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Adjusting the effect of integrating antiretroviral therapy and tuberculosis treatment on mortality for non-compliance: a time-varying instrumental variables analysis

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Abstract

Background: Using intent-to-treat (ITT) comparisons, it has been shown that the integration of antiretroviral therapy (ART) and tuberculosis (TB) treatment improves survival. Because the magnitude of the effect of ART initiation during TB treatment on mortality is less well understood due to non-compliance, we used instrumental variables (IV) analyses.

Methods: We studied 642 HIV-TB co-infected patients from the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial. Patients were assigned to start ART either early or late during TB treatment or after TB treatment completion. We used two-stage predictor substitution and two-stage residuals inclusion methods under additive and proportional hazards regressions with a time-fixed measure of compliance defined as the fraction of time on ART during TB treatment. We moreover developed novel IV methods for additive hazards regression with a time-varying measure of compliance.

Results: ITT results from additive hazards models showed that patients in the early integrated arms had a reduced hazard of −0.05 (95% confidence interval (CI): −0.09 to −0.01) when compared to the sequential arm. Adjustment for noncompliance changed this effect to −0.07 (95%

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Availability of data and code: Dataset and code will be made available upon request but access will be controlled and each request will be considered on a case by case basis.

CI: −0.12 to −0.01). An additional time-varying IV analysis on the overall effect of ART exposure suggested an effect of −0.29 (95 % CI: −0.54 to −0.03).

Conclusion: IV analyses enable assessment of the effectiveness of TB and ART integration, corrected for non-compliance, and thereby enable a better public health evaluation of the potential impact of this intervention.

Keywords

Additive hazards model; instrumental variable; non-compliance; time-varying exposure; HIV; TB

INTRODUCTION

In 2014, an estimated 1.2 million people were co-infected with tuberculosis (TB) and human immunodefiency virus (HIV), around 74% of them living in sub-Saharan Africa.[1] In some parts of South Africa, it is estimated that almost 70% of TB patients are co-infected with HIV.[2] South Africa has the largest antiretroviral therapy (ART) roll-out programme with approximately 3 million people on ART in 2015.[3] Despite the size of the ART roll-out and wide availability of TB treatment, TB and HIV are reported to be the leading causes of death in South Africa in the age-group 15 to 44 years.[4]

Initiation of ART within 4 weeks after the start of TB therapy or within 4 weeks after the completion of the intensive phase of TB therapy has been shown to improve survival,[5,6] especially among patients with low CD4+ cell count.[7,8] In South Africa, TB patients were the first ones to be initiated on ART irrespective of their CD4+ cell count.[9] Patients who develop TB while on ART should continue with ART throughout TB therapy duration. One of the studies that informed guidelines on treatment integration was the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial. SAPiT was an open-label randomized controlled trial (RCT) where patients were randomly assigned to start ART either early or late during TB treatment or after the completion of TB therapy. Irrespective of the randomization arm, patients in the SAPiT study could be started on ART at any time by study clinicians or personal physicians at their discretion. In the current analyses, non-compliance is defined as not starting ART at the correct time with respect to TB treatment, regardless of whether that was enforced by clinicians or by patients themselves.

However, this definition of non-compliance does not take into account any temporary or permanent discontinuation of study drugs as well as adherence. Among the 362 patients who initiated ART in early and late integrated arms of the SAPiT trial, 22.4% did not initiate ART at the correct time.[8] Moreover, following recommendations by data and safety monitoring committee, some patients started ART earlier than the protocol specified time[5] and are regarded as non-compliant.

To preserve the balance brought about by randomization, intent-to-treat (ITT) comparison was used for the primary analyses of the trial. This provides valid estimates of the effect of randomized assignment, but likely underestimates the effectiveness of treatment integration in the presence of non-compliance. To adjust for non-compliance, “as-treated” and “per-protocol” comparisons are commonly made. These contrast study participants according to

their received treatment, regardless of the treatment arm to which they were assigned, or limit the analysis to participants who followed the protocol. Such analyses are generally biased because the subgroups which they compare often lack comparability.

In view of the shortcomings of the “as-treated” and “per-protocol” analyses, our objective was to account for non-compliance by using instrumental variables (IV) analyses to estimate the effect of ART initiation during TB treatment (exposure) on mortality. This will also be referred to as effectiveness. IV analyses enable us to make use of the comparability offered by randomization and thereby have the capability of adjusting for unmeasured and measured confounders; they have the further advantage of yielding results that are less sensitive to random measurement error in the exposure.[10] The key challenge with IV analyses especially in non-randomized studies is obtaining a valid instrument, which must (i) be associated with an exposure, (ii) only affect the outcome through its association with an exposure and (iii) not share common causes with an exposure. We used randomization arm as an instrument, with the exposure being defined as the fraction of time on ART during TB treatment (i.e. months on ART/months on TB therapy).

A limitation of using such fixed exposure over time, is that it cannot capture the full complexity of compliance behaviour and may, moreover, be indirectly influenced by censoring or death. In view of this, we also provide analyses for a time-varying measure of compliance to ART. IV-methodology for the effect of a time-varying exposure on a time-to-event endpoint is currently lacking, with the exception of G-estimation for structural accelerated failure time models.[11] Because this is complex and often performs poorly in the presence of censoring, we developed novel methodology under so-called additive hazard models. The proposed methods can be applied using standard software and do not require specific corrections for non-informative censoring.

METHODS

Dataset

This analysis is based on 642 HIV-TB co-infected patients from the SAPiT open-label randomized trial which was conducted between June 2005 and July 2010 in South Africa. The primary objective of the trial was to determine the optimal timing of ART initiation in patients co-infected with HIV and TB. More details about the study and the results for primary and secondary outcomes have been published in detail elsewhere.[5,8,12,13]

Patients who had confirmed HIV infection and newly diagnosed pulmonary TB were randomly assigned to start ART at the following three different points of their TB therapy. In the first arm, ART was to be initiated within 4 weeks after the start of TB therapy (early integrated arm). In the second arm, ART was to be initiated within 4 weeks after the completion of the intensive phase of TB therapy (late integrated arm). In the third arm, ART was to be initiated within 4 weeks after the completion of TB therapy (sequential arm). All patients received prophylaxis to control opportunistic infections. After a planned interim analysis, on 1 September 2008, almost 2 months after completion of enrollment, the data and safety monitoring committee made a recommendation that all patients in the sequential arm be initiated on ART as soon as possible but stay in follow-up until study completion. The

committee also recommended continuation of the early and late integrated arms without any modifications.

The SAPiT study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (E107/05) and the Medicines Control Council of South Africa (20060157).

Exposure

As mentioned earlier, the fixed exposure, denoted by X, is defined as the fraction of time on ART during TB treatment (i.e. months on ART/months on TB therapy) (Figure 1). This was defined regardless of how long patients were on TB treatment (as some took more than the expected 6 months to complete TB treatment). Patients who were terminated before initiating ART were assigned an exposure of zero.

The rationale for choosing this exposure is as follows. In South Africa, TB and HIV are the leading causes of death in adults,[4] and TB-HIV co-infected patients are supposed to be co-treated by the same healthcare worker for both diseases. However, in resource poor countries like South Africa, this integration has not been fully implemented. Among other things, one constraint is the low uptake of HIV testing among TB patients which deprives patients of treatment integration.[1] For these reasons, this paper focuses on strengthening the evidence of the benefit of integrated therapy on mortality. Our IV analysis based on this exposure will express how, under perfect compliance, the ITT-analysis comparing the early integrated arm (where the exposure is then 1) and the sequential arm (where the exposure is then 0) would have fallen out.

Due to the above explained limitations of a fixed exposure over time, we have moreover developed IV-methodology for a time-varying measure of compliance to ART, which we defined as 1 at time t when the considered patient was on ART at or prior to time t, and 0 otherwise. Our IV analysis based on this exposure will express the effect of continuous ART use versus no ART use (regardless of TB treatment).

Outcome

We will focus on all-cause mortality. The survival time was defined as time from randomization until the date of death. It was censored at the withdrawal date, last visit date for those who were loss to follow-up (LTFU) or date of the 24-month visit for those who completed the study.

Covariates

The association between the fraction of time on ART during TB treatment and all-cause mortality is confounded because patients in poorer conditions (e.g. with lower CD4+ count) were at higher risk of death and thus more likely to initiate ART early irrespective of the study arm. Although the considered IV analysis do not require adjustment for measured confounders, we considered adjustment for CD4+ cell count, gender (0=male; 1=female) and employment status (0=unemployed; 1=employed) to improve precision. The instrument

Z (0 if assigned to sequential arm, 1 if assigned to late integrated arm and 2 if assigned to early integrated arm). This was modelled categorically.

Statistical analysis of fixed exposure

We first performed ITT analyses based on additive hazards models as well as Cox proportional hazards models. These assess the association between assignment Z to one of the arms and all-cause mortality. To investigate the association between the exposure X and all-cause mortality, we next performed instrumental variables analyses.

In particular, we used two-stage predictor substitution (2SPS) and two-stage residuals inclusion (2SRI) methods. Two-stage predictor substitution is a nonlinear extension of the linear two-stage least squares (2SLS). Two-stage residuals inclusion was first introduced by Hausmann,[14] and recently proposed for the analysis of time-to-event endpoints by Terza et al.[15] Both these approaches work by fitting, in a first-stage, univariable or multivariable linear regression models of the association between X and Z. For instance, our results below are based on the multivariable model:

$$X = \alpha_0 + \alpha_z Z + \alpha_m^T \boldsymbol{M} + \varepsilon \quad (1)$$

where **M** is vector of measured covariates such as gender, employment status and CD4+ cell count and where Z was modelled categorically (using dummy coding). The two-stage predictor substitution approach then proceeds by regressing the survival time on the fitted values $\widehat{X}$ from the first-stage regression (1) and on the measured covariates **M** either using additive hazard or Cox proportional hazards regression models. The two-stage residuals inclusion approach proceeds likewise, but regressing additionally on the residuals X-$\widehat{X}$ from the first-stage regression (1).

Tchetgen Tchetgen et al. [16] showed that, under certain conditions specified next, the coefficient of $\widehat{X}$ in the resulting additive hazard model can be interpreted as the exposure effect β_x in the additive hazard model

$$\lambda(t \mid X, U, Z, \boldsymbol{M}) = \lambda_0(t) + \beta_x X + \beta_m^T \boldsymbol{M} + \beta_u(t) U \quad (2)$$

which involves adjustment for possible unmeasured confounders U. Here, exp (-$\beta_x t$) can be interpreted as the relative chance of surviving time t with exposure 1 versus 0; note that it takes the length of the exposure period into account via the value of t. For the two-stage predictor substitution approach, the condition is that the error term ε in the exposure model (1) is independent of randomization arm (given the covariates **M**). For the two-stage residuals inclusion approach, a more subtle additional assumption is needed, which is satisfied when the error term ε equals the unmeasured confounder U apart from (additive) random noise. Because tests of the null hypothesis of no exposure effect are robust against model misspecification in the two-stage predictor substitution approach (unlike the two-stage residuals inclusion approach), we generally recommend the predictor substitution

approach. Both these approaches can be extended to Cox proportional hazard models when the event (all-cause mortality) is rare, which is not well satisfied in the SAPiT trial. Under the rare assumption, then the coefficient of $\widehat{X}$ can be interpreted as the exposure effect β_X in the Cox proportional hazards regression model

$$\lambda(t|X,Z,U,\boldsymbol{M}) = \lambda_0(t)\exp\left(\beta_x X + \beta_m^T \boldsymbol{M} + \beta_u U\right), \quad (3)$$

but not otherwise.

We calculated model-based survival probabilities for ITT and IV analyses under the 2SPS approach of the additive and proportional hazards models. In the IV analyses, the survival probabilities were estimated for three fixed exposure levels of 0 (no exposure), 0.6 (partial exposure) and 1.0 (full exposure). These correspond to what the survival probabilities would have looked like in the sequential, late, and early integrated arms, respectively, had there been perfect compliance.

Standard errors reported below are based on 1000 nonparametric bootstrap samples with replacement, refitting both stages of the procedure each time. We used the bias-corrected and accelerated method[17] to calculate 95% confidence intervals (CIs) for β_X in the second-stage.

Statistical analysis of time-varying exposure

In view of the aforementioned limitations of using a fixed exposure over time, we next extended the two-stage predictor substitution approach to time-varying measures X(t) of compliance (see eAppendix 1). Our results are based on the multivariable model

$$X(t) = \alpha_0(t) + \alpha_z(t)Z + \alpha_m^T(t)\boldsymbol{M} + \varepsilon(t) \quad (4)$$

defined for patients who are alive at time t, which we consider at each observed event time t. Under the assumption that $\varepsilon(t)$ is uncorrelated with Z, conditional on $\boldsymbol{M}$ for patients who are alive at time t, we then show in the eAppendix 1 that the two-stage predictor substitution approach can be extended to an additive hazard regression of the survival time on the fitted values $\widehat{X}(t)$ from the first-stage regression (4) (which is limited to patients who are alive at time t) and on the measured covariates **M**. In particular, we show that the resulting effect β_X of $\widehat{X}(t)$ can be interpreted as the effect of X(t) in the additive hazard model

$$\lambda\left(t \middle| \overline{X}(t), U, Z, \boldsymbol{M}\right) = \lambda_0(t) + \beta_x X(t) + \beta_m^T \boldsymbol{M} + \beta_u(t)U\,. \quad (5)$$

It follows from the eAppendix 2 that the proposed IV approach for time-varying exposure is valid in the presence of unmeasured time-varying confounders, U(t), so long as these are not influenced by previous exposure measurement $\overline{X}(t-1)$; that is, under the data-generating mechanism visualized in eFigure 1. While this is a potentially strong assumption, it is one that is implicit in all standard IV analyses that reduce time-varying exposure to a fixed

exposure, and one that is difficult or impossible to relax. Indeed, without this assumption, there may be pathways from the instrumental variable Z via $\bar{X}(t-1)$ and U(t) towards the time-to-event endpoint, thereby inducing a dependence between the instrumental variable and the unmeasured confounders, and thus violating the instrumental variables assumptions.

We calculated model-based survival probabilities under the proposed additive hazards models for values, 1 (on ART) and 0 (not on ART). Statistical analyses were done using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.4.

RESULTS

Baseline and follow-up

A total of 642 patients were enrolled: 214 in the early integrated arm, 215 in the late integrated arm and 213 in the sequential arm (eFigure 2). Patients in the three study arms had similar baseline demographic and clinical characteristics (eTable 1).

During a median follow-up of 24 months (interquartile range (IQR) 10.5 to 24 months), 69 (10.7%) patients died (17 in each of the early and late integrated arms and 35 in the sequential arm). A total of 417 (65.0%) completed the study [early integrated arm (n=151), late integrated arm (n=139) and sequential arm (n=127)]. A total of 96 (15.0%) were lost to follow-up (early integrated arm (n=26), late integrated arm (n=36) and sequential arm (n=34)); while 60 (9.3%) either withdrew consent or relocated to other areas (early integrated arm (n=20), late-integrated arm (n=23) and sequential arm (n=17)). A total of 16 (7.5%); 51 (23.7%) and 74 (34.7%) patients did not start ART in the early, late-integrated, and sequential arms respectively due to reasons such as death, loss to follow up, relocation, and voluntarily withdrawal (eFigure 2). The baseline and clinical characteristics by study arm are presented in eTable 1, whereas the characteristics of the compliant and non-compliant patients in all arms are shown in eTable 2.

Over 984.79 person–years of follow-up, the mortality rates were 4.9 per 100 person–years (py) (95% confidence interval (CI): 2.9 to 7.9) in the early integrated; 5.2 per 100 py (95% CI: 3.0 to 8.2) in the late integrated and 11.3 per 100 py (95% CI: 7.9 to 15.8) in the sequential arm.

The median (IQR) duration on TB treatment was 6.7 (6.4–8.3) months in each of the three study arms. The mean exposure to ART during TB treatment was 0.78 in the early integrated, 0.39 in the late integrated, and 0.04 in the sequential arm (Table 1, Figure 1).

Additive hazards analysis on the effect of integrating ART and TB treatment

Multivariable results from ITT analyses showed that patients in the early and late integrated arms had a hazard difference of −0.05 (95% CI: −0.09 to −0.01) and −0.06 (95% CI: −0.11 to −0.02) respectively when compared to the sequential arm. This indicates that on average, five and six deaths were averted for each year of follow-up in each 100 patients randomly assigned to early and late integrated arms compared with each 100 patients in the sequential arm (Table 2).

The two-stage predictor substitution analysis of the fixed exposure showed that on average, seven deaths (hazard difference= −0.07; 95% CI: −0.12 to −0.01) were prevented for each year of follow-up in each 100 patients with full exposure to ART during TB treatment (as would be the case under perfect compliance in the early integrated arm) as opposed to 100 patients with no ART exposure during TB treatment (as would be the case under perfect compliance in the sequential arm) (Table 2). The two-stage residuals inclusion method for the fixed exposure resulted in slightly weaker effects (hazard difference = −0.05; 95% CI: −0.11; 0.01). The strong association found between the first-stage residuals and time to death in this analysis provides strong evidence of unmeasured confounding, which the IV-analysis accounted for. The findings from the "as-treated" analyses of the fixed exposure (hazard difference = −0.12; 95% CI: −0.17; −0.07) are thus likely biased (Table 2). Results from proportional hazards regression are shown in the Web Appendix (eTable 6).

Figure 2A shows model-based predicted survival probabilities from univariable ITT and IV (fixed exposure) analyses under the two-stage predictor substitution approach from additive hazards model. Figure 2B shows predicted survival probabilities obtained from the model with time-varying exposure. The survival probabilities for X=1 in both figures are higher than that of the early integrated arm. However, survival probabilities for X=0.6 and X=0 are closer to those for late integrated and sequential arms respectively (Figure 2A). Predicted survival probabilities under proportional hazards models are shown in eFigures 3A and 3B.

Time-varying additive hazards analysis on the effect of ART

The IV-analysis of time-varying ART exposure expresses the effect of continuous ART exposure versus no exposure (hazard difference of −0.29; 95% CI: −0.54 to −0.03) (Table 2). It indicates that an average of 29 deaths were prevented for each year of follow-up in each 100 patients on (continuous) ART, compared with 100 patients not on ART, conditional on gender, employment status, and CD4+ cell count. Corresponding predicted survival probabilities for a patient without ART exposure, X(t)=0 for all t, were very low (Figure 2B). The large differences found between the estimated effects of fixed and time-varying exposures are largely attributable to the different exposure definitions: while the analyses of a fixed exposure focus on the effect on integration of ART and TB treatment (as compared to a background regimen with ART), the analysis of a time-varying exposure focuses on the overall effect of ART. Arguably, the analysis of fixed exposure is also less reliable because of the previously mentioned concern for reverse causality, and the fact that differential ART exposure outside the period of TB treatment may have induced a violation of the exclusion restriction in this analysis. In contrast, also the time-varying IV analysis is subject to a violation of the assumption that the residual in equation (4) is (conditionally) uncorrelated with the IV.

This location shift assumption could be plausible for continuous exposures, but is known to be violated for dichotomous exposures. In view of this, we report the results of limited simulation studies for time-fixed exposures in eTable 7. These show that the degree of bias under violation of this assumption is small under the considered settings. However, we must warn the reader that we cannot guarantee that the proposed approach for time-varying

exposures is (nearly) unbiased when the exposure is dichotomous, unless when the exposure effect is close to, or equal to zero.

DISCUSSION

We have provided IV analyses of the causal effect of exposure to ART (during TB treatment) on time to death, to account for non-compliance as a result of not all patients adhering to randomization and starting ART at the correct time with respect to TB treatment. The SAPiT trial data has been analyzed using ITT methods and showed that integration of ART and TB treatment saves lives.[5] Our results express more precisely how many lives could be saved under perfect compliance. The IV results thus appeal to patients and clinicians who are interested in the benefits of initiating and adhering to received treatment. The results from the “as-treated” analyses showed even higher effectiveness but these results are biased because patients who comply and those who do not comply with the randomized treatment are not always comparable.

The analyses were carried out using the semiparametric additive hazards models. Cox proportional hazards models were used for comparison. Our instrumental variables analysis relies on two key assumptions. The first, that patients on the different arms of the study are exchangeable, is guaranteed by randomization. The second, so-called exclusion restriction, that randomized assignment may only influence all-cause mortality by changing ART exposure, could be violated. One possible cause of violation concerns our definition of exposure, which may not fully capture all relevant components such as adherence which could have an effect on mortality. A second possible reason is that, in the open-label SAPiT trial, being assigned to either of the integrated arms may have enhanced patient’s expectation of success, and in contrast, assignment to the sequential arm might have reduced such an expectation. Moreover, those randomized to integrated arms who did not start ART soon after TB treatment initiation might have deliberately delayed ART initiation because they were still feeling well and did not see the need to integrate TB treatment and ART. Our analysis moreover ignored differential ART exposure outside the TB treatment window. All of this in turn violates the exclusion restriction assumption, which underlies our analysis. The violation of this untestable assumption can lead to biased IV estimates.

We acknowledge several additional limitations in our analyses. Our fixed exposure did not differentiate between patients who were on TB treatment for six months and those who were on TB treatment for a longer period. A patient who was on TB treatment for six months and only took ART for three months had similar exposure level to a patient who was on TB treatment for 12 months and took ART for 6 months. The latter patient is more likely to have drug-resistant TB and thus be more likely to die. Also, for patients who died soon after enrollment and those who did not start ART, the exposure is not ideally defined. We have tried to counteract that limitation by developing an IV-methodology for a time-varying measure of compliance. This analysis answers a different scientific question, but better recognises the complexity of the exposure. Indeed, the magnitude of a summary exposure over the observation period is likely influenced by censoring due to loss to follow-up, and death, and therefore ill defined. In particular, while more reliable, the analysis of time-

varying exposure did not immediately allow us to assess the effectiveness of ART treatment during the TB treatment window.

However, a drawback of our IV-methodology for time-varying exposures is that it relies on a location-shift assumption, which is unlikely to hold for dichotomous exposures. For such exposures, we cannot exclude the possibility of large biases when the exposure effect is large. For time-fixed exposures, Tchetgen Tchetgen et al.[16] were able to circumvent this problem when the instrument is dichotomous; see also Martinussen et al.[18] for general instrumental variables. It is an open question whether their proposals can be extended to time-varying exposures.

Our analysis of time-varying exposure is based on novel IV-methodology which returns effects on the additive hazard scale. While alternative G-estimation strategies have been proposed to infer the effect of a time-varying exposure on a time-to-event endpoint in the presence of an instrumental variable under an alternative class of structural accelerated failure time models,[11] application of these methods in applied research has been relatively infrequent because of their complexity and often poor performance in the presence of censoring.[19] Our proposal overcomes these concerns by being applicable in standard software for additive hazard models, which naturally accommodates non-informative censoring without requiring further adjustments. In contrast to G-estimation, it does have the drawback of making assumptions on the distribution of the exposure [as shown in model (4)].

Further, our analyses infer a treatment effect in the treated, and thereby assume treatment effect homogeneity (i.e., that patients with a given ART exposure level on the different arms on average experience the same benefit of it). We do not infer the effect in compliers, as this would be more difficult to define with a time-varying and/or continuous measure of compliance. Finally, we assumed that censoring is non-informative, given the covariates that we controlled for, and is moreover independent of the exposure and IV.

In conclusion, results from IV analyses demonstrate that survival benefit of fully integrating TB treatment and ART is even higher than what has been reported in the ITT analyses since non-compliance has been accounted for. IV estimates are clinically important because knowing the effectiveness of the TB and ART integration in the absence of non-compliance enables a much better public health evaluation of the potential impact of this intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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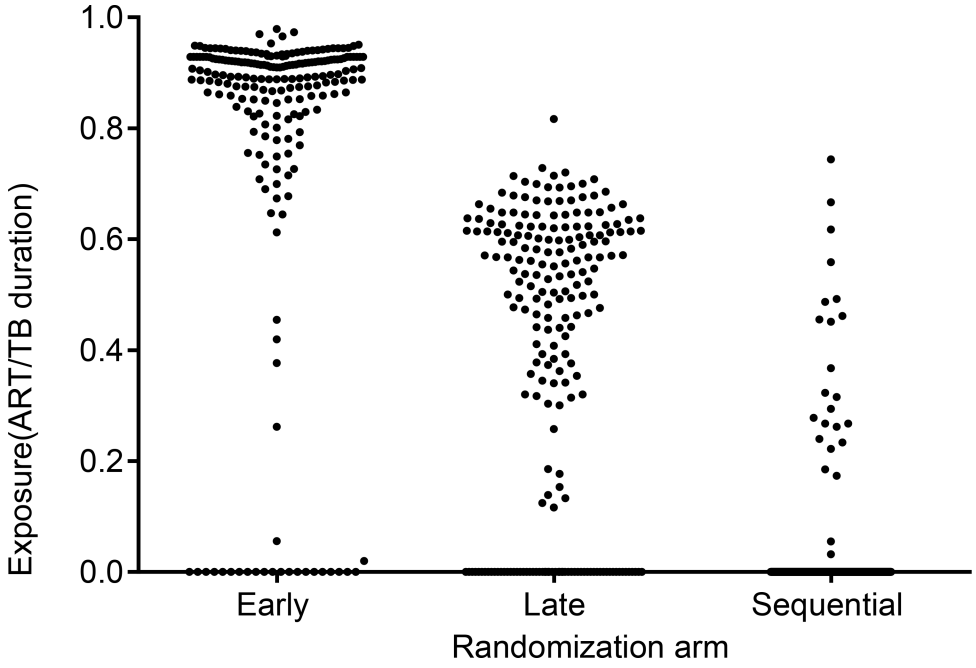

Figure 1:
Exposure (fraction of time on ART during TB treatment) in the three randomized arms.
ART, antiretroviral therapy; TB, tuberculosis

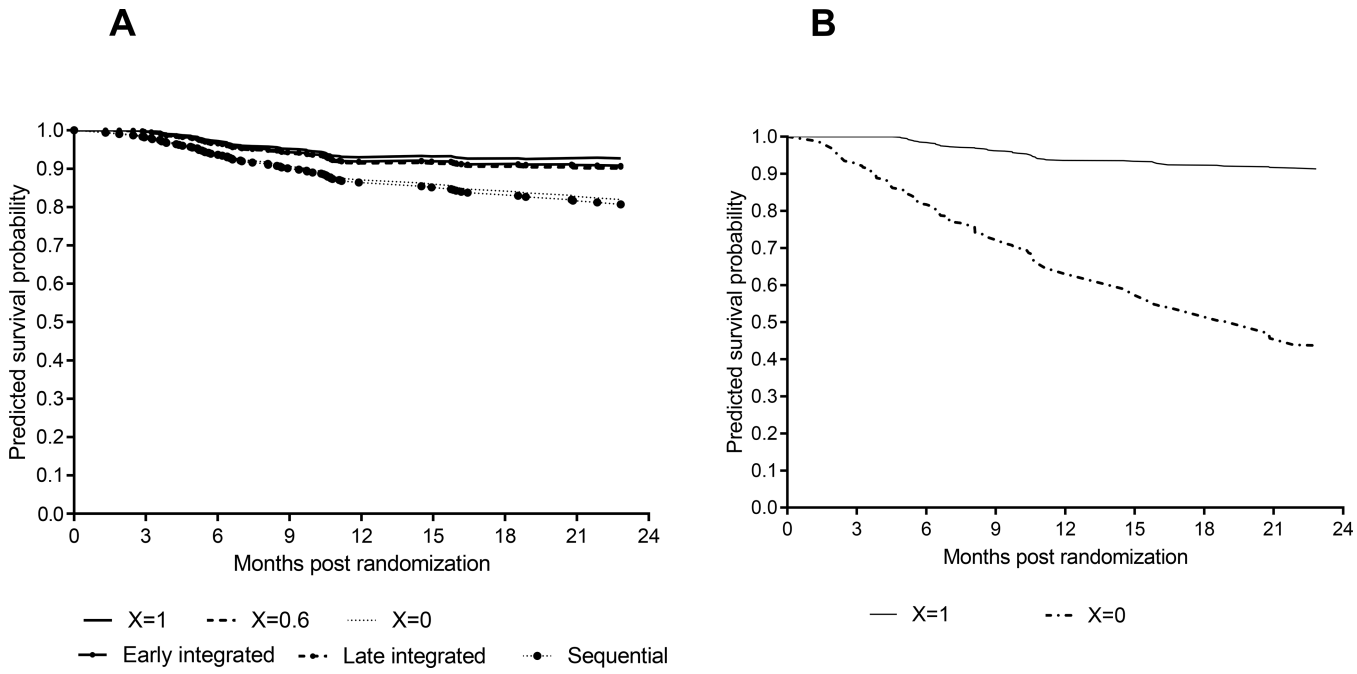

Figure 2:

Predicted survival curves comparing ITT and IV estimates from additive hazards model (A: fixed exposure, B: time-varying exposure). ITT, intent-to-treat; IV, instrumental variables

Table 1:

First-stage linear regression model predicting the fixed exposure

	Univariable		Multivariable[a]	
Effect	**Estimate**	**S.E.**	**Estimate**	**S.E.**
Intercept	0.04	0.02	0.06	0.03
Early integrated arm	0.74	0.02	0.74	0.02
Late integrated arm	0.35	0.02	0.35	0.02
Sequential arm	0		0	
F-value; Partial R2	514.68; 0.62		211.66; 0.62	

S.E.: standard error

[a] adjusted for gender, baseline CD4+ count and employment status

Table 2:

ITT and IV estimates for the effect of study arm and exposure on mortality using additive hazards models

		Univariable	Multivariable[a]
Method/exposure		**β (95%CI)**	**β (95%CI)**
ITT	Early integrated arm	-0.06 (−0.11 to −0.02)	-0.05 (−0.09 to −0.01)
	Late integrated arm	-0.06 (−0.11 to −0.02)	-0.06 (−0.11 to −0.02)
	Sequential arm	0	0
Time-varying exposure			
As-treat	Exposure to ART during follow-up	-0.22 (−0.30 to −0.13)	-0.21(−0.31 to −0.13)
2SPS	Exposure to ART during follow-up	-0.41 (−0.72 to −0.09)	-0.29 (−0.54 to −0.03)
Fixed exposure			
As-treated	Exposure to ART during TB treatment	-0.12 (−0.17 to −0.08)	-0.12 (−0.17 to −0.07)
2SPS	Exposure to ART during TB treatment	-0.08 (−0.14 to −0.03)	-0.07(−0.12 to −0.01)
2SRI	Exposure to ART during TB treatment	-0.06 (−0.13 to −0.01)	-0.05(−0.11 to 0.01)
	First-stage residuals	-0.19(−0.35 to −0.06)	-0.23(−0.43 to −0.09)

[a] adjusted for gender, baseline CD4+ count and employment

ITT, intent-to-treat; IV, instrumental variables