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Antiretroviral Therapy Initiation during Tuberculosis Treatment and HIV-RNA and CD4-T Lymphocyte Responses

Simbarashe Takuva^{1,4}, Daniel Westreich², Colin N. Menezes³, Lynne McNamara¹, Ian Sanne^{1,4}, Liesl Page-Shipp⁴, and Mhairi Maskew¹

¹Clinical HIV Research Unit, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, South Africa

²Department of Obstetrics & Gynecology, Duke Global Health Institute, Duke University, Durham, North Carolina, USA

³Infectious Diseases Unit, Department of Medicine, Helen Joseph Hospital, University of the Witwatersrand, South Africa

⁴Right to Care, Johannesburg, South Africa

Abstract

Setting and Objective—We examined the effect of initiating ART on CD4 and viral response at different time periods during TB therapy (< 14 days; 15–60 days; or > 60 days) using prospectively collected clinical data from a large HIV clinic in South Africa.

Methods—Cohort data analysis for 1499 TB/HIV co-infected patients classified according to timing of ART after the initiation of TB therapy.

Results—In adjusted modified Poisson regression models, CD4 and viral responses showed no significant differences according to timing of ART initiation (failure to increase CD4 by 6 months, <14 days vs. >60 days: RR 1.02 (95% CI 0.85–1.22), 15–60 days vs. >60 days: RR 1.00 (95% CI 0.86–1.15); failure to suppress virus by 6 months, <14 days vs. >60 days: RR 0.98 (95% CI 0.59–1.63), 15–60 days vs. >60 days: RR 0.96 (95% CI 0.66–1.41) and viral rebound at 12 months, 14 days vs. >60 days: RR 1.43 (95% CI 0.50–4.12), 15–60 days vs. >60 days: RR 1.14 (95% CI 0.39–3.34). Similar estimates were found in analysis restricted to patients with severe immunosuppression.

Conclusion—Concerns over the overlapping impact of TB treatment with ART on ART response should not be a reason to delay ART in patients with HIV-associated TB.

Keywords

Timing of ART; CD4 response; Viral response; TB–HIV co-infection

Corresponding Author: Simbarashe Takuva, MBChB, MSc., Clinical HIV Research Unit (CHRU), Department of Medicine, University of the Witwatersrand, Helen Joseph Hospital, P Bag X2600, Houghton 2041, South Africa, Tel: +27112768800; stakuva@witshealth.co.za.

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INTRODUCTION

Mycobacterium tuberculosis (TB) is an important cause of disease progression and death in HIV-infected patients and is estimated to cause more than 60%–70% of all HIV related morbidity and mortality in Southern Africa [1–4]. Antiretroviral Therapy (ART) has proven to successfully reduce the morbidity and mortality from HIV and related opportunistic infections, including TB [4–11].

Overlapping drug toxicities, drug-drug interactions, the risk of developing immune reconstitution syndrome and pill burden may complicate the treatment of HIV-TB co-infected patients [7,12–14]. There have been concerns over pharmacokinetic drug interactions, increased treatment interruptions due to drug intolerance and co-toxicity and variable drug absorption especially between efavirenz and rifampicin. It has been surmised that if these drugs are initiated simultaneously it might lead to suboptimal drug levels resulting in treatment failure or poor treatment outcomes [15–17]. These concerns may complicate or delay the initiation of ART for patients on TB treatment. However, deferring ART among patients on TB treatment may result in faster HIV disease progression and an increased risk of mortality from both infections [3, 5].

In order to inform public health strategies on the management of TB-HIV co-infection, understanding whether the initiation of ART soon after beginning TB medication compromises response to ART is critical. Observational studies and recently, four randomised clinical trials (the SApiT, CAMELIA, the Vietnam TB Meningitis and ACTG 5221 STRIDE clinical trials) that have demonstrated significant reduction or no increased risk of mortality with earlier initiation of ART in these patients [18–24]. These studies further showed no differences in immune and viral responses during follow-up among TB-HIV co-infected patients initiating ART at different times.

We analysed prospectively collected cohort data for HIV-infected patients initiating ART at the Themba Lethu Clinic (TLC), Johannesburg, South Africa, between 01 April 2004 and 31 March 2009 to examine whether the different timing of ART initiation during TB treatment has an impact on early immune and viral responses to first-line ART.

METHODS

Study setting and clinic protocols

This study was conducted in the Themba Lethu Clinic (TLC) in urban Johannesburg, South Africa. The TLC is a cohort of adults initiating ART at one of the largest public clinics providing ART in South Africa. It is adjacent to the TB focal point (TBFP) allowing for easy collaboration and access to HIV and TB services. The TBFP focuses on diagnosis of all forms of TB and prompt initiation of treatment, while also providing simultaneous investigation of HIV co-infection. In addition to its role in TB/HIV collaborative activities, TB patients are referred to the primary health care clinics for continuation of treatment [25, 26]. At the TLC, newly TB diagnosed patients are initiated on a 2 month intensive phase consisting of 600 mg rifampicin (RIF) if patient weight > 55 kg and 450 mg if weight ≤ 55 kg, isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETH) in fixed dose combinations and later on a continuation phase lasting 4 months (consists of RIF and INH). During the course of the study, the South African Department of Health Tuberculosis Treatment guidelines, 2009 were in force [27]. If the client had CD4 count of 50–200 cells/mm³, ART was initiated after completing 2 months of TB treatment. However, if the patient had a CD4 count of < 50 cells/mm³ or other serious HIV-related illness, they completed at least two weeks of TB treatment and then initiated ART.

On initiating ART, most patients start on a combination of efavirenz (EFV), lamivudine (3TC) and stavudine (d4T), a minority of patients initiate with nevirapine or ritonavir-boosted lopinavir rather than EFV. Clinical and laboratory data are collected at all scheduled visits, except for viral load which is not collected at baseline. All data are stored in the Therapy-Edge-HIV™ database.

Eligibility and definitions

We analysed data from ART-naïve adults who initiated ART at the TLC after starting TB treatment between 01 April 2004 and 31 March 2009, and followed up until an event, a competing risk (death or loss to follow-up), or administrative censoring on 31 March 2010. All subjects had baseline CD4 ≥ 350 cells/mm³ and initiated standard first line ART regimens, chiefly d4T-3TC-EFV and d4T-3TC-NVP. Pregnant women were excluded from this study. The main exposure was time of ART initiation after initiation of TB treatment. Patients were classified into three categories: 1) those initiating ART within 14 days of starting TB treatment; 2) those initiating ART between 15–60 days of starting TB treatment; and 3) those initiating ART after at least 60 days of TB treatment.

The measured study outcomes were 1) failure to achieve a CD4 count increase of ≥ 50 cells/mm³ by 6 months after ART initiation; 2) failure to achieve viral suppression 6 months after ART initiation; and 3) viral rebound at 12 months after ART initiation. Viral suppression was defined as achieving a viral load < 400 copies/ml within 6 months of initiating ART. Viral rebound was defined as a viral load measurement ≥ 400 copies/ml at 12 months following initial virologic suppression by 6 months. Additionally, we also defined viral rebound as a measurement of ≥ 1000 copies/ml at 12 months after successful suppression by 6 months.

Statistical analyses

Differences in categorical variables were compared using the Pearson's chi-squared test. Continuous variables were compared by using the Mann-Whitney U test. We used modified Poisson regression models with the robust error variance to estimate the adjusted relative risk (RR) and 95% confidence intervals for the study outcomes [28]. All analyses were done in STATA v.11 (STATA Corp., College Station, TX, USA). The analyses were repeated after stratifying according to the degree of immunosuppression at initiation of ART (CD4 < 50 cells/mm³ vs. CD4 ≥ 50 cells/mm³). To examine the impact of potential selection bias due to missing outcome data (CD4 counts at 6 months and viral load counts at 6 and 12 months), we conducted sensitivity analyses in which we made two different assumptions: 1) that all deaths and LTFU were failure events (i.e. failure to achieve viral suppression, CD4 count response within 6 months and viral rebound at 12 months), and 2) that only death was a failure event and LTFU events were random.

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) and permission to access patient information was obtained from the Superintendent of the Helen Joseph Hospital.

RESULTS

Characteristics of study cohort

Between 01 April 2004 and 31 March 2009, 2120 patients were initiated on ART while on TB treatment at the TLC. Of these, 332 were excluded from the analysis for the following reasons (pregnant, not on standard first-line ART regimens and age < 18 years) and a further 289 patients were excluded for missing laboratory outcome information. This left a total of 1499 patients eligible for analysis. Of these patients, 14.6% (n=219) initiated ART within 14

days of starting TB treatment; 38.6% (n=579) initiated within 15–60 days; and 46.8% (n=701) initiated after 60 days. Median time to ART initiation after beginning TB treatment was 56 days (IQR 28–99 days). Baseline characteristics of these patients are summarized by exposure category in Table 1. Largely, baseline characteristics did not differ by exposure category except for that patients who initiated ART at least after 60 days were likely to have higher CD4 counts than those that were initiated earlier.

By the end of the 12 month follow-up period, 121 patients (8.1%) had died and 200 patients (13.3%) had been lost to follow-up (LTFU); these proportions did not differ by exposure category (Table 1).

In order to understand if there were any significant differences between analysed patients and those excluded for missing laboratory data, we compared the baseline characteristics between these patients. The baseline characteristics were generally similar (Table 2).

Below we present results for each of the three outcomes considered; results are summarized in Table 3.

Effect of timing of ART initiation on CD4 response at 6 months

The proportions of patients failing to achieve absolute CD4 increases ≥ 50 cells/mm³ were similar among the 3 groups; 0–14 days: 44.2%, 15–60 days: 40.8%, and ≥ 60 days: 45.2%. In the adjusted multivariate models (adjusted for CD4 cell count, employment status, BMI and age at initiation), there were no significant differences observed on the outcome according to the different times of ART initiation (however the 95% confidence intervals were relatively wide). The relative risks for failure to achieve CD4 increase ≥ 50 cells/mm³ were as follows: 0–14 days vs. ≥ 60 days: risk ratio (RR) 1.02; 95% confidence interval (CI): 0.85–1.22, 15–60 days vs. ≥ 60 days: RR 1.00; 95% CI: 0.86–1.15.

Effect of timing of ART initiation on viral suppression at 6 months

The proportions failing to achieve virologic suppression after 6 months on ART were similar among the 3 groups: 0–14 days: 12.8%, 15–60 days: 10.3%, and ≥ 60 days: 11.3%. After adjusting for the CD4 count, ALT level, employment status, age and gender, the relative risk estimates for initiating ART during the different time periods on failure to suppress viral load at 6 months were similar, although the 95% confidence intervals were also relatively wide. These adjusted estimates were as follows: 0–14 days vs. ≥ 60 days, RR 0.98 (95% CI: 0.59–1.63) and for 15–60 days vs. ≥ 60 days, RR 0.96 (95% CI: 0.66–1.41).

Effect of timing of ART initiation on viral rebound at 12 months

After 6 months on therapy, 1077 patients (89.8%) had a fully suppressed viral load, of which 823 viral load measurements were available at 12 months. Of these, 38 patients (4.6%) had viral rebounds ≥ 400 copies/ml. Of the patients with viral rebound ≥ 400 copies/ml at 12 months, 3.6% (n=4) were in the group that initiated ART within 0–14 days, 5.4% (n=18) in the 15–60 days group and 4.2% (n=16) in the group that initiated ART at least 60 days after beginning TB treatment. After adjusting for the age at initiation, the relative risk estimates were too imprecise to draw any valid conclusions (0–14 days vs. ≥ 60 days, RR 1.14 (95% CI: 0.39–3.34) and 15–60 days vs. ≥ 60 days, RR 1.43 (95% CI: 0.50–4.12), but there was no evidence of a strong effect of different timing of ART on viral rebound. The risk estimates showed similar trend when we used viral rebound definition of ≥ 1000 copies/ml (0–14 days vs. ≥ 60 days, RR 0.93 (95% CI: 0.31–2.77) and 15–60 days vs. ≥ 60 days, RR 1.28 (95% CI: 0.44–3.78).

Effect of timing of ART initiation on outcomes among severely immunosuppressed patients

We further examined these outcomes in an analysis restricted only to patients with severe immunosuppression (CD4 count at initiation <50 cells/mm³). The proportions of patients in this subgroup failing to achieve the defined CD4 response, failure to achieve viral suppression by 6 months and viral rebound at 12 months (both definitions) were similar among the 3 groups. The adjusted risk estimates for this analysis were similar to those of the main analysis. These results are shown in Table 4.

Results of Sensitivity analyses

In the first sensitivity analysis, we assumed that both death and LTFU were failure events, whereas in the second, we assumed that only death was a failure event. The adjusted RR estimates for both sensitivity analyses showed the same trend in risk for both outcomes in comparison to those computed in the main analysis, and the 95% CIs still remained wide. These results are shown in Table 4. These results suggest that, if any selection bias was present, the adjusted RR estimates were not significantly affected.

DISCUSSION

In this cohort study of HIV infected patients on TB treatment, immune and viral responses at 6 and 12 months did not show any significant association with the timing of ART initiation. Similar results were demonstrated when we restricted the same analysis to patients with severe immunosuppression (baseline CD4 count <50 cells/mm³). These findings from routinely collected clinical data in a typical resource-limited treatment setting outside the clinical trial environment further add to the body of knowledge of understanding the impact of differential timing of ART-TB co-treatment on clinical outcomes.

There have been concerns that the pharmacokinetic interactions of ART and anti-TB drugs and increased risk of treatment interruptions might result in sub-optimal drug levels and, hence, an increased risk of poor immune and viral outcomes. Our findings are in agreement with recently reported data from the SAPIt and the STRIDE clinical trials [21, 23]. In the SAPIt and STRIDE trials, viral suppression (<400 copies/ml) at 48 weeks did not differ between these arms that had initiated ART at different times. Observational studies have also shown that excellent viral outcomes are achievable using EFV-based ART and that these do not differ when compared to responses among non-TB patients receiving the same ART regimen. In a very large analysis by Boulle A et al (2008), viral outcomes were comparable when starting EFV-based antiretroviral therapy (vs. without concurrent tuberculosis) or when tuberculosis developed while taking established NVP- or EFV-based therapies but were inferior when NVP-based antiretroviral therapy was commenced while taking anti-TB treatment (vs. without concurrent tuberculosis) [29]. Our findings also concur with results of an observational study reported by Lawn and co-workers in which they showed that viral loads were suppressed to <400 copies/ml in $>94\%$ of patients, whether the patients received concurrent treatment containing Rifampicin or not [30].

Similarly, Breen and co-workers in a UK case-control study reported similar findings [31]. However in a study of HIV-infected children receiving TB treatment in Johannesburg, South Africa, researchers found that a delay of 30 days or less in starting ART had no effect on viral response (and mortality), but however a delay by more than 60 days lowered the hazards of viral suppression [20].

It has been shown that co-administration of rifampicin reduces the plasma concentrations of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and this pharmacokinetic interaction has resulted in researchers exploring the use of increased doses of either NNRTI

(NVP or EFV)^[32–34]. In this study, most patients (over 95%) were on the standard 600 mg EFV dose. A randomized trial in Thailand did show that standard doses of 600 mg EFV compared to 800 mg adjusted doses did not result in inferior viral outcomes at 48 weeks ^[32].

The study has a number of limitations. First, self selection could lead to systemic bias in determining who ended in each of the 3 groups –e.g. those who are most ill may start the latest on ART. Also, left truncation may potentially bias our results; our inferences are conditional, based on the patient having survived from initiation of TB therapy until the time of initiation of ART. For every person who started TB treatment and ART, there are other patients who may have started TB treatment but died before starting ART; thus, for example, the group who waited 60 days may be enhanced for survivors. Also, the definition of viral rebound as > 400 copies/ml without confirmation i.e. serial viral load measurements or resistance testing may have resulted in a mixture of viral blips and true viral failure being classified as viral rebound. This may have pushed the risk estimates towards the null. Lastly, missing outcome data could have introduced selection bias; however, our sensitivity analysis (Figures 1a, 1b, 1c) addressed these questions. The results of this sensitivity analysis suggest that the missing data was unlikely to qualitatively change our conclusions in this study.

The main strength of this study is its applicability to the real life clinical setting. We used prospectively collected routine programme data on HIV care in a setting with high HIV-TB prevalence; these results are applicable to patients attending treatment programmes in resource limited settings, especially in sub-Saharan Africa. In this population, a significant proportion of the patients use EFV containing regimens and most initiate rifampicin-based TB treatment, hence the ART and TB drug interactions (mainly EFV and rifampicin) are adequately represented.

CONCLUSIONS

In conclusion, these findings from routinely collected clinical data in a resource-limited setting further adds to the current body of knowledge and understanding that concurrent use of TB drugs (containing rifampicin) and ART (containing EFV standard 600 mg dose) does not jeopardize viral and immune responses to ART. Our findings further add weight to recent recommendations that ART should not be delayed in patients with TB ^[35]. However, more studies are needed to continue a detailed explanation of the effect of initiating ART at different time periods on other important clinical outcomes such as IRIS, drug adherence and toxicity.

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Table 1

Characteristics of study cohort at initiation and end of follow-up by time delay among patients initiating ART between April 2004 and March 2009 at the Themba Lethu Clinic, Johannesburg, South Africa.

Characteristics at initiation of ART	Timing of ART			p-value
	0–14 days n=219 (14.6%)	14–60 days n=579 (38.6%)	60 days n=701 (46.8%)	
Age, years; median (IQR)	36 (31–42)	35 (31–41)	36 (31–41)	0.60
Male, n (%)	110 (50.2%)	254 (43.9%)	294 (41.9%)	0.10
Employed, n (%)	86 (39.3%)	213 (36.8%)	260 (37.1%)	0.80
Alcohol, n (%)	19 (8.7%)	45 (7.8%)	80 (11.4%)	0.08
Smoking, n (%)	20 (9.1%)	46 (7.9%)	75 (10.7%)	0.24
Black, n (%)	205 (93.6%)	560 (96.7%)	666 (95%)	0.12
WHO stage IV, n (%)	57 (26.1%)	123 (21.2%)	146 (21.3%)	0.49
EFV-3TC-d4T, n (%)	202 (92.2%)	536 (92.6%)	619 (88.3%)	0.09
Pulmonary TB, n (%)	210 (95.9%)	553 (95.5%)	664 (94.7%)	0.96
CD4 count; median (IQR)	45 (14–108)	42 (18–89)	70 (30–126)	< 0.001
<50 cells/mm ³ , n (%)	117 (53.4%)	310 (53.5%)	264 (37.7%)	
50–200 cells/mm ³	93 (42.5%)	255 (44%)	400 (57.1%)	
>200 cells/mm ³	9 (4.1%)	14 (2.4%)	37 (5.3%)	
Hb, g/dl; median (IQR)	10.2 (8.5–11.5)	10.0 (8.8–11.4)	11.0 (9.6–12.3)	0.37
<10 g/dl, n (%)	103 (47%)	275 (47.5%)	214 (30.5%)	
10 g/dl, n (%)	116 (53%)	304 (52.5%)	487 (69.5%)	
BMI, kg/m ² ; median (IQR)	20 (17.5–22.4)	19.6 (17.6–22)	20.4 (18.3–23.2)	0.11
Status by end of follow-up				
Lost to follow-up, n (%)	33 (15.1%)	71 (12.3%)	96 (13.7%)	0.13
Died, n (%)	21 (9.6%)	53 (9.2%)	47 (6.7%)	0.19

Hb, hemoglobin; BMI, body mass index; EFV, efavirenz; 3TC, lamuvidine; d4T, stavudine.

Table 2

Comparison of patients included in the analysis versus those excluded due to unavailability of 6 month CD4 and viral load results.

Characteristic	Viral load value by 6 months			CD4 count value by 6 months		
	Included n=1211	Excluded n=288	p-value	Included (n=1210)	Excluded (n=289)	p-value
Male	529 (43.7%)	129 (44.8%)	0.73	532 (44.0%)	126 (44.0%)	0.91
Age [†]	35.5 (31–40.7)	35.1 (30.5–42.2)	0.96	35.5 (31.0–40.7)	35.1 (30.3–41.4)	0.73
Employed	464 (38.3%)	95 (33.0%)	0.09	467 (38.6%)	92 (31.8%)	
Alcohol	112 (9.2%)	32 (11.1%)	0.34	113 (9.3%)	31 (10.7%)	0.47
Smoking	118 (9.7%)	23 (8.0%)	0.36	118 (9.8%)	23 (8.0%)	0.35
Black	1162 (96.0%)	267 (92.7%)	0.01	1160 (95.9%)	271 (93.8%)	0.12
Baseline CD4 [†]	56 (21–111)	52 (22–103)	0.31	57 (21–113)	51 (21–98)	0.06
Baseline Hb [†]	11 (9–12)	10 (9–12)	0.07	11 (9–12)	10 (9–11)	0.07
Baseline ALT [†]	24 (17–36)	25 (18–37)	0.50	24 (17–36)	24 (18–37)	0.28
Baseline BMI [†]	20.0 (18.1–22.5)	19.6 (17.7–22.3)	0.21	20.0 (18.1–22.4)	19.7 (17.6–22.7)	0.32
WHO stage IV	254 (21.0%)	75 (26.0%)	0.06	253 (20.9%)	76 (26.3%)	0.05
EFV-3TC-d4T	1101 (90.9%)	256 (88.9%)	0.29	1102 (91.1%)	255 (88.2%)	0.14
Pulmonary TB	1152 (95.0%)	275 (95.5%)	0.79	1147 (94.8%)	280 (96.9%)	0.14

All figures are N(%) except [†] are median (IQR).

CD4 in cells/mm³; ALT, alanine transferase; BMI, body mass index; TB, tuberculosis; Hb, hemoglobin; EFV, efavirenz; 3TC, lamivudine and d4T, stavudine

Table 3

Outcome estimates according to timing of ART among patients initiating ART between April 2004 and March 2009 at the Themba Lethu Clinic, Johannesburg, South Africa.

Timing (days)	Total (N)	Events n (%)	Crude RR (95% CI)	Crude RR (95% CI)
Failure to achieve CD4 increase ≥ 50 cell/mm³ by 6 months				
< 14	172	76 (44.2%)	1.02 (0.85–1.23)	1.02 (0.85–1.22)
15–60	463	189 (40.8%)	0.91 (0.79–1.04)	1.00 (0.86–1.15)
> 60	575	260 (45.2%)	1.	1.
Failure to suppress viral load (< 400 copies/ml) by 6 months				
< 14	171	21 (12.8%)	1.04 (0.65–1.67)	0.98 (0.59–1.63)
15–60	474	49 (10.3%)	0.96 (0.68–1.36)	0.96 (0.66–1.41)
> 60	566	64 (11.3%)	1.	1.
Viral rebound at 12 months (< 400 copies/ml)				
< 14	111	4 (3.6%)	1.17 (0.40–3.43)	1.14 (0.39–3.34)
15–60	333	18 (5.4%)	1.50 (0.52–4.34)	1.43 (0.50–4.12)
> 60	379	16 (4.2%)	1.	1.
Viral rebound at 12 months (< 1000 copies/ml)				
< 14	111	4 (3.6%)	0.95 (0.32–2.86)	0.93 (0.31–2.77)
15–60	333	16 (4.8%)	1.33 (0.46–3.91)	1.28 (0.44–3.78)
> 60	379	13 (3.4%)	1.	1.

RR, relative risk; 95% CI, 95% confidence interval.

Table 4

Results of the analysis restricted to patients with CD4 count < 50 cells/mm³ at initiation of ART and results of the sensitivity analyses among patients initiating ART between April 2004 and March 2009 at the Themba Lethu Clinic, Johannesburg, South Africa. All results are adjusted risk ratios.

	By 6 months		By 12 months	
	Failure to achieve CD4 increase 50 cell/mm ³	Failure to suppress viral load (< 400 copies/ml)	Viral rebound (>400 copies/ml)	Viral rebound (> 1000 copies/ml)
Patients with CD4 count < 50 cells/mm ³ at ART initiation				
<14 days	0.93 (0.66–1.31)	0.74 (0.39–1.41)	1.11 (0.22–5.54)	0.88 (0.17–4.59)
14–60 days	0.93 (0.67–1.30)	0.72 (0.39–1.34)	1.88 (0.43–8.25)	1.57 (0.35–7.12)
> 60 days	1.	1.	1.	1.
Sensitivity analyses 1: all deaths and LTFU are failure events				
<14 days	1.12 (1.00–1.26)	0.99 (0.81–1.22)	0.98 (0.78–1.24)	1.06 (0.53–2.11)
14–60 days	0.92 (0.81–1.05)	0.91 (0.73–1.12)	0.92 (0.73–1.17)	1.40 (0.75–2.61)
> 60 days	1.	1.	1.	1.
Sensitivity analyses 2: death was a failure event and LTFU events were random				
<14 days	1.14 (0.99–1.31)	1.02 (0.76–1.37)	1.11 (0.63–1.97)	0.99 (0.45–2.19)
14–60 days	0.94 (0.80–1.10)	1.06 (0.80–1.42)	1.45 (0.86–2.42)	1.34 (0.66–2.72)
> 60 days	1.	1.	1.	1.