HHS Public Access

Author manuscript

Curr HIV Res. Author manuscript; available in PMC 2016 January 20.

Published in final edited form as:

Curr HIV Res. 2014 ; 12(5): 359–365.

Improved Survival with Co-Trimoxazole Prophylaxis among People Living with HIV/AIDS Who Initiated Antiretroviral Treatment in Henan Province, China§

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Abstract

Objectives—This study aims to evaluate the effect of co-trimoxazole (CTX) prophylaxis on mortality reduction among HIV-infected patients receiving antiretroviral therapy (ART) in Henan Province, China.

Design—We conducted a retrospective study.

Methods—All individuals aged 15 years and older who initiated ART between 2008 and 2010 in Henan Province with completed CTX prophylaxis treatment information were included. The effect of CTX prophylaxis was estimated using Kaplan-Meier survival analysis and multivariate Cox proportional hazard modeling for mortality at 3-months and 12-months after ART initiation.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

Results—Overall mortality among patients receiving both ART and CTX was nearly double at 3-months after ART initiation compared with that at 12-months (12.4 per 100 PY *vs* 6.3 per 100 PY, $p<0.01$). After adjusting for gender, age, TB history, year of ART initiation and CD4 count at ART initiation, CTX was associated with a significant reduction in 12-month mortality (adjusted hazard ratio (AHR) = 0.65, 95% confidence interval (CI): 0.44 – 0.95; $p = 0.027$) compared with persons not receiving CTX. The protective effect was more pronounced in the first 3 months after ART initiation (AHR = 0.53, 95% CI: 0.32 – 0.89; $p = 0.017$).

Conclusion—CTX prophylaxis together with ART reduced mortality of adult HIV patients during the first 12 months of ART in Henan Province, China. The effect was highest in the first 3 months of ART. CTX should be prescribed to all HIV-infected adults who initiate ART.

Keywords

ART; Co-trimoxazole; HIV; mortality; prophylaxis; survival

INTRODUCTION

By 2011, an estimated 780,000 people were living with human immunodeficiency virus (HIV) in China [1]. To respond to the HIV epidemic, the Chinese government started the National Free Antiretroviral Treatment Program (NFATP) in 2003 to provide free antiretroviral therapy (ART) to all eligible patients [2–5]. Overall HIV-associated mortality rate decreased from 39.3% in 2002 to 14.2% in 2009 due to the increasing coverage of NFATP [6]. Yet a substantial number of deaths still occur each year among people living with HIV/acquired immunodeficiency syndrome (AIDS), especially those not on ART and those with only a short treatment history [7]. HIV infection remains the leading cause of death among all notifiable infectious diseases in China [8]. Therefore, it is of great importance to explore additional interventions to further reduce HIV-related deaths.

Co-trimoxazole (CTX) prophylaxis has been associated with a reduction in mortality and morbidity among HIV-infected people both not on ART [9–15] and on ART [16–18]. A meta-analysis of nine articles found CTX prophylaxis reduced mortality by 58% among HIV-infected individuals older than 13 years who were receiving ART [16]. Furthermore, two studies in Africa showed CTX prophylaxis had the most significant effect during the first 3–6 months after ART initiation [17, 18]. In addition, from an economic perspective, CTX prophylaxis is cost-effective in averting mortality among patients on ART [19–22].

In 2005, the Chinese Ministry of Health issued national guidelines on CTX prophylaxis for preventing HIV-related opportunistic infections (OIs) [23]. There has been insufficient data in China to illustrate the actual coverage of CTX prophylaxis among people living with HIV/AIDS. However, a five-year national observational cohort study showed that less than a third (26.2%) of 69,943 HIV-infected individuals who were on ART in China received CTX either for prophylaxis or treatment of opportunistic infections during 2002 to 2009 [6]; these data suggest that implementation of the guidelines has been suboptimal. The aim of this study was to investigate the effect of CTX prophylaxis on survival among HIV-infected adults on ART by utilizing the data from the Henan Provincial Free Antiretroviral Treatment Program database.

MATERIALS AND METHODS

Study Setting

The NFATP in China has been previously described [3–5, 7]. In summary, after a pilot in 2002, the NFATP was scaled up in 2003 among former plasma donors. An electronic database was established in late 2004 [5] to collect information on all ART eligible patients across China through standardized case report forms (CRFs) [5]. The CRFs collect demographic information, laboratory testing results, clinical signs and symptoms at treatment initiation and at follow-up visits. Regimen change and treatment outcome (lost to follow-up, treatment termination and death) are also collected using CRFs during follow-up visits [3]. Self-report of missing any dose of ART during the last 7 days was used as a proxy for non-adherence to ART and CTX prophylaxis. The China Free Antiretroviral Therapy Manual was also developed in 2004 to serve as the national technical guideline of NFATP [4].

Henan Province, located in central China, has the largest HIV cohort caused by unsafe commercial plasma donation in the world [24–26]. It was the site of the first pilot of NFATP [4]. The ART program database of Henan Province, part of the NFATP database, was established in July 2006 [7] and covers all patients receiving free ART in the province. The Henan Provincial free ART program database contains almost half of patients in the NFATP database [5]. CTX prophylaxis eligibility in Henan follows the Chinese national guidelines, which recommend that HIV-infected individuals with CD4 counts less than 200 cells/μl or WHO clinical stage3 or 4 disease [23] be provided CTX prophylaxis to prevent occurrence of opportunistic infections such as Pneumocystis jiroveci pneumonia (PCP).

Study Design and Participants

This was a retrospective study using information extracted from the Henan Provincial free ART program database. The comprehensive electronic database in Henan Province which tracked and monitored the implementation of CTX prophylaxis enables us to explore the effects of CTX on survival. Since the survival information in 2012 is still under verification, therefore we chose 2008–2010 as our study period.

HIV-infected individuals were included for analysis if they were 15 years old or above when enrolled in the NFATP; started ART with first-line regimens between January 1, 2008 and December 31, 2010 in Henan Province; and had CTX prophylaxis information recorded at baseline (yes or no). Those whose CTX prophylaxis information was absent were excluded from the analysis. All recruited patients were followed up for 12 months after starting ART. Patients who self-reported transmission through mother-to-child transmission (4 cases), homosexual behaviors (3 cases), and injection drug use (4 cases) were excluded from analysis due to small sample size.

Outcome Measures

The effect of CTX prophylaxis was evaluated by comparing mortality after ART initiation between patients on ART plus CTX prophylaxis and ART only at 3-months and 12-months. We also performed analysis adjusting for other demographic and medical risk factors for

mortality, such as gender, age at ART initiation, tuberculosis (TB) history, CD4 count at ART initiation and transmission route and the year of ART initiation. Year of ART enrollment was included in the analysis, because in 2008–2010 China raised the immunological criteria for ART initiation from a CD4 count of 200 cells/μl to 350 cells/μl [23].

Statistical Analyses

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 16.0. Continuous variables were expressed using mean (±standard deviation) or median and compared using t-test; categorical variables were estimated by frequency and percentage and compared using Chi-square tests. Mortality was calculated by dividing the number of deaths by the total number of person-years (PY) of observation after ART initiation in the CTX group and non-CTX group for the 0–3 month interval (3-months mortality) and for the 0–12 month interval (12-months mortality), respectively. PY were calculated as time from the date of ART initiation to death or to the date of censoring. Patients were censored at the date of loss follow-up or the administrative censoring date (3-months or 12-months after ART initiation), whichever occurred first. Kaplan-Meier survival analysis was performed to compare cumulative survival probabilities for HIV-infected individuals in the CTX group and non-CTX groups. A log rank test was conducted to test the significance of the difference. Univariate and multivariate Cox proportional hazard (PH) [27] models were used to examine the associations between risk factors and survival. The multivariable Cox PH model was generated using a forward selection approach. Variables were entered and kept in the model based on possible associations in previous literature and *p*-value cut-off value of 0.05 and 0.10, respectively. A *p*-value <0.05 was considered statistically significant.

Ethical Considerations

This study protocol was approved by the Institutional Review Board (IRB) of Henan Provincial Center for Disease Control and Prevention and the IRB of the National Center for AIDS Control and Prevention. The protocol was also reviewed and approved by the Office of the Associate Director of Science of the Center for Global Health, US CDC.

RESULTS

A total of 2,529 eligible HIV-infected individuals were identified with 2,429 person-years (PY) of follow-up. Of these, 2,018 received CTX prophylaxis treatment at ART initiation and 511 did not. By 12 months after ART, 154 patients had died, 50% of whom died within 3 months (21 in the non-CTX group *vs* 56 in the CTX group). Over half the patients were male (54.2%; 58% were infected through plasma donation. Nearly half of the patients (44.2%) were aged between 35 and 54 years (Table 1). Overall, 5.6% had a history of active TB one year prior to ART initiation. A majority (78.9%) had a CD4 count <200 cells/μl at ART initiation. The CTX group had a higher percentage of patients with baseline CD4 count <200 cells/μl (80.8%) than the non-CTX group (71%). The median baseline CD4 count was 91 cells/μl and 132 cells/μl for the CTX group and the non-CTX group, respectively. There

were no significant differences between the two groups in gender, age at ART initiation, proportion with TB history, and transmission route.

Overall mortality at 3-months after ART initiation was nearly doubled that at 12-months (12.4 per 100 PY *vs* 6.3 per 100 PY, $p<0.01$). Univariate analyses demonstrated that patients who were male, aged ≥55 at ART initiation, or had a history of TB prior to ART treatment had a higher probability of death. Patients with a baseline CD4 count < 50 cells/μl had a higher risk of death within one year of treatment. Transmission route was not related to patients' survival. The Kaplan-Meier curve (Fig. 1) showed that patients receiving CTX had higher survival than those without prophylaxis, although this was not statistically significant (log rank =1.14, $p = 0.285$).

The 3-month mortality was 11.3 per 100 PY for patients on CTX at ART initiation and 16.8 per 100 PY for those not on CTX. The 12-month mortality was lower than the 3-month mortality, with 6.1 per 100 PY for the CTX group compared to 7.4 per 100 PY for the non-CTX-group. While these differences were not statistically significant before adjustment, after controlling for other variables, patients who took CTX at ART initiation were less likely to die at one year after ART treatment (AHR: 0.65, 95% CI: 0.44 – 0.95; $p = 0.027$) compared to those who did not take CTX (Table 2). This protective effect was stronger at 3 months after ART initiation (AHR: 0.53, 95% CI: 0.32 – 0.89; $p = 0.017$). Other factors significantly associated with increased risk of death at both at 3-months and 12-months after ART initiation were male sex (3-month mortality AHR 1.99, 95% CI 1.20 – 3.31, $p=0.008$; 12-month mortality AHR 1.56, 95% CI 1.11 – 2.20, $p=0.011$) and TB history in the past year (3-month mortality AHR 3.62, 95%CI 2.00 – 6.54, $p<0.001$; 12-month mortality AHR 2.59, 95% CI 1.63 – 4.14, $p<0.001$). Age ≥55 years at ART initiation was associated with an increased mortality only at 12-months after treatment (AHR 2.21, 95%CI 1.24 – 3.95, $p=0.007$). Higher CD4 cell counts at ART initiation was an independent beneficial factor to patients' survival. Patients with baseline CD4 count of 200 cells/μL or more had a nearly 80% reduction in death both at 3-months and 12-months after ART initiation, compared with those with CD4 count < 50 cells/μL at baseline (3-month AHR 0.22, 95% CI 0.10 – 0.53, $p<0.001$; 12-month AHR 0.21, 95% CI 0.12 – 0.39, $p<0.001$). The protective effect of baseline CD4 count of 50–199 cells/μL was weaker but was still associated with a more than 50% decline both in 3-month and 12-month mortality compared with persons with a baseline CD4 count <50 cells/uL (3-month AHR 0.48 95%CI 0.29 – 0.78, $p<0.001$; 12-month AHR 0.36 95%CI 0.25 – 0.52, $p<0.001$).

DISCUSSION

We found CTX prophylaxis provided an approximately 35% reduction in mortality in the first year of ART among HIV-infected individuals in central China. This result is slightly lower than but consistent with what has been previously reported. Currently there is limited information evaluating the effect of CTX prophylaxis on mortality among HIV-infected patients receiving ART in China. Most publications on CTX prophylaxis in the Asia-Pacific region are from Cambodia and Thailand [28, 29]. Our study provides additional evidence in the region and highlights the benefit of promoting CTX prophylaxis in conjunction with ART to reduce mortality among HIV patients on ART.

Another important finding was that the protective effect of CTX was particularly strong in the first 3 months after ART initiation with a 47% reduction in mortality compared to those not on CTX. Many studies demonstrate that the first three months after ART initiation is a critical period. Lowrance *et al*. reported that a third to half of deaths occurred within three months of ART initiation [17]. Zhang *et al.* showed that mortality (22.6 per 100 PY) was greatest during the first three months of treatment [7]. In Zambia 71% of deaths after initiating ART occurred within 90 days of ART initiation, with an early mortality of 26.0 per 100 PY [30]. Similarly, our study found exactly half of the deaths occurred in the first three months. This high mortality shortly after ART initiation may be mainly attributed to untreated AIDS rather than the immune reconstitution inflammatory syndromes [7].

In our study, we demonstrated that CTX prophylaxis decreased 3-month mortality after ART by nearly half. This is consistent with previously reported data. Walker *et al*. showed mortality among patients on ART with daily CTX prophylaxis was more than halved at 3 months of treatment compared with those not on CTX [18]. The survival difference in the Lowrance paper was apparent as early as 40 to 45 days after ART initiation [17]. A substantial proportion of patients in our cohort had already progressed to advanced HIV with a median CD4 count <200 cells/μl at ART initiation. Even though ART was initiated, these patients were at a high risk for death. Their immune system was being under restoration during the initial ART period and was similar to those not on ART. The beneficial effect of CTX prophylaxis in reducing the risk of death among those patients who have only recently initiated ART was similar to those patients who were not on ART. Although the baseline median CD4 count was lower in the CTX group than that in the non-CTX group (100 cells/μl *vs*130 cell/μl), the risk of death associated with lower baseline immune function was compensated for by CTX prophylaxis.

However, our study has three limitations that need to be considered. First, the majority of participants (58.5%) contracted HIV through commercial plasma donation. This is a manifestation of the unusual nature of the local HIV epidemic in Henan Province. According to the recent Chinese HIV epidemic report unprotected sexual contact is becoming the major transmission route of HIV infections with 46.5% by heterosexual and 17.4% by homosexual contacts, respectively [1]. Therefore, the subjects in our study are not representative of the HIV-infected population in other parts of the country. It is possible that the survival of HIV infected people in Henan Province might be different from those who acquired the infection through sexual transmission since patients in this analysis who were infected by plasma donation in the early 1990s [24] survived without initiating ART for several years until 2003 when ART began to be available in China. However, in the multivariable analysis, we did not identify statistically significant differences in impact of CTX prophylaxis on 3-month or 12-month mortality among different transmission groups. The conclusion of our study provided strong evidence in China to support to scale up CTX prophylaxis together ART to reduce mortality among patients who are eligible for treatment.

Second, CTX adherence was not documented in our study. We used ART dosage as a proxy for overall medication adherence (Table 2), but this may not accurately reflect the adherence to CTX prophylaxis. Last, only information on CTX prophylaxis at ART initiation was collected. Initiating CTX prophylaxis at any time during ART treatment, given that the

criteria for CTX prophylaxis are met, may bring benefits to patients. Some patients may have initiated CTX prophylaxis after ART initiation and been miscategorized as not on CTX in our study. This could lead to an underestimation of the effect of CTX prophylaxis.

Our study demonstrated that CTX significantly reduced the mortality of HIV patients within the first 12 months after ART initiation in Henan Province, China with the strongest impact during the first 3 months. Overall uptake of OI prophylaxis and treatment among eligible HIV-infected individuals in China is low. In 2006, the World Health Organization (WHO) recommended providing CTX prophylaxis to all HIV patients with CD4 count < 350 cells/μl or with WHO clinical stages 2, 3 or 4 disease [31]. However, China is still using the earlier criteria of CD4 count ≤200 cells/μl or WHO clinical 3 or 4 disease [23]. Although our study did not differentiate the effect of CTX prophylaxis in person with CD4 count <350 cells/μl *vs* <200 cells/μl, we would like to recommend updating the Chinese recommendations to be consistent with the current WHO recommended guidelines which suggest initiating CTX prophylaxis at CD4 counts <350 cells/μl. This recommendation not only targets prevention of OIs like *Pneumocystis jiroveci pneumonia* (PCP) and toxoplasmosis but also enteric bacterial infections and isosporiasis and malaria even though there is limited information on these infections among HIV/AIDS patients in China.

Given the consistent results in the literature, CTX prophylaxis, in addition to ART, should be promoted nationwide to all eligible HIV-infected individuals-- both adults and children. This may help to achieve the national goal of reducing HIV-associated mortality by 30% by 2015. More studies are needed to investigate factors that may hinder provision and uptake of CTX prophylaxis, as well as the optimal duration for CTX. To improve CTX prophylaxis monitoring, it is important to add a CTX prophylaxis component in the current web-based HIV case reporting system in China rather than only in the NFATP database.

Acknowledgments

Qian Zhu, Marc Bulterys, Liming Wang and Xiaoyu Wei designed the study. Qian Zhu, Liming Wang and Wen Lin wrote the first draft. Wenjie Yang conducted data analysis. Marc Bulterys and Jonathan Kaplan provided comprehensive review and critical comments during the manuscript development. All authors contributed to subsequent drafts. All authors have read and approved the final draft. The authors thank Dr. Guodong Mi and Dr. Hao Zhu for assistance with data analysis and Dr. Chin-Yih Ou for editorial assistance.

The Global AIDS Program China Office of U.S Centers for Disease Control and Prevention provided funding for the study, project number is 5U2GPS001188.

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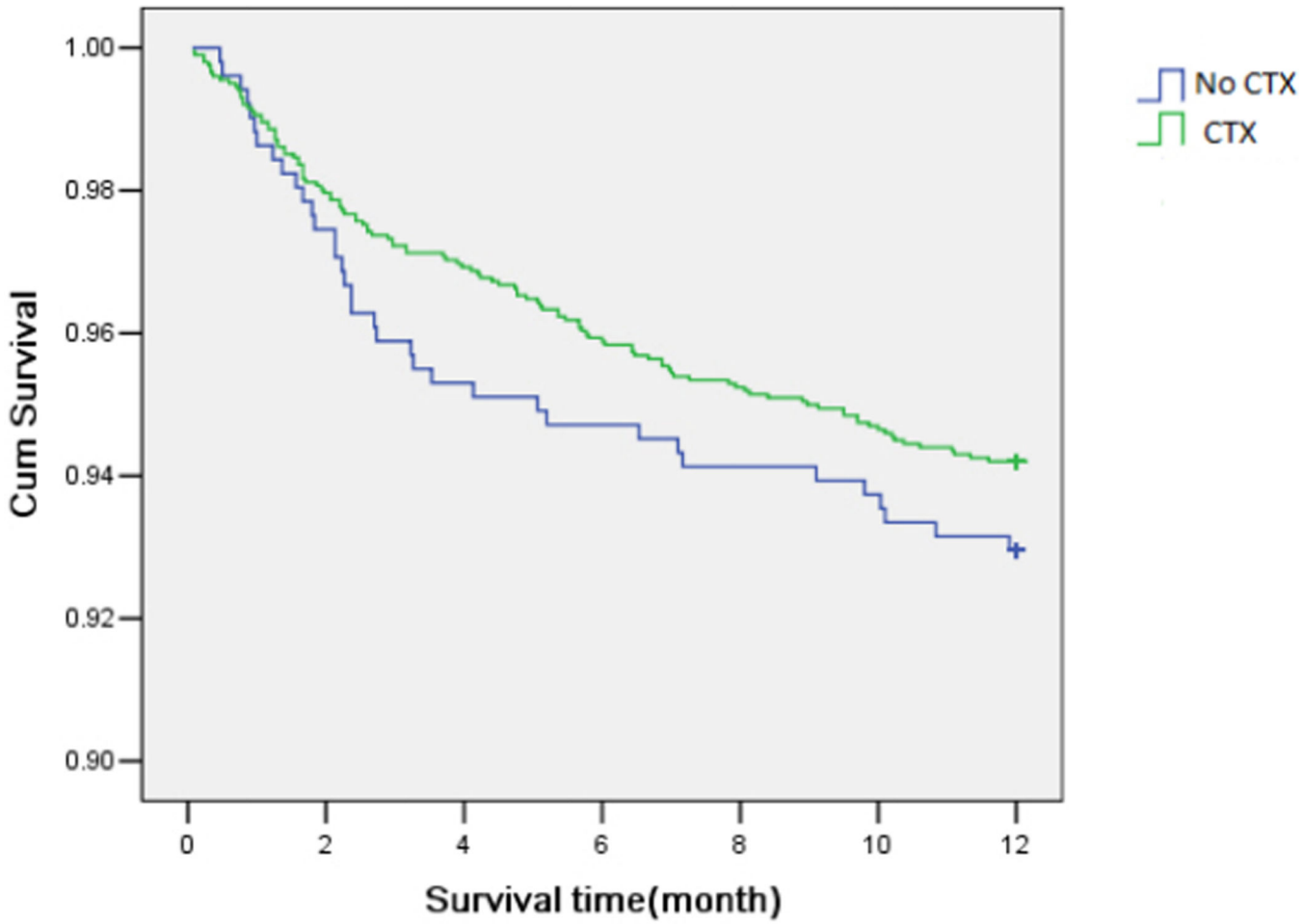

Fig. (1).

Kaplan-Meier survival curve for patients on ART* receiving CTX[#] compared with patients on ART not receiving CTX[#] (log rank = 1.14, df=1; $p = 0.285$).

Table 1

Characteristics of 2,529 HIV Infected Individuals enrolled in the study in Henan Province, 2008–2010.

Characteristics		No CTX at ART Initiation (n=511)		On CTX at ART Initiation (n=2,018)		*p-Value*
		N	%	N	%	
Gender	Female	251	49.1	908	45.0	0.100
	Male	260	50.9	1,110	55.0	
Age at ART initiation	15–34	73	14.3	323	16.0	0.400
	35–44	237	46.4	882	43.7	
	45–54	141	27.6	534	26.5	
	55+	60	11.7	279	13.8	
Transmission route	Plasma Donation	305	59.7	1,174	58.2	0.878
	Blood Transfusion	94	18.4	372	18.4	
	Heterosexual	84	16.4	362	17.9	
	Unknown	28	5.5	110	5.5	
Missing ART dosage in last 7 days	No	506	99.0	1,979	98.1	0.141
	Yes	5	1.0	39	1.9	
TB history in past year	No	489	95.7	1,899	94.1	0.161
	Yes	22	4.3	119	5.9	
CD4 at ART initiation	<50	161	31.5	745	36.9	0.000
	50~199	202	39.5	886	43.9	
	≥200	148	29.0	387	19.2	
Status at 3 months	Alive on ART	482	94.3	1,946	96.4	0.078
	Lost to follow up	0	0.0	0	0.0	
	Stopped completely	8	1.6	16	0.8	
	Dead	21	4.1	56	2.8	
Status at 12 months	Alive on ART	466	91.2	1,859	92.1	0.615
	Lost to follow up	3	0.6	20	1.0	
	Stopped completely	6	1.2	21	1.0	
	Dead	36	7.1	118	5.9	
ART enrollment year	2008	210	41.1	582	28.8	

Characteristics		No CTX at ART Initiation (n=511)		On CTX at ART Initiation (n=2,018)		*p-Value*
		N	%	N	%	
	2009	199	38.9	766	38.0	0.000
	2010	102	20.0	670	33.2	

Abbreviations: ART: antiretroviral therapy; CTX: Co-trimoxazole.

Table 2

Factors Associated with Mortality of HIV-infected Individuals on ART in Henan Province, 2008–2010.

Characteristics		3-Month Mortality					12-Month Mortality				
		Death (D)	Person Years (PY)	Mortality (D/PY, Per 100 PY)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Death (D)	Person Years (PY)	Mortality (D/PY, Per 100 PY)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
CTX at enrollment	No	21	125.28	16.8	1.0	1.0	36	486.58	7.4	1.0	1.0
	Yes	56	497.07	11.3	0.67 (0.41 – 1.11)	0.53 (0.32 – 0.89)	118	1942.48	6.1	0.82 (0.56 – 1.19)	0.65 (0.44 – 0.95)
Gender	Female	21	287.00	7.3	1.0	1.0	50	1128.23	4.4	1.0	1.0
	Male	56	335.23	16.7	2.28 (1.38 – 3.77)	1.99 (1.20 – 3.31)	104	1300.83	8.0	1.78 (1.27–2.49)	1.56 (1.11–2.20)
Transmission Route	Plasma Donation	44	364.42	12.1	1.0	1.0	87	1423.58	6.1	1.0	1.0
	Blood Transfusion	11	114.91	9.6	0.79 (0.41– 1.54)	0.69 (0.35 – 1.35)	26	449.80	5.8	0.96 (0.62 – 1.49)	0.88 (0.56–1.37)
	Heterosexual	18	108.85	16.5	1.37 (0.79 – 2.37)	1.47 (0.84 – 2.58)	33	422.18	7.8	1.29 (0.86 – 1.93)	1.36 (0.91– 2.05)
	Unknown	4	34.18	11.7	0.97 (0.35 – 2.69)	0.75 (0.26 – 2.15)	8	133.48	6.0	0.99 (0.48 – 2.05)	0.79 (0.38 – 1.65)
Missed ART dose in last 7 days	No	75	615.76	12.2	1.0	1.0	150	2387.41	6.3	1.0	1.0
	Yes	2	6.60	30.3	2.50 (0.61– 10.16)	1.95 (0.47 – 8.14)	4	41.64	9.6	1.53 (0.57 – 4.13)	1.71 (0.63– 4.66)
TB history in past year	No	63	589.20	10.7	1.0	1.0	133	2303.02	5.8	1.0	1.0
	Yes	14	33.16	42.2	3.95 (2.2 – 7.04)	3.62 (2.00 – 6.54)	21	126.04	16.7	2.88 (1.82 – 4.56)	2.59 (1.63– 4.14)
CD4 count at ART initiation	<50	46	219.91	20.9	1.0	1.0	97	842.36	11.5	1.0	1.0
	50–199	25	269.32	9.3	0.44 (0.27 – 0.72)	0.48 (0.29 – 0.78)	44	1060.35	4.1	0.36 (0.25 – 0.51)	0.36 (0.25 – 0.52)
	≥200	6	133.13	4.5	0.22 (0.09 – 0.51)	0.22 (0.10 – 0.53)	13	526.34	2.5	0.22 (0.12 – 0.39)	0.22 (0.12 – 0.39)
Age at ART initiation	15–34	13	97.22	13.4	1.0	1.0	20	380.74	5.3	1.0	1.0
	35–44	36	274.78	13.1	0.98 (0.52 – 1.85)	1.06 (0.55 – 2.03)	67	1072.80	6.2	1.19 (0.72 – 1.96)	1.31 (0.79 – 2.18)
	45–54	13	167.19	7.8	0.58 (0.27 – 1.26)	0.67 (0.31– 1.47)	38	655.24	5.8	1.07 (0.62 – 1.85)	1.29 (0.74 – 2.25)

Characteristics	3-Month Mortality						12-Month Mortality				
		Death (D)	Person Years (PY)	Mortality (D/PY, Per 100 PY)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Death (D)	Person Years (PY)	Mortality (D/PY, Per 100 PY)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	55+	15	83.17	18.0	1.35 (0.64 – 2.83)	1.72 (0.80 – 3.66)	29	320.27	9.1	1.71 (0.97 – 3.03)	2.21 (1.24 – 3.95)
ART enrollment year	2008	26	195.16	13.3	1.0	1.0	46	761.42	6.0	1.0	1.0
	2009	19	238.79	8.0	0.60 (0.33– 1.08)	0.58 (0.32 – 1.06)	44	938.30	4.7	0.78 (0.52 – 1.18)	0.76 (0.50 – 1.15)
	2010	32	188.41	17.0	1.28 (0.76 – 2.14)	1.19 (0.69 – 2.04)	64	729.33	8.8	1.43 (0.98 – 2.09)	1.33 (0.90 – 1.07)

Abbreviations: ART: antiretroviral therapy; CTX: Co-trimoxazole; CI: Confidence Interval; HR: Hazard Ratio; TB: Tuberculosis.