INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI®

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

Kaposi's Sarcoma and Sexually Transmitted Disease

Charles Lamar Wiggins

A dissertation submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

University of Washington

1999

Program Authorized to Offer Degree: Department of Epidemiology

Doctoral Dissertation

In presenting this dissertation in partial fulfillment of the requirements for the Doctoral degree at the University of Washington, I agree that the Library shall make its copies freely available for inspection. I further agree that extensive copying of the dissertation is allowable only for scholarly purposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for copying or reproduction of this dissertation may be referred to Bell and Howell Information and Learning, 300 North Zeeb Road, P.O. Box 1346, Ann Arbor, MI 48106-1346, to whom the author has granted "the right to reproduce and sell (a) copies of the manuscript in microform and/or (b) printed copies of the manuscript made from microform."

Signature Charles Lamar Wiggins

Date 6-9-99

University of Washington
Graduate School

This is to certify that I have examined this copy of a doctoral dissertation by

Charles Lamar Wiggins

and have found that it is complete and satisfactory in all respects,
and that any and all revisions required by the final
examining committee have been made

Chair of Supervisory Committee:

David B. Thomas

Reading Committee:

David B. Thomas

Laura A. Koutsky

Noel S. Weiss

Date: 6-9-99

University of Washington

Abstract

Kaposi's Sarcoma and Sexually Transmitted Disease

Charles Lamar Wiggins

Chairperson of the Supervisory Committee

Professor David B. Thomas
Department of Epidemiology

Kaposi's sarcoma (KS) is the most common neoplasm among people infected with human immunodeficiency virus (HIV). A compelling body of evidence suggests that KS is caused by a novel human herpesvirus, referred to as Kaposi's sarcoma-associated herpesvirus (KSHV). The purpose of this investigation was to characterize possible modes of KSHV transmission by examining associations between KS and prior infection with selected pathogens among people with the acquired immunodeficiency syndrome (AIDS).

The HIV/AIDS Reporting System (HARS) was used to identify a cohort of 3,873 residents of thirteen counties in western Washington state who were diagnosed with AIDS during the period 1982-92. Incident cases of KS among cohort members were documented through HARS and by matching the cohort to the Cancer Surveillance System, a population-based cancer registry. Data from communicable disease registries

were linked to the cohort to identify individuals previously infected with *treponema pallidum*, hepatitis-B virus (HBV), hepatitis-A virus (HAV), *salmonella spp.*, *salmonella spp.*, *giardia spp.*, *campylobacter spp.*, and *entamoeba histolytica.*

As documented in earlier studies, the risk of KS in this cohort was far greater among homosexual and bisexual men than other HIV risk groups. By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis, we observed a modest, positive association between KS that occurred following the diagnosis of AIDS and prior infection with *treponema pallidum* (proportional hazards (PH)=1.53, 95 percent confidence interval (CI)=1.18-1.99). We also observed a modest, positive association between KS and prior infection with any of six enteric pathogens examined in this study (PH=1.21, 95 percent CI=0.86-1.70), and individually with five of the six enteric pathogens considered. However, most of the positive associations were modest and were based on a small number of infected individuals. Modest, inverse associations between KS and prior HAV and HBV infection were also observed.

Although some associations observed in this investigation may have been underestimated due to incomplete surveillance in the participating registries, prior infections with these pathogens were not strong or consistent indices of the likely mode of KSHV infection.

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF FIGURES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

LIST OF TABLES

Number

ACKNOWLEDGMENTS

I thank my wife, Andrea, and our sons, Christopher and Jamieson, for their love, patience, and support while I pursued this overwhelming task. I also thank my sister Debbie, who has been a source of inspiration to me since childhood. Thanks to Dad, Barb, Mike, and Amy Wiggins for their love and support. Thanks to Andy Wiggin, Bev and Bob Knecht, Calla and Peter Crowley, Barb and Ross Stevens, Joann Knecht and Guy Reim, and all the cousins: your love and friendship meant a great deal to me throughout this project, and I look forward to spending more time together with you now that it is done.

I especially thank my closest mentors, David Thomas, Laura Koutsky, Noel Weiss, Dave Aboulafia, and Steve Self for their guidance, patience, and support as members of my dissertation committee.

This investigation would not have been possible without the support of the following individuals who now, or at one time or another, worked for the Washington State Department of Health: Maggie Ryland, Leah Cochran, Marcia Goldoft, Larry Klopfenstein, John Kobayashi, Jeanette Stehr-Green, Mariella Cummins, Tim Tyree, Gary Baschuk, Maggie Frederick, Michael Garrick, Dan Jernigan, and Bill Lafferty. Special thanks to Sharon Hopkins, Susan Buskin, and Chris Maden of the Seattle King County Department of Public Health, who were always available to answer my questions and offer useful advice.

Thanks to my friends at the Fred Hutchinson Cancer Research Center who encouraged me and helped me to bring this project to fruition: Lynn Onstad Hawes, Scott Davis, Ken Kopecky, Mary Potts, Diane Guay, Jennifer Hafterson, Nancy Sullivan, Bill Mullin, Paul Maier, Roberta Ray, Peggy Adams Myers, Carol Ure, Janet Daling, Mary Ann Rossing, Margaret Madeleine, and Lynda Voigt. Thanks to the local experts who always found time to guide me during this project, especially Sheila Lukehart, David Koelle, and King Holmes and his worthy assistant, MaryFielder.

Special thanks to my good friend Tom Becker who is, first and foremost, a scientist!

DEDICATION

This dissertation is dedicated to Betty Lou (Reynwald) Wiggins,
Milton Lamar Wiggins, Deborah Lee Wiggins,
and, of course, to Andrea, Christopher, and Jamieson,
with my love

Chapter 1

Background and significance

1.1 Introduction

In 1872, Moritz Kaposi[1] published a report in which he described clusters of small, violateous nodules that occurred primarily on the lower extremities of five men (Kaposi, 1872)[2]. He labeled the condition *idiopathic multiple pigmented sarcoma of the skin*, a term that described the cutaneous lesions and, for more than a century, accurately reflected our knowledge of its etiologic origin. In the years following Kaposi's original report, the medical literature on this subject was comprised largely of case reports and case-series, with a smattering of descriptive epidemiologic studies (Bluefarb 1957). On the basis of this evidence, much of which originated in Europe, Scandinavia, Russia, and the United States, KS was characterized as a rare disease that occurred most often in elderly men of Eastern European, Mediterranean, and Jewish descent.

The occurrence of KS as observed in selected African populations was quite different from that in other parts of the world (Oettlé 1962). The disease tended to occur among relatively young African adults of both sexes, although with a male predominance. A rare, aggressive form of KS was also reported in African children.

---

[1] Moriz Kaposi was born Moritz Kohn in 1837 in the regional trade center of Kaposvár on the river Kapos in southern Hungary (Braun, 1982). Practicing medicine in Vienna, Austria, he changed his surname from Kohn to Kaposi, not wanting to be confused with five other local physicians with the same surname (one of whom had the same first name). In Hungarian, "Kaposi" is the adjective form of Kapos, and thus reflects his birthplace. The correct pronunciation of the name is KOP-osh-ee (Dirckx, 1988).

[2] Although Kaposi's original manuscript focused on the disease in five adult males, it also contains reference to a case in a 10 year-old boy (Kaposi, 1872).

KS was also documented among patients who were iatrogenically immunosuppressed for the purposes of organ transplantation or as treatment for other medical conditions (Penn 1979, Kinlen 1996, Gotti 1997). Only a small percentage these patients developed KS. Nonetheless, these few cases were far more than would have been expected based on KS incidence rates in the general population.

In 1981, reports of KS and pneumocystis pneumonia among young, homosexually active males in the United States heralded the beginning of the AIDS epidemic (Gottlieb 1981, Centers for Disease Control 1981). It later became apparent that the HIV-infected individuals at greatest risk for KS were those who acquired HIV through sexual modes of transmission (Beral 1990). This observation fueled speculation that a sexually transmissible agent, other than HIV, was responsible for KS.

Advances in cellular and molecular biology provided further insight into the mechanisms of this disease. Laboratory scientists developed the ability to grow and sustain large numbers of KS cells in culture (Nakamura 1988, Salahuddin 1988), enabling investigators to demonstrate that cytokines and other chemical messengers exert control over the growth of KS cells *in vitro* (Ensoli 1989). There is now strong evidence that a recently discovered human herpesvirus (HHV8) is a sexually transmitted, etiologic agent of KS (Chang 1996).

This chapter provides a detailed account of the topics summarized in this brief introduction, including the clinical characteristics of KS (Section 1.2), pathogenesis of the disease (Section 1.3), and epidemiologic observations (Section 1.4). Section 1.5

provides an overview of evidence that suggests a sexually transmissible agent, in addition to HIV, is involved in the etiology of KS among people with AIDS. The discovery and subsequent characterization of a novel human herpesvirus that is highly associated with KS is discussed in Section 1.6. The chapter concludes with an overview of the present investigation, including a brief history of the study and research goals (Section 1.8).

1.2 Clinical characteristics of Kaposi's sarcoma

KS is routinely classified into four broad categories based on clinical and epidemiologic characteristics of the disease (Table 1.2.1). Although the clinical presentation and tumor behavior vary among these categories, the histopathology of KS is virtually the same in all affected populations (Friedman-Kien 1990a). The following descriptions of the various types of KS were drawn from reports by Buchbinder (1991) and Friedman-Kien (1990a), unless otherwise noted.

Classical KS, the form of disease first described by Moritz Kaposi in 1872, usually follows a benign, indolent course. Lesions are most often limited to the lower extremities, and are reddish-blue or violet in color. The lesions appear flat to nodular in shape and may form in clusters. In later stages of the disease, the lesions may coalesce to form larger nodules. Extracutaneous sites are sometimes involved, most commonly the gastrointestinal tract and lungs, though other sites may be affected as well. Elderly men of eastern European, Mediterranean, and Jewish ancestry are thought to be at highest risk for this relatively rare form of the disease.

KS is a relatively common tumor in equatorial Africa, accounting for as much as 9 percent of all cancers in some regions (Oettlé 1962). Collectively referred to as the *African endemic* form of the disease, four distinct sub-types of KS have been characterized from the clinical experience with the disease in Africa[3]. *Benign nodular KS* is an indolent form of the disease with a behavior similar to that of Classical KS. *Aggressive KS* is characterized by localized large exophytic nodules and fungating tumors. The aggressive form of the disease may involve multiple lesions with invasion and destruction of underlying tissue and bone. *Florid KS* is characterized by widely disseminated, aggressive nodules which may involve the visceral organs. Benign nodular, aggressive, and florid KS occur primarily in young and middle aged adults. In contrast, *lymphadenopathic* KS is a rapidly progressive form of the disease that primarily affects prepubescent children. There is an absence of cutaneous involvement in these children, and the disease is characterized by rapidly disseminated tumors of the lymph nodes, with occasional visceral involvement. The lymphadenopathic form of KS has not been reported in other regions of the world. African endemic KS primarily effects the Black populations in Africa. White and Asian populations in Africa are at low risk for the disease.

KS has also been recognized as a possible side effect of iatrogenic immunosuppression (Penn 1979, Gotti 1997). Among these patients, KS sometimes

[3] Although HIV-associated KS occurs in Africa, the general categories of disease described here were characterized prior to the advent of the AIDS epidemic.

regressed with the cessation of immunosuppressive therapy (Penn 1988, Trattner 1993), suggesting a role for immunosupression in the development of the disease. KS that develops in this context is referred to as *iatrogenically immunosuppressed KS.*

The epidemic of a fulminant and disseminated form of KS and opportunistic infections among homosexually active young men in California and New York marked the beginning of the AIDS epidemic in the United States (Gottlieb 1981, Centers for Disease Control 1981). This HIV-associated form of the of the disease is referred to as *epidemic KS.* Among people with AIDS, those who acquired their HIV infection via sexual transmission are at the highest risk of developing KS (Beral 1990). In addition to mucocutaneous involvement, epidemic KS is often seen in internal organs. Gastrointestinal KS is common, but is often asymptomatic. Pulmonary disease is slightly less common, and is associated with a poor prognosis. Relatively few AIDS patients die as a direct consequence of KS. However, widely disseminated KS may accompany life-threatening opportunistic infections and other conditions that result from profound immunosuppression induced by HIV.

1.3 Pathogenesis of Kaposi's sarcoma

KS tumors are comprised of spindle-shaped cells, inflammatory cells, endothelial cells, fibroblasts, pericytes, and smooth muscle cells (Roth 1992). The spindle-shaped cells characteristic of this disease are thought to represent the tumor cells of KS (Masood 1993). Because the distinguishing features of a typical KS lesion represent characteristics

of the vascularization process, attention has focused on the cellular constituents of vessels (i.e., endothelial cells, pericytes, and smooth muscle cells) as the possible cells of origin (Rosai 1988). Molecular studies have shown that spindle cells from KS lesions express surface antigens of vascular endothelial cells (Rutgers 1986). Although some discussion persists (Kaplan 1994), the present consensus is that vascular endothelial cells are the most likely cells of origin (Ensoli 1991, O'Connell 1993, Karasek 1994).

Nakamura (1988) and Salahuddin (1988) developed laboratory techniques to sustain the growth of large numbers of KS cells in culture for extended periods of time, which greatly facilitated the study of KS cells *in vitro*. A direct result of these efforts was the identification of numerous cytokines and other factors that mediate the growth of KS cells in culture (Ensoli 1989, Sinkovics 1991, Kaplan 1994). These factors include the HIV *tat* protein (Vogel 1988, Nakamura 1988, Ensoli 1990, Barillari 1993), Oncostatin M (Nair 1992, Miles 1992, Hamilton 1994), interleukin 1 (Nakamura 1988), interleukin 6 (Miles 1990), tumor necrosis factor (Ensoli 1989), granulocyte-macrophage colony-stimulating factor (Ensoli 1989), platelet-derived growth factor (Stürzl 1992), transforming growth factor-beta (Ensoli 1989), and basic fibroblast growth factor (Ensoli 1994). These factors may act in both autocrine and paracrine feedback loops to stimulate the proliferation of KS and some normal tissues (Ensoli 1989, Kaplan 1994, Ensoli 1994).

Evidence that a novel human herpesvirus (HHV8) is an etiologic agent of KS is presented in detail in Section 1.6. Nonetheless, this section would be incomplete without

a brief discussion of the oncogenic potential of this virus. HHV8 has been shown to be highly associated with all forms of KS (i.e., classic, African endemic, iatrogenically immunosuppressed, and AIDS-associated) (Chang 1996). The genetic sequence of HHV8 has largely been determined (Russo 1996, Neipel 1997a), and portions of the HHV8 genome have been shown to be homologous to DNA sequences that are thought to have oncogenic potential. The Bcl-2 family of proteins is known for its ability to modulate apoptosis (i.e., programmed cell death), and HHV8-DNA has been shown to code for an effective Bcl-2 homologue (Cheng 1997). Cyclins are important modulators of the cell cycle, and HHV8-DNA has also been shown to code for a functional cyclin D homolog (Cesarman 1996, Li 1997). The HHV8 genome encodes a G protein-coupled receptor, and some members of this family of proteins have been associated with malignant transformation (Cesarman 1996). HHV8 has also been shown to code for proteins that mimic human cytokine and cytokine response pathways (Moore 1996a), including interleukin 6 (Neipel 1997b). The latter observation may have direct relevance to the autocrine and paracrine signaling mechanisms discussed in the previous paragraph.

1.4 Epidemiologic observations

Scientific investigations of KS in recent years have often focused on the possible role of sexually transmitted agents in the development of the disease (see Section 1.5), the identification of such an agent (see Section 1.6), and on factors that mediate the growth of KS cells in culture (see Section 1.3). Nonetheless, epidemiologic studies have identified

a number of other topics that may be relevant to the development of KS, including the predominance of the disease in males, the association between age and risk of KS, temporal trends in KS incidence rates, KS among homosexually active men without HIV, the association between KS and selected HLA genotypes, and the association between KS and the use of nitrite inhalants.

Sex differences in the risk of KS are well documented (Martin 1993, Beral 1991a). Studies have consistently shown that males are at higher risk for KS than females, though the magnitude of the difference varies by category of disease (Table 1.2.1). Among people with AIDS, the magnitude of the male/female difference varies according to the mode by which HIV was acquired (Table 1.4.1). These observations suggest that sex-specific risk factors, such as hormones, may play a role in the development of KS (Beral 1990). The relationship between selected sex hormones and KS has been examined in a number of studies, with conflicting results. These investigations are summarized in the following paragraphs.

Lunardi-Iskandar (1995a) demonstrated that KS cells *in vivo* and *in vitro* were killed (apparently by apoptosis) by a pregnancy hormone, the β-chain of human chorionic gonadotropin (hCG-β). This observation had the potential for clinical as well as etiologic significance. In clinical trials that were undertaken in response to this research, hCG-β was shown to induce regression of AIDS-related KS lesions in a dose-dependent manner (Gill 1996, Harris 1996, Gill 1997). However, Rabkin and his colleagues (1996) observed no differences in hCG concentrations between cases and controls in a

population-based study of KS in African women. Lunardi-Iskandar et al. (1998) subsequently reported that the anti-KS activity described in their previous report (1995a) was not due to the native hCG heterodimer, but to an associated factor that has not yet been identified.

In one laboratory-based investigation, estradiol was shown to inhibit the production of interleukin-6 from cultured endometrial cell lines (Lahita 1992). This finding is intriguing since interleukin-6 has been shown to stimulate the growth of KS cells *in vitro* (Ensoli 1989, Neipel 1997b).

Christeff (1993) determined the serum concentrations of selected hormones in HIV-positive males with KS (n=62) and without KS (n=34), and for a group of males not infected with HIV (n not reported). Serum levels of dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, testosterone, estrone, and estradiol were compared among the various groups. HIV-positive men with KS had significantly higher levels of all androgens and estrogens than the HIV-negative control group. Levels of DHEA and testosterone were significantly higher in HIV-positive men with KS than those without KS. These findings persisted after the data were stratified by level of CD4 lymphocyte concentration.

Klauke (1995) measured serum levels of testosterone, free testosterone, 17-β-estradiol, luteinizing hormone, and follicle stimulating hormone in HIV-infected males with KS (n=17) and without KS (n=52). The mean serum testosterone and estradiol levels were significantly lower in AIDS patients with KS than in HIV-positive men

without KS. These observations were determined to be independent of tumor stage, level of immunosuppression, and presence of other HIV-related diseases.

Rosenthal (1993) measured serum levels of free testosterone, sex-hormone binding globulin, and dehydroepiandrosterone among 10 AIDS patients with KS, in an unspecified number of AIDS patients without KS, and in HIV-negative controls. Estrogen and progesterone receptors were also compared among the three groups. The groups in this study did not vary with regard to any of these measures, suggesting no association between KS and androgens or estrogens. Similarly, Falutz (1996) found no difference in the levels of testosterone, luteinizing hormone, and follicle stimulating hormone between HIV-positive men with and without KS. Thus, while descriptive epidemiologic studies have repeatedly demonstrated the male predominance of KS, consistent findings regarding possible hormonal mechanisms for this observation have not been demonstrated.

There is wide variation in the age at diagnosis of KS among the various groups at high risk for this disease (Table 1.2.1). Classical KS primarily occurs among the elderly, whereas prepubescent African children are most effected by the lymphadenopathic form of the disease (Friedman-Kien 1990a). The ages of those who developed iatrogenically immunosuppressed-KS reflect the underlying diseases that prompted immunosuppressive therapy. Similarly, the ages of those with AIDS-related KS reflect the groups at risk for infection with HIV. The risk of KS does not appear to vary by age in the group at highest risk for the disease, that is, among homosexually active males with AIDS (Beral 1991a).

For these reasons, it is difficult to interpret the role of age in the development of KS. Nonetheless, it seems prudent to examine the possible effects of age when conducting epidemiologic investigation of this disease.

In the United States, up to 40 percent of homosexual males with AIDS diagnosed in the early 1980's presented with KS at the time of their initial AIDS diagnosis (Beral 1990). Within the first decade of the AIDS epidemic, the percentage of people with AIDS who had KS at the time of their initial AIDS diagnosis decreased to approximately 10-20 percent (Des Jarlais 1987, Haverkos 1990, Rutherford 1990, Beral 1990). Several theories have been proposed to explain this phenomenon, including the expansion of the AIDS case definition to include conditions that may be diagnosed earlier than KS[4], a decrease in the identification or reporting of relatively minor KS lesions, and a decline in exposure to an environmental factor associated with the development of KS (Krown 1997). The interpretation of these studies is limited by the fact that many AIDS patients developed KS in the months and years following their initial AIDS diagnosis, while the surveillance databases on which the investigations were based registered only those cases of KS diagnosed at or near the time of AIDS diagnosis. Therefore, results from these studies did not reflect the full spectrum of AIDS-related KS.

Results from several other investigations suggest that the occurrence of KS among people with AIDS may have been stable over the course of the AIDS epidemic (Jacobson

[4] Beral (1990) adjusted for changes in the AIDS case definition, and continued to observe a temporal decline in the proportion of newly diagnosed AIDS patients with KS.

1990, Muñoz 1993, Montaner 1994, Veugelers 1995, Lundgren 1995). One of these investigations (Lundgren 1995), based on the experience of AIDS patients in Denmark, may reconcile the discrepant findings among the studies. This investigation documented a decline over time in the percentage of patients diagnosed with KS at their initial AIDS diagnosis, from 31 percent among those diagnosed with AIDS prior to 1985 to 13 percent among those diagnosed in 1990. However, the cumulative incidence of KS among cohort members, estimated from time of initial AIDS diagnosis until death or censoring, did not change over the same period of study. Thus, the cumulative incidence of KS remained constant over time but developed later after initial diagnosis of AIDS. Additional research, including retrospective serologic testing for the prevalence of HHV8 in defined cohorts of HIV-infected individuals, may provide further insight into the temporal trends of KS among people with AIDS.

Recent increases in the incidence rates of KS in some populations may have been unrelated to HIV. Some individuals diagnosed with KS early in the AIDS epidemic never became HIV seropositive (Friedman-Kien 1990b). This and other reports of KS among HIV-negative homosexual men (Haverkos 1985, Garcia-Muret 1990) led to speculation that homosexually active males were exposed to an infectious agent, other than HIV, that increased their risk of KS. Similarly, an increase in KS was observed in Sweden in the 1970's, a phenomenon apparently unrelated to HIV (Bendsöe 1990).

There is limited evidence that individuals with selected HLA types are at increased risk of developing KS (Pollock 1983, Prince 1984, Mann 1988, Mann 1990).

However, two population-based studies have failed to confirm these observations (Melbye 1987, Gilles 1987). The relevance of HLA genotype in the development of KS remains unclear.

In response to the emerging AIDS pandemic, and before the discovery of HIV, numerous epidemiologic studies were undertaken to identify risk factors that might explain the new syndrome. Because KS was one of the initial AIDS-defining illness, these studies often sought to identify factors associated with the development of KS. The use of nitrite inhalants emerged from some of these investigations as an important risk factor in the development of KS (Jaffe 1983, Haverkos 1985). Nitrite inhalants were used as sexual stimulants and, as such, were highly correlated with sexual activity. The etiologic agent of KS is thought to be transmitted through sexual contact (Beral 1990), therefore, the association between KS and nitrite inhalants may be explained by the correlation between nitrite inhalants and sexual activity, rather than effects nitrite inhalants themselves (Kaplan 1994, Krown 1997).

1.5 Kaposi's sarcoma and sexually transmitted and enteric pathogens

The hypothesis that an infectious agent is involved in the etiology of KS is not new (Bluefarb 1957, Oettlé 1962)[5]. However, much of the evidence for an association between KS and sexually transmitted and enteric diseases developed following the advent of the AIDS epidemic in the United States and western Europe. This evidence was

[5] Bluefarb (1957) cites an article on this topic that was published in 1902.

initially derived from six studies of KS that involved people with AIDS (Table 1.5.1), though the results from these studies were inconsistent. This hypotheses was eloquently developed in a series of three manuscripts by Dr. Valerie Beral and her colleagues (Beral 1990, Beral 1991b, Beral 1992). Dr. Beral's work and the preceding six studies are summarized in the following paragraphs.

Marmor (1982, 1984) conducted a case-control study of risk factors for the development of KS among homosexually active young men. This case series represented 20 of the first 21 patients with KS to be diagnosed among young homosexually active men at the New York University Medical Center between March, 1979, and August, 1981. Age (± 2 years) and race-matched controls without KS were selected from the practice records of a Manhattan internist whose clientele included a high proportion of homosexually active young men.

All 20 cases and 38 out of 40 controls (95 percent) had positive IgG antibody titers to cytomegalovirus. However, the geometric mean antibody titer in cases (57.5 ± 2.2) was significantly greater than that in controls (27.9 ± 2.5). Antibody titers to Epstein-Barr virus were significantly lower in cases than controls. The levels of IgG antibody to hepatitis A virus, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen were higher in cases than controls, though these differences were not statistically significant.

By univariate analysis, the geometric mean number of partners per month was higher for cases than controls for numerous sexual behaviors. These behaviors included

male homosexual intercourse of any type (Relative Risk (RR)=1.5, p=0.01), insertive oral-genital intercourse (RR=1.3, p=0.05), receptive oral-genital intercourse (RR=1.5, p=0.01), receptive oral-genital intercourse with swallowing of semen (RR=1.9, p=0.003), insertive anal-genital intercourse (RR=1.2, p=0.06), receptive anal-genital intercourse (RR=4.6, p=0.005), receptive anal-genital intercourse with ejaculation of partner (RR=11.3, p=0.0001), occasions of fisting[6] (insertive or receptive) (RR=2.0, p=0.01), and use of amyl nitrate (RR=2.9, p=0.001) and butyl nitrites (RR=2.1, p=0.005).

These observations must be interpreted with caution, given the temporal context of the study. That is, the investigation was conducted early in the AIDS epidemic, prior to the discovery of HIV. Thus, it is likely that the control group was comprised of individuals with and without HIV infection (the authors indicate that two members of the control group were diagnosed with AIDS after being enrolled in the study). In interpreting the results from this investigation, it is not possible to disentangle the risk factors for KS from those for HIV infection. Nonetheless, the study was a valuable contribution at the time, and many of the risk factors for KS that were identified in this investigation were subsequently documented in studies that employed more appropriate control groups.

Goedert (1987) identified a cohort of 86 homosexually active males who were HIV-seropositive at the time they were enrolled for study in May and June of 1982. These individuals, consecutive patients of three primary care physicians in Washington,

---

[6] *Fisting* is the slang term for inserting one's hand and/or a portion of one's arm into a partner's anus.

D.C. and New York City (Manhattan), were followed through June of 1985. Serologic samples were drawn at the beginning of the study, and were examined for evidence of infection with hepatitis B virus, cytomegalovirus, herpes simplex virus (types 1 and 2), Epstein-Barr virus, and syphilis. Eight cases of KS subsequently developed among cohort members during the three-year follow-up period. High levels of antibodies to hepatitis B surface antigen were associated with an increased risk of KS. None of the remaining pathogens were associated with the development of KS. Self-reported behaviors including receptive fellatio, use of enemas, methaqualone use, and pipe smoking were also associated with the development of KS. Seven of the eight KS cases that developed among cohort members were Manhattan residents, which may be relevant to the hypothesis that an infectious agent of KS was more prevalent in the "*epi-centers*" of AIDS infection (i.e., New York, Los Angeles, San Francisco) than in other areas (Beral 1990).

The Vancouver Lymphadenopathy-AIDS Study is an ongoing prospective investigation of homosexually active men who were recruited from six general practices in Vancouver, British Columbia, between November 1982 and February 1984 (Archibald 1990). The investigators conducted a nested case-control study comparing 25 patients with an initial AIDS diagnosis of KS to 48 patients with an initial AIDS diagnosis of other AIDS-defining illnesses.

The study collected self-reported information on history (ever vs. never) of selected sexually transmitted and enteric infections. Positive associations were observed

between KS and a history of syphilis (Odds Ratio (OR)=2.4, 95 percent confidence interval (CI)=0.8 - 6.5) and herpes simplex infection (OR=2.5, 95 percent CI=0.9 - 7.3). There was a negative association between KS and history of giardiasis (OR=0.14, 95 percent CI=0.02 - 0.9). KS did not appear to be associated with prior histories of gonorrhea, nonspecific urethritis, venereal warts, pubic lice, scabies, mononucleosis, hepatitis, amebiasis, or episodes of gay bowel syndrome[7].

Risk of KS was greatest for those with a high number of sex partners, high frequency of sexual contacts occurring in washrooms or parks, and a high frequency of participation in receptive anal intercourse and fisting (both receptive and insertive fisting). KS was also associated with having had sex partners in geographic areas at high risk for AIDS (i.e., San Francisco, Los Angeles, and New York) in the five years prior to enrollment. A strong association was also reported for use of nitrite inhalants.

Similar findings were reported in a subsequent analysis of 353 HIV-seropositive, homosexually active male members of the Vancouver cohort. Archibald (1992) reported associations between the development of KS and use of nitrite inhalants (RR=2.3, 95 percent CI=1.0-5.0) and a high number of sexual contacts during the period 1978-1982 in the AIDS epidemic centers of San Francisco, Los Angeles, and/or New York (RR=3.5, 95 percent CI=1.6-7.6).

---

[7] Gay bowel syndrome is a clinical pattern of anorectal and colon diseases encountered with unusual frequency in homosexually active males (Kazal 1976, Laughon 1988). The clinical diagnosis includes condyloma acuminata, hemorrhoids, nonspecific proctitis, anal fistula, perirectal abscess, anal fissure, amebiasis, benign polyps, viral hepatitis, gonorrhea, syphilis, anorectal trauma and foreign bodies, shigellosis, rectal ulcers, and lymphogranuloma venereum (Kazal 1976).

Self-reported histories of prior sexually transmitted and enteric diseases were similar between San Francisco Clinic Cohort members with and without KS (Lifson 1990a, 1990b). However, this study focused only on those cases of KS that were present at the time of initial AIDS diagnosis.

In the Multicenter AIDS Cohort Study (MACS), Jacobson (1990) examined 391 cohort members who developed AIDS, comparing those with and without KS with regard to prior infections with selected sexually transmitted and enteric pathogens. A higher percentage of patients with KS reported prior oral gonorrhea infection than those without KS (26.2 percent vs. 15.3 percent, respectively, p=0.027). Similarly, those with KS more often reported prior histories of syphilis, shigella or salmonella, amebic dysentery, giardia, and urethral and rectal gonorrhea, though these differences were not statistically significant. In another analysis of MACS data, Armenian (1993) reported an association between KS and multiple episodes of one or more infectious agents.

Results from a study by Moss and colleagues were summarized in a manuscript by Abrams (1990). Though few details of the study methodology are provided in this summary article, the results were presumably derived from a study of gay men in the San Francisco area that was described in a separate manuscript (Moss 1987)[8]. In this study, 151 AIDS patients with KS were compared with 83 AIDS patients who developed opportunistic infections but never had KS. Patients who developed KS were more likely than the comparison group to have had "any parasitic infection" (OR=2.2, p=0.006). In a

[8] These cases appear to be different from those described by Lifson (1990a, 1990b).

multivariable analysis, patients who developed KS were at higher risk than controls for a history of amebiasis, while controls were more likely to have reported a history of other sexually transmitted infections.

In the first of three manuscripts on this topic, Beral (1990) presented data on the occurrence of KS among persons with AIDS in the US. Using data from the CDC's national AIDS surveillance program, Beral and her colleagues characterized the prevalence of KS among people with AIDS according to mode by which they were most likely to have been infected with HIV[9]. For comparison, the investigators estimated the number of KS cases expected to occur among AIDS patients based on 1.) age- and sex-specific incidence rates of KS in the US from 1973-79, and 2.) the percent of transplant recipients in whom KS develops. The investigators interpreted their results as being consistent with an infectious etiology for KS: 1.) people with AIDS who acquired HIV through sexual contact were at much higher risk of KS than other HIV-risk groups, 2.) KS occurred with greater frequency among people with AIDS from major metropolitan areas with a high risk of AIDS ("*epi-centers*" of AIDS) compared to people with AIDS from other regions, suggesting a higher prevalence of the putative etiologic agent in these areas, and 3.) the prevalence of KS at initial AIDS diagnosis declined from 1983 to 1988, suggesting that exposure to the KS agent decreased over time[10].

---

[9] HIV transmission groups included homosexual and bisexual males, heterosexuals born in Caribbean or African countries, "other" heterosexuals (i.e., those not born in the Caribbean or Africa), intravenous drug users, transfusion recipients, and hemophiliacs.

[10] Other interpretations for the decline in prevalence of KS among newly diagnosed AIDS patients were discussed in Section 1.4.

In the second manuscript, Beral (1991b) utilized AIDS surveillance data from Britain. These data included information on the country in which the AIDS patient may have been exposed to HIV, as well as the country of origin of sexual partners who may have been the source of HIV infection. Patients presenting with KS at the time of their AIDS diagnosis were more likely to have acquired their HIV infection in the United States and/or Africa than were AIDS patients without KS. Further, a higher proportion of AIDS patients from the urban center of London (an "*epi-center*" of AIDS) presented with KS than did patients from other areas of Britain.

Finally, in a cohort of homosexually active males with AIDS in Britain, Beral (1992) found that those who were most sexually active were at greatest risk for developing KS. Further, fecal-oral contact, as measured by self-reported participation in selected sexual behaviors such as rimming and fisting were at highest risk of developing KS. The association between fecal-oral contact and KS has been demonstrated in some investigations (Jacobson 1990, Darrow 1992, Grulich 1997), but not others (Lifson 1990a, Lifson 1990b, Elford 1992, Page-Bodkin 1992, van Griensven 1993, Kaldor 1993).

Until 1994, no known agent other than HIV had been consistently associated with the development of KS. The discovery of a new human herpesvirus, highly associated with the disease, ushered in a new era of KS research.

1.6 Discovery of a new herpesvirus highly associated with Kaposi's sarcoma

In December, 1994, Yuan Chang and her colleagues at Columbia University published an article that dramatically changed the direction of KS research (Chang 1994). Using a subtractive hybridization technique, representational difference analysis (RDA)[11], these investigators identified a 330 base-pair DNA sequence that was present in over 90 percent of Kaposi's sarcoma tissue from AIDS patients. In contrast, this DNA sequence was present in less than 15 percent of non-KS tissue from the same AIDS patients, and was not detected in tissue from HIV-negative controls. Portions of this DNA sequence were subsequently determined to be homologous to genes that encode the minor capsid and tegument proteins in two known gammaherpesviruses, the Epstein-Barr virus and herpesvirus saimiri. Both of these viruses are believed to have oncogenic potential[12]. These combined observations suggested the presence of novel human herpesvirus that was strongly associated with Kaposi's sarcoma among people with AIDS.

Numerous PCR-based studies subsequently demonstrated the presence of these DNA sequences in tissue samples from all types of Kaposi's sarcoma, including the classic, African endemic, iatrogenically immunosuppressed, and AIDS-related forms of

---

[11] Representational Difference Analysis (RDA) is used to compare DNA sequences between diseased and non-diseased tissues, and to identify "extra" DNA sequences found only in the diseased tissue (Lisitsyn 1993). This method was first reported less than two years prior to publication of the Chang article (1994), demonstrating the rapid pace of change in the world of molecular biology.

[12] Epstein-Barr virus has been associated with the development of Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal cancer in humans (Mueller 1996). Herpesvirus saimiri has been associated with the development of fulminant polyclonal T-cell lymphoproliferative disorders in some New World monkey species (Rangan 1977).

the disease (Table 1.6.1). Results from these investigations were remarkably consistent. Virtually all KS tissue tested positive by PCR for the target DNA sequences, regardless of the type of KS. The DNA sequences were not as common in non-KS tissue from HIV-positive individuals and were rarely, if ever, detected in non-KS tissue from HIV-negative individuals.

The same DNA sequences were also detected by Cesarman (1995a) in rare body cavity-based lymphomas that occur among people with AIDS (Green 1995), and in Multicentric Castleman's Disease (Soulier 1995), an angiolymphoproliferative disorder that appears to be associated with KS among people with AIDS (Peterson 1993). One study found the DNA sequences in tissue samples from various proliferative skin lesions in HIV-negative, immunosuppressed individuals (Rady 1995). However, these findings were not replicated in subsequent investigations (Adams 1995, Boshoff 1996, Uthman 1996). HHV8 DNA sequences have also been detected in tissue samples from (non-AIDS) patients with multiple myeloma (Rettig 1997, Brousset 1997), leading to speculation that HHV8 may be involved in the etiology of his disease. However, these findings were not replicated in three other investigations (Parravicini 1997, Masood 1997, Whitby 1997). In the latter three studies, serologic evidence (i.e., antibodies) for HHV8 infection was established in only a small percentage of the patients with multiple myeloma, consistent with estimates of HHV8 prevalence in the general population. Further, the descriptive epidemiology of KS differs from that of multiple myeloma (Cottoni 1997), which is inconsistent with a common etiology for both diseases.

Additional research is needed to clarify the association between HHV8 and multiple myeloma.

The initial body of evidence surrounding the discovery of HHV8 DNA in KS lesions was met with both cautious optimism and frank skepticism (Cohen 1995, Levy 1995). Few questioned the evidence in support of a new human herpesvirus. Even before it was isolated and grown in culture, the virus was commonly referred to as HHV8, in recognition of its place as the eighth known human herpesvirus[13]. Rather, at issue was whether or not HHV8 played a role in the etiology of KS. Skeptics cited the fact that the virus was associated with multiple disease entities (KS, body cavity-based lymphoma, Multicentric Castleman's Disease, and proliferative skin lesions) as evidence that HHV8 was a ubiquitous, lymphotrophic, passenger virus that may be reactivated during an immune response. Yet, as evidence accumulated, even the harshest critics were compelled to reevaluate their views.

Whitbey and colleagues (1995) were the first to demonstrate that the presence of HHV8 DNA sequences in subjects without KS was predictive of subsequent development of KS in the same individuals. These investigators tested for the presence of HHV8 DNA sequences in the peripheral blood mononuclear cells (PBMC) of people with AIDS-related KS, HIV-positive individuals without KS, and among HIV-negative controls. HHV8 DNA sequences were detected in 24 of 46 (52 percent) of the AIDS patients with KS, and in 11 of 143 (8 percent) HIV-positive subjects without KS. No evidence of

[13] The virus is also commonly referred to as Kaposi's sarcoma associated herpesvirus (KSHV).

HHV8 infection was found in the HIV-negative controls. The investigators followed the 143 HIV-positive individuals without KS for a median of 30 months from the time their first or only blood sample was drawn. Six of 11 subjects (55 percent) with evidence of HHV8 infection subsequently developed KS. Only 9 percent (12/132) of subjects without evidence of HHV8 infection developed KS in the same time period. Additional prospective investigations have similarly documented that individuals infected with KSHV are at much higher risk of subsequently developing KS than those not so infected (Moore 1996b, Gao, 1996a, Melbye 1998, Grulich 1999).

HHV8 DNA sequences were detected by PCR *in situ* hybridization[14] in endothelial cells and spindle cells from KS lesions, but not in cells from surrounding tissue (Boshoff 1995, Staskus 1997). Spindle cells are thought to represent the tumor cells of KS (Masood 1993). The specificity of infection indicated by studies utilizing the *in situ* hybridization technique suggests that HHV8 is not simply a lymphotrophic passenger virus in these lesions.

Serologic tests for antibodies to HHV8 have now been developed. These assays consistently detected evidence of HHV8 infection in most, but not all, subjects with KS, regardless of the HIV status of the patient.(Table 1.6.2). There is some discrepancy, however, between the various assays in estimating the proportion of the general population that may have been infected with the virus. Estimates for the general

[14] PCR *in situ* hybridization is a technique that amplifies DNA sequences from a specific cell. Results from this test are thought to be highly specific to the contents of the target cell.

population based on antibodies to latency-associated nuclear antigens were consistently in the range of 0-4 percent (Gao 1996a, Kedes 1996, Gao 1996b, Simpson 1996). In contrast, one study based on antibodies to products of the lytic phase of the virus suggested that up to 20 percent of the general population may have been infected with HHV8 (Lennette 1996). Further, a comparison of six antibody assays for HHV8 indicated that the various assays frequently disagreed on the HHV8 status of individual subjects (Rabkin 1998). Additional work is needed to clarify the reasons for these discrepant observations.

HHV8 has been isolated and grown in culture (Renne 1996, Foreman 1997), and the DNA sequence of HHV8 has been largely determined (Russo 1996, Moore 1996c). The HHV8 genome has been shown to harbor sequences that may have oncogenic potential (see Section 1.3). The HHV8 genome codes for homologues of the cellular anti-apoptotic protein Bcl-2 and cellular cyclin D1 (Cesarman 1996, Ganem 1997). It also encodes for proteins related to cellular cytokines, which may be relevant to previous reports regarding the importance of these factors in the growth of KS cells in culture.

Indirect evidence regarding the role of HHV8 in the development of KS also came from a natural experiment that was unwittingly undertaken during the course of the AIDS epidemic. Some AIDS patients have received antiviral therapy for retinitis and other viral-related conditions. There is limited evidence of KS remission in AIDS patients following treatment with anti-herpes agents (Morfeldt 1994, Mocroft 1996, Glesby 1996).

The tools of molecular biology have also provided opportunities to examine possible modes of transmission for HHV8. Investigators have now examined saliva (LaDuca 1998, Blackbourne 1998, Boldogh 1996, Koelle 1997), semen (LaDuca 1998, Huang 1997, Howard 1997, Lin 1995, Ambroziak 1995, Monini 1996), and prostate tissue (Monini 1996) for evidence of HHV8 infection, with varying results. However, as the assays for HHV8 are improved and methods for their application refined, these tools will be invaluable for determining the modes of HHV8 transmission and in further evaluating the role of HHV8 in the development of KS.

1.7 A brief history and research objectives of this investigation

The present study was initially conceived in 1992 as a mechanism to further characterize the association between KS and selected sexually transmitted and enteric pathogens among people with AIDS. At that time, there were no strong candidates for the etiologic agent of KS, though there was compelling evidence that a sexually transmitted agent, in addition to HIV, was involved in the development of the disease among people with AIDS. Numerous disease agents had been investigated, but most studies had been conducted in relatively small cohorts, were not population-based, or relied on self-reports of prior exposure to the pathogens under investigation.

In 1992, surveillance for AIDS, cancer, sexually transmitted diseases, and enteric pathogens was well established in western Washington state. Registries for these diseases, alone and in combination, had already served as the basis for numerous

epidemiologic investigations. The investigators saw an opportunity to address the question of KS etiology with the combined resources of these population-based registries. Initial plans called for a cohort study, with the cohort to be defined as all western Washington residents diagnosed with AIDS. Occurrence of the outcome of interest, KS, among cohort members could be determined through the surveillance efforts of both the HIV/AIDS and cancer registries. Exposures of interest, including syphilis, hepatitis B, *giardia spp.*, *salmonella spp.*, *shigella spp.*, *campylobacter spp.*, and *entamoeba histolytica*, could be documented among cohort members through the registries that conducted surveillance for these diseases.

The investigators worked with representatives from the various disease registries to develop a protocol that would allow the study to be conducted while maintaining the highly confidential nature of these files. A research proposal was agreed upon after many months of negotiation. This proposal was subsequently reviewed, modified, and approved by separate Human Research Review Committees at the Washington State Department of Health, the University of Washington, and the Fred Hutchinson Cancer Research Center. Funding for the study was initially obtained from the University of Washington Royalty Research Fund, and later in the form of an R01 research grant from the National Cancer Institute[15].

[15] The research proposal for this investigation received the highest priority score in its study section at the National Cancer Institute.

As outlined in the original research proposal, the research goals for this investigation included the following:

1. Determine whether serologic evidence of syphilis infection is associated with the development of Kaposi's sarcoma among:
   a. homosexually active men with AIDS
   b. persons with AIDS who are not homosexually active men
2. Assess whether the following parameters of a syphilitic infection are associated with increased risk of Kaposi's sarcoma:
   a. interval between diagnosis of syphilis and Kaposi's sarcoma
   b. syphilis diagnosed and treated in the primary, secondary, and tertiary stage
3. Among homosexually active men with AIDS, determine whether enteric infections including giardiasis, salmonellosis, shigellosis, campylobacterosis, and hepatitis are associated with development of Kaposi's sarcoma among people with AIDS

A compelling body of evidence now supports HHV8 as the etiologic agent of KS, and it is unlikely that syphilis and the other infectious agents under investigation in the present study represent etiologic agents of KS. Nonetheless, this investigation may contribute to the epidemiology of KS by using these agents as surrogates for behaviors that may be relevant to the transmission of HHV8. The results from this investigation must be interpreted in this context.

The second chapter of this dissertation describes the disease registries that contributed to this investigation. Chapter 2 also describes the methods and results of the record linkages that created the research database. Chapter 3 provides information on the types of cancer that were diagnosed among people with AIDS, and discusses issues of surveillance for cancer in this population. The association between KS and selected sexually transmitted and enteric pathogens is presented in Chapter 4. Chapter 5 includes a brief summary of the study results, and a discussion of the strengths and limitations of the investigation.

Table 1.2.1 Clinical and epidemiological manifestations of KS *

Type	*Population at risk*	*Age at onset (years)*	*Male/ female ratio*
Classical	Eastern European Jewish and Mediterranean background	50-80	10-15:1
African endemic			
Sub-types			
Benign nodular	Black African adults	25-40	17:1
Aggressive	Black African adults	25-40	17:1
Florid	Black African adults	25-40	17:1
Lymphadenopathic	Black African children	2-15	3:1
Iatrogenic immunosuppression	Patients on azathioprine, cyclosporin, and cortico-steroids; renal transplant recipients, systemic lupus erythematosus, temporal arthritis	20-60	2.3-1
Epidemic AIDS-related	Homosexual men (95 %) Other risk groups (5 %)	18-65	106:1

* Adapted from Friedman-Kien (1990a) and Martin (1993)

Table 1.4.1. Percentage of people with AIDS who had KS at the time of their initial AIDS diagnosis, by HIV transmission group and sex[•]

HIV transmission group	*Sex*	*Percent with KS*
Homosexual/bisexual	Male	19.8
Homosexual/bisexual *and* injecting drug user	Male	17.1
Born in Caribbean/Africa	Male	6.0
	Female	3.6
Heterosexual partner of person born in Caribbean/Africa	Male	6.2
	Female	5.1
Injecting drug user	Male	2.7
	Female	1.8
Blood transfusion	Male	3.6
	Female	2.1
Hemophilia	Male	2.1
	Female	1.1

[•] From Peterman (1993)

Table 1.5.1 Summary of studies that have investigated the association between KS and prior infections with sexually transmitted and enteric pathogens (*page one of two*)

Investigator, geographic area, and year of report	*Study design*	*Summary of relevant findings*	*Limitations*
Marmor, New York (1982, 1984)	Case-control	KS patients at higher risk than controls for cytomegalovirus and selected antibodies to Hepatitis A and B	Early study of AIDS cases with non-diseased controls; interpretation not strictly comparable to other studies (see text)
Goedert, Washington, DC and New York, NY (1987)	Cohort	KS not associated with serological evidence of syphilis, herpes (types 1 & 2), cytomegalovirus, or Epstein-Barr virus. KS associated with increased levels of antibodies to Hepatitis B surface antigen	Serologic specimens collected at time of enrollment do not provide information regarding the timing of infection relative to the advent of disease. Also, study based on a small number of KS cases (n = 8)
Archibald, Vancouver, BC (1990, 1992)	Nested case-control	Positive associations observed between KS and prior infection with syphilis (OR=2.4, 95 percent confidence interval (CI) = 0.8-6.5), and herpes (type unspecified) (OR=2.5, 95 percent CI=0.9-7.3)	Crude measure of prior infections: self-reported, ever vs. never. No information on timing of exposure relevant to development of KS

continued

Table 1.5.1 continued (*page two of two*)

Investigator, geographic area, and year of report	*Study design*	*Summary of relevant findings*	*Limitations*
Lifson, San Francisco (1990a, 1990b)	Cohort	Persons with KS were not more likely to report a history of selected sexually transmitted or enteric diseases, including syphilis, compared to AIDS patients without KS	Assessment of prior infection based solely on self-reports; no data available on timing of prior infections with regard to development of KS; limited ascertainment of KS cases
Jacobson, Multicenter AIDS cohort: Chicago, Pittsburgh, Baltimore, Los Angeles (1990)	Cohort	AIDS patients with KS were more likely than other AIDS patients to have reported a history of gonorrhea, however, no associations were observed with other sexually transmitted or enteric diseases, including syphilis	Self-reported history of prior infections (ever vs. never), with no information on timing of exposure
Moss, (Summarized in an article by Abrams (1990))	Case-control	AIDS patients who presented with KS were more likely to have had a prior parasitic infection than controls (OR=2.2, p=0.006)	Study apparently limited to KS at time of initial AIDS diagnosis; few details of study reported of study reported

Table 1.6.1 PCR-based investigations that have reported evidence of HHV8-DNA sequences in persons with and without Kaposi's sarcoma (*page one of four*)

Study	*Source of tissue*	*Positive tests/ number tested (percent positive)*
Chang (1994)	• AIDS-related KS	25/27 (93 %)
	• AIDS-related lymphomas	3/27 (11)
	• Lymph nodes from AIDS patients	3/12 (25)
	• Non-AIDS lymphomas	0/29 (0)
	• Non-AIDS lymph nodes	0/7 (0)
	• Vascular tumors	0/5 (0)
	• Opportunistic infections	0/13 (0)
	• Consecutive surgical biopsies	0/49 (0)
Su (1995)	• AIDS-related KS	4/4 (100)
	• Non-AIDS-related KS	2/3 (67)
	• Lymph nodes from AIDS patients	0/5 (0)
	• Other lymphoid lesions (non-AIDS)	0/32 (0)
Huang (1995)	• AIDS-related KS	12/12 (100)
	• Classic KS	7/8 (87)
	• African endemic KS	7/10 (70)
Dupin (1995)	• Classic (Mediterranean) KS	5/5 (100)
	• AIDS-related KS	4/4 (100)
	• HIV-negative controls	0/6 (0)
Collandre (1995)	• Peripheral blood mononuclear cells in HIV-positive individuals:	
	with KS	2/10 (20)
	without KS	0/9 (0)

continued

Table 1.6.1 continued *(page two of four)*

Study	*Source of tissue*	*Positive tests/ number tested (percent positive)*
Boshoff (1995b)	• Classic KS	16/17 (94)
	• KS in iatrogenically immunosuppressed transplant patients	8/8 (100)
	• AIDS-related KS	14/14 (100)
	• KS in HIV-negative homosexual male	1/1 (100)
	• HIV-negative angioma/angiosarcoma	0/4 (0)
	• HIV-negative skin nevi	0/3 (0)
	• HIV-negative granulation tissue	0/4 (0)
Ambroziak (1995)	• HIV-positive homosexual males with KS:	
	KS tissue	12/12 (100)
	non-KS tissue	4/11 (36)
	• HIV-negative homosexual male with KS:	
	KS tissue	1/1 (100)
	non-KS tissue	0/1 (0)
	• Peripheral blood mononuclear cells (PBMC) from HIV-positive subjects with KS	7/7 (100)
	• Peripheral blood mononuclear cells (PBMC) from HIV-negative subjects with KS	3/3 (100)
	• Peripheral blood mononuclear cells (PBMC) from HIV-positive subjects without KS	0/6 (0)
	• Peripheral blood mononuclear cells (PBMC) from HIV-negative subjects without KS	0/14 (0)

continued

Table 1.6.1 continued *(page three of four)*

Study	*Source of tissue*	*Positive tests/ number tested (percent positive)*
Moore (1995)[b]	• AIDS-related KS	10/11 (91)
	• HIV-negative homosexual men with KS	4/4 (100)
	• Classic KS	6/6 (100)
	• PBMC from healthy, HIV-negative subjects	0/10 (0)
	• Skin from healthy subjects undergoing elective plastic surgery	1/11 (9)
Schalling (1995)	• AIDS-related KS in adult African males	11/11 (100)
	• AIDS-related KS in adult African females	5/5 (100)
	• AIDS-related KS in African children	1/1 (100)
	• African endemic KS (HIV-negative) in adult African males	14/14 (100)
	• African endemic KS (HIV-negative) in adult African females	2/2 (100)
	• African endemic KS (HIV-negative) in African children	2/2 (100)
	• AIDS-related KS in adult Swedish males	6/6 (100)
	• AIDS-related KS in adult Swedish females	2/2 (100)
	•"Sporatic" (HIV-negative) KS in adult Swedish males	2/2 (100)
	•"Sporatic" (HIV-negative) KS in adult Swedish females	1/1 (100)
Gluckman (1995)[c]	• HIV-negative, iatrogenically immuno-suppressed female with KS	1/1 (100)

continued

Table 1.6.1 continued *(page four of four)*

Study	*Source of tissue*	*Positive tests/ number tested (percent positive)*
Adams (1995)	• Skin cancer in immunocompetent patients	
	Epithelial cancers	0/28 (0)
	Cutaneous lymphomas	0/13 (0)
Chuck (1996)	• African endemic KS	4/4 (100)
	• KS in HIV-negative homosexual males	1/2 (50)
Utĥman (1996)	• AIDS-related KS	23/23 (100)
	• Non-KS skin lesions in HIV-positive subjects	0/28 (0)
	• KS in HIV-negative subjects	5/5 (100)
	• Non-KS skin lesions in HIV-negative subjects	0/53 (0)
Simon (1996)	• AIDS-related KS	16/16 (100)
	• Classical KS	4/4 (100)
Kemény (1996)	• Classic KS	24/24 (100)
	• HIV-negative patients with	
	basalioma	0/3 (0)
	pyogenic granuloma	0/3 (0)
	hemangioma	0/3 (0)

[a] Ambroziak and his colleagues also examined the cells and cell-free fluids from saliva and semen of KS patients to further characterize possible modes of transmission for HHV8. Evidence of HHV8 was not detected in any of these fluids.

[b] Moore and Chang also determined the DNA sequences for a sample of the KS tissue and determined that the sequences were more than 98 percent identical for the three types of KS. This evidence suggests that the same agent is responsible for all forms of KS.

[c] This was an intriguing case report of an HIV-negative female who developed KS following an allogeneic bone marrow transplant as treatment for acute myeloblastic leukemia. The donor was her HLA-identical brother, who was a healthy, HIV-negative homosexual male.

Table 1.6.2 Results from serologic tests for antibodies to HHV8 antigens among people with and without KS *(page one of eleven)*

Study	*Description of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Miller (1996)	Immunoblot assay used to detect antibodies to p40 antigen *	• AIDS-related KS	32/48 (67)
		• HIV-positive individuals without KS	7/54 (13)
	Immunofluorescence assay used to detect antibodies to p40 antigen *	• AIDS-related KS	31/48 (65)
		• HIV-positive individuals without KS	7/54 (13)
Gao (1996a)	Immunoblot assay to detect antibody to two nuclear antigens (p226, p234) †	• Homosexual men with AIDS-related KS	32/40 (80)
		• HIV-positive homosexual males who died from AIDS but never developed KS	7/40 (18)
		• HIV-positive hemophiliacs without KS	0/20 (0)
		• HIV-negative blood donors	0/122 (0)
		• HIV-negative patients with high titres to EBV capsid antigen	0/22 (0)
Kedes (1996)	Immunofluorescence assay to detect latency-associated nuclear antigen ‡	• AIDS-related KS	37/45 (82)
		• HIV-negative with KS	1/1 (100)
		• HIV-negative blood donors	0/50 (0)
		• College virgins	0/18 (0)

continued

Table 1.6.2 continued *(page two of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Gao (1996b)	Immunofluorescence assay for HHV8 latency-associated nuclear antigen [§]	*North America*	
		• Homosexual men with AIDS-related KS	35/40 (88)
		• Homosexual men who died from AIDS but never had KS	12/40 (30)
		• HIV-positive hemophiliacs without KS	0/20 (0)
		• HIV-negative patients with high titres of EBV capsid antigen	0/69 (0)
		• HIV-negative blood donors	0/122 (0)
		Italy	
		• AIDS-related KS	10/14 (71)
		• HIV-negative with KS	11/11 (100)
		• Blood donors from the general population	4/107 (4)
		Uganda	
		• AIDS-related KS	14/18 (78)
		• HIV-negative KS	1/1 (100)
		• HIV-positive without KS	18/35 (51)
		• HIV-negative without KS	24/47 (51)

continued

Table 1.6.2 continued *(page three of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Gao (1996b) *continued*	Immunoblot assay for HHV8 latency-associated nuclear antigen [§]	*North America*	
		• Homosexual men with AIDS-related KS	32/40 (80)
		• Homosexual men who died from AIDS but never had KS	7/40 (18)
		• HIV-positive hemophiliacs without KS	0/20 (0)
		• HIV-negative patients with high titres of EBV capsid antigen	0/69 (0)
		• HIV-negative blood donors	0/122 (0)
		Italy	
		• AIDS-related KS	11/14 (79)
		• HIV-negative with KS	11/11 (100)
		• Blood donors from the general population	4/107 (4)
		Uganda	
		• AIDS-related KS	16/18 (89)
		• HIV-negative KS	1/1 (100)
		• HIV-positive without KS	25/35 (71)
		• HIV-negative without KS	29/47 (62)

continued

Table 1.6.2 continued *(page four of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Lennette (1996)	Immunofluorescence assay for antibodies to lytic HHV8 antigens	*United States*	
		• AIDS-related KS	84/87 (97)
		• HIV-negative with KS	3/4 (75)
		• HIV-positive homosexual men without KS	87/94 (93)
		• HIV-positive heterosexual IV drug users without KS	3/13 (23)
		• HIV-positive women without KS	7/33 (21)
		• Children under the age of 16 years [1]	10/263 (4)
		• Adults, 16 years of age and older [1]	3/174 (19)
		• Blood donors [1]	9/44 (20)
		• Adult women recruited for prospective studies of HIV	15/54 (28)
		• Hemophiliacs under the age of 18 years	3/35 (9)

continued

Table 1.6.2 continued *(page five of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Lennette (1996) *continued*	*(Immunufluorescence-lytic HHV8)*	*(United States)*	
		• Hemophiliacs of all ages	7/48 (15)
		• Bone marrow recipients	4/38 (11)
		• Hodgkin's disease (adults)	11/52 (21)
		• Non-Hodgkin lymphoma	2/37 (5)
		• Nasopharyngeal carcinoma	2/20 (10)
		• Reactivated Epstein-Barr virus	8/40 (20)
		• Rheumatoid arthritis	5/20 (25)
		Africa	
		• HIV-negative with KS **	28/28 (100)
		• Zimbabwe ‖	12/37 (32)
		• Nigeria ‖	29/52 (56)
		• Zaire ‖	13/16 (82)
		• Uganda ‖	63/82 (77)
		• The Gambia ‖	38/45 (84)
		• Ivory Coast ‖	7/7 (100)

continued

Table 1.6.2 continued *(page six of eleven)*

Study	*Type of assay*	*Source of tissue sample*	***Positive tests/ number tested (percent positive)***
Lennette (1996) *continued*	*(Immunufluorescence-lytic HHV8)*	*Other geographic areas*	
		• Haiti [‖]	15/52 (29)
		• Dominican Republic [‖]	5/40 (13)
		• Guatemala (hemophiliacs)	2/20 (10)
	Immunofluorescence assay for antibodies to latent HHV8 antigens	*United States*	
		• KS (AIDS-related and HIV-negative subjects combined)	47/91 (52)
		• HIV-positive homosexual men without KS	0/94 (0)
		• HIV-positive heterosexual IV drug users without KS	0/13 (0)
		• HIV-positive women without KS	0/33 (0)
		• Children under the age of 16 years [‖]	0/263 (0)
		• Adults, 16 years of age and older [‖]	0/174 (0)
		• Blood donors [¶]	0/44 (0)

continued

Table 1.6.2 continued *(page seven of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Lennette (1996) *continued*	*(Immunufluorescence-latent HHV8)*	*(United States)*	
		• Adult women recruited for prospective studies of HIV	0/54 (0)
		• Hemophiliacs under the age of 18 years	3/35 (0)
		• Hemophiliacs of all ages	0/48 (0)
		• Bone marrow recipients	0/38 (0)
		• Hodgkin's disease (adults)	0/52 (0)
		• Non-Hodgkin lymphoma	0/37 (0)
		• Nasopharyngeal carcinoma	0/20 (0)
		• Reactivated Epstein-Barr virus	0/40 (0)
		• Rheumatoid arthritis	0/20 (0)
		Africa	
		• HIV-negative with KS **	28/28 (100)
		• Zimbabwe ‖	4/37 (11)
		• Nigeria ‖	3/52 (6)
		• Zaire ‖	4/16 (25)

continued

Table 1.6.2 continued *(page eight of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Lennette (1996) *continued*	*(Immunufluorescence-latent HHV8)*	*(Africa)*	
		• Uganda	9/82 (11)
		• The Gambia	11/45 (29)
		• Ivory Coast	4/7 (57)
		Other geographic areas	
		• Haiti	0/52 (0)
		• Dominican Republic	0/40 (0)
		• Guatemala (hemophiliacs)	0/20 (0)

continued

Table 1.6.2 continued *(page nine of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Simpson (1996)	Enzyme-linked immunosorbent assay for antibodies to HHV8 capsid-related proteins	• AIDS-related KS in homosexual men from the US and UK	46/57 (81)
		• HIV-positive homosexual men without KS (US & UK)	5/16 (31)
		• AIDS-related KS in Ugandans	14/17 (82)
		• HIV-positive Ugandans without KS	16/34 (47)
		• HIV-negative Ugandans	6/17 (35)
		• Greek KS cases	17/18 (94)
		• Greek controls without KS	3/26 (12)
		• HIV-positive hemophiliacs	0/28 (0)
		• HIV-negative hemophiliacs	1/56 (2)
		• HIV-positive IV drug abusers	2/38 (5)
		• HIV-negative IV drug abusers	0/25 (0)
		• Blood donors	9/291 (3)
		• HIV-negative attendees of a sexually transmitted disease clinic	
		Homosexual males	*Not done*
		Heterosexual males	*Not done*
		Heterosexual females	*Not done*
		• HIV-positive women of African origin	*Not done*
		• HIV-negative children with rash or fever	*Not done*

continued

Table 1.6.2 continued *(page ten of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Simpson (1996) *continued*	Immunofluorescence assay for HHV8 latent antigens	AIDS-related KS in homosexual men from the US and UK	84/103 (82)
		HIV-positive homosexual men without KS (US & UK)	10/33 (30)
		AIDS-related KS in Ugandans	*Not done*
		HIV-positive Ugandans without KS	18/34 (53)
		HIV-negative Ugandans	9/17 (53)
		Greek KS cases	17/18 (94)
		Greek controls without KS	3/26 (12)
		HIV-positive hemophiliacs	0/26 (0)
		HIV-negative hemophiliacs	*Not done*
		HIV-positive IV drug abusers	0/38 (0)
		HIV-negative IV drug abusers	0/25 (0)
		Blood donors	4/267 (2)
		HIV-negative attendees of a sexually transmitted disease clinic	
		Homosexual males	8/65 (12)
		Heterosexual males	4/75 (5)
		Heterosexual females	2/26 (8)
		HIV-positive women of African origin	3/15 (20)
		HIV-negative children with rash or fever	0/24 (0)

continued

Table 1.6.2 continued *(page eleven of eleven)*

Study	*Type of assay*	*Source of tissue sample*	*Positive tests/ number tested (percent positive)*
Kedes (1997)	Immunofluorescence assay for latency-associated nuclear antigen †† 	HIV-positive ‡‡ HIV-negative	12/302 (4) 1/84 (1)

* The authors identified a 40 kilodalton protein (p40) that was thought to represent a lytic phase product of HHV8.

† The two antigens, p226 and p234, were thought to represent latent nuclear antigens associated with HHV8.

‡ The latency-associated nuclear antigen (LANA) used in this study were derived from the BCBL-1 cell line (body cavity-based B-cell lymphoma) that was latently infected with HHV8 (but not infected with EBV).

§ The investigators developed a new immunofluorescence assay to detect the latent nuclear antigens described in their previous study (Gao 1996a). Both assays were applied to the same groups as in the previous study (Gao 1996a). However, there were additional cases in some study groups in the 1997 study.

‖ The authors indicated that these individuals had been drawn from the general population, but specific sampling methodology was rarely documented.

¶ Blood donors from the San Francisco Bay area.

** These HIV-negative KS patients were from Africa. Specific countries of origin were not listed.

†† The investigators used the same assay as in their previous investigation (Kedes 1996). The study population was composed of HIV-positive women
who were at high risk of HIV infection.

‡‡ Only two of the HIV-positive women in this investigation had KS. Both of these women tested positive for the HHV8 latency-associated nuclear antigen.

Chapter 2

Record linkage methodology and results

2.1 Overview

This investigation was conducted with the combined resources from population-based registries of HIV/AIDS, cancer, syphilis, and other selected communicable diseases that were diagnosed among residents of western Washington state. The study cohort was defined as all residents of thirteen counties[1] in western Washington State who were diagnosed with the acquired immunodeficiency syndrome (AIDS) during the time period 1982-1992 and were registered in the HIV/AIDS Reporting System (HARS). Cohort members were identified through routine AIDS surveillance conducted by the Washington State Office of HIV/AIDS Epidemiology and Evaluation. Occurrences of cancer, syphilis, and other selected communicable diseases among individual cohort members were documented from the corresponding disease registries that serve this geographic region.

This chapter describes each of the component data sets and documents the methods by which their information was combined to create the research data base for this investigation. The research data base was constructed from a series of computer-assisted record linkages among the component data bases. Section 2.2 introduces general concepts and terms relevant to computer-assisted record linkage. The specific record

[1] The thirteen counties are Clallam, Grays Harbor, Island, Jefferson, King, Kitsap, Mason, Pierce, San Juan, Skagit, Snohomish, Thurston, and Whatcom. The study was limited to residents of this geographic region because it represents the area of population-based coverage for the Cancer Surveillance System.

linkage methodology employed in this investigation is summarized in Section 2.3. Characteristics of the component data bases are described in sections 2.4-2.7. Results from each pair-wise linkage of these data bases are documented in Sections 2.8-2.11.

This project was governed by strict guidelines that were designed to maintain the confidentiality of patient records. These guidelines were formalized in a confidentiality agreement among the participating organizations, and are summarized in Section 2.12. Copies of the confidentiality agreement and a subsequent addendum to the agreement are contained in Appendices 1 and 2, respectively.

2.2 Introduction to computer-assisted record linkage

Briefly stated, record linkage "in the present context is simply the bringing together of information from two records that are believed to relate to the same individual or family" (Newcombe 1988). The records to be matched frequently come from separate sources, though record linkage techniques are sometimes used to match records within a single data base. The concept of record linkage is not new (Newcombe 1959), but a formal discussion of its underlying mathematical principles did not appear until 1969 (Felligi 1969). The ability to use record linkage for research purposes was greatly enhanced with the advent of the computer (Newcombe 1959). Record linkages have served as the basis for numerous epidemiologic investigations, both in Washington state (Daling 1982, Emerson 1991, Frost 1992, Demers 1992, Demers 1994, Holt 1997a, Holt 1997b, Doody 1997, Mueller 1997), and nationwide (Potosky 1993, Herman 1997).

Computerized record linkages have been particularly useful in the study of cancer of among people with AIDS (Goedert 1998, Wiggins 1995, Coté 1995, Reynolds 1993, Coté 1991, Reynolds 1990).

The purpose of this section is to define the terminology that is used throughout the manuscript to describe the concepts and methods of computer-assisted record linkage. The term, *component data base*, refers to the source of individual records to be linked. As outlined in Sections 2.4-2.7, the component data bases for this investigation were population-based registries of HIV/AIDS, cancer, syphilis, and other selected communicable diseases. The term, *linkage variable(s)*, designates those data items that, alone or in combination, were used to link records from one data set with those in another. Name, birth date, and Social Security number were used as linkage variables in this investigation. Ideally, every record in the component data base should contain a valid entry for each linkage variable. Linkage variables, alone or in combination, should also uniquely identify individuals within each component data set. Records from separate component data bases are said to *match*, or to be *linked*, when the values for one or more linkage variables in two component data bases are judged to represent the same individual. *Record linkage criteria* are the rules by which two records are determined to match.

Record linkage procedures are broadly categorized as *deterministic* or *probabilistic*, depending on the criteria that are chosen to define a match between two records. In deterministic linkages, records are judged to match if and only if the values

for the linkage variables are the same in both component data sets. In contrast, probabilistic record linkages employ a mathematical algorithm to express the degree of similarity between records from two component data bases, even when the values for one or more the linkage variables do not match exactly. In probabilistic linkages, therefore, the investigator must choose an appropriate algorithm to express the degree of similarity between two records, as well a threshold value below which records will be considered unlikely to match.

All record linkages conducted for the purposes of this investigation were based on deterministic matches. The choice of deterministic rather than probabilistic techniques was a practical decision. Specifically, computer software to conduct probabilistic linkages was prohibitively expensive, and beyond the resources allocated for this investigation. In contrast, tools for conducting deterministic linkages were readily available from standard statistical software packages, as outlined in Section 2.3.

2.3 Record linkage methodology

The first step in the record linkage process was to identify data items common to each of the component data sets that could reasonably serve as linkage variables. To this end, potential linkage variables were judged according to the following criteria: 1.) their ability to uniquely identify members of the component data set, and 2.) availability of valid information recorded in the component data set. Variables from each of the four component data sets were assessed according to these criteria. This exercise was

conducted for individual linkage variables and for selected combinations of linkage variables.

Results from these assessments are summarized in Sections 2.4-2.7 according to the standard tabular format outlined in Table 2.3.1. In this standard format, linkage variables (alone or in combination) are listed in the first column of each table. Information displayed in columns 2-5 characterizes the ability of each linkage variable or combination of variables to uniquely identify a member of the component data set. Subjects without valid information recorded for a specific linkage variable or combination of variables (i.e., *missing* data) are enumerated in column 6.

Name and birth date were two data items that generally met these criteria in all component data sets (specific exceptions are discussed in Sections 2.4-2.7). Social Security number was also available for most records in both the HIV/AIDS Reporting System and Cancer Surveillance System, and served as an additional linkage variable for the union of these two files.

The following example describes the record linkage methodology that was used in this investigation. For the purpose of this example, there are two component data sets that are stored as computer files. These files will be referred to as FILE_A and FILE_B, respectively. Both files contain a variable that uniquely identifies each record in its respective data set. This identification variable is called ID_A in FILE_A and ID_B in FILE_B, and the values for ID_A and ID_B are unrelated. Both files also include a variable called SSN that represents Social Security number. Computer-assisted record

linkage can be used to combine information from the two files for those records that are determined to represent the same individual. Records from FILE_A and FILE_B will be considered to match (i.e., represent the same individual) if the Social Security number recorded in FILE_A has the same value as the Social Security number recorded in FILE_B.

To perform the linkage, a computer is instructed to create a virtual table composed of all Cartesian coordinates formed by the union of records from the two data sets. That is, the first record in FILE_A is combined with each record in FILE_B, the second record in FILE_A is then combined with every record in FILE_B, and so on until all records in FILE_A have been combined with every record in FILE_B. The computer is then instructed to examine all the cells within in this virtual matrix to identify those record-pairs where the Social Security number recorded in FILE_A is the same as that recorded in FILE_B. Finally, the computer creates an output file that contains a single record for each record-pair that met the matching criterion. Every record in the output file includes two unique identification numbers (one from each component data set), as well as the value for Social Security number.

In this investigation, the computer program that performed the linkage operations was written in Structured Query Language (SQL), and was accessed from PROC SQL in the Statistical Analysis System (SAS Institute 1993). An annotated sample program based on the preceding example is shown in Table 2.3.2.

Records from four component data sets were combined in this manner to create the research data base for this investigation. Records from the HARS data set were linked with records from CSS, WSSR, and WSCDR, respectively, in three separate sessions. During each of these three sessions, six separate record linkages were conducted according to the following standard criteria: 1.) first five characters of last name and birth date, 2.) first five characters of last name, month and day of birth, 3.) first five characters of last name, first initial of first name, and birth year, 4.) SOUNDEX[2] code for last name and birth date, 5.) SOUNDEX code for last name, month and day of birth, and 6.) SOUNDEX code for last name, first initial of first name, and birth year. These six steps were conducted in order as listed above. Once two records were determined to have matched according to a given criteria, they were removed from subsequent iterations to minimize the number of records that were reviewed. Additional linkage criteria were applied to accommodate nuances in the component data sets. These special circumstances are presented with the results from the specific record linkage sessions in Sections 2.8-2.11.

After the automated record linkage was completed, each pair of matched records from the output file was manually reviewed to determine if the records from the component data bases represented the same individual. To facilitate the review process, a computer program was developed to display, side by side, the respective patient-

[2] The SOUNDEX code is a phonetic representation of each subject's surname. These codes are particularly useful for linking names that were misspelled, or were spelled differently in the two component data bases. SOUNDEX codes were assigned by the LINKS software package (Wajda 1991).

identifying information from each component data base. Subject name, birth date, social security number, and place of residence (street address, city, county, state, and zip code) were displayed on the screen. The computer program allowed the reviewer to document agreement between specific data items (i.e., indicate whether or not the full name listed in one file was the same as that listed in the other, and so on for birth date, Social Security number, and place of residence). The computer program also allowed the reviewer to enter a summary decision (i.e., match vs. no match), and provided space for written comments. Therefore, the review process and final judgments were fully documented in a computer-accessible format. Furthermore, the record linkage and review process was conducted entirely without the use of printed lists of subjects.

The process of manual record review was inherently subjective. However, to standardize this procedure, all manual record reviews were conducted according to the guidelines listed in Table 2.3.3. These guidelines were developed *a priori* and provided a common structure by which all potential matches were evaluated.

After all possible matches were completed and reviewed, those records that were determined to match were added to the research data base. After the research data base was constructed, a final review was conducted to detect and reconcile duplicate observations.

2.4 HIV/AIDS Reporting System (HARS)

AIDS was designated as a reportable disease in the state of Washington in 1986, and statewide AIDS surveillance has been conducted since that time. Washington Administrative Code requires reporting of symptomatic HIV infection[3] within seven days of diagnosis (State of Washington 1993). Active surveillance for AIDS is conducted through a well-developed network of hospital infection control practitioners, AIDS care coordinators, community clinics, and private practitioners (Sharon Hopkins, D.V.M., M.P.H., Senior Epidemiologist, Seattle-King County Department of Public Health, HIV/AIDS Epidemiology Program, personal communication).

Completeness of AIDS reporting is emphasized both to provide the most accurate epidemiologic data and to maximize funding levels for HIV prevention and care services when such funding is tied to official case counts. Although AIDS surveillance officially began in 1986, case reports of AIDS patients were submitted to the Department of Health since the beginning of the AIDS epidemic in the early 1980's. After AIDS surveillance was officially established, state and local officials made a concerted effort to document AIDS patients diagnosed among Washington state residents prior to 1986. As a result, statewide AIDS surveillance is considered to be reasonably complete from the initial years of the epidemic. Estimates of the completeness of AIDS surveillance vary by methodology and time period, and range from 88 percent to 100 percent complete (Table

[3] Symptomatic HIV infection includes those diseases classified by the Centers for Disease Control and Prevention as AIDS-defining illnesses, as well as other less severe signs and symptoms that were historically referred to as AIDS-related complex, or ARC (Osmond 1994).

2.4.1). Most studies have placed the completeness of AIDS reporting in Washington state above 90 percent, consistent with comparable nationwide estimates from the Center for Disease Control and Prevention (Buehler 1992).

A static copy of the HARS data base was captured for the purposes of this investigation in January, 1995. This file included 5,941 records representing people with symptomatic HIV disease who resided in one of the following western Washington counties at the time of their HIV-related diagnosis: Clallam, Grays Harbor, Island, Jefferson, King, Kitsap, Mason, Pierce, San Juan, Skagit, Snohomish, Thurston, and Whatcom[4]. In January, 1995, AIDS surveillance was considered to be complete[5] for cases diagnosed during calendar years 1982 through 1992, and over 90 percent complete for those diagnosed during calendar year 1993. The file also included cases diagnosed in 1994 and 1995, but surveillance was incomplete for the latter two years when the file was created.

Aliases were listed in the records of 223 (3.8 percent) subjects registered in HARS. For the purpose of record linkage, two separate records were created for each of these individuals, one listing the primary name and the alias in the other. Therefore, a total of 6,164 HARS records were available for linkage.

---

[4] As previously mentioned, these 13 counties correspond to the area of population-based coverage for the Cancer Surveillance System.

[5] In this context, the word *complete* is used to indicate that the HARS data base included all cases of the disease that were likely to have been identified by the prevailing surveillance procedures. In contrast, the word *complete* has been used in this manuscript to refer to the ability of the surveillance system to identify all cases of the disease that were diagnosed.

A valid name was recorded in each of the HARS records[6], and a valid date of birth was available in all but two records (Table 2.4.2). All but 439 records had a valid entry for Social Security number, so that 92.9 percent of these records had valid entries for Social Security number. Valid data were available for the combinations of linkage variables that were used in the record linkage process (Table 2.4.3), and these combinations of variables generally performed well in identifying unique records within the data set.

2.5 Cancer Surveillance System (CSS)

The Cancer Surveillance System (CSS) is a population-based cancer registry that serves the following thirteen counties in western Washington state: Clallam, Grays Harbor, Island, Jefferson, King, Kitsap, Mason, Pierce, San Juan, Skagit, Snohomish, Thurston, and Whatcom. The CSS has been a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program since 1974 (Ries 1997). Incident cancer cases are identified by routine review of medical records, pathology reports, radiation therapy records, and vital records. Over 95 percent of cancer cases are abstracted by members of the CSS field staff who visit hospitals, medical practices, pathology laboratories, and radiation units throughout western Washington.

---

[6] One subject did not have a valid code for the first initial of first name (see Table 2.2.2). This subject did, in fact, have a valid name (both first and last name) recorded in HARS. Unfortunately, the subject's first name was not left justified in the name field, and the computer read the first initial of the first name as a blank space. This error was not detected until after the linkage was completed.

The remaining cases are abstracted by cancer registrars and medical record technicians at institutions within the CSS area of coverage. All data are collected and coded according to standard procedures and definitions developed by the National Cancer Institute (Ries 1997). CSS data are routinely monitored by the SEER Program for accuracy and completeness of coverage. Independent assessments of case ascertainment conducted in previous years have consistently shown that the registry's overall completeness of coverage exceeds 98 percent (Mary Potts, Manager, Cancer Surveillance System, personal communication). It should be noted, however, that completeness of coverage may vary according to type of cancer (Karagas 1991, Wiggins 1994).

For the purposes of this investigation, a static copy of the CSS data base was captured in January, 1995. Coverage of newly diagnosed cancer cases within this geographic area were considered to be complete through calendar year 1993 at the time this file was captured. The CSS static file contained records for 291,356 residents within the CSS area of coverage who were diagnosed with one or more neoplasms during the time period 1974 through 1995. One or more aliases were listed for 4,455 (1.5 percent) cancer patients registered in the CSS (ranging from 3,789 individuals with one alias to 1 individual with 20 aliases). For the purposes of record linkage, separate records were created for each alias. As a result, a total of 296,633 CSS records were available for linkage.

Personal identifying information is routinely collected, recorded, and maintained for each cancer patient registered in the CSS, including the patient's full name, birth date

and, when available, social security number. Every record in the static copy of the CSS data set listed at least one full name for its respective subject (Table 2.5.1). Similarly, year of birth was available for all but two subjects. Complete date of birth (month, day, and year) was available for over 99 percent of all records. Valid data were available for the combinations of linkage variables that were used in the record linkage process (Table 2.5.2), and these combinations of variables generally performed well in identifying unique records within the data set.

2.6 Washington State Syphilis Registry (WSSR)

Syphilis was designated as a reportable disease in Washington state in 1919 (State of Washington 1994). Within the Washington State Department Health, the Office of STD Services maintains the statewide Syphilis Registry and has coordinated surveillance efforts for this disease since the 1970's (Leah Cochran, Coordinator of Informational Support, Washington State Department of Health, Office of STD Services, personal communication). Syphilis surveillance in Washington state is directly tied to the mechanisms by which the disease is diagnosed. Briefly, syphilis is detected in the clinical laboratory with the use of serological tests which fall into one of two general categories: *nontreponemal* or *treponemal* (Chang 1983). Non-treponemal assays are designed to test serum for the presence of antibody that reacts with a cardiolipin-lecithin antigen (Jaffe 1997). In contrast, treponemal tests detect antibody that reacts with the antigenic component of pathogenic members of the genus *Treponema*. Nontreponemal

tests are relatively inexpensive and highly sensitive, but generally have a lower specificity than treponemal tests. For this reason, a diagnosis of syphilis based on a positive nontreponemal test is usually confirmed by a more specific treponemal test. These diagnostic tests require facilities and expertise that are typically found only in a clinical laboratory. Washington state law requires all laboratories in the state to report the results from all tests for syphilis to the State Laboratory or the King County Laboratory, to be verified by a confirmatory test at the latter two institutions. The Washington State Department of Health then receives the results from all such tests from the State Laboratory and the King County Laboratory. Washington State law also allows for the reporting of incident cases of syphilis by health care providers. The Washington State Syphilis Registry is the official repository for all laboratory-based diagnoses and case-reports of syphilis[7].

The Office of STD Services routinely monitors the consistency of syphilis surveillance by comparing the number of syphilis diagnoses independently reported by individual clinical laboratories with the corresponding number of events registered in the WSSR. The laboratory-based surveillance mechanism, augmented by case reports from health care providers, is believed to account for virtually all cases of syphilis diagnosed among Washington residents (Leah Cochran, personal communication).

---

[7] The WSSR is most accurately described as a registry of individuals who have had positive test results for syphilis. For this investigation, only individuals confirmed by a positive treponemal serologic test were considered to have had syphilis, which is the same definition applied for routine reporting of surveillance data.

The WSSR static file was captured in August, 1995. At that time, the WSSR contained records for 79,702 individuals who had received at least one positive test result for syphilis, dating from the 1940s. One or more aliases were listed for 2,477 (3.1 percent) of subjects registered in the WSSR (ranging from 2,203 individuals with one alias to one individual with 10 aliases). For the purposes of record linkage, separate records were created for each alias. As a result, a total of 82,546 WSSR records were available for linkage.

Information regarding date of birth was incomplete in the majority of WSSR records (Table 2.6.1). A total of 12,442 WSSR records (15.1 percent of all WSSR records) contained no information for date of birth. The year of birth was recorded in the remaining 70,104 records, but the month and day of birth was unknown in more than half of these records[8]. Surname was recorded in all WSSR records, and the first name was available in all but 40 records. Therefore, first and last name were the only two variables available for linking the 12,442 WSSR records that had no date of birth recorded; the combination of first and last name uniquely identified most of these records (Table 2.6.1). The six standard combinations of linkage variables outlined in Section 2.3 also uniquely identified the remaining WSSR records (Table 2.6.2). However, combinations of linkage variables that included birth month and day were somewhat limited in their ability to uniquely identify individuals in the data set.

---

[8] In cases where the year of birth was known, but the month and day of birth was unknown, the WSSR entered a value of July 1st (i.e., 07/01/YY, where YY represents the known year of birth).

2.7 Washington State Communicable Disease Registry (WSCDR)

At present, over 50 communicable diseases are reportable by law in the state of Washington (Washington State Department of Health 1995). The Washington State Department of Health's Communicable Disease Epidemiology Section conducts surveillance for these diseases, and serves as the repository for case-reports of individuals with these infections. Communicable disease case-reports originate from clinical laboratories, private health care providers, and local health departments. For the purposes of this investigation, we obtained surveillance records from the WSCDR for the seven pathogens listed in Table 2.7.1. These seven pathogens were selected because their respective modes of transmission were well documented and their corresponding surveillance data were readily available[9].

Surveillance for these seven infections is known to be incomplete since many cases remain asymptomatic and, therefore, never reach the health care and surveillance systems (Marcia Goldoft, M.D., M.P.H., Epidemiologist, Washington State Department of Health, Communicable Disease Epidemiology Section, personal communication). Prior studies have documented the potential for large gaps in the surveillance of hepatitis and other enteric pathogens (Marier 1977, Kimbal 1980, Vogt 1983). For example, Marier (1977) estimated the completeness of coverage to be 11 percent for viral hepatitis, 42 percent for salmonellosis, and 62 percent for shigellosis. The implications of

[9] In addition, some of these pathogens had been associated with the occurrence of KS in previous studies of people with AIDS (see Section 1.5).

incomplete surveillance for these pathogens in interpreting results from this investigation are discussed in Chapter 6.

The WSCDR static file was captured in June, 1997, and included information on 52,301 case-reports for the seven infections of interest[10]. One or more aliases were recorded in 94 of these case reports. Separate records were created to represent each alias, producing a total of 52,403 WSCDR records for the purpose of linkage.

Date of birth was recorded in only 5,110 (9.8 percent) of the WSCDR records that were available for record linkage (Table 2.7.2). First and last names were recorded in each of these 5,110 records. The six standard combinations of linkage variables uniquely identified individual observations within this subset of WSCDR records (Table 2.7.3).

Date of birth was not recorded in the remaining 47,293 (90.2 percent) WSCDR records, presenting a special challenge to the record linkage process. Fortunately, the age of each subject was recorded in all but 57 records. An estimate of birth year was obtained by subtracting the subject's age from the respective year of registration[11]. Surname was recorded in each of these records, and first name was recorded in all but two (Table 2.7.4). Combinations of linkage variables based on name and estimated year of birth uniquely identified individuals within this group of subjects (Table 2.7.4).

---

[10] The availability of these data in computerized format varied by pathogen, and is discussed in detail in Section 5.3.

[11] To assess the validity of this method, this procedure was used to estimate the year of birth for the 5,110 WSCDR records for whom birth date was recorded. The estimated value of birth year fell within ±2 years of the recorded value of birth year in 99 percent of these cases.

2.8 HARS-CSS linkage

The linkage of 6,164 records from HARS with 296,633 records from CSS identified 1,308 individuals who were determined to have been independently registered in both surveillance systems. These linked records were identified through of series of eight separate matching algorithms, as summarized in Table 2.8.1. Social security numbers were recorded in most records from both registries (92.9 percent of HARS records and 92.5 percent of CSS records). For this reason, the two data sets were first matched by social security number, which resulted in the identification of 1,148 linked records (87.8 percent of all linked records that were detected).

Records from HARS and CSS were then linked according to the six standard criteria summarized in Section 2.3. The linkage based on the first 5 characters of last name and birth date identified 150 linked records (11.5 percent). Two records (0.2 percent) were identified on the basis of the first five characters of last name and month and day of birth. Six linked records (0.5 percent) were identified from the first five characters of last name, first initial of first name, and year of birth. No linked records were identified in the remaining three standard algorithms.

Two additional linked records (0.2 percent) were serendipitously identified during a subsequent match between KS cases in the CSS that were not included in the HARS data set and records from the WSSR (see Section 2.11).

During the linkage process, 11 duplicate records were discovered in the HARS data set. When a duplicate record was found, the earliest record was retained in the research data base and the remaining record was excluded.

2.9 HARS-WSSR linkage

A total of 873 individuals registered in HARS were also registered in the WSSR. These subjects were identified through a series of seven separate record linkages, as summarized in Table 2.9.1. All 6,164 records from HARS were matched with the 70,104 WSSR records that contained a valid date of birth, according to the six standard linkage algorithms outlined in Section 2.3. However, many of the WSSR records with valid dates of birth actually contained bogus values for birth month and year (see Section 2.6). This accounts for the disproportionate number of matches that were based on the first five characters of last name, first character of first name, and year of birth. If the full birth date had been recorded in these records, they would probably have linked according to the first five characters of first name and birth date.

The 12,442 records from WSSR without valid birth dates were linked with all 6,164 HARS records to identify those with the same first and last names. Seventy-six record-pairs were identified by this criteria.

As discussed in Section 2.6, not all records registered in the WSSR represent actual cases of syphilis. Accordingly, 730 (83.6 percent) of the 873 individuals identified

in the HARS-WSSR linkage were recorded in WSSR with one or more episodes of syphilis.

2.10 HARS-WSCDR linkage

A total of 769 case-reports from WSCDR were linked with 673 individuals registered in HARS (Table 2.10.1). Of the HARS records that matched, 581 (86.6 percent) linked with a single WSCDR record, 84 (12.5 percent) linked with two WSCDR records, and 6 (0.9 percent) linked with three WSCDR records.

The six standard algorithms described in Section 2.3 were used to link all 6,164 HARS records with the 5,110 WSCDR records for whom a valid birth date was recorded. Twenty-four linked records were identified from these matches (Table 2.10.1, linkages 1-6).

Date of birth was not recorded in 47,293 (90.2 percent) of the WSCDR records. However, the subject's age at diagnosis was recorded in all but 57 (0.1 percent) of these records. As presented in Section 2.7, the year of birth was estimated for individuals whose ages were known. Using this information, two additional linkage criteria were employed to match all 6,164 HARS records with 47,236 WSCDR records for whom year of birth could be estimated (Table 2.10.1, linkages 7-8). The linkage based on the first five characters of first name and year of birth (plus or minus 2 years) identified 714 linked records. The linkage based on the SOUNDEX code for last name and year of birth (plus or minus 2 years) identified a total of 30 linked pairs.

The remaining 54 WSCDR records were matched with all 6,164 HARS records based on two algorithms: 1.) first five characters of last name and the first initial of first name, and 2.) the SOUNDEX code for last name and the first initial of first name (Table 2.10.1, linkages 9-10). One individual who was registered in both data bases was identified by the former of these two criteria.

2.11 Kaposi's sarcoma cases registered in CSS but not in HARS

Record linkages between the HARS and CSS initially identified 1,306 individuals who were registered in both files. However, the CSS static file contained information on an additional 123 individuals with KS who were apparently not registered in HARS. Subsequent review revealed that two of these 123 KS cases were, in fact, registered in HARS, but disparate information recorded in the two registries prevented these cases from matching according to the standard linkage protocol[12]. These two cases were included with the 1,306 subjects who had previously matched, for a total of 1,308 individuals who were registered in both files. The remaining 121 non-linked KS records in the CSS were also matched with records from WSSR and WSCDR, and the combined information from these files was included in the research data base[13]. Aliases were

[12] For these two subjects, information regarding date of birth differed between the two registries, prohibiting a match according to the standard linkage algorithms. Additional information in each registry indicated that these subjects were registered in both CSS and HARS.

[13] Subsequent review of the 121 KS cases registered in CSS but not in HARS suggested that most of these cases were not associated with AIDS. This topic is addressed in detail in Chapter 4.

recorded in two of these cases. Separate records were created for each alias, making a total of 123 records available for the linkage process.

Records representing the additional KS cases registered in CSS were linked with all cases in WSSR and WSCDR according to the criteria use to link the HARS records to these data bases (see Sections 2.9 and 2.10, respectively). Ten of these records (8.0 percent) were also registered in the WSSR, eight of whom were determined to have had syphilis. Five communicable disease case-reports from the from the WSCDR were linked with five individuals registered with KS in the CSS.

2.12 Confidentiality

Confidentiality was of paramount concern in conducting this investigation. Even as the study was formulated, it was clear that a breach of confidentiality, whether real or imagined, could fundamentally undermine disease surveillance in Washington state. For this reason, representatives of the participating organizations, in cooperation with their respective Human Research Review Boards, developed a comprehensive set of guidelines designed to ensure that the confidential nature of these data sets not be compromised. The result of these efforts was a 43-page confidentiality agreement which, along with a subsequent Addendum, governed every aspect of this investigation. Salient points from this agreement are summarized in the following paragraphs. The entire text of the confidentiality agreement and the Addendum are contained in Appendices 1 and 2, respectively.

As summarized in the previous sections, the research data base for this investigation was created by combining the resources of four population-based disease registries through a series of computer-assisted record linkages. All record linkages and subsequent record reviews were conducted at offices of the Washington State Department of Health in Seattle (HARS/CSS linkage) and in Olympia (HARS/WSSR and HARS/WSCDR linkages). Access to these offices was restricted to authorized personnel, and confidential information utilized for the purposes of this investigation were routinely stored in a locked file cabinet within a secure, limited access room. Record review following the linkages was conducted from computerized files (i.e., no paper lists of subjects were generated), and these files were all stored in an encrypted format, as outlined below.

The research data base was constructed from non-confidential information from each of the component data sets. Information from the component data sets was added to the research data base after records from each corresponding data set were linked to the HARS data set. Every record in the research data base was assigned a unique, randomly generated study identification number.[14] After the record linkage process was completed, the investigator created a computer file containing the study identification number, along with corresponding identification numbers from each component data set that was linked with that record. This linkage key was created to allow access to individual records in the

[14] The identification number created for the research data base bore no relationship to any of the unique identifiers maintained in the component data sets.

component data sets, if such a need arose. However, access to the linkage key was limited. The linkage key was administered by personnel at the Office of HIV/AIDS Epidemiology and Evaluation, and was kept at the Department of Health in Olympia.

All computer files that contained confidential information were transported and stored according to a strict set of procedures. In preparation for transportation or storage, all computer files that contained confidential information were placed in a compressed, encrypted, and password protected format with the use of PKZIP software (PKWARE, Incorporated 1992). Following this procedure, each compressed/encrypted file was again encrypted with another software package (Symantec 1994), using a different password. During transportation, computer diskettes containing the double-encrypted files were placed in a locked briefcase, which was always attended by the investigator.

The research data base from this investigation did not contain any patient-identifying information. Nonetheless, the research data base was transported and stored in accordance with the same rules that governed computer files that contained confidential information. The research data base was used only for the purposes outlined in the confidentiality agreement, and access to this data base was limited to the investigator. By mutual agreement among the participating registries, the research data base will be destroyed within a reasonable period of time following the conclusion of this investigation to prevent unauthorized use of these data[15]. Only two copies of the research

[15] Permission for continued use of the research data base has been renewed annually after review by the Washington State Department of Social and Health Services Human Research Review Section.

data base were maintained. One copy was maintained by the investigator, and was stored in a locked, fireproof box within a locked file cabinet, all housed in a locked office in a building that required key-card access. The other copy was maintained at the Department of Health in Olympia, in a locked file cabinet in a secure room with limited access.

The research data base and all other files that resulted from the record-linkage process were maintained solely on a stand-alone microcomputer under the direct control of the investigator. To prohibit unauthorized access this information, the research data base and all other files that resulted from the record-linkage process were never stored on a network disk drive.

No breaches of confidentiality, real or perceived, occurred during the course of this investigation.

Table 2.3.1 Description of standard format for tables included in Sections 2.3-2.6.

Column #	*Column heading*	*Description*
1	Linkage variables *or* Combination of linkage variables	Identifies the variables or combination of variables that were used to link unique observations from two component data bases
2	Number of unique levels	Specifies the number of distinct values that were observed for a given variable. For example, 'male' and 'female' are unique levels for the variable SEX. Therefore, the variable SEX has two unique levels
3	Minimum number of observations per unique level	Specifies the lowest number of observations that occurred among all unique levels of a given variable. For example, consider a fictional data base composed of five males and fifteen females. For this data base, the variable SEX would have two unique levels, and the minimum number of observations per unique level would be five
4	Maximum number of observations per unique level	Specifies the highest number of observations that occurred among all unique levels of a given variable. In the fictional data base outlined in the previous example, the maximum number of observations per unique level of the variable SEX would be fifteen
5	Average number of observations per unique level	The average number of observations that occurred over all unique levels of a given variable or combination of variables. This figure represents the total number of individuals in the component data base divided by the number of unique levels for a given variable
6	Number of subjects missing data for this variable	Specifies the number of observations without a valid entry for a given variable or combination of variables (i.e., "missing" data)

Table 2.3.2 Annotated example of SAS-based computer program that was used to conduct the record linkages for this study* (*page one of two*)

Line #	SAS code	Explanation
01	PROC SQL;	Invoke the SQL language
02	CREATE TABLE STEP1 AS	Create a new data set and call it STEP1
03	SELECT ID_A, SSN FROM FILE_A	Select the variables ID_A and SSN from the existing file called FILE_A, and include them in the new data set, STEP1
04	ORDER BY SSN;	Place the records in STEP1 in order by SSN
05	PROC SQL;	Invoke the SQL language
06	CREATE TABLE STEP2 AS	Create a new data set and call it STEP2
07	SELECT ID_B, SSN FROM FILE_B	Select the variables ID_B and SSN from the existing file called FILE_B, and include them in the new data set, STEP2
08	ORDER BY SSN;	Place the records in STEP2 in order by SSN
09	PROC SQL;	Invoke the SQL language
10	CREATE TABLE STEP3 AS	Create a new data set and call it STEP3
11	SELECT * FROM	Include all variables from STEP1 and STEP 2 in the new data set, STEP3
12	STEP1 INNER JOIN STEP2	Create a virtual table representing all Cartesian coordinates for the union of the two data sets, STEP1 and STEP2
13	ON STEP1.SSN=STEP2.SSN	From the virtual matrix created in the previous step, select those records in which the values of SSN are the same in STEP1 and STEP2, and include them in the new data set, STEP3 †
14	ORDER BY ID_A;	Place the records in STEP3 in order by ID_A

continued

Table 2.3.2 continued (*page two of two*)

Footnotes

---

* This sample SAS program corresponds to the record linkage example described in Section 2.3. The SAS statements listed in this table represent only the specific portion of the program that performs the task of record linkage. In the complete program, these steps would be proceeded by statements that define the input data sets (i.e., FILE_A and FILE_B). The program would also include SAS code to write an output file that contains the records from STEP3.

† For the purposes of this example, records from two component data sets (FILE_A and FILE_B) are considered to match if the values for Social Security Number (SSN) are the same in both records.

Table 2.3.3 Guidelines for determining matches from the manual review of potentially linked records (*page one of two*)

Variable under review	Code	Explanation
Name	0	**No match.** Obvious discrepancy between full names.
	1	**Definite match.** Full names are judged to be the same. Allow for minor differences in spelling and for use of nicknames.
	2	**Possible match.** Elements of the full names are judged to be the same or are similar. Use this code to express doubt regarding the voracity of the match based on name alone.
Date of birth	0	**No match.** Obvious discrepancy between birth dates.
	1	**Definite match.** Birth dates are the same. Allow for transpositions within birth month and day.
	2	**Possible match.** Birth dates are not exactly the same, but one or more elements of birth date match. Use this code if years of birth match, but month and day of birth are *missing* from one file.
Social Security number	0	**No match.** Obvious discrepancy between Social Security numbers, or one or both files does not have a valid entry for social security number.
	1	**Definite match.** Social security numbers are the same. Allow for transpositions and for Social Security numbers that are not exactly, but mostly the same.
	2	**Possible match.** Many elements of SSN were the same, but some items were different.

continued

Table 2.3.3 continued *(page two of two)*

Variable under review	Code	Explanation
Social security number, *continued*	7	For HARS-WSSR linkage *only*. Few records in the WSSR included Social Security number. This code indicates that Social Security number was available in the WSSR record, but did not match the value recorded in the HARS record.
Residence	0	**No match.** No element of the subject's residence matched.
	1	**Definite match.** Requires an exact or reasonably close match on the subject's street address.
	2	**Close match.** Street addresses do not match exactly, but elements of the street address suggest that they match. For example, street names match, but the address numbers differ.
	3	**Area match.** No match on street address, but city, county, and zip code are the same in both component data sets.
	4	**Something matches.** No match as outlined in items 1-3, but one or two of the following items matched: city, county, zip code.
Summary	0	**Judged NO match.**
	1	**Judged a definite match.**
	2	**Judged a possible match.** Limited to linkages between the HARS and WSSR data sets, and between the HARS and WSCDR data sets. Used to identify those cases for whom an exact match on name was the strongest evidence in favor of the match.

Table 2.4.1 Estimates of the completeness of AIDS surveillance in Washington state* (*page one of two*)

Study period	Source of comparison	Estimated completeness	Comments
1982-87	MMIS†	88 %	Statewide; sample of Medicaid patients, including non-hospitalized people with AIDS
1984-85	CHARS‡	96 %	Statewide; hospital-based
1986-87	CHARS‡	100 %	Statewide; hospital-based
1987-88	MMIS†	94 %	Statewide; sample of Medicaid patients, including non-hospitalized people with AIDS
1987-88	Public Health Hospital	90 %	Hospital-based, single institution; based on review of admission list at Public Health Hospital
1989	AIDS clinic at local hospital	92 %	Outpatient clinic, single institution; based on review of outpatient records
1988	CHARS‡	97 %	Hospital-based; SEARCH§ project
1988	Medicaid records	99 %	SEARCH§ project; inpatients
1988	Medicaid records	91 %	SEARCH§ project; outpatients
1991	Respiratory therapy unit	92 %	King county; included non-hospitalized patients

continued

Table 2.4.1 continued (*page two of two*)

Footnotes

---

* Estimates based on comparison of records registered in HARS with records from selected sources that have documentation regarding a diagnosis of AIDS. Source: Seattle/King County Department of Public Health, HIV/AIDS Epidemiology Program.

† MMIS: Medicade Management Information System

‡ CHARS: Comprehensive Hospital Abstract Reporting System

§ SEARCH: Surveillance Evaluation of AIDS Reporting Completeness

Table 2.4.2 Characteristics of linkage variables recorded in the Washington State HIV/AIDS Reporting System*

Linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name	3,613	1	69	1.71	0
SOUNDEX code for last name	1,663	1	77	3.71	0
First initial of first name	25	1	868	246.52	1
Social Security number	5,499	1	3	1.04	439
Birth date (month, day, year)	4,583	1	5	1.34	8
Birth year	81	1	315	76.07	2
Birth month and day	366	4	31	16.82	8
Last name and first name	5,947	1	7	1.04	0

* Based on 6,164 records registered in the Washington State HIV/AIDS Reporting System

† Calculations were limited to subjects with valid codes for each respective variable (i.e., excludes *missing* data)

Table 2.4.3 Characteristics of selected combinations of linkage variables recorded in the Washington State HIV/AIDS Reporting System*

Combination of linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name and birth date	6,052	1	2	1.0172	8
First five characters of last name, month and day of birth	6,005	1	5	1.0251	8
First five characters of last name, first initial of first name, and birth year	6,082	1	3	1.0120	9
SOUNDEX code for last name and birth date	6,043	1	2	1.0187	8
SOUNDEX code for last name, month and day of birth	5,948	1	5	1.0350	8
SOUNDEX code for last name first initial of first name, and birth year	6,019	1	3	1.0226	9

* Based on 6,164 records registered in the Washington State HIV/AIDS Reporting System

† Calculations were limited to subjects with valid codes for each combination of variables (i.e., excludes *missing* data)

Table 2.5.1 Characteristics of linkage variables recorded in the Cancer Surveillance System*

Linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name	41,662	1	3,589	7.12	0
SOUNDEX code for last name	4,512	1	4,189	65.74	0
First initial of first name	26	25	29,784	11,408.96	0
Social Security number	268,352	1	17	1.02	22,216
Birth date (month, day, year)	33,266	1	42	8.87	1,660
Birth year	100	225	7,948	2,966.31	2
Birth month and day	366	206	1,087	805.94	1,658

* Based on 296,633 records registered in the Cancer Surveillance System

† Calculations were limited to subjects with valid codes for each respective variable (i.e., excludes *missing* data)

Table 2.5.2 Characteristics of selected combinations of linkage variables recorded in the Cancer Surveillance System*

Combination of linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name and birth date	291,098	1	12	1.0133	1,660
First five characters of last name, month and day of birth	246,582	1	19	1.1963	1,658
First five characters of last name, first initial of first name, and birth year	271,487	1	16	1.0926	2
SOUNDEX code for last name and birth date	289,171	1	12	1.0201	1,660
SOUNDEX code for last name, month and day of birth	191,717	1	22	1.5386	1,658
SOUNDEX code for last name, first initial of first name, and birth year	242,890	1	16	1.2213	2

* Based on 296,633 records registered in the Cancer Surveillance System

† Calculations were limited to subjects with valid codes for each combination of variables (i.e., excludes *missing* data)

Table 2.6.1 Characteristics of linkage variables recorded in the Washington State Syphilis Registry

Linkage variables	Number of unique levels*	Minimum number of observations per unique level*	Maximum number of observations per unique level*	Average number of observations per unique level*	Number of subjects missing data for this variable
First five characters of last name†	19,186	1	734	3.65	0
SOUNDEX code for last name†	3,658	1	832	19.16	0
First initial of first name†	26	21	8,004	2,694.77	40
Year of birth†	96	12	1,779	730.25	0
Month and day of birth†	366	14	47,601‡	191.54	0
Last name and first name§	12,416	1	4	1.00	6

* Calculations limited to subjects with valid codes for each respective variable (i.e., excludes *missing* data)

† Based on 70,104 records that contained valid information for date of birth

‡ The majority of these records represent subjects for whom the year of birth is known, but month and day of birth were unknown. The Washington State
Syphilis Registry enters the values of July 1st for these individuals (see Section 2.6)

§ Based on 12,442 records that contained no valid information for date of birth

Table 2.6.2 Characteristics of selected combinations of linkage variables recorded in the Washington State Syphilis Registry*

Combination of linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name and birth date	61,085	1	17	1.1476	0
First five characters of last name, month and day of birth	36,411	1	498	1.9254	0
First five characters of last name, first initial of first name, and birth year	67,059	1	6	1.0448	40
SOUNDEX code for last name and birth date	52,808	1	19	1.3275	0
SOUNDEX code for last name, month and day of birth	23,636	1	586	2.9660	0
SOUNDEX code for last name first initial of first name, and birth year	64,493	1	7	1.0864	40

* Based on 70,104 records registered in the Washington State Syphilis Registry

† Calculations were limited to subjects with valid codes for each combination of variables (i.e., excludes *missing* data)

Table 2.7.1 Enumeration of records from the Washington State Communicable Disease Registry that were selected for this investigation, by communicable pathogen

Communicable disease pathogen	*Year of first available surveillance figures in Washington state*	*Number of cases captured in static file**	*Number of records available for linkage †*
Hepatitis A virus	1944	13,101	13,150
Hepatitis B virus	1965	7,380	7,409
Entamoeba histolytica	1920	482	482
Campylobacter spp.	1981	5,891	5,896
Giardia spp.	1974	3,752	3,754
Shigella spp.	1947	7,780	7,789
Salmonella spp.	1947	13,915	13,923
Total	-	52,301	52,403

* Each record represents a unique case-report of the respective disease

† Contains one record for each unique case-report of the respective disease and a separate record for each alias recorded in these records

Table 2.7.2 Characteristics of linkage variables recorded in the Washington State Communicable Disease Registry*

Linkage variables	Number of unique levels	Minimum number of observations per unique level	Maximum number of observations per unique level	Average number of observations per unique level	Number of subjects missing data for this variable
First five characters of last name	2,930	1	45	1.74	0
SOUNDEX code for last name	1,548	1	57	3.30	0
First initial of first name	25	2	651	204.40	0
Date of birth (month, day, year)	4,467	1	5	1.14	0
Year of birth	96	1	196	53.23	0
Month and day of birth (combined)	366	2	27	13.96	0

* Information in this table is based on 5,110 records from the Washington State Communicable Disease Registry that contained valid codes for date of
birth. Comparable information for the remaining 47,293 records that did not contain valid codes for date of birth is shown in Table 2.7.4.

Table 2.7.3 Characteristics of selected combinations of linkage variables recorded in the Washington State Communicable Disease Registry*

Combination of linkage variables	Number of unique levels	Minimum number of observations per unique level	Maximum number of observations per unique level	Average number of observations per unique level	Number of subjects missing data for this variable
First five characters of last name and birth date	5,054	1	2	1.0111	0
First five characters of last name, month and day of birth	5,031	1	3	1.0157	0
First five characters of last name, first initial of first name, and birth year	5,039	1	3	1.0141	0
SOUNDEX code for last name and birth date	5,056	1	2	1.0107	0
SOUNDEX code for last name, month and day of birth	5,003	1	4	1.0214	0
SOUNDEX code for last name first initial of first name, and birth year	5,028	1	3	1.0163	0

* Information in this table is based on 5,110 records from the Washington State Communicable Disease Registry that contained valid codes for date of birth. Comparable information for the remaining 47,293 records that did not contain valid codes for date of birth is shown in Table 2.7.4.

Table 2.7.4 Characteristics of linkage variables (alone and in combination) recorded in the Washington State Communicable Disease Registry*

Linkage variables	Number of unique levels†	Minimum number of observations per unique level†	Maximum number of observations per unique level†	Average number of observations per unique level†	Number of subjects missing data for this variable
First five characters of last name	15,193	1	475	3.11	0
SOUNDEX code for last name	3,295	1	573	14.35	0
First initial of first name	26	14	5,803	1,818.88	2
Estimated year of birth	115	1	1,665	410.75	57
First five characters of last name, first initial of first name, and estimated year of birth	45,105	1	8	1.05	59
SOUNDEX code for last name, first initial of first name, and estimated year of birth	43,763	1	8	1.08	59

* Information in this table is based on 47,293 records from the Washington State Communicable Disease Registry that did not contain valid codes for date of birth. For purposes of record linkage, year of birth was estimated for these records by subtracting the age at diagnosis from the year the case was registered in the registry (refer to Section 6.7)

† Calculations were limited to subjects with valid codes for each combination of variables (i.e., excludes *missing* data)

Table 2.8.1 Summary of record linkages between the Washington State HIV/AIDS Reporting System and the Cancer Surveillance System (*page one of two*)

Linkage #	Linkage criteria	No. records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
1	Social security number	1,227	0	1,227	1,148
2	First five characters of last name and birth date	1,289	1,112	177	150
3	First five characters of last name, birth month, and birth day	5,095	1,301	3,794	2
4	First five characters of last name, first initial of first name, and birth year	1,970	1,264	706	6
5	SOUNDEX code for last name and date of birth	1,335	1,300	35	0
6	SOUNDEX code for last name, birth month, and birth day	10,018	4,746	5,272	0

continued

Table 2.8.1 continued (*page two of two*)

Linkage #	Linkage criteria	No. records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
7	SOUNDEX code for last name, first initial of first name, and birth year	2,856	1,903	953	0
8	Subsequent review*	N/A	N/A	N/A	2
TOTAL				12,164	1,308

* See Section 2.11

Table 2.9.1 Summary of record linkages between the Washington State HIV/AIDS Reporting System and the Washington State Syphilis Registry
(*page one of two*)

Linkage #	Linkage criteria	No. records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
1	First five characters of last name and birth date*	647	0	647	577
2	First five characters of last name, birth month, and birth day*	1,998	647	1,351	16
3	First five characters of last name, first initial of first name, and birth year*	1,211	586	625	161
4	SOUNDEX code for last name and date of birth*	720	639	81	36
5	SOUNDEX code for last name, birth month, and birth day*	3,142	1,959	1,183	0
6	SOUNDEX code for last name, first initial of first name, and birth year*	1,804	1,202	602	7

continued

Table 2.9.1 continued (*page two of two*)

Linkage #	Linkage criteria	# records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
7	Last name and first name[†]	113	0	113	76
TOTAL				4,602	873

* Linkages conducted with all 6,164 records from the Washington State HIV/AIDS Reporting System and only the 70,104 records from the Washington State
Syphilis Registry *with* valid codes for date of birth

† Linkage conducted with all 6,164 records from the Washington State HIV/AIDS Reporting System and only the 12,442 records from the Washington State
Syphilis Registry *without* valid codes for date of birth

Table 2.10.1 Summary of record linkages between the Washington State HIV/AIDS Reporting System and the Washington State Communicable Disease Registry (*page one of three*)

Linkage #	Linkage criteria	# records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
1	First five characters of last name and birth date*	24	0	24	23
2	First five characters of last name, birth month, and birth day*	90	24	66	0
3	First five characters of last name, first initial of first name, and birth year*	50	23	27	0
4	SOUNDEX code for last name and date of birth*	25	24	1	1
5	SOUNDEX code for last name, birth month, and birth day*	177	87	90	0
6	SOUNDEX code for last name, first initial of first name, and birth year*	81	46	35	0

continued

Table 2.10.1 continued (*page two of three*)

Linkage #	Linkage criteria	# records linked	No. records excluded from review, previously reviewed	No. records reviewed	No. new matched record-pairs identified
7	First five characters of last name, first initial of first name, and estimated year of birth ± two years[f]	1,918	0	1,918	714
8	SOUNDEX code for last name, first initial of first name, and estimated year of birth ± two years[f]	3,487	1,776	1,711	30
9	First five characters of last name and first initial of first name[g]	30	0	30	1
10	SOUNDEX code for last name and first initial of first name[g]	41	22	19	0
TOTAL				3,921	769

continued

Table 2.10.1 continued (*page three of three*)

Footnotes

---

* Linkages conducted with all 6,164 records from the Washington State HIV/AIDS Reporting System and only the 5,110 records from the Washington State Communicable Disease Registry *with* valid codes for date of birth.

† Linkage conducted with all 6,164 records from the Washington State HIV/AIDS Reporting System and only the 47,236 records from the Washington State Communicable Disease Registry with *estimated* value for year of birth.

‡ Linkage conducted with all 6,164 records from the Washington State HIV/AIDS Reporting System and only the 57 records from the Washington State Communicable Disease Registry *without* valid codes for date of birth and *without* estimated value for year of birth.

Chapter 3

Methodological issues in combining information from two independent disease registries

3.1 Introduction

The occurrence of cancer among members of the study cohort was determined from the combined resources of the Cancer Surveillance System (CSS) and the HIV/AIDS Reporting System (HARS). Because the surveillance activities of these two registries overlapped in some areas, the investigators were sometimes faced with a choice between different values for the same data item as independently recorded in CSS and HARS. The purpose of this chapter is to describe discrepancies between CSS and HARS for selected data items that were common to both registries, and to document the manner in which these discrepancies were resolved. Section 3.2 provides an overview of the discrepant data items that were examined. Sections 3.3-3.6 summarize the discrepancies that were found and document the steps that were taken to resolve these discrepancies. Finally, with records linked and discrepancies resolved, the study cohort is presented in Section 3.7.

3.2 Combining information from HARS and CSS

Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) were both AIDS defining illnesses during the study period, 1982-92 (Centers for Disease Control 1982, Centers for Disease Control 1985). KS was one of the original AIDS-defining conditions

(Centers for Disease Control 1981, Centers for Disease Control 1982, CDC Task Force 1982, Jaffe 1983). Prior to the discovery of the human immunodeficiency virus (HIV), a diagnosis of KS in anyone under the age of 60 years, with no other indication of immunosuppression, was considered to represent AIDS (Centers for Disease Control 1982). Following the discovery of HIV as the causative agent for AIDS (Barre-Sinoussi 1983, Gallo 1984, Levy 1984), the CDC revised the AIDS case definition to include any diagnosis of KS in an individual who tested positive for HIV (Centers for Disease Control 1985). Although NHL was identified in AIDS patients early in the AIDS epidemic (Centers for Disease Control 1982, Doll 1982, Ziegler 1982, Snider 1983), it was not officially designated by the CDC as an AIDS-defining illness until 1985 (Centers for Disease Control 1985)[1].

Both HARS and CSS conducted surveillance for KS and NHL during the study period, but the scope of surveillance varied between the two registries. AIDS case reports submitted to HARS usually summarized illnesses that were present at or near the time of initial AIDS diagnosis, including KS and NHL. However, no routine efforts were made to ascertain information on diseases that occurred after an AIDS case was entered into the HARS file. In contrast, the CSS attempted to identify all cases of cancer diagnosed among residents within its geographic area of coverage during this time period, including KS and NHL, regardless of HIV status. In combining records from these two registries to

[1] According to the combined resources of HARS and CSS, the first case of NHL in a person with AIDS in western Washington State was diagnosed in 1995.

construct the research data base for this investigation, we were sometimes faced with the task of deciding which information should take precedence when the two registries independently recorded different values for the same data item.

The HARS static file included information on 5,930 individuals[2], 4,981 (84.0 percent) of whom had AIDS[3]. Of the 4,981 people with AIDS, 1,236 (24.8 percent) had one or more cancers registered in the CSS. Among the 1,236 people with AIDS who were registered in the CSS, 1,127 had a diagnosis of KS or NHL recorded in the CSS [4]. As summarized in the in the following four sections, we examined the latter group of 1,127 subjects for possible discrepancies between CSS and HARS for each of the following variables: 1.) AIDS diagnosis date; 2.) age at time of AIDS diagnosis; 3.) KS diagnosis date; and 4.) NHL diagnosis date.

---

[2] The original HARS static file contained information on 5,941 individuals (see Section 2.4). However, 11 duplicate records were discovered during the match between HARS and CSS (see Section 2.8), so that 5,930 individuals are represented in the HARS static file.

[3] Washington Administrative Code requires reporting of symptomatic HIV infection within seven days of diagnosis (State of Washington 1993). Symptomatic HIV infection includes those diseases classified by the Centers for Disease Control and Prevention as AIDS-defining illnesses, as well as other less severe signs and symptoms that were historically referred to as AIDS-related complex, or ARC (Osmond 1994).

[4] Of the 1,127 subjects with KS and/or NHL recorded in the CSS, 297 (26.4 percent) had NHL without KS, 781 (69.3 percent) had KS without NHL, and 49 (4.3 percent) had both KS and NHL.

Section 3.3 Date of AIDS diagnosis

Both KS and NHL were considered to be AIDS-defining illnesses during the study period[5]. For this reason, we compared the dates of AIDS diagnosis as recorded in HARS with the dates of KS and NHL diagnosis as recorded in CSS among the 1,127 subjects for whom both sets of dates were available. For 135 subjects, the diagnosis date for KS or NHL as recorded in CSS preceded the date of AIDS diagnosis as recorded in HARS (Table 3.3.1). These 135 individuals represented 2.7 percent of all people with AIDS registered in HARS, and 12.0 percent of people with AIDS who were registered in the CSS with KS or NHL. For the purposes of this investigation, the date of AIDS diagnosis for these 135 subjects was considered to be the diagnosis date for KS or NHL as recorded in CSS. In most instances, there was little difference between the corresponding dates recorded in HARS and CSS (the median difference was 1 month). In only 10 (7.4 percent) of these cases did the corresponding diagnosis dates vary by more than one year. For the remaining 4,846 people with AIDS, the AIDS diagnosis date as recorded in HARS was considered to represent the true date of AIDS diagnosis.

Section 3.4 Age at AIDS diagnosis

During the study period, HARS routinely documented the age of each subject at the time of their AIDS diagnosis. The CSS similarly documented the age at cancer

---

[5] KS has been an AIDS defining illness since 1982 and NHL has been an AIDS defining illness since 1985 (see Section 3.2).

diagnosis for those cases diagnosed during this period. The age at time of AIDS diagnosis as recorded in the HARS was chosen to represent this variable for the purposes of this study, except for the 135 subjects described in the previous paragraph (Section 3.3)[6]. For these subjects, whose date of AIDS diagnosis was based on information regarding the diagnosis of KS or NHL as recorded in the CSS, the age at time of AIDS diagnosis was represented by the age of the patient at the time of their KS or NHL cancer diagnosis as recorded in the CSS. The age at AIDS diagnosis as recorded in HARS and the age at KS and/or NHL diagnosis from CSS were the same for 99 (73.3 percent) of these subjects. The ages varied by one year for 26 subjects (19.3 percent), by two years for six subjects (4.4 percent), by three years for one subject (0.7 percent), and by four years for two subjects (1.5 percent). For one subject (0.7 percent), the difference in age as recorded in HARS and CSS varied by 12 years. During the record linkage process, this subject was determined to have the same name (first name, middle initial, and surname) and the same month and day of birth recorded in both registries. Further, both registries agreed that this subject had been diagnosed with KS on the same date (month and year). However, the year of birth as recorded in HARS and CSS differed by 12 years. Based on this information, the subject's records from the two registries were

[6] Birth date (month, day, year) was routinely recorded for each person registered HARS. Month and year of KS diagnosis was also routinely documented for those subjects registered with KS in HARS and CSS. Had this information been available in the research data base for this investigation, it would have been possible to calculate the age at AIDS diagnosis for the 135 cases discussed herein. However, to protect the confidentiality of study subjects, date of birth was not included in the research data set.

judged to match, and the subject's age at AIDS diagnosis was assigned based on the (older) age recorded by the CSS.

Section 3.5 Date of KS diagnosis

Four hundred and thirty-seven (437) individuals were registered with a diagnosis of KS in both CSS and HARS. Among these, the date of KS diagnosis (month and year) as recorded in CSS preceded the date of KS diagnosis as recorded in HARS in 100 (22.9 percent) subjects (Table 3.5.1). For the purposes of this investigation, the date of KS diagnosis for these 100 subjects was considered to be the date of KS diagnosis as recorded in CSS. For these subjects, the median difference between the date of KS diagnosis as recorded in HARS and CSS was one month; the difference was greater than one year for 11 subjects (11.0 percent). The date of KS diagnosis as recorded in HARS was considered to be the date of KS diagnosis for the remaining 337 (77.1 percent) of these subjects.

Section 3.6 Date of NHL diagnosis

A diagnosis of NHL was registered in both HARS and CSS for 139 people with AIDS[7]. The diagnosis date for NHL as recorded in the CSS preceded the diagnosis date for NHL as recorded in HARS for 34 (24.5 percent) of these subjects (Table 3.6.1). The

[7] Two subjects were registered in CSS with NHL, and were subsequently registered in HARS with AIDS. However, the diagnosis dates of NHL recorded in the CSS preceded the AIDS diagnosis by more than three years. These two cases of NHL were not considered to be AIDS-associated for the purposes of this investigation.

difference between the two dates was one month for 28 (82.4 percent) of these cases, two months for four cases (11.8 percent), and three months for one case (2.9 percent). For the remaining case, the NHL diagnosis as recorded in CSS preceded the value recorded in HARS by 18 months. For the purposes of this investigation, the date of NHL diagnosis for these 134 subjects was considered to be the date of NHL diagnosis as recorded in CSS. The date of NHL diagnosis as recorded in HARS was considered to be the date of NHL diagnosis for the remaining 105 (75.5 percent) of these subjects.

3.7 Defining the study cohort

The study cohort was defined as all residents of western Washington state who were diagnosed with AIDS during the time period 1982-1992, and who were registered in HARS. This time period was chosen because it includes the year in which an AIDS case was first diagnosed in western Washington state (i.e., 1982) as well as the last calendar year for which HIV/AIDS surveillance was considered to be complete at the time the HARS data set was captured for the purposes of this investigation (i.e., 1992).

Selected characteristics of the 3,899 cohort members are shown in Table 3.7.1. HARS routinely classified incident cases of AIDS according HIV risk group. These risk groups represent the transmission route by which an individual was most likely infected with HIV, based on information from the AIDS case report. The majority of cohort members were male (95.9 percent), most of whom acquired HIV through homosexual contact. Although sexual contact was responsible for most HIV infection among males,

intravenous (IV) drug abuse was also associated with approximately 16 percent of male AIDS cases. IV drug abuse accounted for a much higher percentage of HIV infection among females than males (30.8 percent vs. 4.3 percent, respectively). As in males, sexual contact was the most common mode of HIV transmission in females with AIDS.

Table 3.3.1 Methods for resolving discrepancies between the diagnosis dates for the acquired immunodeficiency Syndrome (AIDS) as recorded in the Cancer Surveillance System (CSS) and the HIV/AIDS Reporting System (HARS)

Discrepancy	Resolution	No. cases effected	Difference in values (months)	
			Median	Range
KS diagnosis date as recorded in CSS preceded AIDS diagnosis date as recorded in HARS	Let KS diagnosis date as recorded in CSS represent AIDS diagnosis date	94	1	1 - 54
NHL diagnosis date as recorded in CSS preceded AIDS diagnosis date as recorded in HARS	Let NHL diagnosis date as recorded in CSS represent AIDS diagnosis date	38	1	1 - 18
Year of KS diagnosis as recorded in CSS preceded year of AIDS diagnosis as recorded in HARS. However, month and day of KS diagnosis were not recorded in CSS	Let year of KS diagnosis as recorded in CSS represent year of AIDS diagnosis. Assigned mid-year (July 15) month and day of AIDS diagnosis	3	36	12, 36, 50*

* For these three subjects, the estimated date of KS diagnosis as derived from the CSS preceded the date of AIDS diagnosis as recorded in HARS by 12 months, 36 months, and 50 months, respectively.

Table 3.5.1. Methods for resolving discrepancies between the diagnosis dates for Kaposi's sarcoma (KS) as recorded in the Cancer Surveillance System (CSS) and the HIV/AIDS Reporting System (HARS)

Discrepancy	Resolution	No. cases effected	Difference in values (months)	
			Median	Range
KS diagnosis date as recorded in CSS preceded KS diagnosis date as recorded in HARS	Let KS diagnosis date as recorded in CSS represent KS diagnosis date	98	1	1 - 54
Year of KS diagnosis as recorded in CSS preceded year of KS diagnosis as recorded in HARS. However, month and day of KS diagnosis were not recorded in CSS	Let year of KS diagnosis as recorded in CSS represent year of KS diagnosis. Assigned mid-year (July 1) month and day of KS diagnosis	2	44	36, 52*
NHL diagnosis date as recorded in CSS preceded NHL diagnosis date as recorded in HARS	Let NHL diagnosis date as recorded in CSS represent NHL diagnosis date	34	1	1 - 18

* For these two subjects, the estimated date of KS diagnosis as derived from the CSS preceded the date of KS diagnosis as recorded in HARS by 36 and 52 months, respectively.

Table 3.6.1. Methods for resolving discrepancies between the diagnosis dates for non-Hodgkin's lymphoma (NHL) as recorded in the Cancer Surveillance System (CSS) and the HIV/AIDS Reporting System (HARS)

Discrepancy	Resolution	No. cases effected	Difference in values (months)	
			Median	Range
NHL diagnosis date as recorded in CSS preceded NHL diagnosis date as recorded in HARS	Let NHL diagnosis date as recorded in CSS represent NHL diagnosis date	34	1	1 - 18

Table 3.7.1 Characteristics of 3,899 western Washington residents who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System

	Males (n = 3,740)				Females (n = 159)			
HIV risk group	No. cases	Percent of total	Median age (years)	Age range (years)	No. cases	Percent of total	Median age (years)	Age range (years)
Homosexual & bisexual males	2,982	79.7	36	18-79	-	-	-	-
Intravenous drug abusers	162	4.3	36	21-71	49	30.8	30	17-50
Homo/bisexual males who were intravenous drug abusers	434	11.6	34	19-67	-	-	-	-
Adult hemophiliacs	33	0.9	33	13-64	2	1.3	35	30-40
Heterosexual contact	24	0.6	35	22-76	65	40.9	34	19-82
Transfusion/transplantation recipients	39	1.0	50	14-82	25	15.7	39	23-83
Adults whose HIV risk factors were unknown	56	1.5	41	21-73	12	7.6	31	24-61
Pediatric hemophiliac	4	0.1	7.5	6-9	0	-	-	-
Child with mother at risk of HIV	6	0.2	0	0-2	6	3.8	0	0-2

Chapter 4

Cancer among people with AIDS in western Washington state

4.1 Introduction

The original purpose of this investigation was to characterize the association between selected sexually transmitted and enteric pathogens and the subsequent development of KS among people with AIDS. However, the combined resources of the HIV/AIDS Reporting System (HARS) and the Cancer Surveillance System (CSS) also provided an opportunity to examine the spectrum of cancers that occurred among people with AIDS. As a population-based cancer registry, CSS routinely conducted surveillance for all malignant neoplasms diagnosed among residents of western Washington state during the study period, 1982-92. Because of interest in KS and NHL as AIDS-defining illnesses, HARS also conducted limited surveillance for these two cancers among people with AIDS during this period[1]. Therefore, the combined HARS/CSS data set also allowed us to examine issues regarding the surveillance of KS and NHL, and to compare and contrast results from the surveillance activities of the two registries.

This chapter begins with an overview of methodologies 1.) for compiling person-years of follow-up for members of the cohort[2], 2.) for calculating cancer incidence rates,

---

[1] HARS primarily documented cases of KS and NHL that occurred at or near the time of initial AIDS diagnosis.

[2] The study cohort consisted of 3,899 residents of 13 counties in western Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). A detailed description of HARS surveillance is summarized in Chapter 2, and the study cohort is described in further detail in Chapter 3.

both in the cohort and in the general population of western Washington state, and 3.) for comparing, by primary cancer site, the number of cases that were observed in the cohort to the number of cases that would have been expected had incidence rates in the general population been observed in the cohort. Section 4.3 describes the distribution of KS among people with AIDS, and compares KS incidence rates in the cohort with those not known to have had AIDS in the general population. Temporal trends in the occurrence of KS among people with AIDS are summarized in Section 4.4. Issues regarding surveillance for KS are presented in Section 4.5. A detailed examination of NHL among people with AIDS is presented in Sections 4.6-4.8, under the same general headings as the three preceding sections on KS. In Section 4.9, we estimate the contribution of HIV to recent increases in incidence rates of NHL in the general population. Finally, Section 4.10 contains a brief description of cancers other than KS and NHL that occurred among members of the cohort.

4.2 General methodology

Incident cancer cases diagnosed among cohort members were identified through the combined resources of HARS and CSS, as documented in the three previous chapters. To summarize the cancer experience among people with AIDS, we calculated age-specific and age-adjusted, primary-cancer-site-specific incidence rates among cohort members. Rates in the study cohort were based on the respective incident cancer cases and the person-years of follow-up that accumulated following the diagnosis of AIDS. For

comparison, age-specific and age-adjusted incidence rates were calculated for the general population that resided within the 13-county CSS area of coverage. This section documents the methods for estimating person-years of follow-up among cohort members. Methods for calculating incidence rates, observed-to-expected ratios, and corresponding statistical measures are also described.

Estimates of person-years of follow-up in the study cohort were based on the following information: 1.) date of AIDS diagnosis, 2.) age at AIDS diagnosis, 3.) date of cancer diagnosis (for those subjects diagnosed with cancer following their AIDS diagnosis), 4.) date of death (for those subjects known to be deceased), and 5.) date the subject was last known to be alive (for those subjects not known to be dead). Date of AIDS diagnosis and corresponding age at AIDS diagnosis were determined for each cohort member from the combined resources of HARS and CSS, as summarized in Sections 3.3 and 3.4, respectively. For analyses where the cancer of interest was KS or NHL, the date of the cancer diagnosis was also determined from the combined resources of HARS and CSS, as summarized in Sections 3.5 and 3.6, respectively. For analyses of cancers other than KS or NHL, the date of cancer diagnosis was that recorded in the CSS. Deaths among cohort members (and corresponding dates of death) were determined through linkages of HARS with death certificate files from the Washington State Bureau of Vital Statistics, and with the National Death Index (Maden 1993). For those subjects

not known to be deceased, HARS maintained information on the date that each person was last known to be alive[3].

For each member of the study cohort, person-years of follow-up were estimated as the time (in years) between the date of AIDS diagnosis and, as appropriate: 1.) the diagnosis date for the cancer of interest (for those who developed the cancer of interest), 2.) the date of death (for subjects known to be deceased), or 3.) date the subject was last known to be alive. Person-years of follow-up were apportioned among nine 10-year year age categories[4], based on the respective age at AIDS diagnosis and the length of follow-up. Individual person-years of follow-up were then summed within each 10-year age category to determine the corresponding total person-years of follow-up for the entire cohort.

Because the research database did not include information on date of birth[5], we assumed that every cohort member was diagnosed at the mid-point of the age-interval represented by their respective age at AIDS diagnosis. The following example demonstrates the apportionment of follow-up time among 10-year age-categories. Consider a hypothetical, HIV-infected individual who was diagnosed with AIDS in May,

---

[3] The three primary sources of active follow-up for people with AIDS not known to be deceased were 1.) an ongoing study of people with AIDS based on routine review of medical records, 2.) periodic linkage with a statewide hospital discharge summary data base, and 3.) periodic telephone contact with health care providers of people with AIDS.

[4] The age categories were 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years.

[5] The confidentiality agreement between the investigators and the State of Washington Department of Health prohibited the inclusion of date of birth in the research database (see Appendix 1).

1982, at the age of 28 years. This person subsequently died from the disease in May, 1989, seven years after being diagnosed with AIDS. Because we do not know this person's date of birth, we assume that the person was diagnosed with AIDS at 28.5 years of age. This individual's seven person-years of follow-up were apportioned among 10-year age-categories as follows: 1.5 years in the 20-29 year age category (0.5 year at age 28 and a full year at age 29) and the remaining 5.5 years in the 30-39 year age category (five full years at ages 30, 31, 32, 33, and 34, and 0.5 year at age 35).

Cohort members with one or more primary cancers may have contributed different person-years of follow-up to separate analyses. For example, a hypothetical cohort member could have been diagnosed with AIDS in May, 1985, diagnosed with KS in May, 1986, and died in May, 1987. For analyses relating to KS, this subject would have contributed one-person year of follow-up (May, 1985 to May, 1986). For analyses of cancers other than KS, this person would have contributed two-person-years of follow-up (May, 1985 to May, 1987), assuming that this individual had no cancers other than KS. Therefore, it was necessary to calculate separate estimates of person-years of follow-up for the analysis of each primary cancer site.

As previously noted, person-years of follow-up represented the time between initial AIDS diagnosis and the date of last information (i.e., date of death or date last known to be alive), as recorded in HARS. However, the date of last information as recorded in HARS was unavailable for 106 (2.7 percent) of the cohort members. Person-years of follow-up were inestimable for an additional 135 cohort members (3.5 percent)

who were diagnosed with AIDS at or shortly before their date of death. Therefore, a total of 241 subjects (6.2 percent) were excluded from all analyses that were based on person-years of follow-up[6].

To assess temporal trends of KS and NHL incidence rates in the general population, average-annual age-specific and age-adjusted incidence rates were calculated for residents of western Washington state for the time period 1975-92. Age-adjusted rates were calculated by the direct method (Rothman 1998), and standardized to the age distribution of the 1970 United States population, as published in Ries (1997). Denominators for the incidence rates in the general population were population estimates by age, sex, year, and county that were produced for use in the SEER Program by the Unites States Bureau of the Census (Ries 1997).

To estimate the contribution of HIV/AIDS to KS incidence rates, three separate sets of rates were calculated based on the following numerators: 1.) all KS cases, 2.) HIV/AIDS-associated cases only, and 3.) KS cases not known to have been associated with HIV/AIDS. For the purposes of this analysis, KS cases were considered to be HIV/AIDS-related if 1.) registered in the CSS with KS and also registered in HARS, 2.) registered in HARS with KS, even if not registered in the CSS with KS, and 3.) the CSS record indicated that a KS case was HIV/AIDS-related, even if not registered in HARS.

---

[6] Of these 241 cohort members, 39 (16.2 percent) had cancer, including 19 (7.9 percent) with KS, 14 (5.8 percent) with NHL, and 6 (2.5 percent) with cancers of other primary sites. The remaining 202 cohort members (83.8 percent) without date of last information recorded in HARS were not known to have had cancer.

The same methodology was also used to assess the contribution of HIV/AIDS to temporal trends in the occurrence of non-Hodgkin's lymphoma[7].

To compare the cancer experience of the study cohort with that of the general population, we estimated the number of cancer cases that would have been expected to occur in the study cohort had they experienced the same incidence rates as the general population. The expected case numbers were estimated by multiplying the age-specific incidence rates from the general population by the corresponding person-years of follow-up observed in the study cohort, and then summing the expected number of cases across all categories of age. Observed-to-expected ratios were then computed for each primary cancer site. Confidence intervals for the observed-to-expected ratios were calculated according to methods described by Bailar III and Ederer (1964).

Average-annual age-specific rates, by primary cancer site, were calculated for residents of western Washington state for the time period 1982-92[8]. These rates served as the basis for the observed-to-expected comparisons. Additionally, age-adjusted rates were calculated by the direct method (Rothman 1998), and were standardized to the percent distribution of person-years accumulated in the study cohort[9]. As in previous calculations, denominators for the incidence rates in the general population were

---

[7] Methodology for examining the contribution of HIV/AIDS to increasing rates of NHL in western Washington state are presented in Section 4.9.

[8] This time period was chosen because it corresponds to the period in which cohort members were diagnosed with AIDS.

[9] This choice of standard population allows for the comparison of the age-adjusted rate for residents of western Washington state with that of the crude rate (all ages combined) in the study cohort.

population estimates by age, sex, year, and county that were produced for use in the SEER Program by the Unites States Bureau of the Census (Ries 1997).

During the period 1982-92, 94.3 percent of incident KS cases and 5.2 percent of incident NHL cases in western Washington state were diagnosed among people with AIDS. For the purposes of comparing cancer incidence rates in the cohort with those in the general population, HIV-associated cases of KS and NHL were excluded from the corresponding rate calculations for the resident population of western Washington state[10]. Because HIV-associated cases constituted only a fraction of the caseload for other primary cancer sites, comparable modifications were not made when incidence rates were calculated for cancers other than KS and NHL.

Crude (all ages combined) and age-specific incidence rates were calculated for the study cohort, by primary cancer site[11]. The numerators for the cohort incidence rates

---

[10] HIV/AIDS-associated cases of KS and NHL were excluded from the numerators of their respective incidence rates. Ideally, these cases should have also been excluded from the denominators of the rates. However, in theory, these cases should have been removed from the denominators only for the specific years preceding AIDS diagnosis in which they were infected with HIV. The research database did not contain sufficient information to estimate the period of HIV infection preceding AIDS for a majority of the cases. Further, HIV/AIDS associated cases of KS and NHL represented a substantial portion of respective cases in the numerators of rates calculations. However, these cases represented only a small fraction of the population represented in the denominator. Therefore, exclusion of these cases from the numerator had substantial impact on the magnitude of the corresponding incidence rates, while exclusion of these cases from the denominators would have had little effect. For these reasons, and to simplify the rate calculation procedure, these cases were excluded from the numerators but not the denominators of the respective rate calculations.

[11] For this analysis, age-adjusted rates from the general population were standardized to the age-specific distribution of person-years accumulated in the cohort. Thus, age-adjusted rates for the general population may be appropriately compared to the crude incidence rates (all ages combined) in the study cohort.

were those cancer cases that occurred following the initial AIDS diagnosis[12]. The accumulated person-years of follow-up for the study cohort, as previously described, served as the denominators for rate calculations.

In supplemental analyses, multiple logistic regression (Breslow 1980, Rothman 1998) was used to characterize the relative risk for developing of KS and NHL by mode of HIV transmission[13], sex, age at AIDS diagnosis, and year of AIDS diagnosis, while simultaneously controlling for the remaining three variables. For these analyses, mode of HIV transmission was categorized as high-risk for KS (homosexual and bisexual men, including homosexual and bisexual men who were also intravenous drug abusers), medium risk for KS (intravenous drug abusers who were not homosexual or bisexual men, heterosexuals, and adults whose HIV risk factors were unknown), and low risk for KS (hemophiliacs, transfusion/transplant recipients, and children whose mothers were at high-risk of HIV infection). Age at AIDS diagnosis was categorized as 00-19 years, 20-29 years, 30-39 years, 40-49 years, and 50+ years. Cohort members were also grouped according to year of AIDS diagnosis, as follows: 1982-86, 1987-89, 1990-92.

Kaplan-Maier curves (Cox 1984, Kalbfleisch 1980) were generated to graphically illustrate the cumulative percent distribution of KS and NHL in cohort members.

---

[12] Some cohort members developed cancer prior to their initial AIDS diagnosis, and some were diagnosed with cancer at the same time as their AIDS diagnosis (for some subjects, KS or NHL may have been their AIDS-defining illness). For the purpose of this investigation, incidence rates were calculated only for those cancers diagnosed following the initial diagnosis of AIDS (see Section 4.10).

[13] Mode of HIV transmission is described in Section 4.3.

Separate curves were produced for individuals diagnosed with AIDS during the periods 1982-86, 1987-89, and 1990-92. Differences among these curves were assessed with the log-rank statistic (Cox 1984, Kalbfleisch 1980).

Cox proportional hazards model (Cox 1984, Breslow 1987, Rothman 1998) was used to examine temporal trends in the cumulative incidence of KS and NHL, while simultaneously adjusting for the effects of age at AIDS diagnosis, mode of HIV transmission, and sex. Variables representing year of AIDS diagnosis, age at AIDS diagnosis, sex, and mode of HIV transmission were coded according to the same scheme that was utilized in the logistic regression analysis, as previously described.

For analyses involving the methods of Kaplan-Maier and Cox, subjects were followed from the time of AIDS diagnosis until they developed the outcome of interest, i.e., KS or NHL, or until they were censored[14]. Because the follow-up time for cohort members diagnosed during the period 1990-92 was limited compared to those diagnosed in earlier time periods, follow-up times were restricted to four-years for these analyses. Cases with follow-up times greater than four years were censored at four years. Cohort members diagnosed with KS and NHL greater than four years after their initial AIDS diagnosis contributed four years of person-years to these analyses, and were censored without contributing to the tally of KS and NHL cases.

---

[14] Cases were censored at the time of death (for those subjects known to have died) or at the time of they were last known to be alive, as recorded in HARS.

4.3 Kaposi's sarcoma among people with AIDS

KS rarely occurred in residents of western Washington state prior to the advent of the AIDS epidemic (Figure 4.3.1). During the period 1975-81[15], KS incidence rates were 0.24 and 0.08 per 100,000 in men and women, respectively. The dramatic increase in KS incidence rates in the 1980's was fueled by hundreds of cases of the disease diagnosed among men with AIDS (Table 4.3.1). There was no apparent temporal variation in KS incidence rates in the general population when the analysis was restricted to cases not known to be associated with HIV/AIDS (Table 4.3.1). In spite of the burgeoning AIDS epidemic, KS incidence rates in the general population that included HIV/AIDS-associated cases of the disease were far lower than those for the most common primary cancer sites[16]. However, KS rates in the general population mask extremely high rates of the disease in men with AIDS. The remaining portion of this section focuses on the occurrence of KS among people with AIDS, as represented by the study cohort.

KS was diagnosed in 863 (22.1 percent) of the 3,899 study cohort members. Because it was an AIDS-defining illness, KS was synonymous with the diagnosis of AIDS for many individuals[17]. Of the 863 KS cases diagnosed among cohort members,

---

[15] 1975-81 was the seven-year period that immediately preceded diagnosis of the first AIDS case in a resident of Washington state in 1982.

[16] For example, during the period 1990-92, the average annual age-adjusted KS incidence rates were 5.2 and 0.07 per 100,000 for males and females, respectively. Comparable rates were 84.1 per 100,000 for male lung cancer, 135.8 for female breast cancer, and 192.5 for prostate cancer.

[17] KS may have been the sole AIDS-defining illness, or one of two or more AIDS-defining illnesses. For the purposes of this report, I will refer to these individuals as those diagnosed with KS at the time of initial AIDS diagnosis.

460 (53.3 percent) were diagnosed at the time of AIDS diagnosis and 403 (46.7 percent) were diagnosed in the months and years following the initial diagnosis of AIDS.

The percentage of AIDS patients ever diagnosed with KS varied by mode of HIV transmission[18], sex, age at AIDS diagnosis, and year of AIDS diagnosis (Table 4.3.2). KS occurred in approximately 25 percent homosexual and bisexual men[19], and was less commonly diagnosed among intravenous drug users (6.6 percent), heterosexuals (3.4 percent), and adults whose risk factors for HIV were unknown (5.9 percent). KS was extremely rare in transfusion/transplantation recipients (1.6 percent), and no cases of KS were diagnosed among the small number of hemophiliacs and children whose mothers were at high risk of AIDS. KS was also much more common among males (23.0 percent) than females (1.3 percent). Most cohort members diagnosed with KS were between the ages of 20-49 at the time of their initial AIDS diagnosis. The proportion of people with AIDS who were diagnosed with KS declined during the study period[20]. The temporal decline in the occurrence of KS among people with AIDS is discussed in detail in Section 4.4.

Risk of KS varied dramatically by mode of HIV transmission, even after simultaneously controlling for age at AIDS diagnosis, sex, and year of AIDS diagnosis

---

[18] HARS routinely documented the most likely mode of HIV transmission for each individual, based on information self-reported by the subject and as reported by health care providers and case-workers.

[19] KS was documented in 25.1 percent of homosexual and bisexual men with no history of intravenous drug abuse, and in 21.7 percent of homosexual and bisexual men who were also intravenous drug abusers.

[20] The decline in proportion of cohort members diagnosed with KS is only partially explained by temporal variations in length of follow-up among cohort members (see Section 4.4).

(Table 4.3.3). Homosexual and bisexual men, including those who were also intravenous drug abusers, were at much greater risk of KS than the comparison group comprised of hemophiliacs, transfusion/transplant recipients, and children whose mothers were at high-risk for HIV infection (odds ratio (OR) = 26.08, 95 percent confidence interval (CI) = 3.42 - 198.7). The combined group of intravenous drug abusers (excluding those who were homosexual or bisexual men), heterosexuals, and adults whose HIV-risk was unknown were also at higher risk of KS than the comparison group (OR = 7.58, 95 percent CI = 0.95 - 60.41), though this difference was not statistically significant.

The high risk of KS in men relative to women was partially explained by the high proportion of male cohort members with KS who were also homosexual and bisexual. Nonetheless, men remained at higher risk for KS than women after simultaneous adjustment for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis (adjusted OR = 5.62, 95 percent CI = 1.29 - 24.44)[21]. There was some variation in risk for KS among those diagnosed with AIDS between the ages of 20-49, but the observed differences were modest and not statistically significant. Subjects less than 20 years of age and those 50 years of age and older at the time of their AIDS diagnosis were at lower risk of KS than the comparison group comprised of 20-29 year olds[22]. The risk

---

[21] The small number of KS cases documented among female members of the study cohort (n=2) restricted our ability to further examine the association between KS and sex.

[22] Cohort members who were 50 years of age or older at the time of their AIDS diagnosis were at approximately one-half the risk for KS of the comparison group of 20-29 year olds (adjusted OR = 0.54, 95 percent CI = 0.37 - 0.78). Only one case of KS was diagnosed among the 26 cohort members who were less than 20 years of age at the time of their AIDS diagnosis. The risk for KS was lower in this group than in the comparison group (adjusted OR = 0.92, 95 percent CI = 0.10 - 8.77), but the magnitude of the difference is difficult to interpret because of the small number of cases under 20 years of age.

of KS declined during the study period, as measured with and without adjustment for age at AIDS diagnosis, sex, and mode of HIV transmission.

As outlined in Section 4.2, person-years of follow-up among cohort members were required for analyses that involved incidence rates, Kaplan-Maier estimates, and Cox regression. Some cohort members were excluded from these analyses because their person-years of follow-up were inestimable or inappropriate. The 460 individuals whose KS occurred at the time of initial AIDS diagnosis were not included in such analyses because they contributed no person-years of follow-up[23]. An additional 227 individuals who had no follow-up information recorded in HARS were also excluded from these analyses[24]. Ten KS cases whose KS diagnosis fell after the date of last information recorded in HARS were treated as non-KS cases for the purposes of these analyses[25]. Therefore, analyses that employed person-years of follow-up were based on the person-years accumulated among the 388 KS cases that were diagnosed subsequent to their

---

[23] For these 460 individuals, the time interval between the diagnosis of AIDS and KS was zero

[24] As documented in Section 4.2, person-years of follow-up represented the time between initial AIDS diagnosis and the date of last information (i.e., date of death or date last known to be alive), as recorded in HARS. However, the date of last information as recorded in HARS was not available for 241 (6.2 percent) of the cohort members. Of these, 14 had KS at the time of initial AIDS diagnosis and 227 did not (although 5 of 227 developed KS following initial AIDS diagnosis).

[25] There were 403 cohort members diagnosed with KS following their initial AIDS diagnosis. In 10 (2.5 percent) of these individuals, the date of KS diagnosis fell after the date of last information as recorded in HARS. For all analyses based on person-years of follow-up, these 10 cohort members contributed person-years only up to the date of last information as recorded in HARS. These ten individuals were not considered to have had KS in the analyses based on person-years of follow-up. Five cohort members who developed KS following their AIDS diagnosis were also excluded from this analysis because we were unable to estimate their person-years of follow-up (date of last information was not recorded in HARS).

initial AIDS diagnosis, and the person-years of follow-up from the 2,814 AIDS patients who were not considered to have had KS.

Average-annual age-specific and age-adjusted KS incidence rates for the cohort are shown in Tables 4.3.4 (males) and 4.3.5 (females). Overall, the 387 incident cases of KS diagnosed among male members of the cohort following their initial AIDS diagnosis far exceeded the 0.0073 cases that would have been expected based on KS incidence rates in the general population (observed/expected ratio = 53,001.3, 95 percent CI = 47,831.6 - 58,536.5). No KS cases occurred among male members of the cohort under 20 years of age[26]. The majority of KS cases in the cohort occurred among males between the ages of 20 and 59 years, ages at relatively low risk of the disease in the general population. KS incidence rates in the general population were highest among men over the age of 60 years. Nonetheless, the 3 cases diagnosed among male cohort members over 60 years of age was far greater than would have been expected to have occurred had the rates of the general population prevailed.

Only one case of KS was diagnosed among a female cohort member following her initial diagnosis of AIDS (Table 4.3.5). Even this single case was far greater than would have been expected based on rates in the general population (observed/expected ratio = 19,630.9, 95 percent CI = 496.6 - 109,060.8).

---

[26] No member of the cohort was under 20 years of age at the time of KS diagnosis. Table 4.3.3 shows that one cohort member with KS was under 20 years of age at his initial AIDS diagnosis. However, this individual did not develop KS until he was 21 years of age.

4.4 Temporal trends in Kaposi's sarcoma among people with AIDS

In San Francisco, the percentage of homosexual and bisexual men with AIDS who presented with KS dropped from 55 percent to 19 percent during the period 1982-88 (Rutherford 1990). As discussed in Section 1.4, similar results have been reported in some studies (Des Jarlais 1987, Haverkos 1990, Beral 1990), but not in others (Jacobsen 1990, Munoz 1993, Montaner 1994, Veugelers 1995, Lundgren 1995). We used data from the combined resources of HARS and CSS to assess the temporal trends of KS among people with AIDS in western Washington state.

As a first step in characterizing temporal trends in the occurrence of KS among people with AIDS, we examined the proportion of people with AIDS that were ever diagnosed with KS, by time period of initial AIDS diagnosis. For the purposes of this analysis, KS cases were categorized into those who were diagnosed at the time of initial AIDS diagnosis (n=460) and those who were diagnosed subsequent to the initial AIDS diagnosis (n=403). Overall, the percentage of people with AIDS ever diagnosed with KS decreased from 32.9 percent of those people diagnosed with AIDS during the period 1982-86 to 19.0 percent of people diagnosed with AIDS during the period 1990-92, a reduction of 42.2 percent (Table 4.4.1). The percentage of people diagnosed with KS at the time of their initial AIDS diagnosis decreased from 22.5 percent of those diagnosed with AIDS during the period 1982-86 to 8.6 percent of those diagnosed with AIDS during the period 1990-92. Among those who did not have KS at the time of their initial AIDS diagnosis, the percent of cases that went on to develop KS following their initial AIDS

diagnosis declined from 13.4 percent of those diagnosed with AIDS during the period 1982-86 to 11.4 percent of those diagnosed with AIDS during the period 1990-92.

Figure 4.4.1 graphically demonstrates that the cumulative percentage of people with AIDS who developed KS following their initial AIDS diagnosis declined during the study period 1982-92[27]. By log-rank test, cohort members diagnosed with AIDS during the period 1982-86 were at significantly greater risk of developing KS following their AIDS diagnosis than were comparable cases diagnosed during the periods 1986-89 ($p<0.01$) and 1990-92 ($p=0.01$). Differences in risk of KS for those diagnosed during the latter two time periods were not statistically significant ($p=0.51$). The Kaplan-Maier curves also suggest that the observed risk differences were established within the first two years following AIDS diagnosis.

By Cox proportional hazards model, the risk of developing KS after initial AIDS diagnosis decreased during the study period[28]. Compared with those diagnosed with AIDS during the period 1982-86, the proportional hazards for developing KS following initial AIDS diagnosis was 0.61 (95 percent CI = 0.43 - 0.86) and 0.66 (95 percent CI = 0.47 - 0.92) for those diagnosed with AIDS during the periods 1987-89 and 1990-92, respectively.

---

[27] Cumulative percentage distribution for KS following the initial diagnosis of AIDS was generated by the Kaplan-Maier product-limit method, as described in Section 4.2.

[28] This model was simultaneously adjusted for age at AIDS diagnosis, sex, and mode of HIV transmission.

A number of modifications were made to the definition of AIDS during the period 1982-92, the two broadest changes having occurred in 1985 and 1987 (Osmond 1994). These changes could potentially influence the interpretation of the observed temporal trends in KS occurrence. The 1985 change in AIDS definition was estimated to have increased the number of AIDS cases by less than one percent (Centers for Disease Control 1985) and, therefore, would have had minimal impact on the observed temporal trends in KS. In contrast, the 1987 change in AIDS definition (Centers for Disease Control 1987) may have increased the number of AIDS cases by as much as 23 percent (Payne 1990). Nonetheless, Beral et al. (1990) estimated that KS declined during the period 1983-88 by approximately 20 percent per year among homosexual men with AIDS and by 10 percent annually among people with AIDS in other HIV risk groups, after controlling for changes in the AIDS definition that occurred during that period. Therefore, changes that broadened the definition of AIDS during the study period are unlikely to fully account for the observed declines in KS reported in this and other investigations.

4.5 Issues regarding surveillance for Kaposi's sarcoma

CSS and HARS conduct surveillance for KS, but their respective efforts differ in scope. To fulfill the role of a population-based cancer registry, CSS staff members conduct routine surveillance for all malignant neoplasms diagnosed among residents of western Washington state, including KS. HARS surveillance for KS stems from interest

in KS as an AIDS-defining illnesses. Thus, HARS conducts surveillance for KS among people with AIDS, and these efforts are usually limited to those KS cases that are diagnosed at or near the time of initial AIDS diagnosis. The combined resources of these two registries provided a unique opportunity to compare and contrast the results of surveillance from these two sources.

This section focuses on surveillance for KS from two perspectives. First, we examined KS diagnosed among people with AIDS, as represented by members of our study cohort. Second, we examined KS surveillance in the general population, specifically, for those cases of the disease diagnosed in residents of western Washington state during the period 1982-92. For the purpose of this presentation, it is important to emphasize the distinction between these two perspectives. While most KS cases identified through the combined resources of HARS and CSS were included in both sets of analyses, some cases were limited to only one analysis or the other. For example, in describing KS surveillance among people with AIDS, it is important to note that the study cohort was defined as all residents of western Washington state who were diagnosed with AIDS during the time period 1982-92, and who were registered in HARS. Cases of KS diagnosed in cohort members may have occurred at or following the initial AIDS diagnosis, and the year of KS diagnosis in this group ranged from 1982-94. In contrast, our review of KS surveillance among residents of western Washington state focused on all KS cases diagnosed among residents of this region during the period 1982-92. Thus, the number of KS cases varies according to the focus of the analysis.

As expected when combining data from two separate sources, there was some variation between dates of KS diagnosis as recorded in HARS and CSS. Our methods for resolving these discrepancies are summarized in Sections 3.5.

During the period 1982-92, 3,899 residents of western Washington state were diagnosed with AIDS. Of these, 863 were also diagnosed with KS, either at the time of their initial AIDS diagnosis (n=460) or in the months and years following their initial AIDS diagnosis (n=403). These individuals formed the study cohort for the purposes of the present investigation.

Of the 863 KS cases diagnosed among members of the study cohort, 405 (46.9 percent) were registered in both the CSS and HARS. Another 372 KS cases (43.1 percent) were identified in cohort members solely from the records of the CSS. The remaining 86 KS cases (10.0 percent) were registered in HARS, but not in the CSS. Figure 4.5.1 demonstrates that most of the KS cases registered in HARS[29] were diagnosed at or near the time of AIDS diagnosis. In contrast, most KS cases diagnosed among cohort members that were solely registered in CSS were diagnosed in the months and years following the initial diagnosis of AIDS.

For the purpose of improving KS surveillance, it would have been useful to investigate further the discrepant KS cases (i.e., those cases registered with KS in one but not both registries) to identify factors that may influence case ascertainment in these

[29] Including those registered solely in HARS (n=86) and jointly registered in CSS and HARS (n=405).

registries. However, the confidentiality guidelines that governed this investigation prohibited the identification of individual cases for this purpose. Nonetheless, we utilized data from the existing research data set to examine some of the discrepant KS cases for clues as to why they were registered in one but not both registries. First, among members of the study cohort, we compared selected characteristics of the 86 KS cases registered solely in HARS with those of the 405 KS cases that were registered in both CSS and HARS. The two groups were compared with respect to age at AIDS diagnosis, year of AIDS diagnosis, sex, county of residence[30], and reporting source[31].

Second, also among members of the study cohort, we examined a subset of the 372 KS cases that were registered solely in the CSS. As previously noted, most of the KS cases registered solely in the CSS were diagnosed in the months and years following the initial AIDS diagnosis. The relatively limited scope of KS surveillance in HARS (i.e., most KS cases registered in HARS occurred at or near the time of initial AIDS diagnosis) may explain why the cases derived solely from CSS were not identified as KS cases in HARS. Nonetheless, 110 of these cases (29.6 percent) were diagnosed within 6 months of initial AIDS diagnoses (39 were diagnosed at the same time as AIDS). We compared selected characteristics of these 110 cases with those of the 405 KS cases that were registered in both registries. These two groups were compared with respect to age at

---

[30] County of residence at the time of initial AIDS diagnosis, as recorded in HARS.

[31] The source of the AIDS case report, as recorded in HARS.

AIDS diagnosis, year of AIDS diagnosis, sex, county of residence[32], and reporting source[33].

Compared with the 405 KS cases recorded in both registries, the 86 KS cases registered solely in HARS were more likely to have been diagnosed with AIDS during the period 1990-92 and were more likely to be non-King county residents (Table 4.5.1). A majority of KS cases in both groups were reported by private health care providers, though the percentage of reports from this source was highest in those cases recorded in both registries. A higher percentage of HARS-only KS cases were derived from death certificates, data from the AIDS spectrum of disease study, and Medicaid records (the latter two sources are not routinely utilized by the CSS). KS cases registered in HARS were classified as definitive vs. presumptive, reflecting to some extent the basis on which the diagnosis of KS was established[34]. A higher percentage of HARS-only KS cases were in the presumptive category than those recorded in both registries. Both of the cohort's female KS cases were registered solely in HARS. There were no appreciable differences in age at AIDS diagnosis between the two groups.

---

[32] County of residence at the time of KS diagnosis, as recorded in the CSS.

[33] The primary source of information relevant to the diagnosis of KS, as recorded in CSS.

[34] The AIDS surveillance case definition contains both "presumptive" and "definitive" criteria for many AIDS-defining conditions, including KS (Centers for Disease Control and Prevention 1992). A diagnosis is considered to be "definitive" if there is evidence that it was based on specific laboratory methods such as histology or culture. A diagnosis is defined as "presumptive" if it was made by a clinician, with no evidence that "definitive" methods were employed.

Few differences were noted between the KS cases registered solely in CSS (that is, in the subset of 110 such cases identified for this analysis) compared with those recorded in both registries (Table 4.5.2). KS cases registered solely in the CSS were more likely to be King county residents, and a slightly higher percentage were identified through pathology laboratories than in the comparison group.

With the combined resources of HARS and CSS, we identified a total of 801 KS cases that were diagnosed among residents of western Washington state during the period 1982-92 (Table 4.5.3). Of these, 373 (46.6 percent) were registered with KS in both CSS and HARS, and 319 (39.8 percent) were registered with KS in the CSS but were registered in HARS without any record of their KS diagnosis. Sixty-one cases (7.7 percent) were registered in HARS with KS, but were not registered with KS in the CSS. Forty-seven cases (5.9 percent) were registered in the CSS with KS but were not registered in HARS. Of the latter 47 cases, only one had evidence of HIV infection recorded in CSS, and the remaining 46 cases were considered unrelated to HIV[35]. In summary, of 801 KS cases diagnosed among residents of western Washington state during the period 1982-92, 755 (94.3 percent) were associated with HIV infection. There was no evidence that the remaining 46 cases (5.7 percent) were associated with HIV infection.

---

[35] We examined the discrepant cases identified in this population-based analysis (i.e., those KS cases registered solely in HARS or CSS, but not in both registries). The results from this analysis were consistent with those from our analysis of such cases in the study cohort, and are not reported here.

4.6 Non-Hodgkin's lymphoma among people with AIDS

NHL was diagnosed in 326 (8.4 percent) of the 3,899 study cohort members. NHL has been an AIDS-defining illness since 1985 (Centers for Disease Control 1985), and 122 (37.4 percent) of the 326 NHL cases had their AIDS diagnosis made at the time this cancer was diagnosed. The remaining 204 NHL cases (62.6 percent) were diagnosed in the months and years following the initial diagnosis of AIDS.

The distribution of NHL cases in cohort members by mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis differed considerably from that of KS cases (Table 4.6.1). NHL occurred most frequently among transfusion/transplant recipients (14.1 percent). No NHL cases were observed in the few pediatric hemophiliacs or children with mothers at high-risk of HIV infection. Among the remaining HIV-risk groups, there was little variation in the percentage of cases with NHL (range 5.7 to 9.0 percent). NHL occurred in a slightly higher percentage of males (8.5 percent) than females (5.7 percent). No cases of NHL were diagnosed in cohort members who were under the age of 20 years or over the age of 80 years at AIDS diagnosis. Otherwise, there was little variation in the percentage of cohort members with NHL by age at AIDS diagnosis. There was no temporal trend in the percentage of AIDS cases diagnosed with NHL during the study period (see Section 4.7).

Logistic regression was used to characterize the associations between NHL and mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis, while simultaneously controlling for each of these factors (Table 4.6.2). Because no

cases of NHL occurred among cohort members under the age of 20 years (n=26), this analysis was limited to the 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis. For this analysis, mode of HIV transmission was grouped according to risk of KS (low, medium, high), as described in Section 4.2.

In contrast to KS, mode of HIV transmission (low, medium, and high KS risk) was inversely related to risk of NHL, to a modest degree. Compared to cohort members whose mode of HIV transmission placed them at low risk for KS, the risk of NHL was somewhat lower in those at medium risk of KS (OR=0.71, 95 percent CI=0.34-1.51) and high risk of KS (OR=0.63, 95 percent CI=0.32.1.24). The odds of developing NHL increased slightly with age at initial AIDS diagnosis and were modestly higher for males than females, but these differences did not achieve statistical significance. The odds of developing NHL remained constant over the study period, with and without simultaneous adjustment for mode of HIV transmission, sex, age at AIDS diagnosis.

As outlined in Section 4.2, person-years of follow-up among cohort members were required for analyses that involved incidence rates, Kaplan-Maier estimates, and Cox regression. Some cohort members were excluded from these analyses because their person-years of follow-up were inestimable or inappropriate. The 122 individuals whose NHL occurred at the time of initial AIDS diagnosis were not included in such analyses because they contributed no person-years of follow-up[36]. An additional 229 individuals

---

[36] For these 122 individuals, the time interval between the diagnosis of AIDS and NHL was zero.

who had no follow-up information recorded in HARS were also excluded from these analyses[37]. Seven NHL cases whose NHL diagnosis fell after the date of last information recorded in HARS were treated as non-NHL cases for the purposes of these analyses[38]. Therefore, analyses that employed person-years of follow-up were based on the person-years accumulated among the 195 NHL cases that were diagnosed subsequent to their initial AIDS diagnosis, and the person-years of follow-up from the 3,353 AIDS patients who were not considered to have NHL.

The average-annual age-adjusted NHL incidence rates in both male and female members of the cohort far exceeded the corresponding rates in residents of western Washington state (Tables 4.6.3 and 4.6.4, respectively)[39]. The 189 NHL cases diagnosed among male members of the cohort were more than were expected based on the incidence rates in the general population (observed/expected ratio = 301.3, 95 percent CI = 259.9-347.5). The risk of NHL was similarly high in female cohort members

---

[37] As documented in Section 4.2, person-years of follow-up represented the time between initial AIDS diagnosis and the date of last information (i.e., date of death or date last known to be alive), as recorded in HARS. However, the date of last information as recorded in HARS was not available for 241 (6.2 percent) of the cohort members. Of these, 12 had NHL at the time of initial AIDS diagnosis, and 229 did not (although 2 of 229 developed NHL following AIDS diagnosis).

[38] There were 204 cohort members diagnosed with NHL following their initial AIDS diagnosis. In 7 (3.4 percent) of these individuals, the date of NHL diagnosis fell after the date of last information as recorded in HARS. For all analyses based on person-years of follow-up, these 7 cohort members contributed person-years only up to the date of last information as recorded in HARS, and were not considered to have had NHL in the analyses based on person-years of follow-up. Two additional NHL cases that occurred following the diagnosis of AIDS were excluded from these analyses because we were unable to estimate their person-years of follow-up (date of last information was not recorded in HARS).

[39] NHL incidence rates for residents of western Washington state excluded cases of the disease known to have been associated with HIV infection (see Section 4.2).

(observed/expected ratio = 307.6, 95 percent CI = 112.7-670.2), though these results were based on only six cases diagnosed in women. In men with AIDS, the absolute incidence of NHL was relatively constant by age at diagnosis, though the magnitude of the observed/expected ratio was inversely related to age at diagnosis.

4.7 Temporal trends in non-Hodgkin's lymphoma among people with AIDS

In contrast to KS, there was no evidence of a temporal trend in the occurrence of NHL among people with AIDS (Table 4.7.1). The cumulative percentage distribution of people with AIDS who developed NHL following their initial AIDS diagnosis is shown in Figure 4.7.1[40]. By log-rank test, the modest differences in risk of NHL among cohort members diagnosed with AIDS during the periods 1982-86, 1987-89, and 1990-92 were not statistically significant (p=0.11). Compared with those diagnosed with AIDS during the period 1982-86, the relative risk of NHL was 0.65 (95 percent CI=0.38-1.08) and 0.86 (95 percent CI=0.53-1.41) for those diagnosed with AIDS during the periods 1987-89 and 1990-92, respectively[41].

4.8 Issues regarding surveillance of non-Hodgkin's lymphoma

In this section, issues regarding surveillance for non-Hodgkin's lymphoma are discussed within the same context as previously outlined for KS (Section 4.5). To briefly

---

[40] Cumulative percentage distribution for NHL following the initial diagnosis of AIDS was generated by the Kaplan-Maier product-limit method, as described in Section 4.2.

[41] By Cox proportional hazards model, adjusted for age at AIDS diagnosis, mode of HIV transmission, and sex.

reiterate, CSS and HARS conduct surveillance for NHL, but their respective efforts differ in scope. CSS strives to identify all malignant neoplasms diagnosed among residents of western Washington state, including NHL, while NHL surveillance in HARS is usually limited to the time period near initial AIDS diagnosis.

The documentation of NHL in HARS is primarily based on information from the AIDS case report form. This form allows for reporting the following three types of NHL in people with AIDS: Burkitt's lymphoma, primary brain lymphoma, and immunoblastic lymphoma[42]. As summarized in Section 2.4, AIDS case report forms are submitted to the Department of Health by health care providers and other professionals. Although the Centers for Disease Control and Prevention (CDC) has guidelines for the reporting of NHL among people with AIDS (CDC 1985), the extent to which these specific guidelines are followed is not known. In contrast, information on each primary cancer recorded in the CSS is collected from medical records by specially trained technicians according to standards promulgated by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (Ries 1987). Tumor histology and cancer primary site are coded by CSS staff members according to the International Classification of Disease for Oncology, Second Edition (ICDO-2).

---

[42] The NHL categories listed here (Burkitt's lymphoma, primary brain lymphoma, and immunoblastic lymphoma) are not mutually exclusive. Nonetheless, in practice, only one of the three categories is usually checked on the AIDS report form. Among the 3,899 residents of western Washington state diagnosed with AIDS during the period, only one individual was reported with more than one type of NHL (see Table 4.8.1).

During the period 1982-92, 5,236 cases of NHL were diagnosed among residents of western Washington state. Of these, 273 (5.2 percent) were determined to have occurred in people infected with HIV. Section 4.9 addresses in detail of contribution of HIV to increasing rates of NHL in the resident population of western Washington state. The remainder of this section focuses on issues of surveillance for NHL among people with AIDS, as represented by members of the study cohort.

Of the 3,899 cohort members, 326 (8.36 percent) were diagnosed with NHL at or following the time of their initial AIDS diagnosis. Of the 326 cohort members with NHL, 123 (37.7 percent) were registered with NHL in both HARS and CSS. Of the remaining NHL cases, 196 (60.1 percent) were registered solely in the CSS, and eight (2.5 percent) were recorded solely in HARS. As with KS, most NHL cases recorded in HARS[43] were diagnosed at or near the time of initial AIDS diagnosis (Figure 4.8.1). Most NHL cases registered solely in CSS were diagnosed in the months and years following the initial AIDS diagnosis.

For comparison purposes, NHLs recorded in the CSS were classified into three categories consistent with those used in HARS. These categories were defined on the basis of tumor histology and primary site as recorded in CSS. NHL cases were considered to represent Burkitt's lymphoma if they were registered in CSS with an ICDO-2 histology code of 9687. NHL cases were considered to have had a primary site

---

[43] NHL cases registered in HARS included those registered in both CSS and HARS (n=123) and those registered solely in HARS (n=8).

in the brain or other parts of the central nervous system (CNS) if their ICDO-2 site categories fell within the ranges C70.0-C70.9 (meninges), C71.0-C71.9 (brain) or C72.0-C72.9 (other central nervous system). The remaining cases were grouped into a general category of NHL (non-Burkitt, non-CNS).

There were discrepancies between the histologic types and primary sites for some cases of NHL registered in both HARS and CSS (Table 4.8.1). Of 15 NHL cases recorded as Burkitt's lymphoma in HARS, only six (40.0 percent) were registered as Burkitt's lymphoma in the CSS. Similarly, of 23 NHL cases registered as primary brain lymphomas in HARS, only 11 (47.8 percent) were recorded as primary brain lymphomas in CSS. Most NHLs registered in HARS were classified as immunoblastic lymphomas, and most of these cases were recorded in CSS as non-Hodgkin's lymphomas other than Burkitt's lymphoma or primary brain lymphoma. Nonetheless, of the latter group of 92 NHL cases recorded in HARS as immunoblastic lymphoma, four (4.3 percent) were registered in CSS as Burkitt's lymphoma, four (4.3 percent) were registered in CSS as primary brain lymphoma, and one (1.1 percent) was registered in CSS as Hodgkin's disease.

4.9 The contribution of HIV/AIDS to the epidemic of non-Hodgkin's lymphoma in the general population of western Washington state, 1975-92

Incidence rates for non-Hodgkin's lymphoma (NHL) have increased in the United States during the past several decades (Devesa 1992, Zheng 1992, Rabkin 1993, Ries

1994). Similar temporal patterns in the occurrence of NHL also have been documented in other countries (Devesa 1992, Cartwright 1992, Martinsson 1992, Coleman 1993, Carli 1994, Hjalgrim 1996). The reasons for the rise in NHL incidence rates are unknown, though many explanations have been offered (Zheng 1992, Rabkin 1993, Holford 1992, Banks 1992, Filipovich 1992, Linet 1992, Kinlen 1992, Mueller 1992, Zahm 1992, Boice 1992, Davis 1992, Pearce 1992).

NHL occurs in approximately 5-10 percent of people with AIDS (Obrams 1991)[44], and the AIDS epidemic has contributed to the increase in NHL incidence rates in the United States (Biggar 1985, Biggar 1987, Biggar 1989, Coté 1997). With combined resources from HARS and CSS, we documented increasing incidence rates of NHL in western Washington state during the period 1975-92, and estimated the contribution of HIV/AIDS to this phenomenon.

All primary cancers with ICDO-2 histology codes 9590-9595 and 9670-9714 were identified for the purposes of this investigation. Both nodal and extranodal primary cancer sites were included in this analysis. Non-malignant tumors and those of questionable malignancy were excluded. This definition is consistent with previous publications of NHL incidence rates from the National Cancer Institute (Ries 1997).

For the purposes of this analysis, NHL cases were considered to be HIV/AIDS-related if 1.) registered in the CSS with NHL and also registered in the HIV/AIDS

---

[44] NHL was diagnosed in 326 (8.4 percent) of the 3,899 cohort members in the present investigation (Section 4.6).

registry, 2.) registered in the HIV/AIDS registry with NHL, even if not registered in the CSS with NHL, and 3.) the CSS record indicated that a case of NHL was HIV/AIDS-related, even if not registered in the HIV/AIDS registry. The remaining NHL cases registered in the CSS with no evidence of HIV/AIDS, as defined above, were considered to be unrelated to HIV/AIDS.

To estimate the contribution of HIV/AIDS to the incidence rates for NHL, separate sets of rates were calculated for all NHL cases, for HIV/AIDS-associated cases only, and for NHL cases not associated with HIV/AIDS. Date of NHL diagnosis was determined from the records of the CSS, except for those NHL cases registered in the HIV/AIDS registry but not in the CSS. For the latter cases, the date of NHL diagnosis was ascertained from the HIV/AIDS registry.

Average annual age-specific and age-adjusted incidence rates per 100,000 were calculated for the time periods 1975-77, 1978-80, 1981-83, 1984-86, 1987-89, and 1990-92 for the entire CSS area of coverage. Because a disproportionate number of people with HIV/AIDS resided in Seattle, separate incidence rates were also calculated for residents of King county (which includes Seattle) and for the remaining 12 counties within the CSS area of coverage, combined. Age-adjusted rates were calculated by the direct method (Rothman 1998), and standardized to the age distribution of the 1970 United States population, as published in (Ries 1997). Denominators for the incidence rates were population estimates by age, sex, year, and county that were produced for use in the SEER Program by the United States Bureau of the Census (Ries 1997).

The combined resources of the CSS and HIV/AIDS registry identified 7,163 incident cases of NHL diagnosed among residents of the thirteen-county CSS area of coverage during the period 1975-92. Of these, 274 (3.8 percent) were diagnosed among people with HIV/AIDS. Among the HIV/AIDS-associated NHLs, 260 (94.9 percent) were registered in both the CSS and the HIV/AIDS registry, five cases (1.8 percent) were registered solely in the CSS, and nine (3.3 percent) were registered solely in the HIV/AIDS registry.

Average annual age-adjusted incidence rates for NHL increased during the period 1975-92, the magnitude of the increase being greater for males than females (Figure 4.9.1). In males, age-specific incidence rates for NHL were lowest among those under the age of 20 years, and there was little or no temporal increase in incidence rates in this age group (Table 4.9.1). No cases of NHL in males under the age of 20 years were associated with HIV/AIDS. In contrast, age-specific incidence rates in 20-49 year-old men increased during the study period, and this increase was almost entirely attributable to HIV/AIDS-associated NHL. NHL incidence rates among men over 50 years of age also increased over time, but few HIV/AIDS-related lymphomas were diagnosed in these older men.

Of 3,242 females diagnosed with NHL during the study period, only nine (0.3 percent) were associated with HIV/AIDS (Table 4.9.2). Temporal patterns in age-specific incidence rates for NHL among females were generally comparable with those of males without HIV/AIDS. NHL incidence rates were lowest among females under 20

years of age, and increased with age. Temporal increases in incidence rates among females were most pronounced in those over 50 years of age.

The contribution of HIV/AIDS to the incidence rates of NHL was greater in King county than in the remaining twelve counties within the CSS area of coverage, reflecting the relatively high prevalence of HIV infection in the Seattle-King county metropolitan area. During the most recent time period, 1990-92, HIV/AIDS-associated NHLs accounted for 59.0 percent of all cases of the disease diagnosed among 20-49 year old males in King county. In contrast, 23.6 percent of all NHL cases were associated with HIV/AIDS among 20-49 year old male residents of the remaining twelve counties during this period.

4.10 Cancers other than KS and NHL among people with AIDS

During the period 1982-92, KS and NHL were the only types of cancer that were considered by the CDC to be AIDS defining conditions[45]. These two types of cancer were, by far, the most common neoplasms diagnosed among members of the study cohort (863 KS cases and 326 NHL cases). Nonetheless, with the combined resources of HARS and CSS, we identified an additional 103 primary cancers, other than KS and NHL, that were diagnosed among cohort members(Table 4.10.1). Of these 103 cases, 99 (96.1 percent) were distributed among 22 primary cancer sites and the remaining four were of

[45] Cervical cancer was added to the list of AIDS-defining illnesses in 1993 (CDC 1992), but was not considered an AIDS-defining illness during the study period.

unknown primary site; 56 (54.4 percent) were diagnosed prior to the initial AIDS diagnosis, six (5.8 percent) were diagnosed at the same time as AIDS, and 40 (38.8 percent) were diagnosed following the diagnosis of AIDS.

Forty cases of cancer other than KS and NHL were diagnosed among cohort members following AIDS diagnosis. Eight of these were non-reportable skin lesions[46], and three were of unknown primary cancer site[47]. The remaining 29 cases were distributed among the 13 primary cancer sites listed in Table 4.10.2. For each of these sites, and for all sites combined (other than KS and NHL), the corresponding age-specific incidence rates from the general population were applied to the person-years of post-AIDS follow-up among cohort members to determine the number of cases that would have been expected had these rates obtained in the cohort (see Section 4.2). The observed-to-expected ratio exceeded unity (i.e., was greater than 1.0) for each of these 13 primary cancer sites.

4.11 Discussion

The cancer experience of our study cohort was consistent with previous reports of cancer among people with AIDS (Coté 1991, Reynolds 1993, Rabkin 1994, Johnson

---

[46] CSS does not conduct routine surveillance for skin cancers that are not included on the list of reportable neoplasms promulgated by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Because surveillance for such lesions is incomplete, we did not calculate the corresponding incidence rates or observed-to-expected ratios.

[47] Incidence rates and observed-to-expected ratios were not calculated for the three cases of unknown primary cancer site. However, these three cases were included in calculations for all cancer sites combined (other than KS and NHL) shown in Table 4.10.2.

1997, Beral 1998, Goedert 1998). KS and NHL were the predominant cancers diagnosed among people with AIDS in western Washington state. Cohort members were also at increased risk for Hodgkin's lymphoma, as well as cancers of the oral cavity and pharynx, anus and anal canal, lung and bronchus, female breast, vulva, and penis. However, incidence rates for cancers other than KS and NHL were based on a small number of cases. Observed-to-expected ratios were highest for KS, NHL, Hodgkin's lymphoma, anal cancer, vulvar cancer, and penile cancer. The etiologies of each of the latter six cancer site/types have been highly associated with infectious agents, and these cancers may thus be a consequence of opportunistic infection in people with AIDS (Beral 1998). Individual primary cancer sites/types are briefly discussed in the following sections.

4.11.a Kaposi's sarcoma

The occurrence of KS and pnuemocystis pneumonia in young homosexually active men marked the beginning of the AIDS epidemic in the United States (Gottlieb 1981, CDC 1981). KS was one of the original AIDS defining conditions (CDC 1981, CDC 1982, CDC Task Force 1985, Jaffe 1983) and, despite an apparent decline in incidence of KS among people with AIDS, it has remained the most common neoplasm in those infected with HIV (Beral 1998).

Among people with AIDS, KS occurs disproportionately among homosexual and bisexual men (Beral 1990). This observation, together with an apparent temporal decline

and geographic variation in the occurrence of the disease in people with AIDS, was the basis for speculation that that KS was caused by a sexually transmissible agent, other than HIV (Beral 1990, Beral 1991b, Beral 1992) (see Section 1.5). There is now compelling evidence that a novel human herpesvirus (HHV8, KSHV)[48] is involved in the etiology of KS (Chang 1994, Chang 1996, Weiss 1998, Moore 1998). Results from recent studies that utilized serologic tests for HHV8 support the hypothesis that this virus may be sexually transmitted (Kedes 1996, Martin 1998, Melbye 1998, Grulich 1999).

4.11.b Non-Hodgkin's lymphoma

As with KS, NHL was recognized early in the AIDS epidemic as a common neoplasm among those infected with HIV (CDC 1982, Doll 1982, Ziegler 1982, Snider 1983, Levine 1984). Unlike KS, NHL occurs in a broad range of HIV-infected individuals of both sexes and with different risk factors for HIV (Obrams 1991, Biggar 1992). Also in contrast to KS, there has been no apparent temporal decline in the occurrence of NHL among those with AIDS.

Prior to the AIDS epidemic, NHL was found to be the most common neoplasm among individuals with genetic- or iatrogenically-induced immunosuppression (Hoover 1973, Penn 1988, Kinlen 1992a, Kinlen 1992b,). Epstein-Barr virus (EBV) has been closely associated with the pathogenesis of NHL (Mueller 1996), especially Burkitt's

---

[48] This virus is the eighth herpesvirus known to infect humans (thus, HHV8), and is also referred to as Kaposi's sarcoma-associated herpesvirus (KSHV).

lymphoma, and is likely to be an important factor in the development of NHL among people with AIDS (Luxton 1991). HIV-induced immunosuppression among individuals at high risk for EBV infection may explain the high rates of NHL in people with AIDS.

It is clear that HIV has contributed to recent increases in incidence rates of NHL in the general population. However, the contribution of HIV was primarily among men between the ages of 20-49 years. In the absence of HIV infection, there were no clear temporal trends in the incidence rates of NHL in the population under 50 years of age. The substantial temporal increase in NHL incidence rates in men and women over 50 years of age began before the AIDS epidemic and continued during the period of this investigation, with relatively little contribution of HIV infection. Factors other than HIV infection are thus largely responsible for the sizable increase in NHL incidence rates in middle-aged and elderly persons. The identification of factors responsible for the increase in NHL cases in the population over 50 years of age should be the subject of additional research.

Highly active antiretroviral therapy (HAART) has led to a dramatic decrease in AIDS-associated morbidity and mortality in recent years (Palella 1998). Incidence rates for AIDS-related KS and NHL have declined following HAART in some cohorts of HIV-infected individuals (Jones 1998, Rabkin 1998, Sporano 1998, Jacobsen 1998), but not others (Jacobsen 1998, Buchbinder 1998). The duration of HIV suppression afforded by HAART is currently not known. Therefore, we do not know if the observed reductions in HIV-associated KS and NHL will be permanent, or if they represent a dramatic but

transient delay in the onset of these malignancies. If HIV-infected individuals remain at high risk for NHL, they will continue to be a major source of NHL cases in young adults, and their contribution to the NHL caseload over 50 years of age may increase in the future.

4.11.c Other cancers

Results from this and other studies indicate that people with AIDS are at relatively high risk of both invasive cervical cancer (Vermund 1991, Kreiss 1992, Bosch 1995) and anal cancer (Melbye 1994, Palefsky 1998). Neoplasms of these two primary sites are believed to be caused by specific strains of human papillomavirus (HPV) which, like HIV, are sexually transmissible agents (IARC 1995, Koutsky 1997). Thus, the high risk of anal and cervical cancer among people with AIDS may be due to the fact that these persons also have an atypically high prevalence of HPV infection. There is also evidence that the carcinogenic potential of HPV may be enhanced in the context of HIV-induced immunosuppression (Sun 1997), which may further contribute to the high risk of HPV-related cancers among people with AIDS.

Cohort members were also at high risk for penile and vulvar cancer, though the observed-to-expected ratios were based on a single case of each cancer. HPV has been associated with penile (Varma 1991, Iwasawa 1993, Malek 1993) and vulvar cancer (Brinton 1990, Madeline 1997). As with anal and cervical cancer, the increased risk of vulvar and penile cancer in HIV-infected individuals may represent a common risk factor

related to sexual activity, and may be effected by the enhanced carcinogenic activity of HPV in an environment of immune incompetence.

Previous studies have documented a high risk of Hodgkin's lymphoma among people with AIDS (Hessol 1992, Reynolds 1993, Lyter 1995, Koblin 1996, Rabkin 1998), though this malignancy occurs at a much lower rate than NHL in people with AIDS. Like NHL, Hodgkin's lymphoma was observed in immunosuppressed patient populations prior to the advent of the AIDS epidemic (Kinlen 1979). Also like NHL, EBV has been implicated in the etiology of Hodgkin's lymphoma (Mueller 1992). Thus, Hodgkin's lymphoma may result from an opportunistic infection in the context of HIV-induced immunosuppression, though further research is warranted in this area.

Members of the study cohort were at high risk for cancers of the breast, lung, and oral cavity. High rates of lung cancer have been documented in some AIDS populations (Tenholder 1993, Johnson 1997), but not others (Reynolds 1993). Nonetheless, it is difficult to interpret observations regarding lung and oral cancer in the absence of data on tobacco use in these groups. Breast and oral cancers have not been well characterized in HIV-infected cohorts. There is limited evidence that HPV infection is associated with cancers of the oral cavity, lung, and breast (IARC 1995, Schwartz 1998). The possible link between HPV and cancers of the lung, breast, and oral cavity is intriguing since people with AIDS are at high risk for other cancers in which the association with HPV has been well established. Again, further research is needed in this area.

4.11.d Surveillance for Kaposi's sarcoma and non-Hodgkin's lymphoma

In our examination of the combined HARS/CSS data set, we found evidence that KS was underreported in the CSS during the period 1982-92. We identified 62 cases of KS diagnosed among residents of western Washington state during this period that were registered in HARS but not in the CSS. Compared to KS cases that were registered in both HARS and CSS, a higher percentage KS cases registered solely in HARS were found to have been diagnosed on the basis of clinical criteria rather than histologic review. Underreporting of KS in central cancer registries has been documented in previous investigations (Reynolds 1990, Reynolds 1991, Coté 1995). This phenomenon may be analogous to underreporting of malignant melanoma that has been observed in some central cancer registries (Karagas 1991, Koh 1991). Karagas et al. (1991) found that up to 25 percent of malignant melanomas diagnosed in residents of western Washington state were not ascertained by the CSS because they were diagnosed in private clinicians offices that were not visited by CSS personnel[49]. As with malignant melanoma, some KS cases may have been diagnosed and treated on an outpatient basis which allowed them to circumvent traditional CSS case finding mechanisms. The confidentiality agreement for this investigation prohibited identification of individual cases, which prevented further examination of this topic. However, cooperative research between registries of cancer and AIDS in future years may provide new insight into the

[49] The CSS subsequently developed new methods to identify the "missing" melanoma cases.

underreporting of KS in the central cancer registry, but only if the confidentiality of such records can be guaranteed.

In contrast to KS, we found few NHL cases that were recorded in HARS but not in CSS. However, for many of the NHLs recorded in both HARS and CSS, we found discrepancies between the classification of NHL recorded in HARS and the corresponding histology and primary cancer sites recorded in CSS. Because these discrepancies may have profound implications for the interpretation of AIDS surveillance data, additional research is needed to reconcile these differences.

Results from this and other investigations demonstrate that population-based AIDS surveillance data alone do not provide a complete picture of the burden of cancer among people with AIDS. Registries of HIV/AIDS primarily ascertain information on cancers that were diagnosed at or near the time of AIDS diagnosis. The relatively large number of cancer cases that are diagnosed following the initial AIDS diagnosis (primarily KS and NHL) are often not reflected in these data. Further, HIV/AIDS surveillance presently includes only those cancers that are classified by the CDC as AIDS-defining conditions[50]. Vague classification of NHL, along with possible inaccuracies in the descriptions NHL primary site and histologic type (as previously discussed), further limit the usefulness of AIDS surveillance data for the purpose of studying AIDS-related neoplasms.

---

[50] During the period of this investigation (1982-92), KS and NHL were the only cancers designated as AIDS-defining conditions. Cervical cancer was added to this list in 1993.

4.11.e Implications for other analyses

Results from this portion of the investigation have implications for analyses of the associations between KS and various sexually transmitted and enteric diseases, the primary focus of the following Chapter. Mode of HIV transmission, sex, and year of AIDS diagnosis are clearly related to the occurrence of KS among people with AIDS. The association between these variables and exposures of interest must be carefully examined and controlled for in the course of these analyses.

Table 4.3.1. Enumeration of incident cases of Kaposis' sarcoma (KS) and corresponding average annual age-adjusted incidence rates per 100,000, residents of western Washington state by sex, HIV status*, and time period of diagnosis, 1975-92

		Year of cancer diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
Sex	Type of case	No.†	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
Male	All	9	0.28	9	0.26	13	0.28	127	2.20	283	4.48	366	5.17
	HIV-related*	0 (-)	-	0 (-)	-	7 (53.8)	0.12	116 (91.3)	1.96	270 (95.4)	4.22	361 (98.6)	5.07
	non-HIV‡	9 (100.0)	0.28	9 (100.0)	0.26	6 (46.2)	0.16	11 (8.7)	0.25	13 (4.6)	0.27	5 (1.4)	0.10
Female	All	3	0.08	3	0.06	7	0.11	2	0.03	3	0.05	3	0.07
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	1 (33.3)	0.02
	non-HIV	3 (100.0)	0.08	3 (100.0)	0.06	7 (100.0)	0.11	2 (100.0)	0.03	3 (100.0)	0.05	2 (66.7)	0.05

* KS cases were assumed to be HIV-positive if they were registered in the HIV/AIDS reporting system, or if Cancer Surveillance System personnel found specific statements in the medical record that documented HIV infection.

† Number of incident cancer cases. *In parentheses:* percentage of cases known or not known to be HIV-related for a given time period and sex.

‡ Cases not known to associated with HIV.

Table 4.3.2 Distribution of Kaposi's sarcoma (KS) among people with AIDS by selected characteristics *(page one of two)*

Characteristic	Category	No. AIDS cases	KS status			
			With KS		*Without* KS	
			No.	Percent	No.	Percent
Mode of HIV transmission*	Homo/bisexual males	2,982	747	25.1	2,235	74.9
	Intravenous drug abusers	211	14	6.6	197	93.4
	Homo/bisexual males who abuse intravenous drugs	434	94	21.7	340	78.3
	Adult hemophiliacs	35	0	-	35	100.0
	Heterosexual contact	89	3	3.4	86	96.6
	Transfusion recipients	64	1	1.6	63	98.4
	Adults with unknown risk factors	68	4	5.9	64	94.1
	Pediatric hemophiliacs	4	0	-	4	100.0
	Children with mothers at high-risk of HIV infection	12	0	-	12	100.0
Sex	Male	3,740	861	23.0	2,879	77.0
	Female	159	2	1.3	157	98.7

continued

Table 4.3.2 continued *(page two of two)*

Characteristic	Category	No. AIDS cases	KS status			
			With KS		*Without* KS	
			No.	Percent	No.	Percent
Age at AIDS diagnosis	00-09 years	16	0	-	16	100.0
	10-19 years	10	1	10.0	9	90.0
	20-29 years	752	167	22.2	585	77.8
	30-39 years	1,888	467	24.7	1,421	75.3
	40-49 years	892	184	20.6	708	79.4
	50-59 years	252	35	13.9	217	86.1
	60-69 years	67	7	10.5	60	89.5
	70-79 years	18	2	11.1	16	89.9
	80+ years	4	0	-	4	100.0
Year of AIDS diagnosis	1982-86	423	139	32.9	284	67.1
	1987-89	1,352	321	23.7	1,031	76.3
	1990-92	2,124	403	19.0	1,721	81.0

* The most likely mode of HIV transmission, as recorded in the HIV/AIDS Reporting System (see text).

Table 4.3.3 Crude and adjusted* odds ratios (OR) for selected risk factors for Kaposis's sarcoma (KS), residents of western Washington state diagnosed with AIDS, 1982-92 (*page one of two*)

Characteristic	Category	No. cases		Crude OR		Adjusted* OR	
		With KS	No KS	OR	95 % confidence interval	OR	95 % confidence interval
Mode of HIV transmission†	Low risk for KS‡	1	114	1.00	Reference	1.0	Reference
	Medium risk for KS§	21	347	6.90	0.92-51.86	7.58	0.95-60.41
	High risk for KS‖	841	2,575	37.23	5.19-267.0	26.08	3.42-198.7
Age at AIDS diagnosis	00-19 years	1	25	0.14	0.01-0.67	0.92	0.10-8.77
	20-29 years	167	585	1.00	Reference	1.00	Reference
	30-39 years	467	1,421	1.15	0.94-1.41	1.07	0.87-1.32
	40-49 years	184	708	0.91	0.72-1.15	0.88	0.69-1.12
	50+ years	44	297	0.52	0.36-0.74	0.54	0.37-0.78
Sex	Female	2	157	1.00	Reference	1.00	Reference
	Male	861	2,879	23.48	5.81-94-90	5.62	1.29-24.44
Year of AIDS diagnosis	1982-86	139	284	1.0	Reference	1.0	Reference
	1987-89	321	1,031	0.64	0.50-0.81	0.67	0.53-0.85
	1990-92	403	1,721	0.48	0.38-0.60	0.51	0.40-0.64

continued

Table 4.3.3 continued (*page two of two*)

---

* Multiple logistic regression model included mode of HIV-transmission, age at AIDS diagnosis, sex, and year of AIDS diagnosis.

† The most likely mode of HIV transmission, as recorded in the HIV/AIDS Reporting System (see text).

‡ Mode of HIV tranmission categories at low risk for KS included hemophiliacs, transfusion/transplant recipients, and children whose mothers were at high-risk for HIV infection.

§ Mode of HIV transmission categories considered at medium risk for KS included intravenous drug abusers who were not homosexual or bisexual men, heterosexuals, and adults whose HIV-risk was unknown.

‖ Mode of HIV transmission categories at high risk for KS included homosexual and bisexual men, including those who abused intravenous drugs.

Table 4.3.4 Comparison of average annual age-specific and age-adjusted incidence rates* for Kaposi's sarcoma (KS) in members of the study cohort† and in residents of western Washington state‡, *males (page one of two)*

Age at KS diagnosis	Cohort rate*†	NW Washington rate*‡	Observed cases§	Expected cases‖	Observed/ expected ratio¶	95 percent confidence interval for observed/expected ratio**
00-09 years	-	-	0	-	-	-
10-19 years	-	-	0	-	-	-
20-29 years	6,415.0	0.10	52	0.00081	64,150.0	47,801.8 - 84,208.5
30-39 years	8,021.2	0.13	221	0.00358	61,701.5	53,800.4 - 70,432.3
40-49 years	6,181.0	0.14	93	0.00211	44,150.3	35,691.5 - 54,079.3
50-59 years	4,551.2	0.07	18	0.00028	65,017.2	38,471.7 - 102,712.7
60-69 years	2,401.0	0.47	2	0.00039	5,108.4	618.5 - 18,442.0
70-79 years	14,285.7	1.35	1	0.00009	10,582.0	267.7 - 58,788.9
80+ years	-	2.67	0	0.00004	0	-
All Ages	6,923.4	0.13	387	0.00730	53,001.3	47,831.6 - 58,536.5

continued

Table 4.3.4 continued *(page two of two)*

Footnotes

---

* Incidence rates per 100,000. Age-specific rates correspond to each of the nine 10-year age categories listed in the first column. Age-adjusted rates are shown in the All Ages category. For the purpose of this analysis, age-adjusted incidence rates were standardized to the percent distribution of person-years in the study cohort (see text).

† The study cohort was comprised of all residents of western Washington state who were diagnosed with AIDS during the period 1982-92, and who were registered in the HIV/AIDS Reporting System. KS incidence rates in the study cohort were based solely on KS cases that occurred *following* the initial diagnosis of AIDS.

‡ KS incidence rates for residents of western Washington state during the period 1982-92 were based solely on those cases not known to be associated with HIV/AIDS.

§ Number of KS cases diagnosed among cohort members following their intial AIDS diagnosis.

‖ Number of KS cases expected to occur in the cohort, estimated by applying the age-specific incidence rates from western Washington state to the person-years of post-AIDS follow-up in cohort members.

¶ Ratio of observed to expected cases of KS in the study cohort.

** 95 percent confidence interval for the observed/expected ratio calculated according to the methods of Bailer III and Ederer (1964).

Table 4.3.5 Comparison of average annual age-specific and age-adjusted incidence rates* for Kaposi's sarcoma (KS) in members of the study cohort† and in residents of western Washington state‡, *females (page one of two)*

Age at KS diagnosis	Cohort rate*†	NW Washington rate*‡	Observed cases§	Expected cases‖	Observed/ expected ratio¶	95 percent confidence interval for observed/expected ratio**
00-09 years	-	-	0	-	-	-
10-19 years	-	0.04	0	<0.00001	0	-
20-29 years	1,543.2	0.03	1	0.00002	51,440.3	1,301.3 - 285,779.4
30-39 years	-	-	0	-	-	-
40-49 years	-	-	0	-	-	-
50-59 years	-	-	0	-	-	-
60-69 years	-	-	0	-	-	-
70-79 years	-	0.50	0	0.00001	0	-
80+ years	-	0.90	0	0.00002	0	-
All Ages	337.9	0.02	1	0.00005	19,630.9	496.6 - 109,060.8

continued

Table 4.3.5 continued *(page two of two)*

Footnotes

---

* Incidence rates per 100,000. Age-specific rates correspond to each of the nine 10-year age categories listed in the first column. Age-adjusted rates are shown in the All Ages category. For the purpose of this analysis, age-adjusted incidence rates were standardized to the percent distribution of person-years in the study cohort (see text).

† The study cohort was comprised of all residents of western Washington state who were diagnosed with AIDS during the period 1982-92, and who were registered in the HIV/AIDS Reporting System. KS incidence rates in the study cohort were based solely on KS cases that occurred *following* the initial diagnosis of AIDS.

‡ KS incidence rates for residents of western Washington state during the period 1982-92 were based solely on those cases not known to be associated with HIV/AIDS.

§ Number of KS cases diagnosed among cohort members following their intial AIDS diagnosis.

‖ Number of KS cases expected to occur in the cohort, estimated by applying the age-specific incidence rates from western Washington state to the person-years of post-AIDS follow-up in cohort members.

¶ Ratio of observed to expected cases of KS in the study cohort.

** 95 percent confidence interval for the observed/expected ratio calculated according to the methods of Bailer III and Ederer (1964).

Table 4.4.1 Enumeration of AIDS patients diagnosed with Kaposi's sarcoma (KS) according to the time of KS diagnosis relative to the initial diagnosis of AIDS, residents of western Washington state diagnosed with AIDS during the period 1982-92

				Time of KS diagnosis relative to that of initial AIDS diagnosis			
		Ever diagnosed with KS		KS diagnosed at time of initial AIDS diagnosis		KS diagnosed following initial AIDS diagnosis	
Year of AIDS diagnosis	No. AIDS cases	No. cases	Percent of total AIDS cases	No.	Percent of total AIDS cases	No.	Percent of AIDS cases *without* KS at initial AIDS diagnosis*
1982-86	423	139	32.9	95	22.5	44	13.4
1987-89	1,352	321	23.7	183	13.5	138	11.8
1990-92	2,124	403	19.0	182	8.6	221	11.4

* For example, 423 residents of western Washington state were diagnosed with AIDS during the period 1982-86. Of these, 139 (32.9 percent) developed KS at or following the time of their initial AIDS diagnosis. Ninety-five (22.5 percent) of these people with AIDS were diagnosed with KS at the time of their initial AIDS diagnosis. Of the remaining 328 people with AIDS who were not diagnosed with KS at the time of their initial AIDS diagnosis, 44 (13.4 percent) were subsequently diagnosed with KS in the months and years following their initial diagnosis of AIDS.

Table 4.5.1 Comparison of selected characteristics between Kaposi's sarcoma (KS) cases registered solely in the HIV/AIDS Reporting System (HARS) and those registered in both HARS and the Cancer Surveillance System (CSS), residents of western Washington state diagnosed with AIDS, 1982-92 (*page one of two*)

		Source of KS surveillance report				
		KS registered in HARS only (*n*=86)		KS registered in both CSS and HARS (*n*=405)		
Characteristic	Category	No.	Percent	No.	Percent	Summary statistical comparison
Age at AIDS diagnosis	00-19	1	1.2	0	-	$\chi^2_{df=4} = 6.12$ p=0.191
	20-29	19	22.1	75	18.5	
	30-39	39	45.4	213	52.6	
	40-49	22	25.6	93	23.0	
	50+	5	5.8	24	5.9	
	mean age	*36.4*		*36.5*		*t-test, p=0.87*
Year of AIDS diagnosis	1982-86	6	7.0	87	21.5	$\chi^2_{df=2} = 10.53$ p=0.005
	1987-89	31	36.0	140	34.6	
	1990-92	49	57.0	178	43.9	
Sex	Male	84	97.7	405	100.0	$\chi^2_{df=1} = 9.46$ p=0.002
	Female	2	2.3	0	-	
County of residence*	King county	64	74.4	336	83.0	$\chi^2_{df=1} = 3.43$ p=0.064
	Other	22	25.6	69	17.0	

continued

Table 4.5.1 continued (*page two of two*)

Characteristic	Category	Source of KS surveillance report: KS registered in HARS only (*n*=86) No.	KS registered in HARS only (*n*=86) Percent	KS registered in both CSS and HARS (*n*=405) No.	KS registered in both CSS and HARS (*n*=405) Percent	Summary of statistical comparison
Basis of KS diagnosis†	Definitive	57	66.3	354	87.4	$\chi^2_{df=1} = 23.22$ p=0.001
	Presumptive	29	33.7	51	12.6	
Reporting source‡	Private physicians and HMOs	56	65.1	338	83.5	$\chi^2_{df=5} = 25.03$ p=0.001
	Death certificate review	5	5.8	12	3.0	
	AIDS spectrum of disease study	9	10.5	14	3.5	
	Medicaid records	4	4.7	7	1.7	
	Tuberculosis registry	2	2.3	0	-	
	Other sources	10	11.6	34	8.4	

* County of residence at time of initial AIDS diagnosis, as recorded in HARS.

† Basis of KS diagnosis as recorded in HARS. A diagnosis was considered to be "definitive" if there was evidence that it was based on specific laboratory methods, such as histology or culture. A diagnosis was classified as "presumptive" if it was made by a clinician with no evidence that "definitive" methods were employed.

‡ Source of AIDS case report as recorded in HARS.

Table 4.5.2 Comparison of selected characteristics between Kaposi's sarcoma (KS) cases registered solely in the Cancer Surveillance System (CSS)* and those registered in both the HIV/AIDS Reporting System (HARS) and CSS, residents of western Washington state diagnosed with AIDS, 1982-92 (*page one of two*)

		Source of KS surveillance report				
		KS registered in CSS only* (n=110)		KS registered in both CSS and HARS (n=405)		
Characteristic	Category	No.	Percent	No.	Percent	Summary statistical comparisons
Age at AIDS diagnosis	20-29	21	19.1	75	18.5	$\chi^2_{df=3} = 0.88$ p=0.831
	30-39	62	56.4	213	52.6	
	40-49	22	20.0	93	23.0	
	50+	5	4.5	24	5.9	
	mean age	*36.0*		*36.5*		t-test, p=0.57
Year of AIDS diagnosis	1982-86	18	16.4	87	21.5	$\chi^2_{df=2} = 1.62$ p=0.446
	1987-89	43	39.1	140	34.6	
	1990-92	49	44.5	178	43.9	
Sex	Male	110	100.0	405	100.0	*Not applicable*
	Female	0	-	0	-	

continued

Table 4.5.2 continued (*page two of two*)

Characteristic	Category	Source of KS surveillance report: KS registered in HARS only (*n*=86) No.	Percent	KS registered in both CSS and HARS (*n*=405) No.	Percent	Summary of statistical comparisons
County of residence†	King county	97	88.2	317	78.3	$\chi^2_{df=3} = 5.97$ p=0.113
	Other areas in western Washington	11	10.0	75	18.5	
	Out-of-state	2	1.8	9	2.2	
	Unknown	0	-	4	1.0	
Reporting source‡	Hospital inpatient	99	90.0	382	94.3	$\chi^2_{df=3} = 3.82$ p=0.282
	Pathology laboratory	8	7.3	17	4.2	
	Private health care provider	1	0.9	4	1.0	
	Autopsy report	2	1.8	2	0.5	

* This analysis was limited to 110 KS cases registered solely in the CSS, who were diagnosed with KS at or within 6 months of their initial AIDS diagnosis (see Section 4.5).

† County of residence at the time of KS diagnosis, as recorded in the CSS.

‡ Summary reporting source as recorded in the CSS.

Table 4.5.3. Enumeration of KS cases diagnosed 1982-92 in residents of western Washington state, by HIV infection status* and registration status in the HIV/AIDS Registration System (HARS) and Cancer Surveillance System (CSS)

Registration status in HARS and CSS	HIV-infection status*								
	HIV-positive			Not known to be HIV-positive			Total KS cases		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Total cases	754	1	755	34	12	46	788	13	801
Registered in both HARS and CSS, KS diagnosis recorded in both registries	373	0	373	-	-	-	373	0	373
Registered in both HARS and CSS, KS diagnosis recorded in CSS but not in HARS	319	0	319	-	-	-	319	0	319
Registered in HARS, KS diagnosis recorded solely in HARS	61	1	62	-	-	-	61	1	62
Registered in CSS but not in HARS, KS diagnosis recorded solely in CSS	1	0	1	34	12	46	35	12	47

* KS cases were assumed to be HIV-positive if they were registered in the HIV/AIDS reporting system, or if Cancer Surveillance System personnel found specific statements in the medical record that documented HIV infection.

Table 4.6.1 Distribution of non-Hodgkin's lymphoma (NHL) among people with AIDS by selected characteristics *(page one of two)*

Characteristic	Category	Total AIDS cases	NHL status			
			With NHL		*Without* NHL	
			No.	Percent	No.	Percent
Mode of HIV transmission*	Homo/bisexual males	2,982	255	8.6	2,727	91.4
	Intravenous drug abusers	211	19	9.0	192	91.0
	Homo/bisexual males who abuse intravenous drugs	434	31	7.1	403	92.9
	Adult hemophiliacs	35	2	5.7	33	94.3
	Heterosexual contact	89	6	6.7	83	93.3
	Transfusion recipients	64	9	14.1	55	85.9
	Adults with unknown risk factors	68	4	5.9	64	94.1
	Pediatric hemophiliacs	4	0	-	4	100.0
	Children with mothers at high-risk of HIV infection	12	0	-	12	100.0
Sex	Male	3,740	317	8.5	3,423	91.5
	Female	159	9	5.7	150	94.3

continued

Table 4.6.1 continued *(page two of two)*

Characteristic	Category	Total AIDS cases	NHL status			
			With NHL		*Without* NHL	
			No.	Percent	No.	Percent
Age at AIDS diagnosis	00-09 years	16	0	-	16	100.0
	10-19 years	10	0	-	10	100.0
	20-29 years	752	51	6.8	701	93.2
	30-39 years	1,888	163	8.6	1,725	91.4
	40-49 years	892	79	8.9	813	91.1
	50-59 years	252	24	9.5	228	90.5
	60-69 years	67	8	11.9	59	88.1
	70-79 years	18	1	5.6	17	94.4
	80+ years	4	0	-	4	100.0
Year of AIDS diagnosis	1982-86	423	33	7.8	390	92.2
	1987-89	1,352	128	9.5	1,224	90.5
	1990-92	2,124	165	7.8	1,959	92.2

* The most likely mode of HIV transmission, as recorded in the HIV/AIDS Reporting System (see text).

Table 4.6.2 Crude and adjusted* odds ratios (OR) for selected risk factors for non-Hodgkin's lymphoma (NHL) among residents of western Washington state diagnosed with AIDS, 1982-92. Note: analysis limited to subjects 20 years of age and older (*page one of two*)

Characteristic	Category	No. cases		Crude OR		Adjusted* OR	
		With NHL	No NHL	OR	95 % confidence interval	OR	95 % confidence interval
Mode of HIV transmission†	Low risk for KS‡	11	83	1.00	Reference	1.00	Reference
	Medium risk for KS§	29	337	0.65	0.31-1.35	0.71	0.34-1.51
	High risk for KS‖	286	3,127	0.69	0.36-1.31	0.63	0.32-1.24
Age at AIDS diagnosis	20-29 years	51	701	1.00	Reference	1.00	Reference
	30-39 years	163	1,725	1.30	0.94-1.80	1.30	0.94-1.81
	40-49 years	79	813	1.34	0.93-1.93	1.33	0.92-1.92
	50+ years	33	308	1.47	0.93-2.33	1.41	0.89-2.24
Sex	Female	9	142	1.00	Reference	1.00	Reference
	Male	317	3,405	1.47	0.74-2.91	1.67	0.77-3.62
Year of AIDS diagnosis	1982-86	33	386	1.00	Reference	1.00	Reference
	1987-89	128	1,208	1.24	0.83-1.85	1.23	0.83-1.84
	1990-92	165	1,953	0.99	0.67-1.46	0.99	0.67-1.46

continued

Table 4.6.2 continued (*page two of two*)

Footnotes

---

* Multiple logistic regression model included mode of HIV-transmission, age at AIDS diagnosis, sex, and year of AIDS diagnosis.

† The most likely mode of HIV transmission, as recorded in the HIV/AIDS Reporting System (see text).

‡ Mode of HIV tranmission categories at low risk for KS included hemophiliacs, transfusion/transplant recipients, and children whose mothers were at high-risk for HIV infection.

§ Mode of HIV transmission categories considered at medium risk for KS included intravenous drug abusers who were not homosexual or bisexual men, heterosexuals, and adults whose HIV-risk was unknown.

‖ Mode of HIV transmission categories at high risk for KS included homosexual and bisexual men, including those who abused intravenous drugs.

Table 4.6.3 Comparison of average annual age-specific and age-adjusted incidence rates* for non-Hodgkin's lymphoma (NHL) in members of the study cohort† and in residents of western Washington state‡, *males (page one of two)*

Age at NHL diagnosis	Cohort rate*†	NW Washington rate*‡	Observed cases§	Expected cases‖	Observed/ expected ratio¶	95 percent confidence interval for observed/expected ratio**
00-09 years	-	0.96	0	0.00013	-	-
10-19 years	-	2.01	0	0.00038	-	-
20-29 years	2,059.4	2.28	19	0.02104	903.2	544.1 - 1,411.3
30-39 years	3,018.9	5.71	99	0.18724	528.7	429.5 - 643.8
40-49 years	3,139.4	13.25	55	0.23213	236.9	178.2 - 308.7
50-59 years	3,026.8	30.77	13	0.13216	98.4	52.3 - 168.2
60-69 years	2,395.2	52.28	2	0.04365	45.8	5.5 - 165.4
70-79 years	10,204.1	92.32	1	0.00905	110.5	2.8 - 614.1
80+ years	-	98.33	0	0.00147	-	-
All Ages	2,903.2	9.68	189	0.62725	301.3	259.9 - 347.5

continued

Table 4.6.3 continued *(page two of two)*

Footnotes

---

* Incidence rates per 100,000. Age-specific rates correspond to each of the nine 10-year age categories listed in the first column. Age-adjusted rates are shown in the All Ages category. For the purpose of this analysis, age-adjusted incidence rates were standardized to the percent distribution of person-years in the study cohort (see text).

† The study cohort was comprised of all residents of western Washington state who were diagnosed with AIDS during the period 1982-92, and who were registered in the HIV/AIDS Reporting System. NHL incidence rates in the study cohort were based solely on NHL cases that occurred *following* the initial diagnosis of AIDS.

‡ NHL incidence rates for residents of western Washington state during the period 1982-92 were based solely on those cases not known to be associated with HIV/AIDS.

§ Number of NHL cases diagnosed among cohort members following their intial AIDS diagnosis.

‖ Number of NHL cases expected to occur in the cohort, estimated by applying the age-specific incidence rates from western Washington state to the person-years of post-AIDS follow-up in cohort members.

¶ Ratio of observed to expected cases of NHL in the study cohort.

** 95 percent confidence interval for the observed/expected ratio calculated according to the methods of Bailer III and Ederer (1964).

Table 4.6.4 Comparison of average annual age-specific and age-adjusted incidence rates* for non-Hodgkin's lymphoma (NHL) in members of the study cohort† and in residents of western Washington state‡, *females (page one of two)*

Age at NHL diagnosis	Cohort rate*†	NW Washington rate*‡	Observed cases§	Expected cases‖	Observed/ expected ratio¶	95 percent confidence interval for observed/expected ratio**
00-09 years	-	0.57	0	0.00010	-	-
10-19 years	-	0.66	0	0.00002	-	-
20-29 years	-	1.88	0	0.00120	-	-
30-39 years	2,463.05	3.39	3	0.00413	726.6	149.8 - 2,124.4
40-49 years	5,300.35	9.24	3	0.00523	573.6	118.3 - 1,677.3
50-59 years	-	20.72	0	0.00199	-	-
60-69 years	-	36.96	0	0.00377	-	-
70-79 years	-	64.44	0	0.00135	-	-
80+ years	-	77.89	0	0.00171	-	-
All Ages	2,095.70	6.72	6	0.01950	307.6	112.7 - 670.2

continued

Table 4.6.4 continued *(page two of two)*

Footnotes

---

* Incidence rates per 100,000. Age-specific rates correspond to each of the nine 10-year age categories listed in the first column. Age-adjusted rates are shown in the All Ages category. For the purpose of this analysis, age-adjusted incidence rates were standardized to the percent distribution of person-years in the study cohort (see text).

† The study cohort was comprised of all residents of western Washington state who were diagnosed with AIDS during the period 1982-92, and who were registered in the HIV/AIDS Reporting System. NHL incidence rates in the study cohort were based solely on NHL cases that occurred *following* the initial diagnosis of AIDS.

‡ NHL incidence rates for residents of western Washington state during the period 1982-92 were based solely on those cases not known to be associated with HIV/AIDS.

§ Number of NHL cases diagnosed among cohort members following their intial AIDS diagnosis.

‖ Number of NHL cases expected to occur in the cohort, estimated by applying the age-specific incidence rates from western Washington state to the person-years of post-AIDS follow-up in cohort members.

¶ Ratio of observed to expected cases of NHL in the study cohort.

** 95 percent confidence interval for the observed/expected ratio calculated according to the methods of Bailer III and Ederer (1964).

Table 4.7.1 Enumeration of people with AIDS diagnosed with non-Hodgkin's lymphoma (NHL) according to the time of NHL diagnosis relative to the initial AIDS diagnosis, residents of western Washington state diagnosed with AIDS during the period 1982-92

				Time of NHL diagnosis relative to that of initial AIDS diagnosis			
		Ever diagnosed with NHL		NHL diagnosed at time of initial AIDS diagnosis		NHL diagnosed following initial AIDS diagnosis	
Year of AIDS diagnosis	No. AIDS cases	No. cases	Percent of total AIDS cases	No.	Percent of total AIDS cases	No.	Percent of AIDS cases *without* NHL at initial AIDS diagnosis*
1982-86	423	33	7.8	13	3.1	20	4.9
1987-89	1,352	128	9.5	56	4.1	72	5.6
1990-92	2,124	165	7.8	53	2.5	112	5.4

* For example, 423 residents of western Washington state were diagnosed with AIDS during the period 1982-86. Of these, 33 (7.8 percent) developed NHL at or following the time of their initial AIDS diagnosis. Thirteen (3.1 percent) of these people with AIDS were diagnosed with NHL at the time of their initial AIDS diagnosis. Of the remaining 410 people with AIDS who were not diagnosed with NHL at the time of their initial AIDS diagnosis, 20 (4.9 percent) were subsequently diagnosed with NHL in the months and years following their initial diagnosis of AIDS.

Table 4.8.1 Comparison of classifications for non-Hodgkin's lymphoma (NHL) as recorded in the HIV/AIDS Reporting System (HARS) and the Cancer Surveillance System (CSS) for 826 residents of western Washington state who were diagnosed with AIDS during the period 1982-92, and were also diagnosed with NHL at or following their initial AIDS diagnosis (*page one of two*)

NHL diagnosis recorded in HARS	NHL diagnosis recorded in CSS				
	Burkitt's lymphoma	Primary lymphoma of brain or other central nervous system site	Other non-Hodgkin's lymphoma*	Other cancer (non-lymphoma)	Non-Hodgkin's lymphoma not recorded in CSS
Burkitt's lymphoma and immunoblastic lymphoma	-	-	1†	-	-
Burkitt's lymphoma	6	-	8	-	1
Primary brain lymphoma	1§	11	8‖	1¶	2
Immunoblastic lymphoma	4	4	78	1**	5
Non-Hodgkin's lymphoma not recorded in HARS	3	83††	110††	-	-

continued

Table 4.8.1 continued (*page two of two*)

Footnotes

---

* Non-Hodgkin's lymphoma other than Burkitt's lymphoma and of primary sites other than the central nervous system.

† This individual was registered in HARS with both Burkitt's lymphoma and immunoblastic lymphoma. This individual was registered in the CSS with malignant lymphoma, not otherwise specified (NOS) (International Classification of Diseases-Oncology, Second Edition (ICDO-2) morphology code 9590). A diagnosis of Burkitt's lymphoma (ICDO-2 morphology code 9687) was not registered in the CSS for this individual.

‡ These eight individuals were registered in CSS with non-Hodgkin's lymphoma other than Burkitt's lymphoma. One case was registered in CSS as malignant lymphoma, NOS (ICDO-2 morphology code 9590); three cases were registered in CSS as malignant lymphoma, large cell, diffuse, NOS (ICDO-2 morphology code 9680), and four cases were registered as malignant lymphoma, small cell, non-cleaved, diffuse (ICDO-2 morphology code 9686).

§ This individual was registered in CSS with Burkitt's lymphoma (ICD0-2 morphology code 9687) originating in the lymph nodes.

‖ Lymph nodes were registered in CSS as the primary site for seven of these individuals. Bone was listed in CSS as the primary site for the remaining individual.

¶ This individual was registered in CSS with an oligodendroglioma (ICDO-2 morphology code 9450).

** This individual was registered in CSS with Hodgkin's lymphoma, mixed cellularity, NOS (ICDO-2 morphology code 9652).

†† One individual was registered in CSS with independent primary lymphomas of different sites. When consulted, CSS staff indicated that this individual represents two separate cases of non-Hodgkin lymphoma. For this reason, the numbers in this table represent 327 primary cancers registered in the CSS among 326 individuals.

Table 4.9.1 Age-specific incidence rates (per 100,000) for non-Hodgkin's lymphoma among *male* residents of western Washington state, by 10-year age group, HIV status*, and time period of diagnosis, 1975-92 (*page one of five*)

		Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
Age group	Type of case	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
00-09	All	8	1.47	8	1.40	5	0.81	5	0.76	7	0.97	11	1.38
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV‡	8 (100.0)	1.47	8 (100.0)	1.40	5 (100.0)	0.81	5 (100.0)	0.76	7 (100.0)	0.97	11 (100.0)	1.38
10-19	All	10	1.44	3	0.43	6	0.89	14	2.23	18	2.82	13	1.91
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV	10 (100.0)	1.44	3 (100.0)	0.43	6 (100.0)	0.89	14 (100.0)	2.23	18 (100.0)	2.82	13 (100.0)	1.91

continued

Table 4.9.1 continued(*page two of five)*

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
20-29	All	15	2.15	20	2.50	19	2.22	20	2.37	28	3.35	46	5.33
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	3 (15.0)	0.36	9 (32.1)	1.08	23 (50.0)	2.67
	non-HIV‡	15 (100.0)	2.15	20 (100.0)	2.50	19 (100.0)	2.22	17 (85.0)	2.01	19 (67.9)	2.27	23 (50.0)	2.67
30-39	All	29	5.77	27	4.35	34	4.66	65	7.99	85	9.51	134	13.86
	HIV-related	0 (-)	-	0 (-)	-	1 (2.9)	0.14	9 (13.8)	1.11	41 (48.2)	4.59	75 (56.0)	7.76
	non-HIV	29 (100.0)	5.77	27 (100.0)	4.35	33 (97.1)	4.53	56 (86.2)	6.88	44 (51.8)	4.92	59 (44.0)	6.10

continued

Table 4.9.1 continued (*page three of five*)

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
40-49	All	39	10.12	49	11.98	60	13.30	81	15.82	97	15.59	134	18.10
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	5 (6.2)	0.98	21 (21.6)	3.38	42 (31.3)	5.67
	non-HIV‡	39 (100.0)	10.12	49 (100.0)	11.98	60 (100.0)	13.30	76 (93.8)	14.85	76 (78.4)	12.22	92 (68.7)	12.42
50-59	All	76	20.35	70	18.06	105	27.00	113	29.85	128	32.26	155	36.02
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	3 (2.7)	0.79	8 (6.3)	2.02	14 (9.0)	3.25
	non-HIV	76 (100.0)	20.35	70 (100.0)	18.06	105 (100.0)	27.00	110 (97.3)	29.05	120 (93.8)	30.25	141 (91.0)	32.76

continued

Table 4.9.1 continued *(page four of five)*

Age group	Type of case	Year of NHL diagnosis: 1975-77 No.	1975-77 Rate	1978-80 No.	1978-80 Rate	1981-83 No.	1981-83 Rate	1984-86 No.	1984-86 Rate	1987-89 No.	1987-89 Rate	1990-92 No.	1990-92 Rate
60-69	All	93	34.70	119	39.96	160	49.19	183	54.27	183	52.64	190	52.64
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	3 (1.6)	0.89	2 (1.1)	0.58	4 (2.1)	1.11
	non-HIV‡	93 (100.0)	34.70	119 (100.0)	39.96	160 (100.0)	49.19	180 (98.4)	53.38	181 (98.9)	52.06	186 (97.9)	51.54
70-79	All	73	54.84	88	58.77	132	78.40	152	81.27	218	103.63	218	94.65
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	1 (0.5)	0.43
	non-HIV	73 (100.0)	54.84	88 (100.0)	58.77	132 (100.0)	78.40	152 (100.0)	81.27	218 (100.0)	103.63	217 (99.5)	94.21

continued

Table 4.9.1 continued (*page five of five*)

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
80+	All	44	83.08	46	82.39	55	92.20	61	93.40	86	115.70	80	96.93
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV‡	44 (100.0)	83.08	46 (100.0)	82.39	55 (100.0)	92.20	61 (100.0)	93.40	86 (100.0)	115.70	80 (100.0)	96.93

* NHL cases were assumed to be HIV-positive if they were registered in the HIV/AIDS reporting system, or if Cancer Surveillance System personnel found specific statements in the medical record that documented HIV infection.

† Number of incident cancer cases. *In parentheses:* percentage of cases known or not known to be HIV-related for a given time period and sex.

‡ Cases not known to associated with HIV.

Table 4.9.2 Average annual age-specific incidence rates (per 100,000) for non-Hodgkin's lymphoma (NHL) among *female* residents of western Washington state, by 10-year age group, HIV status*, and time period of diagnosis, 1975-92 (*page one of five*)

		Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
Age group	Type of case	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
00-09	All	0	-	1	0.18	2	0.34	4	0.64	7	1.02	1	0.13
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV‡	0 (-)	-	1 (100.0)	0.18	2 (100.0)	0.34	4 (100.0)	0.64	7 (100.0)	1.02	1 (100.0)	0.13
10-19	All	4	0.61	3	0.46	1	0.16	5	0.84	2	0.33	7	1.08
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV	4 (100.0)	0.61	3 (100.0)	0.46	1 (100.0)	0.16	5 (100.0)	0.84	2 (100.0)	0.33	7 (100.0)	1.08

continued

Table 4.9.2 continued (*page two of five*)

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate*	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
20-29	All	17	2.57	9	1.19	14	1.74	12	1.51	18	2.29	18	2.21
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	2 (16.7)	0.25	1 (5.6)	0.13	0 (-)	-
	non-HIV‡	17 (100.0)	2.57	9 (100.0)	1.19	14 (100.0)	1.74	10 (83.3)	1.26	17 (94.4)	2.16	18 (100.0)	2.21
30-39	All	21	4.27	20	3.30	28	3.92	31	3.88	34	3.85	33	3.44
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	1 (2.9)	0.11	2 (6.1)	0.21
	non-HIV	21 (100.0)	4.27	20 (100.0)	3.30	28 (100.0)	3.92	31 (100.0)	3.88	33 (97.1)	3.74	31 (93.9)	3.23

continued

Table 4.9.2 continued (*page three of five*)

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
40-49	All	25	6.56	33	8.26	31	7.05	50	9.97	54	8.81	76	10.39
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	3 (3.9)	0.41
	non-HIV‡	25 (100.0)	6.56	33 (100.0)	8.26	31 (100.0)	7.05	50 (100.0)	9.97	54 (100.0)	8.81	73 (96.1)	9.98
50-59	All	63	16.17	50	12.25	77	18.93	97	24.95	79	19.76	93	21.65
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV	63 (100.0)	16.17	50 (100.0)	12.25	77 (100.0)	18.93	97 (100.0)	24.95	79 (100.0)	19.76	93 (100.0)	21.65

continued

Table 4.9.2 continued (*page four of five*)

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
60-69	All	95	31.80	104	31.33	108	29.93	108	28.74	153	38.92	190	46.14
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV‡	95 (100.0)	31.80	104 (100.0)	31.33	108 (100.0)	29.93	108 (100.0)	28.74	153 (100.0)	38.92	190 (100.0)	46.14
70-79	All	86	45.32	115	54.97	137	58.96	151	59.29	180	64.45	219	72.96
	HIV-related	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV	86 (100.0)	45.32	115 (100.0)	54.97	137 (100.0)	58.96	151 (100.0)	59.29	180 (100.0)	64.45	219 (100.0)	72.96

continued

Table 4.9.2 continued (*page five of five)*

Age group	Type of case	Year of NHL diagnosis											
		1975-77		1978-80		1981-83		1984-86		1987-89		1990-92	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
80+	All	53	49.95	65	54.98	85	65.59	114	80.57	108	68.83	153	89.35
	HIV-related†	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-	0 (-)	-
	non-HIV‡	53 (100.0)	49.95	65 (100.0)	54.98	85 (100.0)	65.59	114 (100.0)	80.57	108 (100.0)	68.83	153 (100.0)	89.35

* NHL cases were assumed to be HIV-positive if they were registered in the HIV/AIDS reporting system, or if Cancer Surveillance System personnel found specific statements in the medical record that documented HIV infection.

† Number of incident cancer cases. *In parentheses:* percentage of cases known or not known to be HIV-related for a given time period and sex.

‡ Cases not known to associated with HIV.

Table 4.10.1 Enumeration of cancers diagnosed among people with AIDS by time of cancer diagnosis relative to that of initial AIDS diagnosis *(page one of three)*

Cancer primary site	Histology/primary site categories (ICD-O-2)	Total cases	Time of cancer diagnosis relative to that of initial AIDS diagnosis		
			Pre-AIDS	At-AIDS	Post-AIDS
Hodgkin's lymphoma	Histologies 9650-9657, All sites	8	2	2	4
Leukemia	Histologies 9800-9941	2	0	1	1
Oral cavity and pharynx	Sites C00.0-C14.8, Excluded histologies 9590-9989	6	3	0	3
Colon	Sites C18.0-C18.9, C26.0, Excluded histologies 9590-9989	4	4	0	0
Anus and anal canal	Sites C21.0-C21.2, C21.8, Excluded histologies 9590-9989	12	7	0	5
Larynx	Site C32.0-C32.9, Excluded histologies 9590-9989	2	2	0	0
Lung and bronchus	Site C34.0-C340.9 Excluded histologies 9590-9989	9	3	0	6
Pleura	Site C38.4, Excluded histologies 9590-9989	1	1	0	0
Myeloma	Histologies 9731-9732, Site C42.1	1	1	0	0

continued

Table 4.10.1 continued *(page two of three)*

Cancer primary site	Histology/primary site categories (ICD-O-2)	Total cases	Time of cancer diagnosis relative to that of initial AIDS diagnosis		
			Pre-AIDS	At-AIDS	Post-AIDS
Bone	Sites: C40.0-C41.9 Excluded histologies 9590-9989	1	1	0	0
Soft tissue	Sites: C38.0-C38.8, C47.0-C47.9, C49.0-C49.9, Excluded histologies 9590-9989	1	1	0	0
Non-reportable cancers of the skin	Sites: C44.3, C44.5 Histologies: 8010, 8070, 8071, 8081, 8090	15	7	0	8
Malignant melanoma	Histologies: 8720-8790, Sites: C44.0-C44.9	8	6	0	2
Breast	Sites: C50.0-C50.9 Excluded histologies 9590-9989	2	0	0	2
Cervix (in situ)	Sites: C53.0-C53.9 Excluded histologies 9590-9989 *(In situ cases only)*	7	6	0	1
Vulva (in situ)	Sites: C51.0-C51.9 Excluded histologies 9590-9989 *(In situ cases only)*	1	0	0	1
Prostate	Sites: C61.9 Excluded histologies 9590-9989	4	4	0	0

continued

Table 4.10.1 continued *(page three of three)*

Cancer primary site	Histology/primary site categories (ICD-O-2)	Total cases	Time of cancer diagnosis relative to that of initial AIDS diagnosis		
			Pre-AIDS	At-AIDS	Post-AIDS
Testis	Sites: C62.0-C62.9 Excluded histologies 9590-9989	8	5	2	1
Penis (in situ)	Sites: C60.0-C60.9 Excluded histologies 9590-9989 *(In situ cases only)*	1	0	0	1
Kidney and renal pelvis	Sites: C64.9, C65.9 Excluded histologies 9590-9989	1	0	0	1
Brain	Sites: C71.0-C71.9 Excluded histologies 9530-9539, 9590-9989	3	1	1	1
Thyroid	Sites: C73.9 Excluded histologies 9590-9989	2	2	0	0
Primary cancer site unknown	Site: C80.9 Histologies: 8000, 8010, 8140, 8560	4	1	0	3

Table 4.10.2 Enumeration of observed* and expected† number of cases, observed-to-expected ratios‡, and corresponding 95 percent confidence intervals§ for cancers other than Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL)[I] diagnosed among cohort members following their initial AIDS diagnosis (*page one of two*)

Primary cancer site	Sex	Observed cases*	Expected cases†	O/E ratio‡	95 percent confidence interval§
All sites other than KS and NHL[I]	Both sexes	32	18.74	1.71**	1.2-2.4
	Male	28	10.93	2.56**	1.7-3.7
	Female	4	1.09	3.68**	1.0-9.4
Hodgkin's lymphoma	Male	4	0.28	14.24**	3.9 - 36.4
Leukemia	Male	1	0.38	2.66	0.1 - 14.8
Oral cavity and pharynx	Male	3	0.54	5.56**	1.1 - 16.3
Anus and anal canal					
In situ	Male	3	0.01	219.40**	45.2 - 641.5
Invasive	Male	2	0.04	51.76**	6.3 - 186.9
Lung and bronchus	Male	6	1.70	3.52**	1.3 - 7.7
Malignant melanoma of the skin					
In situ	Male	1	0.20	4.92	0.1 - 27.3
Invasive	Male	1	0.97	1.03	0.0 - 5.7
Breast	Female	2	0.23	8.62**	1.0 - 31.1
Cervix (in situ)	Female	1	0.37	2.70	0.1 - 15.0
Vulva (in situ)	Female	1	0.01	70.55**	1.8 - 391.9

continued

Table 4.10.2 continued (*page two of two*)

Primary cancer site	Sex	Observed cases*	Expected cases†	O/E ratio‡	95 percent confidence interval§
Testis	Male	1	0.78	1.29	0.0 - 7.2
Penis (in situ)	Male	1	0.02	42.36**	1.1 - 235.3
Kidney and renal pelvis	Male	1	0.39	2.55	0.1 - 14.2
Brain	Male	1	0.37	2.70	0.1 - 15.0

* Number of cancer cases diagnosed among cohort members following their intial AIDS diagnosis.

† Number of cancer cases expected to occur in the cohort, estimated by applying the age-specific incidence rates from western Washington state to the person-years of post-AIDS follow-up in cohort members (see text).

‡ Ratio of observed to expected cases of cancer in the study cohort.

§ 95 percent confidence interval for the observed/expected ratio calculated according to the methods of Bailer III and Ederer (1964).

‖ Total includes 3 primary cancers of unknown primary site that are not listed elsewhere in this table. Eight non-reportable skin cancers that were diagnosed among cohort members following their AIDS diagnosis are not included in this table (see text).

** 95 percent confidence interval for the observed-to-expected ratio exluded the null value (1.00).

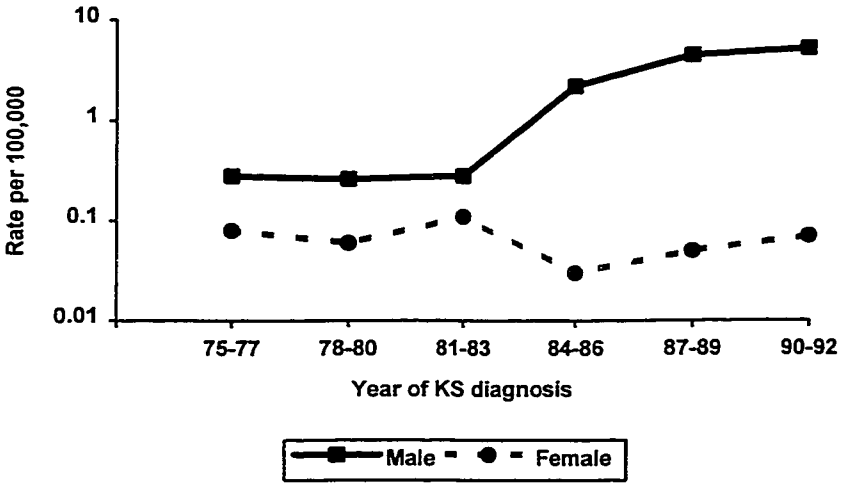


Figure 4.3.1 Average annual age-adjusted incidence rates per 100,000 for Kaposi's sarcoma (KS) in residents of western Washington state, 1975-92, by sex

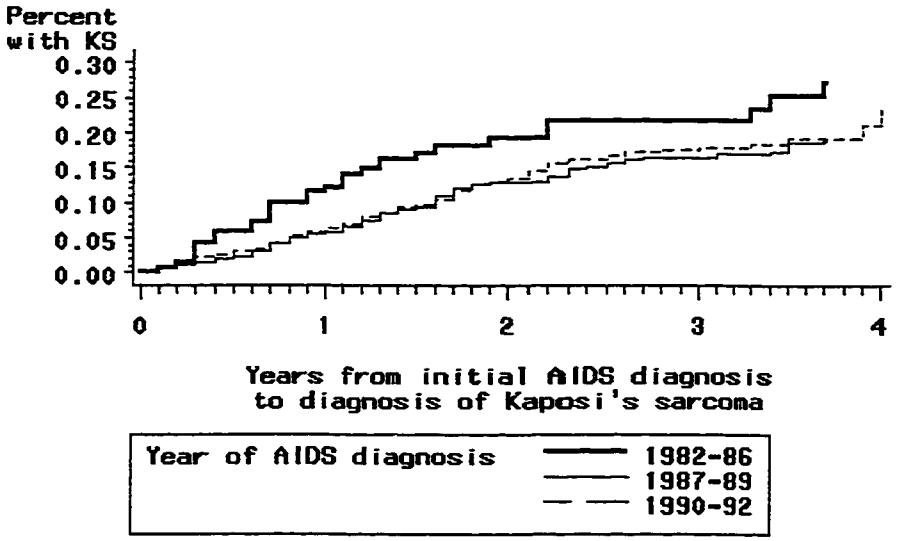


Figure 4.4.1 Cumulative percentage of people with AIDS who developed Kaposi's sarcoma (KS) in the years following initial AIDS diagnosis, by time period of AIDS diagnosis. Residents of western Washington state who were diagnosed with AIDS during the period 1982-92

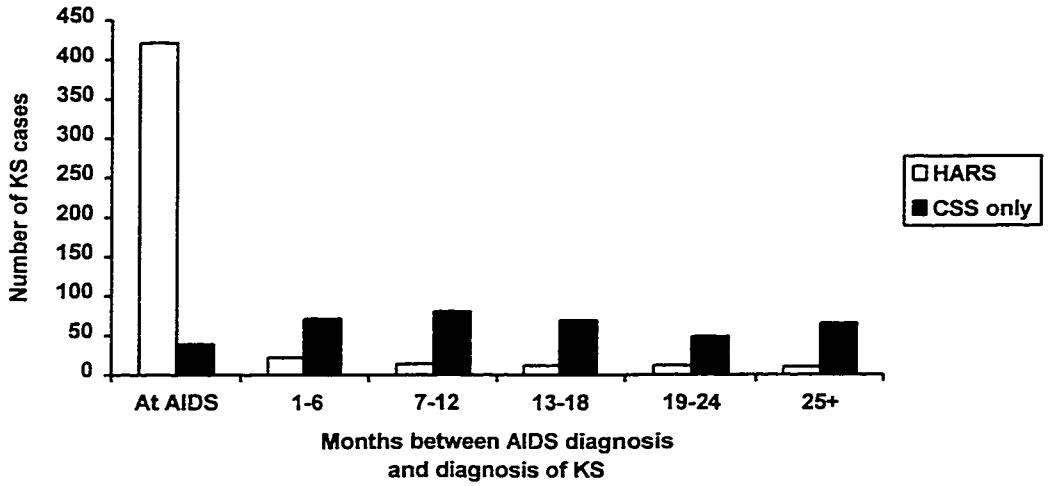


Figure 4.5.1 Distribution of Kaposi's sarcoma (KS) cases diagnosed among people with AIDS according to the date of KS diagnosis relative to the date of initial AIDS diagnosis. Residents of western Washington state diagnosed with AIDS during the period 1982-92

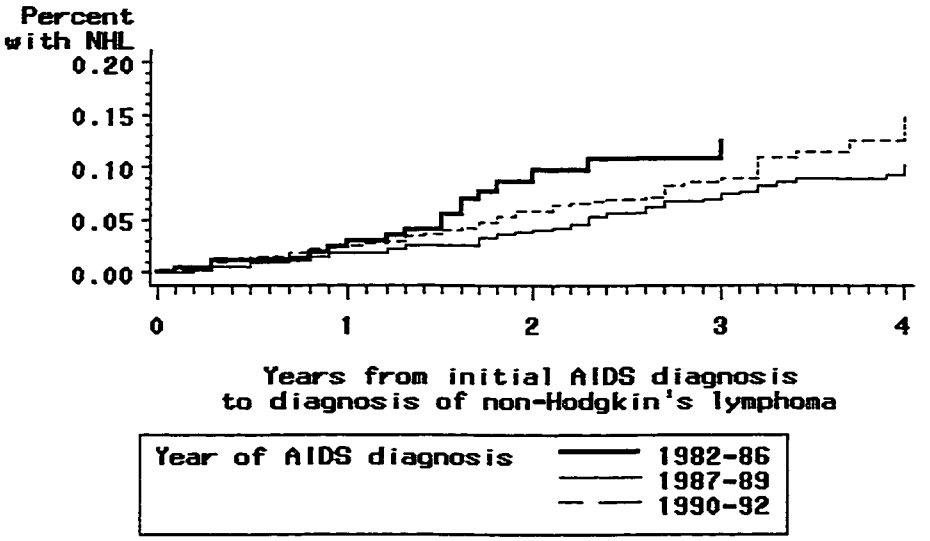


Figure 4.7.1 Cumulative percentage of people with AIDS who developed non-Hodgkin's lymphoma (NHL) in the years following initial AIDS diagnosis, by time period of AIDS diagnosis. Residents of western Washington state who were diagnosed with AIDS during the period 1982-92

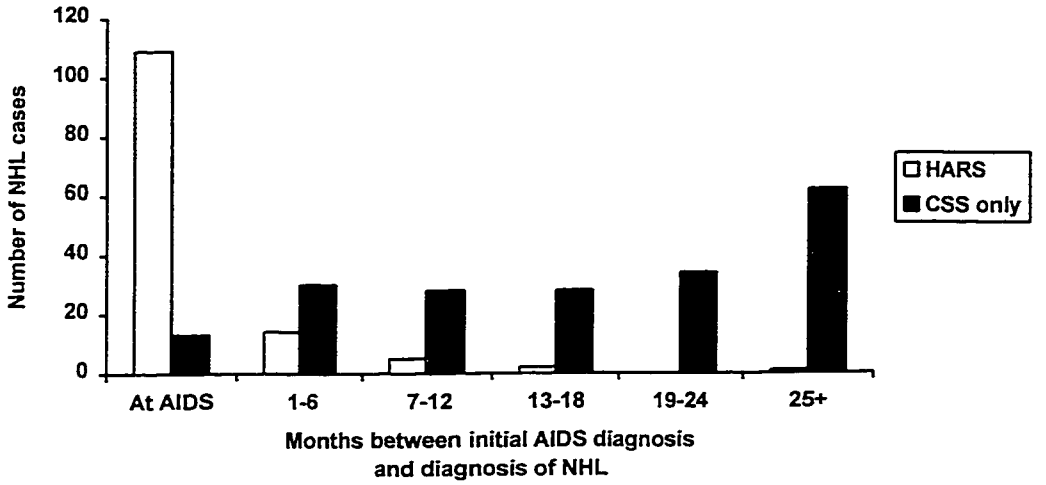


Figure 4.8.1 Distribution of non-Hodgkin's lymphoma (NHL) cases diagnosed among people with AIDS according to the date of NHL diagnosis relative to the date of initial AIDS diagnosis. Residents of western Washington state diagnosed with AIDS during the period 1982-92

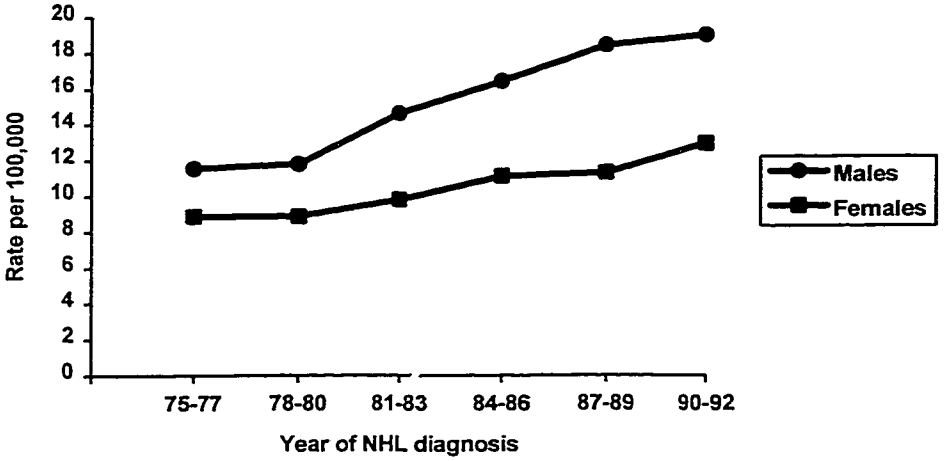


Figure 4.9.1 Average annual age-adjusted incidence rates per 100,000 for non-Hodgkin's lymphoma (NHL) among residents of western Washington state, 1975-92, by sex

5.1 Introduction

We sought to investigate possible associations between the presence of infection with selected pathogens and the subsequent development of Kaposi's sarcoma (KS) among people with the acquired immunodeficiency syndrome (AIDS). The rationale for this endeavor was described in Chapter 1, and is briefly summarized here. Prior to the advent of the epidemic of HIV infection in the United States, KS was a rare disease that occurred primarily among elderly men of Mediterranean ancestry (Krown 1997, Wahman 1991). The dramatic increase in KS incidence that accompanied the epidemic of HIV, along with the disproportionate occurrence of KS among homosexual and bisexual men infected with HIV, fueled speculation that KS was caused by an infectious agent (Beral 1990). At the time this study was formulated, no microbial etiology of KS was known.

This investigation was designed to further elucidate possible modes of transmission for the infectious agent of KS by characterizing the association between KS and selected infectious agents of interest. The eight infectious agents examined in this investigation were selected because their primary modes of transmission were well known and because surveillance data for each of these pathogens was readily available from existing population-based registries (Table 5.1.1). The strength of this approach was that, in contrast to self-reported histories of such infection collected in previous studies, this study was based on laboratory-confirmed diagnoses recorded in routine surveillance data bases. Further, these data were available for a relatively large number of people with AIDS who resided within a defined geographic area.

The analytic strategy and methodology that were employed to address the research objectives of this investigation are described in Section 5.2. The analyses described herein were restricted to selected members of the study cohort, and these restrictions are summarized in Section 5.3. Associations between KS and each of the eight infectious agents of interest are summarized in Sections 5.4-5.11. Results from an analysis of the association between KS and all enteric agents (combined) is reported in Section 5.12. The results of this investigation are briefly summarized in Section 5.13, and a detailed discussion these findings is presented in Chapter 6.

5.2 Analytic strategy and methodology

The following three categories of analysis were undertaken to address to objectives of this investigation: (1) examine the association between each infectious agent of interest and characteristics of the study cohort known to be associated with KS, (2) characterize the association between each infectious agent of interest and KS that was present at the time of AIDS diagnosis (also referred to as "prevalent KS"), and (3) characterize the association between each infectious agent of interest and KS that occurred following the diagnosis of AIDS (also referred to as "post-AIDS KS"). These three categories of analysis were conducted separately for each of the eight infectious agents of interest, and again for an analyses in which all episodes of enteric infection were combined. The corresponding methods for each of the three analyses are summarized in the following paragraphs.

The first set of analyses was designed to examine the association between each infectious agent of interest and selected characteristics of the study cohort that were known to be associated with KS. In Chapter 4, we identified four characteristics that were highly associated with KS among members of the study cohort. These four characteristics were mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis. The occurrence of KS varied markedly by mode of HIV transmission. Homosexual and bisexual men were at highest risk of KS, and cohort members whose HIV infection was unrelated to sexual activity were generally at lowest risk of the disease. Males were at greater risk for KS than females, though this observation was partially explained by male homosexual activity. KS was uncommon in cohort members who were under the age of 20 years and in those over 50 years of age at the time of AIDS diagnosis. There was also evidence that the occurrence of KS in cohort members declined over the study period, 1982-92.

For the first set of analyses, cohort members were classified as having been ever exposed or never exposed to each infectious agent of interest (criteria for this dichotomy is presented later in this section). Infectious disease exposure status was then crosstabulated by each of the four KS-related characteristics discussed in the previous paragraph. Odds ratios and corresponding 95 percent confidence intervals (Rothman 1998) were calculated to express the distribution of each infection of interest across levels of HIV transmission mode, sex, age at AIDS diagnosis, and year of AIDS diagnosis. The χ^2 test for trend (Mantel 1959) was used, as appropriate, to assess linear changes in the

percentage of subjects infected with the agent of interest across levels of individual risk factors (for example, to assess linear changes in the percentage of cohort members infected with the agent of interest by time period of AIDS diagnosis).

The second set of analyses was designed to characterize the association between each of the infectious agents of interest and KS that was prevalent at the time of AIDS diagnosis[1]. For these analyses, cohort members with prevalent KS were compared with the remaining cohort members who did not have KS at the time of their initial AIDS diagnosis[2] with respect to episodes of the infection of interest that occurred prior to the diagnosis of AIDS. The association between exposure (i.e., episodes of the infection of interest that occurred prior to the diagnosis of AIDS) and outcome (i.e., prevalent KS) was expressed as the prevalence odds ratio (POR) (Rothman 1998). We calculated crude (i.e., unadjusted) estimates of the POR, as well as POR estimates independently adjusted for mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis. In the latter stratified analysis, we used the Breslow and Day χ^2 test for homogeneity of odds ratios to assist in our assessment of differences in stratum-specific estimates of the POR (Breslow 1980). Logistic regression (Rothman 1998, Kleinbaum 1994, Breslow 1980) was utilized in some analyses to estimate the POR while simultaneously adjusting

---

[1] Of 3,873 cohort members who were eligible for this analysis (see Section 5.3), 460 (11.9 percent) had KS at the time of their initial AIDS diagnosis. Of the remaining 3,413 eligible cohort members without prevalent KS, 387 (11.3 percent) developed KS following their initial AIDS diagnosis. Thus, a total of 847 eligible cohort members had KS, 460 (54.3 percent) prevalent at AIDS diagnosis and 387 (45.7 percent) that occurred following AIDS diagnosis.

[2] Including 387 eligible cohort members who were known to have subsequently developed KS and 3,026 who were not known to have developed KS.

for mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis. We also examined the association between prevalent KS and (a) number of episodes of the infection of interest, and (b) time (in years) between the most recent episode of the infection of interest and date of AIDS diagnosis (these analyses are discussed in more detail later in this section).

The third set of analyses was designed to characterize the association between each of the infectious agents of interest and KS that occurred following AIDS diagnosis. These analyses were restricted to those cohort members who did not have KS prevalent at the time of AIDS diagnosis (see Section 5.3 for further restrictions). For this analysis, we calculated crude incidence rates of KS for cohort members infected and not known to have been infected with each agent of interest. We calculated rate ratios (RR) and corresponding 95 percent confidence intervals (CI) to compare the crude incidence rates in those infected and not known to have been infected with each agent of interest, according to methods described by Kahn and Sempos (1989). Cox proportional hazards model (Cox 1984, Breslow 1987, Kleinbaum 1996, Rothman 1988) was used to estimate the proportional hazards of developing KS for these two groups (i.e., infected vs. uninfected) while simultaneously controlling for mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis. The latter two methods (i.e., crude incidence rates and Cox proportional hazards model) required estimates of person-years of follow-up, which were calculated according to methods described in Section 4.2. Briefly, for each cohort member who was eligible for this analysis (see Section 5.3),

person-years of follow-up were estimated as the time (in years) between AIDS diagnosis and (1) date of KS diagnosis for those subjects known to have been diagnosed with KS following AIDS diagnosis, or (2) the date of last follow-up information recorded in the HIV/AIDS Reporting System (HARS) for those cohort members not known to have had KS. We also examined the association between post-AIDS KS and (a) the number of episodes of the infection of interest, and (b) time (in years) between the most recent episode of the infection of interest and date of AIDS diagnosis (these analyses are discussed in more detail later in this section).

In each of the three types of analysis described in the preceding paragraphs, cohort members were considered to have been infected with the agent of interest if such infection occurred prior to a specified reference date. The definition of reference date varied by type of analysis, as follows. For the first set of analyses (i.e., those that examined the association between the infectious agent of interest and selected risk factors for KS) and the third set of analyses (i.e., those that examined the association between the infectious agent of interest and KS that occurred following AIDS diagnosis), the reference date was the date of KS diagnosis for those cohort members who had KS[3], or the date of last follow-up information for those cohort members not known to have had KS[4]. For the second set of analyses (i.e., those that characterized the association between

[3] Month and year of KS diagnosis, as determined from the combined records of the HIV/AIDS Reporting System and the Cancer Surveillance System (see Section 3.5).

[4] Month and year of last follow-up information, as recorded in the HIV/AIDS Reporting System.

the infectious agent of interest and prevalent KS), the reference date was the date of AIDS diagnosis[5]. If a cohort member had more than one episode of a specific infection, analyses were based on information that corresponded to the most recent episode of infection that occurred prior to the reference date, unless otherwise specified. Cohort members whose only exposure to an infectious agent of interest occurred after the reference date were considered to have had no such infection for the purpose of the analysis. In some cases, the infectious agent of interest was diagnosed during the same calendar month and year as the reference date. Since only the calendar month and year of each reference date was known, it was not possible to determine if the infection of interest preceded the reference date in these situations. To accommodate such cases, two sets of analyses were performed, one in which no such cases were considered to have been infected with the agent of interest (assumption A) and another in which all such cases were considered to have had the infection of interest (assumption B). In practice, this dilemma occurred in only a small number of instances and there was little difference between the results obtained under assumptions A and B. Unless otherwise specified, all results reported in this chapter were derived from analyses that were conducted under assumption A.

A relatively small number of cohort members were documented to have had multiple episodes of infection with some pathogens of interest. When the number of such cases permitted, we examined the risk of KS associated with multiple occurrences of the

[5] Month and year of AIDS diagnosis as recorded in HARS.

infection of interest that occurred prior to the reference date. The categories for this analysis were defined as follows: (1) not known to have had the infection of interest prior to the reference date; (2) single episode of infection of interest known to have occurred prior to the reference date; (3) two or more episodes of the infection of interest known to have occurred prior to the reference date.

When possible, we also assessed whether or not the association between KS and the infection of interest varied by time (in years) between the onset of the most recent episode infection and date of AIDS diagnosis. For cases with the exposure of interest, we estimated the time period (in years) between the most recent episode of infection and the date of AIDS diagnosis. The data were summarized in the following categories for analysis: (1) not known to have had the infection of interest; (2) onset of most recent episode of infection of interest occurred one or more years prior to AIDS diagnosis; (3) onset of single or most recent episode of infection of interest occurred within one year of AIDS diagnosis (including such infections that occurred following AIDS diagnosis for the analysis of post-AIDS KS).

To further characterize the association between KS and prior exposure to syphilis, we categorized syphilis episodes according to the stage of syphilis infection. Primary and secondary syphilis were considered to represent relatively acute forms of the disease, while the remaining stages collectively were considered represent chronic manifestations of the disease. The data were summarized in the following categories for the purpose of this analysis: (1) not known to have been infected with syphilis prior to the reference

date; (2) primary syphilis as the single or most recent such infection prior to reference date; (3) secondary syphilis as the single or most recent such infection that occurred prior to the reference date; (4) any other stage of syphilis as the single or most recent such infection that occurred prior to the reference date.

All analyses were conducted with standard packages of the Statistical Analysis System (SAS Institute 1989).

5.3 Subjects eligible for analysis

This investigation was based on the experiences of 3,899 residents of northwestern Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in HARS (see Chapter 3). Twenty-six (0.7 percent) of these individuals were under the age of 20 years at the time of AIDS diagnosis, and these individuals were excluded from all analyses reported here for the following reasons. First, no KS was diagnosed among cohort members who were less than 20 years of age. Second, few of the exposures of interest were documented in these young individuals. Finally, WSCDR only provided data on episodes of communicable disease infection[6] that occurred among individuals who were 16 years of age and older. Therefore, 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis served as the

[6] WSCDR data were used to document episodes of the following infections in members of the study cohort: hepatitis-A virus, hepatitis-B virus, *salmonella spp.*, *shigella spp.*, *giardia spp.*, *campylobacter spp.*, and entamoeba histolytica.

basis for all analyses described in this chapter. Some analyses were restricted to subsets of these individuals, as described below.

The research data base for this investigation was constructed through a series of computer-assisted linkages of records from population-based registries of AIDS, cancer, and selected communicable diseases (see Chapter 2). Therefore, information was available for this investigation only if it existed in computerized format. All records from the population-based registries of AIDS and cancer were available in computerized format. Syphilis surveillance in Washington state began early in the twentieth century, and records were generally available from WSSR in computerized format for individuals diagnosed with syphilis since 1959. The availability of computerized surveillance records from WSCDR varied by disease/pathogen. For some communicable diseases, computerized surveillance data was unavailable for cohort members who were diagnosed with AIDS in the early years of the study period, 1982-92. Therefore, some analyses were restricted to AIDS patients who were diagnosed in the latter years of the study period. The availability of computerized communicable disease data is summarized in each of the following sections. Restrictions based on the availability of such data are also documented in each section.

Cox proportional hazards model and crude incidence rates were utilized to examine potential risk factors for the development of KS that occurred following the diagnosis of AIDS (see Section 5.2). Both of these methods required information regarding person-years of follow-up, which was estimated as the time between AIDS

diagnosis and (a) date of KS diagnosis for those subjects who developed KS, and (b) date of last information as recorded in HARS for those cohort members not known to have had KS. KS was prevalent at the time of AIDS diagnosis in 460 cohort members, and these individuals were not included in the analysis of KS that occurred following AIDS diagnosis. The date of last follow-up information was not recorded for 222 (6.5 percent) of the remaining 3,413 cohort members who were otherwise eligible for the analysis KS that occurred following the diagnosis of AIDS. The latter 222 individuals were excluded from this analysis because we were unable to estimate their respective person-years of follow-up. Compared to the remaining 3,191 cohort members who were included in this analysis, the 222 excluded individuals were less likely to have had KS, were slightly older, were more likely to have been diagnosed with AIDS early in the study period, and were more likely to have been transfusion/transplant recipients or adults whose HIV risk factors were unknown (Table 5.3.1).

In summary, and unless otherwise specified[7], analyses that characterized the distribution of the infections of interest in the study cohort were based on 3,873 cohort members who were 20 years of age or older at the time of AIDS diagnosis. Analyses relating to the prevalence of KS at AIDS diagnosis were also based on the same 3,873 individuals. Analyses of KS that developed following AIDS diagnosis were based on

[7] Each presentation of results in Sections 5.4 - 5.12 begins with a summary of the number of subjects included in the respective analysis.

3,191 cohort members who were 20 years of age and older at AIDS diagnosis, and for whom date of last follow-up information was recorded in HARS.

5.4.a Syphilis among members of the study cohort

Computerized records of syphilis infection were available from WSSR for Washington state residents who were diagnosed with the disease during the period 1959-94[8]. Because these records predated the advent of the AIDS epidemic by many years, the ability to document syphilis infection among members of the study cohort was considered to have been as complete as possible within the design of this study. Therefore, all eligible cohort members were included in the analyses that are summarized in Sections 5.4.a -5.4.c.

A history of syphilis infection was documented in 549 (14.2 percent) of 3,873 members of the study cohort who were eligible for the present analysis, which summarizes the distribution of syphilis infection in the cohort. Nine of these individuals were excluded from this analysis because their respective dates of syphilis diagnosis were unknown[9]. The syphilis infection in eight cohort members occurred after the date of last

---

[8] The WSSR computer file that was made available for the purpose of this investigation included some syphilis cases that were diagnosed prior to 1959. However, records of syphilis surveillance in this computer file were clearly incomplete for years prior to 1959.

[9] Because we did not know the date of syphilis diagnosis for these nine individuals, we were unable to determine if their respective syphilis infections occurred during the follow-up period relevant to this investigation (i.e., prior to the date of last information as recorded in HARS). These nine cohort members were excluded from the analysis described in Section 5.4.

follow-up information[10], and these eight individuals were considered to have had no syphilis infection for the purpose of this analysis. Four cohort members were diagnosed with syphilis during the same calendar month as their date of last follow-up, and it was not possible to determine if the syphilis diagnosis was made during the follow-up period of this investigation. The latter four subjects were considered to have had no syphilis for the purpose of this analysis. Thus, of the 3,864 cohort members eligible for this analysis, 528 (13.7 percent) were considered to have been infected with syphilis.

A history of syphilis infection was documented in approximately 15 percent of homosexual and bisexual men (with or without a history of intravenous drug abuse), and cohort members in other HIV risk groups were less likely to have had syphilis (Table 5.4.1). Prior syphilis infection was more common among males (14.1 percent) than females (4.0 percent), reflecting the fact that most male cohort members were homosexual or bisexual and, therefore, more likely to have had syphilis than members of other HIV risk groups.

The percentage of cohort members ever infected with syphilis increased with age at initial AIDS diagnosis (χ^2 test for trend $p<0.01$) (Table 5.4.1). Conversely, the percentage of cohort members ever infected with syphilis declined over the study period (χ^2 test for trend $p<0.01$). Further, the percentage of cohort members ever diagnosed

[10] The date of last follow-up information was defined as the date of KS diagnosis for those subjects known to have had KS, and the date of last follow-up information as recorded in HARS for those subjects not known to have had KS (see Section 5.2).

with syphilis decreased by time period of AIDS diagnosis within each category of age at AIDS diagnosis (data not shown).

5.4.b Syphilis and Kaposi's sarcoma prevalent at AIDS diagnosis

Syphilis infection occurred prior to the diagnosis of AIDS in 499 (90.9 percent) of the 549 cohort members who were documented to have been infected with syphilis. These individuals were considered to have been infected with syphilis for the purpose of examining the association between syphilis and KS prevalent at AIDS diagnosis, as described in this section. Syphilis infection in 27 cohort members occurred after the date of AIDS diagnosis, and these individuals were considered to have had no syphilis infection for the purpose of this analysis. Nine individuals were excluded from this analysis because their respective dates of syphilis diagnosis were unknown. Fourteen cohort members were diagnosed with syphilis during the same calendar month as their initial AIDS diagnosis, and it was not possible to determine which disease (i.e., AIDS or syphilis) was first diagnosed in these individuals. To accommodate the latter 14 subjects, each analysis described in this section was conducted twice, once under the assumption that all 14 subjects had never been infected with syphilis (assumption A) and again under the assumption that all 14 subjects had been infected with syphilis prior to their respective AIDS diagnosis (assumption B), as described in Section 5.2. Because there was little difference between the results obtained under assumptions A and B, the results presented here are those obtained under assumption A.

Syphilis infection was documented in 64 (14.0 percent) of cohort members with KS prevalent at AIDS diagnosis and in 435 (12.8 percent) of the remaining subjects (Table 5.4.2). Thus, there was no appreciable association between KS prevalent at AIDS diagnosis and prior syphilis infection (crude POR=1.11, 95 percent CI=0.84-1.48). Estimates of the POR, adjusted separately by sex, age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission, were similar to the crude POR (Table 5.4.2). Similar results were obtained from an analysis restricted to homosexual and bisexual men (crude POR=1.01, 95 percent CI=0.76-1.35).

There were no appreciable associations between KS prevalent at AIDS diagnosis and the number of prior episodes of syphilis (Table 5.4.3), stage of most recent syphilis infection (Table 5.4.4), and length of time between the most recent syphilis infection and AIDS diagnosis (Table 5.4.5). Similar results were obtained from separate analyses of (a) all eligible cohort members and (b) eligible homosexual and bisexual men only.

5.4.c Syphilis and the development of Kaposi's sarcoma following AIDS diagnosis

Among the 3,191 cohort members who were eligible for the analysis of KS that occurred following the initial AIDS diagnosis, 444 (13.9 percent) were known to have been infected with syphilis prior to the date of last follow-up information. The date of syphilis diagnosis was unknown for five cohort members, and these individuals were excluded from the analysis described in this section. Syphilis was only known to have occurred after the date of last follow-up information in three subjects, and these

individuals were considered to have had no syphilis infection for this analysis. Syphilis was diagnosed during the same calendar month as the date of last follow-up information in two cohort members, but it was unknown if syphilis occurred before or after this date. To accommodate the latter two subjects, all analyses were conducted under assumptions A and B, as described in Section 5.2. The results presented here were obtained under assumption A.

The crude incidence rates of KS were 96.59 and 62.15 per 1,000 person-years of follow-up, respectively, for those previously infected and not known to have been infected with syphilis (RR=1.55, 95 percent CI=1.20-2.01) (Table 5.4.6, part a). Similarly, by Cox proportional hazards model, those with prior syphilis infection were at slightly greater risk of developing KS than those not known to have been infected with syphilis (PH=1.53, 95 percent CI=1.18-1.99), after simultaneous adjustment for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission. Similar results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.4.6, part b).

Cohort members who had two or more episodes of syphilis were at slightly greater risk of KS than those with a single such episode (Table 5.4.7). The risk of KS did not vary appreciably by stage of the most recent syphilis infection (Table 5.4.8). Cohort members with recent syphilis infection[11] were at somewhat greater risk of KS than those

[11] Cohort members whose syphilis diagnosis occurred less than one year prior to the diagnosis of AIDS or after the diagnosis of AIDS.

whose syphilis infections occurred one or more years prior to the diagnosis of AIDS (Table 5.4.9). Similar results were obtained from separate analyses of (a) all eligible cohort members and (b) homosexual and bisexual men only.

5.5.a Hepatitis-B virus infection among members of the study cohort

WSCDR surveillance data for Hepatitis-B virus (HBV) infection were available in computerized format for Washington state residents who were registered with HBV infection during the period 1982-94. Therefore, documentation of HBV infection that preceded AIDS diagnosis was unavailable for most cohort members who were diagnosed with AIDS during the early years of the study period[12]. For this reason, all analyses related to HBV infection were restricted to 3,454 cohort members who were diagnosed with AIDS during the period 1987-92. Due to the nature of HBV infection, the WSCDR data base included a single record of HBV infection per person[13].

HBV infection was documented in 66 (1.9 percent) of 3,454 members of the study cohort who were eligible for this analysis. In 62 (93.9 percent) of these individuals, HBV

---

[12] No HBV infection was documented among cohort members who were diagnosed with AIDS during the years 1982-85. HBV infection was documented in three cohort members who were diagnosed with AIDS in 1986. In contrast, an average of approximately 10 cohort members per year were documented to have had HBV infection in the remaining cohort members who were diagnosed with AIDS during the period 1987-92. Therefore, HBV-related analyses were restricted to cohort members who were diagnosed with AIDS during the period 1987-92.

[13] For the purposes of routine surveillance, HBV infection is considered to be a one-time event. Many people infected with HBV develop antibodies that prevent future infection. HBV infection is not resolved in some individuals, and these become chronic carriers of the virus. Therefore, in contrast to some of the other infectious agents of interest in this investigation, WSCDR maintains a single record for HBV infection per person.

infection occurred prior to the date of last follow-up information as recorded in HARS. These 62 individuals were considered to have been infected with HBV for the purpose of characterizing the distribution of HBV infection in the study cohort, as summarized in this section. HBV infection in one cohort member occurred after the date of last follow-up information, and this individual was considered to have had no HBV infection for this analysis. The date of HBV infection was unknown in three cohort members, but was registered in WSCDR during the same calendar year as the respective date of last follow-up information in each of these individuals. Because we could not determine if HBV infection preceded the date of last follow-up information in the latter three subjects, they were considered to have had no HBV infection for this analysis.

HBV infection was documented in 4.4 percent of intravenous drug abusers, and in a smaller proportion of homosexual/bisexual men and heterosexuals (Table 5.5.1). No HBV infection was documented among cohort members who were adult hemophiliacs, transfusion or transplant recipients, or adults with unknown HIV risk factors. HBV infection was documented in only one female member of the study cohort, an intravenous drug abuser who was not known to have developed KS. The percentage of cohort members infected with HBV varied slightly by age at AIDS diagnosis, and was highest in those under 30 years of age at AIDS diagnosis. The percentage of cohort members infected with HBV did not vary by time period of AIDS diagnosis, though the analysis was restricted to a six-year period.

5.5.b Hepatitis-B virus infection and Kaposi's sarcoma prevalent at AIDS diagnosis

Of 66 HBV-infected cohort members who were eligible for this analysis, 58 (87.9 percent) were known to have been infected with HBV prior to their AIDS diagnosis. These 58 individuals were considered to have been infected with HBV for the analysis of prevalence odds ratios described in this section. HBV infection in three cohort members occurred after the diagnosis of AIDS, and these individuals were considered to have had no HBV infection for this analysis. The date of HBV infection was unknown in five cohort members, but HBV infection was registered in WSCDR for each of these individuals during the same calendar year as their respective AIDS diagnosis. Two sets of analyses were conducted to accommodate the latter five cases (i.e., assumptions A and B, as described in Section 5.2). Results reported here were obtained under assumption A.

Seven (1.9 percent) of 365 cohort members with KS prevalent at the time of AIDS diagnosis were known to have been infected with HBV prior to AIDS diagnosis (Table 5.5.2). Fifty-one (1.7 percent) of 3,089 cohort members without prevalent KS were not known to have been so infected. Thus, there was no overall association between the presence of KS at the time of AIDS diagnosis and prior infection with HBV (crude POR=1.17, 95 percent CI=0.53-2.59)[14]. Summary estimates of the POR, independently adjusted by sex, age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission, did not vary appreciably from the crude POR estimate. However, summary

[14] Similar results were obtained from an analysis restricted to homosexual and bisexual men (crude POR=1.03, 95 percent CI=0.44-2.44).

PORs adjusted for age at AIDS diagnosis and mode of HIV transmission masked stratum-specific variations that merit further consideration in the following two paragraphs.

Modest variations in POR estimates among cohort members who were 20-29, 30-39, and 40-49 years of age at the time of AIDS diagnosis were generally consistent with no association between HBV infection and prevalent KS (Table 5.5.2). HBV infection was highly associated with prevalent KS among cohort members who were 50 years of age and older at the time of AIDS diagnosis (POR=13.65, 95 percent CI=1.83-102.07). However, this observation was based on two HBV-infected cohort members who had KS, both of whom were homo/bisexual males without a history of intravenous drug abuse. This observation should be interpreted with caution because of the relatively small number of observations in this stratum.

There was no association between HBV infection and prevalent KS among homosexual and bisexual men (Table 5.5.2). HBV infection was associated with an elevated risk of prevalent KS among intravenous drug abusers (POR=3.98, 95 percent CI=0.43-37.08), but this observation was based on a relatively small number of subjects. Consequently, the corresponding confidence interval was broad and included the null value. No cohort members from the remaining HIV-risk groups[15] were diagnosed with KS at the time of AIDS diagnosis, and only one individual from these remaining groups had been infected with HBV prior to AIDS diagnosis.

---

[15] Individuals who acquired HIV through heterosexual contact, or who were adult hemophiliacs, transfusion or transplant recipients, or adults whose HIV risk factors were unknown.

There was limited evidence that cohort members infected with HBV less than one year before AIDS diagnosis were at greater risk for having KS prevalent at the time of AIDS diagnosis than those whose HBV infection occurred one or more years prior to AIDS diagnosis (Table 5.5.3). However, this result was based on a small number of observations and must be interpreted with caution. We did not examine the association between multiple episodes of HBV infection and prevalent KS since only one HBV infection per person was documented in WSCDR.

5.5.c Hepatitis-B virus infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 2,901 cohort members who were eligible for analysis of the association between HBV infection and KS that developed following AIDS diagnosis, 53 (1.8 percent) were documented to have been infected with HBV. Further, HBV infection preceded the date of last follow-up information in all 53 of these cohort members. Therefore, no simplifying assumptions were required for this analysis.

The crude incidence rates for KS were 35.34 and 65.05 per 1,000 person-years in those with and without prior HBV infection, respectively (RR=0.54, 95 percent CI=0.17-1.69) (Table 5.5.4, *part a*). By Cox proportional hazards model, those with prior HBV infection were at lower risk of KS than those without prior HBV infection (PH=0.54, 95 percent CI=0.17-1.68), after simultaneous adjustment for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis (Table 5.5.6, *part a*). Similar results

were obtained from an analysis restricted to homosexual and bisexual males (Table 5.5.4, *part b*).

There was little evidence of an association between KS and the timing of HBV infection relative to AIDS diagnosis (Table 5.5.5). We did not examine the association between multiple episodes of HBV infection and KS that occurred following initial AIDS diagnosis since only one HBV infection per person was documented in WSCDR.

5.6.a Hepatitis-A virus infection among members of the study cohort

WSCDR surveillance data for Hepatitis-A virus (HAV) infection were available in computerized format for Washington state residents who were registered with HAV infection during the period 1982-94. Therefore, documentation of HAV infection that preceded AIDS diagnosis was unavailable for most cohort members who were diagnosed with AIDS during the early years of the study period[16]. For this reason, all analyses related to HAV infection were restricted to 3,454 cohort members who were diagnosed with AIDS during the period 1987-92.

HAV infection was documented in 89 (2.6 percent) of 3,454 members of the study cohort who were eligible for this analysis. In 81 (91.0 percent) of these HAV-infected cohort members, the date of HAV infection occurred prior to the date of last follow-up

---

[16] No HAV infection was documented among cohort members who were diagnosed with AIDS during the years 1982-84. HAV infection was documented in one cohort member who was diagnosed with AIDS in 1985, and in two cohort members who were diagnosed with AIDS in 1986. In contrast, HAV infection was documented in 18 cohort members who were diagnosed with AIDS during the period 1987-89 (an average of 6 HAV infections annually), and in 63 cohort members who were diagnosed with AIDS during the period 1990-92 (an average of 21 HAV infections annually). Therefore, HAV-related analyses were restricted to cohort members who were diagnosed with AIDS during the period 1987-92.

information as recorded in HARS. These 81 individuals were considered to have been infected with HAV for the purpose of characterizing the distribution of HAV infection in the study cohort, as summarized in this section. HAV infection occurred after the date of last follow-up information in six cohort members, and these individuals were considered to have had no HAV infection for this analysis. The date of HAV infection was unknown in two cohort members, but was documented in WSCDR during the same calendar year in which AIDS was diagnosed in each individual. Thus, it was unknown whether HAV infection occurred before or after the date of last follow-up information in these two subjects. The latter two subjects were considered to have had no HAV infection for this analysis.

Cohort members with a history of intravenous drug abuse were slightly more likely to have been infected with HAV than were other members of the study cohort (Table 5.6.1). Individuals who acquired HIV through heterosexual contact or through transfusion or transplantation were at similar risk for HAV infection as homosexual/bisexual men without a history of intravenous drug abuse. No HAV infection was documented in adult hemophiliacs or in adults whose HIV risk factors were unknown.

Male cohort members were at slightly greater risk of HAV infection than females, though this observation was based on only two HAV-infected females (Table 5.6.1). HAV infection was most common among cohort members who were under the age of 30 years at the time of AIDS diagnosis. The percentage of cohort members infected with

HAV was greater for those diagnosed with AIDS during the period 1990-92 than for those diagnosed with AIDS in 1987-89.

5.6.b Hepatitis-A virus infection and Kaposi's sarcoma prevalent at AIDS diagnosis

HAV infection occurred prior to AIDS diagnosis in 65 (73.0 percent) of the 89 cohort members in whom HAV infection was documented. All 65 of these individuals were considered to have been infected with HAV for the analysis of prevalence odds ratios described in this section. HAV-infection occurred after the date of AIDS diagnosis in 20 cohort members, and these individuals were considered to have had no HAV infection for the purpose of this analysis. The date of HAV infection was unknown in four cohort members, but these individuals were registered with HAV infection in WSCDR during the same calendar year that they were diagnosed with AIDS. Two sets of analyses were conducted to accommodate the latter four individuals, under assumptions A and B, as described in Section 5.2. Results presented here were obtained under assumption A.

Cohort members who had been infected with HAV prior to developing AIDS were at slightly lower risk for KS prevalent at the time of AIDS diagnosis than those without HAV infection (crude POR=0.86, 95 percent CI=0.37-2.00) (Table 5.6.2). Independent adjustments for sex, age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission had little effect on the summary POR estimate. Similar results

were obtained from an analysis restricted to homosexual and bisexual men (crude POR=0.87, 95 percent CI=0.37-2.04).

We did not examine the association between multiple episodes of HAV infection and prevalent KS because only one HAV infection was documented in the WSCDR for each subject. The time period between HAV infection and AIDS diagnosis was unrelated to KS prevalent at the time of AIDS diagnosis (Table 5.6.3).

5.6.c Hepatitis-A virus infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 2,901 cohort members eligible for the analysis of KS following the diagnosis of AIDS, 76 (2.6 percent) were documented in WSCDR to have been infected with HAV. Of these, 72 (94.7) were infected with HAV prior to the date of last information as recorded in HARS, and were considered to have been infected with HAV for the analysis described in this section. HAV infection in three cohort members occurred after the date of last follow-up information, and these individuals were considered to have had no HAV infection for this analysis. The date of HAV infection was unknown for one cohort member, but was registered in WSCDR during the same calendar year that this subject was diagnosed with AIDS. Two sets of analyses were conducted to accommodate this individual, under assumptions A and B, as described in Section 5.2. Results presented here were obtained under assumption A.

The crude incidence rates for KS were 46.48 and 65.03 per 1,000 person-years of follow-up for cohort members infected and not infected with HAV, respectively (RR=0.71, 95 percent CI=0.32-1.60) (Table 5.6.4, *part a*). Similarly, by Cox proportional hazards model, the risk of developing KS after initial AIDS diagnosis was lower among those who had been infected with HAV than for those who were not so infected (PH=0.68, 95 percent CI=0.30-1.53), after simultaneous adjustment for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis. Comparable results were obtained from an analyses restricted to homosexual and bisexual men (Table 5.6.4, *part b*).

We did not examine the association between multiple episodes of HAV infection and development of KS following AIDS diagnosis since only one episode of HAV infection was documented in the WSCDR for each subject. There was limited evidence that cohort members with recent HAV infection (i.e., HAV infection that occurred <1 year prior to AIDS diagnosis or after AIDS diagnosis) were at lower risk of KS than cohort members infected with HAV one or more years prior to AIDS diagnosis (Table 5.6.5). The latter observation was based on a relatively small number of subjects with both KS and a history of HAV infection.

5.7.a Shigella infection among members of the study cohort

Computerized records of shigella infection were available from WSCDR for Washington state residents who were diagnosed with shigellosis during the period 1975-

96. Thus, records of shigella infection were available for at least six years prior to the first diagnosis of AIDS in a resident of Washington state in 1982. Therefore, all eligible cohort members were included in the analyses that are summarized in Sections 5.7.a-5.7.c.

Shigella infections were documented in 181 (4.7 percent) of 3,873 members of the study cohort who were eligible for the present analysis, which summarizes the distribution of shigella infection in the cohort. Eight cohort members were infected with shigella after the date of last follow-up information as recorded in HARS, and were considered to have had no shigella infection for the purposes of this analysis. Therefore, 173 cohort members (4.5 percent) were considered to have been infected with shigella for this analysis.

Shigella infection was documented in approximately 5 percent of homosexual and bisexual men (with or without a history of intravenous drug abuse), and in 0.5 percent of intravenous drug abusers who were not homo/bisexual men (Table 5.7.1). Shigella infection was not documented in any of the 151 female cohort members. There were small differences in the percentage of cohort members infected with shigella by age at AIDS diagnosis, and the percentage of cohort members so infected decreased over the period of this investigation (χ^2 test for trend $p<0.01$).

5.7.b Shigella infection and Kaposi's sarcoma prevalent at AIDS diagnosis

Of 181 cohort members known to have been infected with shigella, 153 (84.5 percent) were determined to have been so infected prior to the time of AIDS diagnosis. These 153 individuals were considered to have been infected with shigella for analyses of the association between prevalent KS and prior shigella infection, as described in this section. Shigella infection in 24 cohort members (13.3 percent) occurred after AIDS diagnosis, and these individuals were considered to have had no such infection for this analysis. The date of shigella infection was unknown in four cohort members, but was registered in WSCDR during the same calendar year as their respective AIDS diagnoses. Two sets of analyses were conducted to accommodate the latter four individuals, under assumptions A and B, as described in Section 5.2. Results reported here were obtained under assumption A.

Twenty-two (4.8 percent) of the 460 cohort members who had KS prevalent at the time of AIDS diagnosis were documented to have had prior shigella infection. Of the remaining 3,413 cohort members who did not have prevalent KS, 131 (3.8 percent) had previously been infected with shigella. Thus, prior shigella infection was associated with a slight increase in risk of prevalent KS (crude POR=1.26, 95 percent CI=0.79-2.00) (Table 5.7.2). Estimates of the POR independently adjusted by age at AIDS diagnosis and year of AIDS diagnosis were similar to the crude POR estimate. The POR was not adjusted by sex because no female cohort members were documented with shigella infection. Similarly, the POR was not adjusted by mode of HIV transmission since all

but one of those infected with shigella were homosexual or bisexual males[17]. Similar results were obtained from an analysis restricted to homosexual and bisexual males (crude POR=1.13, 95 percent CI=0.71-1.80).

The risk of KS prevalent at the time of AIDS diagnosis was highest in those cohort members who had multiple episodes of shigella infection prior to AIDS diagnosis (χ^2 test for trend p=0.20) (Table 5.7.3). However, multiple episodes of shigella infection were documented in only 11 cohort members, three of whom developed KS. Thus, this observation was based on a relatively small number of subjects and should be interpreted with caution. The time period between the most recent diagnosis of shigella infection and AIDS diagnosis was unrelated to the presence of KS at the time of AIDS diagnosis (Table 5.7.4).

5.7.c Shigella infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 3,191 cohort members eligible for analyses of KS that occurred following the diagnosis of AIDS, 150 (4.7 percent) were registered in WSCDR with one or more episodes of shigella infection. Shigella infection occurred after the date of last follow-up information in six cohort members, and these individuals were considered to have had no shigella infection for this analysis. Therefore, 144 (4.5 percent) of the cohort members

---

[17] In this analysis, all but one member of the study cohort with shigella infection were homosexual or bisexual men. For brevity, mode of HIV transmission was collapsed into the following two categories in Table 5.7.2: (1) homo/bisexual men, including those with and without a history of intravenous drug abuse, and (2) all other groups combined.

eligible for this analysis were considered to have been infected with shigella prior to their respective dates of last follow-up information.

The incidence rates of KS were 92.74 and 65.31 per 1,000 person-years of follow-up in those known to have been infected and not known to have been infected with shigella, respectively (RR=1.42, 95 percent CI=0.93-2.16) (Table 5.7.5, *part a*). By Cox proportional hazards model, those with prior shigella infection were at greater risk of KS than those without such infection (PH=1.25, 95 percent CI=0.82-1.91), after simultaneous adjustment for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis. Similar results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.7.5, *part b*).

There was no compelling evidence that the risk of KS was associated with the number of prior episodes of shigella infection (Table 5.7.6). In contrast to cohort members with a single episode of shigella infection, those with two or more episodes of shigella infection were at slightly lower risk of developing KS compared to those with no such infection. However, only ten cohort members had more than one episode of shigella infection. Further, the confidence intervals corresponding to the PH for the two groups previously infected with shigella overlapped, and both included the null value.

There were modest variations in the risk of KS according the date of most recent shigella infection relative to AIDS diagnosis (Table 5.7.7). A slight increase in risk of KS was observed among cohort members whose most recent shigella infection preceded AIDS diagnosis by one or more years compared with cohort members who were not

infected with shigella. A comparable increase was not observed among cohort members whose most recent shigella infection occurred during the year prior to AIDS diagnosis or after AIDS diagnosis.

5.8.a Salmonella infection among members of the study cohort

Computerized records of salmonella infection were available from WSCDR for Washington state residents who were diagnosed with salmonellosis during the period 1975-96. Thus, records of salmonella infection were available for at least six years prior to the diagnosis of the first person with AIDS in Washington state in 1982. Therefore, all eligible cohort members were included in the analyses that are summarized in Sections 5.8.a-5.8.c.

Salmonella infection was documented in 42 (1.1 percent) of the 3,873 members of the study cohort who were eligible for the present analysis. Salmonella was diagnosed after the date of last follow-up information in seven cohort members, and these individuals were considered to have had no salmonella infection for this analysis. The date of salmonella infection was unknown in four cohort members, but was documented in WSCDR for each of these subjects during the same calendar year as their respective dates of last follow-up information. Nonetheless, we were unable to determine if salmonella infection in these four individuals occurred during the follow-up period of this investigation, and all four were considered to have had no salmonella infection for this

analysis. Thus, of the 3,873 cohort members eligible for this analysis, 31 (0.8 percent) were considered to have been infected with salmonella.

Compared to homosexual and bisexual men[18], cohort members with a history of intravenous drug abuse were at increased risk of salmonella infection. Likewise, cohort members who contracted HIV through heterosexual contact and transfusion/transplant recipients were also at greater risk for salmonella infection than homosexual and bisexual men, though these observations were based on a relatively small number of subjects infected with salmonella. No cases of salmonella were documented in cohort members who were adult hemophiliacs or adults whose HIV risk factors were unknown.

Twenty-nine (0.8 percent) of 3,722 male cohort members were registered in WSCDR with one or more episodes of salmonella (Table 5.8.1). Two (1.3 percent) of the 151 female cohort members were similarly infected. Thus, males were at slightly lower risk of salmonella infection than females (OR=0.59, 95 percent CI=0.14-2.48), though the small number of cases among women limits the interpretation of this observation. Both female cohort members who were infected with salmonella were intravenous drug abusers. Thus, the greater risk of salmonella infection in females than males may be at least partially explained by the high risk of salmonella infection among intravenous drug abusers compared to homosexual and bisexual men.[19]

---

[18] The reference group for this portion of the analysis was homosexual and bisexual men not known to have been intravenous drug abusers.

[19] Approximately 92 percent of the 3,722 male cohort members were homo/bisexual males (n=3,413).

The percentage of cohort members infected with salmonella varied slightly by age at AIDS diagnosis and year of AIDS diagnosis (Table 5.8.1). However, these differences were modest and did not achieve statistical significance.

5.8.b Salmonella infection and Kaposi's sarcoma prevalent at AIDS diagnosis

Salmonella infection preceded the diagnosis of AIDS in 12 (28.6 percent) of the 42 cohort members known to have been infected with salmonella. These 12 individuals were considered to have been infected with salmonella for the purpose of characterizing the association between salmonella and prevalent KS, as summarized in this section. Salmonella infection occurred after AIDS diagnosis in 25 cohort members, and these individuals were considered to have had no salmonella infection for this analysis. The date of salmonella infection was unknown in five cohort members, but the corresponding salmonella case-reports were registered in WSCDR during the same calendar year as their respective AIDS diagnoses. Therefore, we did not know if the salmonella infection in these five individuals occurred before or after the diagnosis of AIDS. Two sets of analyses were conducted to accommodate the latter five individuals, one in which all five were considered to have been infected with salmonella and another in which none were considered to have been so infected (assumptions A and B, as described in Section 5.2).

Under assumption A, none of the 460 cohort members with KS prevalent at the time of AIDS diagnosis were classified as having been infected with salmonella prior to AIDS diagnosis (Table 5.8.2, *part a*). Twelve (0.35 percent) of the cohort members

without KS were documented to have had salmonella infection prior to their initial AIDS diagnosis. Under assumption B, two (0.43 percent) of the 460 cohort members with KS prevalent at the time of initial AIDS diagnosis were classified as having been infected with salmonella prior to AIDS diagnosis (Table 5.8.2, *part b*). Fifteen (0.44 percent) of the cohort members without KS were documented to have had a salmonella infection prior to their initial AIDS diagnosis. Thus, there was no association between salmonella infection prior to the diagnosis of AIDS and the presentation of KS at the time of initial AIDS diagnosis (crude POR=0.99, 95 percent CI=0.23-4.34).

The small number of prevalent KS cases with prior salmonella exposure precluded a detailed examination of the association between KS and the number of salmonella episodes. Of 17 cohort members known to have been infected with salmonella prior AIDS diagnosis, 16 had only a single episode of salmonella infection. The remaining cohort member had two salmonella episodes documented prior to AIDS diagnosis, and did not have KS prevalent at the time of AIDS diagnosis.

The limited number of cohort members infected with salmonella also precluded a detailed examination of the association between prevalent KS and the timing of salmonella infection relative to AIDS diagnosis.

5.8.c Salmonella infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 3,191 cohort members who were eligible for analyses of KS that occurred after initial AIDS diagnosis, 36 (1.1 percent) were registered in WSCDR with one or more episodes of salmonella infection. Salmonella infection in three cohort members occurred after the date of last follow-up information, and these three individuals were considered to have had no salmonella infection for the purpose of the analysis described in this section. The date of salmonella infection was unknown in two cohort members, but was registered in WSCDR during the same calendar year as their respective dates of last follow-up information. Therefore, we did not know if the salmonella infection in these two individuals occurred during the follow-up period of this investigation. Two sets of analyses were conducted to accommodate the latter two individuals, under assumptions A and B, as described in Section 5.2. Results reported here were obtained under assumption A.

The crude incidence rates of KS were 106.67 and 66.22 per 1,000 person-years of follow-up in those infected and not known to have been infected with salmonella, respectively (RR=1.61, 95 percent CI=0.60-4.31) (Table 5.8.3, *part a*). Similarly, by Cox proportional hazards model, those with prior salmonella exposure were at slightly greater risk of KS than those without prior salmonella exposure (PH=1.73, 95 percent confidence interval 0.65-4.64), after simultaneous adjustment for age at AIDS diagnosis, year of

AIDS diagnosis, and mode of HIV transmission. Comparable results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.8.3, *part b*).

Only two cohort members were documented to have had multiple episodes of salmonella infection. Two episodes of salmonella infection were documented in each of these individuals, and one developed KS after AIDS diagnosis while the other did not. Because of the small number of such cases, we did not examine the association between the development of KS following AIDS diagnosis and number of episodes of salmonella infection.

There was limited evidence that cohort members with recent salmonella infection were at greater risk of KS than those whose salmonella infection occurred one or more years prior to the diagnosis of AIDS (Table 5.8.4). However, these results must be interpreted with caution since they were based on a small number of individuals with both KS and salmonella infection.

5.9.a Giardia infection among members of the study cohort

WSCDR surveillance data for giardia infection were available in computerized format for Washington state residents who were registered with giardia infection during the period 1986-94. Therefore, documentation of giardia infection that preceded AIDS diagnosis was unavailable for many cohort members who were diagnosed with AIDS through the midpoint of the study period[20]. For this reason, all analyses related to giardia

[20] Giardia infection was documented in only one of 419 cohort members who were diagnosed with AIDS during the period 1982-86. Giardia infection was documented in 12 cohort members who were diagnosed with AIDS during the period 1987-89 (an average of 4 per year), and in 25 cohort members who were

infection were restricted to 2,118 cohort members who were diagnosed with AIDS during the period 1990-92.

Giardia infection was documented in 36 (1.7 percent) of 2,118 members of the study cohort who were eligible for this analysis. Of these, 25 (69.4 percent) were known to have been infected with giardia prior to the date of last information as recorded in HARS. These 25 individuals were considered to have been infected with giardia for the purpose of characterizing the distribution of giardia infection among members of the study cohort, as described in this section. In six cohort members, giardia infection occurred after the date of last follow-up information, and these individuals were considered to have had no giardia infection for this analysis. The date of giardia infection was unknown in five cohort members, but giardia infection was registered in WSCDR in the same calendar year as the date of last follow-up information for each of these individuals. Thus, we did not know if giardia infection in these subjects occurred during the period of follow-up for this investigation. The latter five individuals were considered to have had no giardia infection for this analysis.

Giardia infection was documented only among homosexual/bisexual men and intravenous drug abusers (Table 5.9.1). No cases of giardia infection were documented among female members of the study cohort. The percentage of cohort members infected with giardia was highest in those who were under 30 years of age at AIDS diagnosis, and

---

diagnosed with AIDS during the period 1990-92 (an average of 8.3 per year). Giardia-related analyses were restricted to cohort members who were diagnosed with AIDS during the period 1990-92.

this percentage declined with age (χ^2 test for trend $p<0.01$). No individuals who were over the age of 50 years at AIDS diagnosis were known to have been infected with giardia.

5.9.b Giardia infection and Kaposi's sarcoma prevalent at AIDS diagnosis

The majority of giardia infections documented among cohort members occurred after the diagnosis of AIDS. Of 36 cohort members who were eligible for this analysis and were known to have been infected with giardia, only six (16.7 percent) were known to have been so infected prior to the diagnosis of AIDS (Table 5.9.2). These six individuals were considered to have been infected with giardia for the analysis of prevalence odds ratios described in this section. Twenty-three cohort members infected with giardia after AIDS diagnosis were considered to have had no giardia infection for this analysis. The date of giardia infection was unknown in seven cohort members, but this infection was registered in WSCDR during the same calendar year as the AIDS diagnosis in this individuals. Two sets of analysis were conducted to accommodate the latter nine subjects, under assumptions A and B, as described in Section 5.2.

Under assumption A, giardia infection was not documented in any of the 182 cohort members with KS present at the time of AIDS diagnosis. Thus, PORs were inestimable under this assumption. Under assumption B, one (0.6 percent) of those cohort members with KS prevalent at AIDS diagnosis had been previously infected with giardia, and 12 (0.6 percent) of the remaining cohort members without prevalent KS were

known to have been so infected (POR=0.89, 95 percent CI=0.12-6.85) (Table 5.9.2). Thus, there was little evidence of an association between KS prevalent at AIDS and prior infection with giardia. No further analyses were conducted since only a single individual with KS was known to have been infected with giardia.

5.9.c Giardia infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 1,823 cohort members who were eligible for the analysis of KS that developed following the onset of AIDS, 33 (1.8 percent) were known to have been infected with giardia. Of these, 25 (75.8 percent) were known to have been infected with giardia prior to the date of last information as recorded in HARS, and these individuals were considered to have been so infected for this analysis. Five cohort members were infected with giardia after the date of last information, and were considered to have had no giardia infection for this analysis. The date of giardia infection was unknown in three cohort members, but this infection was registered in WSCDR during the same calendar year in which the date of last information was recorded for each of these individuals. Two sets of analyses were conducted to accommodate the latter three subjects, under assumptions A and B, as described in Section 5.2. Results reported here were obtained under assumption A.

The crude incidence rates for KS were 218.18 and 67.48 per 1,000 person-years of follow-up in cohort members infected and not known to have been infected with giardia,

respectively (RR=3.23, 95 percent CI=1.44-7.28) (Table 5.9.3, *part a*). By Cox proportional hazards model, cohort members with giardia infection were at greater risk of developing KS following AIDS diagnosis than those who were not so infected (PH=2.61, 95 percent CI=1.15-5.92), after simultaneous adjustment for mode of HIV transmission and age at AIDS diagnosis. Similar results were also obtained from an analysis restricted to homosexual and bisexual men (Table 5.9.3, *part b*).

Of six cohort members eligible for this analysis who developed KS following AIDS diagnosis and were known to have been infected with giardia, all were infected with giardia in the year prior to AIDS diagnosis or following AIDS diagnosis. Therefore, we did not examine the association between KS and time interval between giardia infection and AIDS diagnosis. Similarly, we did not examine the association between KS and multiple episodes of giardia exposure since only one cohort member was known to have had more than one episode of giardia infection (this individual did not have KS).

5.10.a Campylobacter infection among members of the study cohort

WSCDR surveillance data for campylobacter infection were available in computerized format for Washington state residents who were registered with campylobacter infection during the period 1984-94. Therefore, documentation of campylobacter infection that preceded AIDS diagnosis was unavailable for many cohort members who were diagnosed with AIDS during the early years of the study period[21].

[21] No campylobacter infections were documented in cohort members who were diagnosed with AIDS during the period 1982-85, and only one such infection was documented among cohort members diagnosed

For this reason, all analyses related to campylobacter infection were restricted to 3,454 cohort members who were diagnosed with AIDS during the period 1987-92.

Campylobacter infection was documented in 30 (0.9 percent) of 3,454 members of the study cohort who were eligible for this analysis. In 21 (70.0 percent) of these individuals, campylobacter infection was known to have occurred prior to the date of last information as recorded in HARS. These 21 subjects were considered to have been infected with campylobacter for the purposes of characterizing the distribution of this infection among members of the study cohort, as described in this section. In four cohort members, the date of campylobacter infection occurred after the date of last follow-up information, and these individuals were considered to have had no such infection for this analysis. The date of campylobacter infection was unknown in five cohort members, but this infection was registered in WSCDR during the calendar year that corresponded to the date of last information as recorded for each of these individuals. Because we could not determine if campylobacter infection in these five individuals occurred during the follow-up period of this investigation, they were considered to have had no campylobacter infection for this analysis.

All eligible cohort members who were known to have been infected with campylobacter were homosexual or bisexual men (Table 5.10.1). The percentage of cohort members who had been infected with campylobacter varied slightly by age at

---

with AIDS in 1986. In contrast, an average of 3.5 campylobacter infections per year were documented among cohort members diagnosed with AIDS during the period 1987-92. Campylobacter-related analyses were restricted to cohort members diagnosed with AIDS during the period 1987-92.

AIDS diagnosis and by year of AIDS diagnosis, but these differences were modest and did not achieve statistical significance.

5.10.b Campylobacter infection and Kaposi's sarcoma prevalent at AIDS diagnosis

Campylobacter infection was known to have preceded the diagnosis of AIDS in only six (20.0 percent) of the 30 eligible cohort members who had been infected with campylobacter (Table 5.10.2). All six of these individuals were considered to have been infected with campylobacter for the analysis of prevalence odds ratios described in this section. Twenty-one cohort members were infected with campylobacter following the diagnosis of AIDS, and these individuals were considered to have had no campylobacter infection for this analysis. The date of campylobacter infection was unknown for three subjects, but this infection was documented in WSCDR during the same calendar year in which each of these individuals was diagnosed with AIDS. Two sets of analyses were conducted to accommodate the latter three subjects, under assumptions A and B, as described in Section 5.2.

Under assumption A, only one (0.3 percent) of 365 cohort members with KS prevalent at the time of AIDS diagnosis had been previously infected with campylobacter (Table 5.10.2, *part a*). Five (0.2 percent) of the remaining 3,089 cohort members without KS prevalent at AIDS diagnosis had been previously infected with campylobacter. The modest association between KS and campylobacter reported here (POR=1.70, 95 percent CI=0.20-14.54) was based on a relatively small number of individuals with the exposure

of interest. As a result, the corresponding confidence interval was broad and included the null value. Similar results were obtained under assumption B (Table 5.10.2, *part b*). Adjusted estimates of the POR were not calculated due to the small number of subjects with KS prevalent at AIDS diagnosis who were also infected with campylobacter.

5.10.c Campylobacter infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 2,901 cohort members eligible for the analysis of KS diagnosed following the onset of AIDS, 25 (0.9 percent) were documented to have been infected with campylobacter. Nineteen (76.0 percent) of these were known to have been infected with campylobacter prior to the date of last information as recorded in HARS. These 19 individuals were considered to have been infected with campylobacter for this analysis. Two cohort members were diagnosed with campylobacter following the date of last information, and were considered to have had no such infection for this analysis. The date of campylobacter infection was unknown in four cohort members, but the infection was documented in WSCDR during the same calendar year as the date of last information for each of these individuals. Therefore, we did not know if campylobacter infection in these four individuals occurred during the period of follow-up for this investigation. Two sets of analyses were conducted to accommodate the latter four subjects, under assumptions A and B, as described in Section 5.2. Results reported here were obtained under assumption A.

The crude incidence rates for KS were 147.06 and 64.26 per 1,000 person-years of follow-up for cohort members infected and not known to have been infected with campylobacter, respectively (RR=2.29, 95 percent CI=0.73-7.13) (Table 5.10.5, *part a*). By Cox proportional hazards model, the risk of developing KS after AIDS diagnosis was greater for those infected with campylobacter than those not known to have been so infected (PH=1.98, 95 percent CI=0.64-6.20), after simultaneous adjustment for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis. Similar results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.10.5, *part b*).

We did not evaluate the association between multiple episodes of campylobacter infection and subsequent development of KS because no cohort members had more than one documented episode of this infection. There was limited evidence that the risk of KS varied by time interval between campylobacter infection and AIDS diagnosis (Table 5.10.4). Cohort members whose campylobacter infection occurred one or more years prior to AIDS diagnosis were at slightly greater risk of KS than those whose campylobacter infection occurred less than one year prior to AIDS diagnosis or after AIDS diagnosis. However, this observation was based on a relatively small number of cases, and there was a great deal of overlap between the confidence intervals corresponding to these two PH estimates.

5.11.a Entamoeba infection among members of the study cohort

WSCDR surveillance data for entamoeba infection were available in computerized format for Washington state residents who were registered with entamoeba infection during the period 1982-94. Therefore, documentation of entamoeba infection that proceeded the diagnosis of AIDS was unavailable for most cohort members who were diagnosed with AIDS during the early years of the study[22]. For this reason, all entamoeba-related analyses were restricted to 3,454 cohort members who were diagnosed with AIDS during the period 1987-92.

Entamoeba infection was documented in only 20 (0.6 percent) of 3,454 cohort members who were eligible for this analysis. In 17 cohort members, entamoeba infection was known to have occurred prior to the date of last information as recorded in HARS. These 17 individuals were considered to have been infected with entamoeba for the purpose of characterizing the distribution of these infections among members of the study cohort, as described in this section. Entamoeba infection occurred after the date of last follow-up information in two subjects, and these individuals were considered to have had no entamoeba infection for this analysis. The date of entamoeba infection was unknown in one cohort member, but was registered in WSCDR during the same calendar year as this subject's date of last follow-up information. Therefore, we were unable to determine

---

[22] No entamoeba infections were documented in cohort members who were diagnosed with AIDS during the period 1982-86. In contrast, entamoeba infection was documented in an average of approximately 3 cohort members per year among those subjects diagnosed with AIDS during the period 1987-92. All entamoeba-related analyses were restricted to cohort members who were diagnosed with AIDS during the period 1987-92.

if this subject was infected with entamoeba during the follow-up period of this investigation. The latter individual was considered to have had no entamoeba infection for this analysis.

All 17 members of the study cohort who were infected with entamoeba were homosexual or bisexual men, and one infected individual also had a history of intravenous drug abuse (Table 5.11.1). No entamoeba infections were documented in cohort members who were over 50 years of age at the time of AIDS diagnosis. The percentage of cohort members infected with entamoeba was slightly higher for subjects diagnosed with AIDS during the period 1987-89 than for those whose AIDS diagnosis occurred during the period 1990-92.

5.11.b Entamoeba infection and Kaposi's sarcoma prevalent at AIDS diagnosis

Nine cohort members were infected with entamoeba prior to being diagnosed with AIDS (Table 5.11.2), and these individuals were considered to have been infected with entamoeba for the analysis of prevalence odds ratios described in this section. Entamoeba infection in eight cohort members occurred after the diagnosis of AIDS, and these individuals were considered to have had no entamoeba infection for this analysis. The date of entamoeba infection was unknown for three cohort members, but this infection was registered in WSCDR during the respective calendar year that each of these individuals was diagnosed with AIDS. Two sets of analyses were conducted to accommodate the latter three individuals, one in which all were considered to have been

infected with entamoeba (assumption A) and another in which no such infection was assumed (assumption B), as described in Section 5.2.

Under assumptions A and B, none of the 460 cohort members who were diagnosed with KS at the time of their initial AIDS diagnosis were known to have been infected with entamoeba (Table 5.11.2). Thus, the POR was inestimable.

5.11.c Entamoeba infection and the development of Kaposi's sarcoma following AIDS diagnosis

Of 2,901 cohort members who were eligible for the analysis of KS diagnosed following the onset of AIDS, 17 (0.6 percent) were documented in WSCDR with entamoeba infection. Of these, 15 (88.2 percent) were known to have been infected with entamoeba prior to the date of last information as recorded in HARS. These 15 cohort members were considered to have been infected with entamoeba for the purposes of this analysis. One cohort member was infected with entamoeba after the date of last information, and was considered to have had no entamoeba infection for this analysis. The date of entamoeba infection was unknown in one subject, but entamoeba infection was documented in WSCDR during the same year that this subject was diagnosed with AIDS. Two separate analyses were conducted to accommodate the latter subject, under assumptions A and B, as described in Section 5.2. Results reported here were obtained under assumption A.

The crude incidence rates for KS following the diagnosis of AIDS were 86.58 and 64.48 per 1,000 person-years of follow-up in those cohort members infected and not infected with entamoeba, respectively, (RR=1.34, 95 percent CI=0.33-5.39) (Table 5.11.3, *part a*). By Cox proportional hazards model, cohort members who had been infected with entamoeba were at slightly greater risk of developing KS following the onset of AIDS than those not so infected (PH=1.13, 95 percent CI=0.28-4.52). Similar results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.11.5, *part b*).

We did not examine the association between multiple episodes of entamoeba infection and KS since no cohort members had more than one documented episode of entamoeba infection. The small number of cohort members with both KS and entamoeba infection precluded an assessment of the association between KS and timing of entamoeba infection relative to AIDS diagnosis.

5.12.a All enteric infections (combined) among members of the study cohort

In this final set of analyses, selected WSCDR surveillance data were grouped together to determine if infection with a combination of enteric pathogens was associated with the occurrence of KS among members of the study cohort. For this analysis, cohort members were considered to have had an enteric infection if they were documented to have been infected with *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *entamoeba histolytica*, *campylobacter spp.*, or *giardia spp.*, and were so designated in the preceding

analyses based on WSCDR data (i.e., Sections 5.4 and Sections 5.6-5.11). This analysis was restricted to cohort members who were diagnosed with AIDS during the period 1987-92, since WSCDR surveillance data for some enteric pathogens were unavailable for the early years of the AIDS epidemic (see Section 5.3).

Approximately 10 percent of homosexual and bisexual men (with or without a history of intravenous drug abuse) were infected with one or more of the enteric pathogens examined in this investigation (Table 5.12.1). These infections were less common among cohort members who were strictly intravenous drug abusers (5.8 percent), or who acquired HIV through heterosexual contact (4.7 percent infected) or transfusion/transplantation (3.6 percent infected). No enteric infections were documented in cohort members who were adult hemophiliacs or adults whose HIV risk factors were unknown.

Males were much more likely than females to have been infected with one or more enteric infections, reflecting the high risk of such infection among homosexual and bisexual men (Table 5.12.1). Of the four female cohort members infected with one or more enteric pathogens, three were intravenous drug abusers and one acquired HIV through heterosexual contact. None of the latter four women were known to have had KS. Enteric infections were most commonly found in cohort members who were under the age of 30 years at the time of AIDS diagnosis, and the percentage of cohort members so infected decreased with age (χ^2 test for trend $p<0.01$). The percent of cohort members infected with one or more enteric pathogens did not vary over the period of study, though

this analysis was restricted to cohort members who were diagnosed with AIDS during a six year period (1987-92).

5.12.b All enteric pathogens (combined) and Kaposi's sarcoma prevalent at AIDS diagnosis

Of 365 cohort members who were eligible for this analysis and had KS prevalent at the time of AIDS diagnosis, 20 (5.5 percent) had experienced one or more episodes of enteric infection prior to AIDS diagnosis (Table 5.12.2). Of the remaining 3,089 eligible cohort members without KS prevalent at the time of AIDS diagnosis, 191 (6.2 percent) had one or more prior enteric infections. Thus, there was no association between presence of KS at the time of AIDS diagnosis and prior enteric infection (POR=0.88, 95 percent CI=0.55-1.41). Estimates of the POR, independently adjusted by sex, age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission, did not vary appreciably from the crude POR estimate.

The risk of KS prevalent at AIDS diagnosis was slightly lower for cohort members with two or more prior episodes of enteric disease infection than for other cohort members (Table 5.12.3). However, this observation was based on a single cohort member with KS and two or more prior episodes of enteric infection, and should be interpreted with caution.

There was limited evidence that the risk of prevalent KS varied according to the time (in years) between the most recent enteric infection and the diagnosis of AIDS

(Table 5.12.4). Specifically, cohort members whose most recent enteric infection occurred within one year of AIDS diagnosis were at lower risk of prevalent KS than those whose most recent enteric infection occurred one or more years prior to the diagnosis of AIDS. However, this observation was based on only two cases of enteric infection in the former group, and the corresponding confidence intervals overlapped one another and both included the null value. Therefore, this observation should be interpreted with great caution.

5.12.c All enteric infections (combined) and the development of Kaposi's sarcoma following AIDS diagnosis

The crude incidence rates for KS were 83.13 and 62.89 per 1,000 person-years of follow-up among cohort members with and without prior episodes of enteric infection, respectively (RR=1.32, 95 percent CI=0.94-1.86) (Table 5.12.5, *part a*). By Cox proportional hazards model, there was little difference in risk of KS between those with and without prior enteric infection (PH=1.21, 95 percent CI=0.86-1.70), after simultaneous adjustment of mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis. Similar results were obtained from an analysis restricted to homosexual and bisexual men (Table 5.12.5, *part b*).

The risk of KS was unrelated to the number of prior episodes of enteric infection (Table 5.12.6). Minor variations in the risk of KS by time (in years) between the most recent episode of enteric infection and AIDS diagnosis were unremarkable (Table 5.12.7).

5.13 Summary

We found no association between the incidence of a variety of infections prior to AIDS diagnosis and the presence of KS at the time of AIDS diagnosis (Table 5.13.1). This observation was true for each of eight communicable diseases examined in this investigation, and for the combination of six of these agents that were considered to have been enteric pathogens.

We also examined the risk of developing KS following AIDS diagnosis for a selected group of cohort members who did not have prevalent KS (see Sections 5.2 and 5.3). Cohort members with prior syphilis infection were at slightly greater risk of developing KS post-AIDS than were cohort members not so infected (Table 5.13.2). Further, the risk of syphilis increased with the number of prior episodes of syphilis infection. There was limited evidence that cohort members infected with syphilis less than one year prior to AIDS diagnosis or after AIDS diagnosis were at greater risk of post-AIDS KS than those not so infected. We found no association between post-AIDS KS and stage of the most recent syphilis infection.

Prior infection with hepatitis-B virus was inversely associated with the risk of KS following AIDS, though this observation did not achieve statistical significance (Table 5.13.2). There was no evidence that the risk of KS varied according to the time (relative to AIDS diagnosis) of the most recent hepatitis-B infection.

With the exception of hepatitis-A virus, there were positive associations between each of the agents designated as enteric pathogens and the occurrence of KS following

AIDS diagnosis (Table 5.13.2). Most of these associations were modest, with the exceptions those infected with *campylobacter spp.* (adjusted PH=2.29, 95 percent CI=0.73-7.13) and *giardia spp.* (adjusted PH=3.23, 95 percent CI=1.44-7.28). Nonetheless, the confidence intervals were broad for the latter two observations, reflecting the small number of cases available for the respective analyses, and these results must be interpreted with caution. There was a slight increase in risk of post-AIDS KS for cohort members infected with any enteric pathogen (combined). In all analyses of post-AIDS KS, modest variations in risk of KS by number of episodes of infection and by time (in years) between the most recent enteric infection and AIDS diagnosis were largely unremarkable.

A detailed discussion of these findings is presented in Chapter 6.

Table 5.1.1 Selected characteristics of eight infectious agents of interest that were included in this investigation.

Disease	Pathogen	Primary modes of transmission*	Source of surveillance data	Years of available surveillance data†
Syphilis	*Treponema pallidum*	Sexual contact	WSSR‡	1959-94
Shigellosis	*Shigella spp.*	Fecal/oral transmission, direct or indirect	WSCDR§	1975-96
Salmonellosis	*Salmonella spp.*	Ingestion of organisms in food derived from infected food animals or contaminated by feces from an infected animal or person	WSCDR	1975-96
Hepatitis-A	*Hepatitis-A virus*	Person-to-person by the fecal-oral route	WSCDR	1982-94
Hepatitis-B	*Hepatitis-B virus*	Contact with infected blood (and serum-derived fluids), saliva, semen, and vaginal fluids	WSCDR	1982-94
Amebiasis	*Entamoeba histolytica*	Fecal/oral transmission	WSCDR	1982-94
Campylo-bacteriosis	*Campylobacter spp.*	Ingestion of organisms in food or in unpasteurized milk or water, or from contact with infected animals or humans (especially infants and children)	WSCDR	1984-94
Giardiasis	*Giardia spp.*	Hand-to-mouth transfer of cysts from the feces of an infected individual	WSCDR	1986-94

* Summarized from Benenson (1990).

† Availability of surveillance data in a computerized format from the respective source of information.

‡ Washington State Syphilis Registry (WSSR).

§ Washington State Communicable Disease Registry (WSCDR).

Table 5.3.1 Characteristics of selected members of the study cohort,* comparing those with and without date of last information recorded in the HIV/AIDS Reporting System (HARS) *(page one of three)*

		Date of last follow-up information recorded in HARS†				
		Yes		No		
Characteristic	Category	No.	Percent‡	No.	Percent‡	χ^2 test (p-value)
Developed KS after AIDS diagnosis	Yes	387	12.1	5	2.3	$\chi^2_{1\,df}$= 19.912 (p= 0.001)
	No	2,804	87.9	217	97.7	
Sex	Female	7	3.2	143	4.5	$\chi^2_{1\,df}$= 0.871 (p=0.351)
	Male	215	96.8	3,048	95.5	
Age at AIDS diagnosis	20-29 years	635	19.9	32	14.4	$\chi^2_{3\,df}$= 14.383 (p=0.002)
	30-39 years	1,539	48.2	107	48.2	
	40-49 years	737	23.1	48	21.6	
	50+ years	280	8.8	35	15.8	
	median age (years)	*36*		*37*		
Year of AIDS diagnosis	1982-86	290	9.1	34	15.3	$\chi^2_{2\,df}$= 9.898 (p=0.007)
	1987-89	1,078	33.8	75	33.8	
	1990-92	1,823	57.1	113	50.9	

continued

Table 5.3.1 continued (*page two of three*)

Characteristic	Category	Date of last follow-up information recorded in HARS[†]: Yes No.	Yes Percent[‡]	No No.	No Percent[‡]	χ^2 test (p-value)
Mode of HIV transmission	Homosexual or bisexual men	2,414	75.6	166	74.8	$\chi^2_{6\,df}$= 29.790 (p=0.001)
	Intravenous drug abusers	187	5.9	13	5.9	
	Homosexual or bisexual men who were also intravenous drug abusers	371	11.6	16	7.2	
	Adult hemophiliacs	30	0.9	1	0.4	
	Heterosexual contact	82	2.6	4	1.8	
	Transfusion or transplant recipients	54	1.7	9	4.0	
	Adults whose HIV risk factors were unknown	53	1.7	13	5.9	

continued

Table 5.3.1 continued (*page three of three*)

Footnotes

---

* The study cohort included residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in HARS. This table does not include 460 cohort members who had Kaposi's sarcoma prevalent at the time of AIDS diagnosis and 26 cohort members who were under the age of 20 years at AIDS diagnosis.

† Analyses of determinants of KS that occurred following AIDS diagnosis were restricted to members of the study cohort who did not have KS prevalent at the time of AIDS diagnosis and who had date of last follow-up information recorded in HARS (n=3,191) (see text).

‡ Column percent

Table 5.4.1 Distribution of syphilis infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with syphilis†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	441	14.8	2,532	85.2	1.00	(reference)
	Intravenous drug abusers	19	9.1	191	90.9	0.57	0.35-0.93
	Homosexual or bisexual men who were also intravenous drug abusers	62	14.4	369	85.6	0.97	0.72-1.29
	Adult hemophiliacs	0	-	31	100.0	-	-
	Heterosexual contact	0	-	88	100.0	-	-
	Transfusion or transplant recipients	1	1.6	62	98.4	0.09	0.01-0.67
	Adults whose HIV risk factors were unknown	5	7.4	63	92.6	0.46	0.18-1.14

continued

Table 5.4.1 continued (*page two of two*)

Characteristic	Category	Ever infected with syphilis†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	6	4.0	145	96.0	1.00	(reference)
	Male	522	14.1	3,191	85.9	3.95	1.74-8.99
Age at AIDS diagnosis	20-29 years	52	6.9	700	93.1	1.00	(reference)
	30-39 years	210	11.2	1,674	88.8	1.69	1.23-2.32
	40-49 years	183	20.6	705	79.4	3.49	2.52-4.84
	50+ years	83	24.4	257	75.6	4.35	2.99-6.33
Year of AIDS diagnosis	1982-86	90	21.5	328	78.5	1.00	(reference)
	1987-89	207	15.5	1,127	84.5	0.67	0.51-0.88
	1990-92	231	10.9	1,881	89.1	0.45	0.34-0.59

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,864 cohort members who were 20 years of age or older at AIDS diagnosis and whose respective dates of syphilis diagnosis were known (see text).

† Syphilis infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.4.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immunodeficiency syndrome (AIDS) and infection with syphilis prior to AIDS diagnosis, selected members of the study cohort* *(page one of three)*

			Infected with syphilis prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
All cases	Total	Yes	64	14.0	393	86.0	1.11	-
		No	435	12.8	2,972	87.2	(0.84-1.48)	
Sex	Male	Yes	64	14.0	392	86.0	1.07	1.07
		No	431	13.2	2,826	86.8	(0.81-1.42)	(0.81-1.42)
								Breslow-Day¶:
	Female	Yes	0	-	1	100.0	-∞	$\chi^2_{df=1} = 0.029$
		No	4	2.7	146	97.3		p= 0.864
Age at AIDS diagnosis	20-29	Yes	10	11.8	75	88.2	2.41	1.16
		No	35	5.3	632	94.7	(1.15-5.06)	(0.87-1.55)
								Breslow-Day¶:
	30-39	Yes	21	8.7	220	91.3	0.80	$\chi^2_{df=3} = 7.541$
		No	176	10.7	1,467	89.3	(0.50-1.28)	p= 0.057
	40-49	Yes	24	22.6	82	77.4	1.22	
		No	151	19.3	631	80.7	(0.75-1.99)	
	50+	Yes	9	36.0	16	64.0	1.87	
		No	73	23.2	242	76.8	(0.79-4.40)	
Year of AIDS diagnosis	1982-86	Yes	20	21.3	74	78.7	1.02	0.98
		No	68	21.0	256	79.0	(0.58-1.78)	(0.74-1.31)
								Breslow-Day¶:
	1987-89	Yes	26	14.2	157	85.8	0.98	$\chi^2_{df=2} = 0.025$
		No	166	14.4	985	85.6	(0.63-1.54)	p= 0.987
	1990-92	Yes	18	10.0	162	90.0	0.96	
		No	201	10.4	1,731	89.6	(0.58-1.59)	

continued

Table 5.4.2 continued (*page two of three*)

Variable	Category	KS[†]	Infected with syphilis prior to AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratio[‡] Crude (95% CI)	Prevalence odds ratio[‡] Adjusted[§] (95% CI)
Mode of HIV trans-mission	Homo/bi-sexual men	Yes	56	14.1	341	85.9	0.99 (0.73-1.34)	1.02 (0.77-1.35) *Breslow-Day*[‖]: $\chi^2_{df=3} = 0.514$ p = 0.916
		No	366	14.2	2,210	85.8		
	Intravenous drug abusers	Yes	1	10.0	9	90.0	1.60 (0.19-13.60)	
		No	13	6.5	187	93.5		
	Homo/bi-sexual men who were also intra-venous drug abusers	Yes	7	15.2	39	84.8	1.20 (0.51-2.84)	
		No	50	13.0	335	87.0		
	Adult hemophiliacs	Yes	0	-	0	-	-	
		No	0	-	31	100.0		
	Heterosexual contact	Yes	0	-	2	100.0	-	
		No	0	-	86	100.0		
	Transfusion or transplant recipients	Yes	0	-	0	-	-	
		No	1	1.6	62	98.41		
	Adults whose HIV risk factors were unknown	Yes	0	-	2	100.0	-∞	
		No	5	7.6	61	92.4		

continued

Table 5.4.2 continued (*page three of three*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,864 cohort members who were 20 years of age or older at AIDS diagnosis and whose respective dates of syphilis diagnosis were known (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ Adjusted by the corresponding variable listed in column one.

‖ Breslow-Day chi-squared (χ^2) test for homogeneity of odds ratios across strata of the corresponding adjustment variable (Breslow 1980, p 142). Note that strata with a value of zero in two or more cells do not contribute to the calculation of this statistic.

Table 5.4.3 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and the number of syphilis episodes that preceded the diagnosis of AIDS. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Number of syphilis episodes that preceded AIDS diagnosis	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratio† Crude (95% CI)	Prevalence odds ratio† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No syphilis	393	11.7	2,972	88.3	1.00 (reference)	1.00 (reference)
One only	48	12.3	342	87.7	1.06 (0.77-1.46)	0.91 (0.66-1.27)
Two or more	16	14.7	93	85.3	1.30 (0.76-2.23)	1.09 (0.62-1.89)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	380	13.0	2,545	87.0	1.00 (reference)	1.00 (reference)
One only	47	12.6	325	87.4	0.97 (0.70-1.34)	0.90 (0.64-1.25)
Two or more	16	14.9	91	85.1	1.18 (0.69-2.03)	1.09 (0.62-1.90)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,864 cohort members who were 20 years of age or older at AIDS diagnosis and whose respective dates of syphilis diagnosis were known (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.4.4 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and stage of the most recent episode of syphilis that occurred prior to the diagnosis of AIDS. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only *(page one of two)*

Stage of most recent episode of syphilis that occurred prior to AIDS diagnosis	KS prevalent at time of AIDS diagnosis: Yes		KS prevalent at time of AIDS diagnosis: No		Prevalence odds ratio†	
	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted‡ (95% CI)
(a) All eligible cohort members						
No syphilis	393	11.7	2,972	88.3	1.00 (reference)	1.00 (reference)
Primary	10	9.9	91	90.1	0.83 (0.43-1.61)	0.71 (0.36-1.39)
Secondary	22	12.9	149	87.1	1.12 (0.71-1.77)	0.98 (0.61-1.57)
Other	32	14.1	195	85.9	1.24 (0.84-1.83)	1.03 (0.69-1.54)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	380	13.0	2,545	87.0	1.00 (reference)	1.00 (reference)
Primary	9	9.1	90	90.9	0.67 (0.34-1.34)	0.62 (0.31-1.26)
Secondary	22	13.5	141	86.5	1.05 (0.66-1.66)	0.99 (0.62-1.58)
Other	32	14.8	185	85.2	1.16 (0.78-1.71)	1.05 (0.70-1.57)

continued

Table 5.4.4 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,864 cohort members who were 20 years of age or older at AIDS diagnosis and whose respective dates of syphilis diagnosis were known (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.4.5 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and time (in years) between the most recent syphilis episode and date of AIDS diagnosis. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Years between the most recent episode of syphilis and the diagnosis of AIDS	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratio† Crude (95% CI)	Prevalence odds ratio† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No syphilis	393	11.7	2,972	88.3	1.00 (reference)	1.00 (reference)
< 1 year	4	13.8	25	86.2	1.21 (0.42-3.50)	1.10 (0.37-3.23)
1+ years	60	12.8	410	87.2	1.11 (0.83-1.48)	0.94 (0.69-1.27)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	380	13.0	2,545	87.0	1.00 (reference)	1.00 (reference)
< 1 year	4	14.8	23	85.2	1.17 (0.40-3.39)	1.11 (0.38-3.29)
1+ years	59	13.1	393	86.9	1.01 (0.75-1.35)	0.93 (0.68-1.26)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,864 cohort members who were 20 years of age or older at AIDS diagnosis and whose respective dates of syphilis diagnosis were known (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.4.6 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among members of the study cohort*, comparing those infected with syphilis to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Syphilis infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
(a.) All eligible cohort members								
Not infected	2,752	5,084.5	316	62.15	1.00	(reference)	1.00	(reference)
Infected	434	735.1	71	96.59	1.55	1.20-2.01	1.53	1.18-1.99
(b.) Eligible homosexual and bisexual male cohort members								
Not infected	2,366	4,375.8	309	70.62	1.00	(reference)	1.00	(reference)
Infected	414	684.4	71	103.74	1.47	1.14-1.90	1.57	1.21-2.05

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,186 cohort members who were not known to have had KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, whose respective dates of syphilis diagnosis were known and who had a valid entry for date of last follow-up information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.4.7 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and the number of syphilis episodes that preceded the date of last follow-up information*. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Number of syphilis episodes that preceded the date of last follow-up information	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards‡: Crude (95% CI)	Proportional hazards‡: Adjusted§ (95% CI)
(a) All eligible cohort members						
No syphilis	316	11.5	2,436	88.5	1.00 (reference)	1.00 (reference)
One only	53	15.7	285	84.3	1.45 (1.09-1.94)	1.43 (1.07-1.93)
Two or more	18	18.8	78	81.2	1.96 (1.22-3.15)	1.93 (1.19-3.13)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	309	13.1	2,057	86.9	1.00 (reference)	1.00 (reference)
One only	53	16.6	266	83.4	1.38 (1.03-1.85)	1.47 (1.10-1.98)
Two or more	18	18.9	77	81.1	1.76 (1.09-2.83)	1.97 (1.22-3.20)

continued

Table 5.4.7 continued (*page two of two*)

Footnotes

---

* Date of last follow-up information was defined as the date of KS diagnosis for those cohort members with KS, and the date of last follow-up information recorded in the HIV/AIDS Reporting System for cohort members not known to have had KS.

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,186 cohort members who were not known to have had KS prevalent at time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, whose respective dates of syphilis diagnosis were known, and who had a valid entry for date of last follow-up information recorded in HARS (see text).

‡ Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

§ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.4.8 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and stage of the most recent episode of syphilis that occurred prior to the date of last follow-up information*. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Stage of most recent episode of syphilis that occurred prior to the date of last follow-up information	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards‡: Crude (95% CI)	Proportional hazards‡: Adjusted§ (95% CI)
(a) All eligible cohort members						
No syphilis	316	11.5	2,436	88.5	1.00 (reference)	1.00 (reference)
Primary	15	16.9	74	83.1	1.54 (0.92-2.58)	1.56 (0.92-2.63)
Secondary	20	13.9	124	86.1	1.35 (0.86-2.11)	1.22 (0.78-1.92)
Other	36	17.9	165	82.1	1.71 (1.21-2.41)	1.77 (1.25-2.52)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	309	13.1	2,057	86.9	1.00 (reference)	1.00 (reference)
Primary	15	17.4	71	82.6	1.43 (0.85-2.40)	1.57 (0.93-2.66)
Secondary	20	14.4	119	85.6	1.21 (0.77-1.91)	1.24 (0.79-1.96)
Other	36	19.1	153	80.9	1.67 (1.18-2.36)	1.85 (1.30-2.64)

continued

Table 5.4.8 continued (*page two of two*)

Footnotes

---

* Date of last follow-up information was defined as the date of KS diagnosis for those cohort members with KS, and the date of last follow-up information recorded in the HIV/AIDS Reporting System for cohort members not known to have had KS.

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,186 cohort members who were not known to have had KS prevalent at time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, whose respective dates of syphilis diagnosis were known, and who had a valid entry for date of last follow-up information recorded in HARS (see text).

‡ Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

§ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.4.9 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between the most recent syphilis episode and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between the most recent episode of syphilis and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No syphilis	316	11.5	2,436	88.5	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	13	23.6	42	76.4	2.29 (1.31-3.98)	2.51 (1.44-4.38)
1+ years	58	15.3	321	84.7	1.45 (1.10-1.92)	1.40 (1.05-1.86)
(b) Eligible homosexual and bisexual male cohort members only						
No syphilis	309	13.1	2,057	86.9	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	13	27.1	35	72.9	2.57 (1.48-4.48)	2.67 (1.53-4.66)
1+ years	58	15.8	308	84.2	1.33 (1.01-1.76)	1.43 (1.07-1.91)

continued

Table 5.4.9 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,186 cohort members who were not known to have had KS prevalent at time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, whose respective dates of syphilis diagnosis were known, and who had a valid entry for date of last follow-up information recorded in HARS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.5.1 Distribution of hepatitis-B infection among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with hepatitis-B†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	43	1.6	2,586	98.4	1.00	(reference)
	Intravenous drug abusers	9	4.4	197	95.6	2.75	1.32-5.72
	Homosexual or bisexual men who were also intravenous drug abusers	9	2.3	378	97.7	1.43	0.69-2.96
	Adult hemophiliacs	0	-	29	100.0	-	-
	Heterosexual contact	1	1.2	85	98.8	0.71	0.10-5.20
	Transfusion or transplant recipients	0	-	55	100.0	-	-
	Adults whose HIV risk factors were unknown	0	-	62	100.0	-	-

continued

Table 5.5.1 continued (*page two of two*)

Characteristic	Category	Ever infected with hepatitis-B†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	1	0.7	144	99.3	1.00	(reference)
	Male	61	1.8	3,248	98.2	2.70	0.37-19.65
Age at AIDS diagnosis	20-29 years	18	2.7	643	97.3	1.00	(reference)
	30-39 years	32	1.9	1,650	98.1	0.69	0.39-1.24
	40-49 years	8	1.0	806	99.0	0.36	0.15-0.82
	50+ years	4	1.4	293	98.6	0.49	0.16-1.45
Year of AIDS diagnosis	1987-89	25	1.9	1,311	98.1	1.00	(reference)
	1990-92	37	1.8	2,081	98.2	0.93	0.59-1.56

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at the time of AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† Hepatitis-B infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System in those cohort members not known to have had KS.

Table 5.5.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immuno-deficiency syndrome (AIDS) and infection with hepatitis-B prior to AIDS diagnosis, selected members of the study cohort* *(page one of three)*

			Infected with hepatitis-B prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
All cases	Total	Yes	7	1.9	358	98.1	1.17	-
		No	51	1.7	3,038	98.3	(0.53-2.59)	
Sex	Male	Yes	7	1.9	357	98.1	1.14	1.13
		No	50	1.7	2,895	98.3	(0.51-2.52)	(0.51-2.52)
								Breslow-Day‖:
	Female	Yes	0	-	1	100.0	-	$\chi^2_{df=1} = 0.008$
		No	1	0.7	143	99.3		p=0.929
Age at AIDS diagnosis	20-29	Yes	2	3.1	63	96.9	1.32	1.17
		No	14	2.4	582	97.6	(0.29-5.94)	(0.53-2.57)
								Breslow-Day‖:
	30-39	Yes	2	1.1	186	98.9	0.56	$\chi^2_{df=3} = 10.012$
		No	28	1.9	1,466	98.1	(0.13-2.38)	p=0.018
	40-49	Yes	1	1.1	89	98.9	1.15	
		No	7	1.0	717	99.0	(0.14-9.46)	
	50+	Yes	2	9.1	20	90.9	13.65	
		No	2	0.7	273	99.3	(1.83-102.07)	
Year of AIDS diagnosis	1987-89	Yes	4	2.2	179	97.8	1.49	1.18
		No	17	1.5	1,136	98.5	(0.50-4.49)	(0.53-2.65)
								Breslow-Day‖:
	1990-92	Yes	3	1.7	179	98.3	0.94	$\chi^2_{df=1} = 0.320$
		No	34	1.8	1,902	98.2	(0.29-3.08)	p=0.572

continued

Table 5.5.2 continued (*page two of three*)

			Infected with hepatitis-B prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
Mode of HIV trans-mission	Homo/bi-sexual men	Yes	6	1.9	311	98.1	1.22 (0.51-2.92)	1.17 (0.53-2.60) *Breslow-Day:** $\chi^2_{df=3} = 2.286$ p=0.515
		No	36	1.6	2,276	98.4		
	Intravenous drug abusers	Yes	1	11.1	8	88.9	3.98 (0.43-37.08)	
		No	6	3.1	191	96.9		
	Homo/bi-sexual men who were also intra-venous drug abusers	Yes	0	-	35	100.0	-	
		No	8	2.3	344	97.7		
	Adult hemophiliacs	Yes	0	-	0	-	-	
		No	0	-	29	100.0		
	Heterosexual contact	Yes	0	-	2	100.0	-	
		No	1	1.2	83	98.8		
	Transfusion or transplant recipients	Yes	0	-	0	-		
		No	0	-	55	100.0		
	Adults whose HIV risk factors were unknown	Yes	0	-	2	-		
		No	0	-	60	-		

continued

Table 5.5.2 continued (*page three of three*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at the time of AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ Adjusted by the corresponding variable listed in column one.

‖ Breslow-Day chi-squared (χ^2) test for homogeneity of odds ratios across strata of the adjustment variable (Breslow 1980, p 142). Note that strata with a value of zero in two or more cells did not contribute to the calculation of this statistic.

Table 5.5.3 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and time (in years) between the diagnosis of hepatitis-B and date of AIDS diagnosis. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Years between hepatitis-B diagnosis and the diagnosis of AIDS	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratios† Crude (95% CI)	Prevalence odds ratios† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No hepatitis-B	358	10.5	3,038	89.5	1.00 (reference)	1.00 (reference)
< 1 year	2	28.6	5	71.4	3.39 (0.66-17.56)	4.35 (0.78-24.14)
1+ years	5	9.8	46	90.2	0.92 (0.36-2.34)	0.93 (0.37-2.37)
(b) Eligible homosexual and bisexual male cohort members only						
No hepatitis-B	346	11.7	2,620	88.3	1.00 (reference)	1.00 (reference)
< 1 year	2	40.0	3	60.0	5.05 (0.84-30.32)	5.24 (0.84-32.54)
1+ years	4	8.9	41	91.1	0.74 (0.26-2.08)	0.76 (0.27-2.15)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at the time of AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.5.4 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with hepatitis-B to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Hepatitis-B infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	2,848	5,241.8	341	65.05	1.00	(reference)	1.00	(reference)
Infected	53	84.9	3	35.34	0.54	0.17-1.69	0.54	0.17-1.68
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	2,469	4,543.0	334	73.52	1.00	(reference)	1.00	(reference)
Infected	44	69.8	3	42.98	0.58	0.19-1.82	0.56	0.18-1.73

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information as recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.5.5 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between hepatitis-B infection and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between hepatitis-B infection and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No hepatitis-B	341	12.0	2,507	88.0	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	0	-	7	100.0	-	-
1+ years	3	6.5	43	93.5	0.63 (0.20-1.96)	0.58 (0.19-1.81)
(b) Eligible homosexual and bisexual male cohort members only						
No hepatitis-B	334	13.5	2,135	86.5	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	0	-	3	100.0	-	-
1-4 years	3	7.3	38	92.7	0.61 (0.20-1.91)	0.59 (0.19-1.83)

continued

Table 5.5.5 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information as recorded in HARS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.6.1 Distribution of hepatitis-A infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with hepatitis-A†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	56	2.1	2,573	97.9	1.00	(reference)
	Intravenous drug abusers	6	2.9	200	97.1	1.38	0.59-3.24
	Homosexual or bisexual men who were also intravenous drug abusers	16	4.1	371	95.9	1.98	1.13-3.49
	Adult hemophiliacs	0	-	29	100.0	-	-
	Heterosexual contact	2	2.3	84	97.7	1.09	0.26-4.56
	Transfusion or transplant recipients	1	1.8	54	98.2	0.85	0.12-6.26
	Adults whose HIV risk factors were unknown	0	-	62	100.0	-	-

continued

Table 5.6.1 continued (*page two of two*)

Characteristic	Category	Ever infected with hepatitis-A†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	2	1.4	143	98.6	1.00	(reference)
	Male	79	2.4	3,230	97.6	1.75	0.43-7.19
Age at AIDS diagnosis	20-29 years	30	4.5	631	95.5	1.00	(reference)
	30-39 years	39	2.3	1,643	97.7	0.50	0.31-0.81
	40-49 years	7	0.9	807	99.1	0.18	0.08-0.42
	50+ years	5	1.7	292	98.3	0.36	0.14-0.94
Year of AIDS diagnosis	1987-89	18	1.4	1,318	98.6	1.00	(reference)
	1990-92	63	3.0	2,055	97.0	2.25	1.32-3.81

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† Hepatitis-A infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members known to have had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System in those cohort members not known to have had KS.

Table 5.6.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immuno-deficiency syndrome (AIDS) and infection with hepatitis-A prior to AIDS diagnosis, selected members of the study cohort* *(page one of three)*

			Infected with hepatitis-A prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
All cases	Total	Yes	6	1.6	359	98.4	0.86	-
		No	59	1.9	3,030	98.1	(0.37-2.00)	
Sex	Male	Yes	6	1.7	358	98.3	0.85	0.85
		No	57	1.9	2,888	98.1	(0.36-1.98)	(0.36-1.98)
								Breslow-Day‖:
	Female	Yes	0	-	1	100.0	-	$\chi^2_{df=1} = 0.012$
		No	2	1.4	142	98.6		p=0.913
Age at AIDS diagnosis	20-29	Yes	2	3.1	63	96.9	0.87	0.87
		No	21	3.5	575	96.5	(0.20-3.79)	(0.37-2.03)
								Breslow-Day‖:
	30-39	Yes	3	1.6	185	98.4	0.85	$\chi^2_{df=3} = 0.448$
		No	28	1.9	1,466	98.1	(0.26-2.82)	p=0.930
	40-49	Yes	1	1.1	89	98.9	1.35	
		No	6	0.8	718	99.2	(0.16-11.30)	
	50+	Yes	0	-	22	100.0	-	
		No	4	1.5	271	98.5		
Year of AIDS diagnosis	1987-89	Yes	1	0.6	182	99.4	0.63	0.97
		No	10	0.9	1,143	99.1	(0.08-4.94)	(0.42-2.27)
								Breslow-Day‖:
	1990-92	Yes	5	2.8	177	97.2	1.09	$\chi^2_{df=1} = 0.231$
		No	49	2.5	1,887	97.5	(0.43-2.77)	p=0.631

continued

Table 5.6.2 continued (*page two of three*)

			Infected with hepatitis-A prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio[‡]	
Variable	Category	KS[†]	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted[§] (95% CI)
Mode of HIV trans-mission	Homo/bi-sexual men	Yes	6	1.9	311	98.1	1.10 (0.46-2.61)	0.86 (0.37-2.02) *Breslow-Day*‖: $\chi^2_{df=3} = 1.57$ p=0.667
		No	40	1.7	2,272	98.3		
	Intravenous drug abusers	Yes	0	-	9	100.0	-	
		No	4	2.0	193	98.0		
	Homo/bi-sexual men who were also intra-venous drug abusers	Yes	0	-	35	100.0	-	
		No	12	3.4	340	96.6		
	Adult hemophiliacs	Yes	0	-	0	-	-	
		No	0	-	29	100.0		
	Heterosexual contact	Yes	0	-	2	100.0	-	
		No	2	2.4	82	97.6		
	Transfusion or transplant recipients	Yes	0	-	0	-	-	
		No	1	1.8	54	98.2		
	Adults whose HIV risk factors were unknown	Yes	0	-	2	100.0	-	
		No	0	-	60	100.0		

continued

Table 5.6.2 continued (*page three of three*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ Adjusted by the corresponding variable listed in column one.

‖ Breslow-Day chi-squared (χ^2) test for homogeneity of odds ratios across strata of the adjustment variable (Breslow 1980, p 142). Note that strata with a value of zero in two or more cells did not contribute to the calculation of this statistic.

Table 5.6.3 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and time (in years) between the diagnosis of hepatitis-A and date of AIDS diagnosis. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Years between hepatitis-A diagnosis and the diagnosis of AIDS	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratios† Crude (95% CI)	Prevalence odds ratios† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No hepatitis-A	359	10.6	3,030	89.4	1.00 (reference)	1.00 (reference)
< 1 year	0	-	11	100.0	-	-
1+ years	6	11.1	48	88.9	1.06 (0.45-2.48)	1.21 (0.51-2.87)
(b) Eligible homosexual and bisexual male cohort members only						
No hepatitis-A	346	11.7	2,612	88.3	1.00 (reference)	1.00 (reference)
< 1 year	0	-	11	100.0	-	-
1+ years	6	12.8	41	87.2	1.11 (0.47-2.62)	1.31 (0.55-3.13)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission

Table 5.6.4 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with hepatitis-A to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Hepatitis-A infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	2,829	5,197.6	338	65.03	1.00	(reference)	1.00	(reference)
Infected	72	129.1	6	46.48	0.71	0.32-1.60	0.68	0.30-1.53
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	2,450	4,499.0	331	73.57	1.00	(reference)	1.00	(reference)
Infected	63	113.8	6	52.72	0.72	0.32-1.61	0.70	0.31-1.57

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 andwere registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.6.5 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between hepatitis-A infection and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between hepatitis-A infection and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No hepatitis-A	338	11.9	2,491	88.1	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	1	3.8	25	96.2	0.28 (0.04-1.99)	0.26 (0.04-1.84)
1+ years	5	10.9	41	89.1	1.08 (0.45-2.61)	1.06 (0.44-2.58)
(b) Eligible homosexual and bisexual male cohort members only						
No hepatitis-A	331	13.5	2,119	86.5	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	1	4.2	23	95.8	0.28 (0.04-1.97)	0.26 (0.04-1.84)
1+ years	5	12.8	34	87.2	1.11 (0.45-2.68)	1.06 (0.44-2.58)

continued

Table 5.6.5 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.7.1 Distribution of shigella infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with shigella†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	148	5.0	2,832	95.0	1.00	(reference)
	Intravenous drug abusers	1	0.5	209	99.5	0.09	0.01-0.66
	Homosexual or bisexual men who were also intravenous drug abusers	24	5.5	409	94.5	1.12	0.72-1.75
	Adult hemophiliacs	0	-	31	100.0	-∞	-
	Heterosexual contact	0	-	88	100.0	-∞	-
	Transfusion or transplant recipients	0	-	63	100.0	-∞	-
	Adults whose HIV risk factors were unknown	0	-	68	100.0	-∞	-

continued

Table 5.7.1 continued (*page two of two*)

Characteristic	Category	Ever infected with shigella†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	0	-	151	100.0	1.00	(reference)
	Male	173	4.7	3,549	95.3	∞	-
Age at AIDS diagnosis	20-29 years	24	3.2	728	96.8	1.00	(reference)
	30-39 years	91	4.8	1,797	95.2	1.54	0.97-2.43
	40-49 years	46	5.2	846	94.8	1.65	1.00-2.73
	50+ years	12	3.5	329	96.5	1.11	0.55-2.24
Year of AIDS diagnosis	1982-86	35	8.4	384	91.6	1.00	(reference)
	1987-89	66	4.9	1,270	95.1	0.57	0.37-0.87
	1990-92	72	3.4	2,046	96.6	0.39	0.25-0.59

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis (see text).

† Shigella infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.7.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immuno-deficiency syndrome (AIDS) and infection with shigella prior to AIDS diagnosis, selected members of the study cohort* *(page one of two)*

			Infected with shigella prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
All cases	Total	Yes	22	4.8	438	95.2	1.26	-
		No	131	3.8	3,282	96.2	(0.79-2.00)	
Sex	Male	Yes	22	4.8	437	95.2	1.20	*Not calculated*
		No	131	4.0	3,132	96.0	(0.76-1.91)	
	Female	Yes	0	-	1	100.0	-	
		No	0	-	150	100.0		
Age at AIDS diagnosis	20-29	Yes	1	1.2	84	98.8	0.48	1.23
		No	16	2.4	651	97.6	(0.06-3.70)	(0.78-1.96)
								Breslow-Day‖:
	30-39	Yes	14	5.8	228	94.2	1.45	$\chi^2_{df=3} = 1.251$
		No	67	4.1	1,579	95.9	(0.80-2.62)	p=0.741
	40-49	Yes	6	5.6	101	94.4	1.11	
		No	40	5.1	745	94.9	(0.46-2.68)	
	50+	Yes	1	3.9	25	96.1	1.54	
		No	8	2.5	307	97.5	(0.19-12.77)	
Year of AIDS diagnosis	1982-86	Yes	9	9.5	86	90.5	1.37	1.09
		No	23	7.1	301	92.9	(0.61-3.07)	(0.68-1.76)
								Breslow-Day‖:
	1987-89	Yes	8	4.4	175	95.6	1.05	$\chi^2_{df=2} = 0.515$
		No	48	4.2	1,105	95.8	(0.49-2.26)	p=0.773
	1987-92	Yes	5	2.8	177	97.2	0.88	
		No	60	3.1	1,876	96.9	(0.35-2.23)	

continued

Table 5.7.2 continued (*page two of two*)

			Infected with shigella prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio‡	
Variable	Category	KS†	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted§ (95% CI)
Mode of HIV transmission	Homo/bisexual men	Yes	22	4.9	424	95.1	1.13 (0.71-1.80)	*Not calculated*
		No	130	4.4	2,837	95.6		
	Other	Yes	0	-	14	100.0	-∞	
		No	1	0.2	445	99.8		

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ Adjusted by the corresponding variable listed in column one.

‖ Breslow-Day chi-squared (χ^2) test for homogeneity of odds ratios across strata of the corresponding adjustment variable (Breslow 1980, p 142). Note that strata with a value of zero in two or more cells did not contribute to the calculation of this statistic.

Table 5.7.3 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and the number of shigella episodes that preceded the diagnosis of AIDS. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Number of shigella episodes that preceded AIDS diagnosis	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratios† Crude (95% CI)	Prevalence odds ratios† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No shigella	438	11.8	3,282	88.2	1.00 (reference)	1.00 (reference)
One only	19	13.4	123	86.6	1.16 (0.71-1.90)	0.91 (0.55-1.50)
Two or more	3	27.3	8	72.7	2.81 (0.74-10.63)	2.06 (0.53-8.11)
(b) Eligible homosexual and bisexual male cohort members only						
No shigella	424	13.0	2,837	87.0	1.00 (reference)	1.00 (reference)
One only	19	13.5	122	86.5	1.04 (0.64-1.71)	0.91 (0.55-1.51)
Two or more	3	27.3	8	72.7	2.51 (0.66-9.49)	2.00 (0.51-7.89)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.7.4 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and time (in years) between the the most recent shigella episode and date of AIDS diagnosis. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only

Years between the most recent episode of shigella and the diagnosis of AIDS	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratios† Crude (95% CI)	Prevalence odds ratios† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No Shigella	438	11.8	3,282	88.2	1.00 (reference)	1.00 (reference)
< 1 year	2	10.5	17	89.5	0.88 (0.20-3.83)	0.60 (0.14-2.65)
1+ years	20	14.9	114	85.1	1.32 (0.81-2.14)	1.05 (0.64-1.72)
(b) Eligible homosexual and bisexual male cohort members only						
No shigella	424	13.0	2,837	87.0	1.00 (reference)	1.00 (reference)
< 1 year	2	10.5	17	89.5	0.79 (0.18-3.42)	0.61 (0.14-2.70)
1+ years	20	15.0	113	85.0	1.18 (0.73-1.93)	1.05 (0.64-1.72)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and who were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis (see text).

† Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‡ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.7.5 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with shigella to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Shigella infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	3,047	5,573.4	364	65.31	1.00	(reference)	1.00	(reference)
Infected	144	248.0	23	92.74	1.42	0.93-2.16	1.25	0.82-1.91
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	2,642	4,817.5	357	74.10	1.00	(reference)	1.00	(reference)
Infected	143	244.5	23	94.07	1.27	0.83-1.94	1.26	0.83-1.93

* The study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 3,191 cohort members who did not have KS prevalent at initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.7.6 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and the number of shigella episodes that preceded the date of last follow-up information*. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Number of shigella episodes that preceded the date of last follow-up information	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards‡ Crude (95% CI)	Proportional hazards‡ Adjusted§ (95% CI)
(a) All eligible cohort members						
No shigella	364	11.9	2,683	88.1	1.00 (reference)	1.00 (reference)
One only	22	16.4	112	83.6	1.46 (0.95-2.25)	1.32 (0.85-2.02)
Two or more	1	10.0	9	90.0	0.67 (0.09-4.79)	0.60 (0.09-4.30)
(b) Eligible homosexual and bisexual male cohort members only						
No shigella	357	13.5	2,285	86.5	1.00 (reference)	1.00 (reference)
One only	22	16.5	111	83.5	1.31 (0.85-2.01)	1.33 (0.86-2.04)
Two or more	1	10.0	9	90.0	0.59 (0.08-4.21)	0.62 (0.09-4.39)

continued

Table 5.7.6 continued (*page two of two*)

Footnotes

---

* Date of last follow-up information was defined as the date of KS diagnosis for those cohort members with KS, and the date of last follow-up information recorded in the HIV/AIDS Reporting System for cohort members without KS.

† The study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 3,191 cohort members who did not have KS prevalent at initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and had a valid entry for date of last follow-up information recorded in HARS (see text).

‡ Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

§ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.7.7 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between the most recent shigella episode and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between the most recent episode of shigella and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No shigella	364	11.9	2,683	88.1	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	3	8.8	31	91.2	0.81 (0.26-2.51)	0.71 (0.23-2.23)
1+ years	20	18.2	90	81.8	1.56 (0.99-2.45)	1.41 (0.90-2.22)
(b) Eligible homosexual and bisexual male cohort members only						
No shigella	357	13.5	2,285	86.5	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	3	8.8	31	91.2	0.71 (0.23-2.21)	0.74 (0.24-2.31)
1+ years	20	18.3	89	81.7	1.40 (0.89-2.20)	1.42 (0.90-2.22)

continued

Table 5.7.7 continued (*page two of two*)

Footnotes

---

* The study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 3,191 cohort members who did not have KS prevalent at initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.8.1 Distribution of salmonella infection among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

Characteristic	Category	Ever infected with salmonella†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Mode of HIV transmission	Homosexual or bisexual men	18	0.6	2,962	99.4	1.00	(reference)
	Intravenous drug abusers	5	2.4	205	97.6	4.01	1.48-10.92
	Homosexual or bisexual men who were also intravenous drug abusers	5	1.2	428	98.8	1.92	0.71-5.21
	Adult hemophiliacs	0	-	31	100.0	-	-
	Heterosexual contact	2	2.3	86	97.7	3.83	0.87-16.75
	Transfusion or transplant recipients	1	1.6	62	98.4	2.65	0.35-20.20
	Adults whose HIV risk factors were unknown	0	-	68	100.0	-	-

continued

Table 5.8.1 continued (*page two of two*)

Characteristic	Category	Ever infected with salmonella†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	2	1.3	149	98.7	1.00	(reference)
	Male	29	0.8	3,693	99.2	0.59	0.14-2.48
Age at AIDS diagnosis	20-29 years	8	1.1	744	98.9	1.00	(reference)
	30-39 years	14	0.7	1,874	99.3	0.70	0.29-1.66
	40-49 years	6	0.7	886	99.3	0.63	0.22-1.82
	50+ years	3	0.9	338	99.1	0.83	0.22-3.13
Year of AIDS diagnosis	1982-86	3	0.7	416	99.3	1.00	(reference)
	1987-89	14	1.1	1,322	98.9	1.47	0.42-5.14
	1990-92	14	0.7	2,104	99.3	0.92	0.26-3.23

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age and older at the time of AIDS diagnosis (see text).

† Salmonella infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.8.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immunodeficiency syndrome (AIDS) and infection with salmonella prior to AIDS diagnosis, selected members of the study cohort*

	Infected with salmonella prior to AIDS diagnosis				
	Yes		No		
KS†	No.	Pct.	No.	Pct.	Prevalence odds ratio‡
	(a) Analysis conducted under assumption A§				
Yes	0	-	460	100.0	-
No	12	0.3	3,401	99.7	
	(a) Analysis conducted under assumption B§				
Yes	2	0.4	458	99.6	0.99
No	15	0.4	3,398	99.6	(0.23-4.34)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,873 cohort members who were 20 years of age or older at the time of AIDS diagnosis (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Crude prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval

§ In this analysis, the date of salmonella infection was unknown for five cohort members, but was registered in the Washington State Communicable Disease Registry during the same calendar year as the date of AIDS diagnosis in each of these individuals. Therefore, it was not possible to determine if salmonella infection occurred before or after AIDS diagnosis. Under assumption A, none of these five cohort members were considered to have been infected with salmonella prior to AIDS diagnosis. Under assumption B, all five were considered to have been infected with salmonella prior to AIDS diagnosis (see text).

Table 5.8.3 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with salmonella to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Salmonella Infection Status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	3,160	5,783.9	383	66.22	1.00	(reference)	1.00	(reference)
Infected	31	37.5	4	106.67	1.61	0.60-4.31	1.73	0.65-4.64
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	2,762	5,036.2	376	74.66	1.00	(reference)	1.00	(reference)
Infected	23	25.8	4	155.04	2.08	0.78-5.56	1.88	0.70-5.04

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,191 cohort members who first developed KS following their initial AIDS diagnosis and were 20 years of age or older when diagnosed with AIDS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.8.4 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between the most recent salmonella episode and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between the most recent episode of salmonella and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No salmonella	383	12.1	2,777	87.9	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	3	13.6	19	86.4	1.86 (0.60-5.79)	2.20 (0.70-6.87)
1+ years	1	11.1	8	88.9	0.89 (0.13-6.35)	1.06 (0.15-7.54)
(b) Eligible homosexual and bisexual male cohort members only						
No salmonella	376	13.6	2,386	86.4	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	3	18.7	13	81.3	2.55 (0.82-7.94)	2.33 (0.75-7.29)
1+ years	1	14.3	6	85.7	1.09 (0.15-7.78)	1.18 (0.17-8.45)

continued

Table 5.8.4 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,191 cohort members who first developed KS following their initial AIDS diagnosis and were 20 years of age or older when diagnosed with AIDS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.9.1 Distribution of giardia infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with giardia†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	21	1.3	1,571	98.7	1.00	(reference)
	Intravenous drug abusers	1	0.7	143	99.3	0.52	0.07-3.92
	Homosexual or bisexual men who were also intravenous drug abusers	3	1.3	229	98.7	0.98	0.29-3.31
	Adult hemophiliacs	0	-	12	100.0	-	-
	Heterosexual contact	0	-	62	100.0	-	-
	Transfusion or transplant recipients	0	-	28	100.0	-	-
	Adults whose HIV risk factors were unknown	0	-	48	100.0	-	-

continued

Table 5.9.1 continued (*page two of two*)

Characteristic	Category	Ever infected with giardia†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	0	-	102	100.0	1.00	(reference)
	Male	25	1.2	1,991	98.8	-	-
Age at AIDS diagnosis	20-29 years	9	2.3	390	97.7	1.00	(reference)
	30-39 years	13	1.3	1,019	98.7	0.55	0.23-1.30
	40-49 years	3	0.6	514	99.4	0.25	0.07-0.94
	50+ years	0	-	170	100.0	-	-

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 2,118 cohort members who were 20 years of age and older at AIDS diagnosis and were diagnosed with AIDS during the period 1990-92 (see text).

† Giardia infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.9.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immunodeficiency syndrome (AIDS) and infection with giardia prior to AIDS diagnosis, selected members of the study cohort*

	Infected with giardia prior to AIDS diagnosis				
	Yes		No		
KS†	No.	Pct.	No.	Pct.	Prevalence odds ratio‡
	(a) Analysis conducted under assumption A§				
Yes	0	-	182	100.0	-
No	6	0.3	1,930	99.7	
	(a) Analysis conducted under assumption B§				
Yes	1	0.6	181	99.4	0.89
No	12	0.6	1,924	99.4	(0.12-6.85)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 2,118 cohort members who were 20 years of age or older at the time of AIDS diagnosis and were diagnosed with AIDS during the period 1990-92 (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Crude prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval

§ In this analysis, the date of giardia infection was unknown for seven cohort members, but was registered in the Washington State Communicable Disease Registry during the same calendar year as the date of AIDS diagnosis in each of these individuals. Therefore, it was not possible to determine if giardia infection occurred before or after AIDS diagnosis. Under assumption A, none of these seven cohort members were considered to have been infected with giardia prior to AIDS diagnosis. Under assumption B, all seven were considered to have been infected with giardia prior to AIDS diagnosis (see text).

Table 5.9.3 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with giardia to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Giardia infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	1,798	2,993.4	202	67.48	1.00	(reference)	1.00	(reference)
Infected	25	27.5	6	218.18	3.23	1.44-7.28	2.61	1.15-5.92
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	1,535	2,569.4	200	77.84	1.00	(reference)	1.00	(reference)
Infected	24	26.0	6	230.77	2.96	1.32-6.68	2.61	1.15-5.91

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 1,823 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS , were diagnosed with AIDS during the period 1990-92, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission and age at AIDS diagnosis

Table 5.10.1 Distribution of campylobacter infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with campylobacter†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	21	0.8	2,608	99.2	1.00	(reference)
	Intravenous drug abusers	0	-	206	100.0	-	-
	Homosexual or bisexual men who were also intravenous drug abusers	0	-	387	100.0	-	-
	Adult hemophiliacs	0	-	29	100.0	-	-
	Heterosexual contact	0	-	86	100.0	-	-
	Transfusion or transplant recipients	0	-	55	100.0	-	-
	Adults whose HIV risk factors were unknown	0	-	62	100.0	-	-

continued

Table 5.10.1 continued (*page two of two*)

Characteristic	Category	Ever infected with campylobacter†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	0	-	145	100.0	1.00	(reference)
	Male	21	0.6	3,288	99.4	-	-
Age at AIDS diagnosis	20-29 years	5	0.8	656	99.2	1.00	(reference)
	30-39 years	10	0.6	1,672	99.4	0.79	0.27-2.30
	40-49 years	4	0.5	810	99.5	0.65	0.17-2.42
	50+ years	2	0.7	295	99.3	0.89	0.17-4.61
Year of AIDS diagnosis	1987-89	7	0.5	1,329	99.5	1.00	(reference)
	1990-92	14	0.7	2,104	99.3	1.26	0.51-3.14

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† Campylobacter infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.10.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immunodeficiency syndrome (AIDS) and infection with campylobacter prior to AIDS diagnosis, selected members of the study cohort*

	Infected with campylobacter prior to AIDS diagnosis				
	Yes		No		
KS†	No.	Pct.	No.	Pct.	Prevalence odds ratio‡
	(a) Analysis conducted under assumption A§				
Yes	1	0.3	364	99.7	1.70
No	5	0.2	3,084	99.8	(0.20-14.54)
	(b) Analysis conducted under assumption B§				
Yes	2	0.6	363	99.4	2.43
No	7	0.2	3,082	99.8	(0.50-11.72)

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at the time of AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† KS prevalent at the time of AIDS diagnosis.

‡ Crude prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval

§ In this analysis, the date of campylobacter infection was unknown in three cohort members, but this infection was registered in the Washington State Communicable Disease Registry during the same calendar year as the date of AIDS diagnosis in each of these individuals. Therefore, it was not possible to determine if campylobacter infection occurred before or after AIDS diagnosis. Under assumption A, none of these three cohort members were considered to have been infected with campylobacter prior to AIDS diagnosis. Under assumption B, all three were considered to have been infected with campylobacter prior to AIDS diagnosis (see text).

Table 5.10.3 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with campylobacter to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Campylobacter infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
			(a.) All eligible cohort members					
Not infected	2,882	5,306.3	341	64.26	1.00	(reference)	1.00	(reference)
Infected	19	20.4	3	147.06	2.29	0.73-7.13	1.98	0.64-6.20
			(b.) Eligible homosexual and bisexual male cohort members					
Not infected	2,494	4,592.4	334	72.73	1.00	(reference)	1.00	(reference)
Infected	19	20.4	3	147.06	2.02	0.65-6.30	1.92	0.62-6.02

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.10.4 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between campylobacter infection and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members* and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between campylobacter infection and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards† Crude (95% CI)	Proportional hazards† Adjusted‡ (95% CI)
(a) All eligible cohort members						
No campylobacter	341	11.8	2,541	88.2	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	2	13.3	13	86.7	2.10 (0.52-8.45)	1.88 (0.47-7.60)
1+ years	1	25.0	3	75.0	2.64 (0.37-18.79)	2.22 (0.31-15.85)
(b) Eligible homosexual and bisexual male cohort members only						
No campylobacter	334	13.4	2,160	86.6	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	2	13.3	13	86.7	1.86 (0.46-7.47)	1.83 (0.45-7.41)
1+ years	1	25.0	3	75.0	2.34 (0.33-16.63)	2.13 (0.30-15.23)

continued

Table 5.10.4 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last follow-up information recorded in HARS (see text).

† Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.11.1 Distribution of entamoeba infections among selected members of the study cohort* by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

		Ever infected with entamoeba†					
		Yes		No			
Characteristic	Category	No.	Percent	No.	Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	16	0.6	2,613	99.4	1.00	(reference)
	Intravenous drug abusers	0	-	206	100.0	-	-
	Homosexual or bisexual men who were also intravenous drug abusers	1	0.3	386	99.7	0.42	0.06-3.20
	Adult hemophiliacs	0	-	29	100.0	-	-
	Heterosexual contact	0	-	86	100.0	-	-
	Transfusion or transplant recipients	0	-	55	100.0	-	-
	Adults whose HIV risk factors were unknown	0	-	62	100.0	-	-

continued

Table 5.11.1 continued (*page two of two*)

Characteristic	Category	Ever infected with entamoeba†				Odds ratio	95 percent confidence interval
		Yes		No			
		No.	Percent	No.	Percent		
Sex	Female	0	-	145	100.0	1.00	(reference)
	Male	17	0.5	3,292	99.5	-	-
Age at AIDS diagnosis	20-29 years	2	0.3	659	99.7	1.00	(reference)
	30-39 years	10	0.6	1,672	99.4	1.97	0.43-9.02
	40-49 years	5	0.6	809	99.4	2.04	0.39-10.53
	50+ years	0	-	297	100.0	-	-
Year of AIDS diagnosis	1987-89	10	0.8	1,326	99.2	1.00	(reference)
	1990-92	7	0.3	2,111	99.7	0.44	0.17-1.16

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age and older when diagnosed with AIDS and were diagnosed with AIDS during the period 1987-92 (see text).

† Entamoeba infection known to have occurred prior to the diagnosis of Kaposi's sarcoma (KS) in those cohort members with KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS.

Table 5.11.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immunodeficiency syndrome (AIDS) and infection with entamoeba prior to AIDS diagnosis, selected members of the study cohort*

	Infected with entamoeba prior to AIDS diagnosis			
	Yes		No	
KS†	No.	Pct.	No.	Pct.
Yes	0	-	460	100.0
No	9	0.3	3,404	99.7

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

† KS prevalent at the time of AIDS diagnosis.

Table 5.11.3 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with entamoeba to those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only

Entamoeba infection status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH)†	95 percent confidence interval for PH
(a.) All eligible cohort members								
Not infected	2,886	5,303.6	342	64.48	1.00	(reference)	1.00	(reference)
Infected	15	23.1	2	86.58	1.34	0.33-5.39	1.13	0.28-4.52
(b.) Eligible homosexual and bisexual male cohort members								
Not infected	2,498	4,589.7	335	72.99	1.00	(reference)	1.00	(reference)
Infected	15	23.1	2	86.58	1.19	0.30-4.76	1.12	0.28-4.50

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System (HARS). This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, were diagnosed with AIDS during the period 1987-92, and had a valid entry for date of last information recorded in HARS (see text).

† By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.12.1 Distribution of enteric infections* among selected members of the study cohort† by mode of human immunodeficiency virus (HIV) transmission, sex, age at diagnosis of the acquired immunodeficiency syndrome (AIDS), and year of AIDS diagnosis (*page one of two*)

Characteristic	Category	Ever infected with selected enteric agents*: Yes No.	Yes Percent	No No.	No Percent	Odds ratio	95 percent confidence interval
Mode of HIV transmission	Homosexual or bisexual men	236	9.0	2,393	91.0	1.00	(reference)
	Intravenous drug abusers	12	5.8	194	94.2	0.63	0.35-1.14
	Homosexual or bisexual men who were also intravenous drug abusers	43	11.1	344	88.9	1.27	0.90-1.79
	Adult hemophiliacs	0	-	29	100.0	-	-
	Heterosexual contact	4	4.7	82	95.3	0.50	0.18-1.36
	Transfusion or transplant recipients	2	3.6	53	96.4	0.38	0.09-1.58
	Adults whose HIV risk factors were unknown	0	-	62	100.0	-	-

continued

Table 5.12.1 continued (*page two of two*)

Characteristic	Category	Ever infected with selected enteric agents† — Yes: No.	Yes: Percent	No: No.	No: Percent	Odds ratio	95 percent confidence interval
Sex	Female	4	2.8	141	97.2	1.00	(reference)
	Male	293	8.9	3,016	91.1	3.42	1.26-9.32
Age at AIDS diagnosis	20-29 years	73	11.0	588	89.0	1.00	(reference)
	30-39 years	151	9.0	1,531	91.0	0.79	0.59-1.07
	40-49 years	57	7.0	757	93.0	0.61	0.42-0.87
	50+ years	16	5.4	281	94.6	0.46	0.26-0.80
Year of AIDS diagnosis	1987-89	180	8.5	1,938	91.5	1.00	(reference)
	1990-92	117	8.8	1,219	91.2	0.97	0.76-1.24

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *entamoeba histolytica*, *campylobacter spp.*, and *giardia spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

Table 5.12.2 Association between Kaposi's sarcoma (KS) prevalent at the diagnosis of acquired immuno-deficiency syndrome (AIDS) and infection with selected enteric agents* prior to AIDS diagnosis, selected members of the study cohort† *(page one of three)*

			Infected with selected enteric agents* prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio§	
Variable	Category	KS‡	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted‖ (95% CI)
All cases	Total	Yes	20	5.5	345	94.5	0.88	-
		No	191	6.2	2,898	93.8	(0.55-1.41)	
Sex	Male	Yes	20	5.5	344	94.5	0.85	0.85
		No	188	6.4	2,757	93.6	(0.53-1.37)	(0.53-1.37)
								Breslow-Day¶:
	Female	Yes	0	-	1	100.0	-	$\chi^2_{df=1} = 0.018$
		No	3	2.1	141	97.9		p= 0.893
Age at AIDS diagnosis	20-29	Yes	3	4.6	62	95.4	0.71	0.87
		No	38	6.4	558	93.6	(0.21-2.37)	(0.54-1.39)
								Breslow-Day¶:
	30-39	Yes	12	6.4	176	93.6	0.97	$\chi^2_{df=3} = 0.515$
		No	98	6.6	1,396	93.4	(0.52-1.81)	p= 0.916
	40-49	Yes	4	4.4	86	95.6	0.70	
		No	45	6.2	679	93.8	(0.25-2.00)	
	50+	Yes	1	4.6	21	95.4	1.26	
		No	10	3.6	265	96.4	(0.15-10.34)	
Year of AIDS diagnosis	1987-89	Yes	9	4.9	174	95.1	0.84	0.89
		No	67	5.8	1,086	94.2	(0.41-1.71)	(0.56-1.44)
								Breslow-Day¶:
	1990-92	Yes	11	6.0	171	94.0	0.94	$\chi^2_{df=1} = 0.055$
		No	124	6.4	1,812	93.6	(0.50-1.78)	p= 0.815

continued

Table 5.12.2 continued (*page two of three*)

			Infected with selected enteric agents* prior to AIDS diagnosis					
			Yes		No		Prevalence odds ratio[§]	
Variable	Category	KS[‡]	No.	Pct.	No.	Pct.	Crude (95% CI)	Adjusted[‖] (95% CI)
Mode of HIV trans-mission	Homo/bi-sexual men	Yes	19	6.0	298	94.0	0.91 (0.55-1.48)	0.82 (0.51-1.32) *Breslow-Day*¶: $\chi^2_{df=3} = 1.26$ $p = 0.738$
		No	152	6.6	2,160	93.4		
	Intravenous drug abusers	Yes	0	-	9	100.0	-	
		No	7	3.6	190	96.5		
	Homo/bi-sexual men who were also intra-venous drug abusers	Yes	1	2.9	34	97.1	0.34 (0.05-2.58)	
		No	28	8.0	324	92.0		
	Adult hemophiliacs	Yes	0	-	0	-	-	
		No	0	-	29	100.0		
	Heterosexual contact	Yes	0	-	2	100.0	-	
		No	3	3.6	81	96.4		
	Transfusion or transplant recipients	Yes	0	-	0	-	-	
		No	1	1.8	54	98.2		
	Adults whose HIV risk factors were unknown	Yes	0	-	2	100.0	-	
		No	0	-	60	100.0		

continued

Table 5.12.2 continued (*page three of three*)

Footnotes

---

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *entamoeba histolytica*, *campylobacter spp.*, and *giardia spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

‡ KS prevalent at the time of AIDS diagnosis.

§ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

‖ Adjusted by the corresponding variable listed in column one.

¶ Breslow-Day chi-squared (χ^2) test for homogeneity of odds ratios across strata of the corresponding adjustment variable (Breslow 1980, p 142). Note that strata with a value of zero in two or more cells did not contribute to the calculation of this statistic.

Table 5.12.3 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and the number of episodes of selected enteric infections* that preceded the diagnosis of AIDS. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only *(page one of two)*

Number of episodes of selected enteric infections* that preceded AIDS diagnosis	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratio‡: Crude (95% CI)	Prevalence odds ratio‡: Adjusted§ (95% CI)
(a) All eligible cohort members						
No such infections	345	10.6	2,898	89.4	1.00 (reference)	1.00 (reference)
One only	19	9.7	176	90.3	0.91 (0.56-1.48)	0.84 (0.52-1.37)
Two or more	1	6.3	15	93.7	0.56 (0.07-4.25)	0.55 (0.07-4.18)
(b) Eligible homosexual and bisexual male cohort members only						
No such infections	332	11.8	2,484	88.2	1.00 (reference)	1.00 (reference)
One only	19	10.3	165	89.7	0.86 (0.53-1.40)	0.86 (0.53-1.40)
Two or more	1	6.3	15	93.8	0.50 (0.07-3.79)	0.55 (0.07-4.21)

continued

Table 5.12.3 continued *(page two of two)*

Footnotes

---

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *entamoeba histolytica*, *campylobacter spp.*, and *giardia spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.12.4 Association between Kaposi's sarcoma (KS) prevalent at the time of acquired immunodeficiency syndrome (AIDS) diagnosis and time (in years) between the most recent episode of enteric infection* and date of AIDS diagnosis. Prevalence odds ratios and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between the most recent episode of enteric infection* and the diagnosis of AIDS	KS prevalent at time of AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Prevalence odds ratio‡: Crude (95% CI)	Prevalence odds ratio‡: Adjusted§ (95% CI)
(a) All eligible cohort members						
No such infection	345	10.6	2,898	89.4	1.00 (reference)	1.00 (reference)
< 1 year	1	3.2	30	96.8	0.28 (0.04-2.06)	0.25 (0.03-1.81)
1+ years	19	10.6	161	89.4	0.99 (0.61-1.62)	0.93 (0.57-1.53)
(b) Eligible homosexual and bisexual male cohort members only						
No such infection	332	11.8	2,484	88.2	1.00 (reference)	1.00 (reference)
< 1 year	1	3.3	29	96.7	0.26 (0.04-1.90)	0.24 (0.03-1.78)
1+ years	19	11.2	151	88.8	0.94 (0.58-1.54)	0.96 (0.59-1.57)

continued

Table 5.12.4 continued (*page two of two*)

Footnotes

---

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *entamoeba histolytica*, *campylobacter spp.*, and *giardia spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 3,454 cohort members who were 20 years of age or older at AIDS diagnosis and were diagnosed with AIDS during the period 1987-92 (see text).

‡ Prevalence odds ratio and, in parentheses, corresponding 95 percent confidence interval (CI).

§ By logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission.

Table 5.12.5 Occurrence of Kaposi's sarcoma (KS) following the initial diagnosis of acquired immunodeficiency syndrome (AIDS) among selected members of the study cohort*, comparing those infected with one or more enteric infections† and those with no such infection. Separate analyses of (a) all eligible cohort members and (b) eligible homo/bisexual male cohort members only. *(page one of two)*

Enteric disease infection† status	No. eligible cohort members	Person-years of post-AIDS follow-up	No. KS cases diagnoses post-AIDS	Crude incidence rate (per 1,000 person-years)	Incidence rate ratio (RR)	95 percent confidence interval for RR	Proportional hazards (PH) ‡	95 percent confidence interval for PH
(a.) All eligible cohort members								
Not infected	2,634	4,881.6	307	62.89	1.00	(reference)	1.00	(reference)
Infected	267	445.1	37	83.13	1.32	0.94-1.86	1.21	0.86-1.70
(b.) Eligible homosexual and bisexual male cohort members								
Not infected	2,264	4,198.2	300	71.46	1.00	(reference)	1.00	(reference)
Infected	249	414.6	37	89.24	1.25	0.89-1.76	1.23	0.87-1.73

Table 5.12.5 continued (*page two of two*)

Footnotes

---

* The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and were diagnosed with AIDS during the period 1987-92 (see text).

† Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *giardi spp.*, *entamoeba histolytica*, and *campylobacter spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

‡ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.12.6 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and the number of episodes of enteric infection* that preceded the date of last follow-up information†. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members‡ and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Number of episodes of enteric infection* that preceded the date of last follow-up information	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards§ Crude (95% CI)	Proportional hazards§ Adjusted‖ (95% CI)
(a) All eligible cohort members						
No such infection	307	11.7	2,327	88.3	1.00 (reference)	1.00 (reference)
One only	34	14.4	202	85.6	1.39 (0.97-1.98)	1.28 (0.90-1.82)
Two or more	3	9.7	28	90.3	0.81 (0.26-2.53)	0.75 (0.24-2.35)
(b) Eligible homosexual and bisexual male cohort members only						
No such infection	300	13.3	1,964	86.7	1.00 (reference)	1.00 (reference)
One only	34	15.5	185	84.5	1.32 (0.93-1.89)	1.30 (0.91-1.85)
Two or more	3	10.0	27	90.0	0.73 (0.24-2.29)	0.77 (0.25-2.41)

continued

Table 5.12.6 continued (*page two of two*)

Footnotes

---

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *giardi spp.*, *entamoeba histolytica*, and *campylobacter spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† Date of last follow-up information was defined as the date of KS diagnosis for those cohort members with KS, and the date of last follow-up information recorded in the HIV/AIDS Reporting System for cohort members not known to have had KS.

‡ The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and were diagnosed with AIDS during the period 1987-92 (see text).

§ Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

‖ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.12.7 Association between Kaposi's sarcoma (KS) that occurred after diagnosis of the acquired immunodeficiency syndrome (AIDS) and time (in years) between the most recent episode of enteric infection* and date of AIDS diagnosis. Proportional hazards and 95 percent confidence intervals (CI) from separate analyses of (a) all eligible cohort members† and (b) eligible homo/bisexual male cohort members only (*page one of two*)

Years between the most recent episode of enteric infection* and the diagnosis of AIDS	KS occurred following the initial AIDS diagnosis: Yes No.	Yes Pct.	No No.	No Pct.	Proportional hazards‡ Crude (95% CI)	Proportional hazards‡ Adjusted§ (95% CI)
(a) All eligible cohort members						
No such infection	307	11.7	2,327	88.3	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	16	13.3	104	86.7	1.36 (0.82-2.26)	1.26 (0.76-2.10)
1+ years	21	14.3	126	85.7	1.27 (0.82-1.98)	1.17 (0.75-1.82)
(b) Eligible homosexual and bisexual male cohort members only						
No such infection	300	13.3	1,964	86.7	1.00 (reference)	1.00 (reference)
<1 year and post-AIDS	16	14.3	96	85.7	1.30 (0.78-2.15)	1.29 (0.77-2.14)
1+ years	21	15.3	116	84.7	1.20 (0.77-1.87)	1.19 (0.76-1.85)

continued

Table 5.12.7 continued (*page two of two*)

Footnotes

---

* Enteric agents included any of the following pathogens for which surveillance data were available from the Washington State Communicable Disease Registry: *salmonella spp.*, *shigella spp.*, hepatitis-A virus, *giardi spp.*, *entamoeba histolytica*, and *campylobacter spp.*. This analysis was based on infections that occurred prior to the date of KS diagnosis in those cohort members who had KS, or prior to the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those cohort members not known to have had KS (see text).

† The full study cohort included 3,899 residents of 13 counties in northwest Washington state who were diagnosed with AIDS during the period 1982-92 and were registered in the HIV/AIDS Reporting System. This analysis was restricted to 2,901 cohort members who did not have KS prevalent at the time of initial AIDS diagnosis, were 20 years of age or older when diagnosed with AIDS, and were diagnosed with AIDS during the period 1987-92 (see text).

‡ Proportional hazards and, in parentheses, corresponding 95 percent confidence intervals (CI).

§ By Cox proportional hazards model, simultaneously adjusted for mode of HIV transmission, age at AIDS diagnosis, and year of AIDS diagnosis.

Table 5.13.1 Summary of results from an analysis of the risk of Kaposi's sarcoma (KS) at the time of acquired immunodeficiency syndrome (AIDS) diagnosis, comparing those with and without prior episodes of infection with selected communicable pathogens* (*page one of two*)

Communicable pathogen	Crude POR†	No. episodes of infection prior to AIDS diagnosis‡			Time period between the most recent episode of infection and the diagnosis of AIDS‡		
		None	One	Two or more	None	<1 year	1+ years
Treponema pallidum (syphilis)	1.11 (0.84-1.48)	1.00 (reference)	0.91 (0.66-1.27)	1.09 (0.62-1.89)	1.00 (reference)	1.10 (0.37-3.23)	0.94 (0.69-1.27)
Hepatitis-B virus	1.17 (0.53-2.59)	1.00 (reference)	1.17 (0.53-2.59)	*No multiple episodes*§	1.00 (reference)	4.35 (0.78-24.14)	0.93 (0.37-2.37)
Enteric pathogens							
All (combined)	0.88 (0.55-1.41)	1.00 (reference)	0.84 (0.52-1.37)	0.55 (0.07-4.18)	1.00 (reference)	0.25 (0.03-1.81)	0.93 (0.57-1.53)
Hepatitis-A virus	0.86 (0.37-2.00)	1.00 (reference)	0.86 (0.37-2.00)	*No multiple episodes*§	1.00 (reference)	- (0/11)‖	1.21 (0.51-2.87)
Shigella spp.	1.26 (0.79-2.00)	1.00 (reference)	0.91 (0.55-1.50)	2.06 (0.53-8.11)	1.00 (reference)	0.60 (0.14-2.65)	1.05 (0.64-1.72)
Salmonella spp.	0.99 (0.23-4.34)	*Too few cases*¶	-	-	*Too few cases*¶	-	-
Giardia spp.	0.89 (0.12-6.85)	*Too few cases*¶	-	-	*Too few cases*¶	-	-

continued

Table 5.13.1 continued (*page two of two*)

Communicable pathogen	Crude POR†	No. episodes of infection prior to AIDS diagnosis‡			Time period between the most recent episode of infection and the diagnosis of AIDS‡		
		None	One	Two or more	None	<1 year	1+ years
Enteric pathogens (*continued*)							
Campylobacter spp.	1.70 (0.20-14.54)	1.00 (reference)	1.70 (0.20-14.54)	*No multiple episodes*§	*Too few cases*¶	-	-
Entamoeba histolytica	- (0/460)**	*Too few cases*¶	-	*No multiple episodes*§	*Too few cases*¶	-	-

* Summary of analyses based on all eligible cohort members, as described in Sections 5.4-5.12 (see text).

† Crude (unadjusted) prevalence odds ratio (POR) and, in parentheses, corresponding 95 percent confidence interval.

‡ Prevalence odds ratio obtained by logistic regression, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission. Corresponding 95 percent confidence interval in parentheses.

§ No multiple episodes of infection were documented among cohort members for the following pathogens: Hepatitis-B virus, hepatitis-A virus, *campylobacter spp.*, and *entamoeba histolytica* (see text).

‖ None of the eleven cohort members who were infected with hepatitis-A virus in the year prior to AIDS diagnosis were known to have had KS.

¶ Too few KS cases were available within some strata to reasonably conduct this analysis.

** None of 460 cohort members with KS prevalent at the time of initial AIDS diagnosis had been previously infected with *entamoeba histolytica*.

Table 5.13.2 Summary of results from an analysis comparing the risk of developing KS following initial AIDS diagnosis between those with and without prior infections with selected communicable pathogens* (*page one of two*)

Communicable pathogen	Crude rate ratio†	Adjusted proportional hazards‡	No. episodes of infection prior to date of last information§			Time period between the most recent episode of infection and the diagnosis of AIDS‡		
			None	One	Two or more	None	<1 year and post-AIDS	1+ years
Treponema pallidum (syphilis)	1.55 (1.20-2.01)	1.53 (1.18-1.99)	1.00 (reference)	1.43 (1.07-1.93)	1.93 (1.19-3.13)	1.00 (reference)	2.51 (1.44-4.38)	1.40 (1.05-1.86)
Hepatitis-B virus	0.54 (0.17-1.69)	0.54 (0.17-1.68)	1.00 (reference)	0.54 (0.17-1.68)	*No multiple episodes*¶	1.00 (reference)	- (0/7)¶	0.58 (0.19-1.81)
Enteric pathogens								
All (combined)	1.32 (0.94-1.86)	1.21 (0.86-1.70)	1.00 (reference)	1.28 (0.90-1.82)	0.75 (0.24-2.35)	1.00 (reference)	1.26 (0.76-2.10)	1.17 (0.75-1.82)
Hepatitis-A virus	0.71 (0.32-1.60)	0.68 (0.30-1.53)	1.00 (reference)	0.68 (0.30-1.53)	*No multiple episodes*¶	1.00 (reference)	0.26 (0.04-1.84)	1.06 (0.44-2.58)
Shigella spp.	1.42 (0.93-2.16)	1.25 (0.82-1.91)	1.00 (reference)	1.32 (0.85-2.02)	0.60 (0.09-4.30)	1.00 (reference)	0.71 (0.23-2.23)	1.41 (0.90-2.22)
Salmonella spp.	1.61 (0.60-4.31)	1.73 (0.65-4.64)	*Too few cases***	-	-	1.00 (reference)	2.20 (0.70-6.87)	1.06 (0.15-7.54)
Giardia spp.	3.23 (1.44-7.28)	2.61 (1.15-5.92)	*Too few cases***	-	-	*Too few cases***	-	-

continued

Table 5.13.2 continued (*page two of two*)

Communicable pathogen	Crude rate ratio	Adjusted proportional hazards	No. episodes of infection prior to date of last information§			Time period between the most recent episode of infection and the diagnosis of AIDS‡		
			None	One	Two or more	None	<1 year and post-AIDS	1+ years
Enteric pathogens (*continued*)								
Campylobacter spp.	2.29 (0.73-7.13)	1.98 (0.64-6.20)	1.00 (reference)	1.98 (0.64-6.20)	*No multiple episodes*‖	1.00 (reference)	1.88 (0.47-7.60)	2.22 (0.31-15.85)
Entamoeba histolytica	1.34 (0.33-5.39)	1.13 (0.28-4.52)	1.00 (reference)	1.13 (0.28-4.52)	*No multiple episodes*‖	*Too few cases***	-	-

* Summary of analyses based on all eligible cohort members, as described in Sections 5.4-5.12 (see text).

† Crude (unadjusted) rate ratio and, in parentheses, corresponding 95 percent confidence interval.

‡ Cox proportional hazards, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission. Corresponding 95 percent confidence interval in parentheses.

§ Date of last information was the date of KS diagnosis for cohort members with KS, or the date of last follow-up information as recorded in the HIV/AIDS Reporting System for those with no KS. Cox proportional hazards, simultaneously adjusted for age at AIDS diagnosis, year of AIDS diagnosis, and mode of HIV transmission. Corresponding 95 percent confidence interval in parentheses.

‖ No multiple episodes of infection were documented among cohort members for the following pathogens: Hepatitis-B virus, hepatitis-A virus, *campylobacter spp.*, and *entamoeba histolytica* (see text).

¶ None of the seven cohort members diagnosed with hepatitis-B virus infection in the year prior to AIDS diagnosis or after AIDS diagnosis were known to have had KS.

** Too few KS cases were available within some strata to reasonably conduct this analysis.

Chapter 6

Discussion

6.1 Historical context of this investigation

Within the first decade of the AIDS epidemic in the United States, a compelling body of evidence had emerged to suggest that Kaposi's sarcoma (KS) in people with AIDS was caused by a sexually transmitted agent[1]. The cornerstone of this evidence was AIDS surveillance data from the Centers for Disease Control and Prevention which showed that, among people with AIDS in the United States, KS occurred almost exclusively among homosexual and bisexual men (Beral 1990). In contrast, relatively few episodes of KS were documented among people with AIDS who contracted HIV by means other than sexual contact. There was also evidence that, among people with AIDS, the risk of KS was greatest in large urban centers with a high prevalence of HIV infection[2]. Similar patterns of KS occurrence were observed in the United Kingdom, where homosexual and bisexual men also accounted for a disproportionate number of KS cases diagnosed among people with AIDS (Beral 1991b). Further, homosexual men in the United Kingdom whose likely source of HIV infection came from the United States or Africa were at greater risk for developing KS than those whose likely source of HIV infection was domestic (Beral 1991b).

---

[1] This evidence is presented in detail in Chapter 1, and is briefly summarized here.

[2] Beral referred to these areas as "epi-centers" of the AIDS epidemic in the United States (i.e., New York, Los Angeles, and San Francisco), and hypothesized that the prevalence of the putative etiologic agent of KS was highest in these areas.

Most of the numerous investigations that examined potential risk factors for KS among people with AIDS have included components to assess possible associations between KS and level of sexual activity[3], as well as associations between KS and specific sexual behaviors[4] and pathogens. Most of these studies have reported a positive association between KS and high levels of sexual activity (i.e., frequency of sex and number of sex partners), but no single type of sexual act has been consistently associated with an increased risk of KS. Although a variety of specific pathogens have been linked with KS, including cytomegalovirus (Drew 1982) and human papilloma virus (Huang 1992), for more than a decade after the advent of the AIDS epidemic, no single agent consistently emerged as a possible etiologic agent of KS.

Such was the general state of knowledge at the time the present investigation was conceived in 1992-93. The investigators recognized that a system of well-established, population-based registries of HIV/AIDS, cancer, and communicable diseases in western Washington state could be linked to examine possible associations between selected pathogens and the development of KS among people with AIDS[5]. This approach was felt to have two advantages over previous studies. First, information in the various

---

[3] For example, frequency of sexual contact, number of sexual partners within a specified time period, and whether or not one's sexual partners were casual or long-term acquaintances.

[4] These investigations usually examined the association between KS and one or more of the following sexual behaviors: oral-genital contact, anal-genital contact, oral-anal contact ("rimming"), and "fisting" (vernacular term to describe the practice of inserting a hand (and, in some cases, a portion of the forearm) into a partners anus).

[5] We also saw opportunities to further characterize the occurrence of various cancers among people with AIDS through linkage of the Cancer Surveillance System and the HIV/AIDS Reporting System.

surveillance systems was based on relatively objective case reports with laboratory confirmation. Second, in contrast to studies based on case-series and self-selected participants in epidemiologic studies, the combined disease registries in Washington state offered information on a relatively large, population-based study cohort.

6.2 The discovery of Kaposi's sarcoma-associated herpesvirus and implications for interpreting results from the present study

While the present study was in its early stages, Yuan Chang and her colleagues first reported evidence for a novel herpesvirus that was identified from KS tissue (Chang 1994). Subsequent studies found that this virus, referred to as Kaposi's sarcoma-associated herpesvirus (KSHV) and classified as human herpesvirus 8 (HHV8), was highly associated with all forms of KS[6], but was rarely found in persons without the disease (Chang 1996). KSHV has since been isolated and grown in culture (Renne 1996, Foreman 1997), and much of its genome has been mapped (Russo 1996)[7]. Prospective studies of individuals without KS found that the presence of KSHV was highly predictive of subsequent development of KS (Whitby 1995, Moore 1996b, Gao 1996a, Martin 1998, Melbye 1998, Grulich 1999). Studies that have employed serologic tests for KSHV infection have also documented that the prevalence of KSHV infection closely mirrors

---

[6] That is, AIDS-associated KS, African endemic KS, classic KS, and KS in patients who have been iatrogenically immunosuppressed (see Section 1.2).

[7] The HHV8 genome has been shown to include DNA sequences that may have oncogenic potential, as summarized in Section 1.3.

the occurrence of KS in groups at high and low risk of KS (Kedes 1996, Martin 1998, Melbye 1998, Grulich 1999). At present, the accumulated evidence strongly supports a role for KSHV in the etiology of KS.

Results from this investigation must be interpreted in the context of KSHV as a likely etiologic agent of KS. Thus, an association between KS and prior infection with a specific pathogen may indicate that KSHV and the specific pathogen share a common mode of transmission. Similarly, a lack of association between KS and a specific pathogen may indicate that KSHV and the specific pathogen are not transmitted in the same manner. Alternatively, a positive association between KS and a specific pathogen may be interpreted as evidence that the pathogen is a co-factor with KSHV in the development of KS. For example, infection with some sexually transmitted agents is believed to enhance susceptibility to HIV infection (Hitchcock 1999, Cohen 1998, Anderson 1988, Stamm 1988). Although speculative, it is plausible that a co-factor may similarly facilitate the transmission of KSHV.

6.3 Study design and analytic approaches

An ideal study of this type would have followed a group of HIV-infected individuals forward in time from their initial HIV infection, comparing the rates of KS among those previously infected with the pathogens of interest to those not so infected. At the time of this investigation, however, the State of Washington had not conducted routine surveillance of all HIV-infected individuals. Therefore, the study cohort was

limited to the subset of HIV-infected individuals who progressed to AIDS during the period 1982-92[8]. In the absence of knowledge regarding the date of HIV seroconversion, we conducted a cross sectional analysis to determine if the infectious agents of interest were associated with KS as an AIDS-defining event. As a second approach, we also examined associations between infection with selected pathogens and the subsequent development of KS among HIV-infected individuals whose AIDS defining illnesses did not include KS. Both approaches have limitations, as summarized in the following paragraphs.

Section 6.4 Associations between selected pathogens and Kaposi's sarcoma that occurred at AIDS diagnosis

None of the eight communicable agents examined in this investigation were associated with the presence of KS at the time of initial AIDS diagnosis. In contrast, we found modest associations between some pathogens and KS that occurred following AIDS diagnosis. Discrepancies between the results from the two analyses are probably explained by limitations inherent in the analyses performed to calculate prevalence odds ratios (POR). By definition, the POR compares cases of a disease at a given point (or period) in time with those who do not have the disease at the same time (or during the same period). A potential limitation of this study design is that the comparison group

[8] During this period, a majority of HIV-infected individuals eventually developed AIDS. Unfortunately, we had no available information to evaluate whether factors that influence progression to AIDS were associated with the outcome or exposures of interest.

may include a substantial proportion of individuals who are in the process of developing the disease of interest. If a given exposure is truly associated with the disease of interest, the POR may minimize the exposure-disease association if a substantial number individuals in the control group eventually succumb to the disease. Such was the case in this investigation, where the comparison group in the POR analysis (i.e., those cohort members without KS prevalent at AIDS diagnosis) included a sizable number of individuals who went on to develop KS following the initial AIDS diagnosis. Thus, associations between KS and some communicable pathogens that were observed in the analysis of post-AIDS KS may have been underestimated in the POR analysis.

The remainder of this chapter focuses on results from our analysis of KS that occurred following the initial diagnosis of AIDS.

6.5 Associations between selected pathogens and Kaposi's sarcoma that occurred following AIDS diagnosis

We found a modest, positive association between prior infection with *treponema pallidum* (i.e., syphilis) and KS that occurred following the initial diagnosis of AIDS. Results from previous studies that examined the association between KS and prior episodes of syphilis have been inconsistent. A case-control study, conducted with a small number of participants near the beginning of the AIDS epidemic, found a modest association between prior episodes of syphilis and KS (OR=2.4, $p>0.05$, confidence interval not reported) (Marmor 1982). In a cohort of HIV-positive homosexual men in

British Columbia, Archibald et al. (1990) reported an increased risk of KS in those who self-reported prior syphilis infection compared to those not so infected (OR=2.4, 95 percent confidence interval=0.8-6.5). In an Australian cohort of HIV-positive individuals, KS and a history of syphilis were also positively associated (OR=1.48, 95 percent confidence interval=0.79-2.77) (Grulich 1997). However, no association between KS and syphilis was found in other studies of people with AIDS (Goedert 1987, Lifson 1990a, Lifson 1990b, Jacobsen 1990).

We did not observe a statistically significant association between HBV infection and KS that occurred after AIDS diagnosis. In the United States, sexual contact is the most common mode of HBV transmission (Hollinger 1996, Moyer 1994), especially among homosexual and bisexual men (Schreeder 1982). Thus, the absence of a positive association between KS and prior HBV infection contrasts with the association between KS and syphilis described in the previous paragraphs. Some earlier studies reported a positive association between KS and a history of hepatitis-B infection (Marmor 1984, Goedert 1987), although another did not (Jacobsen 1990).

We observed a modest, positive association between KS that occurred following initial AIDS diagnosis and prior infection with one or more enteric pathogens (RR=1.32, 95 percent CI=0.94-1.86) (Section 5.12). When considered separately, an elevated risk of KS was observed for five of the six enteric pathogens that we examined. However, most of the positive associations were modest and all were based on a small number of infected

individuals. HAV was the enteric infection considered that was not associated with an increased risk of KS (RR=0.71. 95 percent confidence interval 0.32-1.60).

These results are discussed in the context of previous studies in Section 6.7.

Section 6.6 Potential limitations of this investigation

The quality of data collection in the participating registries could influence results from this investigation. Incomplete surveillance in one or more of the participating disease registries and/or inability to collect and accurately record key data items may have resulted in biases that could influence the results reported here. Biases could also have been introduced through the record linkage process that was employed to combine data from the various sources. These potential limitations are summarized in the following paragraphs.

6.6.a Selection bias due to incomplete AIDS surveillance

Rothman and Greenland (1998) define selection bias as "distortions [in the measure of association] that result from procedures used to select subjects and from factors that influence study participation." The study cohort for this investigation was defined as all residents of western Washington state who were diagnosed with AIDS during the period 1982-92, as identified through the records in HARS. Incomplete AIDS surveillance could be a potential source of selection bias if (1) potential members of the study cohort were not registered in HARS, and (2) the relationship between exposure and

outcome in the unregistered individuals differed from those who were registered. The presence, direction, and magnitude of such selection bias in the present study is unknown. However, evidence from two sources suggests that such bias was likely to have been minimal. First, previous studies have consistently documented a high level of completeness of AIDS surveillance in Washington state (see Section 2.4). An added benefit of such studies is that they identified AIDS cases not previously registered in HARS and, therefore, contributed to the completeness of AIDS surveillance. Second, results from the linkage of HARS and CSS identified few individuals with AIDS-associated KS who were registered in CSS but not in HARS. Since registration of AIDS-related KS in the CSS was independent of registration of individuals in HARS, this finding provides further evidence of the completeness of AIDS surveillance in western Washington state. Further, we consider it unlikely that the association between KS and the pathogens of interest among the few AIDS cases who may not have been registered in HARS would have been substantially different from those registered in HARS. For these reasons, the possible effects of selection bias were probably minimal and were unlikely to have appreciably influenced the results of this investigation.

6.6.b Information bias due to incomplete surveillance of cancer and/or communicable diseases

Information bias can occur when there are errors in the measurement of subjects (Rothman 1998). In the present study, we were concerned with possible misclassification of (1) the outcome of interest (i.e., KS), (2) the exposures of interest (i.e., the eight communicable diseases examined in Chapter 5), and (3) variables representing characteristics of the study cohort that were simultaneously associated with both exposure and outcome and, thus, may have confounded our interpretation of the association between exposure and outcome[9].

Incomplete surveillance by the participating disease registries could have resulted in information bias in the same manner that it may have contributed to selection bias, as described in the previous paragraphs. Thus, cohort members whose KS was undetected by both HARS and CSS would have been incorrectly classified as not having this disease. We anticipate that the combined resources of CSS and HARS identified the vast majority of KS cases that occurred among cohort members. It is also unlikely that the association between KS and the selected pathogens of interest differed between those KS cases identified in the research data base and those KS cases that may have been missed by both registries. Thus, the likelihood for misclassification of the outcome of interest (i.e., KS) is low and would likely have had little effect on the observed associations.

---

[9] Potential confounding factors examined in this investigation included mode of HIV transmission, sex, age at AIDS diagnosis, and year of AIDS diagnosis.

Similarly, cohort members whose prior infection with one or more communicable pathogens was not documented in the WSSR or WSCDR may have been incorrectly classified with respect to the exposures of interest. Fortunately, syphilis surveillance is believed to be virtually complete for residents of Washington state (see Section 2.6), which would minimize the potential for misclassification of infection with *treponema pallidum*. It is also unlikely that the association between KS and syphilis observed in those cohort members whose syphilis infection may have been undetected would have differed from those cohort members who syphilis was registered in WSSR. Therefore, misclassification of syphilis among cohort members was probably minimal, and would have had little effect on the results from this investigation.

In contrast, available evidence suggests a high potential for underreporting of the infectious agents of interest, other than syphilis. Prior studies have documented major gaps in routine surveillance for some communicable diseases (Marier 1977, Kimbal 1980, Vogt 1983). For example, Marier (1977) estimated the completeness of coverage in Washington, DC, to be 11 percent for viral hepatitis, 42 percent for salmonellosis, and 62 percent for shigellosis. Similar underreporting is thought to exist in the routine surveillance of communicable disease in Washington state (Marcia Goldoft, MD, Epidemiologist, Washington State Department of Health, Communicable Disease Epidemiology Section , personal communication). We anticipate that underreporting of communicable disease was unrelated to the occurrence of KS and, therefore, would result

in non-differential misclassification of disease. Thus, the associations between KS and selected pathogens that were underreported may be spuriously low.

We conducted an analysis to demonstrate the potential effects of incomplete communicable disease surveillance on results obtained from this investigation. Based on the distribution of cohort members reported in Section 5.12 (Table 5.12.5), we estimated the magnitude of rate ratios that would have been observed at various levels of underreporting of enteric pathogens registered in WSCDR. For this analysis, we assumed that the level of underreporting was unrelated to the occurrence of KS (i.e., non-differential misclassification of communicable disease infection with respect to KS)[10]. Even at profound levels of assumed communicable disease underreporting, estimates of the true rate ratio were only modestly higher than the observed rate ratio of 1.32 (Table 6.6.1). Underreporting of communicable diseases thus likely resulted in only a modest underestimate of the true level of association.

---

[10] In Section 5.12, for example, we reported crude KS incidence rates of 83.13 and 62.89 per 1,000 person-years of follow-up for those known to have been previously infected with one or more enteric pathogens and for those not known to have been so infected, respectively (RR=1.32, 95 percent confidence interval=0.94-1.86). These rates were based on 37 KS cases that occurred during 445.10 person-years of follow-up among those with prior episodes of infection with enteric pathogens, and 307 KS cases that occurred during 4,881.60 person-years of follow-up among those not known to have been infected with enteric pathogens. As an example of the methodology we used in this analysis, we divided the 37 KS cases observed among those infected with enteric pathogens by 0.50, to estimate the true number of KS cases that would have been seen in this group if the observed n=37 had represented a 50 percent undercount (37/0.50=74). The corresponding person-years were similarly adjusted (i.e., 445.10 person-years/0.50=890.20 person-years); the number of KS cases and corresponding person-years of follow-up in the group not known to have been infected to enteric pathogens were reapportioned to account for the distribution of cases and person-time, and the rates for each group were recalculated, as were the rate ratios.

6.6.c Information bias due to migration

Routine disease surveillance is conducted in a dynamic population, and migration into or out of a defined geographic area of coverage could potentially influence the results of an investigation that relies on such data. Consider, for example, a hypothetical cohort member with a long history of sexually transmitted disease who moved to Washington state just prior to his/her diagnosis with AIDS and, subsequently, KS. Although this hypothetical individual would likely have been registered in both HARS and CSS, it is possible that no history of sexually transmitted or enteric pathogen would have been documented in the Washington State Syphilis Registry or the Washington State Communicable Disease Registry.

In the context of the present study, migration could potentially have influenced our measures of both disease and exposure, though we do not know the magnitude of this potential problem. In the absence of information to the contrary, we assumed that migration occurred in a manner unrelated to the subsequent occurrence of KS and history of the various communicable diseases of interest. Such non-differential misclassification would have resulted in an underestimate of any true associations between KS and the various pathogens of interest.

6.6.d Information bias due to routine errors in disease surveillance

Routine errors in collecting and recording surveillance data may be an additional source of information bias in this study. Transposition, mistakes in coding, and keying

errors would most likely occur randomly with respect to exposure and disease status. The magnitude of such errors in the research data base is not known. We anticipate these errors would most likely result in non-differential misclassification and would have little impact on the results reported here.

6.6.e Information bias due to record linkage procedures

The record-linkage process itself could have resulted in the misclassification of disease or exposure among members of the study cohort. Such bias could have resulted from combining information from two independent sources that, in truth, did not represent the same individual. Conversely, the record-linkage process may have failed to link records from two independent sources that, in truth, represented the same individual. The opportunity for such error could have been influence by (1) the ability of information from the component data bases to uniquely identify each member registered therein, and (2) inconsistent or arbitrary methods of establishing linkages between component data sets.

As summarized in Chapter 2, each participating disease registry maintained a core set of data items that uniquely identified individuals registered in their respective files, such as patient name and date of birth. In practice, however, there were differences among the participating registries in the availability of valid entries for some of these data items. Patient name (first and last) was available for most records in all data bases[11].

[11] First and last names were recorded in all records in HARS and CSS. Last name was available for all but 6 (<0.01 percent) of the records in WSSR, and first name was available for all but 46 (0.06 percent) of the

Social security number was also recorded in a majority of records in HARS and CSS, and served as a highly unique identifier for combining records from these two sources[12]. Date of birth (month, day, year) was recorded for most records in HARS and CSS[13], but was not recorded in a sizable number of records in WSSR[14] and WSCDR[15]. Fortunately, year of birth (or an estimate thereof) was available for most records in WSSR and WSCDR. Despite these differences, variables from the component databases were combined to provided relatively unique identifiers for linking records among the various registries. To minimize the opportunity for errors of omission and commission, we followed a standard set of procedures for linking records from the component data bases, and all potential linkages were manually reviewed by the primary investigator according to a standardized set of criteria (see Table 2.3.3)[16]. We believe that such possible misclassification of

---

records WSSR. Last name was available for all records in WSCDR, but first name was not available in 2 (<0.01 percent) of WSCDR records. In addition, aliases were recorded for some individuals. For the purpose of record linkage, we created separate records to represent each alias (see Chapter 2)

[12] Social security number was available in 92.9 percent of HARS records and in 92.5 percent of CSS records.

[13] Date of birth (month, day, year) was available in all but eight (0.13 percent) of 6,164 HARS records. Birth year was available in all but two HARS records (0.03 percent). Date of birth available in all but 1,660 (0.56 percent) of 296,633 CSS records. Year of birth was available in all but two CSS records (<0.01 percent).

[14] Date of birth (month, day, year) was recorded in less than half of WSSR records. However, year of birth was available in 84.9 percent of all WSSR records.

[15] Date of birth (month, day, year) was recorded in only 5,110 (9.8 percent) of all WSCDR records. However, we were able to estimate the year of birth for all but 57 (0.12 percent) of the 47,293 WSCDR records in which date of birth was not recorded.

[16] These criteria were determined *a priori* and were applied to each of the three record-linkage sessions that were conducted for this investigation.

exposure and disease were infrequent. If present, they were likely to have occurred independently of exposure and disease status and would, therefore, have resulted in a small underestimation of the observed rate ratios.

6.6.f The use of surrogate measures to infer sexual behavior

This investigation was based on the combined resources of population-based registries of AIDS, cancer, and selected communicable diseases. Information from these existing surveillance systems was combined by computer-assisted record linkage for the purpose of examining possible associations between KS and prior episodes of selected pathogens among people with AIDS. Each participating registry was designed to ascertain relatively specific information for the purpose of routine disease surveillance. For this study, information from these independent data bases was combined to address research questions that were beyond the scope of their intended use. This method of constructing a research data base does not necessarily limit the utility of the research data base, but it does raise a series of issues that must be considered when interpreting the results from the present investigation, as discussed in the following paragraphs.

Previous studies have examined the association between KS and level of sexual activity and participation in specific sexual behaviors, usually based on information obtained from in-person interviews. It would have been useful to have had access to information about frequency of sexual contact and participation in specific sexual behaviors for each member of the study cohort. However, this type of information was

not collected by any of the participating disease registries. Thus, associations between KS and sexual behaviors that have been assessed in previous studies must be inferred from the associations between KS and selected communicable pathogens observed in the present study. For example, we would anticipate that individuals with high levels of sexual activity would have been most likely to contract one or more sexually transmitted diseases. Similarly, we anticipate that individuals whose sexual behaviors involved fecal contact would have been at greatest risk for infection with one or more enteric pathogens[17]. Nonetheless, results from the present study must be interpreted in the context of these underlying assumptions.

6.6.g Other considerations

Some episodes of infection with the selected pathogens examined in this investigation were documented among cohort members near the time of AIDS diagnosis, or after the diagnosis of AIDS. Because AIDS-defining illnesses are the result of profound, HIV-induced immunosuppression, it is likely that some recent episodes of infection with the selected pathogens of interest in this study were facilitated by a compromised immune response. Thus, it is reasonable to question whether cohort members with KS, as a group, were more or less immunocompromised than those who did not develop KS. If so, any observed associations between KS and a given infectious

[17] In turn, these assumptions are premised on complete surveillance for communicable diseases and on the ability to correctly link records from the participating registries. These factors are considered separately later in this chapter.

agent may be due to differences in the degree of immunosuppression between those with and without KS. Unfortunately, the reporting of immune status was inconsistently documented in the records of HARS and, therefore, we were unable to address this concern in the study cohort. Previous reports have suggested that, among people with AIDS, those with KS, as a group, had higher levels of immune competence than those who did not have KS (Crowe 1991). However, KS is also known to be an early manifestation of AIDS, so differences in the level of immune function reported in such studies may have been artifactual (David Aboulafia, M.D., Virginia Mason Medical Center, personal communication). Subjects eligible for the analysis of post-AIDS KS did not have KS as an AIDS defining illness and, therefore, were likely to have been a relatively homogenous group with respect to level of immune suppression at entry into the study cohort. Furthermore, because the associations between KS and selected pathogens reported here were modest, and because some of these associations were positive while others were negative, it is unlikely that differences in the level of immune competence between those with and without KS influenced the results of this investigation.

Section 6.7 Conclusions

With combined resources from population-based registries of AIDS, cancer, and selected communicable diseases, we examined possible associations between the occurrence of KS and prior episodes of infection with selected pathogens among people

with AIDS. The disproportionately high risk for KS among homosexual and bisexual men observed in this and other studies suggests that factors associated with male homosexual behavior may greatly influence the risk of KS. However, results from this and previous investigations do not provide compelling or consistent evidence of increased risk of KS associated with specific pathogens, other than KSHV, or specific sexual behaviors that would further illuminate the mode of transmission for the etiologic agent of KS.

Treponema pallidum and HBV are commonly spread through sexual contact, although parenteral exposure is also an important mode of HBV transmission (Benenson 1995). Infection with the six enteric pathogens examined in this study are most often associated with ingestion of fecal-contaminated food or water in the general population (Benenson 1995). However, numerous studies have documented that these enteric pathogens may also be sexually transmitted among homosexual and bisexual men (Corey 1980, Owen 1979, Bader 1977, Schmerin 1977, Meyers 1977, Mildvan 1977, Dritz 1977). Therefore, all eight of the pathogens examined in this investigation may be considered to be sexually transmitted agents, especially in the context of the present study cohort, which was comprised primarily of homosexual and bisexual men. The inverse association between two of these pathogens, and the modest level of the associations between KS and the other six agents provides only weak evidence that KSHV is preferentially transmitted among homosexual men through behaviors that result in increased risk of sexually transmitted disease.

An association between KS and fecal-oral contact has been found in some investigations (Beral 1992, Darrow 1992, Jacobsen 1990, Lifson 1990a, Lifson 1990b) but not in all studies (Elford 1992, Page-Bodkin 1992, van Griensven 1993, Kaldor 1993). We also evaluated the hypothesis that the etiologic agent of KS may be transmitted through contact with fecal material, under the assumption that cohort members with prior episodes of infection with an enteric pathogen would be more likely to have been exposed to contaminated feces than cohort members without such infection. The inverse association between KS and HAV is not supportive of this hypothesis, although the modest associations between KS and the remaining five enteric pathogens are not inconsistent with the hypothesis that KS is linked to behaviors that would result in an increased risk of enteric infection. However, in the context of KSHV as a likely etiologic agent of KS, it should be noted that KSHV has not been documented in fecal samples from KS patients (LaDuca 1998, Boldogh 1996, Whitby 1995). Since these enteric pathogens are transmitted through sexual behavior in homosexual men, a more likely interpretation of our results is that infection with these pathogens are indices of sexual behavior, and suggest that the etiologic agent of KS is spread through homosexual behavior, but not through contaminated feces per se.

The specific mode of KSHV transmission is presently unknown. PCR-based and serology-based tests for KSHV have shown the virus to be present in many tissues from individuals with KS (LaDuca 1998, summarized in Table 1), including saliva (LaDuca 1998, Blackbourn 1998, Koelle 1997, Boldogh 1996), semen (LaDuca 1998, Huang

1997, Howard 1997), and peripheral blood mononuclear cells (LaDuca 1998, Blackbourn 1998, Huang 1997, Whitby 1995). Nonetheless, results from this and previous investigations have not provided conclusive evidence to delineate risk factors, other than level of sexual activity, for KSHV infection within homosexual groups at high risk for KS.

KSHV infection is not sufficient to cause KS. The prevalence of KSHV infection in the general population has been estimated between 1-3 percent (Ganem 1998). This level of KSHV infection is greater than is reflected in the incidence rates of KS in the general population (approximately 0.25 and 0.08 per 100,000 annually for males and females in western Washington state, respectively) (see Section 4.3). Further, as described in chapter 1, immune suppression appears to be a necessary cofactor in the development of KS. Recent and dramatic declines in the incidence of KS among people with AIDS have been attributed to the widespread use of highly active antiretroviral therapy (HAART) (Wiggins 1999, Aboulafia 1998, Krischer 1998). These therapeutic regimens have, at least temporarily, stopped the progressive decline in immune competence in people with AIDS and, thus, have presumably prevented the occurrence of KS in many individuals. These observations provide further evidence of the importance of immune incompetence in the development of KS.

Rabkin and his colleagues(1998) applied seven different serology assays for KSHV to a standard set of specimens from individuals with and without KS, and documented discrepancies among the results obtained by the various methods.

Additional research is needed to clarify the reasons for these discrepancies and, presumably, to improve the reliability of these tests. Nonetheless, future studies of KS will rely on valid serologic tests and viral isolation to further characterize the mode(s) of KSHV transmission. Such studies should identify new opportunities for prevention and treatment of KS.

Table 6.6.1 Estimates of the rate ratio comparing crude incidence rates of Kaposi's Sarcoma (KS) for those previously infected and not known to have been previously infected with selected enteric pathogens, by assumed levels of completeness of communicable disease surveillance, based on the association between enteric pathogens and post-AIDS KS reported in Section 5.12.

Assumed completeness of surveillance (percent)	Rate Ratio	95 percent confidence interval
100	1.32	0.94-1.86
90	1.33	0.96-1.84
80	1.33	0.98-1.82
70	1.34	1.00-1.80
60	1.35	1.02-1.78
50	1.37	1.06-1.77
40	1.39	1.10-1.77
30	1.45	1.16-1.80
20	1.62	1.31-2.00

* 95 percent confidence intervals calculated according to methods outlined by Kahn and Sempos (1989)

Bibliography

Aboulafia DM. Regression of acquired immunodeficiency syndrome- related pulmonary Kaposi's sarcoma after highly active antiretroviral therapy. Mayo Clinc Procedings 1998; 73:439-443.

Abrams DI. The relationship between Kaposi's sarcoma and intestinal parasites among homosexual males in the United States. Journal of Acquired Immune Deficiency Syndromes 1990; 3:S44-S46.

Adams V, Kempf W, Schmid M, Muller B, Briner J, Burg G. Absence of herpesvirus-like DNA sequences in skin cancers of non- immunosuppressed patients [letter]. Lancet 1995; 346:1715-1716.

Ambroziak JA, Blackbourn DJ, Herndier BG, Glogau RG, Gullett JH, McDonald AR *et al.* Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. Science 1995; 268:582-583.

Anderson RM, May RM. Epidemiological parameters of HIV transmission. Nature 1988; 333:514-519.

Archibald CP, Schechter MT, Craib KJP, Le TN, Douglas B, Willoughby B *et al.* Risk factors for Kaposi's sarcoma in the Vancouver lymphadenopathy-AIDS study. Journal of Acquired Immune Deficiency Syndromes 1990; 3:S18-S23.

Archibald CP, Schechter MT, Le TN, Craib KJP, Montaner JSG, O'Shaughnessy MV. Evidence for a sexually transmitted cofactor for AIDS-related Kaposi's sarcoma in a cohort of homosexual men. Epidemiology 1992; 3:203-209.

Armenian HK, Hoover DR, Rubb S, Metz S, Kaslow R, Visscher B *et al.* Composite risk score for Kaposi's sarcoma based on a case- control and longitudinal study in the Multicenter AIDS Cohort Study (MACS) population. American Journal of Epidemiology 1993; 138:256-265.

Bader M, Pedersen AH, Williams R, Spearman J, Anderson H. Venereal transmission of shigellosis in Seattle-King County. Sexually Transmitted Diseases 1977; 4:89-91.

Bailer JCI, Ederer F. Significance factors for the ratio of a poisson variable to its expectation. Biometrics 1964; 20:639-643.

Banks PM. Changes in diagnosis of non-Hodgkin's lymphoma over time. Cancer Research (Supplement) 1992; 52:5453s-5455s.

Barillari G, Gendelman R, Gallo RC, Ensoli B. The Tat protein of human immunodeficiency virus type 1, a growth factor for AIDS Kaposi sarcoma and cytokine-activated vascular cells, induces adhesion of the same cell types by using integrin receptors recognizing the RGD amino acid sequence. Proceedings of the National Academy of Sciences of the United States of America 1993; 90:7941-7945.

Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J *et al.* Isolation of a T-lymphotrophic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983; 220:868-871.

Bendsoe N, Dictor M, Blomberg J, Agren S, Merk K. Increased incidence of Kaposi sarcoma in Sweden before the AIDS epidemic. Europeon Journal of Cancer 1990; 26:699-702.

Benenson AS. Control of Communicable Diseases Manual, 16th Edition. Washington, DC: American Public Health Association, 1995.

Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet 1990; 335:123-128.

Beral V. Epidemiology of Kaposi's sarcoma. Cancer Surveys 1991a; 10:5-22.

Beral V, Bull D, Jaffe H, Evans B, Gill N, Tillett H *et al.* Is risk of Kaposi's sarcoma in AIDS patients in Britain increased if sexual partners came from United States or Africa? British Medical Journal 1991b; 302:624-625.

Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non- Hodgkin lymphoma. Lancet 1991c; 337:805-809.

Beral V, Bull D, Darby S, Weller I, Carne C, Beecham M *et al.* Risk of Kaposi's sarcoma and sexual practices associated with faecal contact in homosexual or bisexual men with AIDS. Lancet 1992; 339:632-635.

Beral V, Newton R. Overview of the epidemiology of immunodeficiency-associated cancers. Journal of the National Cancer Institute Monographs 1998; 23:1-6.

Biggar RJ, Horm J, Lubin JH, Goedert JJ, Greene MH, Fraumeni JFJr. Cancer trends in a population at risk of acquired immunodeficiency syndrome. Journal of the National Cancer Institute 1985; 74:793-797.

Biggar RJ, Horm J, Goedert JJ, Melbye M. Cancer in a group at risk of acquired immunodeficiency syndrome (AIDS) through 1984. American Journal of Epidemiology 1987; 126:578-586.

Biggar RJ, Burnett W, Mikl J, Nasca P. Cancer among New York men at risk of acquired immunodeficiency syndrome. International Journal of Cancer 1989; 43:979-685.

Biggar RJ, Rabkin CS. The epidemiology of acquired immunodeficiency syndrome-related lymphomas. Current Opinion in Oncology 1992; 4:883-893.

Blackbourn DJ, Lennette Evelyne T., Ambroziak J, Mourich DV, Levy JA. Human herpesvirus 8 detection in nasal secretions and saliva. Journal of Infectious Disease 1988; 177:213-216.

Bluefarb SM. Kaposi's Sarcoma: Multiple Idiopathic Hemorrhagic Sarcoma. Springfield, IL: Charles C. Thomas, 1957.

Boice JD Jr. Radiation and non-Hodgkin's lymphoma. Cancer Research (Supplement) 1992; 52:5489s-5491s.

Boldogh I, Szaniszlo P, Bresnahan WA, Flaitz CM, Nichols MC, Albrecht T. Kaposi's sarcoma herpesvirus-like DNA sequences in the saliva of individuals infected with Human Immunodeficiency Virus. Clinical Infectious Diseases 1996; 23:406-407.

Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto AJ. Prevalence of human papillomavirus in cervical cancer: A worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) study group. Journal of the National Cancer Institute 1995; 87:796-802.

Boshoff C, Shulz TF, Kennedy MM, Graham AK, Fisher C, Thomas A *et al.* Kaposi's sarcoma-associated herpesvirus infects endothelial and spindle cells. Nature Medicine 1995a; 1:1274-1278.

Boshoff C, Whitby D, Hatziioannou T, Fisher C, van der Walt J, Hatzakis A *et al.* Kaposi's-sarcoma-associated herpesvirus in HIV- negative Kaposi's sarcoma [letter]. Lancet 1995b; 345:1043-1044.

Boshoff C, Talbot S, Kennedy M, O'Leary J, Shulz T, Chang Y. HHV8 and skin cancers in immunosuppressed patients [letter]. Lancet 1996; 347:338-339.

Braun M. Classics in oncology: Moriz Kaposi, M.D. CA-A Cancer Journal for Clinicians 1982; 32:340-341.

Breslow NE, Day NE. Statistical Methods in Cancer Research. Volume I. The Analysis of Case-Control Studies. IARC Scientific Publication No. 32. Lyon, France: International Agency for Research on Cancer, 1980.

Breslow NE, Day NE. Statistical Methods in Cancer Research. Volume II. The Design and Analysis of Cohort Studies. IARC Scientific Publication No. 82. Lyon, France: International Agency for Research on Cancer, 1987.

Brinton LA, Nasca PC, Mallin K, Baptiste MS, Wilbanks GD, Richart RM. Case-control study of cancer of the vulva. Obstetrics and Gynecology 1990; 75:859-866.

Brousset P, Meggetto F, Attal M, Delsol G. Kaposi's sarcoma- associated herpesvirus infection and multiple myeloma [Technical Comment]. Science 1997; 278:1972.

Buchbinder A, Friedman-Kien AE. Clinical aspects of epidemic Kaposi's sarcoma. Cancer Surveys 1991; 10:39-52.

Buchbinder SP, Vittinghoff E, Colfax G, Holmberg S. Declines in AIDS incidence associated with highly active anti-retroviral therapy (HAART) are not reflected in KS and lymphoma incidence [abstract]. Presented at the Second National AIDS Malignancy Conference. Bethesda, MD. Available from: http://healthcg.com/hiv/2ndnciconf/. Abstract no. S7. 1998.

Buehler JW, Berkelman RL, Stehr-Green JK. The completeness of AIDS surveillance. Journal of Acquired Immune Deficiency Syndromes 1992; 5:257-264.

Carli PM, Boutron MC, Maynadie M, Bailly F, Caillot D, Petrella T. Increase in the incidence of non-Hodgkin's lymphomas: Evidence for a recent sharp increase in France independent of AIDS. British Journal of Cancer 1994; 70:713-715.

Cartwright RA. Changes in the descriptive epidemiology of non- Hodgkin's lymphoma in Great Britain. Cancer Research (Supplement) 1992; 52:5441s-5442s.

Centers for Disease Control. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men - New York City and California. Morbidity and Mortality Weekly Report 1981; 30:305-308.

Centers for Disease Control. Update on acquired immune deficiency syndrome (AIDS) - United States. Morbidity and mortality weekly report 1982; 31:507-514.

Centers for Disease Control. Revision of the case definition of acquired immunodeficiency syndrome for national reporting - United States. Morbidity and Mortality Weekly Report 1985; 34: 373-374.

Centers for Disease Control. Revision of the CDC surveillance case definition of acquired immunodeficiency syndrome. Morbidity and Mortality Weekly Report (Supplement 1) 1987; 36:S1-S15.

Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity and Mortality Weekly Report 1992; 41(RR-17):4-19.

Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. New England Journal of Medicine 1982; 306:248-252.

Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. New England Journal of Medicine 1995; 332:1186-1191.

Cesarman E, Nador RG, Bai F, Bohenzky RA, Russo JJ, Moore PS *et al.* Kaposi's sarcoma-associated herpesvirus contains G protien- coupled receptor and cyclin D homologs which are expressed in Kaposi's sarcoma and malignant lymphoma. Journal of Virology 1996; 70:8218-8223.

Chang Y. A guideline to serologic tests for syphilis. Diagnostic Medicine 1983:51-54.

Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM *et al.* Identification of Herpesvirus-like DNA sequences in AIDS- associated Kaposi's sarcoma. Science 1994; 266:1865-1869.

Chang Y, Moore P. Kaposi's sarcoma (KS)-associated herpesvirus and its role in KS. Infectious Agents and Disease 1996; 5:215-222215- .

Cheng EH-Y, Nicholas J, Bellows DS, Hayward GS, Guo H, Reitz MS *et al.* A Bcl-2 homolog encoded by Kaposi sarcoma-associated virus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. Proc Natl Acad Sci USA 1997; 94: 690-694.

Christeff N, Thobie N, Nunez EA. Differences in the androgens of HIV positive patients with and without Kaposi's sarcoma. Proceedings of the 9th International Conference on AIDS 1993; Abstract No. 400.

Chuck S, Grant RM, Katongole-Mbidde E, Conant M, Ganem D. Frequent presence of a novel herpesvirus genome in lesions of human immunodeficiency virus-negative kaposi's sarcoma. Journal of Infectious Disease 1996; 173:248-251.

Cohen J. Controversy: Is KS really caused by new herpesvirus? (Research News). Science 1995; 268:1847-1848.

Cohen MS. Sexually transmitted diseases enhance HIV transmission: No longer a hypothesis. Lancet 1998; 351 (supplement III):5-7.

Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in Cancer Incidence and Mortality (IARC Scientific Publication No. 121). Lyon, France: World Health Organization, International Agency for Research on Cancer, International Union Against Cancer, International Association of Cancer Registries., 1993.

Collandre H, Ferris S, Grau O, Montagnier L, Blanchard A. Kaposi's sarcoma and new herpesvirus [letter]. Lancet 1995; 345: 1043.

Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men. New England Journal of Medicine 1980; 302:435- 438.

Cote TR, Howe HL, Anderson SP, Martin RJ, Evans B, Francis BJ. A systematic consideration of the neoplastic spectrum of AIDS: registry linkage in Illinois. AIDS 1991; 5:49-53.

Cote TR, O'Brien TR, Ward JW, Wilson SE, Blattner WA. AIDS and cancer registry linkage: Measurement and enhancement of registry completeness. Preventive Medicine 1995; 24:375-377.

Cote TR, Biggar RJ, Rosenberg PS, Devesa SS, Percy C, Yellin FJ. Non-Hodgkin's lymphoma among people with AIDS: Incidence, presentation, and public health burden. International Journal of Cancer 1997; 73:645-650.

Cottoni F, Uccini S. Kaposi's sarcoma-associated herpesvirus infection and multiple myeloma [Technical Comment]. Science 1997; 278:1972.

Cox DR, Oakes D. Analysis of Survival Data. London: Chapman and Hall, 1984.

Crowe SM, Carlin JB, Stewart KI, Lucas CR, Hoy JF. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. Journal of Acquired Immune Deficiency Syndromes 1991; 4: 770-776.

Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R. Correlates of homosexual behavior and the incidence of anal cancer. Journal of the American Medical Association 1982; 47:1988-1990.

Darrow WW, Peterman TA, Jaffe HW, Rogers MF, Curran JW. Kaposi's sarcoma and exposure to faeces [letter]. Lancet 1992; 339:685.

Davis S. Nutritional factors and the development of non-Hodgkin's lymphoma: A review of the evidence. Cancer Research (Supplement) 1992; 52:5492s-5495s.

Demers PA, Vaughan TL, Checkoway H, Weiss NS, Heyer NJ, Rosenstock L. Cancer identification using a tumor registry versus death certificates in occupational cohort studies in the United States. American Journal of Epidemiology 1992; 136:1232-1240.

Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L. Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). Cancer Causes and Control 1994; 5:129-135.

Des Jarlais DC, Stoneburner R, Thomas P, Friedman SR. Declines in proportion of Kaposi's sarcoma among cases of AIDS in multiple risk groups in New York City. Lancet 1987; 2:1024-1025.

Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Research (Supplement) 1992; 52:5432s-5440s.

Dirckx JH. On the Name Kaposi (Chapter 3, pp. 25-26). In: Gottlieb GJ and Ackerman AB (eds). Kaposi's Sarcoma: A Text and Atlas. Philadelphia, PA: Lea and Febiger, 1988.

Doll DC, List AF. Burkitt's lymphoma in a homosexual [letter]. Lancet 1982; 1:1026-1027.

Doody DR, Patterson MQ, Voigt LF, Mueller BA. Risk factors for the recurrence of premature rupture of the membranes. Paediatric and Perinatal Epidemiology 1997; 11:96-106.

Drew WL, Conant MA, Miner RC, Huang E, Ziegler JL, Groundwater JR *et al.* Cytomegalovirus and Kaposi's sarcoma in young homosexual men. Lancet 1982; 2:125-127.

Dritz SK, Ainsworth TE, Back A, Boucher LA, Garrard WF, Palmer RD *et al.* Patterns of sexually transmitted enteric diseases in a city. Lancet 1977; 2:3-4.

Dupin N, Grandadam M, Calvez V, Gorin I, Aubin JT, Harvard S *et al.* Herpesvirus-like DNA sequences in patients with Mediterranean Kaposi's sarcoma. Lancet 1995; 345:761-762.

Elford J, Tindall B, Sharkey T. Kaposi's sarcoma and insertive rimming [letter]. Lancet 1992; 339:938.

Emerson JC, Malone KE, Daling JR, Starzyk P. Childhood brain tumor risk in relation to birth characteristics. Journal of Clinical Epidemiology 1991; 44:1159-1166.

Ensoli B, Nakamura S, Salahuddin SZ, Biberfeld P, Larsson L, Beaver B *et al.* AIDS-Kaposi's sarcoma-derived cells express cytokines with autocrine and paracrine growth effects. Science 1989; 243:223-226.

Ensoli B, Barillari G, Salahuddin SZ, Gallo RC, Wong-Staal F. Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. Nature 1990; 345:84-86.

Ensoli B, Barillari G, Gallo RC. Pathogenesis of AIDS-associated Kaposi's sarcoma. Hematology/Oncology Clinics of North America 1991; 5:281-295.

Ensoli B, Gendelman R, Markham P, Fiorelli V, Colombini S, Raffeld M *et al.* Synergy between basic fibroblast growth factor and HIV-1 Tat protein in induction of Kaposi's sarcoma. Nature 1994; 371:674-680.

Falutz J. Lack of association of low testosterone with HIV- associated Kaposi's sarcoma. AIDS 1996; 10:794-795.

Fellegi IP, Sunter AB. A theory for record linkage. Journal of the American Statistical Association 1969; 64:1183-1210.

Filipovich AH, Mathur A, Kamat D, Shapiro RS. Primary immunodeficiencies: Genetic risk factors for lymphoma. Cancer Research (Supplement) 1992; 52:5465s-5467s.

Foreman KE, Friborg JJr, Kong W, Woffendin C, Polverini PJ, Nickoloff BJ *et al.* Propagation of a human herpesvirus from AIDS- associated Kaposi's sarcoma. N Engl J Med 1997; 336:163-171.

Friedman-Kien AE, Saltzman BR. Clinical manifestations of classical, endemic African, and epidemic AIDS-associated Kaposi's sarcoma. Journal of the American Academy of Dermatology June, 1990a; 22:1237-1250.

Friedman-Kien AE, Saltzman BR, Cao YC,NMS, Mirabile M, Jian JL, Peterman TA. Kaposi's sarcoma in HIV-negative homosexual men [letter]. Lancet 1990b; 335:168-169.

Frost F, Taylor V, Fries E. Racial misclassification of Native Americans in a Surveillance, Epidemiology, and End Results cancer registry. Journal of the National Cancer Institute 1992; 84:957- 962.

Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF *et al.* Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patient with AIDS and at risk for AIDS. Science 1984; 224:500-503.

Ganem D. Human herpesvirus 8 and AIDS-related neoplasms. In: The 4th Annual Epidemiology and Prevention of Infectious Diseases: Emerging Pathogens in the United States and Worldwide. San Francisco, CA: Department of Epidemiology and Biostatistics, University of California School of Medicine at San Francisco, 1997.

Ganem D. Human herpesvirus 8 and its role in the genesis of Kaposi's sarcoma. Current Clinical Topics in Infectious Disease 1998; :237-251.

Gao S, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A *et al.* Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. New England Journal of Medicine 1996a; 335:233-241.

Gao S, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J *et al.* KSHV antibodies among Americans, Italians, and Ugandans with and without Kaposi's sarcoma. Nature Medicine August, 1996b; 2:925- 928.

Garcia-Muret MP, Pujol RM, Puig L, Moreno A, De Moragas JM. Disseminated Kaposi's sarcoma not associated with HIV infection in a bisexual man. Journal of the American Academy of Dermatology 1990; 23:1035-1038.

Gill PS, Lunardi-Iskandar Y, Louie S, Tulpule A, Zheng T, Espina BM *et al.* The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. New England Journal of Medicine 1996; 335:1261-1269.

Gill PS, McLaughlin T, Espina BM, Tulpule A, Louie S, Lunardi- Iskandar Y *et al.* Phase I study of human chorionic gonadotropin given subcutaneously to patients with Acquired Immunodeficiency Syndrome-related mucocutaneous Kaposi' sarcoma. Journal of the National Cancer Institute 1997; 89:1797-1802.

Gilles K, Louie L, Newman B, Crandall J, King MC. Genetic susceptibility to AIDS: Absence of an association with group specific component (Gc) [letter]. New England Journal of Medicine 1987; 317:630-631.

Glesby MJ, Hoover DR, Weng S, Graham NMH, Phair JP, Detels R *et al.* Use of antiherpes drugs and the risk of Kaposi's sarcoma: Data from the Multicenter AIDS Cohort Study. Journal of Infectious Diseases 1996; 173:1477-1480.

Gluckman E, Parquet N, Scieux C, Deplanche M, Traineau R, Betheau P *et al.* KS-associated herpesvirus-like DNA sequences after allogeneic bone-marrow transplantation [letter]. Lancet 1995; 346:1558-1559.

Goedert JJ, Biggar RJ, Melbye M, Mann DL, Wilson S, Gail MH *et al.* Effect of T4 count and cofactors on the incidence of AIDS in homosexual men infected with human immunodeficiency virus. Journal of the American Medical Association 1987; 257:331-334.

Goedert JJ, Cote TR, Virgo P, Scoppa SM, Kingma DW, Gail MH *et al.* Spectrum of AIDS-associated malignant disorders. Lancet 1998; 351:1833-1839.

Gotti E, Remuzzi G. Post-transplant Kaposi's sarcoma. Journal of the American Society of Nephrology 1997; 8:130-137.

Gottlieb MS, Schroff R, Schanker HM. Pneumocytis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: Evidence of a new acquired cellular immunodeficiency. New England Journal of Medicine 1981; 305:1425-1431.

Grulich AE, Kaldor JM, Hendry O, Luo K, Bodsworth NJ, Cooper DA. Risk of Kaposi's sarcoma and oroanal sexual contact. American Journal of Epidemiology 1997; 145:673-679.

Grulich AE, Olsen SJ, Luo K, Hendry O, Cunningham P, Cooper DA *et al.* Kaposi's sarcoma-associated herpesvirus: A sexually transmitted infection? Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1999; 20:387-393.

Hamilton AS, Radka SF, Bernstein L, Gill PS, Gonsalves M, Naemura JR *et al.* Relationship of serum levels of oncostatin M to AIDS- related and classic Kaposi's sarcoma. Journal of Acquired Immune Deficiency Syndromes 1994; 7:410-414.

Harris PJ. Human chorionic gonadotropin hormone is antiviral. Medical Hypotheses 1996; 47:71-72.

Haverkos HW, Drotman DP. Prevalence of Kaposi's sarcoma among patients with AIDS [letter]. New England Journal of Medicine 1985; 312:1518.

Haverkos HW, Friedman-Kien AE, Drotman DP, Morgan WM. The changing incidence of Kaposi's sarcoma among patients with AIDS. Journal of the American Academy of Dermatology 1990; 22:1250- 1253.

Herman AA, McCarthy Brian J., Bakewell JM, Ward RH, Mueller BA, Maconochie NE *et al.* Data linkage methods used in maternally- linked birth and infant death surveillance data sets from the United States (Georgis, Missouri, Utah, and Washington State), Israel, Norway, Scotland, and Western Australia. Paediatric and Perinatal Epidemiology 1997; 11:5-22.

Hessol NA, Katz MH, Liu JY, Buchbinder SP, Rubino CJ, Holmberg SD. Increased incidence of Hodgkin's disease in homosexual men with HIV infection [comment]. Annals of Internal Medicine 1993; 118:313.

Hitchcock P, Fransen L. Preventing HIV infection: Lessons from Mwanza and Raka. Lancet 1999; 353:513-515.

Hjalgrim H, Frisch M, Begtrup K, Melbye M. Recent increase in the incidence of non-Hodgkin's lymphoma among young men and women in Denmark. British Journal of Cancer 1996; 73:951-954.

Holford TR, Zheng T, Mayne ST, McKay LA. Time trends of non- Hodgkin's lymphoma: Are the real? What do they mean? Cancer Research (Supplement) 1992; 52:5443s-5446s.

Hollinger FB. Hepatitis B Virus. In: Fields BN, Knipe DM, Howley, et al. (eds): Fields Virology, Third Edition. pp 2739- 2807. Philadelphia: Lippincott-Raven, 1996.

Holt VL, Danoff NL, Mueller BA, Swanson MW. The association of change in maternal marital status between births and adverse pregnancy outcomes in the second birth. Paediatric and Perinatal Epidemiology 1997; 11:31-40.

Holt VL, Mueller BA. Attempt and success rates for vaginal birth after Caesarean section in relation to complications of the previous pregnancy. Paediatric and Perinatal Epidemiology 1997; 11:63-72.

Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. Lancet 1973; 2:55-57.

Howard MR, Whitby D, Bahadur G, Suggett F, Boshoff C, Tenant- Flowers M *et al.* Detection of human herpesvirus 8 DNA in semen from HIV-infected individuals but not healthy semen donors. AIDS 1997; 11:F15-F19.

Huang YQ, Li JJ, Rush MG, Poiesz BJ, Nicolaides A, Jacobson M *et al.* HPV-16-related DNA sequences in Kaposi's sarcoma. Lancet 1992; 339:515-518.

Huang YQ, Li JJ, Kaplan MH, Poiesz B, Katabira E, Zhang WC *et al.* Human herpesvirus-like nucleic acid in various forms of Kaposi's sarcoma. Lancet 1995; 345:759-761.

Huang Y, Li JJ, Poiesz BJ, Kaplan MH, Friedman-Kien AE. Detection of the herpesvirus-like DNA sequences in matched specimens of semen and blood from patients with AIDS-related Kaposi's sarcoma by polymerase chain reaction in situ hybridization. American Journal of Pathology 1997; 150:147-153.

Humphrey RW, O'Brien T, Newcomb FM, Nishihara H, Wyvill KM, Ramos GA *et al.* Kaposi's sarcoma(KS)-associated herpesvirus-like DNA sequences in peripheral blood mononuclear cells: Association with KS and persistence in patients receiving anti-herpesvirus drugs. Blood 1996; 88:297-301.

International Agency for Research on Cancer. Human Papillomaviruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 64. Lyon, France: World Health Organization, 1995.

Iwasawa A, Kumamoto Y, Fujinaga K. Detection of human papillomavirus deoxyribonucleic acid in penile carcinoma by polymerase chain reaction and in situ hybridization. Journal of Urology 1993; 149:59-63.

Jacobson LP, Munoz A, Fox R, Phair JP, Dudley J, Obrams GI *et al.* Incidence of Kaposi's sarcoma in a cohort of homosexual men infected with the Human Immunodeficiency Virus Type 1. Journal of Acquired Immune Deficiency Syndromes 1990; 3:S24-S31.

Jacobson LP. Impact of highly effective anti-retroviral therapy on the incidence of malgnancies among HIV-=infected individuals [abstract]. Presented at the Second National AIDS Malignancy Conference. Bethesda, MD. Available from: http://healthcg.com/ hiv/2ndnciconf/. Abstract no. S5. 1998.

Jaffe HW, Bregman DJ, Selik RM. Acquired immune deficiency syndrome in the United States: First 1,000 cases. Journal of Infectious Disease 1983; 148:339-345.

Jaffe HW, Musher DM. Management of the reactive syphilis serology. In: Holmes KK, Mardh P-A, Stamm WE, Wasserheit J, Sparling PF, Lemon SM, Piot P (eds). Sexually Transmitted Diseases. USA: McGraw-Hill, 1997.

Johnson CC, Wilcosky T, Kvale P, Rosen M, Stansell J, Glassroth J *et al.* Cancer incidence among an HIV-infected cohort. American Journal of Epidemiology 1997; 146:470-475.

Jones JL, Hanson DL, Ward JW. Effect of antiretroviral therapy on recent trends in cancers among HIV-infected persons [abstract]. Presented at the Second National AIDS Malignancy Conference. Bethesda, MD. Available from: http://healthcg.com/hiv/2ndnciconf/ . Abstract no. S3. 1998.

Kahn HA, Sempos CT. Statistical Methods in Epidemiology. New York: Oxford University Press, 1989.

Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: Wiley, 1980.

Kaldor JM, Tindall B, Williamson P. Factors associated with Kaposi's sarcoma in a cohort of homosexual and bisexual men. J AIDS 1993; 6:1145-1149.

Kaplan LD. Pathogenesis of HIV-associated Kaposi's sarcoma (Chapter 7.2, pp. 7.2-1 - 7.2-5). In: Cohen PT, Sande MA, and Volberding PA (eds): The AIDS Knowledge Base. A Textbook on HIV Disease from the University of California, San Francisco, and the San Francisco General Hospital. Boston, New York, Toronto, London: Little, Brown and Company, 1994.

Kaposi M. Idiopathic multiple pigmented sarcoma of the skin. CA-A Cancer Journal for Clinicians 1982; 32:342-347 (reprinted from Archiv Fur Dermatologie Und Syphillis 1872; 4:265-273).

Karagas MR, Thomas DB, Roth GJ, Johnson LK, Weiss NS. The effects of changes in health care delivery on the reported incidence of cutaneous melanoma in western Washington state. American Journal of Epidemiology 1991; 133:58-62.

Karasek MA. Origin of spindle-shaped cells in Kaposi sarcoma. Lymphology 1994; 27:41-44.

Kazal HL, Sohn N, Carrasco JI, Robilotti JG, Delaney WE. The gay bowel syndrome: Clinico-pathologic correlation in 260 cases. Annals of Clinical and Laboratory Science 1976; 6:184-192.

Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma- associated herpesvirus): Distribution of infection in KS risk groups and evidence for sexual transmission. Nature Medicine 1996; 2:918-924.

Kedes DH, Ganem D, Ameli N, Bacchetti P, Greenblatt R. The prevalence of serum antibody to human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) among HIV-seropositive and high- risk HIV-seronegative women. Journal of the American Medical Association 1997; 277:478-481.

Kemeny L, Kiss M, Gyulai R, Dobozy A, Adam E. Herpesvirus-like nucleic acid sequences in patients with eastern European sporadic Kaposi's sarcoma [letter]. Journal of Investigative Dermatology 1996; 106:381.

Kimball AM, Thacker SB, Levy ME. Shigella surveillance in a large metropolitan area: Assessment of a passive reporting system. American Journal of Public Health 1980; 70:164-166.

Kinlen LJ, Sheil AGR, Peto J, Doll R. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. British Journal of Medicine 1979; 2: 1461-1466.

Kinlen LJ. Immunosuppression and cancer (pp. 237-253). In: Vainio H, Magee PN, McGregor DB, McMichael AJ (eds): Mechanisms of Carcinogenesis in Risk Identification. Lyon, France: International Agency for Research on Cancer, 1992a.

Kinlen LJ. Malignancy in autoimmune diseases. Journal of Autoimmunity 1992b; 5:363-371.

Kinlen L. Immunosuppressive therapy and acquired immunological disorders. Cancer Research (Supplement) 1992c; 52:5474s-5476s.

Klauke S, Schoefer H, Althoff PH, Michels B, Helm EB. Sex hormones as a cofactor in the pathogenesis of epidemic Kaposi's sarcoma. AIDS 1995; 9:1295-1296.

Kleinbaum DG. Logistic Regression. A Self-Learning Text. New York: Springer-Verlag, 1994.

Kleinbaum DG. Survival Analysis. A Self-Learning Text. New York: Springer-Verlag, 1996.

Koblin BA, Hessol NA, Zauber AG, Taylor PE, Buchbinder SP, Katz MH *et al.* Increased incidence of cancer among homosexual men, New York City and San Francisco, 1978-90. American Journal of Epidemiology 1996; 144:916-923.

Koelle DM, Huang M, Chandran B, Vieira J, Piepkorn M, Corey L. Frequent detection of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in saliva of human immunodeficiency virus-infected men: Clinical and immunologic correlates. Journal of Infectious Diseases 1997; 176:94-102.

Koh HK, Clapp RW, Barnett JM, Nannery WM, Tahan SR, Geller AC *et al.* Systematic underreporting of cutaneous malignant melanoma in Massachusetts. Journal of the American Academy of Dermatology 1991; 24:545-550.

Koutsky LA. Epidemiology of genital human papillomavirus infection. American Journal of Medicine 1997; 102:3-8.

Kreiss JK, Kiviat NB, Plummer FA, Roberts PL, Waiyaki P, Ngugi E *et al.* Human immunodeficiency virus, human papillomavirus, and cervical intraepithelial neoplasia in Nairobi prostitutes. Sexually Transmitted Diseases 1992; 19:54-59.

Krischer J, Rutschmann O, Hirschel B, Vollenweider-Roten S, Saurat J, Pechere M. Regression of Kaposi's sarcoma during therapy with HIV-1 protease inhibitors: A prospective pilot study. Journal of the American Academy of Dermatology 1998; 38: 594-598.

Krown SE. Acquired Immunodeficiency Syndrome-associated Kaposi's sarcoma. Medical Clinics of North America 1997; 81:471-494.

LaDuca JR, Love JL, Abbott LZ, Dube S, Freidman-Kien AE, Poiesz BJ. Detection of human herpesvirus 8 DNA sequences in tissues and bodily fluids. Journal of Infectious Diseases 1998; 178:1610- 1615.

Lahita RG. The effects of sex hormones on the immune system in pregnancy. American Journal of Reproductive Immunology 1992; 28: 136-137.

Laughon BE, Druckman DA, Vernon A, Quinn TC, Polk BF, Modlin JF *et al.* Prevalence of enteric pathogens in homosexual men with and without acquired immunodeficiency syndrome. Gastroenterology 1988; 94:984-993.

Lennette ET, Blackbourn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. Lancet 1996; 348:858-861.

Levine AM, Meyer PR, Begandy MK, Parker JW, Taylor CR, Irwin L *et al.* Development of B-cell lymphoma in homosexual men. Clinical and immunologic findings. Annals of Internal Medicine 1984; 100: 7-13.

Levy JA, Hoffman AD, Kramer SM, Landis JA, Shimabukuro JM, Oshiro LS. Isolation of lymphocytopathic retroviruses from San Franciso patients with AIDS. Science 1984; 225:840-842.

Levy JA. A new human herpesvirus: KSHV or HHV8? (Commentary). Lancet 1995; 34:786.

Li M, Lee H, Yoon D, Albrecht J, Fleckenstein B, Neipel F *et al.* Kaposi's sarcoma-associated herpesvirus encodes a functional cyclin. Journal of Virology 1997; 71:1984-1991.

Lifson AR, Darrow WW, Hessol NA, O'Malley PM, Barnhart JL, Jaffe HW *et al.* Kaposi's sarcoma in a cohort of homosexual and bisexual men. American Journal of Epidemiology 1990a; 131:221- 231.

Lifson AR, Darrow WW, Hessol NA, O'Malley PM, Barnhart L, Jaffe HW *et al.* Kaposi's sarcoma among homosexual and bisexual men enrolled in the San Francisco City Clinic Cohort Study. Journal of Acquired Immune Deficiency Syndromes 1990b; 3:S32-S37.

Lin JC, Lin SC, Mar EC, Pellett P, Stamey FR, Stewart JA *et al.* Is Kaposi's-sarcoma-associated herpesvirus detectable in semen of HIV-infected homosexual men? Lancet 1995; 346:1601-1602.

Linet MS, Pottern LM. Familial aggregation of hematopoietic malignancies and risk of non-Hodgkin's lymphoma. Cancer Research (Supplement) 1992; 52:5468s-5473s.

Lisitsyn N, Lisitsyn N, Wigler M. Cloning the differences between two complex genomes. Science 1993; 259:946-951.

Lunardi-Iskandar Y, Bryant JL, Zeman RA, Lam VH, Samaniego F, Besnier JM *et al.* Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. Nature 1995; 375:64-68.

Lundgren JD, Melbye M, Pedersen C, Rosenberg PS, Gerstoft J. Changing patterns of Kaposi's sarcoma in Danish acquired immunodeficiency syndrome patients with complete follow-up. American Journal of Epidemiology 1995; 141:652-658.

Luxton J, Thomas JA, Crawford DH. Aetiology and pathogenesis of non-Hodgkin lymphoma in AIDS. Cancer Surveys 1991; 10:103-119.

Lyerly HK, Matthews TJ, Langlois AJ, Bolognesi DP, Weinhold KJ. Human T-cell lymphotropic virus IIIB glycoprotein (gp120) bound to CD4 determinants on normal lymphocytes and expressed by infected cells serves as target for immune attack. Proceedings of the National Academy of Sciences of the United States of America 1987; 84:4601-4605.

Lyter DW, Bryant J, Thackeray R, Rinaldo CR, Kingsley LA. Incidence of human immunodeficiency virus-related and nonrelated malignancies in a large cohort of homosexual men. Journal of Clinical Oncology 1995; 13:2540-2546.

Madeleine MM, Daling JR, Carter JJ, Wipf GC, Schwartz SM, McKnight B *et al.* Cofactors with human papillomavirus in a population-based study of vulvar cancer. Journal of the National Cancer Institute 1997; 89:1516-1523.

Maden C, Hopkins SG, Smyser M, Lafferty WE. Survival after AIDS diagnosis in Washington state: Trends through 1989 and effect of the case definition change of 1987. Journal of Acquired Immune Deficiency Syndromes 1993; 6:1157-1161.

Malek RS, Goellner JR, Smith TF, Espy MJ, Cupp MR. Human papillomavirus infection and intrepithelial, in situ, and invasive carcinoma of penis. Urology 1993; 42:159-170.

Mann DL, Murray C, Yarchoan R, Blattner WA, Goedert JJ. HLA antigen frequencies in HIV-1 seropositive disease-free individuals and patients with AIDS. Journal of Acquired Immune Deficiency Syndromes 1988; 1:13-17.

Mann DL, Murray C, O'Donnell M, Blattner WA, Goedert JJ. HLA antigen frequencies in HIV-1-related Kaposi's sarcoma. Journal of Acquired Immune Deficiency Syndromes 1990; 3:S51-S55.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959; 22:719-748.

Marier R. The reporting of communicable diseases. American Journal of Epidemiology 1977; 105:587-590.

Marmor M, Friedman-Kien AE, Laubenstein L, Byrum RD, William DC, D'Onofrio S *et al.* Risk factors for Kaposi's sarcoma in homosexual men. Lancet 1982; 1:1083-1087.

Marmor M, Friedman-Kien AE, Zolla-Pazner S, Stahl RE, Rubinstein P, Laubenstein L *et al.* Kaposi's sarcoma in homosexual men. A seroepidemiologic case-control study. Annals of Internal Medicine 1984; 100:809-815.

Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes D. Sexual transmission and the natural history of human herpesvirus 8 infection. New England Journal of Medicine 1998; 338:948-954.

Martin RW III., Hood AF, Farmer ER. Kaposi sarcoma. Medicine 1993; 72:245-261.

Martinsson U, Glimelius B, Sundstrom C. Lymphoma incidence in a Swedish county during 1969-87. Acta Oncology 1992; 31:275-282.

Masood R, Cai J, Law R, Gill P. AIDS-associated Kaposi's sarcoma pathogenesis, clinical features, and treatment. Current Opinion in Oncology 1993; 5:831-834.

Masood R, Zheng T, Tulpule A, Arora N, Chatlynne L, Handy M *et al.* Kaposi's sarcoma-associated herpesvirus infection and multiple myeloma [Technical Comment]. Science 1997; 278:1970- 1971.

Melbye M, Kestens L, Biggar RJ, Schreuder GMT, Gigase PL. HLA studies of endemic African Kaposi's sarcoma patients and matched controls: No association with HLA-DR5. International Journal of Cancer 1987; 39:182-184.

Melbye M, Cote TR, Kessler L, Gail M, Biggar RJ. High incidence of anal cancer among AIDS patients. The AIDS/Cancer Working Group. Lancet 1994; 343:636-639.

Melbye M, Cook PM, Hjalgrim H, Begtrup K, Simpson GR, Biggar RJ *et al.* Risk factors for Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981-1996. International Journal of Cancer 1998; 77:543-548.

Meyers JD, Kuharic HA, Holmes KK. Giardia lamblia infection in homosexual men. British Journal of Venereal Disease 1977; 53:54- 55.

Mildvan D, Gelb AM, William D. Venereal transmission of enteric pathogens in male homosexuals: Two case reports. Journal of the American Medical Association 1977; 238:1387-1389.

Miles SA, Rezai AR, Salazar-Gonzalez JF, Vander Meyden M, Stevens RH, Logan DM *et al.* AIDS Kaposi sarcoma-derived cells produce and respond to interleukin 6. Proceedings of the National Academy of Sciences of the United States of America 1990; 87:4068-4072.

Miles SA, Martinez-Maza O, Rezai A, Magpantay L, Kishimoto T, Nakamura S *et al.* Oncostatin M as a potent mitogen for AIDS- Kaposi's sarcoma-derived cells. Science 1992; 255:1432-1434.

Miller G, Rigsby MO, Heston L, Grogan E, Sun R, Metroka C *et al.* Antibodies to butyrate-inducible antigens of Kaposi's sarcoma- associated herpesvirus in patients with HIV-1 infection. New England Journal of Medicine 1996; 334:1292-1297.

Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. AIDS 1996; 10:1101-1105.

Monini P, DeLellis L, Fabris M, Rigolin F, Cassai E. Kaposi's sarcoma-associated herpesvirus DNA sequences in prostate tissue and human semen. New England Journal of Medicine 1996; 334:1168- 1172.

Montaner JSG, Le T, Hogg R, Ricketts M, Sutherland D, Strathdee SA *et al.* The changing spectrum of AIDS index diseases in Canada. AIDS 1994; 8:693-696.

Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and those without HIV infection. New England Journal of Medicine 1995; 332:1181-1185.

Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. Science 1996a; 274:1739-1744.

Moore PS, Kingsley LA, Holmberg SD, Spira T, Gupta P, Hoover DR *et al.* Kaposi's sarcoma-associated herpesvirus infection prior to onset of Kaposi's sarcoma. AIDS February, 1996b; 10:175-180.

Moore PS, Gao S, Dominguez G, Cesarman E, Lungu O, Knowles DM *et al.* Primary characterization of a herpesvirus agent associated with Kaposi's sarcoma. Journal of Virology January, 1996c; 70: 549-558.

Moore PS, Chang Y. Kaposi's sarcoma (KS), KS-associated herpesvirus, and the criteria for causality in the age of molecular biology. American Journal of Epidemiology 1998; 147: 217-221.

Morfeldt L, Torssander J. Long-term remission of Kaposi's sarcoma following foscarnet treatment in HIV-infected patients. Scand J Infect Dis 1994; 26:749-752.

Moss AR, Osmond D, Bacchetti P, Chermann J, Barre-Sinoussi F, Carlson J. Risk factors for AIDS and HIV seropositivity in homosexual men. American Journal of Epidemiology 1987; 125:1035- 1047.

Moyer LA, Mast EE. Hepatitis B: Virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. American Journal of Preventive Medicine 1994; 10 (Supplement):45-55.

Mueller BA, Schwartz SM. Risk of recurrence of birth defects in Washington State. Paediatric and Perinatal Epidemiology 1997; 11: 107-118.

Mueller NE, Mohar A, Evans A. Viruses other than HIV and non- Hodgkin's lymphoma. Cancer Research (Supplement) 1992; 52:5479s- 5481s.

Mueller NE, Evans AS, London WT. Viruses. In: Schottenfeld D, Fraumeni JF (eds): Cancer Epidemiology and Prevention, Second Edition (pp 502-531). New York, NY: Oxford University Press, 1996.

Munoz A, Schrager LK, Bacellar H, Speizer I, Vermund SH, Detels R *et al.* Trends in the incidence of outcomes defining acquired immunodeficiency syndrome (AIDS) in the Multicenter AIDS Cohort Study: 1985-1991. Am J Epidemiol 1993; 137:423-438.

Nair BC, DeVico AL, Nakamura S, Copeland TD, Chen Y, Patel A *et al.* Identification of a major growth factor for AIDS-Kaposi's sarcoma cells as Oncostatin M. Science 1992; 255:1430-1432.

Nakamura S, Salahuddin SZ, Biberfeld P, Ensoli B, Markham PD, Wong-Staal F *et al.* Kaposi's sarcoma cells: Long-term culture with growth factor from retrovirus-infected CD4+ T cells. Science 1988; 242:426-430.

Neipel F, Albrecht JC, Fleckenstein B. Cell-homologous genes in the Kaposi's sarcoma-associated rhadinovirus human herpesvirus 8: Determinants of its pathogenicity? Journal of Virology 1997a; 71: 4187-4192.

Neipel F, Albrecht JC, Ensser A, Huang YQ, Li JJ, Friedman-Kien AE *et al.* Human herpesvirus 8 encodes a homolog of interleukin 6. Journal of Virology 1997b; 71:839-842.

Newcombe HB, Kennedy JM, Axford SJ, James AP. Automatic linkage of vital records. Science 1959; 130.

Newcombe HB. Handbook of Record Linkage. Methods for Health and Statistical Studies, Administration, and Business. New York: Oxford University Press, 1988.

Obrams GI, Grufferman S. Epidemiology of HIV associated non- Hodgkin lymphoma. Cancer Surveys 1991; 10:91-102.

O'Connell KA, Rudmann AA. Cloned spindle and epitheliod cells from murine Kaposi's sarcoma-like tumors are of endothelial origin. Journal of Investigative Dermatology 1993; 100:742-745.

Oettle AG. Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes. Unio Internationalis Contra Cancrum 1962; 18:330-363.

Osmond DH. Classification and staging of HIV disease. In: Cohen PT, Sande MA, Volberding PA (eds): The AIDS Knowledge Base. A Textbook on HIV Disease from the University of California, San Francisco, and the San Francisco General Hospital. Second Edition (pp 1.1-1 to 1.1-15). Boston, MA: Little, Brown, and Company, 1994.

Owen RL, Dritz SK, Wibbelsman CJ. Venereal aspects of gastroenterology. Western Journal of Medicine 1979; 130:236-246.

Page-Bodkin K, Tappero J, Samuel M, Winkelstein W. Kaposi's sarcoma and faecal-oral exposure [letter]. Lancet 1992; 339:1490.

Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. Journal of the National Cancer Institute Monographs 1998; 23:15- 20.

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. New England Journal of Medicine 1998; 338:853-860.

Parravicini C, Lauri E, Baldini L, Neri A, Poli F, Sirchia G *et al.* Kaposi's sarcoma-associated herpesvirus infection and multiple myeloma [Technical Comment]. Science 1997; 278:1969- 1970.

Payne SF, Rutherford GW, Lemp GF, Clevenger AC. Effect of the revised AIDS case definition on AIDS reporting in San Franciso: Evidence of increased reporting in intravenous drug users. AIDS 1990; 4:335-339.

Pearce N, Bethwaite P. Increasing incidence of non-Hodgkin's lymphoma: Occupational and environmental factors. Cancer Research (Supplement) 1992; 52:5496s-5500s.

Penn I. Kaposi's sarcoma in organ transplant recipients: A report of 20 cases. Transplantation 1979; 27:8-11.

Penn I. Cancers following cyclosporine therapy. Transplantation 1987; 43:32-35.

Penn I. Secondary neoplasms as a consequece of transplantation and cancer therapy. Cancer Detection and Prevention 1988; 12:39- 57.

Penn I. Incidence and treatment of neoplasia after transplantation. Journal of Heart and Lung Transplantation 1993; 12:S328-S336.

Peterman TA, Jaffe HW, Beral V. Epidemiologic clues to the etiology of Kaposi's sarcoma. AIDS 1993; 7:605-611.

Peterson BA, Frizzera G. Multicentric Castleman's Disease. Seminars in Oncology 1993; 20:636-647.

PKWARE Incorporated. PKZIP 2 User Guide, Tutorial, and Command Reference. Brown Deer, WI.: PKWARE Incorporated., 1992.

Pollock MS, Safai B, Dupont B. HLA-DR5 and DR2 are susceptibility factors for acquired immunodeficiency syndrome with Kaposi's sarcoma in different ethnic subpopulations. Disease Markers 1983; 1: 135-139.

Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. Medical Care 1993; 31: 732-748.

Prince HE, Schroff RW, Ayoub G. HLA studies in acquired immune deficiency syndrome patients with Kaposi's sarcoma. J Clin Immunol 1984; 4:242-245.

Rabkin CS, Devesa SS, Zahm SH, Gail MH. Increasing incidence of non-Hodgkin's lymphoma. Seminars in Hematology-Oncology 1993; 30: 286-296.

Rabkin CS, Yellin F. Cancer incidence in a population with a high prevalence of infection with Human Immunodeficiency Virus Type 1. Journal of the National Cancer Institute 1994; 86:1711-1716.

Rabkin CS, Chibwe G, Muyunda K, Musaba E. Kaposi's sarcoma in pregnant women. Nature 1995; 377:21.

Rabkin CS. Association of non-acquired immunodeficiency syndrome- defining cancers with human immunodeficiency virus infection. Journal of the National Cancer Institute Monographs 1998a; 23: 23-25.

Rabkin CS, Testa MA, Fischl MA,VRJ. Declining incidence of Kaposi's sarcoma in AIDS Clinical Trial Group (ACTG) trials [abstract]. Presented at the Second National AIDS Malignancy Conference. Bethesda, MD. Available from: http://healthcg.com/ hiv/2ndnciconf/. Abstract no. S4. 1998b.

Rady PL, Yen A, Rollefson JL, Orengo I, Bruce S, Hughes TK *et al.* Herpesvirus-like DNA sequences in non-Kaposi's sarcoma skin lesions of transplant patients. Lancet 1995; 345:1339-1340.

Rangan SR, Martin LN, Enright FM, Abee CR. Herpesvirus saimiri- induced lymphoproliferative disease in howler monkeys. Journal of the National Cancer Institute 1977; 59:165-171.

Renne R, Zhong W, Herndier B, McGrath M, Abbey N, Kedes D *et al.* Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nature Medicine 1996; 2:342-346.

Rettig MB, Ma HJ, Vescio RA, Pold M, Schiller G, Belson D *et al.* Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients. Science 1997; 276:1851-1854.

Reynolds P, Layefsky ME, Saunders LD, Lemp GF, Payne SF. Kaposi's sarcoma reporting in San Francisco: A comparison of AIDS and cancer surveillance systems. Journal of the Acquired Immune Deficiency Syndromes 1990; 3:S8-S13.

Reynolds P, Saunders LD, Layefsky ME, Lemp GF. An update on Kaposi's sarcoma reporting in San Francisco [letter]. Journal of Acquired Immune Deficiency Syndromes 1991; 4:825-826.

Reynolds P, Saunders LD, Layefsky M, Lemp GF. The spectrum of Acquired Immunodeficiency Syndrome (AIDS)-associated malignancies in San Francisco, 1980-87. American Journal of Epidemiology 1993; 137:19-30.

Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK. SEER CAncer Statistics Review, 1973-1994. Bethesda, MD: National Cancer Institute, 1997.

Rosai J. A riddle within a puzzle (Chapter 1, pp. 3-7). In: Gottlieb GJ and Ackerman AB (eds). Kaposi's Sarcoma: A Text and Atlas. Philadelphia, PA: Lea and Febiger, 1988.

Rosenthal E, Formanto JL, Giudicelli J, Hoffman P, Milano G, Cassuto JP. Estrogen, progesterone, and androgen and their receptors in epidemic Kaposi's sarcoma. Proceedings of the 9th International Conference on AIDS 1993; Abstract No. 403.

Roth WK, Brandstetter H, Sturzl M. Cellular and molecular features of HIV-associated Kaposi's sarcoma. AIDS 1992; 6:895- 913.

Rothman KJ, Greenland S. Modern Epidemiology. Second Edition. Philadelphia: Lippincott-Raven, 1998.

Russo JJ, Bohenzky RA, Chien M, Chen J, Yan M, Maddalena D *et al.* Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proc Natl Acad Sci USA 1996; 93:14862-14867.

Rutgers JL, Wieczorek R, Bonetti F, Kaplan KL, Posnett DN, Friedman-Kien AE *et al.* The expression of endothelial cell surface antigens by AIDS-associated Kaposi's sarcoma. Am J Pathol 1986; 122:493-499.

Rutherford GW, Payne SF, Lemp GF. The epidemiology of AIDS- related Kaposi's sarcoma in San Francisco. Journal of Acquired Immune Deficiency Syndromes 1990; 3:S4-S7.

Salahuddin SZ, Nakamura S, Biberfeld P, Kaplan MH, Markham PD, Larsson L *et al.* Angiogenic properties of Kaposi's sarcoma- derived cells after long-term culture in vitro. Science 1988; 242:430-433.

SAS Institute I. SAS/STAT User's Guide, Version 6, Fourth Edition, Volumes 1 and 2. Cary, NC: SAS Institute, Inc., 1989.

SAS Institute Incorporated. SAS Guide to the SQL Procedure: Usage and Reference, Version 6, First Edition. Cary, NC.: SAS Institute Incorporated, 1993.

Schalling M, Ekman M, Kaaya EE, Linde A, Biberfeld P. A role for a new herpes virus (KSHV) in different forms of Kaposi's sarcoma. Nature Medicine 1995; 1:707-708.

Schmerin MJ, Gelston A, Jones TC. Amebiasis: An increasing problem among homosexuals in New York City. Journal of the American Medical Association 1977; 238:1386-1387.

Schreeder MT, Thompson SE, Hadler SC, Berquist KR, Zaidi A, Maynard JE *et al.* Hepatitis B in homosexual men: Prevalence and infection and factors related to transmission. Journal of Infectious Diseases 1982; 146:7-15.

Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM *et al.* Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. Journal of the National Cancer Institute 1998; 90:1626-1636.

Simon M, Kind P, Kaudewitz P, Graf A, Schirren CG, Raffeld M *et al.* Detection of herpesvirus-like DNA in HIV-associated and classical Kaposi's sarcoma. Archives of Dermatological Research 1996; 288:402-404.

Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L *et al.* Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 1996; 348:1133- 1138.

Sinkovics JG. Kaposi's sarcoma: Its oncogenes and growth factors. Critical Reviews in Oncology/Hematology 1991; 11:87-107.

Snider WD, Simpson DM, Aronyk KE, Nielsen SL. Primary lymphoma of the nervous system associated with acquired immune-deficiency syndrome [letter]. New England Journal of Medicine 1983; 308:45.

Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P *et al.* Kaposi's sarcoma-associated herpesvirus-like DNA sequences in Multicentric Castleman's Disease. Blood 1995; 86: 1276-1280.

Sporano JA, Anand K, Mitnick R. Effect of protease inhibitor therapy on the incidence of HIV-associated malignancies at tn urban medical center [abstract]. Presented at the Second National AIDS Malignancy Conference. Bethesda, MD. Available from: http://healthcg.com/hiv/2ndnciconf/. Abstract no. S9. 1998.

Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. Journal of the American Medical Association 1988; 260:1429-1433.

Staskus KA, Zhong W, Gebhard K, Herndier B, Wang H, Renne R *et al.* Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. Journal of Virology 1997; 71: 715-719.

State of Washington. Washington Administrative Code. Chapter 246-100, Communicable and certain other diseases. Section WAC 246-100-076(c)(i), Reportable diseases and conditions (p. 15). Olympia, WA: State of Washington, 1993.

State of Washington. Revised Code of Washington. Title 70 RCW: Public Health and Safety. Chapter 70:24. (p. 23). Olympia, WA: State of Washington, 1994.

Sturzl M, Roth WK, Brockmeyer NH, Zietz C, Speiser B, Hofschneider PH. Expression of platelet-derived growth factor and its receptor in AIDS-related Kaposi sarcoma in vivo suggests paracrine and autocrine mechanisms of tumor maintenance. Proceedings of the National Academy of Sciences of the United States of America 1992; 89:7046-7050.

Su I, Hsu Y, Chang Y, Wang I. Herpesvirus-like DNA sequence in Kaposi's sarcoma from AIDS and non-AIDS patients in Taiwan [letter]. Lancet 1995; 345:722-723.

Sun X, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TCJr. Human papillomavirus infection in women infected with the human immunodeficiency virus. New England Journal of Medicine 1997; 337:1343-1349.

Symantec Corporation. The Norton Utilities User's Guide. Cupertino, CA.: Symantec Corporation, Peter Norton Group., 1994.

Tenholder MF, Jackson HD. Bronchogenic carcinoma in patients seropositive for human immunodeficiency virus. Chest 1993; 104: 1049-1053.

Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. Cancer 1993; 72: 1779-1783.

Uthman A, Brna C, Weninger W, Tschachler E. No HHV8 in non- Kaposi's sarcoma mucocutaneous lesions from immunodeficient HIV- positive patients [letter]. Lancet 1996; 347:1700-1701.

van Griensven GJP, de Vroome EMM, Goudsmit J, Coutinho RA. Changes in sexual behaviour and the fall in incidence of HIV infection among homosexual men. British Medical Journal 1989; 289:218-221.

van Griensven GJ, Boucher EC, Coutinho RA. Oro-anal sex and the occurrence of Kaposi's sarcoma. Genitourinary Medicine 1993; 69:77-78.

Varma VA, Sanchez-Lanier M, Unger ER, Clark C, Tickman R, Hewan- Lowe K *et al.* Association of human papillomavirus with penile cancer: A study using polymerase chain reaction and in situ hybridization. Human Pathology 1991; 22:908-913.

Vermund SH, Kelley KF, Klein RS, Feingold AR, Schreiber K, Munk G *et al.* High risk of human papillomavirus infection and cervical squamous intraepithelial lesions among women with symptomatic human immunodeficiency virus infection. American Journal of Obstetrics and Gynecology 1991; 165:392-400.

Veugelers PJ, Strathdee SA, Moss AR, Page KA, Tindall B, Schechter MT *et al.* Is the human immunodeficiency virus-related Kaposi's sarcoma epidemic coming to an end? Insights from the Tricontinental Seroconverter Study. Epidemiology 1995; 6:382-386.

Vogel J, Hinrichs SH, Reynolds RK, Luciw PA, Jay G. The HIV tat gene induces dermal lesions resembling Kaposi's sarcoma in transgenic mice. Nature 1988; 335:606-611.

Vogt RL, LaRue D, Klaucke DN, Jillson DA. Comparison of an active and passive surveillance system of primary care providers for hepatitis, measles, rubella, and salmonellosis in Vermont. American Journal of Public Health 1983; 73:795-797.

Wahman A, Melnick SL, Rhame FS, Potter JD. The epidemiology of classic, African, and immunosuppressed Kaposi's sarcoma. Epidemiologic Reviews 1991; 13:178-199.

Wajda A, Roos LL, Layefsky M, Singleton JA. Record linkage strategies. Part 2: Portable software and deterministic matching. Methods of Information in Medicine 1991; 30:210-214.

Washington State Department of Health. Annual Communicable Disease Report, 1995. Seattle, WA: Washington State Department of Health, Office of Epidemiology, Communicable Disease Epidemiology Section, 1995.

Weiss RA, Whitby D, Talbot S, Kellam P, Boshoff C. Human herpesvirus type 8 and Kaposi's sarcoma. Journal of the National Cancer Institute Monograph 1998; 23:51-54.

Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C *et al.* Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-

infected individuals and progression to Kaposi's sarcoma. Lancet 1995; 346:799-802.

Whitby D, Boshoff C, Luppi M, Torelli G. Kaposi's sarcoma- associated herpesvirus infection and multiple myeloma [Technical Comment]. Science 1997; 278:1971-1972.

Wiggins CL, Thomas DB, Koutsky LA, Frederick M, Maden C. An evaluation of Kaposi's sarcoma surveillance. Presented at the Annual Meeting of the North American Association of Central Cancer Registries. 1994; .

Wiggins CL, Thomas DB. The use of computerized record linkages to study cancer among people with AIDS. Journal of Registry Management 1995; 22:80-84.

Wiggins CL, Aboulafia DM, Ryland LM, Buskin SE, Hopkins SG, Thomas DB. Decline in HIV-associated Kaposi's sarcoma and non- Hodgkin's lymphoma following the introduction of highly active antiretroviral therapy [abstract]. Presented at the Third National Malignancy Conference. Bethesday, MD. 1999.

Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Research (Supplement) 1992; 52:5485s-5488s.

Zheng T, Mayne ST, Boyle P, Holford TR, Liu WL, Flannery J. Epidemiology of non-Hodgkin lymphoma in Connecticut. Cancer 1992; 70:840-849.

Ziegler JL, Drew WL, Miner RC, Mintz L, Rosenbaum E, Gershow J *et al.* Outbreak of Burkitt's-like lymphoma in homosexual men. Lancet 1982; 2:631-633.

Appendix 1

Confidentiality agreement between the investigators
and the Washington State Department of Health

STATE OF WASHINGTON
DEPARTMENT OF SOCIAL AND HEALTH SERVICES
Olympia, Washington 98504-0095
Human Research Review Section, MS: 45205

December 28, 1994

TO: Chuck Wiggins

FROM: Mike Garrick

SUBJECT: FINAL CONFIDENTIALITY AGREEMENT

Attached is the final version of the Confidentiality Agreement for your project. The Agreement incorporates the comments in your December 27 memo, as well as Jeanette's request that the "linkage key" be stored and maintained at her Office. I have also attached "ATTACHMENT 1" which you sent to me on November 14.

Please obtain the signatures of the researchers, as well as Dr. Stehr-Green's signature if that is convenient. When you send the signed Agreement back to me, I'll request the remaining signatures from persons located in Olympia. When completed, I'll return a copy of the signed Agreement to you and to Dr. Stehr-Green.

Call me at 753-0424 if you have any questions.

DEPARTMENT OF HEALTH

COMMUNITY AND FAMILY HEALTH

Olympia, Washington 98504

CONFIDENTIALITY AGREEMENT

Agreement made between Laura Koutsky, Ph.D., Associate Director, Center for AIDS and STD, University of Washington, David B. Thomas, M.D., Dr.P.H., Head, Program in Epidemiology, Fred Hutchinson Cancer Research Center, and Charles Wiggins, M.S.P.H., Doctoral Student, Department of Epidemiology, University of Washington and Research Associate, Fred Hutchinson Cancer Research Center (hereinafter referred to as "RESEARCHERS"), and Maxine Hayes, M.D., Assistant Secretary, Community and Family Health, Jeanette Stehr-Green, M.D., Director, Office of HIV/AIDS Epidemiology and Evaluation, and Larry Klopfenstein, M.P.A., Director, Office of STD Services (hereinafter referred to as "DOH").

WHEREAS the RESEARCHERS have submitted a written research proposal entitled "Supplemental Class IV HIV Surveillance" to DOH dated April 24, 1992, and an addendum to this research entitled "Kaposi's Sarcoma and Sexually Transmitted Diseases" to DOH dated April 25, 1994, copies of which are annexed hereto and made a part hereof; and

WHEREAS the DSHS/DOH Human Research Review Board has reviewed said proposal, has determined that it clearly specifies the purposes of the research and the information sought and is of importance in terms of the agency's program concerns, that the research purposes cannot be reasonably accomplished without disclosure of information in individually identifiable form and without waiver of the informed consent of the person to whom the record pertains or the person's legally authorized representative, that disclosure risks have been minimized and that remaining risks are outweighed by anticipated health, safety or scientific benefits, and has approved said proposal with respect to scientific merit and the protection of human subjects; and

WHEREAS the RESEARCHERS have declared to be in receipt of the department's policy for the protection of human subjects (Guide to DSHS/DOH Policy on Protection of Human Research Subjects, Revised March 1, 1990) and the Washington State law on the disclosure of personal records for research purposes (RCW 42.48),

NOW THEREFORE, IT IS AGREED AS FOLLOWS:

1. DOH authorizes the RESEARCHERS to access, and use for purposes described in their study addendum dated April 25, 1994, HIV/AIDS Reporting System (HARS) records, and Washington State Syphilis Registry (WSSR) records. All records in each database will be disclosed to the RESEARCHERS. Data elements listed in Attachment 1 to this Agreement will be disclosed to the RESEARCHERS. DOH authorizes the

RESEARCHERS to link the HARS and WSSR records with Cancer Surveillance System (CSS) records maintained by the Fred Hutchinson Cancer Research Center (FHCRC) to create a "Research Database."

2. The RESEARCHERS will:

(a) Use the "Research Database" only to characterize the association between infection with treponema pallidum and subsequent development of Kaposi's sarcoma among individuals with AIDS;

(b) Follow the procedures specified in Attachment 1 to this Agreement to create, transport, store, maintain and analyze the "Research Database";

(c) Create "static file" versions of the HARS, CSS, and WSSR, and use confidential data items (i.e., patient identifying information) listed in Tables 1, 3, and 5 in Attachment 1 for purposes of linking records in the "static files";

(d) Use FHCRC linkage software to produce a file that lists the record identification numbers from each "static file" that meet predetermined linkage criteria;

(e) With the assistance of DOH staff designated by the DOH signatories to this Agreement, review and verify the potential matches, and link the "static file" records to create the "Research Database", which includes only non-confidential data items (listed in Tables 2, 4, and 6 in Attachment 1), and which contains no patient identifying information;

(f) Create one "linkage key" which contains an arbitrary record identification number for each record in the "Research Database" and the corresponding record identification numbers from HARS, CSS, and WSSR, but which contains no patient identifying information, and store and maintain the "linkage key" at the DOH Office of HIV/AIDS Epidemiology and Evaluation;

(g) Maintain a Checklist of Record Linkage Activities to document that each step outlined in Attachment 1 to this Agreement has been completed, and submit a signed copy of the Checklist to the DSHS/DOH Human Research Review Board at the completion of each stage of the linkage;

(h) Restrict access to the "static files," all temporary files created during the linkage, the files of potential matches, the "Research Database" and the "linkage key" to persons who have signed this Agreement and to those DOH staff who are designated by the DOH signatories to this Agreement;

(i) Create only one copy of the "Research Database", with the original maintained by Charles Wiggins at the Fred Hutchinson Cancer Research Center, and the copy maintained by Jeanette Stehr-Green at the Office of HIV/AIDS Epidemiology and Evaluation;

(j) Store and transport all files in an encrypted format with password protection, and maintain them in secure locked locations, as specified in Attachment 1 to this Agreement;

(k) Notify the DSHS/DOH Human Research Review Board if other identifiable data not specified in this Agreement are needed for the study;

(l) Report and publish findings in a manner that does not permit identification of persons whose records are used in the research;

(m) Destroy the "linkage key", all temporary files created during the linkage, the files of potential matches, and all individual identifiers associated with DOH records or record information when study purposes have been accomplished, and provide written certification to the DSHS/DOH Human Research Review Board that this requirement has been fulfilled.

3. The RESEARCHERS will not:

(a) Link DOH records or record information, or study database records, with information obtained from other sources without the express written permission of the DSHS/DOH Human Research Review Board;

(b) Contact or attempt to contact any person identified in records provided by DOH, or access their medical records, or contact their health care providers, without the express written permission of the DSHS/DOH Human Research Review Board;

(c) Disclose, publish, provide access to, or otherwise make known any individually identifiable information in DOH records released under this Agreement, or in study database records created under this Agreement, except as provided in RCW 42.48.040;

(d) Copy, duplicate or otherwise retain individually identifiable information provided or created under this Agreement for any use after study purposes have been accomplished.

4. The RESEARCHERS agree to use the information provided by DOH for no purposes other than those described in their proposal to DOH. Any changes in study design and methods, and changes that may affect approved study purposes, will be subject to prior

review and approval by the DSHS/DOH Human Research Review Board and by DOH Directors who have signed this Agreement;

5. DOH assume no responsibility for the accuracy or integrity of data derived or created from the source data provided under this Agreement, or for the accuracy or integrity of the source data once the RESEARCHERS have altered or modified the data, or linked the data with other data files;

6. DOH assumes no responsibility for the accuracy or validity of published or unpublished conclusions based in whole or in part on analyses of data provided to the RESEARCHERS.

7. The RESEARCHERS agree that DOH shall have the right, at any time, to monitor, audit, and review activities and methods in implementing this Agreement in order to assure compliance therewith. The RESEARCHERS agree to fully comply with all such requests in a timely manner.

8. In the event the RESEARCHERS fail to comply with any terms of this Agreement, DOH shall have the right to take such action as it deems appropriate, including termination of this Agreement. If the Agreement is terminated, the RESEARCHERS will forthwith return all information provided by DOH, including all materials derived from this information, or make such alternative disposition of provided and derived information as directed by DOH. The exercise of remedies pursuant to this paragraph shall be in addition to all sanctions provided by law, and to legal remedies available to parties injured by unauthorized disclosure.

9. The RESEARCHERS will hold DOH harmless from any damage or other liability which might be assessed against DOH as a result of the uses by researchers of any information received pursuant to this Agreement.

10. Unauthorized disclosure of any identifiable information provided under this Agreement is a gross misdemeanor and may also result in a civil penalty of not more than ten thousand dollars for each violation, under the provisions of RCW 42.48.050.

11. This Agreement becomes effective on the date it is signed by the DOH official authorized to approve disclosure of identifiable records or record information for research purposes. This Agreement remains in effect until September 30, 1996, at which time authority to use data disclosed under this Agreement expires. The terms of this Agreement remain in effect until such time that the RESEARCHERS provide written certification to the DSHS/DOH Human Research Review Board that all DOH records and record information provided under this Agreement, and all copies of the "Research Database" created in whole or in part from DOH records or record information, have been destroyed or returned to DOH.

Confidentiality Agreement
Koutsky, Thomas & Wiggins/Hayes, Stehr-Green & Klopfenstein
Page 5 of 5

In Witness Whereof, the parties have signed their names hereto on the dates appearing with their signatures.

Maxine Hayes, M.D., Assistant Secretary
DOH Community and Family health — Date

Jeanette Stehr-Green, M.D., Director
DOH Office of HIV/AIDS Epidemiology and Evaluations — Date

Larry Klopfenstein, M.P.A., Director
DOH Office of STD Services — Date

Laura Koutsky
Laura Koutsky, Ph.D. Associate Director
UW Center of AIDS and STD — 1/18/95 Date

David B. Thomas
David B. Thomas, M.D., Dr.P.H., Head
FHCRC Program in Epidemiology — 1/18/95 Date

Charles Wiggins
Charles Wiggins, M.S.P.H., Graduate Student
UW Department of Epidemiology — 1/18/95 Date

STEPS FOR DATABASE LINKAGE

ATTACHMENT 1
DOH Project A-042492-H
Agreement 94.13

Contents *Page*

INTRODUCTION

Under the auspices of DOH-Project A-042492-H, "Supplemental Class IV HIV Surveillance," we conducted a computerized linkage of the Washington State HIV/AIDS Reporting System (HARS) and the Cancer Surveillance System (CSS). The original linkage was completed in strict compliance with the confidentiality agreement previously approved for this project, with no breach of confidentiality. We now propose to conduct a second linkage of these databases, using a more sophisticated software package, according to the guidelines outlined in this document. We also propose to link the HARS with records of the Washington State Syphilis Registry (WSSR). Successful completion of this link will allow us to evaluate the possible association between infection with treponema pallidum and subsequent development of Kaposi's sarcoma among individuals with AIDS.

LIST OF ABBREVIATIONS USED IN THIS DOCUMENT

AIDS	Acquired Immunodeficiency Syndrome
HARS	Washington State HIV/AIDS Reporting System. A population-based surveillance system that includes all AIDS patients diagnosed among residents of Washington state since 1982
CDC	United States Centers for Disease Control and Prevention
CSS	Cancer Surveillance System. A population-based cancer registry that covers 13 counties in western Washington state
DOH	Washington State Department of Health
HRRB	Washington State Department of Health Human Research Review Board
KS	Kaposi's sarcoma. One of the original AIDS-defining illnesses, and the most common neoplasm diagnosed among people with AIDS
WSSR	Washington State Syphilis Registry. A laboratory-based repository for all persons with a reactive serologic test for syphilis including, but not limited to, cases of syphilis diagnosed among residents of Washington State. The Washington State Syphilis Registry contains records that date from the 1940's to the present
STD	Sexually transmitted disease

GLOSSARY OF SELECTED TERMS

Confidential data items	Any data item that, in and of itself, uniquely identifies an individual member from one or more of the participating surveillance databases. Examples of confidential data items include name, address, telephone number, and social security number. Identification numbers from the participating surveillance databases *are not* considered to be confidential data items because they must be combined with other data items to uniquely identify individual members of the database.
Confidential data file	A computer data file that contains confidential data items.
Static file	A computer file that captures all data items in a given database at a specific point in time. Each participating organization will create a static file of their respective database to serve as the basis for the research outlined in this proposal.
Linkage key	A computer data file that includes the identification numbers from each of the participating surveillance databases.

PARTICIPATING ORGANIZATIONS AND INVESTIGATORS

University of Washington Center for AIDS and STD. DOH-Project A-042492-H, "Supplemental Class IV HIV Surveillance," is under the direction of Laura Koutsky, Ph.D.. Dr. Koutsky is Associate Director of the University of Washington Center for AIDS and STD, and is Assistant Professor of Epidemiology at the University of Washington.

Cancer Surveillance System/Fred Hutchinson Cancer Research Center. David B. Thomas, M.D., Dr.P.H. is Head of the Program in Epidemiology at the Fred Hutchinson Cancer Research Center. Dr. Thomas is the Principal Investigator for the Cancer Surveillance System, a population-based cancer registry that serves thirteen counties in western Washington state. Dr. Thomas is also Professor of Epidemiology at the University of Washington. Charles Wiggins, M.S.P.H. is a doctoral student in the Department of Epidemiology at the University of Washington. Under the guidance of Drs. Thomas and Koutsky, Mr. Wiggins has developed the research project entitled, "Kaposi's sarcoma and sexually transmitted diseases." Mr. Wiggins will be primarily responsible for the activities outlined in this document.

Office of HIV/AIDS Epidemiology and Evaluation, Washington State Department of Health, Division of HIV/AIDS and STD. This project was initiated under the guidance of William Lafferty, M.D., who was the Director of the Office of HIV/AIDS Epidemiology and Evaluation until 1993. Following Dr. Lafferty's departure from the position, Mike Smyser, M.P.H., and Anne Shields, R.N., M.H.A., served for brief periods as Acting Director. The initial HARS/CSS link was completed during Ms. Shields' tenure. John Peppert served as Acting Director from January through May, 1994. Jeanette Stehr-Green, M.D., assumed the role of Director in May, 1994.

Seattle-King County Department of Public Health, Epidemiology Unit, HIV/AIDS Section. Sharon Hopkins, D.V.M., M.P.H., has provided expertise and guidance during the initial phases of this investigation.

Washington State Syphilis Registry, Office of STD Services, Washington State Department of Health, Division of HIV/AIDS and STD. Larry Klopfenstein, M.P.A., and Leah Cochran, B.A., Office Director and Data Support Coordinator, respectively, of the Office of STD Services, will provide guidance on the use and interpretation of data from the Washington State Syphilis Registry.

SECTION 1.

OUTLINE OF PROPOSED LINKAGES

1.1 Overview

The following sections describe, in detail, each step involved in conducting this linkage. Confidentiality of patient records is of paramount concern. This protocol has been designed to assure that the confidentiality of each patient record is maintained during the computerized linkage of the databases and in subsequent analyses. The *Research Database* will contain no confidential information.

1.2 Administrative agreements

1.2.a. The Directors of the participating organizations will review this document and will sign a letter of intent stating that they have reviewed the enclosed protocol and will follow the procedures outlined therein (see Appendix 1). In the letter of intent, each respective Director will identify the staff member(s) they anticipate will participate in the research, including the name of one individual who will serve as the liaison for this project.

1.2.b. Michael Garrick, Ph.D., Executive Secretary of the DSHS/DOH Human Research Review Board, will prepare a confidentiality agreement to govern this research project. The following individuals will serve as signatories to that agreement: Maxine Hayes, M.D., Assistant Secretary, DOH Community and Family Health; Jeanette Stehr-Green, M.D., Director, Office of HIV/AIDS Epidemiology and Evaluation; David B. Thomas, M.D., Dr.P.H., Head, Program in Epidemiology, Fred Hutchinson Cancer Research Center; Laura Koutsky, Ph.D., Associate Director, UW Center for AIDS and STD; and Charles Wiggins, M.S.P.H., Research Associate, Fred Hutchinson Cancer Research Center. By signing this agreement, these individuals indicate that they will strictly follow the guidelines and procedures outlined therein.

1.2.c. All personnel who participate in this project must adhere to the confidentiality policies as required by the State of Washington (RCW 70.24.105, WAC 246-100-016, and WAC 246-100-091) and the Fred Hutchinson Cancer Research Center. Participating personnel will also agree to follow the confidentiality policies in effect at the respective participating organizations.

1.3 Steps for linking the HARS with the CSS

All activities outlined in this section will be conducted in strict accordance with guidelines for the handling of confidential files as outlined in Section 3 (below). A checklist will be maintained to document when each step of the linkage process has been completed (See Appendix 3).

1.3.a. Define the HARS static file capture date. Representatives of the Office of HIV/AIDS Epidemiology and Evaluation and the CSS will agree upon a date at which time a static copy of the entire HARS database will be captured and stored on a computer disk(s). This date will be referred to as the *HARS static file capture date*. The *HARS static file capture date* will be documented in a brief memo to be signed by the Directors or Acting Directors of the Office of HIV/AIDS Epidemiology and Evaluation and the CSS.

1.3.b. Capture and store a static copy of the HARS file. On the *HARS static file capture date*, a representative of the Office of HIV/AIDS Epidemiology and Evaluation will capture and store a copy of the entire HARS database on a computer disk (or disks, as space requires). This file will be referred to as the *HARS static file*. A copy of the *HARS static file* will be stored at the Office of HIV/AIDS Epidemiology and Evaluation until September 30, 1996. The *HARS static file* may be stored beyond this date with the written approval of the HRRB. The *HARS static file* will not be destroyed before September 30, 1996.

1.3.c. Define the CSS static file capture date. Representatives of the Office of HIV/AIDS Epidemiology and Evaluation and the CSS will agree upon a date at which time a static copy of the entire CSS database will be captured and stored on a computer disk(s). This date will be referred to as the *CSS static file capture date*. The *CSS static file capture date* will be documented in a brief memo to be signed by the Directors or Acting Directors of the Office of HIV/AIDS Epidemiology and Evaluation and the CSS.

1.3.d. Capture and store a static copy of the CSS file. On the *CSS static file capture date*, a representative of the CSS will capture and store a copy of the entire CSS database on a computer disk (or disks, as space requires). This file will be referred to as the *CSS static file*. A copy of the *CSS static file* will be stored at the CSS until September 30, 1996. The *CSS static file* may be stored beyond this date with the written approval of the HRRB. The *CSS static file* will not be destroyed before September 30, 1996.

1.3.e. Linking the files. At a mutually agreeable date, representatives of the Office of HIV/AIDS Epidemiology and Evaluation and the CSS will link the *HARS* and *CSS static files*. The computerized linkage will take place at the Office of HIV/AIDS Epidemiology and Evaluation in Seattle, Washington. The *HARS* and *CSS static files* will be linked with the use of software to be provided by the CSS. Confidential data items from the HARS and the CSS that will be used in the linkage process are listed in Tables 1 and 3, respectively (Appendix 2).

1.3.f. Destroy all temporary work files that were created during the linkage. The linkage software creates temporary work files during the linkage process. Immediately upon completion of the HARS/CSS linkage, all relevant temporary files will be deleted from the host machine, using software that erases files according to U.S. Department of Defense standards (i.e., Norton utilities).

1.3.g. Reviewing the linked records. The output from the linkage program outlined in step 1.3.e (above) will be a computer file listing the records from each registry that meet predetermined matching criteria. The file that contains possible matches from this linkage will be kept on-site at the Office of HIV/AIDS Epidemiology and Evaluation in Seattle during the entire time period required to review and verify the linked records. Charles Wiggins will be responsible for reviewing and verifying the potential matches, with assistance from staff members from the participating organizations. This review will take place on-site at the Office of HIV/AIDS Epidemiology and Evaluation in Seattle.

1.3.h. Deleting the list of potential matches. All copies of the computerized file of potential matches between The HARS and the CSS will be deleted once the integrity of the linkage has been established, or six months following the date of the initial linkage, whichever comes first. This deadline may be extended with written approval from DOH-HRRB.

1.4 Steps for linking the HARS with the WSSR

All activities outlined in this section will be conducted in strict accordance with guidelines for the handling of confidential files as outlined in Section 3 (below). A checklist will be maintained to document when each step of the linkage process has been completed (See Appendix 3).

1.4.a. Define the WSSR static file capture date. Representatives of the Office of HIV/AIDS Epidemiology and Evaluation, the WSSR, and the CSS will agree upon a date at which time a copy of the entire WSSR database will be captured and stored on a computer disk(s). This date will be referred to as the *WSSR static file capture date*. The *WSSR static file capture date* will be documented in a brief memo to be signed by the Directors or Acting Directors of the Office of HIV/AIDS Epidemiology and Evaluation, the WSSR, and the CSS.

1.4.b. Capture and store a static copy of the WSSR file. On the *WSSR static file capture date*, a representative of the WSSR will capture and store a copy of the entire WSSR database on a computer disk (or disks, as space requires). This file will be referred to as the *WSSR static file*. A copy of the *WSSR static file* will be stored at the WSSR until September 30, 1996. The *WSSR static file* may be stored beyond this date with the written approval of the DOH-HRRB. The *WSSR static file* will not be destroyed before September 30, 1996.

1.4.c. Linking The HARS and WSSR files. At a mutually agreeable date, representatives of the Office of HIV/AIDS Epidemiology and Evaluation , WSSR, and CSS will link the *HARS* and *WSSR static files*. The computerized linkage will take place at the WSSR office in Olympia, Washington. The *HARS* and the *WSSR static files* will be linked with the use of software to be provided by the CSS. The confidential data items from the HARS and the WSSR that will be used in the linkage process are listed in Tables 1 and 5, respectively (Appendix 2).

1.4.d. Destroy all temporary work files that were created during the linkage. The linkage software creates temporary work files during the linkage process. Immediately upon completion of the HARS/WSSR linkage, all such temporary files will be deleted from the host machine, using software that erases files according to U.S. Department of Defense standards (i.e., Norton utilities).

1.4.e. Reviewing the linked records. The output from the linkage program outlined in step 1.4.c (above) will be a computer file listing the records from each registry that meet predetermined matching criteria. The file that contains possible matches from this linkage will be kept on-site at the WSSR in Olympia during the entire time period required to review and verify the linked records. Charles Wiggins will be responsible for reviewing and verifying the potential matches, with assistance from HARS and WSSR staff members. This review will take place on-site at the WSSR in Olympia.

1.4.f. Deleting the list of potential matches. All copies of the computerized file of potential matches between the HARS and the WSSR will be deleted once the integrity of the linkage has been established, or at six months following the date of the initial linkage, whichever comes first. This deadline may be extended with written approval from HRRB.

SECTION 2.

CREATING AND MAINTAINING THE RESEARCH DATABASE

2.1.a. The Research Database. The assemblage of selected non-confidential data items from the linked files of the HARS, CSS, and WSSR will be referred to as the *Research Database*.

2.1.b. Exclude confidential information. The *Research Database* will contain no confidential information. Specifically, the file will exclude patient name, address (street, city), telephone number, and social security number. The "Miscellaneous" data item from the WSSR, which sometimes contains confidential patient information, will not be included in the *Research Database*. The *Record Identification Number* outlined in item 2.1.d (below) will not, in and of itself, allow for the identification of an individual patient.

2.1.c Contents of the research database. The non-confidential data items from the HARS, CSS, and WSSR to be included in the *Research Database* are listed in Tables 2, 4, and 6, respectively (Appendix 2).

2.1.d. Record Identification Number. Each record in the *Research Database* will be assigned a unique *Record Identification Number*. The *Record Identification Number* will contain no components of patient identifying information, nor bear any resemblance to identification numbers from the HARS, CSS, WSSR, or any other component databases.

2.1.e. Linkage Key. We propose to maintain a computer file to serve as a *Linkage Key* to the component databases in the event that questions arise concerning data items from these databases. The *Linkage Key* will contain the *Record Identification Number* from the *Research Database*, as well as the corresponding identification numbers from the HARS, CSS, and WSSR. The *Linkage Key* will be stored in a secure place on-site at the Office of HIV/AIDS Epidemiology and Evaluation in Seattle. Access to the Linkage Key will be granted to Charles Wiggins by the Director/Acting Director of the Office of HIV/AIDS Epidemiology (or her designate) solely for the purpose of verifying/updating potentially erroneous data items in the *Research Database*. The *Linkage Key* will not be used by any person for purposes other than those outlined in this document. The *Linkage Key* will be maintained in strict accordance with the protocol outlined in Section 3 (below). The *Linkage Key* will not be destroyed until the Directors or Acting Directors agree to do so, and sign a joint memo to that effect. The DOH-HRRB may request that the *Linkage Key* be destroyed after consulting with the Directors/Acting Directors.

2.1.f. Location and maintenance of the Research Database. The original/working copy of the *Research Database* will be kept in the office of Charles Wiggins at the Fred Hutchinson Cancer Research Center. Although the *Research Database* contains no confidential information, the file will be maintained in strict accordance with the protocol outlined in Section 3 (below). Mr. Wiggins will coordinate all updates to the *Research Database*.

2.1.g. Other and subsequent uses of the Research Database. The *Research Database* will not be used for purposes other than those approved in DOH-Project A-042492-H, "Supplemental Class IV HIV Surveillance." When the present research has been completed, all copies of the *Research Database* will be destroyed, unless otherwise specified by a joint agreement of the Directors or Acting Directors.

2.1.h. Access to the Research Database. The researchers will create the original and one copy of the *Research Database*. Charles Wiggins will be responsible for the original *Research Database*, which will be kept at the Fred Hutchinson Cancer Research Center. Jeanette Stehr-Green will be responsible for the single copy of the Research Database to be kept at the Office of HIV/AIDS Office of Epidemiology and Evaluation.

SECTION 3.

PROTOCOL FOR FILE MAINTENANCE DURING TRANSPORTATION, STORAGE, AND ANALYSIS

3.1.a Copies of the Research Database. Charles Wiggins will be responsible for the original *Research Database*, which will be kept at the Fred Hutchinson Cancer Research Center. Jeanette Stehr-Green will be responsible for the single copy of the Research Database to be kept at the Office of HIV/AIDS Office of Epidemiology and Evaluation.

3.1.b. File storage when files are not in use. When not in use, all files will be stored on a computer diskette in an encrypted format with password protection. The computer diskettes on which these files reside will be kept in a locked receptacle within a protected building with restricted access. The name(s) assigned to each computer file will contain no reference to the file contents.

3.1.c. File storage when files are in transit. When in transit, all files will be stored on a computer diskette in an encrypted format with password protection. At no time while in transit will the diskette(s) be left unattended. The name(s) assigned to each computer file will contain no reference to the file contents.

3.1.d. File access during linkage, review, and analysis. At no time will files with confidential information be left unattended or unsecured. If, for any reason, the research personnel must leave the files with confidential information unattended, the files must be secured in accordance with item 3.1.a (above). Files with non-confidential information (i.e., the *Research Database*) may be left unattended for brief periods during the working day, provided that the file is being used within a work area with restricted access. The *Research Database* will be used only on a stand alone computer system and will not be accessible from a LAN or other network.

APPENDIX 1

LETTER OF INTENT

We, the undersigned, have reviewed the contents of this proposal and agree to follow the procedures outlined herein. The staff members who will be working on this project are specified below, including the individual who will serve as liaison for each participating organization.

Office of HIV/AIDS Epidemiology and Evaluation

_____ _____
Jeanette Stehr-Green, M.D. Date
Director, Office of HIV/AIDS
Epidemiology and Evaluation

Designated contact person: _____

Specify other personnel who will work on this project:

_____

_____

Cancer Surveillance System, Fred Hutchinson Cancer Research Center

David B. Thomas 1/18/95
David B. Thomas, M.D., Dr.P.H. Date
Head, Program in Epidemiology

Designated contact person: Charles Wiggins, M.S.P.H.

Specify other personnel who will work on this project:

Mary Potts, Diane Guay, Paul Maier

_____

Washington State Syphilis Registry

_____ _____
Larry Klopfenstein, M.P.A. Date
Office Director, Office of STD Services

Designated contact person: Leah Cochran

Specify other personnel who will work on this project:

_____

_____

Epidemiology Unit, HIV/AIDS Section
Seattle-King County Department of Public Health

Sharon Hopkins DVM, MPH 1/18/95
Sharon Hopkins, D.V.M., M.P.H. Date
Director, Epidemiology Unit

Designated contact person: _____

Specify other personnel who will work on this project:

_____

_____

University of Washington Center for AIDS and STD

Laura Koutsky

Laura Koutsky, Ph.D.
Associate Director

1/18/95
Date

Designated contact person: Laura Koutsky, Ph.D.

Specify other personnel who will work on this project:

_____

_____

APPENDIX 2

Table 1. Variables from the Washington State HIV/AIDS Reporting System to be used for linkage to the Cancer Surveillance System

Variable name	*Description*	*Justification*
BIRTH	Date of birth (month, day, year)	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
NAME	Patient name (first, middle, last)	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
SSN	Social security number	Will be used to supplement the initial computerized linkage of datasets and for subsequent manual review of potentially linked records
ADDRESS	Patient's street address at AIDS diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
RCITY	Patient's city of residence at AIDS diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
RCOUNTY	Patient's county of residence at AIDS diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
CURRCITY	Patient's current city of residence (if deceased, city of residence at time of death)	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
CURRCNTY	Patient's current county of residence (if deceased, county of residence at time of death)	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records

Table 1. Variables from the Washington State HIV/AIDS Reporting System to be used for linkage to the Cancer Surveillance System (continued)

Variable name	*Description*	*Justification*
ZIP_CODE	Patient's zip code at AIDS diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
STATENO	HARS identification number	Will be used to construct linkage key for research database

Table 2.2 Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database*

Variable name	*Description*	*Justification*
STATENO	HARS identification number	Will serve as the linkage key for the research database until the *Record Identification Number* is established, at which time STATENO will be removed from the *Research Database*
AGEYEARS	Age in years at time of AIDS diagnosis	Necessary to determine if exposure/disease associations vary by age of patient. Also important for assessing disease risk for cohort members
SEX	Patient's gender	Necessary to determine if exposure/disease associations vary by gender
RACE	Patient's race/ethnicity	Necessary to determine if exposure/disease associations vary by race/ethnicity of patient
ST	State of residence at AIDS diagnosis	Necessary to distinguish in-state from out-of-state cases
RCOUNTY	County of residence at AIDS diagnosis	Will allow for evaluation of surveillance by geographic area
FORM	Type of reporting form (Adult vs. Pediatric)	Allows differentiation between type of reporting form
BRES_ST	State of residence at birth	Because of the potential high mobility of AIDS patients, we anticipate conducting sub-analyses on patients who are likely to have been life-long residents of Washington State. This variable will be used to help define this subset of individuals
STAT	Current mortality status of patient	Necessary to determine the patient's vital status, which is of key importance in identifying "censored" observations for cohort analyses

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
DTHMONTH DTHYEAR	Date of patient death (Month and year, ONLY)	Necessary for determining "end-point" for cohort analyses
F16	Censor date (date of last information)	Necessary for determining "end-point" for cohort analyses
DXMOYR	Date of first AIDS diagnosis	Necessary for defining "starting-point" for cohort analyses
TH_MOYR	Date of first CD4 count <200 or CD4 < 14 percent of total	Necessary for characterizing immunologic status
F8	Flag for AIDS/non-AIDS cases	Necessary to distinguish AIDS from pre-AIDS patients.
FAC_TYPE	Type of facility where diagnosis occurred (inpatient vs. outpatient)	This item will be of use in evaluating the completeness of the surveillance data. Specifically, it will assist in further characterizing eligible patients who were not ascertained by standard case-finding mechanisms
SOURCER	Source of AIDS report	This item will be of use in evaluating surveillance, especially in examining discrepancies between the HARS and CSS
F1	Expanded information on SOURCE	See SOURCE

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
HIVPMOYR	Date of first positive of all HIV tests	The ability to estimate the length of time between seroconversion and development of AIDS will assist in further characterizing the exposure/disease association. This variable, along with HIVNMOYR will allow us to estimate this time interval
COMPLTED	Date form completed	Will facilitate identification of cases reclassified following the change in AIDS case definition (May 1993)
ENTERED	Date entered into HARS	See COMPLTED
MODE	Transmission mode to patient	Necessary to determine if observed exposure/disease associations vary according to primary risk category of patient. MODE provides a summary of the transition mode, however, it may be useful to examine subsets of these categories that may be masked in the summary variable. For that reason, we are requesting the related variables listed below
MODEX	Transmission mode (expanded information)	See MODE

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Regional Database* (Continued)

Variable name	*Description*	*Justification*
SEX_MALE	Sexual relations with male	See MODE
SEX_FMLE	Sexual relations with female	See MODE
IV	IV drug user	See MODE
BLDPRD	Blood product received	See MODE
TRANSFUS	Received blood or blood components	See MODE
TRANPLNT	Tissue/transplant recipient	See MODE
S_IV	Sex with IV drug user	See MODE
S_BI	Sex with bisexual man	See MODE
S_HEMO	Sex with hemophiliac	See MODE
S_TX	Sex with transfusion recipient	See MODE
S_TRNPLT	Sex with transplant recipient	See MODE
S_HIV	Sex with person with AIDS/HIV, risk not specified	See MODE
OTH_RISK	Other risk behavior	See MODE

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
OTH_IMM	Presence of other disqualifying immunodeficiency	It will be important to identify patients with other sources of immunodeficiency. It may be necessary to perform all analyses both with and without these patients
OI_MOYR	Date of diagnosis for first opportunistic infection	Important for characterizing the timing of opportunistic infections while evaluating the exposure/disease relationship
CATEG	Earliest CDC surveillance definition that the patient meets	Will help us to compare cases across different CDC surveillance definitions
TH(1-9)CNT TH(1-9)MOTY TH(1-9)PCT	First (thru 9th) CD4 count Date of 1st (thru 9th) CD4 count Percent of 1st (thru 9th) CD4 count	These variables will be a key element in determining whether or not CD4 count is relevant in the association between exposure and disease
BACT BACTMOYR	Bacterial infections Date of diagnosis, BACT	It will be important to identify whether or not other AIDS-defining illnesses modify the association between STD exposures and development of Kaposi's sarcoma. Also, it may be useful to determine if STD exposure is associated to other AIDS-defining illnesses in addition to Kaposi's sarcoma

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
CANDLUNG	Candidiasis, bronchi, trachea, lung	See BACT
CLNGMOYR	Date of diagnosis, CANDLUNG	
CANDESOP	Candidiasis, esophageal	See BACT
CESOMOYR	Date of diagnosis, CANDESOP	
COCCI	Coccidioidomycosis	See BACT
CCMOYR	Date of diagnosis, COCCI	
CRYPTOCO	Cryptococcosis, extrapulmonary	See BACT
CTCCMOYR	Date of diagnosis, CRYPTOCO	
CRYPTOSP	Cryptosporidiosis, chronic intestinal	See BACT
CRYPMOYR	Date of diagnosis, CRYPTOSP	
CMV	Cytomegalovirus disease	See BACT
CMVMOYR	Date of diagnosis, CMV	
CMVRET	Cytomegalovirus retinitis	See BACT
CMVRMOYR	Date of diagnosis, CMVRET	
DEMENTIA	HIV encephalopathy	See BACT
DEMMOYR	Date of diagnosis, DEMENTIA	
HS	Herpes simplex	See BACT
HSMOYR	Date of diagnosis, HS	

Table 2. 7-4. Variables from the Washington State HIV/AIDS Reporting System to be Included in the *Research Database* (Continued)

Variable name	*Description*	*Justification*
HISTO	Histoplasmosis	See BACT
HISTMOYR	Date of diagnosis, HISTO	
ISO	Isoporiasis, intestinal	See BACT
ISOMOYR	Date of diagnosis, ISO	
LIP	Lymphoid interstitial pneumonitis	See BACT
LIPMOYR	Date of diagnosis, LIP	
MAVIUM	Mycobacterium avium complex or M. kansasii	See BACT
MAVMOYR	Date of diagnosis, MAVIUM	
PULM_TB	M. tuberculosis, pulmonary	See BACT
PTBMOYR	Date of diagnosis, PULM_TB	
TB	M. tuberculosis, disseminated or extrapulmonary	See BACT
TBMOYR	Date of diagnosis, TB	
MYCO	Mycobacterium of other or unidentified species	See BACT
MYCOMOYR	Date of diagnosis, MYCO	
PC	Pneumocystis carinii pneumonia	See BACT
PCMOYR	Date of diagnosis, PC	

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
RP	Pneumonia, recurrent, in 12 month period	See BACT
RPMOYR	Date of diagnosis, RP	
PML	Progressive multifocal leukoencephalopathy	See BACT
PMLMOYR	Date of diagnosis, PML	
SALS	Salmonella septicemia, recurrent	See BACT
SALSMOYR	Date of diagnosis, SALS	
TP	Toxoplasmosis of brain	See BACT
TPMOYR	Date of diagnosis, TP	
WASTING	Wasting syndrome due to HIV	See BACT
WASTMOYR	Date of diagnosis, WASTING	
F3	Other symptomatic (non-AIDS) HIV-associated illnesses	See BACT
CERVIDIS	Carcinoma, invasive cervical	Information about other (non-KS) cancers will be used to evaluate the completeness of surveillance for both the HARS and the CSS. If time permits, we may explore the possible etiologic role of STDs in the development of these cancers, particularly non-Hodgkin's lymphoma
CDISMOYR	Date of diagnosis, CERVDIS	
BURKL	Lymphoma, Burkitt's	See CERVIDIS
BURKMOYR	Date of diagnosis, BURKL	

Table 2. Variables from the Washington State HIV/AIDS Reporting System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
IBL	Lymphoma, immunoblastic	See CERVIDIS
IBLMOYR	Date of diagnosis, IBL	
PLB	Lymphoma, primary in brain	See CERVIDIS
PLBMOYR	Date of diagnosis, PLB	
KS	Kaposi's sarcoma	As with the information on other (non-KS) neoplasms, this variable will allow us to assess the completeness of surveillance for both the HARS and CSS. Preliminary analyses have documented some under-reporting of KS in both registries
KSMOYR	Date of diagnosis, KS	
SYMPMOYR	Date of earliest known B1/B2 condition	Allows us to characterize early disease patterns

Table 3. Variables from the Cancer Surveillance System to be used for linkage to the Washington State HIV/AIDS Reporting System

Variable name	*Description*	*Justification*
BRTHDATE	Date of birth (month, day, year)	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
NAME	Patient name (last, first, middle initial)	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
SSN	Social security number	Will be used to supplement the initial computerized linkage of datasets and for subsequent manual review of potentially linked records
STREET	Patient's street address at time of cancer diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
CITY	Patient's city of residence at time of cancer diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
COUNTY	Patient's county of residence at time of cancer diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
ZIP	Patient's zip code at time of cancer diagnosis	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
CRF	CSS patient identification number	Will be used to construct linkage key for the research database

Table 4.1. Variables from the Cancer Surveillance System to be included in the *Research Database*

Variable name	*Description*	*Justification*
BIRTHPL	Place of birth	Because of the potential high mobility of AIDS patients, we anticipate conducting sub-analyses on patients who are likely to have been life-long residents of Washington State. This variable will be used to help define this subset of individuals
AGE_DX	Age at time of cancer diagnosis	Will be used to augment HARS data. Exposure/disease associations will be stratified to determine if observed associations vary by age
SEX	Patient's gender	Will be used to augment HARS data. Exposure/disease associations will be stratified to determine if observed associations vary by gender
RACE SPANISH	Race Spanish surname	Will be used to augment HARS data. Exposure/disease associations will be stratified to determine if observed associations vary among racial/ethnic groups
VIT_STAT	Vital status (alive, dead)	Will be used to augment HARS data. Vital status is of key importance in identifying "censored" observations in cohort analyses
LASTDATE	Date of last follow-up (month, year)	Will be used to augment HARS data. Necessary for determining "end-point" for cohort analyses
COUNTY	Patient's county of residence at time of cancer diagnosis	For evaluation of completeness of surveillance. Also for quality-control cross-check with HARS database
HIST	Histology, grade, and behavior of tumor	Necessary to accurately characterize the tumor's histologic type, grade, and behavior.

Table 4.3. Variables from the Cancer Surveillance System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
SITE	Primary site of cancer	Necessary for determining the primary site of the tumor. Will be used to help evaluate the completeness of CSS/HARS surveillance and for quality control
DXDATE	Date of cancer diagnosis (month, day, year)	Date of cancer diagnosis will be a key element in evaluating the association between exposure and subsequent development of cancer. Also, this variable will be useful in determining whether a cancer diagnosis should have been included in the HARS record (i.e., if it occurred near the time of AIDS diagnosis)
SEQUENCE	Sequence of tumor for patients with more than one primary cancer site	Distinguishes between primary cancer sites for patients with more than one cancer
EOD	Extent of disease. Includes detailed information about the tumor stage, size, metastasis (if applicable)	This variable allows us to examine tumor stage and metastasis at the time of diagnosis. It may be of particular interest to determine if the aggressive forms of Kaposi's sarcoma are related to STD exposure
STAGE	Summary stage of disease of diagnosis.	same as EOD
SOURCE	Type of reporting source	Important for evaluating surveillance mechanisms. For example, this variable will assist in characterizing the type of patients who are "missed" by the HARS
BASIS_DX	Basis of diagnosis (i.e., histology, clinical diagnosis, x-ray, etc.)	Important for evaluating surveillance mechanisms. For example, this variable will assist in characterizing the type of patients who are "missed" by the HARS

Table 4: Variables from the Cancer Surveillance System to be included in the *Research Database* (continued)

Variable name	*Description*	*Justification*
MARITAL	Marital status	For evaluation of prior surveillance reports of Kaposi's sarcoma that have relied on "single" marital status as a surrogate marker for homosexually active men at risk of developing AIDS-related cancers
RX	First course of cancer-directed treatment	May be of use in evaluating subsequent outcomes (other cancers, death)

Table 5. Data items from the Washington State Syphilis Registry to be used for linkage with the HIV/AIDS Reporting System

Variable name	*Description*	*Justification*
PATIENTNO	Patient number	Will be used to construct the linkage key for the research database
LASTNAME	Patient's last name	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
FIRSTNAME	Patient's first name	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
MI	Patient's middle initial	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records
AKA AKAONLY	Other names this patient may be known by	Will be used to supplement the initial computerized linkage of datasets and for subsequent manual review of potentially linked records
MISC	Miscellaneous information about this patient (may include social security number)	Will be used to supplement the initial computerized linkage of datasets and for subsequent manual review of potentially linked records
DOB	Date of birth (month, day, year)	Necessary for initial computerized linkage of datasets and for subsequent manual review of potentially linked records

Table 5. Data items from the Washington State Syphilis Registry to be used for linkage with the HIV/AIDS Reporting System (continued)

Variable name	*Description*	*Justification*
STREET1	First line of patient's street address	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
STREET2	Second line of patient's street address	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
CITY	City of residence	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
COUNTYCODE	County of residence (FIPS code)	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
STATE	State of residence	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records

Table 5. Data items from the Washington State Syphilis Registry to be used for linkage with the HIV/AIDS Reporting System (continued)

Variable name	*Description*	*Justification*
ZIP	Zip code of residence	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
SEX	Patient's gender	Will be used to supplement the initial computerized linkage of datasets and for subsequent manual review of potentially linked records
P_STREET1	Previous street address-patient's old address	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records
P_CITY	Previous city-patient's old address	Although not used in the computerized linkage, this item provides additional information for the subsequent manual review of potentially linked records

Table 6. Data items from the Washington State Syphilis Registry to be used in the *Research Database*

Variable name	*Description*	*Justification*
EVENTS	Number of events for this patient	Will be useful in identifying patients with multiple events
COUNTYCODE	County of residence (FIPS code)	Will allow for evaluation of data by geographic area
STATE	State of residence	Necessary to distinguish in-state from out-of-state patients
DOB	Date of birth (month, day, year)	Useful for determining age at diagnosis; will supplement data from CSS and HARS
AGE	Age at diagnosis	Will be used to supplement data from the HARS and CSS; necessary to determine if exposure/disease associations vary by age
KNOWNYEAR	Year in which age is known/approximated	Will supplement data on AGE and DOB
KNOWNMNTH	Month in which age is known/approximated	Will supplement data on AGE and DOB
RACE	Patient's race	Will be used to supplement data from the HARS and CSS; necessary to determine if exposure/disease associations vary by race/ethnicity
ETHNICITY	Patient's ethnicity	Will be used to supplement data from the HARS and CSS; necessary to determine if exposure/disease associations vary by race/ethnicity

Table 6. Data items from the Washington State Syphilis Registry to be used in the *Research Database* (continued)

Variable name	*Description*	*Justification*
SEX	Patient's gender	Will be used to supplement data from the HARS and CSS; necessary to determine if exposure/disease associations vary by gender
DATEWRIT	Date record was last modified	May be useful in the event that discrepant information is identified
TIMEWRIT	Time record was last modified	May be useful in the event that discrepant information is identified
MARITAL	Patient's marital status	Will be used to supplement data from the HARS and CSS; for evaluation of prior surveillance reports of Kaposi's sarcoma that relied on "single" marital status for surrogate marker for homosexually active males
SYPHCNTR	Number of syphilis records	Useful for identifying patients with multiple records
MORBCNTR	Number of morbidity records	Useful for identifying patients with multiple records
INTVCNTR	Number of inventory records	Useful for identifying patients with multiple records
ORDER	Order of this patient's records	Necessary for determining the correct order of entries for patients with multiple records

Table 6. Data items from the Washington State Syphilis Registry to be used in the *Research Database* (continued)

Variable name	*Description*	*Justification*
RECVDATE	Date received	Useful for characterizing events related to the diagnosis of syphilis
LAS	Submitting laboratory provider code	Useful for characterizing events related to the diagnosis of syphilis
PROVIDER	Provider code	Useful for characterizing events related to the diagnosis of syphilis
TESTDATE	Date tested	Useful for characterizing events related to the diagnosis of syphilis
TESTTYPE	Type of test	Useful for characterizing events related to the diagnosis of syphilis
RESULT	Result of test	Necessary for establishing the diagnosis of syphilis
ACTION	Action taken	Useful for characterizing events related to the diagnosis of syphilis
C_TEST	Confirmatory test	Necessary for identifying patients who had a test to confirm their diagnosis
SUBLAB	Submitting laboratory	Useful for characterizing events related to the diagnosis of syphilis
CFS_PREG	CFS pregnant test	Useful for characterizing events related to the diagnosis of syphilis

Table 6.5. Data items from the Washington State Syphilis Registry to be used in the *Research Database* (continued)

Variable name	*Description*	*Justification*
DIAGNOSIS	Diagnosis	Necessary for characterizing the diagnosis
TREATDATE	Date of treatment	Necessary for identifying patients who were treated or not treated for disease. Also, may be important to establish whether or not treatment is related to timing of subsequent AIDS diagnosis

APPENDIX 3

Checklist of record linkage activities

Part A. *Linkage of HARS and CSS databases*

Task		*Date completed*	*Witnesses*
A.1	Review of HARS database completed	_____	_____ HARS representative
			_____ CSS representative
A.2	HARS *static file* captured	_____	_____ HARS representative
			_____ CSS representative
A.3	- Review of CSS database completed	_____	_____ HARS representative
			_____ CSS representative
A.4	CSS *static file* captured	_____	_____ HARS representative
			_____ CSS representative

Part A. Linkage of HARS and CSS databases (continued)

Task		*Date completed*	*Witnesses*
A.5	Linkage of HARS and CSS databases	_____	_____ HARS representative
			_____ CSS representative
A.6	Temporary linkage files deleted	_____	_____ HARS representative
			_____ CSS representative
A.7	Record review initiated	_____	_____ HARS representative
			_____ CSS representative
A.8	Record review completed	_____	_____ HARS representative
			_____ CSS representative
A.9	List of potential HARS/CSS matches deleted	_____	_____ HARS representative
			_____ CSS representative

Part B. Linkage of HARS and WSSR databases

Task		*Date completed*	*Witnesses*
B.1	Review of WSSR database completed	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative
B.2	WSSR *static file* captured	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative
B.3	Linkage of HARS and WSSR databases	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative
B.4	Temporary linkage files deleted	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative

Part B. Linkage of HARS and WSSR databases (continued)

Task		*Date completed*	*Witnesses*
B.5	Record review initiated	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative
B.6	Record review completed	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative
B.7	List of potential HARS/WSSR matches deleted	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative

Part C. Construction of the Research Database

Task		*Date completed*	*Witnesses*
C.1	Non-confidential HARS data added to the *Research Database*	_____	_____ HARS representative
			_____ CSS representative
C.2	Non-confidential CSS data added to the *Research Database*	_____	_____ HARS representative
			_____ CSS representative
C.3	Non-confidential WSSR data added to the *Research Database*	_____	_____ WSSR representative
			_____ HARS representative
			_____ CSS representative

Appendix 2

First addendum to the
confidentiality agreement between the investigators
and the Washington State Department of Health

STATE OF WASHINGTON

DEPARTMENT OF SOCIAL AND HEALTH SERVICES

Human Research Review Section, P.O. Box 45205, Olympia, WA 98504-5205

March 28, 1997

TO: Charles Wiggins

FROM: Lilly Moneer

SUBJECT: CONFIDENTIALITY AGREEMENT - ADDENDUM

Enclosed is a copy of your Confidentiality Agreement with all signatures in place. You are free to proceed with your study as planned. Any additional changes in the study purposes, design, or methods are subject to prior review and approval by the Review Board.

Thank you for keeping the Board informed of changes in your study.

94.13

DEPARTMENT OF HEALTH

EPIDEMIOLOGY AND HEALTH STATISTICS
COMMUNITY AND FAMILY HEALTH

FIRST ADDENDUM

CONFIDENTIALITY AGREEMENT

First Addendum to the January 23, 1995 Agreement made between Laura Koutsky, Ph.D., Associate Director, Center for AIDS and STD, University of Washington, David B. Thomas, M.D., Dr.P.H., Head, Program in Epidemiology, Fred Hutchinson Cancer Research Center, and Charles Wiggins, M.S.P.H., Doctoral Student, Department of Epidemiology, University of Washington and Research Associate, Fred Hutchinson Cancer Research Center (hereinafter referred to as "RESEARCHERS"), and Maxine Hayes, M.D., Assistant Secretary, Community and Family Health, Jeanette Stehr-Green, M.D., Director, Office of HIV/AIDS Epidemiology and Evaluation, and Larry Klopfenstein, M.P.A., Director, Office of STD Services, and now to include Elizabeth Ward, Assistant Secretary, Epidemiology and Health Statistics, (hereinafter referred to as "DOH").

NOW THEREFORE, IT IS AGREED AS FOLLOWS:

1. The January 23, 1995 Agreement shall remain in effect until May 21, 1998.

2. DOH will create a "static file" on computer disk(s) from the Washington State Communicable Disease Registry (WSCDR) of all persons aged 16 and older whose records indicate a diagnosis of hepatitis B, hepatitis A, *Entamoeba histolytica*, *Campylobacter spp.*, *Giardia spp.*, *Shigella spp.*, or *Salmonella spp.* during the period January 1, 1974 through December 31, 1994. A copy of this subset of the WSCDR will be retained at the Public Health Laboratory until December 31, 1997. This WSCDR subset file will be linked to the static file of the HIV/AIDS Reporting System (HARS) created for this research and described in the January 23, 1995 Agreement. This linkage will be performed at the Office of Infectious Diseases and Reproductive Health in Olympia, Washington. The confidential data elements from WSCDR used for this linkage are listed in Table A.1; confidential data elements from the HARS database to perform this linkage are listed in the January 23, 1995 Agreement. For all matching records, non-confidential elements of the WSCDR will be extracted for inclusion in the research database; these elements are listed in Table A.2. All temporary work files created during the record linkage process will be destroyed immediately upon completion of the linkage. All copies of the computerized file of potential matching records between HARS and WSCDR will be deleted once the integrity of the linkage has been established.

3. The RESEARCHER will identify cases of non-Hodgkins lymphoma in the Cancer Surveillance System (CSS) static file described in the January 23, 1995 Agreement. The RESEARCHER will identify the non-AIDS-related cases by using the linkage key from the initial HARS/CSS linkage, as described in the January 23, 1995 Agreement. Only non-confidential data elements from CSS for these cases will be added to the research database. This linkage will be performed at the Office of Infectious Diseases and Reproductive Health in Olympia, Washington, where the linkage key for HARS/CSS is held.

4. The RESEARCHERS agree that all terms of their January 23, 1995 Agreement with DOH remain in effect and apply to the additional data disclosed under this Addendum.

In Witness Whereof, the parties have signed their names on the dates appearing with their signatures.

Elizabeth Ward — 3/28/97
Elizabeth Ward, Assistant Secretary
Epidemiology and Health Statistics
Date

Maxine Hayes — 3/20/97
Maxine Hayes, M.D., Assistant Secretary
Community and Family Health
Date

Charles Wiggins — 3/11/97
Charles Wiggins, M.S.P.H., Graduate Student
UW Department of Epidemiology
Date

Table A.1. Data items for HARS/WSCDR record linkage

Variable name	*Type*	*Length*	*Description*
LAST	Char	20	Surname
FIRST	Char	20	First name
MIDDLE	Char	20	Middle name or initial
NICKNAME	Char	20	Nickname
SUFFIX	Char	02	Name suffix (i.e., Jr, Sr., etc.)
BIRTHDATE	Date	08	Date of birth
SEX	Char	01	Sex of subject
RACE	Char	01	Race of subject
STREET_1 STREET_2	Char	30	Subject's street address at time of disease report
CITY	Char	30	Subject's city of residence at time of disease report
COUNTY	Char	02	Subject's county of residence at time of disease report
ZIPCODE	Char	05	Subject's zip code of residence at time of disease report
NUM_WASH	Char	05	Unique identification number used to identify a specific disease report

Table A.2. Data items from the WSCDR to be included in the Research Database

Variable name	*Type*	*Length*	*Description*
DISEASE	Char	02	Two-character code that identifies the disease being registered
COUNTY	Num	02	Identifies the county of residence at time of disease diagnosis
SEX	Char	01	Specifies the subject's sex
RACE	Char	01	Subject's race
DECEASED	Char	01	Indicates the vital status of the subject
DATE_ONS	Date	08	Date of disease onset
DATE_REP	Date	08	Date of report
AGE_YEAR	Num	2	Age in years (> 1 year of age)
OCCUP	Char	30	Occupation (text)

Table A.2. *continued.*

Variable name	*Type*	*Length*	*Description*
DIAGNOSE	Char	1	Additional information regarding the disease diagnosis
MILK_PAT	Char	1	Flag to indicate patient exposed to raw milk
MILK_HSE	Char	1	Flag to indicate household contact of patient exposed to raw milk
DAYC_PAT	Char	1	Flag to indicate patient exposed at day care facility
DAYC_HSE	Char	1	Flag to indicate household contact of patient exposed at day care facility
HOSPLIZE	Char	1	Flag for hospitalization
HOSPCODE	Char	3	Code for specific facility where treated
DATE_ADM	Date	8	Date of admission to hospital
FOOD_HAND	Char	1	Flag for food handler
ENTERIC	Num	1	Enteric disease flag: YES/NO
DATE_LHD	Date	8	Date report received from local health department
DATE_STATE	Date	8	Date report received from state health department

CURRICULUM VITAE

Charles L. Wiggins

Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, MP-474
Seattle, WA 98109
(206) 667-4111

DATE OF BIRTH	February 14, 1956
PLACE OF BIRTH	Denver, Colorado
MARITAL STATUS:	Married, two children

EDUCATION

1999	Ph.D. Epidemiology	University of Washington Seattle, Washington
1983	M.S.P.H. Epidemiology	University of Alabama-Birmingham Birmingham, Alabama
1978	B.S. Health Education	University of New Mexico Albuquerque, New Mexico

PROFESSIONAL EMPLOYMENT

1990-1999	Research Associate Fred Hutchinson Cancer Research Center Seattle, Washington
1983-1990	Epidemiologist New Mexico Tumor Registry University of New Mexico Cancer Center Albuquerque, New Mexico
1986-1989	Project Epidemiologist Belen Sleep Project University of New Mexico School of Medicine Albuquerque, New Mexico

PROFESSIONAL EMPLOYMENT, *continued*

1982-1983	Administrative Assistant to the Department Head Department of Epidemiology University of Alabama - Birmingham Birmingham, Alabama
1978-1982	Reporting Assistant New Mexico Tumor Registry University of New Mexico Cancer Center Albuquerque, New Mexico

PROFESSIONAL ACTIVITIES

1994-present	Member, Network for Cancer Control Research among American Indian and Alaskan Native Populations
1993, 1995	Reviewer, Indian Health Service Tribal Management Grant Ad Hoc Review Committee
1993	Chair, Task Force on Data Analysis. American Association of Central Cancer Registries Task Force to Develop a Standards Document

PROFESSIONAL TRAINING

1995	Participant, Student Workshop Sponsored by the Society for Epidemiologic Research Snowbird, Utah
1992	Histopathobiology of Neoplasia The Edward A. Smuckler Memorial Workshop Sponsored by the National Cancer Institute Keystone, Colorado

PROFESSIONAL TRAINING, *continued*

1986 Epidemiology Summer Session
Sponsored by the New England Epidemiology Institute
Tufts University
Medford, Massachusetts
Courses: Regression and Categorical Data Methods
Epidemiologic Basis of Public Health Policy and Law
Theory and Practice of Case-Control Research
Data Acquisition and Management

1984 Population Estimate Methodology
Sponsored by the U. S. Census Bureau
San Antonio, Texas

1983 Epidemiology Summer Session
Sponsored by the New England Epidemiology Institute
University of Massachusetts
Amherst, Massachusetts
Courses: Multivariate Methods in Epidemiologic Analysis
Cancer Epidemiology
Environmental and Occupational Epidemiology

1982 Epidemiology Summer Session
Sponsored by the New England Epidemiology Institute
University of Massachusetts
Amherst, Massachusetts
Courses: Theory and Practice of Epidemiology, Level 1
Biostatistics for Epidemiologists
Cancer Epidemiology

1981 Biostatistics for Epidemiology
Sponsored by the Tumor Registry Training Program and
Conferences for Personnel of Cancer Patient Data Systems,
Cancer Research Institute, University of California-San Francisco
College of William and Mary
Williamsburg, Virginia

MEMBERSHIPS

Society for Epidemiologic Research
American Association for the Advancement of Science

PUBLICATIONS

01.) Samet JM, Key CR, Kutvirt DM, Wiggins CL. Respiratory disease mortality in New Mexico's American Indians and Hispanics. American Journal of Public Health 1980; 70:492-497.

02.) Coultas DB, Samet JM, Wiggins CL. Altitude and mortality from chronic obstructive pulmonary disease in New Mexico. Archives of Environmental Health 1984; 39:355-359.

03.) Black WC, Wiggins C. Melanoma among Southwestern American Indians. Cancer 1985; 55:2899-2902.

04.) Coultas DB, Samet JM, Wiggins CL, Butler C, Sweeney ES, Parzyck T. Clinical features of a population-based series of patients with lung cancer presenting with a solitary nodule. American Review of Respiratory Disease 1986; 133:302-306.

05.) Sewell CM, Castle SP, Hull HF, Wiggins CL. Testicular cancer and employment in agriculture and oil and natural gas extraction. Lancet 1986; 1:553 (letter to the editor).

06.) Duncan MH, Wiggins CL, Samet JM, Key CR. Childhood cancer epidemiology in New Mexico's American Indians, Hispanic whites, and non-Hispanic whites, 1970-82. Journal of the National Cancer Institute 1986; 76:1013-1018.

07.) Greenberg MA, Wiggins CL, Kutvirt DM, Samet JM. Cigarette use among Hispanic white and non-Hispanic white school children, Albuquerque, New Mexico. American Journal of Public Health 1987; 77:621-622.

08.) Lerchen ML, Wiggins CL, Samet JM. Lung cancer and occupation in New Mexico. Journal of the National Cancer Institute 1987; 79:639-645.

09.) Black WC, Goldhahn RT, Wiggins CL. Melanoma within a Southwestern Hispanic population. Archives of Dermatology 1987; 123:1331-1334.

10.) Samet JM, Wiggins CL, Humble CG, Pathak DR. Cigarette smoking and lung cancer in New Mexico. American Review of Respiratory Disease 1988; 137:1110-1113.

11.) Samet JM, Wiggins CL, Key CR, Becker TM. Mortality from lung cancer and chronic obstructive pulmonary disease in New Mexico, 1957-82. American Journal of Public Health 1988; 78:1182-1186.

PUBLICATIONS, *continued*

12.) Becker TM, Wiggins CL, Key CR, Samet JM. Ischemic heart disease mortality in Hispanics, American Indians, and non-Hispanic whites in New Mexico, 1958-82. Circulation 1988; 78:302-309.

13.) Wiggins CL, Becker TM, Key CR, Samet JM. Stomach cancer among New Mexico's American Indians, Hispanic whites, and non-Hispanic whites. Cancer Research 1989; 49:1595-1599.

14.) Becker TM, Wiggins CL, Key CR, Samet JM. Ethnic differences in mortality from acute rheumatic fever and chronic rheumatic heart disease in New Mexico, 1958-82. Western Journal of Medicine 1989; 150:46-50.

15.) Sewell CM, Becker TM, Wiggins CL, Key CR, Hull HF, Samet JM. Injury mortality in New Mexico's American Indians, Hispanics, and non-Hispanic whites, 1958-82. Western Journal of Medicine 1989; 150:708-713.

16.) Olson LM, Becker TM, Wiggins CL, Key CR, Samet JM. Injury mortality in American Indian, Hispanic, and non-Hispanic white children in New Mexico, 1958-82. Social Science and Medicine 1990; 30:479-486.

17.) Schmidt-Nowara WW, Coultas DB, Wiggins CL, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Archives of Internal Medicine 1990; 150:597-601.

18.) Becker TM, Wiggins CL, Key CR, Samet JM. Symptoms, signs, and ill-defined conditions: A leading cause of death among minorities. American Journal of Epidemiology 1990; 131:664-668.

19.) Becker TM, Wiggins C, Peek C, Key CR, Samet JM. Mortality from infectious diseases among New Mexico's American Indians, Hispanic whites, and other whites, 1958-87. American Journal of Public Health 1990; 80:320-323.

20.) Wiggins CL, Schmidt-Nowara WW, Samet JM. Comparison of self- and spouse reports of snoring and other symptoms associated with sleep apnea syndrome. Sleep 1990; 13:245-252.

21.) Becker TM, Wiggins CL, Key CR, Samet JM. Violent death in the West: Suicide and homicide in New Mexico, 1958-87. Suicide and Life Threatening Behavior 1990; 20:324-334.

22.) Peek C, Wiggins CL, Becker TM. Pedestrian fatalities in New Mexico's American Indians, Hispanics, and other whites, 1958-87. Morbidity and mortality weekly report 1991; 40:312-314.

PUBLICATIONS, *continued*

23.) Olson LM, Troutman W, Wiggins CL, Becker TM. Fatal poisoning among American Indian, Hispanic, and non-Hispanic white children in New Mexico, 1958-82. Ethnicity and Disease 1991; 1:257-262.

24.) Foucar K, Duncan MH, Stidley CA, Wiggins CL, Hunt WC, Key CR. Survival of children and adolescents with acute lymphoid leukemia: A study of American Indians, Hispanic whites, and non-Hispanic whites treated in New Mexico, 1969-86. Cancer 1991; 67:2125-2130.

25.) Becker TM, Wiggins CL, Key CR, Samet JM. Changing trends in mortality among New Mexico's American Indians, 1958-1987. International Journal of Epidemiology 1992; 21:690-700.

26.) Carter JS, Wiggins CL, Becker TM, Key CR, Samet JM. Diabetes mortality among New Mexico's American Indian, Hispanic, and non-Hispanic white populations, 1958-87. Diabetes Care 1993; 16:306-309.

27.) Wiggins CL, Becker TM, Key CR, Samet JM. Cancer mortality among New Mexico's Hispanics, American Indians, and non-Hispanic whites, 1958-87. Journal of the National Cancer Institute 1993; 85: 1670-1678.

28.) Eidson M, Becker TM, Wiggins CL, Key CR, Samet JM. Breast cancer among Hispanics, American Indians, and non-Hispanic Whites in New Mexico. International Journal of Epidemiology 1994; 23: 231-237.

29.) Wiggins CL, Thomas DB. The use of computerized record linkages to study cancer among people with AIDS. Journal of Registry Management 1995; 22:80-84.

30.) Wiggins CL. Issues to consider when choosing a computer program to assist Native American collection of accurate cancer data. Cancer. 1996; 78(Supplement):1569-1573.

31.) Mahoney MC, Michalek AM, Wiggins CL, Tenney M, Bad Wound D, Burhansstipanov L. Native American Cancer Conference III: Cognitive correlates and impressions of attendees. Cancer. 1996; 78(Supplement):1533-1537.

32.) Wiggins CL, Aboulafia DM, Ryland LM, Buskin SE, Hopkins SG, Thomas DB. Declining incidence of HIV-associated Kaposi's sarcoma and non-Hodgkin's lymphoma following introduction of highly active antiretroviral therapy. Submitted for publication.

MONOGRAPHS

01.) Wiggins CL, Thomas DB, Potts MS. Cancer in Western Washington State, 1974-1991. Fred Hutchinson Cancer Research Center, 1993.

02.) Becker TM, Wiggins CL, Elliott RS, Key CR, Samet JM. Ethnic Patterns of Disease in New Mexico. University of New Mexico Press, 1993.

ABSTRACTS

01.) Key CR, Black WC, Wiggins CL. Malignant melanoma in New Mexico. Fourth International Symposium on the Prevention and Detection of Cancer. London, 1980.

02.) Coultas DB, Wiggins CL, Parzyck T, Samet JM. Survival in a population-based series of patients with malignant solitary pulmonary nodules. American College of Chest Physicians. Chicago, 1983.

03.) Samet JM, Wiggins CL. Defining Hispanic populations for epidemiologic studies: Census-based definitions. Fifth Annual Epidemiological Research Exchange. Denver, 1985.

04.) Schmidt-Nowara WW, Coultas DB, Wiggins CL, Skipper BE, Samet JM. Prevalence and determinants of symptoms of sleep apnea syndrome in a population-based survey of adults. Fifth International Congress of Sleep Research. Copenhagen, 1987.05.) Schmidt-Nowara WW, Coultas DB, Wiggins CL, Skipper BE, Samet JM. Prevalence and correlates of snoring in an adult population. First International Congress on Snoring Diseases. Paris, 1987.

06.) Schmidt-Nowara WW, Wiggins CL, Samet JM, Coultas DB. Comparison of sleep apnea symptoms derived from subjects and their spouses in a population survey. Second Annual Meeting of the Association of Professional Sleep Societies. San Diego, 1988.

07.) Wiggins CL, Becker TM, Key CR, Samet JM. Stomach cancer among New Mexico's American Indians, Hispanic whites, and non-Hispanic whites. Eighth Annual Epidemiological Research Exchange. Denver, 1988.

08.) Sewell CM, Becker TM, Wiggins CL, Key CR, Samet JM. Injury mortality in New Mexico's American Indians, Hispanics, and Anglos. Eighth Annual Epidemiological Research Exchange. Denver, 1988.

ABSTRACTS, *continued*

09.) Schmidt-Nowara WW, Wiggins CL, Skipper BE, Samet JM. Prevalence of sleep apnea in a population-based sample of Hispanic-American adults. American Thoracic Society. Cincinnati, 1989.

10.) Chavez L, Becker TM, Wiggins CL, Key CR, Samet JM. Alcohol-related mortality in New Mexico's Hispanics, American Indians, and non-Hispanic whites, 1958-82. American College of Physicians. Carmel, 1989.

11.) Becker TM, Wiggins CL, Key CR, Samet JM. Violent death in the old west: Suicides and homicides in New Mexico, 1958-87. American College of Physicians. Albuquerque, 1989.

12.) Wiggins CL, Koutksy LA, Boisvert JF, Handsfield HH. Trends in sexual diseases (STDs) among homosexually active men attending an urban STD clinic, 1980-88. Society for Epidemiologic Research. Minneapolis, 1992.

13.) Allen-Barash N, Wiggins CL, Thomas DB, Davis S, Vaughan TL. The effect of mouthwash use on the risk of oral cancer. Society for Epidemiologic Research. Keystone, 1993.

14.) Wiggins CL, Thomas DB, Koutsky LA, Frederick M, Maden C. An evaluation of Kaposi's sarcoma surveillance. North American Association of Central Cancer Registries Annual Meeting. Niagara on the Lake, 1994.

15.) Wiggins CL. Computer programs that assist Native American collection of accurate cancer data. Native American Cancer Conference III: Cancer Risk Factors, Outreach, and Intervention Strategies. Seattle, 1995.

16.) Potts MS, Wiggins CL, Guay DR, Hafterson JL, Thomas DB. An automated system to assist cancer registry collection of treatment information. North American Association of Central Cancer Registries Annual Meeting. Minneapolis, 1996.

17.) Davis S, Wiggins C. Exposure to soil contaminants via soil ingestion. American Association for the Advancement of Science Annual Meeting. Seattle, 1997.

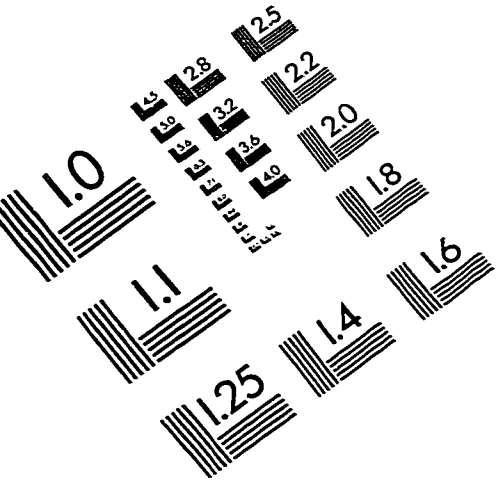
ABSTRACTS, *continued*

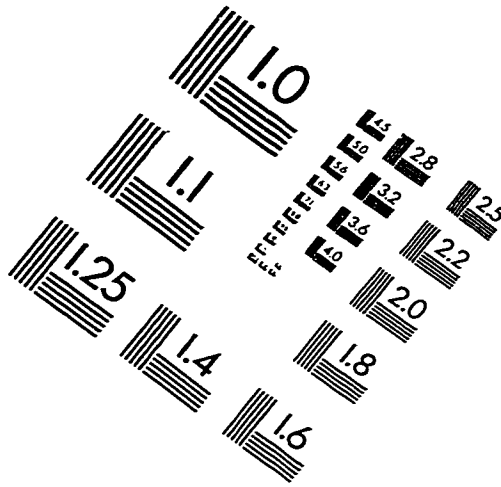
18.) Wiggins CL, Kamineni A, Mueller BA, Stanford JL, Potts MS, Thomas, DB. An assessment of occupational information recorded in a population-based central cancer registry in northwestern Washington state. North American Association of Central Cancer Registries Annual Meeting. Vancouver, 1998.

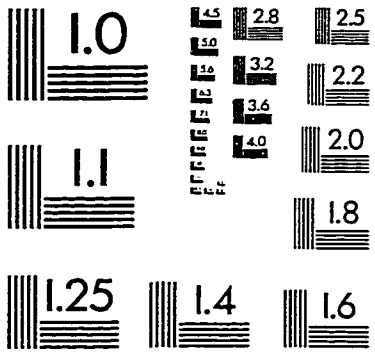
19.) Wiggins CL, Aboulafia DM, Ryland LM, Buskin SE, Hopkins SG, Thomas DB. Decline in HIV-associated Kaposi's sarcoma and non-Hodgkin's lymphoma following the introduction of highly active antiretroviral therapy. Third Annual AIDS Malignancy Conference. Bethesda, 1999.

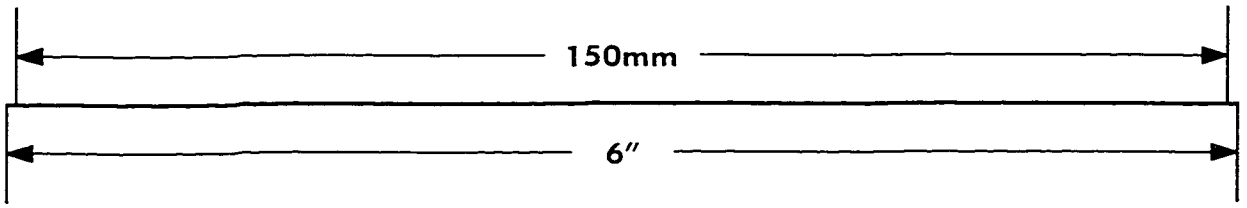
CLW: June 1999

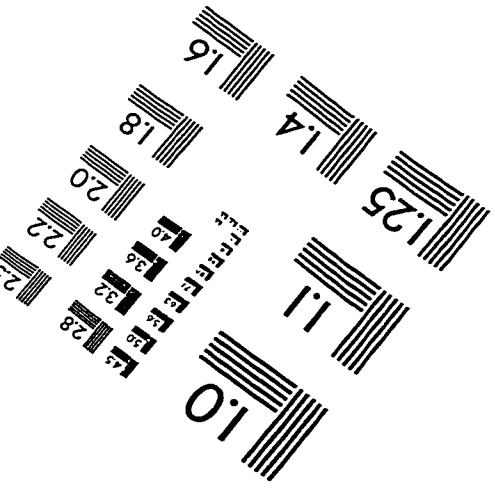
IMAGE EVALUATION TEST TARGET (QA-3)

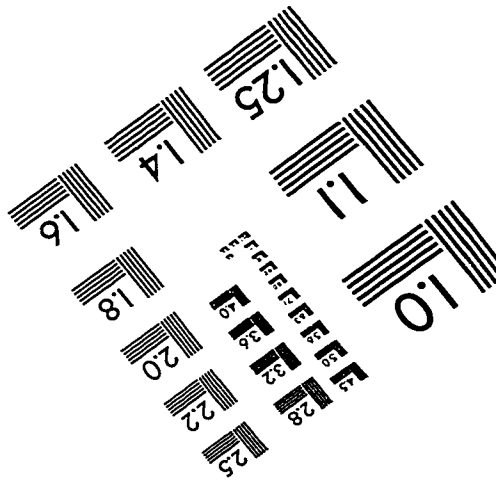












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989