Cofactors and Outcomes of Infant HIV Diagnosis in PMTCT versus Hospital

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

Master of Public Health

University of Washington
2012

Committee:

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Program Authorized to Offer Degree:
Public Health—Epidemiology

University of Washington

Abstract

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Background: Many HIV-infected infants remain undiagnosed until they present with severe illness and hospitalization. Defining cofactors and outcomes associated with late pediatric HIV diagnosis can inform new approaches to identify HIV infected children before severe illness.

Methods: A cohort of HIV-infected infants was recruited from PMTCT clinics and pediatric wards in Nairobi, Kenya during the pre-randomization phase of a clinical trial. Infants were diagnosed with HIV and referred to the study; infants initiated antiretroviral therapy (ART) and were followed for 2 years. Univariate logistic regression was used to identify cofactors for diagnosis site (hospital versus PMTCT), and survival analysis, chi-squared tests, and independent T-tests were used to compare infant survival, retention, hospitalization, and ART initiation between the two sites.

Results: At recruitment sites, HIV prevalence was significantly higher among infants tested in hospital than in PMTCT programs (41% vs 11%, $p<0.001$). Among screened infants ages 0-12 months, infants diagnosed in hospital were significantly older than those diagnosed in PMTCT (5.5 vs 2.3 months, respectively, $p<0.001$). Among 99 infant-caregiver pairs enrolled in the study, 37% were diagnosed in a PMTCT clinic and 63% in hospital. Infants diagnosed in hospital were 81% less likely to have received PMTCT (95%CI=0.071-0.52), and their mothers were 83% less likely to have received ART or PMTCT (95%CI=0.061-0.48) compared to infants diagnosed within a PMTCT program. Infants diagnosed in hospital were more likely to be later disease stage (WHO 3 or 4) (OR=33, 95%CI=8.3-184), and had higher median HIV viral loads (6.7 versus 6.2 $\log_{10}$, respectively). Infants diagnosed in hospital were more

than 3 times as likely to die as infants diagnosed in PMTCT (HR=3.1, 95%CI=1.3-7.6), a relationship that persisted after controlling for CD4% at enrollment (aHR=2.7, 95%CI=1.1-6.8). The two groups did not differ in time to ART initiation, loss to follow-up, or subsequent hospitalization.

Conclusions: Infant HIV diagnosis in hospital was associated with failure to access PMTCT and more advanced disease. Infants diagnosed in hospital were at a higher risk for mortality, underscoring the critical importance of earlier diagnosis.

I. Introduction

During the past decade in sub-Saharan Africa, prevention of mother-to-child HIV transmission (PMTCT) programs have expanded coverage with corresponding decreases in new infant HIV infections [1]. In Kenya, the percentage of women accessing HIV testing during antenatal care rose from 31% in 2005, to 83% in 2010; however only 43% received an appropriate PMTCT regimen, and only 64% of HIV-exposed infants received a virologic test by 2 months of age [1]. Among infants who are infected with HIV, early infant diagnosis (EID) and initiation of treatment is still uncommon [2-4]. The WHO estimates that in 2010 only 28% of infants globally who were exposed to HIV received a virologic HIV test within the recommended first 2 months of life [1]; fewer still returned for test results and initiated ART where indicated [2, 3]. Just 21% of Kenyan children eligible for ART received it in 2010 [1]. Despite the clear benefits of early treatment, late identification of HIV-infected infants, who often present for care in a hospital setting when already symptomatic, is still common in many African settings [5, 6].

Early infant HIV diagnosis and initiation of treatment are critical for child survival [7, 8]. A randomized trial in South Africa found that initiation of ART between 6-12 weeks of age, prior to disease progression, improved infant survival by 76% and reduced disease progression by 75% compared to delayed ART initiation [9]. Children who are diagnosed with HIV after they are ill have a poorer response to antiretroviral therapy (ART), markedly higher mortality rates, and impaired neurologic and physical development [5, 10, 11].

Both individual and program-level factors likely contribute to incomplete HIV testing coverage of HIV-exposed infants. A study of Kenyan facilities in 2008 reported several systems and structural facility-level barriers to early infant HIV testing including lack of PCR testing capacity, lack of universal antenatal HIV testing, along with limited physical infrastructure, limited laboratory quality control procedures, and staff shortages [12]. While program-level factors affecting infant HIV testing [3, 12], and structural interventions to improve infant testing [13] have been described, individual-level factors delaying diagnosis are not well defined.

A better understanding of factors leading to delayed infant HIV diagnosis could inform targeting of specific groups to improve infant testing, or inform allocation of resources to overcome structural barriers. In this paper, we compare infant HIV disease stage, socioeconomic status, and caregiver characteristics between infants who were diagnosed with HIV within PMTCT versus hospital settings. We subsequently compare infant morbidity, mortality, time to ART initiation, and loss to follow-up (LTFU) based on HIV diagnosis site. This analysis is based on the recruitment, enrollment, and pre-randomization data from the Optimizing Pediatric HAART (OPH03) randomized control trial of HAART interruption (NCT00428116).

II. Materials & Methods

This study was approved by the University of Washington Institutional Review Board in Seattle, WA and the Kenyatta National Hospital (KNH) Ethics & Research Committee in Nairobi, Kenya. Recruitment was based at KNH and Nairobi City Council Clinics (NCCC), which provide HIV testing and treatment services. Infants who presented for care at KNH pediatric wards were tested for HIV. Infants who tested positive in this hospital setting were referred to the study staff for enrollment in the study.

Recruitment and Screening Newly diagnosed HIV-infected infants were recruited between 2007 and 2009. Infants ages 0 through 12 months were screened; infants between 0 and 4.5 months were eligible for the OPH03 study and older infants were eligible for a separate study. Infants were considered eligible for OPH03 if they tested HIV positive by two HIV DNA filter paper tests, and their caregiver planned to remain in Nairobi for at least 3 years and was willing and able to provide sufficient locator information. Infants were considered ineligible if they had previous ART exposure, aside from ART as part of PMTCT, or were suspected to have active tuberculosis.

Study Population Eligible infants were enrolled in the pre-randomization cohort and were followed for 2 years before being randomized as part of the OPH03 trial (NCT00428116) [10]. All data considered in this paper were collected prior to study randomization. At enrollment, a full physical examination was

performed on all infants, socio-demographic information and medical history were obtained from caregivers, and blood samples were collected from infants and caregivers for virologic testing. Viral loads were obtained by APTIMA HIV RNA Qualitative test (GenProbe, San Diego, CA) and CD4 count and CD4 percent were determined by flow cytometry. Following enrollment, caregivers received infant HAART adherence counseling and infants initiated HAART; infants who were identified in a hospital setting began HAART after they had been stabilized. HAART regimens consisted of the following drugs: lamivudine, zidovudine, and either nevirapine or lopinavir-boosted ritonavir if the infant had been exposed to nevirapine as part of PMTCT. Infants and caregivers had monthly follow-up visits with OPH study staff. Self-report of hospitalization events and infant mortality since the last visit were collected by questionnaire during these visits.

Statistical Analysis All analyses were conducted using STATA 11.2 IC (StataCorp, College Station, TX). Independent T-tests were used to test for differences in prevalence of HIV and age at HIV diagnosis between hospital and PMTCT sites during recruitment. Univariate logistic regression and chi-squared tests were used to compare baseline infant and caregiver characteristics by diagnosis site.

Infant outcomes were compared by diagnosis site using chi-squared analysis and included hospitalization after ART initiation, overall loss to follow-up (LTFU), and LTFU after ART initiation. Time to death (overall, pre-, and post-ART initiation), time to ART initiation, and time to first hospitalization after ART initiation by infant diagnosis site were compared between diagnosis sites using Cox proportional hazards regression and the log rank test. In all analyses, infants were censored at the time they were LTFU, deceased, or randomized into the clinical trial. The independent T-test was used to compare the incidence of hospitalization after ART initiation by infant diagnosis site. All tests were two-tailed, with alpha=0.05.

III. Results

HIV prevalence during recruitment screening Overall, 8,824 infants and their mothers were screened in hospital and PMTCT clinics; of 6,420 mothers with HIV test results, 1,083 were HIV-infected (16.9%).

Among the 8,095 (92%) screened mother-infant pairs with data regarding recruitment site, 6,027 were screened in hospital pediatric wards and 2,068 were screened in PMTCT clinics. Among those 830 infants screened in a hospital setting who had HIV test results, 341 (41.1%) were HIV-infected. Among those 1,030 infants screened in a PMTCT clinic who had HIV test results, 111 (10.8%) were HIV-infected (Figure 1).

Among HIV-infected infants ages 0-12 months who were screened, infants diagnosed in a hospital setting were significantly older than infants diagnosed in a PMTCT clinic (5.5 (IQR=4.1, 8.3) vs 2.5 (IQR=2.2, 3.4) months, respectively, p<0.001). However, time between testing and delivering infant test results was shorter among hospital-diagnosed infants than PMTCT-diagnosed infants (7 (IQR=5, 9) vs 25 (IQR=21, 38) days, respectively, p<0.001). Due to age restrictions in the eligibility criteria for OPH03, the age differences between hospital- and PMTCT-diagnosed infants observed during the screening process were not different in the cohort of enrolled infants (p=0.09).

Participant characteristics Among 99 enrolled infants, 37 were diagnosed at PMTCT and 62 were diagnosed in a hospital setting (Figure 1). A majority of primary caregivers were the infant's biological mother (97%), most were in a monogamous marriage (78%), and were either unemployed or worked as a housewife (83%). Most fathers were of unknown HIV status (as reported by the primary caregiver) (62%), and only 11% were reported to be HIV negative. At diagnosis, infants were, on average, just under 4 months old, had low CD4% (median of 19%), high viral loads (median of 6.5 $\log_{10}$ viral load) and nearly half were WHO clinical stage 3 or 4 (Table 1).

Predictors for diagnosis of HIV in a hospital setting Among the 99 infants enrolled in the cohort, the age of infants at the time of HIV diagnosis was similar between infants diagnosed in PMTCT and hospital (3.7 vs 3.6 months, respectively, p = 0.09; Table 2). Age, partner and income status, education, and symptomatic disease were similar between infants diagnosed in hospital and PMTCT (p>0.05 for each comparison). Knowledge that the infant's father was HIV-infected was significantly associated with being diagnosed in hospital (OR=4.9, 95%CI=1.4-21), as was male infant sex (OR=3.3, 95%CI=1.3-8.6). Infants

diagnosed in hospital had more advanced disease, with an average 0.5 $\log_{10}$ higher HIV viral load at diagnosis (OR per $\log_{10}$=2.0, 95%CI=1.2-2.6) and with a greater likelihood of being WHO clinical stage 3 or 4 (OR=33, 95%CI=8.3-184). Finally, infants diagnosed in hospital were less likely to have received any PMTCT (OR=0.17, 95%CI=0.061-0.48) and had mothers who were less likely to have had a history of ART for HIV treatment or PMTCT (OR=0.19, 95%CI=0.071-0.52).

Outcomes for infants diagnosed in a hospital setting We compared survival, hospitalization, and loss to follow-up (LTFU) between infants diagnosed in PMTCT and those diagnosed in hospital (Table 3) (Figure 2). Infants diagnosed in hospital were three times as likely to die as infants diagnosed through PMTCT (HR=3.1, 95%CI=1.3-7.6) (Figure 3). When we controlled for infant CD4% at enrollment, we noted persistent differences in mortality risk between the two groups (aHR=2.7, 95%CI=1.1-6.8). We previously described the incidence and predictors of mortality in this cohort of infants [10]. Infants in the two groups had similar rates of LTFU both overall and following ART initiation. Additionally, they did not differ in the incidence of hospitalization after ART initiation, time to first hospitalization after ART initiation, and time to ART initiation ($p>0.05$ for each comparison).

IV. Discussion

During recruitment we observed a higher prevalence of infants with HIV infection in hospital than in PMTCT settings and noted that HIV-infected infants in hospital were older than their PMTCT-diagnosed counterparts. In the enrolled cohort, we found that a lack of prior PMTCT interventions, advanced infant disease, male infant sex, and having a father known to be HIV-infected were significantly associated with infants being diagnosed in hospital rather than in a PMTCT clinic. Hospital diagnosis was associated with increased mortality compared to PMTCT diagnosis; however, the two groups did not differ in terms of hospitalization, time to ART initiation, or LTFU.

During recruitment, HIV prevalence was higher among hospital-tested infants than in PMTCT-tested infants. This is likely due to the use of highly efficacious prophylaxis regimens in urban Nairobi; and is

consistent with recent reports noting that HIV testing in hospital pediatric wards identifies a large number of HIV-infected children in high prevalence areas [14] and that the prevalence of HIV infection is higher among hospitalized infants than infants tested in a PMTCT clinic [15]. The older age among hospital-diagnosed infants is consistent with previous studies comparing inpatient to outpatient settings [16] and suggests that despite recent scale-up of PMTCT services in Nairobi, mothers and infants continue to fall through the cracks of PMTCT programs, and being diagnosed later in a hospital setting.

To our knowledge, this is among the first reports to examine cofactors of hospital vs PMTCT diagnosis in infants, though previous papers have examined cofactors for late stage vs early stage diagnosis in children [6] and inpatient versus outpatient diagnosed children [16]. Infants diagnosed in hospital were sicker than their PMTCT-diagnosed counterparts and were less likely to have received ART as part of PMTCT. However, it is notable that a quarter of hospital-diagnosed infants had received PMTCT drugs and a third of their mothers either received ART as part of PMTCT or were on HAART for their own health. Attrition of children at risk for HIV infection from PMTCT programs and subsequent presentation in hospital has been noted in other settings [17]. Infants in our study who had at least some PMTCT contact but were diagnosed with HIV in hospital may have been brought to the hospital because they were symptomatic with HIV, as noted by higher $\log_{10}$ viral load and higher proportion at WHO clinical stage 3 or 4. Previous studies have noted that children who were WHO clinical stage 3 or 4 when they initiated ART were less likely to have had PMTCT than children who were WHO stage 1 or 2 at initiation [6]. Males were overrepresented among hospital-diagnosed infants and underrepresented among PMTCT-diagnosed infants, despite a roughly equal sex distribution in our overall cohort. While there are no immediate explanations for this observation, sex differences may be present in both disease transmission and progression [18-22] as well as parental care-seeking behaviors [23]. Previous studies have not noted similar relationships between infant sex and late stage diagnosis [6] and only showed a trend towards significance between infant sex and EID program retention [24].

Caregiver sociodemographic characteristics were not strong predictors of infant diagnosis site in our study; a previous study in Uganda noted that younger caregiver age, caregiver unemployment, and high

cost of transportation to clinic were associated with late stage pediatric diagnosis [6]. While there are limited data assessing sociodemographic predictors of pediatric HIV diagnosis in hospital, there are several studies in African countries with sociodemographic predictors of EID uptake; independent income, larger family size, further distance from clinic, maternal HAART [4], older maternal age [24, 25], higher education and higher socio-economic status [26] were all associated with completion of EID. The lack of such a relationship between diagnosis site and sociodemographic characteristics in our study likely suggests limited power to detect such an association, perhaps due to relative homogeneity of caregiver sociodemographic characteristics.

The significant association between knowledge that the infant's father was HIV-infected and infant diagnosis in hospital is unexpected, considering previous reports that male partner testing is associated with greater uptake of PMTCT and improved HIV-free survival in infants [27, 28]. Unfortunately, although we ascertained paternal HIV status at enrollment, we did not ask mothers when their partners were diagnosed with HIV. It is possible that fathers were tested for HIV after their children were diagnosed with HIV in hospital but before completing study enrollment. However, paternal history of ART medication was associated with infant hospital diagnosis and showed a trend towards significance, which suggests that this potential reverse causality does not completely explain the observed association. Further studies should be conducted to assess the impact of paternal HIV status on PMTCT enrollment and infant diagnosis site.

Infants who were diagnosed in hospital were more than 3 times as likely to die as their PMTCT-diagnosed counterparts, a relationship which persisted after HAART initiation. This is consistent with literature noting associations between infant CD4% or viral load and mortality [5, 10, 29]. However, there were differences in mortality between the two groups that persisted after adjusting for baseline CD4%, suggesting that the relationship between diagnosis site and mortality is not completely explained by infant's disease status at baseline. A study in Malawi observed that the difference in mortality between HIV-infected infants from outpatient and inpatient settings, while in the direction that we would expect, did not reach statistical significance [16]. The differences in mortality risk between infants diagnosed at PMTCT and hospital did

not disappear once infants initiated ART; the hazard ratios (HR) for pre-ART initiation, post-ART initiation, and overall mortality were comparable, though we were underpowered to detect a true difference during pre- and post-ART sub-periods. Our observed persistent risk of mortality is consistent with previous reports, which have noted that infants who are already symptomatic upon ART initiation do not respond to ART as rapidly as their asymptomatic counterparts [10, 11].

Strengths of this study include including longitudinal and systematic ascertainment of infant morbidity and mortality following diagnosis, high retention, and detailed ascertainment of caregivers. However, the small sample size limits our ability to detect differences in some predictors and outcomes of diagnosis in hospital. Additionally, as this is a historic cohort that was recruited from 2007-2009 in Nairobi, the coverage rates of PMTCT and patterns of parental testing and treatment may differ from those seen in 2012 and/or patterns in other geographic areas of Kenya. Finally, selection into this cohort was influenced by the larger study enrollment criteria—being willing to participate in a clinical research trial, planning to reside in Nairobi for 3 years, willing to provide detailed locator information—which may limit generalizability of the observations.

Despite being crucial for infant survival, there are many drop-off points along the EID “cascade”, which leave HIV-exposed infants untested [2, 3, 16]. The findings from this study reinforce the importance of diagnosing infants early before they become symptomatic and are unable to respond well to treatment. While many of the infants in this study received PMTCT drugs, a significant portion did not, a proportion that is likely higher in the segment of the population without access to primary or acute health centers. Additionally, many older children, who acquired HIV before the recent PMTCT scale-up, remain undiagnosed in the community. This group of occult HIV-infected children may have high risk for morbidity and mortality as long as they remain undiagnosed, which suggests a need for a more aggressive programmatic approach to finding these undiagnosed children and linking them to care.

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Table 1: Characteristics of study cohort at enrollment		**N**	**Median (IQR) or n(%)**
Primary Caregiver Characteristics			
	Primary caregiver (mother)	99	96(97)
	Age	96	26(23-30)
	Marital Status	99	
		Married (monogamous)	77(78)
		Married (polygamous)	1(1)
		Single	9(9)
		Steady boyfriend	1(1)
		Widow	4(4)
		Separated	7(7)
	Employment	98	
		Casual	13(13)
		Housewife	50(51)
		Unemployed	31(32)
		Other	4(4)
	Education (highest achieved)	99	
		None	1(1)
		Primary	59(60)
		Secondary	37(37)
		College	2(2)
	Mother had any PMTCT or was on ARVs	98	48(49)
Father Characteristics			
	Father know about child's status	99	58(59)
	Father's HIV status	99	
		Known positive	27(27)
		Known negative	11(11)
		Unknown	61(62)
Infant Characteristics			
	Infant age at diagnosis	99	3.7(2.9-4.0)
	Infant received PMTCT drugs	91	38(42)
	Infant CD4%	96	18(14-24)
	Infant CD4% <25	96	76(79)
	Infant VL	86	6.5(6.0-7.0)
	Infant WHO stage 3 or 4	96	47(49)
	Infant sex (male)	99	50(51)
SES Characteristics			
	Share a toilet	99	86(87)
	Number of people per room in house	99	3(3-4)
	Monthly rent (in 1000 Ksh)	95	1.5(1.0-2.5)

Table 2: Cofactors of Diagnosis in Hospital and PMTCT

Cofactors at enrollment	PMTCT		Hospital		OR (95% CI)	p-value
	N	Median (IQR) or n(%)	N	Median (IQR) or n(%)		
Caregiver Cofactors						
Age	37	25(22-30)	59	26(23-30)	1.0 (0.93, 1.1)	>0.9
Partner and Income	37		61			
Has partner and indep income		2(5)		6(10)	0.66 (0.073, 6.1)	0.7
No partner but indep income		5(14)		4(7)	0.18 (0.024,1.3)	0.09
Has partner but no indep income		28(76)		42(69)	0.33 (0.067, 1.7)	0.2
No partner and no indep income		2(5)		8(15)	ref	ref
Achieved secondary education or higher	37	12(32)	62	27(44)	1.6 (0.69, 3.8)	0.3
Mother sick recently [$]	37	3(8)	62	7(10)	1.4 (0.30, 9.2)	0.6
Mother had PMTCT or ARVs	37	27(73)	61	21(34)	0.19 (0.071, 0.52)	**0.0002**
Thinks child will benefit from ARVs	37	36(97)	62	61(98)	1.7 (0.021, 135)	0.7
Father Cofactors						
Father's HIV status	37		62			
Known positive		4(11)		23(37)	4.9 (1.4, 21)	**0.005**
Known negative or unknown		33(89)		39(63)	ref	ref
Father sick recently [$]	37	4(11)	62	9(15)	1.4 (0.35, 6.7)	0.6
Father ever on ARVs	36	0(0)	60	5(8)	--	0.08
Infant Cofactors						
Infant had PMTCT drugs	36	24(67)	55	14(25)	0.17 (0.061, 0.47)	**0.0001**
Infant age at diagnosis	37	3.7(3.1-3.9)	62	3.6(2.4-4.0)	0.62 (0.36, 1.1)	0.09
Infant $\log_{10}$VL	32	6.2(5.6-6.7)	54	6.7(6.3-7.2)	2.0 (1.2, 3.6)	**0.01**
Infant CD4%	37	20(15-24)	59	18(14-22)	0.97 (0.93, 1.0)	0.3
Infant CD4% <25	37	29(78)	59	47(80)	1.1 (0.34, 3.3)	0.9
Infant WHO stage 3 or 4	37	3(8)	59	44(75)	33 (8.3, 184)	**<0.0001**
Infant sex (male)	37	12(32)	62	38(61)	3.3 (1.3, 8.6)	**0.006**
Family Cofactors						
Any other children with HIV	37	3(8)	62	1(2)	0.19 (0.0035, 2.5)	0.1
SES Cofactors						
Shared toilet	37	34(92)	62	52(84)	0.46 (0.076, 2.0)	0.3
Number of people per room in house	37	3.5(3-5)	62	3(3-4)	0.89 (0.68, 1.2)	0.4
Monthly rent (in 1000 Ksh)	36	1.5(1.0-2.0)	60	1.7(1.0-2.8)	1.0 (0.88, 1.2)	0.8

[$] Sick recently refers to self report of any of the following symptoms: fever, cough, or diarrhea >1 month, oral thrush longer than 2 weeks, weight loss greater than 5 kg, or generalized itchy rash

Table 3: Differences in Mortality, Hospitalization, and LTFU between Hospital and PMTCT

Outcome of Interest	PMTCT		Hospital		RR or HR (95%CI)	p-value
	N	Median (IQR) or n(%)	N	Median (IQR) or n(%)		
Overall Mortality	37	6(16)	62	24(39)	3.1 (1.3, 7.6)	**0.01**
Mortality pre-ART	37	2(5)	62	10(16)	2.9 (0.64, 13)	0.2
Mortality post-ART	33	4(12)	47	14(30)	2.9 (0.94, 8.7)	0.06
Ever hospitalized after ART	37	6(16)	62	13(21)	1.3 (0.54, 3.1)*	0.6
Time to first hospitalization after ART	32	109.5(103-357)[$]	43	55(28-189)[$]	2.0 (0.76, 5.3)	0.2
Incidence of hospitalization after ART (per 1,000 person-years)	60.75[^]	8(132)[#]	82.78[^]	20(242)[#]	1.8 (0.77, 4.8)**	0.1
Time to start ART (enrollment to ART initiation in days)	37	8 (7-20)[&]	62	14 (7-20)[&]	0.80 (0.51, 1.3)	0.3
Overall LTFU	37	6(16)	63	4(6)	0.39 (0.12, 1.3)*	0.1
LTFU after ART initiation	34	4(12)	47	3(6)	0.54 (0.12, 2.2)*	0.5

[*] Relative risk

[**] Incidence rate ratio

[$] Median time to hospitalization among those children hospitalized (N = 6 for PMTCT, N = 13 for Hospital)

[^] Person-years

[#] Number of hospitalizations (Incidence)

[&] Median time to ART initiation among those children who initiated ART (N = 33 for PMTCT, N = 47 for Hospital)

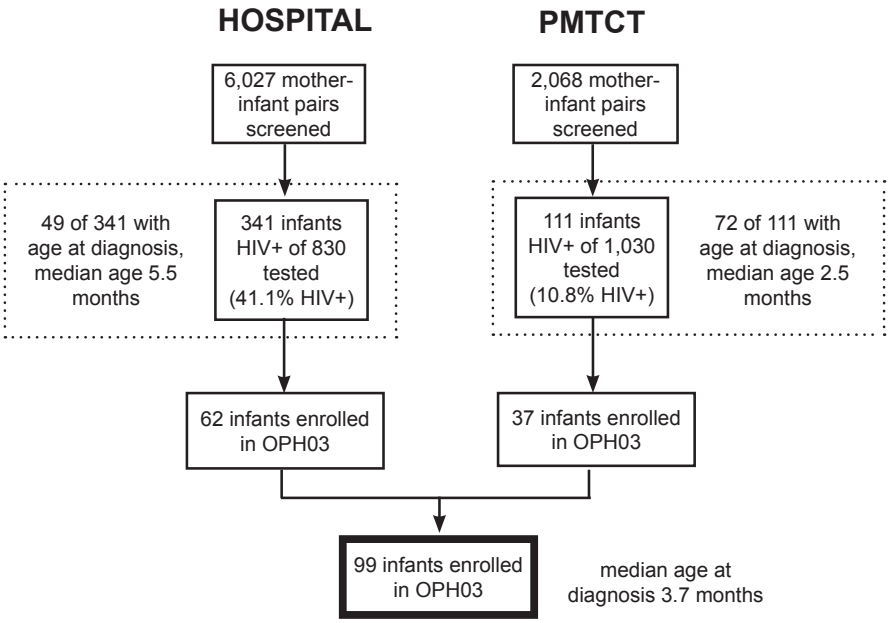

Figure 1: Study recruitment

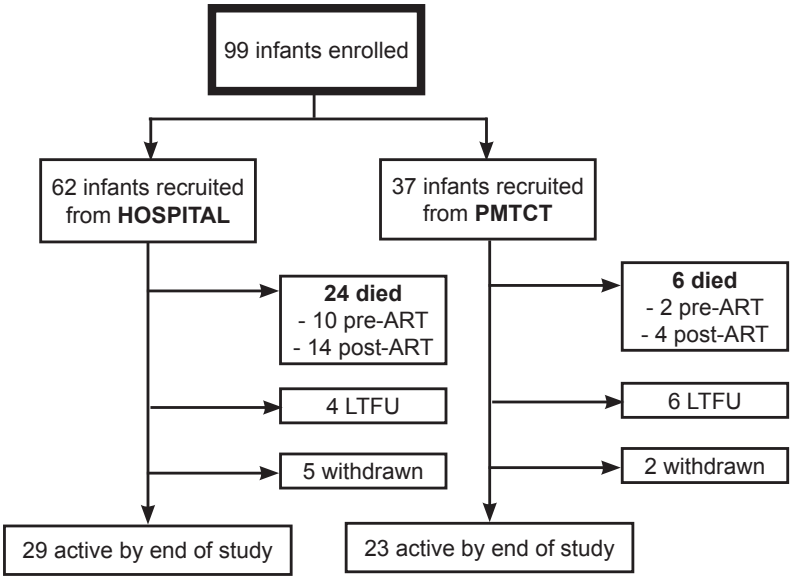

Figure 2: Outcomes by diagnosis site

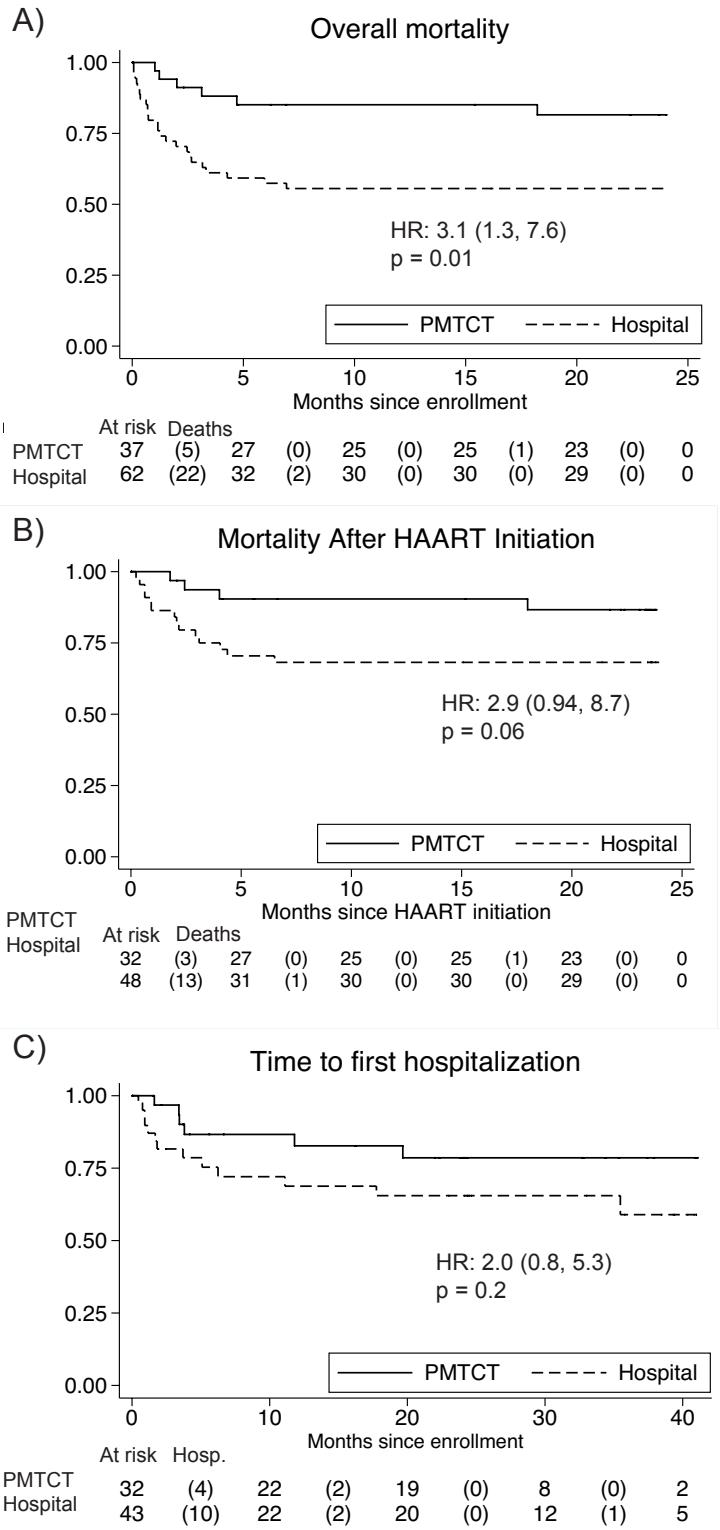

Figure 3: Mortality and time to hospitalization by infant diagnosis site