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RESEARCH ARTICLE

SURVIVAL AND LOSS TO FOLLOW UP AMONG HIV AND TUBERCULOSIS CO-INFECTED CHILDREN BELOW 3 YEARS OF AGE INITIATING ANTI-TUBERCULOSIS TREATMENT IN WESTERN KENYA

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Abstract

Background:
The optimal strategy for treating young children co-infected with HIV and tuberculosis is unknown. We compared mortality and loss to follow-up (LTFU) among HIV-infected children aged three years and below who received anti-tuberculosis treatment (anti-TB) and combination antiretroviral therapy (cART) in various sequences.

Methods: We conducted retrospective analysis of longitudinal data of HIV-infected children initiating anti-TB at less than 3 years who had not been initiated on cART at anti-TB initiation enrolled in the USAID-Academic Model Providing Access to Healthcare (AMPATH) Partnership in Kenya between 2001 and 2009. Survival outcomes were analyzed by Kaplan-Meier methods. Cox proportional hazard models were used to evaluate the risk factors associated with death or a composite outcome of death and/or LTFU.

Results:

Of the 365 eligible subjects, 52% were female, 66% were initiated on cART, 15.9% were LTFU and 6.9% died. Sixty-four were initiated on cART less than 8 weeks after starting on anti-TB, 64 between 8-24 weeks, and 237 after 24 weeks. Being female was associated with a higher chance of initiating

cART. Children on cART and anti-TB had better survival compared to those not on anti-TB but never on cART, (HR 0.336 95%CI 0.149-0.757). There was no survival or LTFU difference between the three cART initiation timing groups.

Conclusions:

For young HIV-TB co-infected children, there was no statistical difference in mortality, LTFU or mortality & LTFU when initiation on cART was staggered depending on the severity of clinical or immunologic stage within 8 weeks, 8-24 weeks or after completion of anti-TB. HIV-TB co-infected children on both cART and anti-TB had better survival.

Introduction

Tuberculosis (TB) remains the leading cause of death for those living with HIV/AIDS globally, including children [1, 2]. The risk of progression from TB infection to TB disease is greatest in the very young, in those infected with HIV, and in those with other forms of immune compromise such as severe malnutrition.[3-5] TB progression is also most rapid for very young children (less than two years), who are immune immature.[6] TB is a major cause of morbidity and mortality among HIV-infected children over 1 year of age, accounting for 20-32 percent of deaths among HIV-infected children over age 1 year in Zambia [7, 8], Cote d'Ivoire,[9] and South Africa.[10, 11]

These vulnerable populations, those with HIV and young children, have a substantially increased risk of mortality when treatment for TB is delayed due to the inability to make a timely diagnosis. [12-15] Treatment of TB/HIV co-infection is complex because of the possibility of cumulative toxicity when combining anti-retroviral drugs and TB therapies, poor drug absorption, drug interactions, pill burden, and, in children, lack of appropriate drug formulations.[16] Rifampicin, an essential first-line drug and a backbone of anti-Tuberculosis (anti-TB) therapy, affects levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI), the cornerstones of combination antiretroviral therapy (cART).[17] Trials to evaluate the pharmacokinetics, toxicity, or efficacy of anti-TB drugs have less often been performed in children.[18, 19] Because it is difficult to isolate an organism in pediatric TB, verifiable microbiological endpoints are often unavailable to accurately measure treatment success. Appropriate dosing may be even more of a challenge when children are co-infected with TB and HIV; there is a paucity of data on how concurrent cART impact the pharmacokinetics of anti-TB drugs in children. There is equally limited epidemiologic data to indicate the outcomes of current regimens being used in TB and HIV co-infected children.[20, 21] A paper by some of the authors shows the incidence of TB in HIV infected children below 14 years to be 17.5 per 100CY. In that study, the incidence of TB was reduced by 85% in children started on cART.[22]

Kenya is a country in sub-Saharan Africa that has a substantial disease burden from both HIV and TB. Moi University, in collaboration with Moi Teaching & Referral Hospital (MTRH), Indiana University School of Medicine and the United States Agency for International Development (USAID), established the USAID-Academic Model Providing Access to Healthcare (AMPATH) Partnership to a provide a comprehensive HIV care program for western Kenya.[23, 24] The AMPATH program, based in Eldoret, Kenya, and serving 25 clinic sites and additional 40 satellites in western Kenya, offers a comprehensive care package that includes provision of cART, prevention of opportunistic infections and treatment of HIV-associated diseases including TB. Drawing on the large pediatric cohort treated within the AMPATH partnership, we sought to examine the outcomes from six years of experience treating children under 3 years of age for TB and HIV co-infection. Comparing the results of various TB and HIV co-treatment strategies and differences in outcomes of loss to follow-up and death will inform treatment strategies for young co-infected children in similar resource-limited settings.

METHODS

Study Design

We conducted a retrospective cohort study using prospectively collected, de-identified data stored in the computerized medical records of pediatric patients enrolled in the AMPATH clinic sites in western Kenya. We identified the cohort of HIV-infected children under the age of 3 years who were also diagnosed with TB. Within this cohort, we described and compared three different groups of children based on when they initiated combination

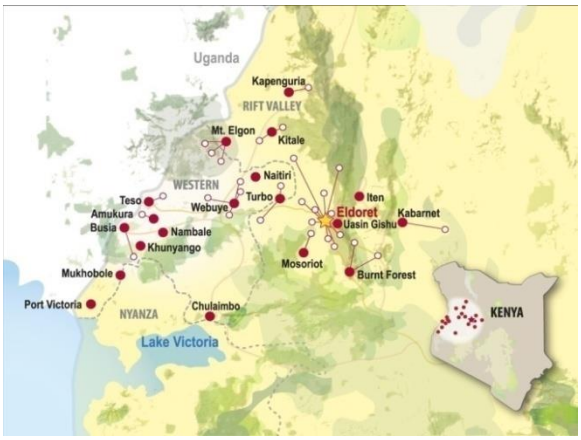
antiretroviral therapy (cART) in relationship to initiating anti-tuberculosis therapy: 1) initiating cART within 8 weeks after starting anti-TB therapy, 2) initiating cART between 8 weeks and 24 weeks after initiating anti-TB therapy, and 3) initiating cART after 24 weeks on anti-TB. The study was approved by the Institutional Research and Ethics Committee of the Moi University College of Health Sciences (Eldoret, Kenya) and the Institutional Review Board of the Indiana University School of Medicine (Indianapolis, USA).

Study Population:

Patients were eligible for this study if they were HIV-infected children under the age of 3 years, were enrolled at any one of the 18 AMPATH clinic sites operational between November 2001 and January 2009, had been diagnosed with TB and initiated on anti-TB therapy at some point in their follow-up. Being on anti-TB therapy was used as proxy for TB diagnosis in this analysis.

The AMPATH clinic sites included several urban clinics, the largest of which is located at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya, and multiple rural clinics across western Kenya. MTRH is the hospital hosting the Moi University College of Health Sciences (MUCHS), the second medical school in Kenya, and is one the first hospitals to start the family-based management of HIV-infected and affected people in Kenya. The other outpatient AMPATH clinics are located in several districts in western Kenya and North Rift. (Fig 1)

Figure 1: The AMPATH Clinics



Clinical procedures:

Protocols consistent with World Health Organization (WHO) guidelines (http://www.who.int/hiv/topics/arv/en/scaling_exe_summary.pdf) for the treatment of HIV-infected pediatric patients were developed locally and followed for the duration of the study. HIV infection was documented by DNA-PCR (Amplicor, Roche) for children less than18 months and by two parallel HIV rapid ELISA tests using Determine and Unigold for children18 months old or more. Indications for initiating cART in the children less than 3 years of age were having a CD4 cell percentage of less than 20% or WHO clinical stage 3 and 4 disease or CDC stage C. Tuberculosis was diagnosed using Keith Jones scoring criteria and Kenyan Ministry of Health guidelines that are modified from WHO guidelines. The standard initial cART and anti-TB regimens are shown in Chart 1 below.

Counseling and education about the cART and anti-TB drugs were provided to the adult who accompanied the patient during the clinic session that medications were initiated. Patients receiving cART or anti-TB therapy were seen for two visits two weekly after initiation of therapy and then every month thereafter. Those who were on both anti-TB therapy and cART at two weeks were followed up two weekly for two months. For those requiring both anti-TB therapy and cART at the same time, as per the national and AMPATH guidelines, the anti-TB drugs were started and used for at least two weeks before cART was initiated. For the ill, defined as severely low CD4% for age or WHO stage 4, the anti-TB drugs were used for two months before cART was initiated. The healthy – as defined by normal or mildly decreased CD4% for age, or WHO stage 3disease because of only TB - were treated for TB to completion before cART was commenced. During these visits, patients underwent clinical and adherence assessments and were dispensed anti-TB and antiretroviral drugs as necessary. Laboratory testing for HIV-infected children was based on local protocols and clinical necessity. Per protocol for patients initiating on cART, a complete blood count, an alanine aminotransferase, and a creatinine was performed at baseline and then every three

months. CD4 cell counts and percentages were obtained at baseline and then every six months. Mortality data was passively collected at the HIV clinics while data on patients admitted to MTRH was actively collected. At the time of this report, the outreach department in the program routinely actively tracked patients who did not return for scheduled HIV clinic visits. Data for loss to follow-up were also collected. This was defined as having no clinic visit for 3 months for those on cART and 6 months for those not on cART.

Data collection and management

Clinicians completed standard initial and return paper encounter forms at all AMPATH clinic visits. (http:// amrs.iu-kenya.org/download/forms) The initial encounter form included standard demographic, historical (including birth history and maternal prophylaxis), dietary, social, physical, and laboratory data, as well as data on medications provided (antiretroviral drugs and opportunistic infection prophylaxis). Follow-up data were collected on inter-current symptoms including drug side-effects, medication adherence, new diagnoses, laboratory data, and modifications in drug regimens. Dedicated data entry clerks entered this information into the electronic AMPATH Medical Record System, which initially used an MS-ACCESS Database (Microsoft Corp., Redmond Washington, USA) [25] but currently uses the OpenMRS platform.[26, 27]

Chart 1: cART and anti-TB Regimen

Child Characteristics	**Recommended cART Regimen**
A. Child previously NOT exposed to Nevirapine for PMCT HIV transmission	
Age < 3 years or weight < 10kg	Zidovudine(AZT) + Lamivudine (3TC) + Nevirapine (NVP)/Efavirenz (EFV)*
Age > 3 years and weight > 10kg	AZT or Stavudine(D4T) + Lamivudine (3TC) + Nevirapine (NVP)/Efavirenz (EFV)*
B. Child previously exposed to only single dose Nevirapine for PMCT HIV	
All ages	As above, substitute Nevirapine with Kaletra (LPV/r)
Child Characteristics	**Recommended anti-TB Regimen**
A. Child with non-severe TB	
	2months RHZ Rifampicin(R)/Isoniazid(H)/Pyrazinamide(Z) + 4 months RH
B. Severe or re-treatment TB	
	2 months SRHZE Streptomycin(S)/Rifampicin(R)/Isoniazid(H) /Pyrazinamide(Z)/Ethambutol(E) + 1 month RHZE+ 5 months RHE

*If the child is on anti-TB treatment:

- EFV should be used in place of NVP (preferred)
- Use boosted LPV/r (double the dose)if on LPV/r as 1st line
- Use 3 NRTI's (AZT/3TC/ABC) then change to LPV/r+2NRTI's at TB completion

Statistical Analysis

All statistical analyses were performed using STATA version 10.0. For continuous variables, comparisons were made using Kruskal-Wallis (Wilcoxon test) a non-parametric statistical test. Subjects were included in the analysis if they met the inclusion criteria of having a CD4% within the window period of 9 months prior and one month post TB treatment initiation. Timing of cART was defined as starting cART at a specific time period after being on TB treatment and was grouped as follows: 1) starting cART within 8 weeks after initiating anti-TB, 2) starting cART between 8-24 weeks, and 3) starting cART after 24 weeks of anti-TB therapy. All statistical tests were evaluated at the 0.05 level of significance. Pearson's Chi-square test was used to compare selected baseline characteristics of

subjects by cART timing group. Survival time was defined as duration from start of anti-TB treatment to death or loss to follow-up. Subjects were administratively censored at their last visit date if the patient did not die or become lost to follow-up during study period. If the duration to the event of interest was zero, then it was replaced by an infinitesimally small value enabling us to have a high power in the study. In our case, mortality & lost to follow-up was the main composite outcome variable of interest and was further categorized into three groups. In this study we evaluated one-year, two-year and overall mortality and lost to follow-up survival outcomes. The outcome variable was stratified in this manner because it was hypothesized that mortality outcomes of the subjects would vary depending on the duration of follow-up. In addition, because patients initiating cART at 8-24 weeks and at more than 24 weeks could only have the event of death or LTFU after those periods, we analyzed the survival or LTFU for all the groups after 30 weeks of initiating anti-TB therapy, excluding those who had not been followed up for 30 weeks after TB initiation.

Cox proportional hazards model and its associated covariates were used to evaluate the risk factors associated with mortality & lost to follow-up among subjects being started on cART while on or soon after completing anti-TB treatment. To estimate one-year, two-year and overall survival outcomes, Kaplan-Meier method and Cox regression model were employed. The main outcome variable was analyzed while controlling for factors such as age, sex, type of clinic, CDC class at start of anti-TB treatment, CD4% at start of anti-TB treatment and cART timing group. Differences in survival curves were compared using the log-rank test.

To address the issue of confounding by indication, a weighted cox regression model was fit to adjust for non random allocation to treatment. The weights were computed based on the model for time to start of cART from start of anti-TB treatment. To adjust for nonrandom allocation to treatment, a marginal Cox proportional hazards model was used to adjust for nonrandom allocation to treatment. The weights were computed based on a Cox model for time to initiation of cART adjusting for baseline covariates.

RESULTS

Patient characteristics

Data were available for 430 HIV-infected children under three years who had been initiated on anti-TB therapy prior to initiation of cART and were followed between November 2001 and January 2009. The mean age at initiation of anti-TB for the eligible 365 subjects was 1.71 years (SD 0.71); 190 (52.0%) were female; 35 (9.6%) were orphaned and the majority of patients, 209 (57.3%) were enrolled at urban clinics. During the study period, 58 (15.9%) subjects were lost to follow-up and 25 (6.9%) died. The median follow up period for the subjects who were LTFU or died was 1.36 years. Sixty-four were initiated on cART within 8 weeks of starting on anti-TB treatment, 64 between 8-24 weeks and 237 were initiated on cART after 24 weeks on anti-TB therapy or not at all. (Table 1)

Characteristics by cART Timing

In uni-variable analysis, those initiating cART within 8 weeks were more likely to be LTFU, p=0.016. Those initiating cART after 24 weeks were more likely to have a CD4% > 20%. (Table 1) Being female was associated with higher overall chances of initiating on cART (hazard ratio (HR) 1.44, CI 1.05-1.98), whereas there was a lower chance of initiating cART among those with a CD4% > 20% (HR 0.38, CI 0.25-0.56) or a high weight-for-age Z-score (WAZ) (HR 0.84, CI 0.72-0.98). (Table 2)

Overall unadjusted survival characteristics

The cumulative survival time from start of anti-TB was 6676.47 person months (556.37 person years) with a median survival of 16.43 months. There was no survival difference between the three cART initiation groups namely those who initiated cART after being on anti-TB therapy for 0-8 weeks, 8-24 weeks and more than 24 weeks (Figure 2F). Neither was there a difference in the composite endpoint of mortality and loss to follow-up between the three groups. (Figure 2E) During the entire follow-up period, subjects who were initiated on cART (n=283) had much better survival compared to those who were never started on cART (n=189) (p=0.0058) (Figure 2A). Similarly, subjects who had CD4% measurements greater than 20% had much better survival when compared to those with CD4% less than 20% (p=<0.0001). (Figure 2B)

One year survival (Mortality and LTFU):

There was no two year survival difference for the composite outcome of mortality and LTFU between the three cART timing groups, either before or after adjusting for baseline covariates including gender, CD4%, clinic type, CDC category and orphan status. (Table 3)

Two year survival (Mortality and LTFU):
There was no two year survival difference for the composite outcome of mortality and LTFU between the three cART timing groups, either before or after adjusting for baseline covariates including gender, CD4%, clinic type, CDC category and orphan status. (Table 4; Figures 2C and 2D). However, subjects starting cART after 24 weeks had some tendency for better survival early on in the follow-up period (HR 0.77, CI 0.37-1.63). (Table 4; Figures 2C and 2D). There was no survival difference for the composite outcome of mortality and LTFU among the three cART timing groups when we adjusted for the bias of late follow-up for those initiating cART in the later two categories and for selected covariates including gender, CD4%, clinic type, CDC group and orphan status.

Weighted cox regression model (to adjust for non random allocation to treatment)
From the results, we observe that there is a reduction in the hazard for death or lost to follow up at both one year and two years among those that started cART in the interval 8-24 weeks compared to those who initiated cART in the interval 0-8 weeks. There was a similar trend when controlling for those with missing exposure (no cART). However, there was no change in the direction for those that started cART after 24 weeks.(Tables 3 & 4)

Table 1: Patient characteristics by timing of cART initiation

	timing of cART(weeks)			
Characteristic	**0-8, (N=64)**	**8-24, (N=64)**	**>24, (N=237)**	**P-value**
Gender	**n=64**	**n=64**	**n=237**	
Male	25 (39.1)	28 (43.8)	122 (51.5)	
Female	39 (60.9)	36 (56.2)	115 (48.5)	0.160[1]
Age (yrs) at enrolment	**n=64**	**n=64**	**n=237**	
Median (range)	1.68 (0.01,2.92)	1.51 (0.03,2.86)	1.38 (0.01,2.96)	0.1815[3]
Duration of follow-up on TB treatment(months)	**n=64**	**n=64**	**n=237**	
Median (range)	17.59 (0.23,46.05)	18.25 (0.46,53.52)	13.95 (0.23,66.15)	0.8059[3]
Age (yrs) at start of TB treatment	**n=64**	**n=64**	**n=237**	
Median (range)	1.96 (0.35,2.95)	1.87 (0.42,2.97)	1.71 (0.12,2.98)	0.2011[3]
Type of Clinic	**n=64**	**n=64**	**n=237**	
Urban	28 (43.7)	24 (37.5)	104 (43.9)	
Rural	36 (56.3)	40 (62.5)	133 (56.1)	0.647[1]
	n=64	**n=64**	**n=237**	
Lost to follow-up	17 (26.6)	12 (18.8)	29 (12.2)	0.016[1]
	n=64	**n=64**	**n=237**	
Deceased	4 (6.3)	6 (9.4)	15 (6.3)	0.678[2]
Weight (kg) at start of TB treatment	**n=64**	**n=63**	**n=236**	
Median (range)	8.45 (3.4,13)	8.35 (3.3,15.50)	8.00 (3,15)	0.9099[3]
Weight-for-height at start of TB treatment	**n=60**	**n=61**	**n=218**	
Median (range)	-1.42 (-4.53,1.91)	-1.53 (-4.39,2.08)	-1.14 (-4.84,3.47)	0.065[3]

CDC stage at start of TB treatment	**n=58**	**n=64**	**n=231**	
N or A	7 (12.1)	4 (6.2)	36 (15.6)	
B or C	51 (87.9)	60 (93.8)	195 (84.4)	0.148[2]
cd4% category at start of TB treatment	**n=51**	**n=48**	**n=154**	
0-20	43 (84.3)	41 (85.4)	85 (55.2)	
>20	8 (15.7)	7 (14.6)	69 (44.8)	<0.0001[1]

[1]Chi-square test

[2]Fishers exact test

[3]Kruskal-wallis test

Table 2: Adjusted Cox Proportional hazard regression model of time to start of cART

Covariate	**Hazard Ratio**	**p-value**	**95% Conf. Interval**
Gender			
Male*	1		
Female	1.44	**0.025**	(1.048 to 1.980)
Age at TB Treatment start	1.02	0.864	(0.800 to 1.304)
Clinic type			
Rural*	1		
Urban	0.94	0.684	(0.676 to 1.292)
CDC group			
N or A*	1		
B or C	1.49	0.186	(0.826 to 2.675)
Cd4% categories			
<=20%*	1		
>20%	0.38	**<0.001**	(0.254 to 0.555)
Weight-for-Age Z-Score	0.84	**0.024**	(0.715 to 0.977)
Weight-for-Height Z-Score	1.07	0.356	(0.924 to 1.248)
Orphan status			
Not orphan*	1		
Orphan	0.83	0.528	(0.466 to 1.479)
Missing status	1.12	0.505	(0.802 to 1.567)

*** Reference category**

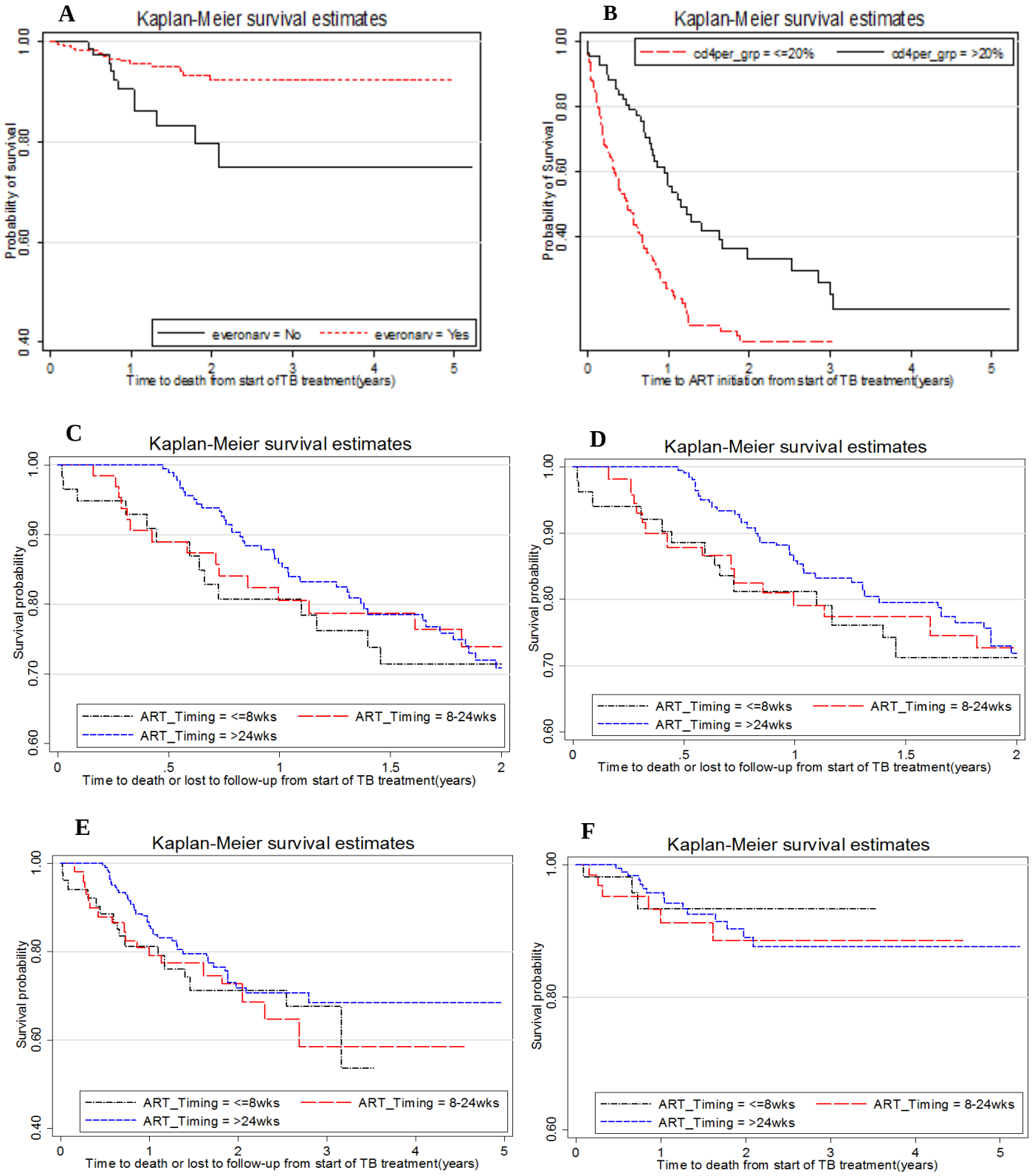
Table 3: Unadjusted and Adjusted Cox proportional cox models at one year

	cART timing (weeks)		
	< 8*(ref)	**(8-24)**	**>24**
1) 1 Year mortality			
Unadjusted	1	1.32 (0.315-5.519)	0.59 (0.152-2.275)
Adjusted	1	1.93 (0.350-10.620)	0.47 (0.065-3.356)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
2) 1 year mortality with LTFU			
Unadjusted	1	0.96 (0.414-2.221)	0.61 (0.291-1.271)
Adjusted	1	1.07 (0.403-2.825)	0.56 (0.225-1.416)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			
3) 1 Year mortality with Marginal Structural Modeling (MSM)			
Unadjusted	1	1.32 (0.315-5.519)	0.59 (0.152-2.275)
MSM	1	1.43 (0.322-6.328)	0.47 (0.111-1.955)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
4) 1 Year mortality with MSM at 30 week cutoff			
Unadjusted	1	0.79 (0.111-5.616)	1.20 (0.259-5.564)
MSM	1	0.84 (0.110-6.335)	1.22 (0.240-6.230)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
5) 1 year mortality + lost to follow-up at 30 week cut-off			
Unadjusted	1	0.60 (0.208-1.727)	0.89 (0.404-1.973)
Adjusted	1	0.62 (0.196-1.940)	0.93 (0.375-2.311)
MSM	1	0.63 (0.211-1.906)	0.84 (0.363-1.921)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			
6) 1 year mortality with LTFU with MSM & MSM with missing exposure			
Unadjusted	1	0.96 (0.414-2.221)	0.61 (0.291-1.271)
Adjusted	1	1.07 (0.403-2.825)	0.56 (0.225-1.416)
MSM	1	1.07 (0.429-2.665)	0.63 (0.280-1.414)
MSM with missing exposure	1	1.53 (0.817-2.866)	0.70 (0.386-1.252)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			

Table 4: Unadjusted and Adjusted Cox proportional cox models at two years

	cART timing (weeks)		
	< 8*(ref)	**(8-24)**	**>24**
1) 2 Year mortality			
Unadjusted	1	1.63 (0.408-6.524)	1.27 (0.365-4.434)
Adjusted	1	1.98 (0.357-10.953)	1.21 (0.226-6.506)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
2) 2 year mortality with LTFU			
Unadjusted	1	0.88 (0.423-1.815)	0.83 (0.449-1.509)
Adjusted	1	0.93 (0.398-1.165)	0.77 (0.365-1.628)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			
3) 2 Year mortality with Marginal Structural Modeling (MSM)			
Unadjusted	1	1.63 (0.408-6.524)	1.27 (0.365-4.434)
MSM	1	1.84 (0.426-7.952)	1.06 (0.277-4.060)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
4) 2 Year mortality with MSM at 30 week cut-off			
Unadjusted	1	1.25 (0.209-7.499)	1.88 (0.423-8.340)
MSM	1	1.48 (0.229-9.576)	1.80 (0.363-8.905)
*reference category, controlling for gender, CD4%, Clinic type, WAZ & WHZ score			
5) 2 year mortality+lost to follow-up at 30 week cut-off			
Unadjusted	1	0.94 (0.380-2.304)	1.14 (0.547-2.373)
Adjusted	1	0.84 (0.304-2.324)	1.04 (0.443-2.441)
MSM	1	1.03 (0.395-2.686)	1.13 (0.507-2.542)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			
6) 2 year mortality with LTFU with MSM & MSM with missing exposure			
Unadjusted	1	0.88 (0.423-1.815)	0.83 (0.449-1.509)
Adjusted	1	0.9 (0.398-1.165)	0.77 (0.365-1.628)
MSM	1	0.95 (0.421-2.129)	0.81 (0.408-1.590)
MSM with missing exposure	1	1.33 (0.724-2.430)	0.82 (0.473-1.409)
*Reference category, controlled for: gender, CD4%, Clinic type, CDC group, WAZ score, WHZ score & Orphan status			

Figure 2. Kaplan-Meier graphs showing time to death or lost to fup from start of TB treatment (A) whether child was ever on cART ; (B) time to cART start by cd4% category; (C) unweighted KM plot of time to 2-year lost tofup or death by cART groups; (D) weighted KM plot of time to 2-year lost to fup or death by cART groups ; (E) Overall KM plot of mortality+lost to follow-up by cART timing groups and (F)Overall mortality KM plot by cART timing groups



DISCUSSION:

In this large pediatric retrospective cohort study, we demonstrate that co-administering cART and anti-TB therapy results in favorable outcomes for children in Kenya despite the complexity associated with pediatric dosing and formulations and formidable barriers to care, such as poverty and orphan status. This young cohort of co-infected children had relatively good overall, annual and biannual survival, better than in some other studies. [10, 13, 28]

Children initiating cART at any time during the anti-TB treatment had better survival than those on anti-TB alone but not on cART. This provides further evidence that cART improves immunity, thereby reducing opportunistic infections and their severity and leading to fewer deaths. Several studies in Africa have demonstrated similar results. (10, 12, 16) Children with higher CD4% had better survival in this cohort, again indicating the value of having a better immune status for better survival as shown in other studies.[29] Older children with TB and HIV co-infection had a tendency to better survival, although this was not statistically significant. These findings are similar to those of other studies, reinforcing policies that push for shorter time to initiation of cART for younger children, [30] This may be explained by the fact that older children have better immunity and are therefore able to contain the multiplication and dissemination of the bacteria.[31]

Children initiating cART after completion of anti-TB treatment had a tendency to better survival although this was not statistically significant. This may result from a combination of factors. Confounding by indication may explain this phenomenon, since sicker children are initiated on cART early and will not survive due to severity of disease. This is supported by the weighting analysis we performed that shows a tendency to reversal of survival trends between the 0-8 week and 8-24 week cART timing categories. This means that if you were to randomly allocate the various categories of patients to treatment without considering the severity of infection, there is a tendency to reversing the confounding effect. Those with lower weight-for-age and lower CD4% also had earlier initiation of cART. This could reflect a good understanding of the protocols by the practicing clinicians. The AMPATH program emphasizes consistent training for clinical officers and nurses, with a week of didactic training for clinicians, followed by 2 months of working under mentorship. Clinicians may have been more likely to recognize the need for cART initiation in these sicker, more malnourished patients. Female patients were more likely to be initiated on cART. This may be an incidental finding, but may also reflect efforts not discriminate against the female gender. Additionally, the government's policy on gender parity has ensured that various ministries and departments increase participation of the girl child in all spheres of life and development. This has resulted in the girl child increasingly receiving increasing opportunities for education, less biased involvement in performing home chores and better and balanced access to healthcare as the government scales up gender equality and this may be a reflection of that increased awareness of gender equality.

Co-infected children initiating cART between 0-8 weeks had a trend to higher mortality and LTFU although not statistically significant. This trend may reflect that these patients are usually severely immune-suppressed and have advanced disease.

Even if cART is initiated, it would take 3 months before one would see a drop in viral load and up-to more than one year to see a rise in CD4%. In this period before CD4% improves, these children are still predisposed to opportunistic infections as in the pre-cART period. Mortality is therefore not as dramatically impacted in this group. This is similar to an earlier evaluation of the same program where those with poor CDC staging and immunity were more likely to be LTFU.[32] This may need further evaluation of the reasons for LTFU is needed since these may actually be patients who die. In a study in the same population of children by some of the authors, we found that children who were LTFU were either dead (11%) or had disclosure and discrimination issues influencing their inability or unwillingness to return to clinic for care. (24%).[33]

In this study, there was no statistically significant difference between the three groups of initiating cART at 0-8, 8-24 and > 24 weeks even after performing Marginal Structural Modeling (MSM) and Inverse Proportional Weighting to account for confounding by indication. In these statistical procedures, the treatment initiation is randomly allocated to control for confounding by treatment by indication. No differences were seen with mortality as the outcome of interest and or with mortality and LTFU as a composite outcome. However, there was a tendency to lesser mortality for those initiating cART after completion of anti-TB therapy. Most of these would be patients who are otherwise stable and healthier by virtue of either not being severely immune-suppressed or not having other WHO stage 3 or 4 conditions. There may be no clear policy implications of this observation given the small sample

size but it may be that all HIV-infected children who have been diagnosed with TB, irrespective of clinical stage, can be initiated on cART at the earliest convenient and tolerable time after initiating anti-TB therapy. The tendency to higher mortality for those initiating on cART early on in their anti-TB therapy may be severely immune-suppressed and therefore dying from other co-morbid conditions in-spite of initiating cART.

One of the commonest causes of mortality in HIV infected adults worldwide is TB. In such orphaned children, we postulated that they may get TB from their late parents and would likely subsequently have poor access to care and support. When we looked at orphan status and TB outcomes we found no statistical difference between the two groups in this study.

The staggering of initiation on cART depending on the severity of clinical or immunologic stage is not supported by the outcomes of this study. This may be explained by the small number of outcomes of interest in this cohort; in this small population, the power of the study is low and therefore small differences may not be statistically significant. We hope to follow up a bigger population of under 3 years to determine if this tendency is significant.

The study was performed in an 18-site treatment program in western Kenya. Our results may therefore not be generalizable to other treatment programs in sub-Saharan Africa for a number of reasons beyond cultural ones, including access to medical attention, differences in cART and anti-TB treatment protocols etc. On the other hand, this was a relatively large cohort of young children, and the findings may be more similar to those from other resource-limited settings. The second limitation is the fact that TB diagnosis in children utilizes scoring criteria rather than microscopic confirmation as happens in adults. We therefore used the initiation of anti-TB as proxy for TB diagnosis. It is possible some of the children may not have been infected with TB. The third limitation to the analysis is the unmeasured confounding since we might not have accounted for all the factors that clinicians took into account when making the decision to treat. However, we did attempt to factor in the most common criteria included in guidelines for treating TB-HIV co-infections, including nutritional status, WHO clinical and immunologic stage and age. In addition, we controlled for clinic type and did weighting (assuming a random allocation to treatment) but did not see a difference between the groups. The fourth limitation was the exclusion of patients who died or were lost to follow-up prior to initiation of cART. This group of patients may contribute to selection bias.

Conclusions

This study confirms that TB-HIV co-infected children on cART have better survival and that those with lower CD4% and lower WAZ are more likely to be initiated on cART compared with those with higher baseline WAZ scores or CD4%. There was, however, no difference in mortality between initiating cART before 8 weeks on anti-TB therapy, between 8-24 weeks on anti-TB therapy or after completion of anti-TB treatment.

The staggering of initiation on cART depending on the severity of clinical or immunologic stage is not supported by the outcomes of this study

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