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Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa

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Abstract

Objective—Routine monitoring of plasma HIV RNA among HIV-infected patients on antiretroviral therapy (ART) is unavailable in many resource-limited settings. Alternative monitoring approaches correlate poorly with virologic failure and can substantially delay switch to second-line therapy. We evaluated the impact of delayed switch on mortality among patients with virologic failure in Africa.

Design—A cohort.

Methods—We examined patients with confirmed virologic failure on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens from four cohorts with serial HIV RNA monitoring in Uganda and South Africa. Marginal structural models aimed to estimate the effect of delayed switch on mortality in a hypothetical trial in which switch time was randomly assigned. Inverse probability weights adjusted for measured confounders including time-updated CD4⁺ T-cell count and HIV RNA.

Results—Among 823 patients with confirmed virologic failure, the cumulative incidence of switch 180 days after failure was 30% [95% confidence interval (CI) 27–33]. The majority of patients (74%) had not failed immunologically as defined by WHO criteria by the time of virologic failure. Adjusted mortality was higher for individuals who remained on first-line therapy

than for those who had switched [odds ratio (OR) 2.1, 95% CI 1.1–4.2]. Among those without immunologic failure, the relative harm of failure to switch was similar (OR 2.4; 95% CI 0.99–5.8) to that of the entire cohort, although of borderline statistical significance.

Conclusion—Among HIV-infected patients with confirmed virologic failure on first-line ART, remaining on first-line therapy led to an increase in mortality relative to switching. Our results suggest that detection and response to confirmed virologic failure could decrease mortality.

Keywords

antiretroviral; cohort studies; HIV; HIV RNA level; inverse probability weight; marginal structural model; time-dependent confounding; treatment failure; viral load

Introduction

First-line nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens save the lives of millions of HIV-infected patients globally; however, resistance to these regimens results in increased viral replication (virologic failure). In resource-rich settings, HIV RNA levels are monitored regularly and the threshold to switch regimens after virologic failure is detected is low [1]. However, in Africa, delayed switch following failure is common due to several factors. First, routine plasma HIV RNA monitoring is often unavailable and alternative CD4⁺ T-cell and clinical criteria provide poor surrogates [2–7]. Second, until recently, WHO guidelines suggested that HIV RNA levels below 5000 or 10000 copies/ml did not warrant immediate regimen switch [8,9]. Third, second-line regimens are expensive, and in the absence of compelling data that switching immediately is needed, the resources to fund such regimens have been limited. Finally, when patients have confirmed HIV RNA rebound, clinicians may be hesitant to switch patients with perceived poor adherence.

Although delayed switch following virologic failure exposes patients to accumulation of resistance mutations and advanced immunosuppression, the clinical effect of delayed switch in resource-limited settings has not been adequately quantified [10–13]. To date, four randomized trials found no significant reduction in mortality among individuals monitored with routine HIV RNA compared to those with access to clinical monitoring only, CD4⁺ and clinical monitoring, or CD4⁺ and clinical monitoring with discretionary HIV RNA levels [14–18]. However, the excellent adherence and limited follow-up time in these studies, and thus few virologic failures and deaths, resulted in attenuated power.

There are several lines of indirect evidence that routine HIV RNA monitoring and prompt switching are important. In multisite observational studies in southern Africa, patients treated in programmes with routine HIV RNA monitoring had higher switch rates, higher CD4⁺ T-cell counts at switch and lower mortality than patients treated in programmes without routine HIV RNA levels [19,20]; however, clinics with HIV RNA testing may have had additional resources or infrastructure, confounding observed associations. Delayed switch following failure has been associated with lower rates of virologic suppression on second-line therapy in South Africa; however, prior analyses did not quantify mortality impact nor did they adjust for confounding by time-updated CD4⁺ cell count, HIV RNA level or other factors [21].

In order to evaluate the impact of delayed switch to second-line therapy following confirmed virologic failure on mortality in Africa, we used data from adult patients treated with first-line NNRTI-based antiretroviral therapy (ART) in four African clinics where serial HIV RNA monitoring was carried out. We analysed a large number of patients with confirmed virologic failure treated in routine care settings and controlled in analysis for clinic. Finally, we used inverse probability weights to adjust for confounding by time-varying CD4⁺ T-cell count and plasma HIV RNA level, factors that are affected by prior antiretroviral treatment and thus not amenable to traditional regression-based adjustment [22].

Materials and methods

Patient population

We examined data from HIV-infected adults who initiated first-line NNRTI-based ART between 2002 and 2011 in one of four prospective cohorts: Uganda AIDS Rural Treatment Outcomes (UARTO), a research cohort in Mbarara, Uganda; Infectious Diseases Institute (IDI), a research cohort in Kampala, Uganda; Rakai Health Sciences Program (RHSP), a clinic-based cohort in Rakai, Uganda; and, Gugulethu, a clinic-based cohort in Cape Town, South Africa. At the time of analysis, UARTO included 484 ART initiators, RHSP included 1665 initiators, IDI included 559 initiators and Gugulethu included 5267 initiators. Patients followed in these cohorts were managed by clinics that followed concurrent WHO guidelines. All cohorts serially measured plasma HIV RNA level.

Measurements

Patients who experienced confirmed virologic failure while on first-line NNRTI-based ART were included in primary analyses. Virologic failure could occur any time at least 16 weeks after ART initiation and was defined as two consecutive 'failing' HIV RNA levels measured fewer than 270 days apart. HIV RNA levels measured between 12 and 24 weeks after ART initiation were classified as 'failing' if they were more than 1000 copies/ml; HIV RNA levels measured after 24 weeks of ART were classified as failing if they were more than 400 copies/ml [11]. In sensitivity analyses, we analysed patients with confirmed rebound (confirmed virologic failure with at least one prior HIV RNA level <400 copies/ml) and unconfirmed rebound (a single HIV RNA level ≥ 400 copies/ml with at least one prior HIV RNA level <400copies/ml).

Secondary analyses evaluated patients without immunological failure prior to or concurrent with virologic failure. Immunologic failure was defined as meeting either of the WHO 2013 criteria: CD4⁺ cell count less than or equal to pretherapy baseline or CD4⁺ cell count less than 100 cells/μl after at least 6 months of ART [9]. In addition to serial HIV RNA and CD4⁺ cell count measurements, all cohorts recorded age, sex and clinical stage at ART initiation. Switch to second-line therapy was defined as initiation of a protease inhibitor (boosted lopinavir). Deaths were ascertained via linkage to a national death registry (Gugulethu) or active tracking in the community (the East African cohorts).

Ethics

The study was approved by all appropriate local and national Institutional Review Boards. Analyses were conducted with de-identified data.

Analysis

Time zero was defined as date of virologic failure confirmation. Cumulative incidence of switch to second-line therapy following confirmed virologic failure was estimated treating death as a competing event [23,24]. For remaining analyses, data were discretized into 30-day intervals, with time-varying variables coded as the most recent measurement available to guide clinical decision-making at the start of an interval. Unadjusted associations of each potential confounder with mortality and switch were calculated using pooled logistic regression models with robust standard error estimates to account for repeated measures [25].

Marginal structural models were used to investigate how delayed switch to second-line therapy impacted mortality over time. Analyses targeted a hypothetical trial in which individuals were enrolled at the time of confirmed failure and were assigned a random switch time, ranging from switch immediately (first 30 days following confirmation of failure) to never switch. Marginal structural models were used to summarize how use of first versus second-line therapy (switch status) at the end of an interval affected probability of dying in the following interval [11,22,26]. We fit pooled logistic regression models that included time since failure and switch status as main terms, as well as models with an additional interaction term between time and switch status and models with a natural cubic spline on time with knots at the 25th, 50th, and 75th percentiles.

Several time-varying variables, including CD4⁺ cell count, HIV RNA and clinic visit frequency, influence decisions whether and when to switch therapy, as well as affecting mortality; thus adjustment for confounding by these variables is needed. These same variables, however, are affected by prior switching decisions and mediate the effect of exposure to failing first-line therapy on mortality. Hence, adjustment via standard regression will bias results [11,22,26]. Inverse probability weighting (IPW) was therefore used to adjust for measured confounders [22,27].

In primary analyses, individuals were censored at reported transfer to an outside clinic or database closure, an appropriate approach under the assumptions of complete death ascertainment and transfer reporting. In secondary analyses, we relaxed this assumption by censoring at the first of database closure, transfer or 270 days without a recorded visit or laboratory test, with 270 chosen to reflect at least two consecutive missed visits and to reduce censoring of patients with a missed visit who subsequently returned to care. An additional weight was used to adjust for measured sources of potentially informative censoring, with separate components for each cause of censoring.

All treatment and censoring weights were estimated using Super Learner, a data adaptive approach that used 10-fold cross-validation to learn the optimal weighted combination of a library of algorithms [28]. The library included multivariate adaptive polynomial spline regression combined with initial screening to limit adjustment variables to those either

associated with mortality ($P < 0.2$) or considered *a priori* to be important confounders (CD4⁺ cell count, HIV RNA level and clinic), as well as five candidate parametric logistic regression models *a priori* specified on the basis of background knowledge [29–31]. The set of candidate confounders included clinic, age, sex, baseline WHO stage, calendar date of failure, virologic suppression prior to failure, CD4⁺ cell count and HIV RNA level at the time of failure and a range of time-varying summaries (including nadirs, zeniths and change over time) of CD4⁺ cell count, HIV RNA level and recorded visit frequency (Table 2). In sensitivity analysis, we excluded WHO stage at ART initiation from the adjustment set.

All weights were stabilized [22]. Standard errors were estimated using the robust sandwich estimator [25].

Results

Among 7975 patients on first-line NNRTI-based ART, 823 patients experienced confirmed virologic failure. Among these patients, 52% of first-line regimens contained efavirenz and 48% contained nevirapine. Of the 358 patients who had their therapy switched to second-line protease inhibitor based ART, the median time to switch was 116 days after confirmation of failure [interquartile range (IQR) 63–198 days]. Cumulative incidence of switch by 30, 90 and 180 days after failure was 3% [95% confidence interval (CI) 2–4], 16% (95% CI 14–19) and 30% (95% CI 27–33), respectively (Fig. 1a). Most patients (74%) had not failed immunologically (as defined by WHO criteria) by the time of virologic failure; 140 individuals (17% of failures) experienced at least one HIV RNA level less than 400 copies/ml after confirmed failure and while still on first-line therapy.

Among 823 patients with confirmed failure, a median of 79 days passed between first and confirmatory failing HIV RNA levels (IQR 53–115 days). The confirmatory failing HIV RNA measurement occurred a median of 1.4 years after ART initiation (IQR 0.8–2.6 years). Median values at the time of failure were 220 CD4⁺ T cells/ μ l and 6214 plasma HIV RNA copies/ml; 197 (24%) of individuals with confirmed virologic failure had not previously suppressed HIV RNA level below 400 copies/ml (Table 1).

Predictors of switch and mortality

In unadjusted analyses, switch to second-line therapy was associated with lower CD4⁺ cell count at treatment initiation and most recent measurement, lower nadir and peak CD4⁺ cell counts (including CD4⁺ cell count prior to ART initiation), greater percentage decline in CD4⁺ cell count since failure, higher HIV RNA level at most recent measurement, higher nadir HIV RNA level, baseline WHO clinical stage III or IV, and shorter duration between ART start and virologic failure (Table 2).

We observed 49 deaths among 823 persons, followed for a median of 2.1 years after failure (2.5 deaths per 100 person-years, Fig. 1b); 32 deaths (65%) occurred while still on first-line ART. Median CD4⁺ cell count at death was 107 cells/ μ l (IQR 46–211 cells/ μ l), measured a median of 90 days before death (IQR 34–136 days). Of the 17 deaths after switch, 14 had an HIV RNA level measured after switch. Of these, last measured HIV RNA level, measured a median of 134 days before death (IQR 72–205 days), was less than 400 copies/ml for four

patients and less than 1000 copies/ml for seven patients. In unadjusted analyses, significant predictors of mortality included lower CD4⁺ cell count at the most recent measurement, lower nadir CD4⁺ cell count, greater percentage decline in CD4⁺ cell count since failure, higher HIV RNA level at the most recent measurement and at the time of failure, higher nadir and peak HIV RNA level, older age, male sex and recorded visit within prior 90 days (Table 2).

Before adjustment for confounding, the discrete hazard of death was not significantly different among patients who remained on first-line therapy compared with patients who had switched. Assuming a constant relative odds over time, the relative odds of death among individuals on first-line therapy was 1.5 (95% CI 0.8, 2.6) compared with those on second-line. When an interaction term between switching status and time was included, remaining on first-line therapy was associated with elevated mortality, although the magnitude of this association declined nonsignificantly over time (Table 3).

Estimated effect of delayed switch

Adjustment for measured confounders increased the estimated magnitude of harm due to delayed switch (Table 3). Assuming a constant relative odds over time, the adjusted relative odds of death among individuals still on first-line therapy compared with those who had switched was 2.1 (95% CI 1.1–4.2). When an interaction term between switching status and time was included, for the first 28 months following failure those individuals who remained on first-line therapy had a higher probability of dying than those who had switched; the protective effect of switch declined nonsignificantly over time since failure ($P = 0.09$) (Table 3, Fig. 2a). Exclusion of the 197 patients without at least one HIV RNA level less than 400 copies/ml prior to failure resulted in similar estimates (Table 3). Inclusion of time since failure as a restricted cubic spline and exclusion of baseline stage from the adjustment set had a minimal impact on all estimates (data not shown).

The majority of patients (74%) had not failed immunologically (as defined by WHO criteria) by the time of virologic failure. Median CD4⁺ cell count among these 610 patients at virologic failure was 258 cells/ μ l (IQR 179–340 cells/ μ l). Among the 293 who subsequently switched, median CD4⁺ cell count at switch was 253 cells/ μ l (IQR: 168–328 cells/ μ l). Seventy-one of these patients subsequently failed immunologically and 27 died. Among the 15 patients who died on first-line therapy, median CD4⁺ cell count at death was 107 cells/ μ l (IQR 48–209 cells/ μ l), measured a median of 90 days before death. Among the 12 patients who died on second-line therapy, median CD4⁺ cell count at death was 124 cells/ μ l (IQR 35–264 cells/ μ l), measured a median of 183 days before death. After adjustment for measured confounders of switch, estimated mortality in this subpopulation was lower than in the full cohort (Fig. 2b). Assuming a constant relative odds over time, the adjusted relative odds of death among individuals still on first-line therapy compared to those who had switched was 2.4 (95% CI 0.99–5.8), similar to that of the full cohort, although of borderline significance ($P = 0.052$) (Table 3).

Three hundred and fifty-one (43%) patients experienced at least one episode of 270 days or more without a recorded visit, a median of 510 days after virologic failure (IQR 300–855 days). Using this definition of ‘loss to follow up’, 39 deaths prior to loss, transfer or

database closure were observed. The estimated effect of delayed switch was similar to estimates that censored only at database closure or reported transfer (Table 3).

Nonconfirmed virologic rebound, defined as a single HIV RNA level of at least 400 copies/ml with at least one preceding HIV RNA level less than 400 copies/ml, was observed in 1337 patients. Of these, 1153 (86%) had at least one subsequent HIV RNA level measured on first-line therapy, measured a median of 84 days after initial unsuppressed HIV RNA level (IQR 56–126 days). The majority (55%) of these confirmatory RNA levels were less than 400 copies/ml. Among individuals with nonconfirmed rebound, in both unadjusted and adjusted analyses mortality was no higher among individuals who remained on first-line therapy than among those on second-line (Table 3).

Discussion

When to switch therapy for treatment ‘failure’ in resource-poor regions remains controversial. Much of the debate has been informed by cost concerns and practical issues, as well as by several randomized clinical studies in which most patients did well and follow-up time was limited (median 1.5–3 years following ART initiation), making it hard to evaluate clinical outcomes among the small numbers of failures [14–18]. In this study, we identified a large number of individuals with confirmed virologic failure in routine clinical practice, followed for a median of 4.3 years after ART initiation (2.2 years after confirmed failure). We found that switching to second-line protease inhibitor based therapy was delayed in many patients, a practice that others have found to be common, even in settings in which routine HIV RNA monitoring and second-line therapy are available [32–35]. We found, after adjustment for measured confounders, that remaining on first-line therapy following confirmed virologic failure significantly increased mortality. The estimated effect of delayed switch was similar among individuals without evidence of immunologic failure at the time of virologic failure, although of borderline statistical significance.

Several factors may have contributed to delayed switch in our study cohorts. First, clinician access to HIV RNA results was likely delayed in many cases, particularly in cohorts in which HIV RNA levels were drawn for research purposes. Second, during much of the study period, the WHO recommended an HIV RNA threshold of 5000 or 10 000 copies/ml, ideally with confirmation, for switching [8,9]. Third, clinicians may have delayed switch in patients with perceived adherence lapses or with tuberculosis treated with rifampicin due to concern for pharmacological interactions with ritonavir, or may have prioritized use of costly and scarcer second-line drugs for patients deemed most likely to benefit. Fourth, initiation of second-line therapy may have required scheduling and attendance at a subsequent visit.

We required confirmation of failure in order to improve specificity for true virologic failures rather than ‘blips’ or falsely elevated HIV RNA levels due to laboratory error [36]. Among patients who achieved a suppressed HIV RNA level, the majority of initial HIV RNA measurements of at least 400 copies/ml were followed by a consecutive HIV RNA measurement of less than 400 copies/ml, and we were unable to detect any effect of delayed switch on mortality among patients with nonconfirmed virologic rebound. These

observations support the use of a confirmatory HIV RNA level for switching, at least at the lower threshold for suppression [37].

Patients in our cohort initiated ART at low CD4⁺ cell counts. This may have contributed to high mortality resulting from failure to switch. The impact of delayed switch following confirmed virologic failure may differ among patients initiating ART more recently and at higher CD4⁺ cell counts.

As has been observed by others, a substantial proportion of individuals with confirmed failure had at least one subsequent HIV RNA level of less than 400 copies/ml while still on first-line therapy [17,34]. In the absence of resistance testing, which is unlikely to be widely available in this region, any definition of virologic failure will include some patients with transient loss of suppression. Our analyses suggest that in the absence of resistance testing, prompt switch to second-line therapy following confirmed failure has the potential to save lives.

Our estimates of the impact of delayed switch on mortality rely on measured variables to adjust for confounding. We were not able to adjust for time-updated WHO stage following ART initiation, as this measure was not introduced until 2010 and remains inconsistently applied in practice [8]. Sensitivity analyses excluding baseline WHO stage from the adjustment set had a minimal impact on estimates, suggesting that the baseline measure provides little additional confounding control after other measured covariates (including serial CD4⁺ cell count and HIV RNA) are adjusted for. However, unmeasured confounding by disease severity and perceived adherence not captured by CD4⁺ cell count and HIV RNA measures might result in either under or overestimates of the harm of delayed switch.

Nonetheless, use of inverse probability of treatment weighting rather than standard regression made it possible to adjust for measured sources of time-varying confounding and informative censoring, including serial CD4⁺ cell counts and HIV RNA levels (the latter of which correlates with adherence). We further minimized potential bias due to model misspecification through use of data-adaptive methods when estimating the weights and through use of alternative marginal structural model specifications in sensitivity analyses [28]. Further, although all cohorts had some form of active outcome ascertainment, both death ascertainment and transfer reporting may have been incomplete, resulting in bias not amenable to adjustment without supplementary data [38]. Sensitivity analyses in which patients were censored after 270 days without a clinic visit resulted, however, in similar estimates of increased mortality due to delayed switch.

We investigated the potential benefit of routine HIV RNA level monitoring compared with CD4⁺ cell count monitoring alone by estimating the effect of delayed switch among patients who had not met WHO immunologic failure criteria by the time of confirmed virologic failure, and thus who would not yet have been switched under CD4⁺ cell count criteria. Point estimates of the effect of delayed switch in these patients were similar to the larger group, but had less statistical precision. These secondary analyses are subject to several limitations, however. First, we had limited power to detect an effect in this subgroup. Second, these analyses do not directly quantify the impact of routine HIV RNA level

monitoring, as data were not available to assess WHO clinical failure criteria, and a minority of patients subsequently failed immunologically and thus would have experienced a delayed switch with CD4⁺ cell count monitoring alone. Although dynamic regime methods address the latter concern, they typically require larger samples [39,40]. Third, our analyses underestimate the benefits of routine viral monitoring in that they do not account for reduction in unneeded switches due to poor specificity of immunologic failure criteria, improved opportunity for targeted adherence interventions, decreased acquired and transmitted resistance, or reduced infectivity [3,7,41–44]. Although simulation models can investigate these broader health, transmission and costing implications, such models rely on understanding the mortality impact of deferred switch following virologic failure; our analyses contribute to this knowledge base [45–49].

Conclusion

To the best of our knowledge, our study is the first to estimate the impact of delayed switch to second-line therapy following confirmed virologic failure on mortality among patients treated in a resource-limited setting, taking into account time-varying confounders of switching. Many individuals did not switch to second-line therapy following confirmation of virologic failure, or switched only after substantial delay, and these delays increased mortality relative to immediate switch. Our findings support the importance of detection and response to virologic failure.

Acknowledgments

M.P. conceived the study, planned and supervised the analysis, interpreted results and wrote the manuscript. L.T. implemented the analysis and contributed to interpretation and writing. S.D. and J.M. contributed to study conception, data collection, planning and interpretation of analyses, and writing. E.G., S.R., A.K., R.W., D.B. and C.Y. contributed to data collection, interpretation of analyses and writing.

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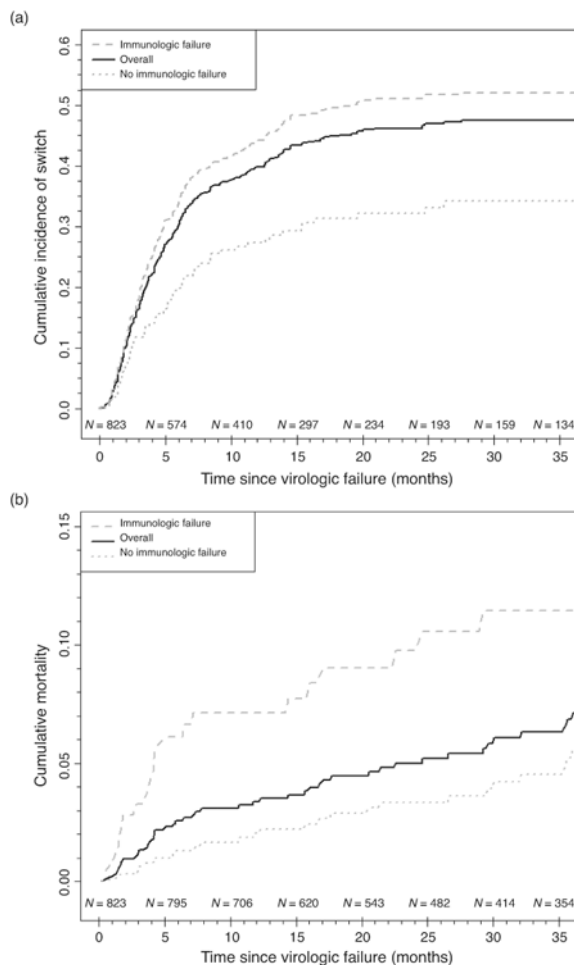


Fig. 1. Cumulative incidence of switch to second-line antiretroviral therapy (ART) (a) and mortality (b) following confirmed virologic failure on first-line NNRTI-based ART, among 823 patients with confirmed virologic failure, overall and stratified by WHO immunological failure at or before time of virologic failure
N refers to full cohort (not stratified by immunologic failure).

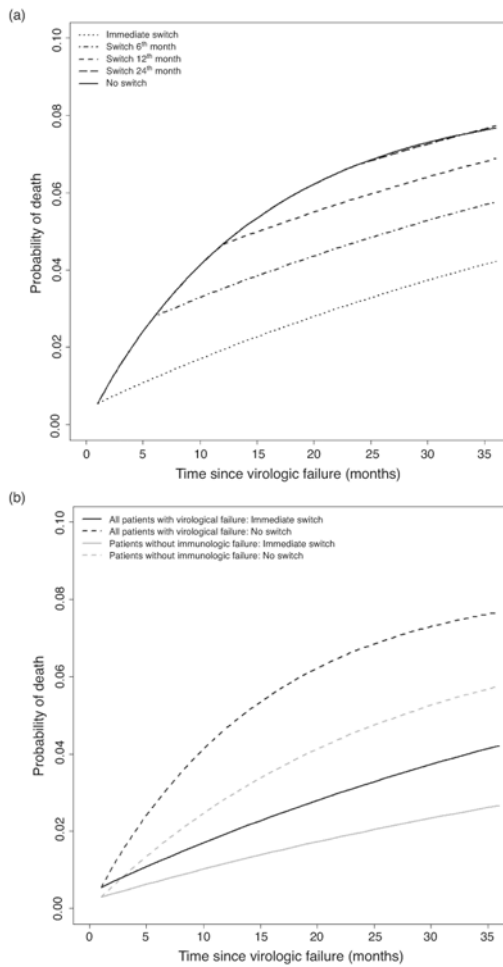


Fig. 2. Counterfactual mortality curves following confirmed virologic failure on first-line NNRTI-based ART, estimated using inverse probability weighting of marginal structural models (a) Among all patients with confirmed virologic failure ($N=823$) under a range of hypothetical delays before switching to second-line antiretroviral therapy, ranging from immediate switch (within 30 days of confirmed virologic failure) to never switch, (b) Among all patients with confirmed virologic failure ($N=823$) and only those patients without WHO immunologic failure at or before time of virologic failure ($N=610$), under immediate switch (within 30 days of confirmed virologic failure) and never switch.

Table 1
Characteristics of 823 patients with confirmed virologic failure on first-line nonnucleoside reverse transcriptase inhibitor based antiretroviral therapy, at the time of antiretroviral therapy initiation and at time of confirmed virologic failure, and extent of postfailure follow up^a

	At time of ART start				At time of confirmed virologic failure ^b			
	UARTO N = 31	IDI N = 61	RHSP N = 57	Gugulethu N = 674	UARTO N = 31	IDI N = 61	RHSP N = 57	Gugulethu N = 674
Age (years)								
<30	9 (29%)	22 (36%)	24 (42%)	259 (38%)	9 (29%)	21 (34%)	13 (23%)	185 (27%)
30–39	14 (45%)	21 (34%)	23 (40%)	287 (43%)	14 (45%)	22 (36%)	30 (53%)	330 (49%)
40	8 (26%)	18 (30%)	10 (18%)	128 (19%)	8 (26%)	18 (30%)	14 (25%)	159 (24%)
Median (IQR)	33 (27–39)	32 (27–40)	31 (29–37)	31 (27–37)	34 (28–40)	33 (28–41)	33 (31–39)	34 (30–40)
Sex								
Female	19 (61%)	37 (61%)	37 (65%)	469 (70%)	19 (61%)	37 (61%)	37 (65%)	469 (70%)
CD4 cell count (cells/ μ L) ^c								
<100	13 (50%)	36 (59%)	23 (40%)	357 (54%)	3 (10%)	11 (18%)	3 (5%)	97 (14%)
100–199	8 (31%)	19 (31%)	22 (39%)	244 (37%)	11 (35%)	31 (51%)	8 (14%)	194 (29%)
200–349	4 (15%)	5 (8%)	11 (19%)	58 (9%)	13 (42%)	9 (15%)	28 (49%)	269 (40%)
350–499	1 (4%)	1 (2%)	1 (2%)	1 (0%)	1 (3%)	6 (10%)	12 (21%)	89 (13%)
500	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (10%)	4 (7%)	6 (11%)	25 (4%)
Median (IQR)	101 (62–187)	53 (9–142)	125 (47–187)	90 (42–157)	213 (138–254)	172 (110–215)	294 (214–419)	222 (138–316)
Plasma HIV RNA (copies/ml) ^d								
<1 K	0 (0%)	0 (0%)	1 (2%)	8 (1%)	3 (10%)	9 (15%)	9 (16%)	82 (12%)
1 K–5 K	0 (0%)	1 (2%)	5 (9%)	11 (2%)	15 (48%)	8 (13%)	14 (25%)	232 (34%)
5 K–10 K	1 (3%)	0 (0%)	2 (4%)	30 (5%)	1 (3%)	3 (5%)	7 (13%)	86 (13%)
10 K–100 K	7 (24%)	9 (15%)	11 (21%)	286 (49%)	11 (35%)	18 (30%)	20 (35%)	214 (32%)
>100 K	21 (72%)	51 (84%)	34 (64%)	325 (49%)	1 (3%)	23 (38%)	7 (12%)	60 (9%)
Median (IQR)	228K (93K–731 K)	241 K (138K–677K)	182K (50K–411 K) 98K (34K–230K)	4K (1K–18K)	29K (3K–225K)	9K (2K–41K)	6K (2K–24K)	514 (76%)
Prior suppression (HIV RNA <400 copies/ml)								
					26 (84%)	34 (56%)	52 (91%)	

	At time of ART start				At time of confirmed virologic failure ^b			
	UARTO N = 31	IDI N = 61	RHSP N = 57	Gugulethu N = 674	UARTO N = 31	IDI N = 61	RHSP N = 57	Gugulethu N = 674
WHO clinical stage ^e								
I/II	12 (39%)	3 (5%)	22 (39%)	178 (26%)				
III/IV	19 (61%)	39 (64%)	13 (23%)	495 (73%)				
Time from ART start to failure (months)								
Median (IQR)					11 (8–16)	9 (7–14)	21 (17–28)	17 (10–35)
								Follow-up after virologic failure ^f
Duration follow up after failure (months)								
Median (IQR)		19.7 (12.9–27.2)		48.5 (39.6–52.6)		17.0 (7.5–30.4)		30.5 (15.7–47.3)
Plasma HIV RNA after failure								
Median # measurements (IQR)		6 (3–8)		5 (2–7)		3 (2–5)		4 (2–8)
Median months between measurements (IQR)		2.8 (2.7–3.1)		5.5 (2.8–5.6)		5.6 (5.6–5.6)		3.7 (2.1–4.2)
CD4 ⁺ T-cell counts after failure								
Median # measurements (IQR)		6 (4–9)		5 (2–7)		3 (1–5)		3 (1–7)
Median months between measurements (IQR)		2.8 (2.7–3.1)		5.4 (2.8–5.6)		5.6 (5.6–6.1)		3.8 (3.5–4.6)

IQR, interquartile range.

^a % of nonmissing values reported.

^b Most recent measurement date of confirmatory failing HIV RNA level.

^c 19 patients (2%) missing CD4⁺ cell count at ART start.

^d 20 patients (2%) missing HIV RNA at ART start.

^e 42 patients (5%) missing WHO stage at ART start.

^f From date of confirmed virologic failure to death, transfer or database closure.

Table 2
Unadjusted predictors of switch to second-line antiretroviral therapy and mortality^a

	Relative odds of switch (95% CI)	Relative odds of death (95% CI)
Age (per 10 years)	0.91 (0.78–1.07)	1.80* (1.30–2.51)
Male sex	0.81 (0.62–1.05)	1.93* (1.09–3.43)
CD4 ⁺ T cell count (per 100 cells/μl)		
At ART start	0.71* (0.62–0.81)	0.95 (0.69–1.30)
Nadir	0.66* (0.55–0.78)	0.56* (0.36–0.88)
Peak	0.88* (0.83–0.94)	0.87 (0.73–1.05)
At virologic failure	0.95 (0.87–1.04)	0.77 (0.56–1.06)
Most recent measurement	0.86* (0.80–0.94)	0.53* (0.37–0.76)
CD4 ⁺ cell count decline since failure (per 10%)	1.06* (1.01–1.11)	1.17* (1.09–1.27)
Plasma HIV RNA level (per log 10copies/ml)		
At virologic failure	1.11 (0.98–1.26)	1.78* (1.22–2.61)
Peak	0.94 (0.76–1.15)	2.79* (1.71–4.57)
Nadir	1.13* (1.03–1.24)	1.41* (1.04–1.91)
Most recent measurement	1.57* (1.43–1.73)	2.02* (1.50–2.74)
Suppression prior to failure ^b	0.86 (0.66–1.12)	1.00 (0.53–1.88)
WHO clinical stage at ART Start		
Stage I/II	Ref	Ref
Stage III/IV	1.51* (1.17–1.95)	2.52 (0.98–6.46)
ART start to failure (per 180 days)	0.91* (0.87–0.96)	1.01 (0.91–1.13)
Seen in prior 90-day interval	0.89 (0.71–1.11)	1.82* (1.02–3.27)
Time since last recorded visit (per 180 days)	0.87 (0.66–1.15)	0.68 (0.46–1.02)

ART, antiretroviral therapy; CI, confidence interval.

* P<0.05.

^aIn addition to the above variables, candidate predictors for estimated switching and censoring weights included: square root and categorical transformations of CD4⁺ cell count values; categorical transformations of HIV RNA values; indicators of whether an HIV RNA or CD4⁺ cell count test was performed in the previous 90-day interval; WHO immunologic failure criteria; time since failure; calendar date of failure; and clinic.

^bDefined as at least one HIV RNA < 400copies/ml after starting ART and prior to confirmed failure.

Table 3
Unadjusted and inverse probability weighted estimates of the association between switch to second-line therapy following confirmed virologic failure and mortality^a

Patient population/censoring definition	Main term model ^b	Model including interaction with time ^c	
	Main term for switch status (OR for mortality on first-line versus second-line therapy) ^d (95% CI); <i>P</i> value	Main term for switch status ^e (95% CI); <i>P</i> value	Interaction term between switch status and time since failure ^f (95% CI); <i>P</i> value
Confirmed virologic failure (<i>N</i> = 823) ^g	Unadjusted: 1.47 (0.83–2.60); <i>P</i> = 0.19 IPW: 2.12 (1.09–4.15); <i>P</i> = 0.027	Unadjusted: 3.19 (1.24–8.20); <i>P</i> = 0.016 IPW: 4.18 (1.54–11.32); <i>P</i> = 0.005	Unadjusted: 0.95 (0.90–1.00); <i>P</i> = 0.068 IPW: 0.95 (0.90–1.01); <i>P</i> = 0.086
Confirmed virologic failure (<i>N</i> = 823); censored at 9 months without visit ^h	Unadjusted: 1.75 (0.89–3.42); <i>P</i> = 0.10 IPW: 2.46 (1.17–5.17); <i>P</i> = 0.017	Unadjusted: 3.62 (1.28–10.19); <i>P</i> = 0.015 IPW: 5.46 (1.87–15.95); <i>P</i> = 0.002	Unadjusted: 0.93 (0.85–1.01); <i>P</i> = 0.090 IPW: 0.91 (0.82–1.02); <i>P</i> = 0.096
Confirmed virologic failure without prior immunologic failure (<i>N</i> = 610) ⁱ	Unadjusted: 1.31 (0.63–2.72); <i>P</i> = 0.47 IPW: 2.40 (0.99–5.82); <i>P</i> = 0.052	Unadjusted: 2.60 (0.82–8.24); <i>P</i> = 0.10 IPW: 3.43 (0.99–11.88); <i>P</i> = 0.052	Unadjusted: 0.96 (0.91–1.01); <i>P</i> = 0.14 IPW: 0.98 (0.93–1.03); <i>P</i> = 0.40
Confirmed virologic failure with prior viral suppression (<i>N</i> = 626) ^j	Unadjusted: 1.19 (0.63–2.26); <i>P</i> = 0.59 IPW: 1.93 (0.87–4.28); <i>P</i> = 0.11	Unadjusted: 3.13 (1.12–8.69); <i>P</i> = 0.029 IPW: 4.24 (1.42–12.63); <i>P</i> = 0.010	Unadjusted: 0.93 (0.86–1.00); <i>P</i> = 0.054 IPW: 0.94 (0.87–1.01); <i>P</i> = 0.094
Nonconfirmed virologic rebound (<i>N</i> = 1337) ^k	Unadjusted: 0.59 (0.33–1.06); <i>P</i> = 0.078 IPW: 0.96 (0.44–2.08); <i>P</i> = 0.92	Unadjusted: 1.18 (0.43–3.25); <i>P</i> = 0.76 IPW: 1.09 (0.30–3.95); <i>P</i> = 0.89	Unadjusted: 0.97 (0.94–1.01); <i>P</i> = 0.087 IPW: 0.99 (0.95–1.04); <i>P</i> = 0.77

CI, confidence interval; OR, odds ratio.

^aInverse probability weighted (IPW) estimates adjust for measured confounders of switch and measured causes of potentially informative censoring using inverse probability weights.

^b $P(Y_{switch, time}(t) = 1 | Y_{switch, time}(t-1) = 0) = \exp(it(\beta_0 + \beta_1)(switch.time > t) + \beta_2t)$.

^c $P(Y_{switch, time}(t) = 1 | Y_{switch, time}(t-1) = 0) = \exp(it(\alpha_0 + \alpha_1)(switch.time > t) + \alpha_2t + \alpha_3((switch.time > t) \times t))$: Corresponding mortality functions plotted in Figure 2.

^d $\exp(\beta_1)$.

^e $\exp(\alpha_1)$.

^f $\exp(\alpha_3)$.

^gFollow-up until death, database closure or reported transfer. Mean weights = 0.93; range: 0.02–10.

^hFollow-up until death, database closure, reported transfer or 270 days without recorded visit. Mean weights = 0.91; range: 0.001–18.

ⁱPatients had not met any of WHO immunologic failure criteria at or before time of confirmed virologic failure. Follow up until death, database closure or reported transfer. Mean weights = 1.05; range: 0.03–22.

^jPatients with at least one HIV RNA level <400 copies/ml prior to confirmed virologic failure. Follow up until death, database closure, or reported transfer. Mean weights = 0.94; range: 0.10–17.

^kNonconfirmed rebound defined as an HIV RNA level ≥ 400 copies/ml, preceded by at least one HIV RNA level <400 copies/ml. Follow-up until death, database closure or reported transfer. Mean weights = 0.96; range: 0.10-8.