Informing Strategies for Effective HIV Treatment and Prevention

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Abstract

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HIV continues to challenge individual and public health throughout the world. Ensuring HIV-infected and high-risk individuals are aware of their infection status, engage in care, and receive effective treatment and prevention tools as early as possible is key to improving health outcomes, disrupting transmission, and reducing the burden of disease globally. To best combat the HIV epidemic, it is crucial to determine if guidelines and practices are effective, understand barriers to successful implementation of recommendations, and ascertain how to optimize interventions. One barrier to effective HIV treatment is pre-antiretroviral treatment (ART) drug resistance (PDR). PDR to first line regimens has shown to contribute to treatment failure, which is especially problematic in setting where resistance testing is unavailable and alternative regimens are limited. Understanding PDR prevalence and associated risk-factors can inform policy to best manage care and ensure treatment effectiveness. Additionally, despite efforts to treat infected individuals early in the course of disease progression, many seek treatment only when they are symptomatic at later stages of infection. Investigating the extent to which individuals seek treatment late in disease progression and factors associated with early mortality

can help programs target high-risk individuals, address contributing factors, and improve health outcomes. While interventions can successfully improve diagnosis rates, treatment uptake, and prevention, it is important to evaluate effective strategies to ensure they are optimized, especially when resources are limited.

To investigate the prevalence and risk factors of PDR in a low resource setting in Kenya, we conducted a cross-sectional analysis of ART-eligible HIV-infected participants in 2013-2014. We found an overall PDR-prevalence of 10%, and the highest prevalence (22%) among ARV-naïve women 18-24 years old. Given our observed PDR-prevalence, resistance-testing and/or alternative ARVs may be warranted in high HIV prevalence settings, with special attention to young women. We also conducted a longitudinal survival analysis to estimate incidence and identify risk factors of early mortality following ART initiation at similarly managed rural and urban clinics in Kenya. We found that the rural clinic had a 2-fold greater risk of mortality than the urban clinic (unadjusted hazard ratio 2.20; 95% CI 1.29-3.76; P = 0.004), despite a lower average baseline CD4 count among the urban cohort. Mortality risk associated with low CD4 count, low BMI, and PDR was also greater in the rural setting. Other statistically significant ($p<0.05$) predictors of mortality included male gender, older age, fewer years of education, unemployment, low body mass index, low CD4 count, and PDR. Efforts to engage patients, especially men, earlier in HIV infection remain critical, and interventions to improve BMI and target less educated patients could improve health outcomes, especially in rural areas with high infectious disease burdens. PDR may influence short-term mortality and further studies to optimize management will be important in settings with increasing PDR.

Additionally, we evaluated an effective partner services (PS) program for bacterial sexually transmitted diseases (STDs) that includes integrated HIV-objectives (HIV-testing, pre-

exposure prophylaxis promotion, and re-linkage to care) in a higher resource setting, Washington state (WA). We assessed STD PS costs, including time, and identified modifiable areas to improve efficiency at three WA health jurisdictions (King, Pierce, and Spokane counties) using activity-based micro-costing that included interviews, observational time-studies with disease intervention specialists (DIS) and other program staff, and individual case time tracking. We also collected program expenditures and analyzed surveillance and service delivery data to determine costs of program objectives. In King, Pierce, and Spokane, respectively, DIS spent approximately 6.5, 6.4, and 28.8 hours per syphilis case and 1.5, 1.6, and 2.9 hours per GC/CT case. Difficult-to-reach heterosexuals (including many reported methamphetamine drug users) comprised 68% of syphilis cases in Spokane, which increased the time required for case-finding, whereas most cases in King (88%) and Pierce (82%) were among easier to reach men who have sex with men. In all jurisdictions, time-consuming DIS activities included provider contact (9%) data entry (20%), record searches to locate cases/partners (19%), and contacting cases/partners (32%). Time spent on expedited partner therapy (EPT) for STDs and HIV-related objectives was minimal (30 seconds-5 minutes per interview). In 2016, DIS interviewed 363, 97, and 104 syphilis and 1,929, 1,948, and 280 GC/CT cases in King, Pierce, and Spokane, respectively. Cost-per-interview ranged from $516-$2,155 for syphilis, $215-$472 for GC, and $161-$533 for CT. We found that STD PS resource needs depend on epidemic characteristics and program models. Electronic reporting and medical records access could improve efficiency. Integrating HIV-objectives minimally impacted STD PS specific program costs. These data are necessary for program planning, budget impact analysis, and estimating the cost-effectiveness of PS.

Overall, the work presented in this dissertation contributes to our understanding of barriers and strategies for successful HIV treatment and prevention and can be used to improve health outcomes and combat the HIV epidemic in Kenya and the United States.

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DEDICATION

To my inspirational family
Dr. Marian Silverman, Dr. Gary Silverman, Dr. Natalie Silverman, and Dr. Clay Wright

Chapter 1. Introduction

Human immunodeficiency virus type-1 (HIV) infection remains a major global health threat, and has had major adverse health effects in sub-Saharan Africa [1] and among high-risk populations in the United States [2]. Efforts to increase promotion and uptake of prevention strategies among high-risk individuals, and diagnose, treat, and engage infected individuals as early as possible, remain crucial to disrupting transmission and improving health outcomes [3]. To best achieve these objectives, it is vital to understand and assess barriers to successful implementation of recommendations, and ascertain how to optimize strategies and implement well-informed effective interventions.

One important barrier to successful ART treatment programs is pre-antiretroviral treatment (ART) drug resistance (PDR). PDR has been shown to contribute to treatment failure [4-6], which is especially problematic in setting where drug resistance testing is unavailable and alternative regimens are limited. Understanding PDR prevalence and associated risk factors can inform policy to best manage care and ensure treatment is effectively suppressing viral load to improve health outcomes and prevent transmission. Additionally, it is recognized that starting infected individuals on ART as early as possible improves health outcomes and reduces transmission [3]. However, despite efforts to diagnose and treat infected individuals early, many are diagnosed and seek treatment only when they are symptomatic at later stages of infection [7-9], contributing to early mortality [10, 11]. Investigating the extent to which individuals seek treatment late in disease progression and factors associated with early mortality can help programs target higher-risk individuals, improve health outcomes, and prevent transmission through earlier treatment and better management.

Additionally, further control of the HIV epidemic depends on improving diagnosis rates, engagement in care, and treatment uptake among infected individuals, as well as increasing

uptake of prevention strategies like pre-exposure prophylaxis (PrEP) among high-risk individuals. Evaluating effective strategies to address these objectives is essential to program implementation and optimization, especially when resources are limited. Individuals, particularly men who have sex with men (MSM), diagnosed with a bacterial STD are at increased risk for subsequent HIV acquisition [12], making them an important target for interventions. Partner services (PS) for sexually transmitted diseases (STDs) are recommended by the Centers for Disease Control and Prevention (CDC) as an effective strategy to ensure cases and partners are tested and treated appropriately and prevent subsequent transmission [13]. Integrated HIV-related objectives within STD PS can improve HIV case finding, linkage to care, and prevention [14, 15]. Evaluating a program that has successfully implemented HIV-objectives within its STD PS program can inform budget impact, operational activities and costs, and identify areas to improve efficiency to optimize service delivery. Results can also inform program implementation at other health jurisdictions and cost-effectiveness analyses.

The studies included in this dissertation investigate the prevalence and risk factors of PDR in Kenya, examine early mortality risk following ART initiation in Kenya, and evaluate STD partner services with integrated HIV-related objectives in Washington State. These projects can inform ART policy and management, help programs mitigate poor health outcomes and better target high-risk individuals, and assist implementation of effective and efficient STD PS programs. Results can be used to inform programs internationally to help reduce disease burdens of STDs and HIV in their communities.

Chapter 2: Prevalence and Risk Factors of Pre-treatment Drug in Kenya

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Individuals with drug-resistant (DR) HIV are at increased risk for treatment failure leading to poor health outcomes and higher risk of HIV transmission [2-4]. This is especially problematic in low resource settings where DR to publicly available regimens is increasing [3], DR testing is not routinely performed or available [16-18], and alternative regimen options are limited [19-24]. Given the importance of ensuring ART regimens are effective, understanding the burden and epidemiology of PDR in these populations is vital for determining when and how to modify programmatic ART strategies. For this aim, we present a cross-sectional analysis of risk factors associated with PDR in a large cohort of HIV-infected individuals initiating ART at one rural and two urban clinics in Kenya between May 2013 and November 2014. Our analyses included young women of childbearing age who may be at especially high-risk for PDR with implications for prevention of mother-to-child-transmission (PMTCT).

Chapter 3: Predictors of Short-term Mortality Following ART Initiation

Substantial efforts have been made to accelerate diagnosis of HIV infection and start infected individuals on ART as soon as possible [16-18]. However, many HIV-infected individuals continue to delay testing and/or treatment until they are symptomatic with advanced HIV [7-9], often leading to early mortality [10, 11]. Investigating the extent to which patients seek care late in infection and characteristics associated with early mortality after ART initiation can help programs better prevent early mortality and other poor health outcomes. For this aim, we conducted a nested prospective study to assess the risk and predictors of short-term mortality among individuals participating in a randomized clinical trial (RCT). Participants initiated ART in 2013-2014 at two treatment clinics managed by Coptic Hospital (with the same clinical procedures and protocols), one in urban Nairobi and one in rural Maseno, in Western Kenya.

Chapter 4: Costing and Time Study of STD Partner Services in Washington State

Partner services (PS) for bacterial sexually transmitted diseases (STDs) including syphilis, gonorrhea (GC), and chlamydia (CT) infection are routinely provide through health departments in the United States to help prevent transmission and ensure infected individuals are treated. STD PS throughout the United States vary in methods, available resources, and coverage [15, 19-21]. The STD PS program in Washington (WA) State has several unique features including PS interviews primarily conducted via telephone, expedited partner therapy (EPT) for heterosexual GC and CT cases, and HIV-related interventions for MSM. For this aim, we assessed the costs, including time, associated with different components of STD PS at high-burden health jurisdictions in WA. This information can be used to optimize and/or implement STD PS programs in health jurisdictions in WA and across the United States, as well as inform cost-effectiveness analyses.

Summary

The work presented in this dissertation contributes to our understanding of barriers for successful HIV treatment and prevention, and optimization of strategies that address key challenges. Specific topics include estimating prevalence and risk factors of pre-treatment drug resistance to commonly used first-line ART regimens in Kenya, investigation of early mortality risk and correlates following ART initiation in Kenya, and evaluation of STD partner services programs with integrated HIV-related objectives in WA State. We hope the results of this work will be used to inform policies and programs to better combat the HIV epidemic internationally.

Chapter 2. Prevalence and Risk Factors of Pre-treatment Drug Resistance in Kenya

Prevalence of Pre-antiretroviral Treatment Drug Resistance by Gender, Age, and Other Factors in HIV-infected Individuals Initiating Therapy in Kenya, 2013-2014

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Running Title: Pre-Treatment HIV Drug Resistance, Kenya

Summary: HIV-infected participants initiating first-line antiretroviral therapy (ART) in Kenya were tested for pre-treatment drug resistance (PDR) using an oligonucleotide ligation assay (OLA). PDR was detected in 9.6% (95% CI=7.9%, 11.6%), including 19.5% (95% CI=8.8%, 34.9%) of all 18-24 year-old women.

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Abstract

Background. Pre-antiretroviral-treatment drug resistance (PDR) is a predictor of HIV treatment failure. We determined PDR-prevalence and correlates in a Kenyan cohort.

Methods. We conducted a cross-sectional analysis of antiretroviral (ARV) treatment-eligible HIV-infected participants in 2013-2014 at three clinics. PDR was defined as ≥2% mutant-frequency in a participant's HIV-quasispecies at pol codons K103N, Y181C, G190A, M184V, or K65R by oligonucleotide ligation assay. Low-frequency mutations were verified using Illumina sequencing. PDR-prevalence was calculated by age, gender, clinic location, and codon, stratifying by prior ARV-experience. Poisson regression was used to estimate prevalence-ratios.

Results. The PDR-prevalences (95% CI) in 815 ARV-naïve adults, 136 ARV-experienced adults, and 36 predominantly ARV-naïve children were 9.4% (7.5%, 11.7%), 12.5% (7.5%, 19.3%), and 2.8% (0.1%, 14.5%), respectively. Median detected mutant-frequency within an individual's HIV-quasispecies was 67%. PDR-prevalence in ARV-naïve women 18-24 years old was 21.9% (9.3%, 40.0%). Multivariable regression found only age in females associated with PDR: A 5-year age decrease was associated with an adjusted PDR prevalence ratio of 1.20 (95% CI=1.06, 1.36; p=0.004).

Conclusions. Given the high PDR-prevalence, resistance-testing and/or alternative ARVs may be warranted in high HIV prevalence settings, with attention to young women, likely to have recent infection and higher rates of resistance.

Key Words: Pre-treatment drug resistance, transmitted drug resistance, HIV, Kenya, oligonucleotide ligation assay, antiretroviral therapy

Introduction

Human immunodeficiency virus type-1 (HIV) infection continues to be a serious health threat globally, particularly in low-resource countries. While antiretroviral (ARV) therapy (ART) has significantly improved the health and quality of life of HIV-infected individuals [18, 22], the selection and transmission of drug-resistant HIV have increased with increasing time since ART "roll-out" [5]. Individuals with drug-resistant HIV (DR-HIV) are at increased risk for treatment failure leading to poor health outcomes and higher risk of transmitting HIV [4-6]. While testing for DR-HIV is performed in resource-rich countries to guide clinicians in the selection of ART, most lower-resource countries do not routinely test for DR-HIV [23-25]. In lower-resource settings, first-line combination therapies containing non-nucleoside transcription inhibitors (NNRTIs) are provided gratis, and those who experience first-line treatment failure are prescribed second-line combination therapies with protease inhibitors (PIs). Should treatment failure to second-line combinations occur, third-line combinations are generally available only to individuals with the means to purchase the drugs [16, 17, 26-29]. Thus, understanding the burden and epidemiology of DR-HIV in these populations is important for evaluating the effectiveness of currently dispensed ART and for determining when and how to modify programmatic ART strategies.

The World Health Organization (WHO) defines pre-antiretroviral-treatment drug resistance (PDR) as DR-HIV in adult populations starting ART, and transmitted drug resistance (TDR) as DR-HIV in recently infected populations [30]. TDR is often defined more broadly as DR-HIV infection among those who were previously uninfected with HIV [5]. Generally, PDR includes, but is not limited to, TDR. These terms are distinct from acquired drug resistance (ADR),

which refers to likely selection of DR-HIV in ART-experienced individuals, usually after virologic failure [5, 30].

On average, younger HIV-infected adults have been infected for less time than older individuals [31]. Therefore, in communities with increasing prevalence of DR-HIV, it logically follows that those infected with HIV more recently may be more likely to have TDR. Young women, who account for 25% of all new HIV infections in sub-Saharan Africa [32], may also be at a particularly high risk of TDR in the region, as they are more likely to have been infected with HIV via older partners [33, 34] with potentially higher likelihoods of ART use due to longer duration of infection. An additional risk factor for DR-HIV is prior ARV experience, which may occur in women and children with a history of using mono- or dual-therapy ARVs previously recommended for prevention of mother-to-child transmission (PMTCT) [35-39]. Geographic locations may differ in the risk of PDR. For example, persons in urban centers may have a higher DR-HIV prevalence compared with rural communities due to earlier ART scale-up [29].

To address an objective of the WHO 2016-2021 Global Action Plan For HIV Drug Resistance, and generate evidence to inform policy [5], we report our analysis of risk factors associated with PDR in a large cohort of HIV-infected individuals initiating ART at 3 sites, one rural and two urban clinics, in Kenya between May 2013 and November 2014, including among women of childbearing age, who may be at especially high risk of PDR. Understanding the burden of PDR is crucial to ensuring that pregnant and breastfeeding women receive effective HIV treatment for PMTCT.

Methods

Study Setting and Design

We conducted a cross-sectional analysis of PDR using pre-ART baseline data collected from individuals initiating ART at the Coptic Hope Center for Infectious Diseases, a network of HIV treatment clinics that administer care based on Kenya national guidelines [40]. In 2013-2014, Hope Center patients who were 2 years of age and older and eligible to initiate ART were invited to enroll into a randomized clinical trial (RCT) examining the use of a sensitive point mutation assay to detect and manage PDR (RCT name: Oligonucleotide Ligation Assay (OLA) Resistance Study; ClinicalTrials.gov identifier: NCT01898754). This RCT was implemented at three Coptic Hope Center clinic sites, two located in urban Nairobi and the third in rural Maseno in Western Kenya. Participants with a history of prior use of ARV administered from another clinic, for PMTCT, or post-exposure prophylaxis (PEP), were not excluded. At enrollment, prior to clinicians prescribing ART, blood samples were collected along with sociodemographic information, medical history, and risk behaviors. For this analysis, information regarding prior ARV use was obtained from the study enrollment form and the Hope Center medical records. All participants provided written informed consent prior to study enrollment as approved by Human Subjects' Committees at Seattle Children's Hospital in Seattle, Washington, and Kenyatta National Hospital in Nairobi, Kenya.

Pre-ART peripheral blood mononuclear cells (PBMC) underwent nested PCR of HIV *pol* to generate amplicons for oligonucleotide ligation assay (OLA) to detect point mutations K103N, Y181C, G190A, M184V, and K65R. Our and others previous studies have shown that virologic failure during ART with NNRTIs nevirapine (NVP) or efavirenz (EFV) is associated with mutations K103N, Y181C, and G190A, to the NRTIs lamivudine (3TC) and emtricitabine (FTC) by M184V, and to the NRTI tenofovir disoproxil fumarate (TDF) by K65R [4, 41-43]. PBMC were used because we have found that OLA detection of DR-HIV is similar to plasma among

untreated individuals, and testing of PBMC is less costly compared to testing plasma. For OLA, the proportion of mutant in each participant's HIV-quasispecies was estimated by comparing optical densities to standards containing 0%, 2%, 5%, 10%, 25%, 50%, 75% or 100% mutant, with PDR defined by ≥2% mutant [4, 43, 44]. In addition, Illumina sequencing was performed to confirm PDR for low level mutations (<25%) and for selected specimens with high frequency mutations detected via OLA for validation purposes. For Illumina sequencing, two ~330bp regions of HIV *pol* encoding reverse transcriptase were amplified from ~1,000 HIV DNA copies, quantified by an in-house qPCR assay targeting the long terminal repeat (LTR) region. 1st round PCR amplicons were generated as previously described [4], except for using a high-fidelity PCR enzyme (FastStart, Roche Diagnostics, Mannheim, Germany). 2nd round PCR primers targeting the regions of interest were synthesized with forward and reverse adapter sequences allowing subsequent tagging of PCR product from distinct study participants with a unique combination of index sequences. Indexed amplicons were then pooled together and ~300bp were bi-directionally sequenced on an Illumina Miseq. Trimming at the 5' and 3' ends of raw sequence reads used a sliding window of 9 base pairs and an average Phred quality score of less than 30. Trimmed reads <75bp in length or containing fully degenerate bases were filtered from the final data set. High-quality filtered reads were aligned to the HXB2 reference HIV sequence using the Burrows-Wheeler algorithm [45]. Nucleotide variants (single-nucleotide polymorphisms and insertion-deletions) were called at relevant codons associated with resistance and filtered for statistical significance using the open-source LoFreq* [46] and FreeBayes [47] software. Remaining variants were annotated using SNPEff [48] indicating their frequency within the overall viral sequence population and their effects on encoded amino acids. PCR and sequencing error rates at each nucleotide generated from a plasmid DNA control were assessed by a perl script developed in-

house to allow more accurate estimation of genuine PDR populations. The average mismatch error rate for this PCR and sequencing method ranged from 0.6-0.65%, so a conservative cut-off of 1% mutant detected by Illumina was used as a minimum frequency to confirm the presence of mutant via OLA. Mutations detected by OLA but not confirmed via Illumina were defined as wild-type.

Statistical Analyses

PDR prevalence and 95% binomial exact confidence intervals (CIs) by age, gender, clinic location, prior ARV-experience and specific *pol* codon mutations were calculated. Age was defined as a continuous variable (years) and, to identify associations by age groups, categorized into five age groups (children <18, and adults 18-24, 25-35, 35-50, and over 50 years of age). Clinic locations were defined as urban (Ngong Road and Industrial Area) or rural (Maseno). "ARV-experienced" was defined as any ARV use prior to study as reported by the participant at enrollment and/or by review of the Coptic Hope Center clinic and pharmacy records, and analyzed as a binary variable. Socioeconomic, health care access, and sexual risk-behavior variables were evaluated to investigate other potential correlations with PDR in exploratory analyses. Poisson regression with robust standard errors was used to conduct univariable and multivariable regression analyses to estimate the prevalence ratios of PDR (≥2% mutant virus at any *pol* codon) by potential correlates (alpha=0.05). The unadjusted prevalence ratio was estimated for all variables. For regression analyses, age was defined as a continuous variable, and location was defined both as a categorical variable (three clinic sites) and as a binary variable (rural vs. two urban clinics combined) in separate analyses. Multivariable regression analyses were conducted to estimate the prevalence ratio of PDR by gender, age, and location adjusted for potential confounding variables, and to explore other potential correlates of PDR. An interaction term

between age and gender was included in separate regression analyses to investigate differences in the effect of age by gender. Gender-stratified analyses were conducted to further investigate our hypothesis that younger women have a higher prevalence of PDR. In addition to investigating the full cohort, all analyses were also stratified by prior ARV-experience to potentially differentiate between ADR and TDR. Children (<18 years old) were excluded from regression analyses due to a paucity of socioeconomic and demographic data. Participants ≥16 years of age were included in sensitivity analyses to investigate the impact of older adolescents on our results.

Results

Enrollment and Eligibility

Between May 25, 2013 and November 5, 2014, 1,198 HIV infected Hope Center patients over 2 years of age, who qualified to initiate first-line ART by Kenya national guidelines, were screened for eligibility into the parent RCT. Of these, 991 (82.7%) enrolled. OLA testing was successful on the entry specimen from 987 (99.6%) participants. Of the 987 individuals included in analyses, prior ARV use was identified in 138 (14.0%) participants either by self-report or through Hope Center clinic and/or pharmacy records, including 2 children. Overall, 815 of 951 (85.7%) adults and 34 of 36 (94.4%) children were defined as ARV-naïve at enrollment.

Participant Characteristics

Of participants with a successful OLA test, the median age was 37 years (IQR 31-45), 642 (65.1%) were female, and 849 (86.0%) were ARV-naïve. Of the ARV-naïve and ARV-experienced participants, 519/849 (61.1%) and 123/138 (89.1%) were women, respectively. ARV-experienced were slightly younger than ARV-naïve participants (median 34 vs. 38 years). Most

participants (76.7%) were enrolled at the urban study sites in Nairobi (67.5% from Ngong Road, 9.2% from Industrial Area). Table 1 presents descriptive statistics by ARV-experience and PDR for adults. Of the 36 children, 20 (55.6%) were female and the median age was 10 years (IQR 7-15 years). Unlike adults, children were enrolled in similar proportions from study sites in urban Nairobi (38.9% Ngong Road, 11.1% Industrial Area) and rural Maseno (50.0%).

Illumina Confirmation of OLA

Samples from 67 participants with mutations detected via OLA were re-tested via Illumina and 49 (73%) were confirmed at a frequency >1%. Of these, 14 had mutations detected via OLA at <10% mutant frequency, 18 between 10% and 24%, and 17 between 25% and 100%. Across a total of 71 mutant codons for these 49 samples, the median difference in mutant frequency between OLA and Illumina was 4.5% (interquartile range: 1.4% to 13.8%). Of the 18 (27%) samples that were not confirmed via Illumina, the median mutant frequency detected via OLA was 2% (range 2% to 6%). These 18 were considered "wild-type" in all analyses.

Pre-Antiretroviral-Treatment Drug Resistance (PDR)

PDR was detected by OLA in 94 adults (9.9%; 95% CI = 8.1%, 12.0%) with 130 total mutant codons, and only one child (2.8%; 95% CI = 0.1%, 14.5%), a 16-year-old ARV-naïve male (Table 2). Among those with PDR, the median frequency of mutant virus within an individual's HIV-quasispecies was 67% by OLA (range 2%-100%; IQR 14%-92%). Of the 95 participants with PDR, 30 (32%) had a mutant frequency <20% (11 women and 3 men, all >24 years old) and 16 (17%) had <10% (all women >24 years old) detected via OLA. The majority (96.8%) with PDR had at least one NNRTI mutation, and relatively fewer had NRTI mutations (16.8% with M184V

and 9.5% with K65R). Among the 815 ARV-naïve adults, OLA detected mutants in 77 (9.4%; 95% CI=7.5%, 11.7%) participants with a total of 111 mutant codons and a median mutant frequency in their quasispecies of 80% (range 2%-100%; IQR 15%-92%); and in the child, Y181C was detected at 24%. PDR was 2.9% more prevalent among the 136 ARV-experienced vs. –naïve adults, with 17 (12.5%; 95% CI=7.5%, 19.3%) participants harboring 19 mutant codons, though this was not statistically significant (Chi^2 p-value = 0.270). The median mutant frequency among ARV-experienced adults was 30% (range 4%-100%; IQR 10%-83%), 50% lower than the ARV-naïve adult median, though this was not statistically significant (Wilcoxon rank-sum p-value = 0.244).

Women 18-24 years of age (N=41) had the highest PDR prevalence (19.5%; 95% CI=8.8%, 34.9%), with similar prevalence among ARV-naïve 18-24 year old women (n=32) (21.9%; 95% CI=9.3%, 40.0%). Figure 1 illustrates PDR prevalence by gender, age category, and ARV-experience, and shows a declining trend in PDR prevalence with increasing age among women, specifically in the ARV-naïve group who were the majority cohort of women in this study.

In univariable and multivariable regression (Table 3), the PDR prevalence among all adult women was 1.63 times greater than men (95% CI = 1.04, 2.56; p-value = 0.033). ARV-experienced adults had a PDR prevalence 1.32 times greater than ARV-naïve adults, though this was not statistically significant (95% CI = 0.81, 2.17; p-value = 0.226). A 5-year decrease in age was associated with a 1.14-fold greater PDR prevalence (95% CI = 1.02, 1.27; p = 0.033) among all adults, a 1.11-fold greater PDR prevalence (95% CI = 0.99, 1.25; p-value = 0.082) among ARV-naïve adults, and a 1.35-fold greater PDR prevalence (95% CI=1.00, 1.83; p-value = 0.054) among ARV-experienced adults (Table 3). The interaction term between age and gender was statistically

significant among all adults (p-value = 0.026) and among ARV-naïve (p-value = 0.039), though not for ARV-experienced (p-value = 0.571).

When stratifying by gender, a 5-year decrease in age in adult women was associated with a 1.20-fold greater PDR prevalence (95% CI = 1.06, 1.36; p-value =0.004), including a 1.18-fold greater prevalence (95% CI = 1.03, 1.35; p-value = 0.016) among ARV-naïve women and a 1.36-fold greater prevalence (95% CI = 0.97, 1.91; p-value = 0.076) among ARV-experienced women, though the latter was not statistically significant (Table 3). Age was not associated with PDR prevalence among men. Similar results for gender and age associations were found in multivariable regression that included gender, age, and location (Table 3), and in exploratory models that also included marital/partner status, years of education, unemployment status, type of toilet, and age of sexual debut (results not shown). The increased prevalence of PDR by decreasing age remained similar in magnitude and was statistically significant only among females in all analyses.

Among all adult participants, being unemployed was associated with a 1.68-fold greater prevalence of PDR (95% CI = 1.11, 2.55; p-value = 0.015), though this was attenuated and not statistically significant in multivariable analyses (results not shown). Among ARV-experienced adults, being unemployed was associated with a 2.56-fold greater PDR prevalence (95% CI = 1.07, 6.15; p-value = 0.035), and a one-person increase of the number of people living with the participant was associated with a 1.18-fold greater PDR prevalence (95% CI = 1.00, 1.40; p-value = 0.045). No other statistically significant associations were detected between PDR and clinic location, socioeconomic status, access to care, or sexual risk behavior variables regardless of prior ARV use (Table 3). Sensitivity analyses that additionally included 8 participants ≥16 years old (7 women and 1 man), resulted in a slight attenuation of the associations between PDR and age overall and among women, but did not impact the overall interpretation of the results.

Discussion

In this study, we observed a high prevalence of PDR to currently recommended first-line ARVs [16, 17, 26-29] among individuals initiating ART in Kenya. PDR prevalence was highest among HIV-infected young women, 18-24 years old, particularly among ARV-naïve women. This is consistent with younger women accounting disproportionately for incident HIV infections in sub-Saharan Africa [32], and younger adults becoming HIV-infected more recently, and thus at a time with greater transmission of HIV-DR, compared with older individuals [31]. The observed prevalence of PDR in young women in our study exceeds the 10% threshold at which the WHO recommends re-assessment and modifications to the ART strategy [49]. While a high PDR prevalence was found in the population as a whole (10%), PDR may be especially problematic for young women and their children, as PDR may adversely affect the effectiveness of first-line ART that is recommended for ARV-naïve pregnant women for PMTCT.

The statistically significant association between lower age and higher PDR prevalence among women remained after controlling for potential confounders. The absence of an association in men may be due to differences in risk factors for HIV acquisition. The increased PDR prevalence among young women compared with young men, could be due to differences in their partners and their likelihood of DR-HIV, with women having greater acquisition of infection from older, potentially ARV-experienced men [33, 34], or due to unreported prior ARV use. Additionally, our study is limited by the small number of younger men (n=8 between age 16 and 24 years), and further research is needed to investigate PDR prevalence by age and other factors in this group. Very little PDR was observed in children, which may indicate that untreated children

were infected by mothers with lower rates of DR-HIV or that resistance had decayed to undetectable levels by the time of evaluation.

As expected, we found a higher PDR prevalence among ARV-experienced compared to ARV-naïve individuals. The 2.9% difference we observed is slightly lower than the 6% difference found in Zimbabwe (12% in ARV-experienced participants and 6% in ARV-naïve) [35]. The Zimbabwean study was conducted in 2008-2010, with likely less time since ART "roll-out" compared to our study cohort that enrolled more recently in 2013-2014, which correlates with prevalence of resistance [50]. PDR prevalence among ARV-experienced participants in our cohort was lower than what has been found in studies of mothers and children who received mono- or dual-ARVs for PMTCT (~36%) [36, 38]. This could be due to greater decay of mutant viruses [51, 52] in our study compared with other cohort studies, resulting from a longer time-interval between ARV use and DR testing; although TDR to NNRTI has been shown to persist at high frequencies for years [53].

We found a similar PDR prevalence (9%-13%) across urban and rural sites, which was contrary to our expectation that PDR prevalence would be lower at the rural than the urban clinics. While some previous studies have generally found lower PDR in rural settings [54-64], our more recent results may reflect improved access to ART in the rural regions. Our observed 12% PDR prevalence among 212 adult participants (11% among ARV-naïve) at the rural Maseno clinic was slightly higher than the 9% TDR prevalence observed in another recently published study of 87 ARV-naïve participants conducted in 2012 also based in Western Kenya [65], providing further evidence of PDR in this rural setting. In addition, the higher HIV incidence and prevalence in Western Kenya suggests a greater proportion of recent infections among these subjects, which may have contributed to rate of PDR.

Our study has several limitations. Relatively few 18-24 year-old males and few children limit the precision of PDR estimates in these subgroups. Prior ARV-experience was based on self-report, clinic and pharmacy records and could be subject to misclassification. Additionally, OLA testing may have underestimated PDR because only 5 codons were examined for mutations as opposed to more comprehensive testing. While our previous studies at these sites did not find that mutations at other codons were associated with virologic failure [4], if mutations were missed, PDR may actually be higher than what was detected. While we found unemployment to be correlated with PDR prevalence in unadjusted analyses, no other socioeconomic status or sexual risk behaviors were identified as potential correlates. Because those we defined as unemployed included women who considered themselves to be housewives, a category for which there is no male equivalent, the association is likely in part due to more unemployed participants being women. Our study may be underpowered to detect associations and larger surveillance cohorts that allow for multiple comparison adjustment may be necessary to identify other risk factors of PDR transmission.

Strengths of this study include its relatively large, representative cohort of HIV-infected Kenyans who initiated ART in 2013-2014, and testing for PDR by a sensitive method, with results available from 99.7% of participants. This study provides recent evidence of a high prevalence of PDR in Kenyan patients. The especially high prevalence in young women could compromise the outcomes of ART programs for women's health and interventions given for PMTCT. ART outcome data is needed to determine whether testing for PDR and/or if scale up of alternative ARV combinations without NNRTI-cross-resistance should be implemented throughout Kenya or within PMTCT programs.

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Footnotes

Conflict of Interest Statement: No authors have an association that might pose a conflict of interest to this study.

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Table 1. Characteristics of participants ≥18 years of age initiating 1st-line-ART[a] by history of ARV-use and PDR detected by OLA[b]

Variables[c]	Total (N=951)		ARV-naïve (n=815)		ARV-exposed (n=136)	
	No PDR (n=857, 90%)	PDR (n=94, 10%)	No PDR (n=738, 91%)	PDR (n=77, 9%)	No PDR (n=119, 88%)	PDR (n=17, 12%)
ARV-exposure status						
ARV-naïve	738 (90.6%)	77 (9.4%)	-	-	-	-
ARV-exposed	119 (87.5%)	17(12.5%)				
Demographic						
Age in years	38 (32, 46)	34 (29, 42)	39 (32, 47)	35 (30, 44)	34 (30, 40)	32 (27, 36)
18-24	40 (83.3%)	8 (16.7%)	32 (82.1%)	7 (17.9%)	8 (88.9%)	1 (11.1%)
25-34	269 (87.1%)	40 (12.9%)	217 (87.9%)	30 (12.1%)	52 (83.9%)	10 (16.1%)
35-49	410 (92.6%)	33 (7.5%)	359 (93.0%)	27 (7.0%)	51 (89.5%)	6 (10.5%)
50+	138 (91.4%)	13 (8.6%)	130 (90.9%)	13 (9.1%)	8 (100%)	0 (0.0%)
Female	551 (88.6%)	71 (11.4%)	444 (89.0%)	55 (11.0%)	107 (87.0%)	16 (13.0%)
Male	306 (93.0%)	23 (7.0%)	294 (93.0%)	22 (7.0%)	12 (92.3%)	1 (7.7%)
Location						
Study Site						
Ngong Rd Clinic in Nairobi,	594 (91.1%)	58 (8.9%)	526 (91.8%)	47 (8.2%)	68 (86.1%)	11 (13.9%)
Industrial Area Clinic in Nairobi	76 (87.4%)	11 (12.6%)	62 (84.9%)	11 (15.1%)	14 (100%)	0 (0.0%)
Maseno Clinic in rural Nyanza	187 (88.2%)	25 (11.8%)	150 (88.8%)	19 (11.2%)	37 (86.1%)	6 (14.0%)
Socioeconomic						
Married/steady partner	521 (60.8%)	59 (62.8%)	442 (59.9%)	46 (59.7%)	79 (66.4%)	13 (76.5%)
Education in years	11 (8, 13)	10 (8, 12)	11 (8, 13)	10 (8, 12)	12 (8, 14)	11 (8, 15)
Unemployed	157 (18.3%)	27 (28.7%)	130 (17.6%)	19 (24.7%)	27 (22.7%)	8 (47.1%)
Monthly rent in US$[d]	22 (0, 66)	22 (0, 66)	28 (0, 66)	22 (0, 66)	22 (0, 66)	28 (0, 56)
Flush toilet[d]	404 (47.2%)	41 (43.6%)	352 (47.8%)	33 (42.9%)	52 (43.7%)	8 (47.1%)
Persons living in house	4 (2, 5)	4 (3, 5)	3 (2, 5)	3 (2, 5)	4 (3, 5)	4 (4, 5)
Access to care						
Cost of travel ≥US$2[d]	402 (47.6%)	45 (48.9%)	336 (46.3%)	36 (47.4%)	66 (55.9%)	9 (56.3%)
Travel time to clinic in hrs	1 (0.5, 2)	1 (0.5, 1.5)	1 (0.5, 2)	1 (0.5, 1.5)	1 (0.5, 2)	1 (1, 2)
Sexual risk behavior						
Age of sexual debut in yrs[d]	18 (16, 20)	18 (16, 20)	18 (16, 20)	18 (16, 20)	18 (16, 20)	17 (15, 18)
Lifetime sexual partners[§]	3 (2, 5)	4 (2, 5)	3 (2, 5)	4 (2, 5)	3 (2, 5)	4 (2, 5)
Ever exchange money for sex	46 (5.4%)	4 (4.3%)	42 (5.7%)	3 (3.9%)	4 (3.4%)	1 (5.9%)
Sexual risk in 18-24 yr-old girls	**n=31 (3.7%)**	**n=7 (8.6%)**	**n=23 (2.9%)**	**n=6 (8.4%)**	**n=8 (7.1%)**	**n=1 (4.6%)**
Age of sexual debut in yrs[d]	18 (15, 19)	18 (15, 19)	17 (15, 19)	18 (15, 19)	19 (18, 20)	15
Lifetime sexual partners[d]	2 (1, 3)	1 (1, 4)	2 (1, 3)	2 (1, 4)	2 (1, 3)	1
Ever exchange money for sex	1 (3.0%)	0 (0%)	1 (4.0%)	0 (0%)	0 (0.0%)	0 (0.0%)
Laboratory						
Median CD4 cells/uL[d]	230 (116, 311)	224 (73, 296)	211 (103, 306)	155 (69, 270)	277 (227, 332)	308 (257, 400)

Abbreviations: ART, Antiretroviral therapy; ARV, Antiretroviral; PDR, Pre-treatment-drug-resistance; OLA, oligonucleotide ligation assay

[a] 1st-line-ART indicates non-nucleoside-reverse-transcriptase-inhibitor-based antiretroviral treatment.

[b] Oligonucleotide ligation assay is a point mutation test designed to detect K103N, Y181C, M184V, G190A, and K65R.

[c] For continuous variables, the median (interquartile range) are presented. For ARV-exposure status, age category, gender, and study site, the N (%) with and without PDR is shown. For other categorical variables, the N (%) within that category is shown.

[d] Data are complete for all variables except the following: Monthly rent (N=927, 834 PDR-, 93 PDR+); Type of toilet (N=950, 856 PDR-, 94 PDR+); Cost of travel ≥$2.00 (N=936, 844 PDR-, 92 PDR+); Age of sexual debut (N=891, 803 PDR-, 88 PDR+); Lifetime sexual partners (N=893, 807 PDR-, 86 PDR+); CD4 count (N=948, 855 PDR-, 93 PDR+).

Table 2. Frequency of PDR detected by oligonucleotide ligation assay[a] in participants qualifying for 1st-line-ARTb by history of ARV-use (N=987)

Mutant Codon[c]	ARV-naive (N=849)[d]	ARV-experienced (N=138)	Total (N=987)
K103N	38 (4.5%)	11 (8.0%)	49 (5.0%)
Y181C	5 (0.6%)	2 (1.5%)	7 (0.7%)
G190A	5 (0.6%)	2 (1.5%)	7 (0.7%)
M184V	1 (0.1%)	0 (0.0%)	1 (0.1%)
K65R	2 (0.2%)	0 (0.0%)	2 (0.2%)
K103N + Y181C	4 (0.5%)	2 (1.5%)	6 (0.6%)
K103N + G190A	5 (0.6%)	0 (0.0%)	5 (0.5%)
K103N + M184V	8 (0.9%)	0 (0.0%)	8 (0.8%)
Y181C + K65R	2 (0.2%)	0 (0.0%)	2 (0.2%)
G190A + M184V	2 (0.2%)	0 (0.0%)	2 (0.2%)
K103N + Y181C + M184V	1 (0.1%)	0 (0.0%)	1 (0.1%)
K103N + M184V + K65R	1 (0.1%)	0 (0.0%)	1 (0.1%)
Y181C + M184V + K65R	2 (0.2%)	0 (0.0%)	2 (0.2%)
G190A + M184V + K65R	1 (0.1%)	0 (0.0%)	1 (0.1%)
K103N + Y181C + G190A + K65R	1 (0.1%)	0 (0.0%)	1 (0.1%)
Total cases of PDR	**78 (9.2%)**	**17 (12.3%)**	**95 (9.6%)**

Abbreviations: PDR, Pre-treatment-drug-resistance; OLA, oligonucleotide ligation assay; ART, Antiretroviral therapy; ARV, Antiretroviral

[a] OLA is a point mutation test designed to detect K103N, Y181C, M184V, G190A, and K65R
[b] 1st-line-ART = non-nucleoside-reverse-transcriptase-inhibitor-based antiretroviral treatment
[c] 1 ARV-naïve child had PDR detected at Y181C. All other mutations were detected in adults
[d] ARV-naïve includes 815/951 adults and 34/36 children

Table 3. Prevalence Ratios of PDR in participants ≥18 years of age (N=951) by history of prior ARV-use using Poisson regression with robust standard errors[a]

Variables	Total (N=951)		ARV-Naïve (N=815)		ARV-Experienced (N=136)	
	Univariable Regression	Multivariable Regression[b]	Univariable Regression	Multivariable Regression[b]	Univariable Regression	Multivariable Regression[b]
	PR (95% CI); p-value	PR (95% CI); p-value	PR (95% CI); p-value	PR (95% CI); p-value	PR (95% CI); p-value	PR (95% CI); p-value
Demographic						
Gender (female vs. male)	**1.63 (1.04, 2.56); 0.033**	1.48 (0.95, 2.32); 0.086	1.58 (0.98, 2.54); 0.058	1.48 (0.93, 2.37); 0.100	1.69 (0.24, 11.83); 0.597	1.19 (0.17, 8.51); 0.864
Age (5-year decrease)						
Total	**1.14 (1.02, 1.27); 0.022**	**1.12 (1.01, 1.24); 0.037**	1.11 (0.99, 1.25); 0.082	1.10 (0.98, 1.22); 0.110	1.35 (1.00, 1.83); 0.054	1.34 (0.99, 1.80); 0.056
Males	0.93 (0.78, 1.12); 0.465	0.94 (0.79, 1.13); 0.522	0.92 (0.77, 1.12); 0.418	0.94 (0.78, 1.12); 0.475	1.20 (0.89, 1.61); 0.234	1.20 (0.82, 1.75); 0.339
Females	**1.20 (1.06, 1.36); 0.004**	**1.20 (1.06, 1.36); 0.004**	**1.18 (1.03, 1.35); 0.016**	**1.18 (1.03, 1.35); 0.016**	1.36 (0.97, 1.91); 0.076	1.35 (0.97, 1.87); 0.072
Location						
Study Site (clinic)						
Ngong Rd (Nairobi, urban)	Ref		Ref			
Industrial Area (Nairobi, urban)	1.42 (0.78, 2.60); 0.255	-	1.83 (1.00, 3.38); 0.051	-	-	-
Maseno (Nyanza, rural)	1.32 (0.85, 2.06); 0.212		1.37 (0.83, 2.27); 0.221			
Study Site (clinic location)[c]						
Nairobi (Ngong Rd + Industrial)	Ref	Ref	Ref	Ref	Ref	Ref
Maseno	1.26 (0.82, 1.94); 0.289	1.22 (0.79, 1.89); 0.364	1.25 (0.77, 2.04); 0.368	1.23 (0.75, 2.02); 0.405	1.18 (0.47, 2.99); 0.728	1.10 (0.45, 2.70); 0.831
Socioeconomic						
Married/steady partner vs. single	1.08 (0.72, 1.60); 0.710	-	0.99 (0.64, 1.53); 0.979	-	1.55 (0.53, 4.51); 0.417	-
Education (1 years increase)	0.96 (0.92, 1.01); 0.118	-	0.95 (0.91, 1.01); 0.082	-	1.00 (0.89, 1.11); 0.934	-
Unemployed vs. employed	**1.68 (1.11, 2.55); 0.015**	-	1.46 (0.90, 2.38); 0.125	-	**2.56 (1.07, 6.15); 0.035**	-
Monthly rent ($1 increase)	1.00 (1.00, 1.00); 0.889	-	1.00 (1.00, 1.00); 0.909	-	1.00 (1.00, 1.00); 0.975	-
Flush toilet vs. pit latrine	0.88 (0.60, 1.30); 0.516	-	0.84 (0.54, 1.29); 0.420	-	1.12 (0.46, 2.75); 0.795	-
Persons living in house	1.03 (0.94, 1.12); 0.537	-	0.99 (0.90, 1.09); 0.907	-	**1.18 (1.00, 1.40); 0.045**	-
Access to Care						
Cost of travel ≥$2.00 vs. <$2.00	1.05 (0.71, 1.54); 0.815	-	1.04 (0.68, 1.60); 0.857	-	1.01 (0.40, 2.56); 0.981	-
Travel time to clinic (1 hr increase)	0.92 (0.78, 1.10); 0.365	-	0.89 (0.72, 1.11); 0.321	-	1.05 (0.72, 1.53); 0.814	-
Sexual risk behavior						
Age of sexual debut (1 yr increase)	0.97 (0.92, 1.04); 0.421	-	0.99 (0.93, 1.06); 0.825	-	0.88 (0.72, 1.07); 0.188	-
Lifetime sex partners (1 increase)	1.00 (1.00, 1.00); 0.400	-	1.00 (1.00, 1.00); 0.285	-	0.99 (0.98, 1.01); 0.436	-
Ever exchange money for sex	0.80 (0.31, 2.09); 0.651	-	0.69 (0.23, 2.12); 0.520	-	1.64 (0.27, 10.1); 0.595	-

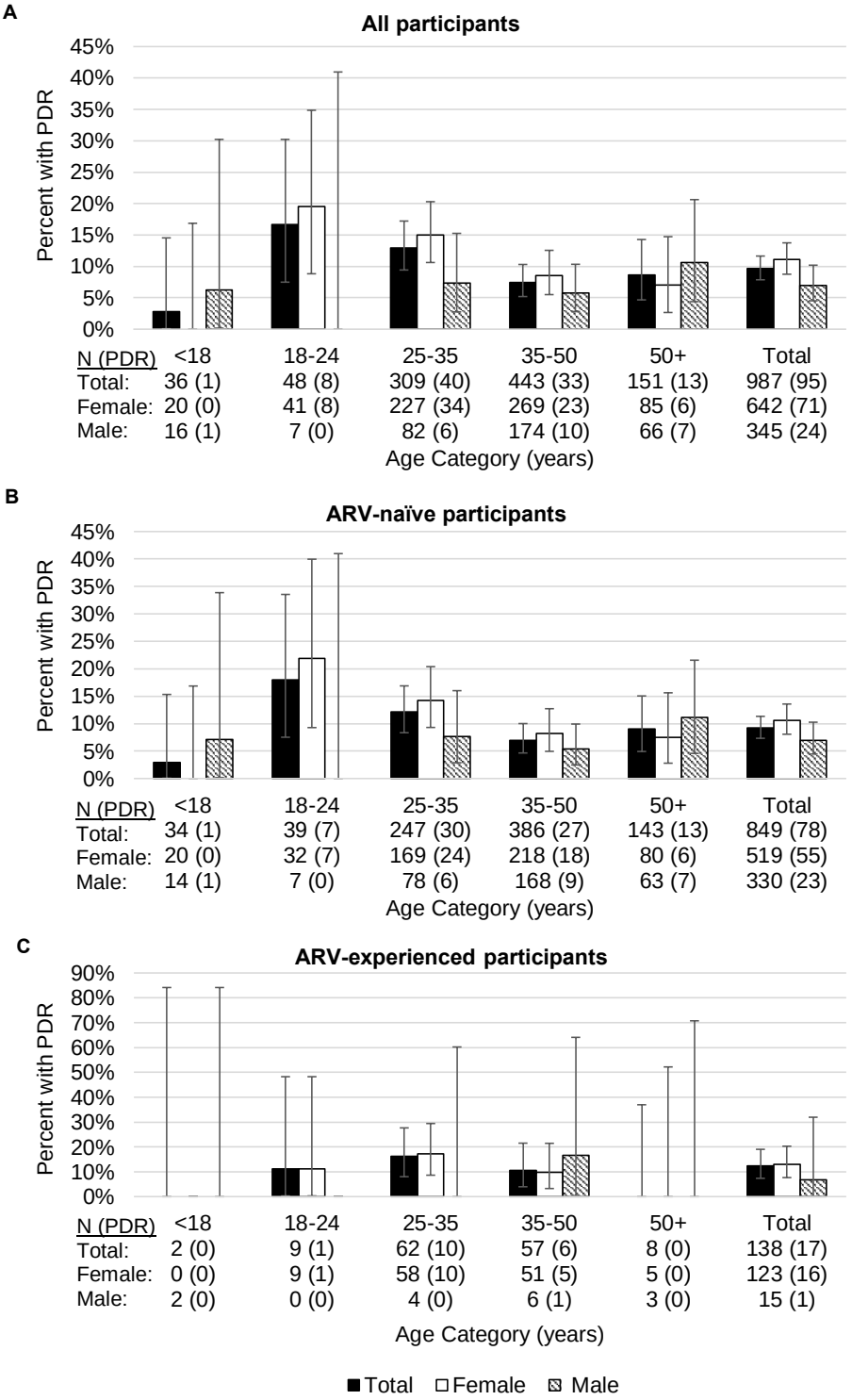
Abbreviations: PDR, Pre-treatment-drug-resistance; ARV, Antiretroviral; PR, prevalence ratio.

[a] PRs with p-value<0.05 are shown in bold.

[b] The PDR PR by location was adjusted for both age and sex in multivariable regression. The PDR PR by location stratified by sex and adjusted for age showed similar results and are not presented. Analyses adjusting for additional variables showed similar results to univariate analyses and are not presented.

[c] Industrial Area had no ARV-experienced participants with PDR so location was defined Maseno vs. Nairobi in multivariable analyses.

Figure 1. Pre-treatment HIV-drug-resistance (PDR) by age, gender and ARV-experience



Bar charts illustrate the prevalence of pre-treatment HIV-drug-resistance (PDR) and 95% CIs by 5 age categories (<18, 18-24, 25-35, 35-50, and 50 and older in years). Data are shown for all 987 study participants (panel A), 849 antiretroviral (ARV)-naïve participants (panel B), and 138 ARV-experienced participants (panel C). In each panel, data are shown stratified by gender (total in solid black, female in solid white, male in diagonal stripe).

Chapter 3. Predictors of Short-term Mortality Following ART Initiation in Kenya

Predictors of Mortality Within First Year of Initiating Antiretroviral Therapy in Urban and Rural Kenya

Running Title: Early Mortality Risk Post-ART in Kenya

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Abstract

Objective: To investigate predictors of early mortality following ART initiation among HIV-infected individuals.

Design: Nested prospective cohort study within a randomized clinical trial (RCT) of adult patients initiating ART in Kenya from 2013-2016.

Methods: Data from participants at HIV treatment clinics managed by Coptic Hospital in urban Nairobi and rural Maseno were analyzed to determine mortality incidence rates. Cox proportional hazards regression was used to identify predictors of mortality within 12 months of ART initiation.

Results: Among 207 Maseno and 612 Nairobi participants initiated on ART, mortality incidence rates (per 100 person-years) were 12.78 (95% CI 8.49-19.23) and 5.72 (95% CI 4.05-8.09) [unadjusted hazard ratio (HR): 2.20 (95% CI 1.29-3.76, P=0.004)]. Other statistically significant (P<0.05) predictors of mortality included male gender (HR=1.74), age (HR=1.04 for 1-year increase), fewer years of education (0.92 for 1-year increase), unemployment (HR=1.89), low body mass index (BMI<18.5 m/kg2; HR=4.99), CD4 count <100 (HR=11.67) and 100-199 (HR=3.40) vs. 200-350 cells/μL, and pre-treatment drug resistance (PDR; HR=2.49). Despite similar baseline CD4 counts across locations, mortality risk associated with low CD4 count, low BMI, and PDR was greater in Maseno than Nairobi.

Conclusions: High short-term post-ART mortality was observed, partially due to low CD4 count and BMI at presentation, especially in the rural setting. Male gender, older age, and markers of lower socioeconomic status were also associated with greater mortality risk. Engaging patients earlier in HIV infection remains critical. PDR may influence short-term mortality and further studies to optimize management will be important in settings with increasing PDR.

Keywords: Kenya; HIV and AIDS; antiretroviral therapy (ART); mortality; pre-treatment drug resistance (PDR); body mass index (BMI)

Background

Substantial efforts have been made to accelerate diagnosis of HIV infection and start infected individuals on ART as soon as possible [16-18]. However, many HIV-infected individuals continue to delay testing and/or treatment until they are symptomatic with advanced HIV [7-9], increasing their risk of early mortality [10, 11]. Prior studies in sub-Saharan Africa and other settings have identified sociodemographic predictors of early mortality including male gender [10, 66-68] and older age [10, 66, 67]. Measures of lower socioeconomic status [69, 70] and single marital status [70] have also been identified in some, though not all [71, 72] studies that investigated these factors. Clinical predictors of mortality include low CD4 count [10, 66, 67, 73] and low body mass index (BMI), weight loss, and malnutrition [10, 73]. Pre-treatment drug resistance (PDR) was observed to impact longer-term mortality (>6 months post-ART initiation) in one study [74], but was not associated with mortality within 1 and 2 years post-ART in another [75]. In Kenya, some rural areas have lower rates of HIV testing, greater delays in treatment, higher HIV prevalence, higher HIV-related mortality [76-78], and greater burdens of other infections including diarrheal diseases, tuberculosis and other respiratory diseases, and malaria both generally and among HIV-infected individuals [76, 79-82].

In this nested prospective study, we assessed the risk and predictors of short-term mortality among individuals participating in a randomized clinical trial (RCT) who initiated ART in 2013-2014 at two treatment clinics implemented by the same program (with the same clinical procedures and protocols), one in urban Nairobi, the capital city, and one in rural Maseno, Kisumu in Western Kenya. We examined sociodemographic and clinical correlates of mortality overall and across these sites. We ultimately aimed to gain greater understanding of factors

driving short-term mortality risk among HIV-infected individuals initiating ART in high disease-burden areas in Kenya and similar settings.

Methods

Study Design and Setting

We nested a prospective cohort study within a randomized clinical trial (RCT) investigating resistance testing-informed versus standard of care (SOC) treatment (RCT name: Oligonucleotide Ligation Assay (OLA) Resistance Study; ClinicalTrials.gov identifier: NCT01898754). Enrolled patients received care through the Coptic Hospital Hope Center for Infectious Diseases at three locations in Kenya, which provides HIV care [40, 83], standardized across clinic locations. For this RCT [50, 84], HIV-infected patients were enrolled from May 28th, 2013 to November 5th, 2014 at two clinics located in urban Nairobi (Ngong Road and Industrial Area) and one in rural Maseno, Kisumu. Participants received a CD4 test and health assessment through the Hope Center and were referred to the study if eligible for the RCT. Enrollment criteria for the RCT included that participants were over two years of age, willing to initiate ART, and eligible to initiate ART based on Kenyan National Guidelines at the time of enrollment. The CD4 count threshold for ART eligibility from 2011 through mid-2014 was 350 cells/μL [28] and increased to 500 cells/μL in 2014 [27]. For this analysis, we included participants who were 18 years and older and excluded those enrolled in the Industrial Area of Nairobi due to small numbers of participants and differences in socioeconomic characteristics compared to Ngong Road participants [84]. All participants provided written informed consent prior to study enrollment as approved by Human Subjects' Committees at Seattle Children's Hospital in Seattle, Washington, and Kenyatta National Hospital in Nairobi, Kenya.

At enrollment, participants completed a baseline questionnaire and a blood sample was collected. The baseline questionnaires collected sociodemographic, economic, and health information. Participants were randomized at enrollment, prior to ART initiation, to either SOC non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, or were tested for PDR using an OLA to inform their initial ART regimen. The OLA is point mutation test designed to detect ≥2% mutant-frequency in a participant's HIV-quasispecies at *pol* codons K103N, Y181C, G190A, M184V, and K65R [4, 43, 44, 50, 76, 84]. Low-level mutations <25% of an individual's HIV quasispecies were confirmed using Illumina sequencing described elsewhere [84]. Those in the OLA arm with ≥10% drug resistance detected were initiated on protease inhibitor (PI)-based treatment recommended for second-line ART. ART initiation began at the first follow-up study visit scheduled approximately two weeks from enrollment. Baseline samples from participants randomized to the SOC arm were later tested for PDR and results were available at the end of follow-up. Participants attended study visits for 12 months, either monthly or every two months per clinician discretion, and attended an exit visit at 15 months to receive their final results. Participants who missed a visit and did not respond to several phone call attempts, received a home visit by a trained community health worker to ascertain their status and attempt to re-engage them in the study and treatment. Dates and causes of illnesses, hospitalizations, and deaths were obtained during follow-up from medical records and/or verbal autopsy via a patient's relative or other contact when available.

Statistical Analyses

Baseline sociodemographic, economic, and health characteristics among adult enrolled patients seeking ART initiation were compared by clinic site (Nairobi vs. Maseno) to assess

differences by location using a t-test assuming unequal variance for continuous variables and a chi^2 test for binary and categorical variables. Correlates associated with not initiating ART were assessed by logistic regression to understand difference between enrolled, ART eligible, participants who did and did not attend the ART initiation visit due to known death, withdrawing from the study, or loss to follow-up.

We compared mortality incidence rates among patients who attended their first follow-up visit to initiate ART, from ART initiation visit to death date. Participants who withdrew from the study or were lost to follow-up were censored at the date of their last attended visit and those who completed follow-up were censored at 365 days after ART initiation. Participants who transferred to a different clinic location were censored at the date of their last visit attended at the clinic at which they enrolled. Deaths caused by unexpected injuries (e.g. motor vehicle accidents), rather than illnesses, were excluded as outcomes and these individuals were censored at their date of death. Deaths with unknown causes were included as outcomes.

Potential correlates investigated included location (Maseno vs. Nairobi), age group (18-24, 25-34, 35-49, ≥50), gender (male vs. female), relationship status (married or attached vs. single), years of education (0-11 vs. ≥12), employment status (unemployed vs. employed), sanitation access (flush toilet vs. pit latrine), and travel time to clinic (continuous). Unemployment may be associated with illness in addition to socioeconomic status, so was excluded from multivariable analyses due to issues of directionality. We also investigated mortality risk by baseline health indicators including BMI category (<18.5 m/kg^2 [underweight], 18.5-24.9 m/kg^2 [healthy], ≥25 m/kg^2 [overweight/obese]), CD4 lymphocyte count (<100, 100-199, 200-349, ≥350 cells/μL), and PDR (vs. wild-type). To investigate the potential impact of the RCT intervention, we compared mortality among those with ≥10% PDR detected at enrollment (randomized to receive resistance-

guided-treatment) by study arm. Cox proportional hazards regression with robust standard errors was used to compare mortality risk by these potential correlates in unadjusted analyses. To investigate the independent relationship between these variables and mortality, we adjusted for combinations of likely correlates in multivariable Cox proportional hazards regression models. Age and years of education were included as continuous variables in regression. We also stratified analyses by location to investigate differences in mortality correlates and risk between Maseno and Nairobi.

Kaplan-Meier survival curves show survival from ART initiation visit by select correlates identified in regression. Curves were stratified by location for correlates with an association that differed by clinic site.

Results

Participant Characteristics

Descriptive statistics on demographics, socioeconomics, and baseline health and laboratory information are shown by clinic location among 655 adults enrolled at the Nairobi (Ngong Road) clinic, and 212 at the Maseno clinic (Table 4). Age was similar between clinics, with a median of 38 years. More women enrolled in Maseno than Nairobi (73% vs. 64%; $P<0.05$). Nairobi participants had greater median number of years of education compared to Maseno (12 vs. 8 years; $P<0.001$). More participants in Maseno were unemployed than in Nairobi (38% vs. 14%; $P<0.001$) and fewer had access to a flush toilet (6% vs. 61%; $P<0.001$). Cost of and time spent traveling to the clinic were slightly greater in Nairobi ($P<0.05$). More participants were underweight (BMI <18.5 kg/m^2) in Maseno than Nairobi (28% vs. 13%; $P<0.001$). More participants in Nairobi had a CD4 cell count <50 cells/μL than in Maseno (16% vs. 9%; $P<0.05$), and fewer ≥350 cells/μL

(12% vs. 18%; $P<0.05$). Slightly more participants in Maseno than Nairobi had PDR (12% vs. 9%) but this was not statistically significant.

Enrollment, ART Initiation, and Follow-up Summary

Of the 867 enrolled participants, 20 (2%) were known to have died and 28 (3%) withdrew or were lost to follow-up prior to initiating ART. Overall, 612 (93%) in Nairobi and 207 (98%) initiated ART in Maseno. Of those who initiated ART, 56 (7%) died (including 1 auto accident), 52 (6%) withdrew or were lost to follow-up, and 8 (1%) transferred clinics within 12 months (Figure 2). Causes and/or symptoms reported at time of death are described (Supplemental Table 1). Among those who initiated ART, the average time from enrollment to ART initiation was 22 days in Nairobi (median 17 days; IQR: 14-23), and 18 days in Maseno (median 14 days; IQR: 14-21). Those who did not initiate ART (n=48) were more likely to be in Nairobi ($P=0.026$), unemployed ($P=0.001$), and have CD4 count <100 cells/μL ($P=0.035$), compared to those who initiated ART (Supplemental Table 2); among these, 20 (42%) were known mortalities.

Mortality Incidence and Correlates of Mortality Risk Following ART Initiation

Of the participants who initiated ART, 55 (7%) died from a non-injury related cause within 365 days of ART initiation, including 32 (5%) in Nairobi and 23 (11%) in Maseno. The median time to death from ART initiation was 74 days (IQR: 30-189) in Nairobi and 70 days (IQR: 26-182) in Maseno. Overall, of those who died within a year from initiating ART, 18 (33%), 25 (45%), 37 (67%), and 44 (80%) died within 30, 60, 90, and 180 days from ART initiation. The overall mortality incidence rate within a year of initiating ART was 7.44 per 100 person-years (95% CI 5.71, 9.69).

In unadjusted Cox proportional hazards regression, older age, male gender, fewer years of education, unemployment, low CD4 count, low BMI, and PDR were associated with increased mortality risk within a year of ART initiation (Table 5a; Figure 3a). Increased risk of mortality associated with age (HR 1.04 for a one-year increase; 95% CI 1.02, 1.07; $P<0.001$) persisted in models adjusted for location, gender, education, PDR, CD4 count, and BMI (Table 5b). Males had 1.74-fold increased risk of mortality than females (95% CI 1.02-2.95; $P=0.041$), which remained when adjusting for location, age, education and PDR, but not when adjusting for BMI and/or CD4 count. A one-year increase in education was associated with a decreased risk of mortality (HR 0.92; 95% CI 0.88, 0.97; $P=0.002$), which remained when adjusting for other variables. Unemployment was associated with an increased risk in unadjusted analyses (HR 1.89; 95% CI 1.05, 3.40; $P=0.033$). Participants with a CD4 count <100 had a 11.67-folder increased risk of mortality compared to those with 200-349 cells/μL (95% CI 4.93, 27.65; $P<0.001$). Participants with a low BMI (<18.5 m/kg^2) vs. healthy BMI (18.5-24.9 m/kg^2) had a 4.99-fold increased risk (95% CI 2.79, 8.92; $P<0.001$). The associations between CD4 and BMI with increased mortality risk persisted in multivariable analyses. Those with PDR (≥2% detected via OLA) had a 2.49-fold increased risk of mortality than those with wild-type virus (95% CI 1.29-4.79; $P=0.006$), which remained when adjusting for location, age, gender, education, and BMI, but not when adjusting for CD4 count. There was no statistically significant difference in mortality risk between those who received the RCT intervention. There was no significant association for relationship status and mortality risk. Sanitation (type of toilet) was collinear with location (see Table 4), so was excluded from this analysis.

Maseno had a 2.20-fold greater risk of mortality than Nairobi (95% CI 1.29, 3.76; $P=0.004$) (Table 5a; Figure 3a). This association remained when adjusting for age, gender, education, PDR,

and CD4 count, but not when adjusting for BMI (Table 5b). When stratifying by location (Table 6) we found CD4 count and BMI were associated with mortality at both locations, while older age and male gender were only statistically significantly associated with mortality in Nairobi. PDR was only associated with mortality in Maseno. When adjusting for the other variables (Table 6), the association between CD4 count and BMI remained for both sites, as did older age and male gender for Nairobi, and PDR for Maseno. Lower education in Nairobi, and age and female gender in Maseno were associated with mortality in adjusted stratified analyses. The association between CD4 count, BMI, and PDR with increased mortality risk was greater in Maseno than in Nairobi in unadjusted analyses (Figure 3b). Adjusted associations between mortality and CD4 count and PDR remained greater in Maseno than Nairobi, though were similar across locations for BMI; only effect modification by location for CD4 count was statistically significant ($P<0.001$).

Discussion

In this study of mortality following ART initiation in Kenya in 2013/14, 7% of patients were known to have died within a year of initiating ART. This is similar to the 9% incidence estimated in a 2011 meta-analysis of studies from sub-Saharan Africa [66]. Compared to a large study of patients in Europe and North America [85], the mortality rates within a year were an order of magnitude higher in our study for those with a low CD4 count <100, but similar at CD4 counts >200 cells/μL. The majority (67%) of deaths in our study occurred within 3 months of initiating ART. This elevated risk of mortality within the first few months of ART initiation is consistent with other studies in sub-Saharan Africa and globally [70, 85-88]. Interventions to modify the risk of early mortality may be most effective by targeting this time-frame, in addition to efforts to diagnose and treat individuals earlier in HIV disease progression.

We found that a low CD4 lymphocyte count, low BMI, rural location, increased age, male gender, fewer years of education, unemployment, and PDR were associated with greater risk of mortality. Low CD4, low BMI, and PDR were associated with a greater risk of mortality at the rural location compared to those at the urban location. Because the clinics were designed and managed by the Coptic Hospital to provide the same high level of services and programs [40, 83], differences by location are more likely due to regional or rural/urban disparities in underlying health and infectious disease burden [76]. The higher risk of death in rural Maseno compared to urban Nairobi remained even when controlling for CD4 count, but not when controlling for BMI indicating that poor nutrition may explain some of the higher risk of mortality in this rural setting. Stratified analyses suggest that the consequences of poor nutrition, low pre-ART CD4 count, and drug resistance may be more severe in rural settings where the risk of coinfections is higher [79-82]. Providing ARV-naïve individuals with point-of-use water filtration and/or long-lasting insecticide-treated bed nets has been shown to prevent diarrheal disease and malaria and delay HIV disease progression [89, 90]. While evidence is needed to determine if such interventions would be effective at reducing short-term mortality among individuals with more advanced HIV initiating ART, more aggressive management of coinfections has been shown to be beneficial in the REALITY trial and could improve outcomes for late presenters [91].

Our results are generally consistent with previous studies investigating post-ART mortality among HIV-infected adults in sub-Saharan Africa. Similar to other studies, older age was associated with mortality [10, 66, 67] and is consistent with older adults being diagnosed and presenting for treatment later, with less immune recovery during treatment [92]. Male gender has been associated with higher post-ART mortality in many studies [10, 66-68] including those conducted in coastal and Western Kenya [71, 93]. We previously found males to be at higher risk

of attrition from clinic attendance at the same Coptic Hope Center in Nairobi [94]. HIV-infected men have been shown to have later diagnoses and ART initiation, worse engagement, poorer adherence, and more severe outcomes including mortality than women throughout low- and middle-income countries [68, 95]. The results of our study add to the expanding body of literature demonstrating high mortality risk among HIV-infected men and underscore the continued need to engage and retain men in care.

The independent association we found between low BMI and mortality is also consistent with prior studies [66, 96-99]. Even among ARV-naïve patients with less advanced HIV (CD4 ≥350 cellsμ/L), low BMI was associated with increased mortality risk in a study in Uganda [100]. Weight loss was found to be associated with mortality in studies of patients initiating [86] or currently on ART [101] and weight gain is associated with greater survival [98, 102, 103]. While nutritional supplementation and food assistance have effectively increased BMI in some [104-107], but not all studies [108], such interventions have not been shown to significantly decrease short-term mortality risk in HIV-infected adults [108, 109]. However, evidence is limited and nutritional supplementation has been shown to be cost-effective for reducing mortality in severely underweight individuals [110].

There is limited evidence regarding PDR and short-term mortality risk in previously published studies. While PDR was not statistically significantly associated with mortality within one and two years of ART initiation in a study across in Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe [75], it was found to be associated with death among those on ART for at least 6 months in one study conducted in Malawi, Kenya, Uganda, and Cambodia [74]. In adjusted analysis in our study, the association between PDR and mortality remained statistically significant only among rural Maseno participants. Further study is needed to understand the mechanisms by

which PDR contributes to early morality after ART initiation. Given the substantial evidence of virologic failure and poor health outcomes among patients with PDR initiating ART in resource limited settings [4, 6, 23, 74] and observed increases in PDR prevalence [50, 111], scale-up of resistance testing and/or alternative ARV combinations may be warranted. Utilizing ARVs like dolutegravir with a higher barrier of resistance [112] could be beneficial in Kenya and similar settings where first-line regimen recommendations currently include NNRTI based ART [17, 26].

There is mixed evidence regarding the association between socioeconomic status and short-term mortality among HIV-infected individuals initiating ART [69-72]. We found that greater years of education and employment were protective, and unemployment was also associated with not initiating ART (many non-initiators were known mortalities). While unemployment may be associated with underlying severe illness leading to both inability to work and early mortality, the independent association found with education suggests less educated individuals may require additional support to mitigate their higher risk of short-term mortality. There is mixed evidence that single marital status may be associated with higher risk of HIV-related mortality [70, 71], and we did not observe an association in our study.

Study limitations include that baseline viral loads were not determined on all subjects who died or were lost to follow-up and use of a single pre-enrollment CD4 count measurement [113, 114]. However, CD4 count has commonly been used in clinical settings to define the health and severity of HIV-infected individuals [9, 17, 85, 115, 116]. More direct measures of socioeconomic status, like income, were unavailable for our analyses. Our study also did not investigate the impact of poor adherence to medications nor quantify non-fatal indicators of poor health. Data to specifically identify immune reconstitution inflammatory syndrome (IRIS) were not collected, though the timing of most deaths suggests that looking for IRIS may be an important intervention.

Although our study was nested in an RCT, 82.7% of screened participants were enrolled [84] suggesting reasonable coverage of the population in care. We also found no significant difference in mortality risk due to the RCT intervention. Our study has notable strengths as a large prospective cohort study with careful follow-up and tracking, assessment of mortality, and high retention. The Coptic Hospital Hope Center clinics are designed to provide uniform high standard of care [40, 83] across regional locations, allowing us to look beyond health service delivery as a contributor of differences in mortality. Using a prospective longitudinal study design with monthly/bi-monthly follow-up visits, we were able to control for losses to follow-up and minimize biases in our analyses using Cox proportional hazards regression.

Conclusions

We found a high proportion of HIV-infected patients initiating ART with low CD4 counts, indicative of delayed treatment and increased risk for poor health outcomes and transmission to others. This study identifies multiple potentially modifiable risk factors associate with increased mortality within the first year of ART. Targeted interventions to patients with a low CD4 count at presentation, as well as to those who are older, male, less educated and unemployed, and those with low BMI or PDR may help mitigate the risk of early mortality in Kenya and similar populations, especially in rural areas.

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Table 4. Characteristics of enrolled adult participants eligible to initiate ART by clinic location

Characteristics[a]	Urban Nairobi (n=655)	Rural Maseno (n=212)	Total (n=867)
Demographic			
Age in years	38 (32, 45)	39 (30, 47)	38 (31, 46)
Female	421 (64%)	155 (73%)*	576 (66%)
Socioeconomic			
Married/steady partner	396 (60%)	135 (64%)	531 (61%)
Education in years[b]	12 (8, 14)	8 (7, 10)**	11 (8, 13)
Unemployed[b]	89 (14%)	80 (38%)**	169 (19%)
Monthly rent in US$[b]	39 (0, 89)	0 (0, 0)**	22 (0, 66)
Flush toilet[b]	396 (61%)	12 (6%)**	408 (47%)
Persons living in house	3 (2, 5)	4 (3, 5)**	4 (2, 5)
Access to Care			
Cost of travel in US$[b]	2.22 (1.11, 2.77)	2.10 (1.11, 3.32)*	2.22 (1.11, 2.88)
Travel time to clinic in hours	1 (0.67, 2.00)	1 (0.50, 1.50)*	1 (0.67, 2.00)
Health & Laboratory (at Baseline)			
BMI (kg/m^2)	23 (20, 26)	21 (18, 23)**	22 (19, 25)
<18.5 (underweight)	85 (13%)	60 (28%)**	158 (18%)
18.5-24.9 (healthy)	355 (56%)	114 (54%)	468 (54%)
25-29.9 (overweight)	136 (21%)	34 (16%)	170 (20%)
≥30 (obese)	59 (9%)	4 (2%)**	68 (8%)
CD4 count (cells/μL)[b]	224 (97, 305)	233 (135, 323)	227 (105, 308)
<50	102 (16%)	19 (9%)*	121 (14%)
50-99	63 (10%)	22 (10%)	85 (10%)
100-199	135 (21%)	43 (20%)	178 (21%)
200-349	276 (42%)	88 (42%)	364 (42%)
350-499	63 (10%)	39 (18%)**	102 (12%)
≥500	14 (2%)	0 (0%)*	14 (2%)
Viral load (log10, copies/mL)[b]	4.75 (4.08, 5.30)	4.41 (3.76, 5.12)**	4.67 (3.97, 5.23)
Drug resistance ≥2%, OLA[b, c]	58 (9%)	25 (12%)	83 (10%)
Drug resistance ≥10%, OLA[b, c]	50 (8%)	19 (9%)	69 (8%)
Study Intervention and ART initiation			
Randomized at enrollment to OLA informed ART	329 (50%)	112 (53%)	441 (51%)
Randomized at enrollment to OLA & had drug resistance ≥10%	30 (5%)	11 (5%)	41 (5%)
ART initiation visit attended	612 (93%)	207 (98%)*	819 (94%)

Abbreviations: ART, Antiretroviral therapy; OLA, oligonucleotide ligation assay (point mutation test designed to detect K103N, Y181C, M184V, G190A, and K65R)

[a] For continuous variables, median (interquartile range) are presented. For binary and categorical variables, the number (%) within that category is shown.

[b] Data is complete except for the following variables for Nairobi: Monthly rent (n=633), Type of toilet (n=654), Cost of travel (n=642), BMI (n=635), CD4 count (n=653), Viral load (n=548), Drug resistance (n=652); Data is complete for Maseno except for Viral load (n=177). Viral load testing was not performed for participants who completed fewer than 4 months of follow-up.

[c] OLA is a point mutation test designed to detect K103N, Y181C, M184V, G190A, and K65R). Percent resistant is defined by the highest frequency of viral variant with a mutant codon detected within an individual's HIV-quasispecies.

* T-test assuming unequal variance for continuous variables and a chi2 test for binary and categorical variables used to compare across locations. For BMI and CD4 count categories, proportions are compared within each category across locations with chi2 test. *p<0.05, **p<0.001

Table 5a. Unadjusted incidence rates and hazard ratios (HR) of mortality following ART initiation (N=811)[a]

Variables		Deaths/ person-years	Incidence (per 100 person-years)	HR (95% CI); p-value[b]
Location	Nairobi	32/559	5.72 (4.05, 8.09)	Ref
	Maseno	23/180	12.78 (8.49, 19.23)	2.20 (1.29, 3.76); **0.004**
Age	18-24	0/35	-	Ref
	25-34	16/238	6.71 (4.11, 10.95)	
	35-49	21/349	6.02 (3.93, 9.24)	1.03 (0.54, 1.98); 0.918
	≥50	18/117	15.35 (9.67, 24.37)	2.59 (1.33, 5.05); **0.005**
	1-year increase	-	-	1.04 (1.02, 1.07); <**0.001**
Gender	Female	30/502	5.97 (4.17, 8.54)	Ref
	Male	25/237	10.60 (7.14, 15.63)	1.74 (1.02, 2.95); **0.041**
Relationship Status	Single	20/284	7.04 (4.54, 10.92)	Ref
	Married/attached	35/455	7.69 (5.52, 10.71)	1.09 (0.63, 1.88); 0.766
Education Years	0-11	36/379	9.49 (6.85, 13.16)	Ref
	≥12	19/360	5.28 (3.37, 8.28)	0.56 (0.32, 0.98); **0.042**
	1-year increase	-	-	0.92 (0.88, 0.97); **0.002**
Employment Status	Employed	39/609	6.40 (4.68, 8.76)	Ref
	Unemployed	16/30	12.32 (7.55, 20.12)	1.89 (1.05, 3.40); **0.033**
BMI Category (m/kg^2)	<18.5 (underweight)	27/103	26.25 (18.00, 38.28)	4.99 (2.79, 8.92), <**0.001**
	18.5-24.9 (healthy)	20/405	4.94 (3.19, 7.65)	Ref
	≥25 (overweight/obese)	6/215	2.79 (1.25, 6.22)	0.57 (0.23, 1.41); 0.224
CD4 Count (cells/μL)	<100	35/156	22.40 (16.08, 31.20)	11.67 (4.93, 27.65); <**0.001**
	100-199	10/157	6.35 (3.42, 11.81)	3.40 (1.24, 9.34); **0.018**
	200-349	6/326	1.84 (0.83, 4.09)	Ref
	≥350	3/99	3.04 (0.98, 9.41)	1.63 (0.41, 6.47); 0.491
PDR	0% (wild-type)	44/673	6.54 (4.86, 8.78)	Ref
	≥2%	11/66	16.68 (9.24, 30.12)	2.49 (1.29, 4.79); **0.006**
	2-9%	4/9	43.87 (16.47, 116.90)	6.17 (2.44, 15.59); <**0.001**
	10-100%[c]	7/57	12.32 (5.87, 25.84)	1.86 (0.83, 4.13); 0.129
Intervention	PDR 10-100%, OLA arm	5/32	15.49 (6.45, 37.21)	Ref
	PDR 10-100%, SOC arm	2/25	8.15 (2.04, 32.58)	0.54 (0.10, 2.80); 0.462

Abbreviations: ART, Antiretroviral therapy; HR, Hazard ratio; CI, confidence interval; BMI, Body mass index; PDR, Pre-treatment drug resistance; OLA, Oligonucleotide ligation assay; SOC, Standard of care; Ref, reference category.

[a]See Footnote in Table 1 for information on missing variable information.
[b]HRs estimated using Cox proportional hazards regression with robust variance estimates. P-values<0.05 are in bold.
[c]Approximately 50% of these individuals were randomized to OLA testing for PDR, and those with ≥10% drug resistant variants in their HIV-quasispecies were initiated on protease-inhibitor-based ART (which was shown to reduce their rate of virologic failure (submitted))

Table 5b. Adjusted hazard ratios (HR) of mortality following ART initiation (N=811)[a]

Variables	Model 1 (N=811)	Model 2 (N=810)	Model 3 (N=792)	Model 4 (N=791)
	HR (95% CI); p-value[b]	HR (95% CI); p-value[b]	HR (95% CI); p-value[b]	HR (95% CI); p-value[b]
Maseno vs. Nairobi	1.84 (1.06, 3.19); **0.029**	2.09 (1.17, 3.74); **0.013**	1.31 (0.73, 2.33); 0.364	1.55 (0.82, 2.95); 0.181
Age (1-year increased)	1.04 (1.01, 1.06); **0.003**	1.03 (1.01, 1.05); **0.002**	1.04 (1.02, 1.06); <**0.001**	1.03 (1.01, 1.05); <**0.001**
Male vs. female	1.79 (1.02, 3.13); **0.041**	1.18 (0.63, 2.20); 0.606	1.43 (0.80, 2.55); 0.233	1.11 (0.59, 2.10); 0.747
Education (1-year increased)	0.95 (0.90, 1.00); **0.049**	0.93 (0.88, 0.98); **0.008**	0.96 (0.91, 1.01); 0.101	0.93 (0.89, 0.98); **0.010**
PDR ≥2%	2.76 (1.43. 5.32); **0.002**	1.69 (0.90, 3.21); 0.105	2.49 (1.32, 4.68); **0.005**	1.46 (0.75, 2.86); 0.266
CD4 count category (cells/μL)				
<100		11.37 (4.72, 27.39); <**0.001**		7.97 (3.20, 19.87); <**0.001**
100-199	-	3.53 (1.29, 9.65); **0.014**		2.82 (1.01, 7.88); **0.049**
200-349		Ref		Ref
≥350		1.28 (0.30, 5.48); 0.735		1.39 (0.33, 5.94); 0.653
BMI Category (m/kg^2)				
<18.5 (underweight)	-		4.41 (2.51, 7.75); <**0.001**	3.11 (1.69, 5.74); <**0.001**
18.5-24.9 (healthy)			Ref	Ref
≥25 (overweight/obese)			0.59 (0.23, 1.47); 0.257	0.87 (0.34, 2.24); 0.779

Abbreviations: ART, Antiretroviral therapy; HR, Hazard ratio; CI, confidence interval; BMI, Body mass index; PDR, Pre-treatment drug resistance; OLA, Oligonucleotide ligation assay; SOC, Standard of care; Ref, reference category.

[a]Of those who initiated ART, CD4 count was missing for 1 participant and BMI information was missing for 19 participants.
[b]HRs were estimated using Cox proportional hazards regression with robust variance estimates. For each model, we adjusted for all variables with results presented. P-values<0.05 are in bold.

Table 6. Univariable and multivariable Cox proportional hazards regression for mortality from ART initiation visit by location (N=811)[a]

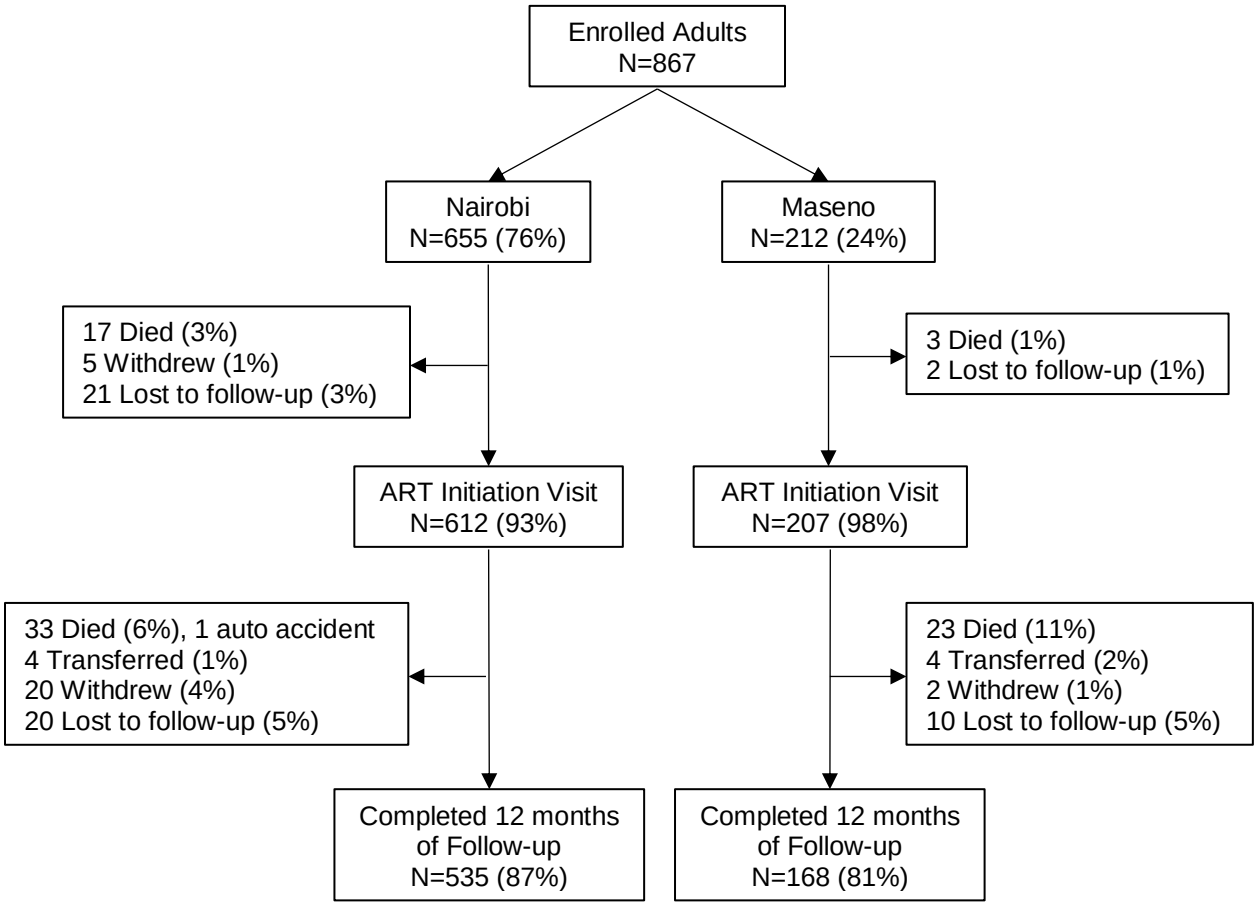
Variable	Nairobi (N=606)		Maseno (N=205)	
	Unadjusted HR[b]	Adjusted HR[b]	Unadjusted HR[b]	Adjusted HR[b]
Age (1yr increase)	1.05 (1.02, 1.08); **0.003**	1.05 (1.01, 1.08); **0.009**	1.03 (1.00, 1.06); 0.062	1.04 (1.01, 1.07); **0.002**
Male vs. Female	2.16 (1.08, 4.31); **0.030**	2.21 (1.01, 4.82); **0.047**	1.50 (0.64, 3.49); 0.348	0.26 (0.10, 0.64); **0.003**
Married/Attached	1.24 (0.60, 2.57); 0.566	-	0.85 (0.37, 1.95); 0.695	-
School years (1yr increase)	0.94 (0.88, 1.00); 0.051	0.90 (0.83, 0.97); **0.005**	0.96 (0.87, 1.05); 0.345	0.91 (0.82, 1.02); 0.095
Unemployed	1.76 (0.72, 4.26); 0.213	-	1.32 (0.58, 3.02); 0.510	
Flush toilet vs. pit	0.83 (0.41, 1.66); 0.597	-	-	-
Time to clinic (1min increase)	0.88 (0.64, 1.20); 0.407	-	1.12 (0.76, 1.67); 0.561	-
PDR ≥2%	1.55 (0.55, 4.40); 0.408	0.63 (0.17, 2.35); 0.495	3.41 (1.43, 8.16); **0.006**	3.46 (1.62, 7.40); **0.001**
PDR 10-100%, OLA arm	Ref	-	Ref	-
PDR 10-100%, SOC arm	0.69 (0.06, 7.72); 0.764		0.42 (0.05, 3.77); 0.437	
CD4 count category				
<100	7.01 (2.79, 17.59); **<0.001**	5.30 (1.90, 14.84); **0.001**	21.64 (6.33, 74.00); **<0.001**	20.53 (4.68, 89.98); **<0.001**
100-199	3.00 (1.01, 8.92); **0.047**	2.08 (0.62, 6.95); 0.234	2.94 (0.58, 14.80); 0.191	4.36 (0.81, 23.50); 0.087
≥200	Ref	Ref	Ref	Ref
BMI Category				
<18.5 (underweight)	3.15 (1.41, 7.03); **0.005**	3.62 (1.47, 8.90); **0.005**	7.59 (2.79, 20.62); **<0.001**	3.57 (1.11, 11.52); **0.033**
18.5-24.9 (healthy)	Ref	Ref	Ref	Ref
≥25 (overweight/obese)	0.57 (0.21, 1.55); 0.270	0.93 (0.32, 2.70); 0.889	0.58 (0.07, 4.84); 0.614	0.35 (0.06, 2.18); 0.262

Abbreviations: ART, Antiretroviral therapy; HR, Hazard ratio; CI, confidence interval; BMI, Body mass index; PDR, Pre-treatment drug resistance; OLA, Oligonucleotide ligation assay; SOC, Standard of care; Ref, reference category.

[a]See footnote in Table 1 for information on missing variables. For adjusted models, N=586 for Nairobi & N=205 for Maseno.

[b]HRs estimated using Cox proportional hazards regression with robust variance estimates. Adjusted HR controls for all other variables with results presented. P-values <0.05 are in bold.

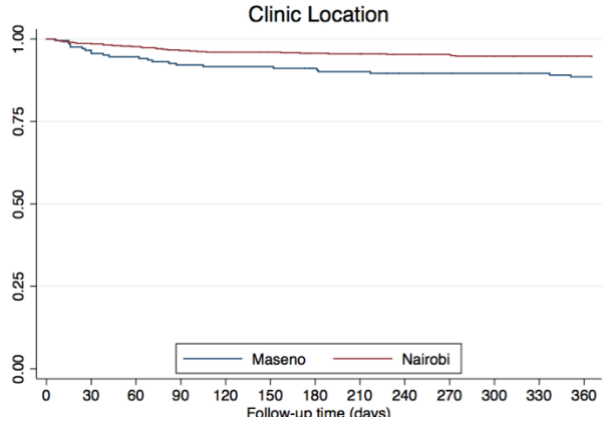
Figure 2. Flow Chart from enrollment of adult participants



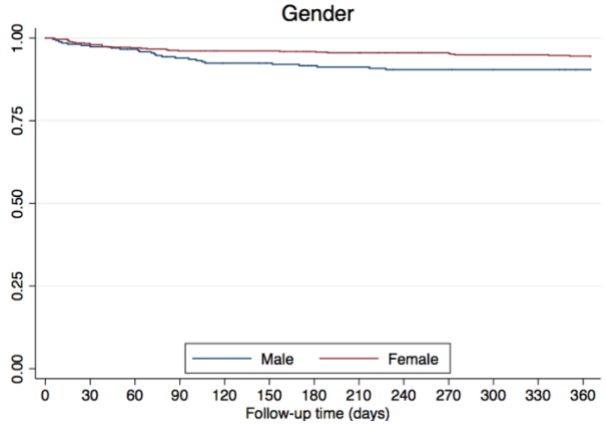
Flow chart diagraming overall study follow-up and attrition before and after ART initiation by location (Nairobi and Maseno).

Figure 3a. Kaplan-Meier Curves from ART initiation to death by correlates of mortality

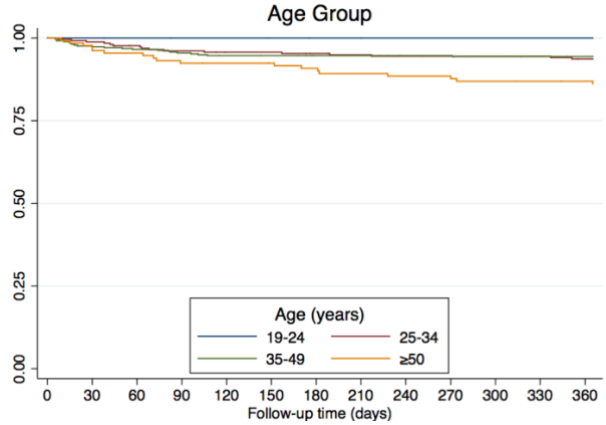
i.



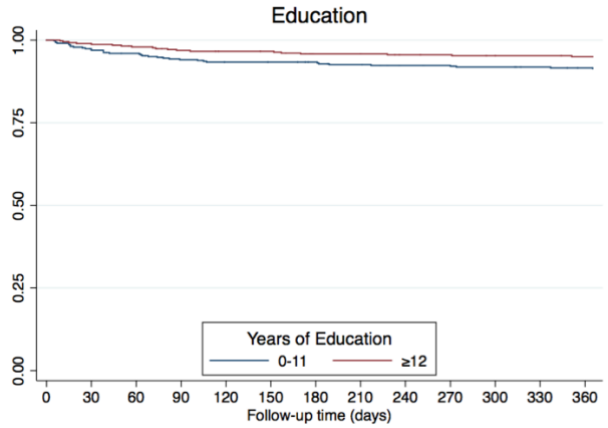
ii.



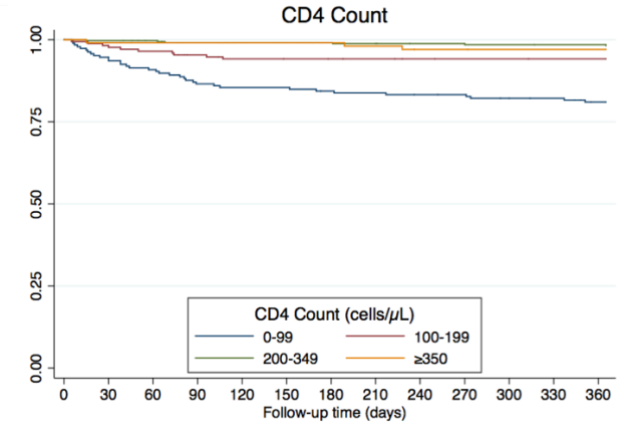
iii.



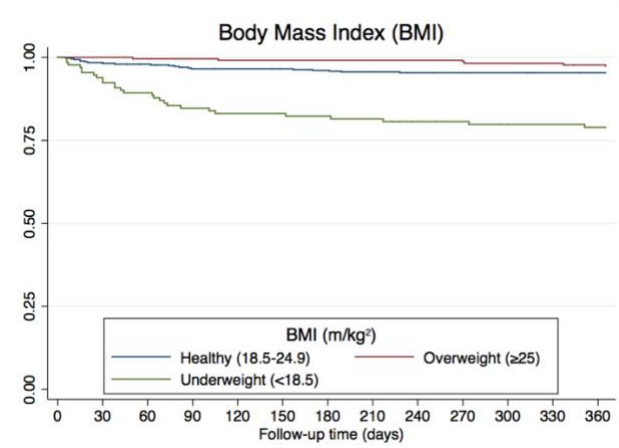
iv.



v.



vi.



vii.

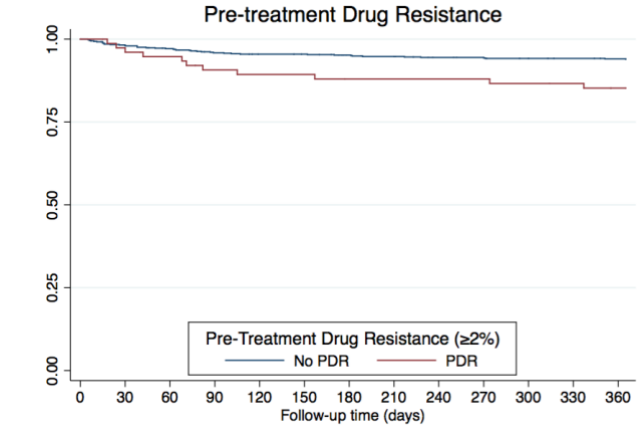
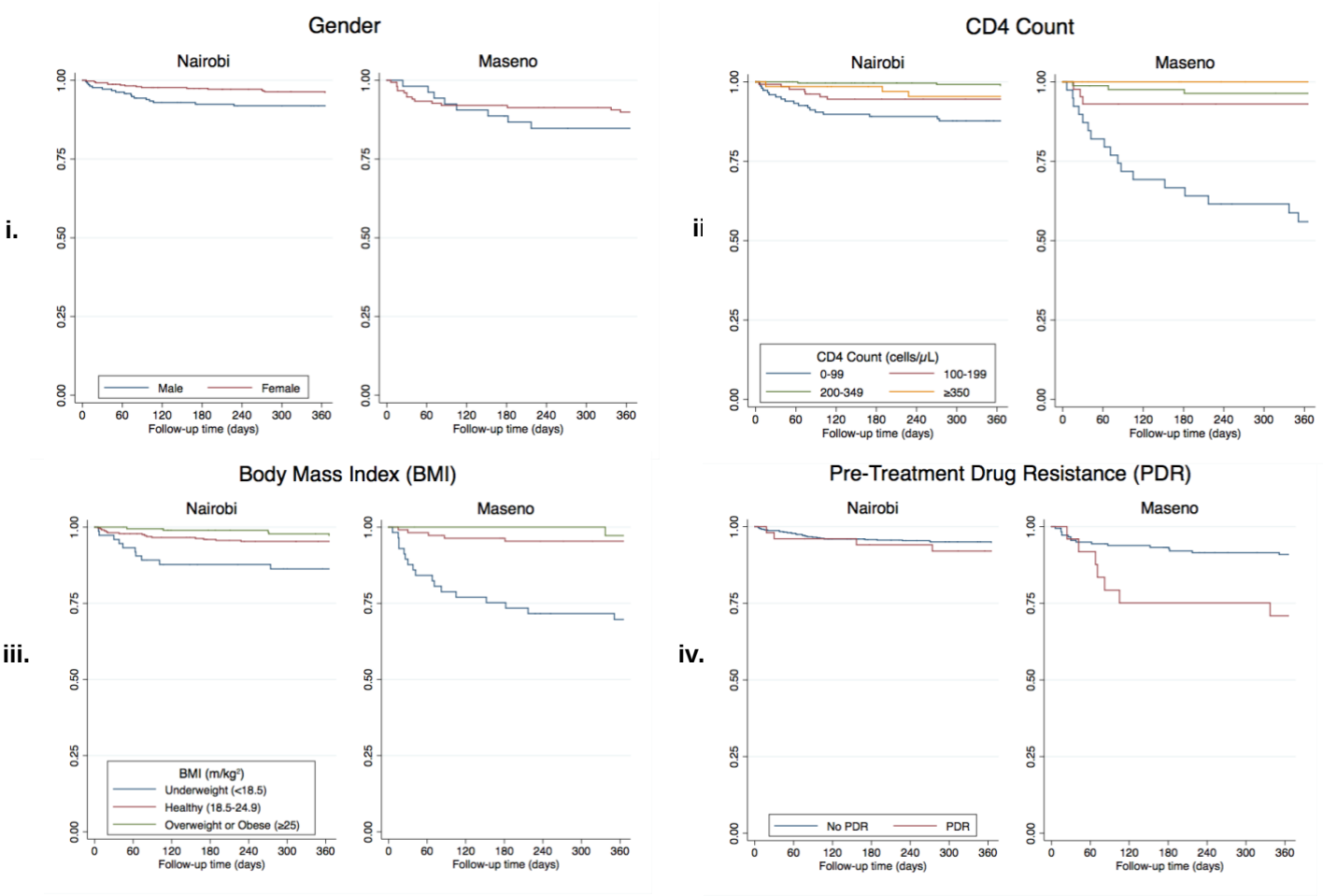


Figure 3b. Kaplan-Meier Curves from ART initiation to death by correlates of mortality stratified by location



Kaplan-Meier survival curves from ART initiation by correlates of mortality. Figure 3a describes survival in the combined cohort by i) location, ii) gender, iii) age group, iv) education, v) CD4 count, vi) body mass index (BMI), and vii.) pre-treatment drug resistance (PDR). Figure 3a describes survival stratified by clinic location (Nairobi and Maseno) cohort by correlates of mortality that differed in their association by location including i) gender, ii) CD4 count, iii) BMI, and iv) PDR.

Table S1. Baseline correlates & cause/symptom summary at time of death (n=81)

A. Nairobi (n=52)

ART Initiated	Gender	Age	BMI (m/kg^2)	CD4 Count (cells/μL)	PDR	Days from Enrollment to Death	Days from ART start to Death	Simple Summary of Cause/ Symptoms at Death
No	Female	27	16.5	52	unknown	20		Severe anemia
No	Female	27	21.9	4	wildtype	66		General body weakness, difficulty breathing, sweating profusely
No	Female	30	19.1	14	wildtype	31		TB
No	Female	35	19.7	6	wildtype	4		Kidney disease, tuberculosis (TB)
No	Female	35	11.1		wildtype	22		Severe anemia, esophageal candidiasis, lower respiratory tract infection, genital ulcer disease
No	Female	38	21.6	43	wildtype	29		TB
No	Female	39	33.2	7	wildtype	105		Collapsed and died
No	Female	44	unknown	135	wildtype	36		TB, difficulty breathing, chest pain, cough, swollen left leg and arm
No	Female	48	18.2	214	wildtype	231		Cervical cancer
No	Male	30	17.8	471	wildtype	6		Collapsed and died
No	Male	33	16.9	81	wildtype	15		Diarrhea & vomiting postprandial associated with dysphagia, sick looking, pale, oral thrush
No	Male	36	19.3	4	wildtype	26		Difficulty breathing
No	Male	37	23.2	31	wildtype	18		Anemia & pneumonia
No	Male	38	19.8	196	wildtype	400		Unknown (weakness)
No	Male	40	19.4	14	wildtype	179		Unknown
No	Male	47	22.5	24	wildtype	3		TB, headache & generalized body aches
No	Male	52	15.2	176	wildtype	20		TB
Yes	Female	29	18.7	4	wildtype	52	38	Body weakness, anemia, headache, chronic diarrhea, & vomiting
Yes	Female	30	23.9	473	wildtype	203	189	Kidney disease (anemia and dialysis)
Yes	Female	31	13.6	56	10-100%	394	375	Unknown
Yes	Female	34	18.7		10-100%	192	157	Diarrhea, general body malaise, vomiting, weight loss, reduced appetite, cachexic & dehydrated
Yes	Female	37	22.5	20	wildtype	40	20	Anemia & oral candidiasis & swelling/weakness of lower limbs
Yes	Female	37	28.4	68	wildtype	291	271	Postprandial vomiting, epigastric abdominal pains, anemia
Yes	Female	39	22.1	21	10-100%	32	18	Headache, general body malaise, diarrhea, vomiting, dehydration
Yes	Female	41	15.9	118	wildtype	74	38	General body weakness, body itchiness, rash, & wounds
Yes	Female	44	16.5	44	wildtype	17	6	Chest congestion, difficulty breathing, underweight, anemia
Yes	Female	45	20.1	57	wildtype	93	81	TB
Yes	Female	49		64	wildtype	72	57	Pneumonia
Yes	Female	52	17	22	2-9%	288	274	Cancer: Kaposi's Sarcoma (possibly)
Yes	Female	54	26.4	321	wildtype	290	270	Kidney disease
Yes	Female	57	26.6	292	wildtype	382	365	TB
Yes	Female	61	15.6	76	wildtype	78	64	Cryptococcal meningitis, oral candidiasis, & moderate anemia.
Yes	Female	62	20.3	80	wildtype	105	89	Unknown (general illness)
Yes	Male	32	16.6	77	wildtype	195	44	Meningitis (severe headache/paralysis on one side)
Yes	Male	33	17	318	wildtype	77	63	Edema of lower limbs, difficulty breathing, & unconscious episodes
Yes	Male	33	18.1	44	wildtype	21	7	General malaise
Yes	Male	34	19.8	42	wildtype	127	78	Cancer: Kaposi's Sarcoma, possible metastasis to the lungs & pneumonia (PCP)
Yes	Male	35	unknown	153	wildtype	143	96	Leg weakness & resting tremors; paralysis of one side
Yes	Male	35	18.8	142	wildtype	88	74	Yellowing eyes & urine, general body malaise, fever
Yes	Male	37	27.4	136	wildtype	129	107	Pneumonia (PCP) & TB
Yes	Male	37	24.2	246	10-100%	444	431	Cancer: Kaposi's Sarcoma, metastasis to chest
Yes	Male	39	18.3	14	wildtype	115	101	Cancer: Kaposi's Sarcoma
Yes	Male	40	25.2	150	wildtype	70	50	Cough, severe vomiting (blood stained)
Yes	Male	42	21.3	114	wildtype	21	5	TB, acute renal illness, & UTI
Yes	Male	47	27.7	101	wildtype	431	411	Ruptured pancreas
Yes	Male	48	20.3	10	wildtype	28	11	Poor appetite, weight loss, & anemia
Yes	Male	50	20.2	543	wildtype	246	228	Collapsed and died
Yes	Male	50	19	21	wildtype	200	170	TB
Yes	Male	51	15.5	32	10-100%	44	30	Diarrhea, weakness
Yes	Male	52	17	134	wildtype	89	73	Severe pneumonia & severe anemia
Yes	Male	58	20.8	24	wildtype	69	9	Lower abdominal pains, difficulty breathing, & low blood glucose
Yes	Male	60	24.2	1560	wildtype	39	15	Diabetes

B. Maseno (n=29)

ART Initiated	Gender	Age	BMI (m/kg^2)	CD4 Count (cells/µL)	PDR	Days from Enrollment to Death	Days from ART start to Death	Simple Summary of Cause/ Symptoms at Death
No	Female	34	14.7	unknown	wildtype	10		Persistent diarrhea, difficulty breathing, & severe chest pain
No	Male	29	18.8	80	wildtype	31		Difficulty breathing, severe chest pain, general body malaise
No	Male	56	17.2	29	wildtype	30		Dizziness, generalized malaise, anorexia, severe dehydration, immuno-suppression, & esophageal candidiasis
Yes	Female	23	13.9	300	wildtype	409	395	Wasted & anorexic, vomiting, bilateral edema, yellow eyes, oral sores, skin excoriation, very weak, inability to walk unaided
Yes	Female	28	14.1	26	wildtype	365	351	Emaciated, vomiting, diarrhea & had yellow eyes
Yes	Female	29	18	98	2-9%	56	42	Psychological symptoms, collapsed and died, possible TB meningitis
Yes	Female	29	17.4	263	10-100%	82	68	Vomiting, anorexic, diarrhea, & cough
Yes	Female	30	17.4	116	wildtype	54	26	Severe cough (2 weeks), chest congestion, & difficulty breathing
Yes	Female	30	25.1	4	2-9%	351	337	Cryptococcal meningitis
Yes	Female	32	17.1	151	wildtype	37	16	Vomiting, appetite loss, immobility, severe dehydration (gastroenteritis)
Yes	Female	37	18.3	23	2-9%	96	82	Anorexia, general malaise, weight loss, bilateral lower limb swelling, & inability to walk
Yes	Female	39	16.2	133	wildtype	65	30	Severe diarrhea, vomiting, lower limb edema
Yes	Female	39	16.4	39	wildtype	29	15	Oral candidiasis, gastroenteritis/dehydration, anemia
Yes	Female	46	19.8	243	wildtype	29	15	Diarrhea & difficulty breathing
Yes	Female	47	18.3	51	wildtype	17	6	Anorexia, general body malaise
Yes	Female	48	16.8	45	wildtype	42	16	Severe headache, vomiting, dehydration, gasping
Yes	Female	54	21.9	6	wildtype	51	30	Anemia
Yes	Female	56	20.3	341	wildtype	195	181	Unknown
Yes	Female	56	16.2	38	wildtype	52	38	Vomiting blood, blood stained diarrhea, both feet became swollen, peptic ulcer disease
Yes	Male	25	14.9	5	wildtype	231	217	Diarrhea, vomiting, general malaise
Yes	Male	25	15.9	33	wildtype	456	442	TB, loss of appetite, coughing, weakness
Yes	Male	32	16.9	20	10-100%	119	105	Unknown
Yes	Male	34	19.8	69	wildtype	85	62	TB, liver failure
Yes	Male	39	18.2	135	wildtype	469	455	Abdomen swelling, low appetite, difficulty breathing, general weakness, pedal edema
Yes	Male	47	19.3	95	wildtype	101	87	Vomiting & headache, TB
Yes	Male	51	14.5	32	10-100%	84	71	Severe diarrhea
Yes	Male	62	18.2	42	10-100%	39	24	Dyspnea, chest pain, & herpes zoster
Yes	Male	71	17.5	48	wildtype	198	182	Cancer: throat, swollen mouth, aphasia, & anorexia
Yes	Male	85	17.1	47	wildtype	166	152	Pneumonia

Table S2. Correlates of enrollees not returning to study to initiate ART*

Variables	Odds ratio for not initiating ART
Clinic Location	
Nairobi	Ref
Maseno	0.34 (0.13, 0.88); **0.026**
Age (1-year increase)	0.98 (0.96, 1.01); 0.192
Gender	
Female	Ref
Male	1.32 (0.73, 2.39); 0.365
Single	Ref
Married/Attached	0.88 (0.49, 1.59); 0.670
Education years	0.99 (0.92, 1.06); 0.721
Employment Status	
Employed	Ref
Unemployed	2.92 (1.60, 5.35); **0.001**
Type of Toilet	
Pit	Ref
Flush	1.35 (0.75, 2.42); 0.316
Time to clinic	1.00 (0.92, 1.08); 0.924
BMI (kg/m^2)	
<18.5 (underweight)	1.61 (0.81, 3.21); 0.175
18.5-24.9 (healthy)	Ref
≥25 (overweight/obese)	0.51 (0.22, 1.18); 0.116
CD4 Count (cells/μL)	
<100	1.95 (1.05, 3.63); **0.035**
≥100	Ref
Pre-Treatment Drug Resistance	
Wild-type (no PDR)	Ref
PDR ≥2%	1.48 (0.61, 3.62); 0.387
SOC arm	Ref
OLA arm	1.05 (0.59, 1.89); 0.862

*Unadjusted logistic regression for death, withdraw, or lost to follow-up prior to ART start visit

Chapter 4. Costing and Time Study of STD Partner Services in Washington State

Time Study and Costing of STD Partner Services in Washington State, 2016

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Number of Tables (4); Figures (2); Supplemental Tables (2)

Summary: Cost-assessment of partner services for sexually transmitted diseases found high variability in activities and costs across three health jurisdictions in Washington state. HIV-related objectives had minimal impact on program costs.

Abstract

Background: STD partner services (PS) prevent disease, transmission, and promote HIV prevention, but their costs are not well understood. We assessed STD PS costs and identified areas to improve efficiency.

Methods: Through Washington State (WA) STD PS, disease intervention specialists (DIS) conduct telephone-based interviews, offer expedited partner therapy (EPT) to heterosexuals with gonorrhea (GC) or chlamydia (CT), and promote HIV-testing, pre-exposure prophylaxis, and re-linkage to care. At three health jurisdictions (King, Pierce, and Spokane counties), we conducted activity-based micro-costing of PS including: Interviews, observational time-and-motion studies with DIS and program staff, and tracking time spent working individual cases. We analyzed program costs, surveillance and service delivery data to determine costs per program objectives.

Results: In King, Pierce, and Spokane, respectively, DIS spent 6.5, 6.4, and 28.8 hours per syphilis case and 1.5, 1.6, and 2.9 hours per GC/CT case. Difficult-to-reach heterosexuals, (specifically methamphetamine users) comprised 68% of syphilis cases in Spokane, which increased the time required for case-finding, whereas most cases in King (88%) and Pierce (82%) were among easier to reach men who have sex with men. In all jurisdictions, time-consuming DIS activities included provider contact (9%) data entry (20%), record searches to locate cases/partners (19%), and contacting cases/partners (32%). Time spent on EPT and HIV-related objectives was minimal (30 seconds-5 minutes per interview). In 2016, DIS interviewed 363, 97, and 104 syphilis and 1,929, 1,948, and 280 GC/CT cases in King, Pierce, and Spokane, respectively. Cost-per-interview ranged from $516-$2,155 for syphilis, $215-$472 for GC, and $161-$533 for CT.

Discussion: Resources required for STD PS depend on epidemic characteristics and program models. Electronic reporting and access to medical records could improve efficiency. Integrating HIV prevention objectives minimally impacted STD PS specific program costs. These data are necessary for program planning, budget impact analysis, and estimating the cost-effectiveness of PS.

Key words: STD Partner Services; Bacterial sexually transmitted infections (Syphilis, Gonorrhea, Chlamydia); HIV; Costing

Background

The Centers for Disease Control and Prevention (CDC) recommends that partner services (PS) be provided to individuals diagnosed with bacterial sexually transmitted diseases (STDs) including syphilis, gonorrhea (GC), and chlamydia (CT) infection. CDC recommends STD PS include in-person interviews with infected persons to obtain contact information for exposed partners to ensure they are tested and/or treated appropriately [13]. Health departments in the United States routinely provide these services with variable methods, available resources, and coverage [15, 19-21]. Additionally, expedited partner therapy (EPT) is recommended as part of partner services programs for heterosexual (HET) cases to improve treatment uptake and prevent reinfection within partnerships [117], with varying uptake nationwide [118]. STD PS also provides a unique point at which to also implement HIV prevention interventions among men who have sex with men (MSM) at high-risk for acquiring and transmitting STDs and HIV [12, 14].

In Washington (WA) State, STD PS has several unique features. These include PS interviews primarily conducted over the telephone, EPT for HET GC and CT cases, and HIV specific interventions for MSM with an STD diagnosis or exposure. HIV interventions include routine HIV testing of all index cases, linkage to treatment for HIV infected individuals, and linkage to pre-exposure prophylaxis (PrEP) for high-risk HIV negative individuals. STD PS in WA State is provided to all cases of early syphilis, and select cases of GC and CT, including pregnant, MSM, youth and adolescent, and untreated cases. GC and CT cases are often prioritized based on risk factors including anatomic site of infection and HIV status.

In this study, we assess the costs, including time, associated with different components of STD PS at high-burden health jurisdictions in WA that represent the geographic and resource diversity of the state. This study informs the operational activities, costs, areas to improve

efficiency, and budget impact of STD PS in WA. This information can also inform STD PS program implementation at other health jurisdictions and cost-effectiveness analyses.

Methods

Study Setting & Summary

This study estimates the costs for STD PS service delivery from the perspective of the partner services program at three local health jurisdictions in WA State: Seattle/King County, Pierce County, and Spokane County. We conducted a micro-costing analysis over 2016-2017 to estimate staff time allocation for specific components of STD PS delivery for each STD. Analyses included a time study, financial expenditure assessment, and utilized surveillance and programmatic data to estimate health service delivery indicators. Results are stratified by health jurisdiction to investigate heterogeneity in disease burden, population characteristics, and costs.

Health Service Delivery Indicators

To determine the burden of disease and number of cases served through the STD PS programs, we extracted annual 2016 estimates from county level surveillance and DIS reporting data collected during case interviews and follow-up. Indicators include total diagnosed STD cases, cases served and assigned for STD PS DIS follow-up, successfully interviewed cases, partners named and identified, partners notified by DIS or their partner following the case interview, and partners tested and treated. We also estimated the number of cases provided with EPT, cases and partners tested for HIV, HIV uninfected cases referred to PrEP, and HIV infected cases linked to HIV care following the DIS interview when available. Cases with multiple STDs (coinfections)

were counted as the higher priority STD, with syphilis being highest, followed by gonorrhea, and chlamydia only as the lowest priority.

Time-Study

We conducted a time-study of disease intervention specialists and other supportive staff that contribute to STD partner services. The first component was an observational-based study conducted by an independent observer to assess time-allocation for each staff member on routine activities and specific interventions such as EPT, HIV prevention, and linkage to care, and to identify potentially modifiable areas to improve efficiency. Casework on extreme outliers was excluded from these estimates. To supplement observations, each staff member was interviewed to gain a more complete understanding of work-flow, time allocation for key activities and specific STDs, and areas they felt could be made more efficient. The second component was individual case tracking in which STD PS staff recorded case-specific activities from report and assignment of the case through casework completion.

Combined time-study information was used to estimate hours spent per week on key activities performed by administrative staff and DIS by STD and annual personnel costs spent on each activity. Tracking form data is also summarized to present the average, and variability of, time spent per case by STD and risk group.

Financial Expenditures Assessment

We collected information on financial expenditures at each health jurisdiction. Estimates were adjusted for time allocated to STD PS specific work as defined by their job description and reported through staff interviews. Costs were stratified by STD based on time allocation estimates

for each staff member and their disease focus when applicable. Activities and time unrelated to STD PS casework & service delivery were excluded from analyses and costing results. The adjusted financial expenditures were divided by health service indicator estimates to determine the average cost per outcome and service attempted and successfully delivered. Costs were adjusted for inflation to 2016 US dollars.

Results

Work-flow Summary

At all three jurisdictions, administrative/data entry staff process laboratory and case reports for all gonorrhea (GC) and chlamydia (CT) cases. Once the initial case report is completed and entered into the system, cases are assigned to disease intervention specialists (DIS) for STD PS. Not all cases are assigned depending on available resources, STD, treatment status, and other risk criteria. Specifically, untreated, MSM, HIV positive, pregnant, and youth/adolescent cases of CT receive PS, as do the majority of GC cases. Syphilis cases, including all positive serology lab results, are assigned directly by the state department of health (DOH) to DIS to review and probable new infections are assigned to DIS.

Observations were conducted on select days between October-November 2016 in King county, May 2017 in Pierce county, and September 2017 in Spokane county. At the time of the observations, pre-assignment administrative and data entry work for GC and CT was conducted by three staff members at King county, and one staff member each at Pierce and Spokane counties. There were 7, 5, and 4 DIS working on STD PS and King, Pierce, and Spokane counties, respectively. While DIS generally focused on specific STDs and patient risk group at all locations,

case assignments varied depending on staff availably and leave, case load, preferred language of the case, and disease burden.

At King County, one DIS worked full-time on syphilis STD PS, one split their time between syphilis and GC/CT, and 4 worked primarily on GC/CT, 2 of whom were assigned to STD PS part-time at 50% of full time employment (FTE). All King county DIS also provided STD results through the clinic as part of their job responsibilities, which we considered unrelated to STD PS work and estimated to account for approximately 10% of their time. At Pierce county, GC/CT cases were generally assigned to 3 DIS and syphilis to one DIS. DIS at Pierce county also worked approximately half of their time on clinic work, which we estimated accounted for approximately 35% of their time on average as they did some low intensity STD PS work during this time (15%) when not seeing patients. At Spokane county, 1 DIS focused primarily on Syphilis cases (and HIV only work that was excluded from analysis), and 2 were split between GC/CT and syphilis. Spokane casework for syphilis was also heavily supported by a state DOH consulting staff member assigned to the region, who reported 90% of her work-time was devoted to syphilis work (case-assignment and STD PS) in Spokane at the time of observations. The majority of case-work was conducted within the office at all three locations and field work was conducted when other modes of contact were unsuccessful. Most field work at King county was performed by a designated DIS one day a week for all cases regardless of DIS assignment. In Pierce and Spokane county, field work was generally performed by all DIS for their assigned cases, often in pairs of DIS.

Time Study Observations & Interviews

Time spent per week on STD PS activities by health jurisdiction are presented (Figure 4, Supplemental Table 3). We estimated that in 2016, data entry/administrative staff spent a total of 120, 38, and 30 hours on GC/CT related casework in King, Pierce, and Spokane counties, respectively completing and entering case-report and laboratory data for approximately 273, 132, and 64 cases, respectively, per week. DIS spent a total of 73, 17, and 73 hours on syphilis specific STD PS work and 142, 88, and 27 hours on GC/CT specific work, at King, Pierce, and Spokane counties, respectively. Approximately 11, 3, and 3 syphilis and 96, 55, and 9 GC/CT cases were assigned to DIS per week. This corresponds to 6.5, 6.4, and 28.8 hours per syphilis and 1.5, 1.6, and 2.9 hours per GC/CT case.

Administrative work was consistent for all GC/CT cases regardless of if the case was subsequently assigned to DIS. The majority of administrative staff time at all three jurisdictions was spent on data entry of GC/CT case reports and labs (>53%). King county administrative staff spent a higher percentage of time (17%) than Pierce and Spokane counties (<3%) contacting health care providers to obtain and complete case reports. Similarly, DIS in King county also spent more of their time (9%) contacting health care providers regarding GC/CT cases than in Pierce (0.4%) and Spokane (3%) counties. A similar percentage of time was observed for provider contact regarding syphilis cases in King (22%) and Pierce (23%), but less in Spokane (8%). The additional time spent contacting providers is largely due to electronic medical record accessibility, which allows to staff to look up case information directly rather than contacting providers, waiting on hold, and leaving messages. DIS working on GC/CT in Spokane and Pierce spent of their more time using electronic resources like medical record to locate patients, and it was observed they utilized Facebook to locate and contact patients and partners more often than did DIS in King County, though this resource was generally used after other methods (like phone calls and texting)

were unsuccessful. Spokane also often utilized police blotters, which was not observed at the other jurisdictions. We estimated that case interviews and partner contacting accounted for 6%, 46%, and 11% of syphilis DIS work, and 21%, 42%, and 17% of GC/CT DIS work in King, Pierce, and Spokane, respectively. We also observed that King County DIS spent a higher percentage of time consulting on syphilis cases and results with other staff (other DIS and DOH staff) to discuss case management.

Time Spent per Case on Casework

Results of individual case tracking by health jurisdiction, STD, and risk group are presented (Table 7). In King, Pierce, and Spokane, administrative staff tracked 17, 10, and 5 CT/CT cases, respectively. On average, they spent 18 (range: 2-70), 9 (5-12), and 14 (5-25) minutes per case, and a median of 12 (IQR 7-25), 9 (7-10), and 12 (10-20) minutes per case. DIS tracked 16, 11, and 12 GC/CT cases, spending on average 17 (range: 10-195), 37 (20-93), and 33 (11-51) minutes per case, and a median of 19 (IQR 17-30), 27 (26-34), and 27 (17-36) minutes per case. DIS tracked 8, 2, and 12 syphilis cases, spending on average 65 (23, 160), 144 (142, 146), and 166 (22, 960) minutes per case, and a median of 63 (24, 74), 144 (143, 145), and 75 (48, 117) minutes per case. Across health jurisdictions, syphilis casework took more DIS time than GC/CT. DIS work for HET cases took more time than MSM cases in King county, but similar amounts of time in Spokane (no GC/CT MSM cases were tracked in Pierce). When drug use information was available, casework on reported methamphetamine (meth) users took longer than non-users for Spokane syphilis cases (limited data for meth use in King and Pierce Counties). It was reported in Spokane that the majority of syphilis cases were among heterosexual meth users who are especially difficult to locate possibly due to distrust of government and legal concerns, and require additional efforts to

reach and ensure they and their partners are successfully treated. In comparison to the heterosexual epidemic in Spokane, most syphilis cases in King and Pierce counties were among MSM, who are reportedly relatively easier to engage. Additionally, while complicated high-priority cases like neurological and neonatal syphilis are rare, DIS spend a much larger amount of time conducting related casework resulting in extreme outliers for time-spent per case.

From the observations, enhanced STD PS objectives took minimal time relative to overall work (30 seconds to 2 min per topic per interview). Often, clients already had a documented HIV test, were not HIV positive, or were already linked to care if they were HIV positive, so additional DIS efforts were unnecessary. In King county especially, many clients eligible for PrEP had already discussed it with their provider. When PrEP referrals were observed, they generally only took a few minutes to document and refer patients to the on-site PrEP coordinator.

Financial Expenditures Summary

Overall annual costs for STD PS work were estimated at $798,141, $416,098, and $400,757 in King, Pierce, and Spokane, respectively (Table 8). At the time of observations, GC and CT STD PS related casework accounted for 72% and 88% of STD PS work at King and Pierce counties but only 43% of work in Spokane, compared to Syphilis cases that accounted for 28%, 12%, and 57%. In Spokane, syphilis work was heavily supported by a state DOH consultant, whose associated personnel costs were included in this estimate. While information on epidemiology support was not available for Pierce and Spokane, the cost was likely minimal and provided by the state DOH rather than the local jurisdiction, which is done in King county. Vehicle and fuel costs for field work was unavailable for Pierce, but costs were likely minimal compared to personnel costs.

Health Service Delivery Indicators

Health service delivery indicators and estimated costs per service are presented for 2016 (Table 9, Supplemental Table 4). For each jurisdiction, King, Pierce, and Spokane counties respectively, estimated program costs per case interview were $305, $219, and $484 for GC cases, $288, $164, and $547 for CT only cases, and $608, $526, and $2,210 for syphilis cases. Costs per partner notification (by DIS or the case following their interview) were $683 for GC, $565 for CT only, and $908 for syphilis cases in King County (partner data was unavailable for Pierce and Spokane counties). Testing STD cases for HIV following DIS interview cost between $749 and $51,017 depending on the STD and health jurisdiction. However, the small number of post-interview HIV tests was due to common simultaneous HIV testing with their STD test, rendering a subsequent HIV test unnecessary. In King county, cost per accepted PrEP referral was $3,727 for GC/CT and $5,365 for syphilis cases (PrEP referral data was unavailable for Pierce and Spokane).

Staffing Requirements Summary

We estimated that every 100 cases of GC/CT cases reported per week required approximately 44, 28, and 47 hours of administrative time, and 150, 159, and 288 hours of DIS time if all cases were assigned to STD PS in King, Pierce, and Spokane. If 10 cases of Syphilis were reported and assigned per week, we estimated this would require 65, 64, and 288 hours of DIS time per week (Table 10). Differences in staffing requirements likely stem from multiple factors, including staff experience, provider case-report quality, access to electronic medical records, and population characteristics, as described below.

Discussion

Costing summary

We estimated that the cost per interview was between $215 to $472 for GC cases, $161 to $533 for CT only cases, and $516 to $2,155 for syphilis cases depending on the health jurisdiction. A costing analysis for STD PS in New York State found similar trends in relative costs between STDs, estimating that the cost per interview was $608, $635, and $1,072 for GC, CT, and Syphilis, respectively [119]. Assuming enhanced STD PS accounts for 5 minutes of a 15-minute interview (30%), this corresponds to an added cost of $65-$142, $48-$160, and $155-$647 per GC, CT, and syphilis interview, respectively and is likely over-estimating the time necessary for the majority of cases based on our observations.

Considerations for program implementation and cost-savings

When implementing an STD PS program, there are multiple factors to consider (Figure 5). Specifically, understanding the disease burden and population characteristics is crucial in determining staff needs. We observed large differences in time and resources required to reach cases and partners across health jurisdictions, that were anecdotally ascribed to population characteristics such as methamphetamine use among heterosexual cases and associated mistrust of public health officials seen in other marginalized groups [120]. Serious infections such as neuro- and congenital-syphilis required immediate DIS response and a large allocation of staff resources and time. If recent increasing national trends in syphilis and other STDs continue [121], STD prevention and treatment programs will need additional resources to meet public health needs and efforts to improve efficiency can help best utilize limited resources. Studies have shown that

telephone based STD PS are highly effective, time-saving, and less costly compared to more intensive field-based casework [122]. Additionally, web-based partner notification has shown to be a useful and efficient tool in Australia [123] and the Netherlands [124] and it may be worth-wile to investigate implementing similar tools in the United States.

Understanding surveillance mechanisms is also integral to any STD PS program. The better health care providers and laboratories are at timely and complete case reporting, the more efficient STD PS work can be conducted. Additionally, we observed a significant amount of administrative and DIS work-time spent contacting providers via time-consuming phone calls when electronic medical records were not accessible. Access to electronic medical records would save both STD PS staff and health care providers valuable time. Additionally, an electronic reporting system to submit case-reports could greatly reduce the burden on health department staff and healthcare providers. Given the high amount of time spent on data entry, the easier and more efficient the database, the more time that can be spent on casework. Allowing quick input of duplicate data, such as when a partner tests positive and becomes a new case, would also reduce the data entry burden.

It was observed that not all staff have the same level of access to restricted data sources, requiring them to contact and interrupt other staff to obtain essential case information. Allowing all relevant staff access to restricted databases such as Accurint ®, state DOH STD surveillance, and syphilis databases would save time and improve efficiency. Additionally, better data sharing between the state DOH and across neighboring health jurisdictions would facilitate faster casework, as cases and partners often cross jurisdictions.

Finally, we observed the majority of DIS work was spent on data entry and searching for cases and partners prior to successfully interviewing cases and contacting partners. Interventions,

such as HIV testing and PrEP referrals, that occur during this client contact take only a small fraction of overall work-time and can have big rewards in terms of disease treatment and prevention [12, 14, 15]. Programs should consider integrating such interventions into their programs.

Strengths and Limitations

This study has several strengths including direct observations and case tracking across multiple high disease burden health jurisdictions across Washington State. This allowed us to understand factors that can influence STD PS programs within a state, describe what goes into delivering services, and identify potentially modifiable areas in which to improve efficiency and better utilize often limited resources. Limitations include the qualitative nature of the time-study data. Given the highly variable nature of STD PS work, observations may have missed some work or incorrectly estimated the average time spent on various activities that may have been more accurately captured through a longer observation period. Additionally, extrapolating the time-study results to the reported hours of full-time employment may have imprecisely estimated time spent on activities. Additionally, STD PS work depends heavily on case load and personnel availability, which varies over time and is not captured well by short observation periods. Resources provided by the state DOH were included in our estimates, but may not reflect the available budgets within a jurisdiction to meet the population level needs. Additionally, though efforts were made to minimize imposition and impact of the time-study itself, staff likely work slightly differently while being observed than in normal practice. Data availability also varied between jurisdictions. However, by integrating interviews, case-tracking forms, and observations and stratifying by health jurisdiction, we attempted to minimize bias in our estimates.

Conclusions

We found that there was large variability in the time required to interview STD cases within and across STD infection type and health jurisdictions. We found that casework for syphilis costs more than for GC/CT, partially due to the work being done exclusively by highly-trained DIS, but also because syphilis cases are often at higher-risk for complications and require additional efforts to reach.

Our results can inform the operational costs, areas to improve efficiency, and budget impact of STD PS health jurisdictions in Washington State and can be utilized for program implementation across the United States. Given that the lifetime cost of one HIV case is estimated to be $400,000 [125], efforts to integrate interventions to prevent HIV transmission within STD PS can be highly cost-effective, especially given the relatively small amount of time required for STD PS staff to deliver services like HIV testing and PrEP referrals to high-risk patients. A cost-effectiveness analysis of STD PS that will balance incurred costs against savings from HIV prevention is needed.

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Table 7. Time (Minutes) Per Case, by STD, Risk group, and Health Jurisdiction

STD	Type of Casework, STD & Risk group	King			Pierce			Spokane		
		N	Median (IQR)	Mean (min-max)	N	Median (IQR)	Mean (min-max)	N	Median (IQR)	Mean (min-max)
GC/CT	**Admin Work**	17	12 (7, 25)	18 (2-70)	10	9 (7, 10)	9 (5-12)	5	12 (10, 20)	14 (5-25)
	DIS Case-work	16	25 (17, 30)	37 (10-195)	11	27 (26, 34)	37 (20-93)	12	27 (17, 36)	33 (11-51)
	Infection									
	CT only	2	24 (20, 27)	24 (17-30)	6	26 (23, 27)	26 (20-33)	1	113	113
	GC only	7	17 (16, 57)	52 (10-195)	5	34 (28, 72)	51 (26-93)	7	22 (16, 29)	23 (11-34)
	GC/CT co-infection	7	28 (22, 31)	26 (10-40)	0	-	-	4	30 (22, 37)	29 (14- 44)
	Risk/exposure									
	MSM	6	19 (12, 22)	20 (10-40)	0	-	-	2	34 (29, 38)	34 (25-42)
	Meth use*	0	-	-	0	-	-	0	-	-
	HET	8	30 (28, 45)	56 (16-195)	8	28 (26, 33)	33 (22-72)	7	29 (16, 37)	37 (13-113)
	Meth use*	1	28	28	0	-	-	0	-	-
	Unknown	2	16 (16, 17)	16 (15-17)	3	26 (23, 60)	46 (20-93)	3	22 (17, 28)	22 (11-34)
	DIS Partner-work	6	30 (28, 32)	33 (19, 58)	3	18 (15, 27)	22 (12-36)	5	12 (11,14)	15 (7-30)
Syphilis	**DIS Case-work**	8	63 (34, 74)	65 (23, 160)	2	144 (143, 145)	144 (142-146)	12	75 (48, 117)	166 (28-960)
	Risk/exposure									
	MSM	5	35 (30, 71)	47 (23-75)	2	144 (143, 145)	144 (142-146)	3	80 (54, 93)	71 (28-105)
	Meth use*	4	48 (28, 82)	63 (23-133)	0	-	-	0	-	-
	HET	3	74 (65, 117)	96 (55-160)	0	-	-	8	81 (64, 190)	217 (105-960)
	Meth use*	1	74	74	0	-	-	4	262 (183, 467)	388 (70-960)
	DIS Partner-work	15	15 (9, 19)	16 (6, 35)	7	44 (13, 90)	52 (12-106)	13	45 (25, 50)	46 (13-127)
Enhanced STD PS Activities**										
EPT (discussion)		1	2	2	13	3 (2, 4)	2.85 (1-5)	1	2 min	2 min
HIV test (discuss/verify)		13	1 (0.5, 1)	0.92 (0.5-2)	8	1 (1, 1)	1.06 (0.5-2)	0	-	-
HIV care (discuss/verify)		1	2	2	1	1	1	0	-	-
PrEP (discussion)		17	1 (0.5, 1)	1.28 (0.25-4)	0	-	-	0	-	-
PrEP referral		0	-	-	0	-	-	1	6 min	6 min

Abbreviations: STD, sexually transmitted disease; PS, Partner Services; GC, gonorrhea; CT, chlamydia; Admin, administrative/data entry; DIS, disease intervention specialist; Meth, methamphetamine; EPT, expedited partner therapy; PrEP, pre-exposure prophylaxis; IQR, interquartile range

*Drug use was often unknown or client refused to answer.

**Collected during observations. All other data was collected by staff for all case work on tracked cases and named partners. Tracked data for DIS work include data for cases/partners from assignment to close, not necessarily successfully interviewed or contacted.

Table 8. 2016 Annual Financial Expenditures[a] of the STD PS Program and Total Expenditures by STD

Category	King	Pierce	Spokane
Salary & Benefits	$643,098 (81%)	$342,163 (82%)	$327,757 (82%)
Overhead	$149,736 (19%)	$73,935 (18%)	$70,738 (18%)
Salary, Benefits, Overhead Total	$792,834 (100%)	$416,098 (100%)	$398,495 (100%)
Admin/Data Entry	$107,261 (14%)	$35,738 (9%)	$25,528 (6%)
DIS	$633,140 (80%)	$360,193 (87%)	$275,561 (69%)
Supervisor	$45,588 (6%)	$20,167 (5%)	$97,405 (24%)
Epidemiology support	$6,845 (1%)	N/A	N/A
Vehicle & Fuel	$5,306 (0.7%)	N/A	$2,262 (0.6%)
Total	$798,141 (100%)	$416,098 (100%)	$400,758 (100%)
By STD[c]			
GC	$391,089 (49%)	$179,866 (43%)	$111,837 (28%)
CT	$186,475 (23%)	$185,215 (45%)	$59,053 (15%)
Syphilis	$220,576 (28%)	$51,017 (12%)	$229,869 (57%)

Abbreviations: STD, sexually transmitted disease; PS, Partner Services; GC, gonorrhea; CT, chlamydia; Admin, administrative; DIS, disease intervention specialist

[a]Includes only staff costs for work on cases that receive STD PS (costs for data entry and other work on cases that are not assigned to STD PS or otherwise followed by DIS are excluded)

[c]Based on %FTE for all personnel for each STD estimated through interviews.

Table 9. Annual Reported Cases and Health Service Delivery Indicators by STD and Health Jurisdiction (2016)

STD*	Indicators and Outcomes	King Co.		Pierce Co.		Spokane Co.	
		Number of Cases	Cost per Outcome	Number of Cases	Cost per Outcome	Number of Cases	Cost per Outcome
Gonorrhea	Diagnoses						
	Reported Cases	3,377	-	1,181	-	511	-
	Men who have sex with men (MSM)	1,768 (52%)	-	214 (18%)	-	79 (15%)	-
	Women	810 (24%)	-	523 (44%)	-	228 (45%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	2,846 (84%)	$133	1,119 (95%)	$161	231 (66%)	$330
	Interviewed by DIS	1,282 (45%)	$305	821 (73%)	$219	172 (68%)	$484
	Identifiable Partners (partner index)	826 (0.64)	-	N/A	-	N/A	-
	Partner Notified**	573 (69%)	$683	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	75 (6%)	$5,215	240 (29%)	$749	23 (10%)	$4,862
	New case HIV diagnosis	2 (0.2%)	$195,545	0 (0%)	-	1 (0.4%)	$11,837
	HIV cases identified as out of care	72 (6%)	$5,432	4 (0.5%)	$44,966	3 (1%)	$37,279
	Cases re-linked to HIV care after interview	14 (1%)	$27,159	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	18 (2%)	$21,727	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	1 (0.1%)	$391,089	N/A	N/A	N/A	N/A
	Total Costs	-	$391,089	-	179,866	-	$11,837
Chlamydia	Diagnoses						
	Reported Cases	8,624	-	4,611	-	2,306	-
	MSM	1,485 (17%)	-	138 (3%)	-	66 (3%)	-
	Women	4,950 (57%)	-	3,108 (67%)	-	228 (45%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	1,357 (16%)	$137	1,312 (28%)	$141	179 (8%)	$330
	Interviewed by DIS	647 (48%)	$288	1,127 (86%)	$164	108 (60%)	$547
	Identifiable Partners (partner index)	630 (0.97)	-	N/A	-	N/A	-
	Partner Notified**	359 (57%)	$565	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	34 (5%)	$5,485	158 (14%)	$1,172	7 (6%)	$8,436
	New case HIV diagnosis	5 (0.8%)	$37,295	1 (0.1%)	$185,215	3 (3%)	$19,684
	HIV cases identified as out of care	25 (4%)	$6,430	2 (0.2%)	$93,607	4 (4%)	$14,763
	Cases re-linked to HIV care after interview	5 (0.8%)	$37,295	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	5 (0.8%)	$37,295	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	1 (0.2%)	$186,475	N/A	N/A	N/A	N/A
	Total Costs	-	$186,475	-	$185,215	-	$59,053
Gonorrhea/ Chlamydia	Enhanced STD PS outcome						
	Cases Accepting EPT from DIS	4 (0.6%)	$134,819	N/A	N/A	N/A	N/A
	Cases Accepting PrEP referral from DIS	155 (8%)	$3,727	N/A	N/A	N/A	N/A
Syphilis	Diagnoses						
	Reported Cases	516	-	116	-	114	-
	MSM	455 (88%)	-	95 (82%)	-	43 (38%)	-
	Women	17 (3%)	-	8 (7%)	-	33 (29%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	493 (96%)	$447	114 (98%)	$448	112 (98%)	$2,052
	Interviewed by DIS	363 (74%)	$608	97 (85%)	$526	104 (93%)	$2,210
	Identifiable Partners (partner index)	375 (1.03)	-	-	-	-	-
	Partner Notified**	243 (65%)	$908	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	10 (3%)	$22,058	1 (1%)	$51,017	12 (12%)	$19,156
	New case HIV diagnosis	1 (0.3%)	$220,576	0 (0.0%)	-	1 (1%)	$229,869
	HIV cases identified as out of care	25 (7%)	$8,623	5 (5%)	$10,203	3 (3%)	$76,623
	Cases re-linked to HIV care after interview	5 (1%)	$44,115	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	73 (19%)	$3,022	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	2 (0.5%)	$110,288	N/A	N/A	N/A	N/A
	Cases Accepting PrEP referral from DIS	41 (11%)	$5,365	N/A	N/A	N/A	N/A
	Total Costs	-	$220,576	-	$51,017	-	$229,869

Abbreviations: STD, sexually transmitted disease; PS, Partner Services; GC, gonorrhea; CT, chlamydia; Admin, administrative/data entry; DIS, disease intervention specialist; EPT, expedited partner therapy; PrEP, pre-exposure prophylaxis; N/A, data not available

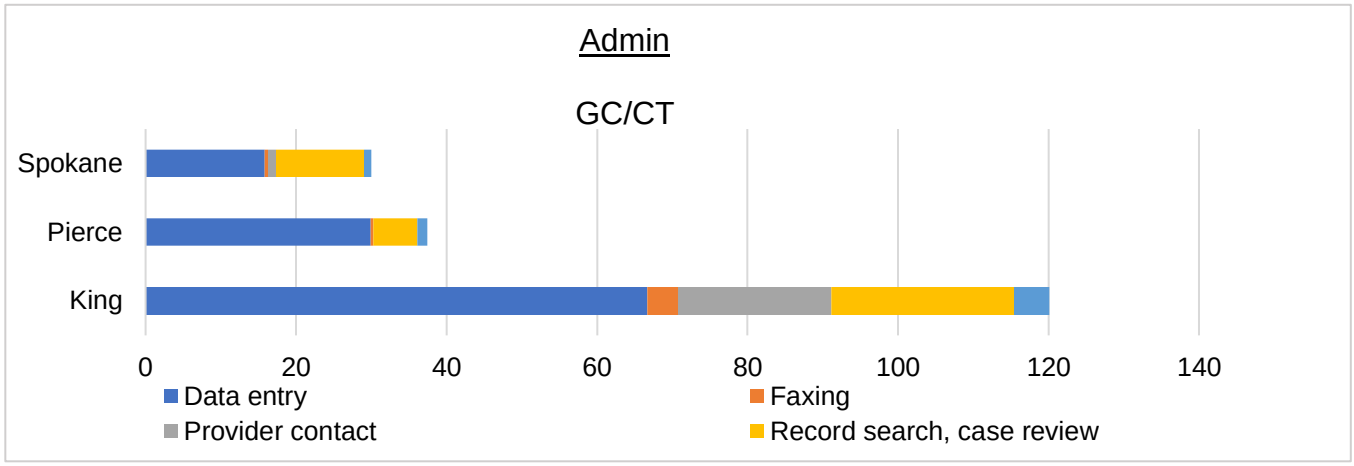
*Syphilis may include coinfections with GC and/or CT. GC may include coinfections with CT. CT refers to CT only infections.
**By DIS or Partner after DIS interview

Table 10. Estimated number of staff hours required to work 100 cases of GC/CT and 10 cases of syphilis reported and assigned for STD PS per week, by health jurisdiction.

	King			Pierce			Spokane		
STD	% MSM	Admin (hrs/wk)	DIS (hrs/wk)	% MSM	Admin (hrs/wk)	DIS (hrs/wk)	% MSM	Admin (hrs/wk)	DIS (hrs/wk)
GC/CT (100 cases/wk)	27%	44	150	6%	28	159	5%	47	288
Syphilis (10 cases/wk)	88%	-	65	82%	-	64	38%	-	288

Abbreviations: STD, sexually transmitted disease; PS, Partner Services; GC, gonorrhea; CT, chlamydia; Admin, administrative/data entry; DIS, disease intervention specialist

Figure 4. Aggregated Weekly Time Allocation by Staff, STD, and Health Jurisdiction



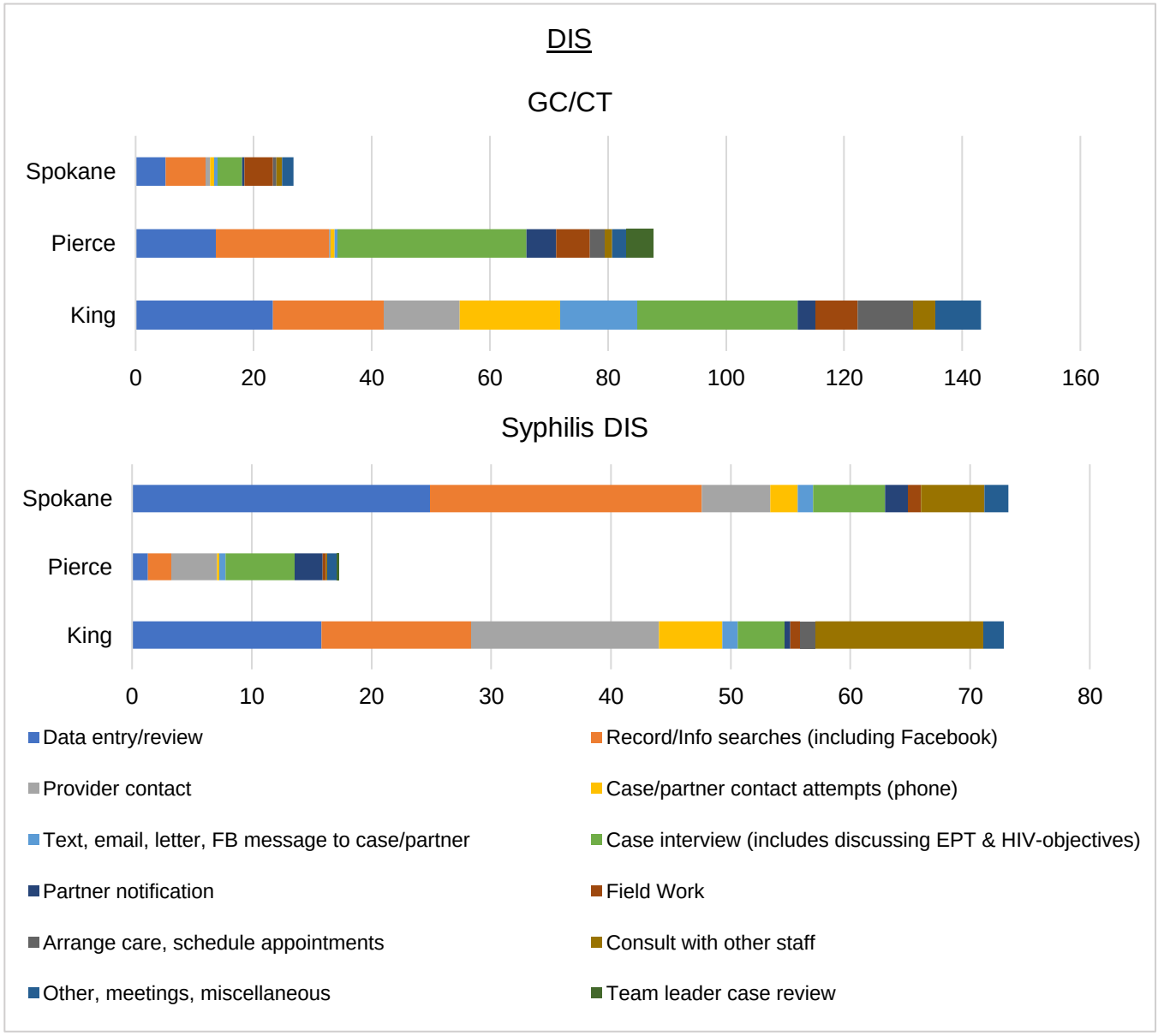


Figure 5. Summary of considerations for STD PS program development and implementation

Figure 5. What to Consider when Developing STD PS?
• Disease Burden and Population Characteristics • Methods to locate contact clients (phone/text, Facebook, dating apps, fieldwork) • Prioritization of cases • Case reporting quality and access to electronic medical records • Access to restricted databases (e.g. Accurint) • Database simplicity and efficiency • Data sharing between DOH and other Jurisdictions • Effective interventions to implement within client contact

Table S3. Time Study Summary: Activities Worked and Associated Time Per Week by Health Jurisdiction and Staff and STD Focus, Based on Observations, Interviews, and Case-Tracking Forms

	Health Jurisdiction	King Co.	Pierce Co.	Spokane Co.
Case-work flow stage	Activity	Hrs/wk (%)	Hrs/wk (%)	Hrs/wk (%)
CT/GC Case Work* Pre-Assignment (Data Entry, Admin)	Data entry	66.7 (56%) [a]	29.9 (80%) [a]	15.8 (53%) [b,c,d]
	Faxing	4.1 (3%) [a]	0.4 (1%) [b]	0.5 (2%) [b]
	Provider contact	20.3 (17%) [a]	0 (0%) [b]	1 (3%) [b]
	Record search, case review	24.3 (20%) [a]	5.8 (16%) [a]	11.7 (39) [b,c,d]
	Other, meetings, miscellaneous	4.7 (4%) [a,b]	1.3 (4%) [b]	1.0 (3%) [b]
	Total Administrative Work	120 (100%)	37.5 (100%)	30 (100%) [b]
CT/GC Case Work Post-Assignment (DIS)	Data entry/review	23.3 (16%) [a]	13.6 (15%) [a,b]	5.1 (19%) [a]
	Record/Info searches (including Facebook)	18.7 (13%) [a]	19.1 (22%) [a,b]	6.7 (25%) [a]
	Provider contact	12.9 (9%) [a]	0.3 (0.4%) [a,b]	0.8 (3%) [a]
	Case/partner contact attempts (phone)	17.0 (12%) [a]	0.7 (0.8%) [a,b]	0.7 (3%) [a]
	Text, email, letter, FB message to case/partner	13.1 (9%) [a]	0.5 (0.6%) [a,b]	0.6 (2%) [a]
	Case interview	27.1 (19%) [a]	32.0 (37%) [a,b]	4.1 (15%) [a]
	Partner notification	3.0 (2%) [a]	5.0 (6%) [b,c,d]	0.4 (1%) [a]
	Field Work	7.2 (5%) [a,b,d]	5.7 (7%) [b,d]	4.9 (18%) [b,d]
	Arrange care, schedule appointments	9.4 (7%) [a]	2.5 (3%) [a,b]	0.5 (2%) [b]
	Consult with other staff	3.7 (3%) [a]	1.3 (1%) [a,b]	1.0 (4%) [a]
	Other, meetings, miscellaneous	7.8 (5%) [a,b]	2.4 (3%) [a,b]	1.9 (7%) [a,b]
	Team leader case review	N/A	4.6 (5%) [b,c,d]	N/A
	Total DIS work-hours/week for GC/CT cases	143.2 (100%)	87.8 (100%)	26.8 (100%) [a]
Syphilis Case-Work Pre- & Post-Assignment (DIS)	Data entry/review	15.8 (22%) [a]	1.3 (8%) [a]	24.9 (34%) [a]
	Record/Info searches (including Facebook)	12.5 (17%) [a]	2 (12%) [a]	22.7 (31%) [a]
	Provider contact	15.7 (22%) [a]	3.8 (23%) [a]	5.7 (8%) [a]
	Case/partner contact attempts (phone)	5.3 (7%) [a]	0.2 (466%) [a]	2.3 (3%) [a]
	Text, email, letter to case/partner	1.3 (2%) [a]	0.5 (3%) [a]	1.3 (2%) [a]
	Case interview	3.9 (5%) [a]	5.8 (35%) [a]	6.0 (8%) [a]
	Partner notification	0.5 (0.7%) [c,d]	2.3 (14%) [b,c,d]	1.9 (3%) [a]
	Field Work	0.8 (1%) [b,d]	0.3 (2%) [b,d]	1.1 (1%) [b,c,d]
	Arrange care, schedule appointments	1.3 (2%) [a,b]	0 (0%)	0 (0%)
	Consult with other staff (DIS, Clinicians, DOH)	14.0 (19%) [a]	0.1 (0.5%) [a]	5.3 (7%) [a]
	Other, meetings, miscellaneous	1.7 (2%) [a,b]	0.8 (5%) [a]	2 (3%) [a,b]
	Team leader case review	N/A	0.2 (1%) [b,c,d]	N/A
	Total DIS work-hours/week for Syphilis cases	72.8 (100%)	16.5 (100%)	73.2 (100%)
Management	Manager/supervisor work allocated to STD PS	12 hours	22 hours	27
Epi Support	Epidemiologist Data Quality Assurance	2 hours	N/A	N/A

Data source (weighted to total work time per week): a. observations; b. interviews; c. tracking forms; d. surveillance *Not all cases are worked for STD PS.

Table S4. Reported Cases and Health Service Delivery Indicators by STD and Health Jurisdiction (2016)

STD*	Indicators and Outcomes	King Co.		Pierce Co.		Spokane Co.	
		Number of Cases	Cost per Outcome	Number of Cases	Cost per Outcome	Number of Cases	Cost per Outcome
Gonorrhea	Diagnoses						
	Reported Cases	3,377	-	1,181	-	511	-
	Men who have sex with men (MSM)	1,768 (52%)	-	214 (18%)	-	79 (15%)	-
	Men who have sex with women (MSW)	544 (16%)	-	346 (29%)	-	137 (27%)	--
	Men (unknown)	255 (8%)	-	98 (8%)	-	67 (13%)	-
	Women	810 (24%)	-	523 (44%)	-	228 (45%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	2,846 (84%)	$137	1,119 (95%)	$161	231 (66%)	$330
	Interviewed by DIS	1,282 (45%)	$305	821 (73%)	$219	172 (68%)	$484
	Identifiable Partners (partner index)	826 (0.64)	-	N/A	-	N/A	-
	Partners Notified by DIS	511 (62%)	$765	N/A	N/A	N/A	N/A
	Partners Notified by Partner after DIS interview	62 (8%)	$6,308	N/A	N/A	N/A	N/A
	Partner Notified by DIS or Partner after DIS interview	573 (69%)	$683	N/A	N/A	N/A	N/A
	Partner tested after interview	39 (5%)	$10,028	N/A	N/A	N/A	N/A
	Partner treated after interview	64 (8%)	$6,111	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	75 (6%)	$5,215	240 (29%)	$749	23 (10%)	$4,862
	New case HIV diagnosis	2 (0.2%)	$195,545	0 (0%)	-	1 (0.4%)	$11,837
	HIV cases identified as out of care	72 (6%)	$5,432	4 (0.5%)	$44,966	3 (1%)	$37,279
	Cases re-linked to HIV care after interview	14 (1%)	$27,159	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	18 (2%)	$21,727	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	1 (0.1%)	$391,089	N/A	N/A	N/A	N/A
	Total Costs	-	$391,089		$179,866		$11,837
Chlamydia	Diagnoses						
	Reported Cases	8,624	-	4,611	-	2,306	-
	MSM	1,485 (17%)	-	138 (3%)	-	66 (3%)	-
	MSW	544 (18%)	-	933 (20%)	-	368 (16%)	-
	Men (unknown)	666 (8%)	-	432 (9%)	-	231 (10%)	-
	Women	4,950 (57%)	-	3,108 (67%)	-	228 (45%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	1,357 (16%)	$137	1,312 (28%)	$141	179 (8%)	$330
	Interviewed by DIS	647 (48%)	$288	1,127 (86%)	$164	108 (60%)	$547
	Identifiable Partners (partner index)	630 (0.97)	-	N/A	-	N/A	-
	Partners Notified by DIS	330 (52%)	$565	N/A	N/A	N/A	N/A
	Partners Notified by Partner after DIS interview	29 (5%)	$6,430	N/A	N/A	N/A	N/A
	Partner Notified by DIS or Partner after DIS interview	359 (57%)	$519	N/A	N/A	N/A	N/A
	Partner tested after interview	49 (8%)	$3,806	N/A	N/A	N/A	N/A
	Partner treated after interview	65 (10%)	$2,869	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	34 (5%)	$5,485	158 (14%)	$1,172	7 (6%)	$8,436
	New case HIV diagnosis	5 (0.8%)	$37,295	1 (0.1%)	$185,215	3 (3%)	$19,684
	HIV cases identified as out of care	25 (4%)	$7,459	2 (0.2%)	$92,607	4 (4%)	$14,763
	Cases re-linked to HIV care after interview	5 (0.8%)	$37,295	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	5 (0.8%)	$37,295	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	1 (0.2%)	$186,475	N/A	N/A	N/A	N/A
	Total Costs	-	$186,475	-	$185,215	-	$59,053
Gonorrhea/ Chlamydia	Enhanced STD PS outcome						
	Cases Accepting EPT from DIS	4 (0.6%)	$134,819	N/A	N/A	N/A	N/A
	Cases Accepting PrEP referral from DIS	155 (8%)	$3,727	N/A	N/A	N/A	N/A
Syphilis	Diagnoses						
	Reported Cases	516	-	116	-	114	-
	MSM	455 (88%)	-	95 (82%)	-	43 (38%)	-
	MSW	20 (4%)	-	10 (9%)	-	37 (32%)	-
	Men (unknown)	24 (5%)	-	3 (3%)	-	1 (1%)	-
	Women	17 (3%)	-	8 (7%)	-	33 (29%)	-
	STD PS Services & Outcomes						
	Assigned to STD PS	493 (96%)	$447	114 (98%)	$448	112 (98%)	$2,052
	Interviewed by DIS	363 (74%)	$608	97 (85%)	$526	104 (93%)	$2,210
	Identifiable Partners (partner index)	375 (1.03)	-	N/A	-	N/A	-
	Partners Notified by DIS	107 (29%)	$2,061	N/A	N/A	N/A	N/A
	Partners Notified by Partner after DIS interview	136 (36%)	$1,622	N/A	N/A	N/A	N/A
	Partner Notified by DIS or Partner after DIS interview	243 (65%)	$908	N/A	N/A	N/A	N/A
	Partner tested after interview	108 (29%)	$2,042	N/A	N/A	N/A	N/A
	Partner treated after interview	93 (25%)	$2,372	N/A	N/A	N/A	N/A
	Enhanced STD PS outcomes						
	Cases Tested for HIV after Interview	10 (3%)	$22,058	1 (1%)	$51,017	12 (12%)	$19,156
	New case HIV diagnosis	1 (0.3%)	$220,576	0 (0.0%)	-	1 (1%)	$229,869
	HIV cases identified as out of care	25 (7%)	$8,823	5 (5%)	$10,203	3 (3%)	$76,623
	Cases re-linked to HIV care after interview	5 (1%)	$44,115	N/A	N/A	N/A	N/A
	Partners Tested for HIV after interview	73 (19%)	$3,022	N/A	N/A	N/A	N/A
	New partner HIV diagnosis	2 (0.5%)	$110,288	N/A	N/A	N/A	N/A
	Cases Accepting PrEP referral from DIS	41 (11%)	$5,365	N/A	N/A	N/A	N/A
	Total Costs	-	$220,576	-	$51,017	-	$229,869

*Syphilis may include coinfections with GC and/or CT. GC may include coinfections with CT. CT refers to CT only infections. N/A, data not available

Chapter 5. Conclusion

This dissertation addressed challenges to effective HIV treatment and prevention including pre-treatment drug resistance (PDR), early mortality following ART initiation, and evaluation of a STD partner services programs with integrated HIV-objectives designed to increase case-finding, linkage to care, and PrEP uptake. Results of these studies can help inform policies and interventions to overcome barriers to effective treatment and prevention including drug resistance, delayed diagnosis and treatment, and accessible prevention tools like PrEP.

Pre-treatment drug resistance

In aim 1, we found that the prevalence of PDR to recommended first-line therapies was high overall (10%) and similar across clinic locations, potentially reflecting improved access to ART across urban and rural regions in Kenya. PDR prevalence was especially high among young women 18-24 years old (20%), including those who reported no prior ARV exposure (22%). These results are consistent with younger women accounting disproportionately for incident HIV infections in sub-Saharan Africa [32], and younger adults becoming HIV-infected more recently when HIV-DR is increasingly more common [50, 111]. Because PDR can limit the effectiveness of ARVs, our results have potentially serious implications for individual health and HIV transmission, especially for ART programs for women's health and PMTCT. The prevalence of PDR in young women in our study is double the 10% threshold at which the WHO recommends re-assessment and modifications to the ART strategy [49]. Data is needed to determine whether routine PDR testing and/or scale up of alternative ARVs could effectively prevent treatment failure associated with PDR in low resource settings.

Early mortality after ART initiation

In aim 2, we found that many individuals (24%) presented for treatment with a CD4 count <100 cells/μL, a marker of advanced HIV disease. We also identified additional predictors

of short-term mortality including older age, male gender, less education, unemployment, low BMI, and PDR. Although the average CD4 count at presentation was slightly lower among participants in urban Nairobi than in rural Maseno, mortality incidence was greater in Maseno. Furthermore, we found that in Maseno, low CD4, low BMI, and PDR were associated with a greater risk of mortality than in Nairobi. Given that clinics were similarly managed by the Coptic Hospital, differences by location are more likely due to regional or rural/urban disparities in underlying health and infectious disease burden, rather than the clinic services. Though evidence is mixed regarding the association of PDR on early mortality [74, 75], the association between PDR and increased risk of treatment failure and other poor health outcomes is well documented [4, 6, 23, 74]. Given widespread increases in PDR prevalence to commonly available first-line therapies in low resource countries [50, 111], it may be warranted to scale-up resistance testing and/or alternative therapies like dolutegravir with a higher barrier of resistance [112] in these settings to mitigate poor health outcomes associated with PDR. Overall, results suggest that interventions targeting patients with a low CD4 count at presentation, as well as to those who are older, male, less educated and unemployed, and those with low BMI or PDR may help reduce the risk of early mortality in Kenya and similar settings, especially in rural areas.

Costing and Evaluation of STD Partner Services Programs

In aim 3, we evaluated STD Partner Services programs with integrated HIV-objectives in Washington State (WA). We observed large variability in time required for STD casework within and across STD infection types and jurisdictions. Syphilis cases required more resources than GC/CT due in part to work performed exclusively by highly-trained DIS and because syphilis cases are usually higher-priority due to the severity of untreated disease and often required greater efforts to reach. Spokane allocated over four times the staffing resources than

King and Pierce to syphilis casework. This disparity may largely be explained by the Spokane syphilis epidemic predominantly occurring among more difficult to reach and high-priority heterosexual, meth-using cases, whereas King and Pierce cases occurred primarily among MSM who were easier to reach. The majority of DIS work was spent on data entry and case and partner finding prior to successful contact. Interventions like HIV testing and PrEP referrals, which occurred during client contact, took only a small fraction of overall STD PS work-time and can have big rewards for HIV treatment and prevention [12, 14, 15].

Increases in efficiency could allow staff to devote more resources to client-contact to reach more STD cases and improve treatment and prevention of STDs and HIV in the community. Expanding staff access to electronic medical records and other restricted databases at all jurisdictions would reduce time spent obtaining crucial client information. More efficient data entry through electronic reporting and upload/input of existing electronic information would reduce the staff resources required for data entry. Given recent increases in STD incidence [121], improved efficiency in this highly effective public health service [13] can help best utilize limited recourses to meet growing public health needs.

Results of this study can inform the operational costs, areas to improve efficiency, and budget impact of STD PS in health jurisdictions in WA and can be utilized for program development across the United States. Given that the lifetime cost of one HIV case is estimated to be $400,000 [125], programs that integrate HIV-objectives within STD PS have potential to be highly cost-effective, especially given the relatively small amount of time required for STD PS staff to deliver HIV testing and PrEP referrals to high-risk patients. To estimate STD PS cost-effectiveness, we will combine results of this costing study with a mathematical model (currently in development) that will balance incurred program costs against savings from HIV prevention.

Conclusions

Our results add evidence that PDR prevalence to first-line therapies in Kenya exceeds the WHO threshold for program reassessment and is particularly high among young women, which could negatively impact HIV treatment effectiveness. Scale-up of PDR testing and alternative ARV regimens may be warranted to ensure ART is effective in this and similar settings. Additionally, to promote better health outcomes, continued efforts are needed to diagnose and treat infected individuals earlier in disease. Our results suggest that interventions targeting patients with a low CD4 count at presentation, and those who are older, male, less educated, unemployed, and those with low BMI or PDR may help mitigate the risk of early mortality, especially in rural areas. Finally, in evaluating STD PS programs in Washington State, we identified areas to improve efficiency, such as expanded database access, and electronic case-reporting and data entry. We also described important factors that may heavily influence resource needs for successful program implementation and service delivery, such as epidemic characteristics like illicit drug use. We found that integrated HIV-objectives required a small fraction of STD PS staff resources, with large potential benefits in terms of HIV case finding, linkage-to-care, and prevention. These results can inform program implementation to better address growing STD epidemics and gaps in HIV treatment and prevention. Overall, the results of the studies presented in this dissertation can inform policies and help programs overcome diverse challenges to effective HIV treatment and prevention.

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85. May MT, Vehreschild JJ, Trickey A, et al. Mortality According to CD4 Count at Start of Combination Antiretroviral Therapy Among HIV-infected Patients Followed for up to 15 Years After Start of Treatment: Collaborative Cohort Study. Clin Infect Dis **2016**; 62:1571-7.
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91. Hakim J, Musiime V, Szubert AJ, et al. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. N Engl J Med **2017**; 377:233-45.
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107. Rawat R, Kadiyala S, McNamara PE. The impact of food assistance on weight gain and disease progression among HIV-infected individuals accessing AIDS care and treatment services in Uganda. BMC Public Health **2010**; 10:316.
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109. Grobler L, Siegfried N, Visser ME, Mahlungulu SS, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. Cochrane Database Syst Rev **2013**:CD004536.
110. Koethe JR, Marseille E, Giganti MJ, Chi BH, Heimburger D, Stringer JS. Estimating the cost-effectiveness of nutrition supplementation for malnourished, HIV-infected adults starting antiretroviral therapy in a resource-constrained setting. Cost Eff Resour Alloc **2014**; 12:10.
111. Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis **2017**.
112. Wainberg MA, Han YS. Will drug resistance against dolutegravir in initial therapy ever occur? Front Pharmacol **2015**; 6:90.
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Curriculum Vitae

RACHEL A. SILVERMAN

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EDUCATION

Doctor of Philosophy (PhD), Epidemiology 2013-2018
University of Washington School of Public Health, Seattle, WA
Dissertation: Informing Strategies for Effective HIV Treatment and Prevention

Master of Science (ScM), Epidemiology 2009-2011
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Infectious Disease
Thesis: Evaluation of Anemia as an Indicator of Malaria Disease Burden in a Region of Declining Malaria Transmission in Southern Zambia

Bachelor of Arts (BA), Biochemistry 2004-2008
Oberlin College, Oberlin, OH
Distinctions: Elected to Sigma Xi

Study Abroad Program, Alcalá de Henares, Spain Jun-Jul 2007
Bowling Green State University, Bowling Green, OH

PROFESSIONAL EXPERIENCE

Research Assistant, University of Washington, Jan 2016-present
Department of Global Health, Dr. Ruanne Barnabas

- Conduct time and motion studies to collect detailed information on activities performed by local health department staff involved with STD partner services (PS) to be used in cost-effectiveness analyses.
- Design and analyze a dynamic compartmental mathematical model investigating the population level impact and cost-effectiveness of enhanced STD PS on HIV related outcomes, using data from King County, WA.

Student Epidemic Action Leaders (SEAL) Team, University of Washington, Sep 2016-Jan 2017
Department of Epidemiology, Dr. Janet Baseman

- Assisted with infectious disease outbreak response with the Department of Public Health - Seattle King County (PHSKC).
- Zika Virus Response (20 hours): Advised healthcare providers on testing guidelines and prevention recommendations. Approved/denied test requests based on exposure and risk criteria. Verified samples testing was conducted appropriately. Answered general provider and resident questions. Followed-up with providers regarding negative results and recommendations.
- Mumps Outbreak Response (20 hours): Conducted case interviews via phone. Followed-up with healthcare providers and WA state department of health regarding approvals for cases meeting criteria for state funded mumps testing.

Teaching Assistant, University of Washington, Department of Epidemiology Oct-Dec 2016;
Introduction to Epidemic Modeling for Infectious Diseases, Dr. Ruanne Barnabas Oct-Dec 2015

- Presented lecture on modeling sexually transmitted diseases and PrEP.
- Helped develop lab assignments using STELLA software.
- Created slides to guide hands-on mathematical modeling activities.
- Assisted students with homework assignment final projects completing a mathematical model based on an infectious disease of their choice.
- Graded assignments and created assignment keys.

Teaching Assistant, University of Washington, Department of Pharmacy Oct 2015-Dec 2015
Design and Analysis of Medical Studies, Dr. Beth Devine

- Provided general assistance to the lead instructor with the goal of training pharmacy students to understand basic statistical and epidemiologic methods, and to critically assess medical literature.
- Created and graded homework assignments and exams.
- Assisted students with material.

Research Assistant/Assistant Study Coordinator, University of Washington Jul 2014-Oct 2015
Department of Global Health, Dr. Michael Chung.

- Served as the assistant study coordinator for a clinical trial investigating the implementation of a point-of-clinical-care oligonucleotide ligation assay (OLA) used to detect drug resistant HIV in patients initiating HAART at three clinic sites in Kenya.
- Conducted data cleaning, and assist with the development of syntax and protocols to improve and maintain data quality.
- Conducted data analysis and contribute to posters and manuscript preparation.
- Worked on-site in Nairobi from July-August 2014 to become familiar with study protocols and assist the study coordinator as needed.
- Participated in weekly meetings with the laboratory and data staff via Skype.
- Assisted with preparing IRB documentation for Seattle and Kenya based institutions.
- Conducted data analysis and prepared closed and open reports for the Data Safety Monitoring Board (DSMB).

Research Assistant, University of Washington Oct 2013-Jun 2014
Department of Global Health, Dr. Michael Chung.

- Using data from the Coptic Hospital Hope Center HIV treatment clinics in Kenya, performed data analysis to evaluate HIV treatment and monitoring.
- Conducted data analyses using datasets from multiple studies investigating medication adherence in HIV positive patients in Nairobi.
- Modified SPSS syntax as needed to clean, merge, and organize datasets used by Hope Center staff and other researchers.

Consultant, EpiMetrix, Inc. Aug 2011-Oct 2013

- Conducted comprehensive searches and reviews of epidemiologic literature.
- Synthesized literature and prepared summary reports as requested by clients.
- Prepared manuscripts for publication submission.

Epidemiologist I, Maryland Department of Health and Mental Hygiene Sep 2011-Aug 2013
Center for HIV Surveillance, Epidemiology and Evaluation.

- Analyzed HIV/AIDS surveillance data and presented results for use in fact sheets, periodic reports, and customized data requests.
- Combined multiple data sources and conducted data analyses to better inform HIV prevention and surveillance programs.
- Spatially presented HIV/AIDS surveillance and other project data using ArcGIS to target outreach programs.
- Assisted in the development and implementation of integrated security and confidentiality guidelines to facilitate improved data sharing between centers within the Maryland state and local health departments.

Research Assistant, Johns Hopkins Bloomberg School of Public Health Jun 2010-Sep 2011
Epidemiology Department, Dr. William Moss.

- Cleaned, analyzed, and interpreted data for a multi-year, community-based malaria study in Southern Zambia.

Research Assistant, Johns Hopkins Bloomberg School of Public Health Aug 2010-Aug 2011
Environmental Health Sciences Department, Dr. Peter Lees.

- Collaborated with health departments in the Chesapeake Bay region to investigate the underreporting of *Vibrio vulnificus* infections

Study Interviewer, Johns Hopkins Bloomberg School of Public Health Aug-Dec 2010
BESURE, Dr. Danielle German.

- Administered questionnaire for the Behavioral Surveillance Research (BESURE) study investigating health behaviors of heterosexuals at high-risk of HIV infection in the Baltimore area, part of the National HIV Behavioral Surveillance (NHBS) study.

Teaching Assistant, Johns Hopkins Bloomberg School of Public Health Jun-Aug 2010
Epidemiology Department, Principles of Epidemiology.

- Instructed during lab sections and held office hours to answer questions.
- Graded assignments and exams, and proctored exams.

Junior Specialist, University of California, Davis Nov 2008-Aug 2009
Neurobiology, Physiology, & Behavior Department, Dr. James Trimmer.

- Performed lab research to better understand the effects of seizures on neurophysiology by inducing seizures in rats and analyzing brain samples using protein concentration assays, SDS PAGE, and Western blotting.
- Trained new lab members, ordered supplies, and presented research at weekly meetings.

Research Assistant, Oberlin College Jan-May 2008;
Biology Department, Dr. Yolanda Cruz. Jun-Aug 2006

- Performed dissections and immuno-histochemistry on embryos of *Monodelphis domestica* to identify protein expression during embryonic development.
- Collected, analyzed, and presented data regarding growth trends of small opossums, *Monodelphis domestica*.
- Was responsible for animal husbandry of mice and small opossums.

PUBLICATIONS

Silverman RA, Beck IA, Kiptinness C, Levine M, Milne R, McGrath CJ, Bii S, Richardson BA, John-Stewart G, Chohan B, Sakr SR, Kiarie JN, Frenkel LM, Chung MH. Prevalence of Pre-antiretroviral-Treatment Drug Resistance by Gender, Age, and Other Factors in HIV-Infected Individuals Initiating Therapy in Kenya, 2013-2014. *J Infect Dis*. 2017 Dec 19;216(12):1569-1578.

Kanthula R, Rossouw T, Feucht UD, Van Dyk G, Beck IA, **Silverman R**, Olson S, Salyer C, Cassol S, Frenkel LM. Persistence of HIV-drug-resistance among South African Children given Nevirapine to Prevent Mother-to-Child-Transmission. *AIDS*. 2017 May 15;31(8):1143-1148.

Chung MH, **Silverman R**, Beck IA, Yatich N, Dross S, McKernan-Mullin J, Bii S, Tapia K, Stern J, Chohan B, Sakr SR, Kiarie JN, Frenkel LM. 2016. Increasing HIV-1 Drug Resistance among

Antiretroviral-Naïve Adults Initiating Treatment between 2006 and 2014 in Nairobi, Kenya. *AIDS.* 2016 Jun 19;30(10):1680-2.

Rousmaniere H, **Silverman R**, White RA, Sasaki MS, Wilson SD, Morrison JT, Cruz YP. 2010. Husbandry of *Monodelphis domestica* in the study of mammalian embryogenesis. *Lab Animal (NY)* 39(7):219-26.

POSTER PRESENTATIONS

Rachel Silverman, David Katz, Matthew Golden, Teal Bell, Dawn Spellman, Carol Levin, Ruanne Barnabas. Cost and Impact of STI Partner Services (PS) in Seattle, WA. 2017. Poster presentation at IUSTI 2017 in Helsinki, Finland

Chambers LC, Manhart LE**, Silverman RA**, Barnabas RV. Potential Impact of Testing for Mycoplasma genitalium Infection and Macrolide Resistance: A Mathematical Modeling Analysis. Poster presentation at ISSTDR 2017 in Rio de Janeiro, Brazil.

Roberts ST, Katz DA, Golden MR, **Silverman RA**, Bell TR, Barnabas RV. Population-Level Effectiveness and Cost-Effectiveness of Enhanced Partner Services for Curable Sexually Transmitted Infections: A Systematic Review. 2016. Poster presentation at IUSTI 2016 in Marrakesh, Morocco

Michael Chung, Ingrid Beck, Molly Levine, Catherine Kiptiness, James Munyao, **Rachel Silverman**, Christine McGrath, Bhavna Chohan, Samah Rafie Sakr, Lisa Frenkel. 2016. Prospective randomized HIV drug resistance testing of Kenyans before 1st-line ART. Poster presentation at CROI 2016 in Boston, MA

Rachel Silverman, Michael Chung, James Kiarie, Nelly Yatich, Julia Njoroge, Catherine Kiptiness, Samah Sakr, Grace John-Stewart, Lisa Frenkel. 2015. Mortality Across Two ART Trials Enrolling at ≤200 verses ≤350 CD4 cells/uL in Kenya. Poster presentation at CROI 2015 in Seattle, WA

Rachel Silverman, Lisa Frenkel, Nelly Yatich, Ingrid Beck, Catherine Kiptinness, Julia Njoroge, James Kiarie, Michael Chung. 2015. Higher Risk of Pre-Treatment HIV Drug Resistance among Younger ART-Naïve Adults in Kenya. Poster presentation at the International HIV Drug Resistance Workshop 2015 in Seattle, WA

PEER REVIEW ACTIVITIES

Journal Reviewer for BMC Medicine – 2017
Journal Reviewer for PLOS ONE – 2016

COMPUTER SKILLS

Proficient with Stata, SAS, SPSS, ArcGIS, STELLA, EndNote, & Microsoft Office.
Some experience with R.