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Immunological failure of first-line antiretroviral therapy (ART) and switch to second-line ART among HIV-infected persons in Tanzania: Analysis of national routinely-collected data

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Abstract:	Objectives: Rates of first-line treatment failure and switches to second-line therapy are key indicators for national HIV programs. We assessed immunological treatment failure (ITF) defined by World Health Organization criteria among persons in the Tanzanian national HIV program. Methods: We included adults initiating first-line therapy in 2004-2011 with a pre-treatment CD4 count, and ≥6 months' follow-up. We assessed sub-hazard ratios (SHR) for ITF, and subsequent switch to second-line therapy, using competing risks methods to account for deaths. Results: Among 121,308 adults, 8,384 (7%) experienced ITF, and 2,486 (2%) died without observed ITF, over median 1.7 years. The six-year cumulative probability of ITF was 19.0% (95% CI 18.5,19.7) and death 5.1% (4.8,5.4). ITF predictors included earlier year of treatment initiation (p<0.001), initiation in lower-level facilities (SHR=2.23 [2.03,2.45] for dispensaries versus hospitals), being male (1.27 [1.19,1.33]) and initiation at low or high CD4 counts (for example, 1.78 [1.65,1.92] and 5.33 [4.65,6.10] for <50 and ≥500 versus 200-349 cells/mm3, respectively). Of 7,382 participants in the time-to-switch analysis, 416 (6%) switched, while 355 (5%) died before switching. Four years after ITF, the cumulative probability of switching was 7.3% (6.6,8.0) and death 6.8% (6.0,7.6). Those who immunologically-failed in dispensaries, health centers and

	government facilities were least likely to switch. Conclusions: ITF rates and unmet need for second-line therapy are high in Tanzania; virological monitoring, at least for persons with ITF, is required to minimize unnecessary switches to second-line therapy. Lower-level government health facilities need more support to reduce treatment failure rates and improve second-line therapy uptake to sustain the benefits of increased coverage.

Response to reviewers

Reviewer #1:

-Major concern is that no indication of numbers or potential impact (especially bias) from those not having regular CD4 follow-up. Would be good to include a flow chart of the analytic frame and some sensitivity analysis of risks assuming different impacts of the loss to follow-up. The paper is slightly unclear regarding the confirmatory CD4 result but clearly incomplete data (as you point out) could have major implications regarding bias and important to clarify how important this could be. Flow chart should highlight who of the 121000 does not contribute to the outcomes (ie has a CD4 gap of more than 12 months and is lost and/or remains in f/u without further CD4, who has a failing CD4 but no confirmatory CD4 etc).

Response: We would like to confirm that a patient's follow up was censored if they had not had a CD4 count for more than 12 months, but that patient could re-enter later if/when they had a subsequent CD4 recorded, as explained in the manuscript (Methods/Statistical methods, paragraph 2): "If a CD4 count was not recorded for >12 months, then follow-up was censored at 12 months after the last CD4 count, but that person could re-enter the risk set if another CD4 count was subsequently recorded." We have added text to the manuscript to describe the amount of censored follow-up (Results, paragraph 3): "Nearly two-thirds of participants (65%) did not have any gaps in their follow-up due to CD4 counts not being recorded for >12 months, while 28%, 6%, <1% and <1% of participants had one, two, three or four such gaps in their follow-up, respectively. Across all gaps, the median gap length was 7 months, with an interquartile range of 3-13 months."

Patients who had one CD4 count suggesting ITF, but then died, would have been dealt with appropriately by the competing risks model, ie such patients experienced the competing risk of death before ITF was observed. The reviewer is correct that IFT *may* be missed if a patient had a single CD4 count suggested IFT but was then lost to follow up (LTFU). This is an interesting topic in itself, and we plan to do further work in this area. We felt that the best way to address this concern in this paper was to consider what the results would have looked like if we had only required one CD4 count to determine ITF (ie no confirmatory CD4 count). We have now performed this analysis and amended the manuscript as follows:

- **Methods/Definition of ITF: "We also considered a less strict definition of ITF, which did not require a confirmatory CD4 count (except for the criterion of CD4 count <100 cells/mm^3, since the WHO guidelines explicitly define ITF among individuals with CD4 counts "persistently" <100 cells/mm^3)."**
- **Results/Immunological failure, paragraph 2: "Under the less strict ITF definition, 19,380 (16.0%) participants would have been considered to have experienced ITF, with cumulative probability of 23.8% (23.5,24.2) by three years and 40.6% (39.8,41.5) by six years."**
- **Discussion, paragraph 2: We have revised the comparison to the Nigeria paper and added: "The differences in the estimated IFT rates between definitions requiring and not requiring a confirmatory CD4 count are large. CD4 count measurement is known to have large variability and CD4 count trajectories may display transient changes, thus we believe that it is unlikely that the IFT rates are as high as suggested by the unconfirmed criteria, hence reinforcing the importance of a confirmatory CD4 count, which is typically what clinicians seek in practice."**
- **Discussion, paragraph 8: We have added: "However, the IFT rates indicated by our less strict definition, which did not require a confirmatory CD4 count, were implausibly high."**

Please give justification and implications of the assumption that 12 months after last CD4 should be taken as censorship point rather than date of last CD4 as well as choice of 12 months as date of failure in those found to have failed later but with >12 month gap.

Response: In Tanzania, the current guidelines for patients on ART is for CD4 count to be taken every 6 months, therefore censoring cannot be less than 6 months (under the current guidelines).

For participants without a CD4 count for >12 months, we believe that those 12 months should pass before the participant is declared LTFU with respect to their CD4 counts (i.e. it cannot be known at the time of their last CD4 count that they will become LTFU), therefore we took the date of censoring as 12 months after the last CD4 count.

For those participants who reappeared with a CD4 count more than 12 months after the last one, and whose CD4 count at that point indicated ITF, it was necessary to choose somehow a date to declare ITF. We chose 12 months after the date of last CD4 count for comparability with the LTFU definition above. An alternative would have been to use the date of the confirmatory CD4 (>12 months after the first CD4 indicating ITF) but we felt that this may greatly overestimate the time to ITF, since it is likely that the participant would have reached ITF somewhere between the two CD4 counts, if only the CD4 count had been measured during that time.

We have now performed a sensitivity analysis, using 6 months instead of 12 months, and have amended the manuscript accordingly:

- **Methods/Statistical methods, paragraph 2: "We performed a sensitivity analysis using 6 instead of 12 months for censoring follow-up."**
- **Results/Predictors of ITF, paragraph 2: "Sensitivity analyses censoring follow-up after 6 rather than 12 months … yielded broadly similar results."**

Reference to WHO supplement to guidelines from March 2014 would be important, including detail on new recs regarding CD4/VL monitoring

Response: We thank the reviewer for this suggestion and have amended the text accordingly (Discussion, paragraph 6; changes are highlighted here in grey), including reference to the WHO supplement guidelines of March 2014: "However, in a setting without routine or targeted viral-load monitoring, switching decisions must be made based on the immunological evidence, and this is the situation in many countries across sub-Saharan Africa. New and cheaper viral load tests, using dried blood spots, would ideally be used to perform targeted monitoring of persons with ITF in order to minimize unnecessary switches to second-line treatment, as recommended by the WHO (2). Switching persons who have ITF but not virological failure has individual and economic implications, and such persons would be unlikely to benefit from second-line therapy, therefore it would be important to assess viral load before switch."

The statement on page 12 regarding 'routine viral load monitoring' and immunological monitoring as only alternative fails to mention the standard recommendation (and cost-efficacy) of targetted viral load to reduce unnecessary switches.

Response: We have made the amendments as above with respect to highlighting the recommendations for targeted viral load to reduce unnecessary switch, and indeed the final sentence of the paper reiterates this point (we have amended to include the word "targeted"): "In

order to sustain the benefits of increased coverage, there is a priority to address the need for second-line therapy, and (targeted) virological monitoring is required to minimize unnecessary switches to second-line therapy."

Unclear whether conclusions regarding risks take into account wide differences between early and late (2004 and 2011) cohorts. For example, have you shown that risk related to facility (you suggest some have higher rates of failure) is not confounded by differing time period cohorts in the different facility types?...and fully account for differences in completeness of follow-up data. Would be risky to suggest one type is better than another without clear provisos.

Response: We have adjusted for confounders in the multivariable analysis: the results show that after adjusting for year of ART initiation (among other variables), there remains an association between health facility level and ITF. We considered looking at the interaction between year of ART initiation and health facility level, but we were concerned that there might be a colinearity problem (since in earlier years, participants would have mainly initiated in hospitals, and only later in health centres and dispensaries). We therefore re-ran the final model restricted to participants who initiated ART in 2009 or later, and found broadly similar results. We have added text to the manuscript as follows:

- **Methods/Statistical methods, paragraph 2: "We performed a second sensitivity analysis including only data from 2009 or later (due to concerns about the changes in ART provision, with more being provided by health centres and dispensaries in later years)."**
- **Results/Predictors of ITF, paragraph 2: "Sensitivity analyses … including only participants who initiated in 2009 or later … yielded broadly similar results."**
- **Discussion, paragraph 7: "In addition, our results were robust to sensitivity analyses."**

If possible include more detail and comment on time to switch among those who switched to second line

Response: Results on the time to switch are included in the paragraph in the Results entitled "Switch to second-line therapy", and includes details on the number of participants who were observed to switch and who died before switching, as well as the cumulative probabilities of switch and death. Further results are presented in Figure 2 and Table 3 (and described in the section "Predictors of switch to second-line therapy"). We have provided further comment on the switching rates in the Discussion (paragraph 3; see also below).

Conclusions/discussion would ideally include a little more on role of routine and targetted VL and of barriers and approaches to increasing second line access (ie decentralisation, pricing, supply etc).

Response: We thank the reviewer for these suggestions. As indicated above, we have amended the text to highlight the role of targeted viral load testing. We have added further text to discuss some of the barriers and approaches related to access to second-line ART (Discussion, paragraph 3): "Our results likely reflect what clinicians are doing in practice, regardless of national policies, due to barriers in accessing second-line therapy such as lack of availability and higher cost. Approaches to increase coverage to ART, such as decentralization, could be harnessed to increase access to second-line therapy."

Reviewer #2:

This is an excellently written manuscript. However I have one major comment and a number of minor comments

Major comment:

The outcome here for the competing risks analysis is Immunological Treatment Failure (ITF). This is defined using the CD4 count at treatment initiation and the current CD4 count. There is thus a structural relationship between ITF and CD4 count. I therefore feel that it is inappropriate to use either initial CD4 count or current CD4 count and strongly recommend that they be removed from the model for time to ITF. It is however appropriate to include CD4 count in the model for starting second line treatment

Response: We thank the reviewer for this comment. We have considered this issue very carefully, and agree that the incorporation and interpretation of the time-dependent variables (not just CD4 count) is challenging, as highlighted by Fisher & Lin (1). For this reason, and the relationship between time-dependent CD4 and the IFT outcome, as raised by the reviewer, we have decided to omit the time-dependent variables from the model. We believe this amendment enhances the paper, making it more accessible. We have made revisions throughout the paper accordingly.

Regarding baseline CD4 count, the reviewer states below that "those with a higher initial CD4 are more likely to fail". This is not intuitive to us, and we are not aware of any published data that would suggest this. Furthermore, this relationship is exactly what we are attempting to assess by including baseline CD4 count in the model. Indeed, one could argue that participants with a low initial CD4 count are more likely to experience ITF; for example, participants starting with CD4 <100 cells/mm^3 might be more likely to fail, by having two subsequent CD4 counts <100 cells/mm^3 (even if higher than baseline).

1. **Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health. 1999;20:145–57.**

Minor comments:

In the title it might be appropriate to specify "anti-retroviral therapy (ART)" and later just ART, rather thna just "therapy"

Response: We have amended the title accordingly.

Methods

"First line treatment consists of 2 nucleotide reverse transcriptase inhibitors ..." In fact the only nucleotide reverse transcriptase inhibitor in common use is Tenofovir - Stavudine, AZT and 3TC/FTC are all nucleoside transciptase inhibitors. This should be corrected in the text. Also NNRTI should be described in full the first time it is used.

Response: We have amended the text to read "nucleoside/nucleotide-reverse transcriptase inhibitors" (Methods/HIV care and treatment in Tanzania, paragraph 2). We refer to NNRTI in that paragraph as non-NRTI (NRTI having being defined), and the term NNRTI is not subsequently used.

In the methods it would be useful to have a couple of sentences describing what competing risk analysis actually does, as a number of readers might not be familiar with this method.

Response: We have added text to the Methods section (Statistical methods, paragraph 1; along with a further helpful reference): "Death is a competing risk for IFT because its occurrence prevents us from observing ITF. In such situations, standard Cox proportional-hazards models are not appropriate, and instead competing risks models are required. Such models yield sub-hazards ratios which, although statistically-speaking are different, may be interpreted in the same way as hazard ratios derived from Cox models."

Results

The analysis is based on 121,308 out of 243,844 adults initiating first line ART. SO just over half of potential participants are excluded. The authors should indicate if all 348 clinics are still included in the analysis and in the discussion address possible selection bias effects due to the inclusion criteria.

Response: All 348 clinics are still included in the analysis, and we have clarified this in the text (Results, paragraph 1): "Of the remaining 121,308 participants (representing all 348 clinics)…". In the Results section (paragraph 1), we already indicate why patients are removed from the analysis, and we have now added text to the Discussion (paragraph 8) to discuss the key issue of missing baseline CD4 counts: "Due to the definition of ITF, we were not able to include nearly a third of registered participants since they did not have a baseline CD4 count; it is difficult to know whether this selection has led to bias in our results."

Predictors of ITF

"Compared to persons who were married or cohabiting at treatment initiation, single and divorced or widowed persons ..." This should read "divorced or separated" not "divorced or widowed".

Response: We have corrected this in the text (Results/Predictors of ITF, paragraph 1).

Note that the explanation of the CD4 effect could be completely structural - those with a higher initial CD4 are more likely to fail as there is then more potential to have a subsequent CD4 lower than the initial CD4. This underlines my assertion that inclusion of either CD4 count at treatment initiation or current CD4 count is inappropriate.

Response: Please see the response above.

There is a sentence

"Variable selection to obtain a parsimonious model (removing variables with P<0.05) yielded similar results to the full model"

a) presumably this should be P>0.05 not P<0.05.

b) the authors should indicate whether this was done in a stepwise fashion or simultaneously.

Response: We have corrected the sign in the text (Results/Predictors of ITF, paragraph 3) and clarified that the selection was done in a stepwise fashion.

Immunological failure of first-line antiretroviral therapy (ART) and switch to second-line ART among HIV-infected persons in Tanzania: Analysis of national routinely-collected data

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ABSTRACT

Objectives: Rates of first-line treatment failure and switches to second-line therapy are key indicators for national HIV programs. We assessed immunological treatment failure (ITF) defined by World Health Organization criteria among persons in the Tanzanian national HIV program.

Methods: We included adults initiating first-line therapy in 2004-2011 with a pre-treatment CD4 count, and ≥6 months' follow-up. We assessed sub-hazard ratios (SHR) for ITF, and subsequent switch to second-line therapy, using competing risks methods to account for deaths.

Results: Among 121,308 adults, 8,384 (7%) experienced ITF, and 2,486 (2%) died without observed ITF, over median 1.7 years. The six-year cumulative probability of ITF was 19.0% (95% CI 18.5,19.7) and death 5.1% (4.8,5.4). ITF predictors included earlier year of treatment initiation (p<0.001), initiation in lower-level facilities (SHR=2.23 [2.03,2.45] for dispensaries versus hospitals), being male (1.27 [1.19,1.33]) and initiation at low or high CD4 counts (for example, 1.78 [1.65,1.92] and 5.33 [4.65,6.10] for <50 and ≥500 versus 200-349 cells/mm^3, respectively). Of 7,382 participants in the time-to-switch analysis, 416 (6%) switched, while 355 (5%) died before switching. Four years after ITF, the cumulative probability of switching was 7.3% (6.6,8.0) and death 6.8% (6.0,7.6). Those who immunologically-failed in dispensaries, health centers and government facilities were least likely to switch.

Conclusions: ITF rates and unmet need for second-line therapy are high in Tanzania; virological monitoring, at least for persons with ITF, is required to minimize unnecessary switches to second-line therapy. Lower-level government health facilities need more support to reduce treatment failure rates and improve second-line therapy uptake to sustain the benefits of increased coverage.

INTRODUCTION

The year 2012 saw the largest annual increase of HIV-positive persons receiving antiretroviral therapy (ART), with 9.7 million people in low- and middle-income countries on ART (1). In 21 African countries with the highest HIV burden, two-thirds of people in need of treatment in 2012 were receiving ART (1). Furthermore, with recent treatment guideline changes, the number of people eligible for first-line treatment will increase (2). While work remains to reach all persons in need of treatment, focus has shifted to the implications of providing long-term treatment for what, under the right care, has become a chronic condition.

Monitoring persons on ART for treatment failure is essential to ensure that their treatment remains potent and to enable timely switches from first- to second-line therapy. In South Africa, where routine viral-load monitoring is performed, the proportion of persons switching by 3-5 years after treatment initiation was ~10% (3,4), whereas in settings without routine viral-load monitoring, such as Malawi and Zambia prior to 2011, switching rates were much lower (~2% by 3 years) (4). Delayed switching increases the risk of drug resistance (5,6) and subsequent higher viral load (7–9) and hence impairs clinical outcomes (2), while early, unnecessary switching may reduce treatment options and increase costs. The World Health Organization (WHO) recommends routine viral load monitoring for persons on ART (2), but this remains too expensive for resource-limited countries such as Tanzania. In the absence of viral-load monitoring, treatment failure is diagnosed using immunological and clinical criteria (2), as implemented in Tanzanian policy (10–12). To date, there is a paucity of data on the rates and predictors of first-line treatment failure, and the use of second-line therapy, within national programs using immunological and/or clinical criteria.

Tanzania had an estimated 1.3 million HIV-infected adults in 2011 (13). Of these, ~370,000 adults (28%) were enrolled in care, and ~260,000 were receiving ART, representing 65% in need of treatment (13). Our aim was to investigate the rate and predictors of immunological treatment

failure (ITF), and subsequent switch to second-line therapy, among HIV-infected adults receiving therapy through the Tanzania government program.

METHODS

HIV care and treatment in Tanzania

The Tanzanian National AIDS Control Program (NACP) provides HIV prevention, care and treatment services. In late 2003, the first HIV/AIDS Care and Treatment Plan was launched, and free ART was rolled out from 2004. By the end of 2011, >1100 facilities were approved to provide care and treatment services, estimated to enable >1 million persons potentially to access ART (13).

HIV-positive persons enrolling in care and treatment clinics are assessed for ART eligibility, defined pre-2012 (data collection period) as CD4 count <200 cells/mm^3, or CD4 count <350 cells/mm^3 and WHO stage III, or WHO stage IV regardless of CD4 count (10,11). Persons not yet eligible for ART are encouraged to attend clinics six-monthly for pre-treatment monitoring, while those on treatment attend monthly. First-line treatment consists of 2 nucleoside/nucleotide-reverse transcriptase inhibitors (NRTIs) and a non-NRTI, while second-line therapy included 2 NRTIs plus a protease inhibitor. Individual paper-based records, including unique, nationally-attributed patient identifiers, are maintained at each facility, and subsequently electronically-entered by data entry clerks before being regularly submitted to the national database.

Study population

We included data from clinics reporting electronic, individual-level data to the end of 2011. We included persons who initiated first-line ART in 2004-2011 aged ≥15 years with a pre-ART CD4 count available, and who completed ≥6 months of follow-up.

Definition of ITF

The Tanzanian 2005 National Guidelines for the Clinical Management of HIV and AIDS defined ITF as CD4 count <30% of peak on-treatment value or <pre-treatment levels (10); this definition was revised in 2009 to CD4 count <50% of peak value within 6 months or <pre-treatment levels (11). This resembles the WHO 2010 Antiretroviral Therapy for HIV Infection in Adults and Adolescents guidelines which defined ITF as CD4 count <50% of peak value or <pre-treatment levels, or persistently <100 cells/mm^3 (14); the WHO guidelines were revised in 2013 to remove the criterion of a 50% drop (2). For this analysis, we used the WHO 2010 guidelines, with a second consecutive confirmatory CD4 count for the definition of ITF, to rule out transient drops in CD4 counts due to other infections or measurement error. ITF was only defined ≥6 months after treatment initiation (2). We also considered a less strict definition of ITF, which did not require a confirmatory CD4 count (except for the criterion of CD4 count <100 cells/mm^3, since the WHO guidelines explicitly define ITF among individuals with CD4 counts "persistently" <100 cells/mm^3).

Statistical methods

We assessed ITF and death rates and predictors using competing risks methods to account for deaths. Death is a competing risk for IFT because its occurrence prevents us from observing ITF. In such situations, standard Cox proportional-hazards models are not appropriate, and instead competing risks models are required. Such models yield sub-hazards ratios which, although statistically-speaking are different, may be interpreted in the same way as hazard ratios derived from Cox models (15,16) . Among those with ITF, we assessed switch to second-line therapy, using similar methods. Loss to follow up was considered uninformative. Body mass index (BMI) was not included in multivariable models, as it was missing for ~70% of visits, mainly due to missing height.

Data were censored at 31 December 2011. If a CD4 count was not recorded for >12 months, then follow-up was censored at 12 months after the last CD4 count, but that person could re-enter the risk set if another CD4 count was subsequently recorded. If the person reappeared with ITF, then

he/she was considered to have immunologically-failed at 12 months after the last CD4 count recorded before the gap. Time-dependent variables at ART initiation or switch were defined as the closest up to 3 months earlier, and if none then up to 2 weeks after (except for CD4 count at treatment initiation, which permitted up to 4 weeks after, to allow for delayed reporting of CD4 counts). We performed a sensitivity analysis using 6 instead of 12 months for censoring follow-up. We performed a second sensitivity analysis including only data from 2009 or later (due to concerns about the changes in ART provision, with more being provided by health centres and dispensaries in later years).

For the analysis of switch to second-line therapy, individuals who changed to an unknown ART regimen were censored at that time; those with missing ART information were considered to still be continuing on their first-line regimen. Intermittent regimens of duration ≤14 days were ignored. Individuals with missing ART information from the date when they were last known to be on first-line therapy until the date they switched to second-line therapy were assumed to have switched at the mid-point between these dates. Participants who changed therapy on the day of ITF were given one day of follow-up. Analyses were conducted using Stata version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP). P-values are 2-sided.

Ethical considerations

This analysis was conducted on routinely-collected data under the auspices of the NACP and approved by the London School of Hygiene & Tropical Medicine ethics committee. Unique patient identifiers were used to preserve anonymity, and all names and personal identifiers were removed before analysis.

RESULTS

In 348 clinics, 243,844 adults initiated first-line ART. Of these, 71,285 (29%) participants did not have a pre-treatment CD4 count recorded: 23,038 (32%) were WHO stage IV (among whom treatment should have been initiated regardless of CD4 count as per treatment guidelines (10,11)), but 5,608 (8%) did not have WHO stage recorded, and 26,599 (37%), 11,180 (16%) and 4,860 (7%) were WHO stages I, II and III, respectively (perhaps suggesting missing CD4 count data). Of the remaining 172,559 participants, 11,397 (7%) died within the first six months after treatment initiation, 13,625 (8%) initiated treatment in the last six months of 2011 and therefore had <6 months of follow-up, and 26,229 (15%) were lost to follow-up within six months; these participants are excluded.

Of the remaining 121,308 participants (representing all 348 clinics), 73% initiated ART in hospitals and 67% initiated in government-run facilities (Table 1). Two-thirds of participants were female, 55% were married or cohabiting, and 89% were working. 26% of participants initiated ART with low BMI (<18.5 kg/m^2), 16% with WHO stage IV and 73% with low CD4 count (<200 cells/mm^3). The most common first-line ART regime was stavudine-based (61%), mainly driven by data from earlier years. The use of zidovudine, lamivudine and nevirapine or efavirenz increased from 8% and 10% respectively in 2008, to 36% and 40% respectively in 2011, following the elimination of stavudine in 2010 (Supplementary Table 1).

Nearly two-thirds of participants (65%) did not have any gaps in their follow-up due to CD4 counts not being recorded for >12 months; 28%, 6%, <1% and <1% of participants had one, two, three or four such gaps in their follow-up, respectively. Across all gaps, the median gap length was 7 months, with an interquartile range of 3-13 months.

Immunological failure

Subsequent to the first six months on ART, 8,384 (7%) participants experienced ITF and 2,486 (2%) died without ITF being observed, over a median of 1.7 years (maximum eight years). Of those

experiencing ITF, 1,995 (24%) participants had CD4 counts <pre-treatment levels, 1,400 (17%) <50% of on-treatment peak, 2,625 (31%) <100 cells/mm^3, and 2,364 (28%) had a combination of these components (Supplementary Table 2). The cumulative probability of ITF by six years (to when we had sufficient data for reliable estimation) was 19.0% (95% CI: 18.5,19.7) and of death (without ITF) was 5.1% (4.8,5.4; Figure 1).

Under the less strict ITF definition, 19,380 (16.0%) participants would have been considered to have experienced ITF, with cumulative probability of 23.8% (23.5,24.2) by three years and 40.6% (39.8,41.5) by six years.

Predictors of ITF

Using the definition of IFT with confirmatory CD4 count, in adjusted analyses, higher risk of ITF was found among those who initiated treatment in lower-level facilities and in "other" facilities, which predominantly included institutional facilities with restricted access (*P*<0.001; Table 2). However, those in "other" facilities had lowest death rate (0.6 versus 1.1/100 person-years in hospitals). The ITF risk was lower in private versus government facilities facilities (sub-hazard ratio, SHR=0.59 [95% confidence interval, CI: 0.50,0.69]), with no difference for faith-based facilities (SHR=1.01 [0.95,1.07]). There was lower ITF risk with later year of treatment initiation (*P*<0.001), and death rates decreased from 1.2/100 to 0.5/100 person-years among those who initiated treatment pre-2006 and in 2011, respectively. Females had lower ITF risk than men (SHR=0.79 [0.75,0.84]). Compared to persons who were married or cohabiting at treatment initiation, single persons were at higher ITF risk (SHR=1.12 [1.05,1.20]), but there was no evidence of a difference for those divorced or separated, or widowed.

Persons initiating treatment with lower weight were at somewhat higher risk of ITF (SHR=1.07 [0.99,1.16] and 1.08 [1.02,1.14] for <45 and 45-<55 versus ≥55 kg, respectively). There was some

difference in ITF risk by WHO stage at treatment initiation (p=0.03), although no clear trend across the stages. Of note, the competing risk of death varied by stage (0.5 versus 1.5/100 person-years for WHO stage I and IV, respectively). Persons who initiated with the lowest CD4 counts were at higher risk of ITF (SHR=1.78 [1.65,1.92] for <50 versus 200-349 cells/mm^3). However, persons initiating with high CD4 counts were also at higher ITF risk (SHR=2.51 [2.20,2.86] and 5.33 [4.65,6.10] for 350-499 and ≥500 versus 200-349 cells/mm^3, respectively). In the unadjusted model, persons who initiated on zidovudine-based regimens had a lower ITF risk versus stavudine-based regimens; this relationship was reversed once we adjusted for confounders (SHR=1.14 [1.06,1.21]). Persons who initiated treatment with other regimens had much higher ITF risk (SHR=6.12 [4.90,7.65] versus stavudine-based). There was no evidence of a difference in ITF risk by age (*P*=0.58) or functional status (*P*=0.21). Variable selection to obtain a parsimonious model (removing variables in a stepwise fashion with *P*>0.05) yielded similar results to the full model. Sensitivity analyses censoring follow-up after 6 rather than 12 months, or including only participants who initiated in 2009 or later, yielded broadly similar results.

Switch to second-line therapy

Of 8,384 persons who immunologically-failed on first-line therapy, 135 (2%) had previously used second-line therapy, 276 (3%) had previously taken an unknown regimen and 591 (7%) had an ITF date estimated at 12 months after the last CD4 count before a gap of >12 months; these persons are excluded from the following analyses. Of the remaining 7,382 (88%) participants, 40% had been on first-line ART for <1 year, 34% for 1-<2 years and 27% for ≥2 years (Table 1). The distribution of participant characteristics at the time of ITF broadly reflected those at ART initiation. The proportions of participants with CD4 counts of <50, 50-199, 200-349, 350-499 and ≥500 cells/mm^3 at ITF were 25%, 50%, 18%, 5% and 2%, respectively.

Overall, 416 (6%) persons were observed to subsequently switch to second-line therapy, while 355 (5%) died before switching. By four years after ITF, the cumulative probability of switching was 7.3% (95% CI: 6.6,8.0) and of death 6.8% (6.0,7.6; Figure 2).

The most common second-line regimen to which people switched was abacavir, didanosine and ritonavir-boosted lopinavir (n=343; 82%), followed by tenofovir, emtricitabine and ritonavir-boosted lopinavir (43; 10%). The reasons for switch were not reported for 162 (39%) individuals; of those given, the most common reasons were ITF (184; 72%) or clinical treatment failure (20; 8%).

Predictors of switch to second-line therapy

In adjusted analyses, there were large differences in the switching rates by facility level and type, with those who immunologically-failed in health centers and dispensaries being less likely to switch than those in hospitals (SHR=0.43 [95% CI: 0.26,0.71] and 0.50 [0.27,0.93], respectively), and those in "other" facilities more likely to switch (SHR=2.27 [1.52,3.39]). People who experienced ITF in faith-based facilities were much more likely to switch than those in government facilities (SHR=2.29 [1.79,2.91]). We observed less frequent switching with later year of ITF (P<0.001). Women were less likely to switch than men (SHR=0.77 [0.60,0.97]). Persons at lower WHO stage at treatment initiation were more likely to switch (P<0.001; for example, SHR=1.64 [1.18,2.28] for WHO stage I versus III). Persons with lower CD4 count at ITF were much more likely to switch (P<0.001; for example, SHR=6.33 [4.03,9.95] for <50 versus 200-349 cells/mm^3). Persons who had initiated ART on zidovudine-based therapy were more likely to switch than those on stavudine-based regimens (SHR=1.76 [1.36,2.29]). There was increasing probability of switch with increasing time on therapy (P<0.001). There was no evidence of a difference in switching rates by age (P=0.76), marital status (P=0.35), functional status (P=0.34) or weight (P=0.54).

DISCUSSION

In this study of >120,000 HIV-infected adults initiating first-line therapy in Tanzania, the need for second-line therapy was high, with ITF rates of 19% by 6 years after treatment initiation. The analysis was restricted to persons with ≥6 months of follow-up, excluding the 7% of people who died within 6 months; nonetheless, over the following 6 years, there was a 5% cumulative probability of death without observed ITF. Following ITF, the cumulative probability over 4 years of switching to second-line therapy was 7%, which was approximately the same as that of death (7%).

To our knowledge, this is the first study to assess ITF rates and switches to second-line therapy among adults on first-line ART using national routinely-collected data. In a recent study from Nigeria, which used the same WHO criteria for ITF but without a confirmatory CD4 count, the cumulative probability of ITF was ~35% by 3 years, similar to our estimation of 24% under the less strict ITF definition (17). When a confirmatory CD4 count was incorporated in the Nigerian analysis, the overall proportion of participants experiencing ITF reduced from 32% to 10% and therefore the cumulative ITF probability when incorporating a confirmatory CD4 count (not directly reported) is likely to be similar to that observed under the main IFT definition in our study. The differences in the estimated IFT rates between definitions requiring and not requiring a confirmatory CD4 count are large. CD4 count measurement is known to have large variability and CD4 count trajectories may display transient changes, thus we believe that it is unlikely that the IFT rates are as high as suggested by the unconfirmed criteria, hence reinforcing the importance of a confirmatory CD4 count, which is typically what clinicians seek in practice.

Encouragingly, ITF rates dropped with later calendar year of ART initiation, with 72% lower risk among those who initiated in 2011 versus 2008, which may be attributable to improvements in care and drug efficacy. Switching rates also decreased over time, with 59% lower “risk” of switching among those who immunologically-failed in 2011 versus 2008, perhaps suggesting that the national program in Tanzania has not yet organized itself for widespread second-line therapy use. The overall

low switching rates observed in this study indicate that there is a large unmet need for second-line therapy, and so this should be a future priority for the ART program if excess morbidity and mortality among persons on ART are to be minimized. Our results likely reflect what clinicians are doing in practice, regardless of national policies, due to barriers in accessing second-line therapy such as lack of availability and higher cost. Approaches to increase coverage to ART, such as decentralization, could be harnessed to increase access to second-line therapy.

We found important differences in the rates of both ITF and switching by the types of facilities participants were attending. The Tanzanian HIV program has successfully devolved care to lower-level clinics, and there are calls for similar initiatives for the management of other chronic diseases (18). However, the higher ITF rates and lower switching rates in lower-level and particularly government-owned facilities highlights that adequate training and support is required for front-line health-care workers, along with a stable drug supply chain and adequate equipment, to ensure that consistent services are provided.

We have identified key sub-groups of the population who may be at higher ITF risk, including men, single persons, and those with lower weight at ART initiation. Men typically have poorer healthcare-seeking behaviors than women, as illustrated by mean lower CD4 counts at enrolment to HIV care (5,13), poorer ART uptake (19), and the higher ITF risk observed in this study. In contrast, we found that women were less likely to switch to second-line therapy than men; the reasons for this are unclear and this finding warrants further investigation. The drivers behind the higher ITF risk with zidovudine-based and other first-line regimens, compared to stavudine-based therapy, are unclear. Stavudine has been phased out since 2010, and tenofovir-based regimens are now recommended. Although only a small percentage of participants initiated tenofovir in this cohort, its use is increasing. Both low and high CD4 count at ART initiation were associated with higher ITF risk. Participants starting treatment with CD4 counts <100 cells/mm^3 would have met the definition for

ITF if they had two subsequent CD4 counts <100 cells/mm^3, even if higher than their baseline value. Individuals initiating treatment at high CD4 counts were likely to be different in some way; for example, they may be presenting for care due to an opportunistic infection. While we have controlled for the confounders routinely captured in the national data, such as WHO stage, there may remain residual confounding.

Lower CD4 count at ITF was strongly associated with switching; nonetheless, our results indicate that there remains a large need for second-line therapy which is not being met, with the probability of switch among those who have immunologically-failed being only 7% by 4 years. The poor predictive ability of ITF for virological failure is well-known (17,22–26), meaning that persons with a low CD4 count may not necessarily have virologically-failed. However, in a setting without routine or targeted viral-load monitoring, switching decisions must be made based on the immunological evidence (2), and this is the situation in many countries across sub-Saharan Africa. New and cheaper viral load tests, using dried blood spots, would ideally be used to perform targeted monitoring of persons with ITF in order to minimize unnecessary switches to second-line treatment, as recommended by the WHO (27). Switching persons who have ITF but not virological failure has individual and economic implications, and such persons would be unlikely to benefit from second-line therapy, therefore it would be important to assess viral load before switch.

A strength of this study is the use of appropriate statistical methodology, namely competing risks analysis, to take into account the correlation between death and ITF. A naïve approach would be to use proportional hazards regression, ignoring the competing risk of death for ITF. Such an approach underestimates the ITF rate, due to deaths occurring in those with unobserved ITF. This under-estimation may be greater in a resource-poor setting with less-intensive CD4 monitoring. In addition, our results were robust to sensitivity analyses.

While we included over 120,000 persons in this analysis, the 348 clinics included do not represent every region in Tanzania, as the analysis was restricted to clinics who submitted electronic data in 2011. Due to the definition of ITF, we were not able to include nearly a third of registered participants since they did not have a baseline CD4 count; it is difficult to know whether this selection has led to bias in our results. Attrition rates from care and treatment clinics in Tanzania are high (28), and it is likely that many deaths remain unreported, therefore our mortality rates will be underestimates. While we attempted to address incompleteness of immunological data by censoring follow-up when no CD4 count had been recorded for >12 months, it may be that incomplete data contributes to the deaths without ITF. Information on causes of death might help inform this question further, but these data are not currently captured. We used the WHO 2010 ITF criteria, covering the majority of the data collection period (14); application of the WHO 2013 guidelines would yield lower ITF rates (2). The implications of different definitions could be explored, including the incorporation of persons who initiated at WHO stage IV without CD4 measurements recorded. Further, interpretations of ITF were required for analysis, for example related to "persistent" CD4 count <100 cells/mm^3. This raises questions about how the guidelines are interpreted in clinical practice. The guidelines state that transient drops in CD4 count should be ignored and we attempted to address this by requiring a confirmatory CD4 count for ITF, but we may therefore have underestimated the ITF rate. However, the IFT rates indicated by our less strict definition, which did not require a confirmatory CD4 count, were implausibly high. Detailed information on clinical treatment failure was not captured, although the number of persons switching to second-line therapy in the absence of ITF was low, suggesting perhaps that clinical failure – which may be more complex to diagnose – may not be adequately assessed in clinics. This study does not attempt to address the optimal time to switch to second-line therapy to minimize adverse outcomes, which is of importance and should be considered for future work. As second-line therapy use increases, work should address outcomes after switch, particularly as a substantial proportion of persons may be expected not to achieve virological suppression (7,29).

In summary, we have used national routinely-collected data to investigate ITF rates in Tanzania; such rates are high, and the need for second-line treatment is not currently being met. The Tanzanian national control program has successfully focused on ART roll-out, and this remains crucial, particularly with new WHO guidelines recommending earlier initiation (2). In order to sustain the benefits of increased coverage, there is a priority to address the need for second-line therapy, and (targeted) virological monitoring is required to minimize unnecessary switches to second-line therapy.

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TABLES

Table 1. Participant characteristics at ART initiation and immunological treatment failure.

		At ART initiation [1]		At immunological failure [1,2]	
		N=121,308		N=7,382	
Health facility level	Hospital	87,770	(72.7%)	4,712	(64.3%)
	Health center	16,798	(13.9%)	1,189	(16.2%)
	Dispensary	13,131	(10.9%)	1,027	(14.0%)
	Other [3]	2,995	(2.5 %)	397	(5.4 %)
Health facility type	Government	74,789	(66.7%)	4,696	(68.8%)
	Faith-based	28,343	(25.3%)	1,712	(25.1%)
	Private	8,947	(8.0 %)	413	(6.1 %)
Year	Up to end 2005	5,951	(4.9 %)	42	(0.6 %)
	2006	12,181	(10.0%)	471	(6.4 %)
	2007	19,770	(16.3%)	954	(12.9%)
	2008	26,158	(21.6%)	1,396	(18.9%)
	2009	25,726	(21.2%)	1,559	(21.1%)
	2010	22,121	(18.2%)	1,581	(21.4%)
	2011	9,401	(7.7 %)	1,379	(18.7%)
Sex	Male	40,055	(33.0%)	2,630	(35.6%)
	Female	81,250	(67.0%)	4,752	(64.4%)
Age, years	15-29	23,412	(19.3%)	953	(12.9%)
	30-39	50,750	(41.8%)	3,063	(41.5%)
	40-49	31,848	(26.3%)	2,263	(30.7%)
	≥50	15,278	(12.6%)	1,099	(14.9%)
Marital status [4]	Single	24,757	(22.2%)	1,648	(25.2%)
	Married or cohabiting	61,586	(55.3%)	3,493	(53.4%)
	Divorced or separated	11,866	(10.7%)	635	(9.7 %)
	Widowed	13,156	(11.8%)	765	(11.7%)
Functional status	Working	102,301	(88.7%)	6,980	(96.9%)
	Ambulatory	11,866	(10.3%)	177	(2.5 %)
	Bed-ridden	1,177	(1.0 %)	49	(0.7 %)
Weight, kg	<45	21,754	(18.1%)	690	(9.4 %)
	45-<55	47,019	(39.1%)	2,292	(31.2%)
	≥55	51,633	(42.9%)	4,365	(59.4%)
BMI [5]	Underweight	11,035	(26.2%)	427	(13.4%)
	Normal	25,097	(59.6%)	2,030	(63.7%)
	Overweight	6,002	(14.2%)	732	(23.0%)
WHO stage [4]	I	11,586	(10.4%)	562	(9.0 %)
	II	27,636	(24.9%)	1,445	(23.0%)
	III	53,603	(48.3%)	3,169	(50.5%)
	IV	18,158	(16.4%)	1,102	(17.6%)
CD4 count, cells/mm^3	<50	24,339	(20.1%)	1,822	(24.7%)
	50-199	64,753	(53.4%)	3,684	(49.9%)
	200-349	27,375	(22.6%)	1,333	(18.1%)
	350-499	3,250	(2.7 %)	383	(5.2 %)
	≥500	1,591	(1.3 %)	158	(2.1 %)
First ART regimen [4]	Stavudine-based	73,402	(60.5%)	5,287	(71.6%)
	Zidovudine-based	46,739	(38.5%)	2,008	(27.2%)
	Other first-line	1,167	(1.0 %)	87	(1.2 %)
Time on first-line ART, years	<1			2,950	(40.0%)
	1-<2			2,475	(33.5%)
	≥2			1,957	(26.5%)

ART=antiretroviral therapy. BMI=body mass index. [1] Values are number (% of those with non-missing data). [2] Restricted to those included in the switching analysis (see main text). [3] "Other" facilities predominantly included institutional facilities with restricted access. [4] At ART initiation (not updated at immunological failure; marital status only recorded at enrolment into care). [5] BMI categorized as underweight (<18.5 kg/m^2), normal (18.5-<25.0 kg/m^2) or overweight (≥25 kg/m^2).

Table 2. Associations of participant characteristics at ART initiation with immunological treatment failure and death, after first-line treatment initiation.

	Immunological failure			Death (before immunological failure)			Sub-hazard ratio (95% confidence interval) for immunological failure			
	Rate per 100 person-years	N events	Person-years	Rate per 100 person-years	N events	Person-years	Univariable models		Full multivariable model	
Health facility level							*P*<0.001		*P*<0.001	
Hospital	3.2	5,776	179,186	1.1	1,911	179,186	1		1	
Health center	3.3	966	28,865	1.0	302	28,865	1.05	0.98, 1.12	1.19	1.10,1.29
Dispensary	4.8	1,133	23,735	0.9	214	23,735	1.51	1.41, 1.61	2.23	2.03,2.45
Other [1]	5.8	448	7,763	0.6	50	7,763	1.75	1.59, 1.93	1.73	1.54,1.95
Health facility type							*P*=0.01		*P*<0.001	
Government	3.5	5,169	147,962	1.0	1,455	147,962	1		1	
Faith-based	3.3	1,996	59,877	1.2	714	59,877	0.94	0.89, 0.99	1.01	0.95,1.07
Private	3.1	540	17,209	0.8	145	17,209	0.91	0.83, 0.99	0.59	0.50,0.69
Year							*P*<0.001		*P*<0.001	
Up to end 2005	5.2	1,029	19,724	1.2	228	19,724	2.06	1.90, 2.24	2.47	2.22,2.73
2006	4.8	1,732	35,781	1.2	421	35,781	1.86	1.74, 1.99	1.90	1.75,2.07
2007	3.9	1,986	50,880	1.1	553	50,880	1.42	1.33, 1.52	1.41	1.31,1.52
2008	2.8	1,610	56,696	1.1	597	56,696	1		1	
2009	3.2	1,376	43,500	1.0	423	43,500	1.1	1.02, 1.18	0.88	0.81,0.97
2010	2.3	612	27,165	0.8	230	27,165	0.84	0.76, 0.92	0.60	0.54,0.68
2011	0.6	39	6,875	0.5	34	6,875	0.39	0.28, 0.54	0.28	0.20,0.40
Sex							*P*<0.001		*P*<0.001	
Male	4	3,017	76,151	1.4	1,065	76,151	1		1	
Female	3.3	5,367	164,463	0.9	1,421	164,463	0.82	0.79, 0.86	0.79	0.75,0.84
Age, years							*P*=0.60		*P*=0.58	
15-29	3.4	1,537	44,600	0.9	411	44,600	0.98	0.93, 1.04	0.95	0.89,1.03
30-39	3.5	3,587	101,822	0.9	932	101,822	1		1	
40-49	3.5	2,254	64,512	1.0	669	64,512	0.99	0.94, 1.04	1.01	0.94,1.07
≥50	3.4	1,002	29,648	1.6	474	29,648	0.95	0.89, 1.02	0.98	0.90,1.07
Marital status							*P*<0.001		*P*=0.004	
Single	3.8	1,888	49,109	1.1	517	49,109	1.14	1.08, 1.21	1.12	1.05,1.20
Married or cohabiting	3.3	3,955	118,396	1.0	1,155	118,396	1		1	
Divorced or separated	3.2	736	22,679	1.1	239	22,679	0.97	0.90, 1.05	1.06	0.97,1.16
Widowed	3.2	860	26,536	0.9	252	26,536	0.97	0.90, 1.04	1.05	0.96,1.14
Functional status							*P*=0.83		*P*=0.21	
Working	3.4	6,774	196,437	0.9	1,852	196,437	1		1	
Ambulatory	3.4	863	25,060	1.6	394	25,060	0.98	0.91, 1.05	0.92	0.85,1.01
Bed-ridden	3.4	80	2,335	1.9	45	2,335	0.97	0.78, 1.21	0.99	0.78,1.25
Weight, kg							*P*<0.001		*P*=0.03	
<45	3.8	1,600	42,615	1.4	615	42,615	1.14	1.08, 1.21	1.07	0.99,1.16
45-<55	3.6	3,258	91,619	1.0	961	91,619	1.09	1.04, 1.14	1.08	1.02,1.14
≥55	3.3	3,430	104,635	0.8	887	104,635	1		1	
BMI [2]							*P*=0.001			
Underweight	4.2	1,022	24,193	0.9	227	24,193	1.12	1.04, 1.20		
Normal	3.8	2,095	55,456	0.6	338	55,456	1			
Overweight	3.5	474	13,516	0.5	63	13,516	0.93	0.84, 1.03		
WHO stage							*P*<0.001		*P*=0.03	
I	2.8	638	22,513	0.5	119	22,513	0.83	0.76, 0.90	0.92	0.84,1.01
II	3.2	1,630	51,678	0.8	431	51,678	0.93	0.87, 0.98	1.04	0.98,1.11
III	3.4	3,589	104577	1.1	1,122	104,577	1		1	
IV	3.7	1,288	34,879	1.5	529	34,879	1.07	1.01, 1.14	0.94	0.88,1.02
CD4 count, cells/mm^3							*P*<0.001		*P*<0.001	
<50	5.8	2,741	47,534	1.4	649	47,534	1.95	1.83, 2.08	1.78	1.65,1.92
50-199	2.5	3,402	133,708	1.0	1,330	133,708	0.86	0.80, 0.91	0.78	0.72,0.84
200-349	2.9	1,496	51,208	0.8	411	51,208	1		1	
350-499	6.8	382	5,623	1.0	58	5,623	2.36	2.11, 2.64	2.51	2.20,2.86

≥500	14.2	363	2,548	1.5	38	2,548	4.96	4.44, 5.55	5.33	4.65,6.10
First ART regimen							*P*<0.001		*P*<0.001	
Stavudine-based	3.6	6,059	167,123	1.1	1,840	167,123	1		1	
Zidovudine-based	3.1	2,233	72,418	0.9	637	72,418	0.9	0.85, 0.94	1.14	1.68,1.21
Other first-line	8.5	92	1,080	0.8	9	1,080	3.36	2.73, 4.13	6.12	4.90,7.65

ART=antiretroviral therapy. BMI=body mass index. "1" indicates the reference category. [1] "Other" facilities predominantly included institutional facilities with restricted access. [2] BMI categorized as underweight (<18.5 kg/m^2), normal (18.5-<25.0 kg/m^2) or overweight (≥25 kg/m^2).

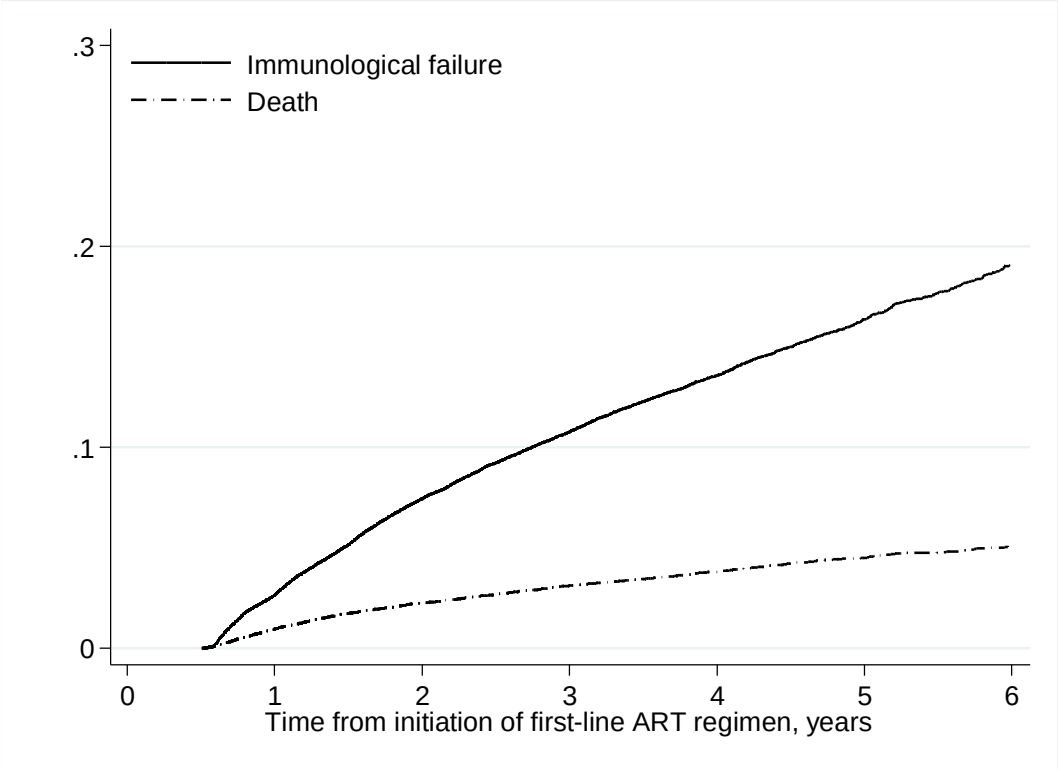
Table 3. Rates and predictors of switching, after immunological treatment failure.

	Rate per 100 person-years	N events	Person-years	Sub-hazard ratio (95% confidence interval) Univariable models		Full multivariable model	
Health facility level				*P*<0.001		*P*<0.001	
Hospital	2.7	315	11,462	1		1	
Health center	1.3	27	2,075	0.42	0.29, 0.63	0.43	0.26,0.71
Dispensary	1.1	21	1,964	0.31	0.20, 0.48	0.50	0.27,0.93
Other [1]	5.9	53	900	2.02	1.50, 2.71	2.27	1.52,3.39
Health facility type				*P*<0.001		*P*<0.001	
Government	2.1	226	10,917	1		1	
Faith-based	4.8	176	3,667	2.26	1.86, 2.75	2.29	1.79,2.91
Private	1.2	10	825	0.53	0.28, 0.99	[2]	[2]
Year				*P*=0.004		*P*<0.001	
Up to end 2005	3.6	8	223	1.70	0.83, 3.49	1.08	0.35,3.32
2006	1.8	39	2,211	0.87	0.61, 1.26	1.21	0.76,1.90
2007	2.0	75	3,676	0.90	0.67, 1.21	1.25	0.88,1.77
2008	2.7	111	4,184	1		1	
2009	3.0	100	3,339	0.90	0.69, 1.19	0.86	0.62,1.19
2010	2.4	52	2,186	0.55	0.39, 0.76	0.47	0.31,0.70
2011	4.7	31	666	0.65	0.43, 0.97	0.41	0.25,0.65
Sex				*P*=0.005		*P*=0.03	
Male	3.1	174	5,668	1		1	
Female	2.2	242	10,818	0.76	0.62, 0.92	0.77	0.60,0.97
Age, years				*P*=0.23		*P*=0.76	
15-29	3.0	67	2,253	1.32	1.00, 1.76	1.07	0.75,1.52
30-39	2.3	160	7,003	1		1	
40-49	2.5	123	4,984	1.06	0.84, 1.34	0.94	0.72,1.23
≥50	2.9	65	2,231	1.19	0.89, 1.58	0.86	0.61,1.23
Marital status [3]				*P*=0.21		*P*=0.35	
Single	2.9	102	3,483	1.20	0.94, 1.53	1.21	0.93,1.59
Married or cohabiting	2.4	180	7,442	1		1	
Divorced or separated	2.0	27	1,349	0.83	0.55, 1.25	0.92	0.60,1.42
Widowed	2.8	48	1,698	1.20	0.87, 1.65	1.24	0.87,1.75
Functional status				*P*=0.43		*P*=0.34	
Working	2.6	394	15,126	1		1	
Ambulatory	1.6	7	439	0.64	0.30, 1.35	0.50	0.20,1.26
Bed-ridden	1.6	2	123	0.67	0.16, 2.74	0.94	0.22,4.08
Weight, kg				*P*=0.92		*P*=0.54	
<45	2.7	39	1,446	0.99	0.71, 1.39	1.05	0.70,1.59
45-<55	2.5	124	4,939	0.96	0.77, 1.19	0.87	0.67,1.14
≥55	2.5	253	10,058	1		1	
WHO stage [3]				*P*<0.001		*P*<0.001	
I	4.2	51	1,201	1.73	1.27, 2.37	1.64	1.18,2.28
II	3.0	86	2,867	1.16	0.89, 1.50	1.11	0.84,1.47
III	2.5	171	6,882	1		1	
IV	1.6	37	2,288	0.63	0.44, 0.89	0.56	0.38,0.81
CD4 count, cells/mm^3				*P*<0.001		*P*<0.001	
<50	2.9	115	3,975	2.16	1.51, 3.11	6.33	4.03,9.95
50-199	3.0	255	8,543	2.31	1.65, 3.23	3.70	2.42,5.67
200-349	1.3	39	2,927	1		1	
≥350	0.7	7	1,041	0.48	0.21, 1.06	0.52	0.20,1.36
First ART regimen [3]				*P*=0.07		*P*<0.001	
Stavudine-based	2.3	301	13,018	1		1	
Zidovudine-based	3.4	115	3,414	1.22	0.99, 1.52	1.76	1.36,2.29
Other first line	0	0	55	[4]		[4]	
Time on first-line ART, years				*P*<0.001		*P*<0.001	
<1	1.2	101	8,378	1		1	
1-<2	2.9	155	5,433	2.12	1.65, 2.72	2.34	1.72,3.17
≥2	6.0	160	2,674	3.58	2.80, 4,58	5.34	3.84,7.44

ART=antiretroviral therapy. "1" indicates the reference category. [1] "Other" facilities predominantly included institutional facilities with restricted access. [2] Not reliably estimable since few switches to second-line therapy, therefore omitted this category from the model. [3] At ART initiation rather than immunological failure (marital status only recorded at CTC enrolment). [4] Omitted from the model since no-one in this category was observed to switch to second-line therapy.

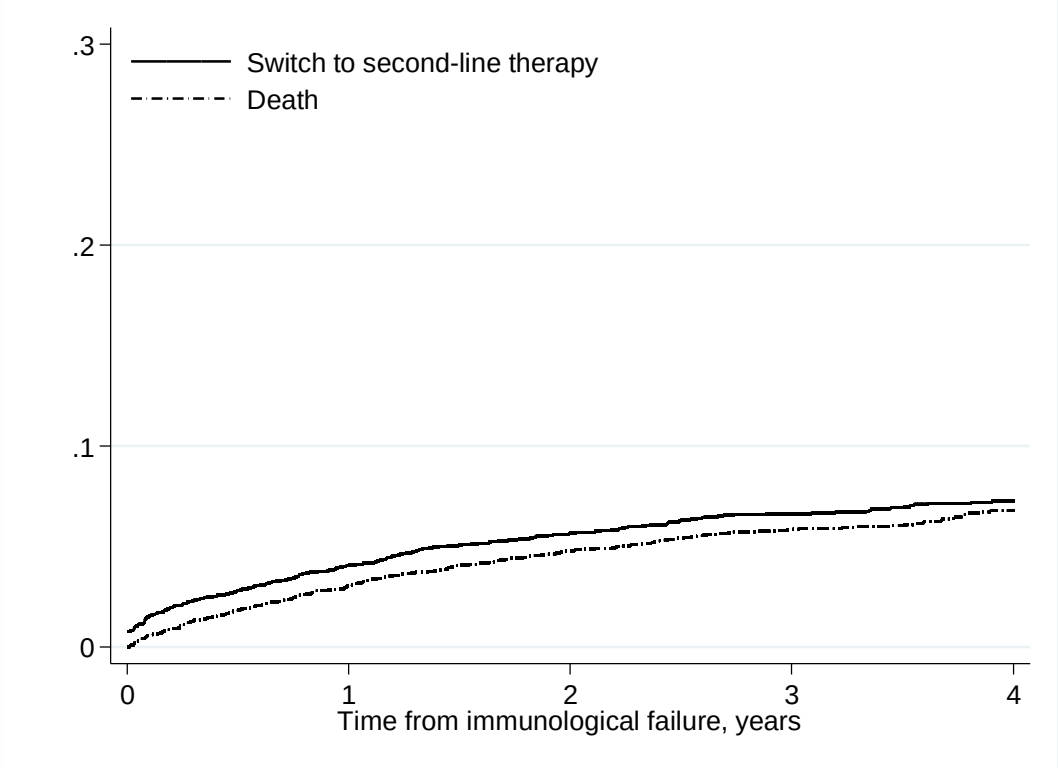
FIGURES

Figure 1. Probability of immunological treatment failure or death, following initiation of first-line ART.



ART=antiretroviral therapy. Y-axis truncated at 0.3. Persons with <6 months of follow-up (including due to death) were excluded from the analyses. Immunological failure was not defined until at least 6 months after treatment initiation.

Figure 2. Probability of switch from first- to second-line ART or death, following immunological treatment failure.



ART=antiretroviral therapy. Y-axis truncated at 0.3. Participants who changed therapy on the day of immunological failure were given 1 day of follow-up, so that they were included in the time-to-event analyses.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. First-line ART regimen by year of treatment initiation.

	Up to end 2005	2006	2007	2008	2009	2010	2011
	N=5,951	N=12,181	N=19,770	N=26,158	N=25,726	N=22,121	N=9,401
Stavudine, lamivudine, nevirapine	5,081 (85%)	10,251 (84%)	15,422 (78%)	20,290 (78%)	11,938 (46%)	4,411 (20%)	1,497 (16%)
Stavudine, lamivudine, efavirenz	191 (3%)	712 (6%)	1,122 (6%)	1,162 (4%)	834 (3%)	382 (2%)	109 (1%)
Zidovudine, lamivudine, nevirapine	428 (7%)	547 (4%)	1,190 (6%)	2,149 (8%)	4,104 (16%)	6,382 (29%)	3,351 (36%)
Zidovudine, lamivudine, efavirenz	251 (4%)	671 (6%)	2,035 (10%)	2,555 (10%)	8,767 (34%)	10,533 (48%)	3,776 (40%)
Tenofovir-based first line	0 (0%)	0 (0%)	1 (0%)	2 (0%)	80 (0%)	401 (2%)	616 (7%)
Other first line	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	12 (0%)	52 (1%)

ART=antiretroviral therapy.

Supplementary Table 2. Immunological criteria met, for the 8,384 persons who were observed to have immunological treatment failure, by CD4 count at treatment initiation.

CD4 count at treatment initiation, cells/mm^3	Criterion				Total
	CD4 count <CD4 count at treatment initiation	CD4 count <50% of on-treatment peak CD4 count	CD4 count <100 cells/mm^3	Combination of criteria	
<50	0 (0%)	362 (13%)	1,792 (65%)	587 (21%)	2,741 (100%)
50-199	583 (17%)	854 (25%)	833 (24%)	1,132 (33%)	3,402 (100%)
200-349	931 (62%)	173 (12%)	0 (0%)	392 (26%)	1,496 (100%)
349-499	263 (69%)	10 (3%)	0 (0%)	109 (29%)	382 (100%)
≥500	218 (60%)	1 (<1%)	0 (0%)	144 (40%)	363 (100%)
Total	1,995 (24%)	1,400 (17%)	2,625 (31%)	2,364 (28%)	8,384 (100%)

Some cells are zero by design. For example, if a person initiated treatment with a CD4 count <100 cells/mm^3 and subsequently had two consecutive CD4 counts below the value at treatment initiation, then that person would be considered as having immunologically-failed with CD4 count both (a) below the CD4 count at treatment initiation and (b) <100 cells/mm^3, i.e. that person could not fall solely into the category of <CD4 count at treatment initiation.

Immunological failure of first-line antiretroviral therapy (ART) and switch to second-line ~~therapy~~ ART among HIV-infected persons in Tanzania: Analysis of national routinely-collected data

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Figures: 2

Tables: 3

ABSTRACT

Objectives: Rates of first-line treatment failure and switches to second-line therapy are key indicators for national HIV programs. We assessed immunological treatment failure (ITF) defined by World Health Organization criteria among persons in the Tanzanian national HIV program.

Methods: We included adults initiating first-line therapy in 2004-2011 with a pre-treatment CD4 count, and ≥6 months' follow-up. We assessed sub-hazard ratios (SHR) for ITF, and subsequent switch to second-line therapy, using competing risks methods to account for deaths.

Results: Among 121,308 adults, 8,384 (7%) experienced ITF, and 2,486 (2%) died without observed ITF, over median 1.7 years. The six-year cumulative probability of ITF was 19.0% (95% CI 18.5,19.7) and death 5.1% (4.8,5.4). ITF predictors included earlier year of treatment initiation (p<0.001), initiation in lower-level facilities (SHR=2.23~~1.46~~ [2.03,2.45~~1.36,1.56~~] for dispensaries versus hospitals), being male (1.~~1~~27 [1.10~~9~~,1.33~~18~~])~~, lower current weight (1.32 [1.23,1.42] for <45 versus ≥55kg) and lower current CD4 count (1.67 [1.53,1.83] for <50 versus 200-349 cells/mm^3)~~ and initiation at low or high CD4 counts (for example, 1.78 [1.65,1.92] and 5.33 [4.65,6.10] for <50 and ≥500 versus 200-349 cells/mm^3, respectively). Of 7,382 participants in the time-to-switch analysis, 416 (6%) switched, while 355 (5%) died before switching. Four years after ITF, the cumulative probability of switching was 7.3% (6.6,8.0) and death 6.8% (6.0,7.6). Those who immunologically-failed in dispensaries, health centers and government facilities were least likely to switch.

Conclusions: ITF rates and unmet need for second-line therapy are high in Tanzania; virological monitoring, at least for persons with ITF, is required to minimize unnecessary switches to second-line therapy. Lower-level government health facilities need more support to reduce treatment failure rates and improve second-line therapy uptake to sustain the benefits of increased coverage.

INTRODUCTION

The year 2012 saw the largest annual increase of HIV-positive persons receiving antiretroviral therapy (ART), with 9.7 million people in low- and middle-income countries on ART (1). In 21 African countries with the highest HIV burden, two-thirds of people in need of treatment in 2012 were receiving ART (1). Furthermore, with recent treatment guideline changes, the number of people eligible for first-line treatment will increase (2). While work remains to reach all persons in need of treatment, focus has shifted to the implications of providing long-term treatment for what, under the right care, has become a chronic condition.

Monitoring persons on ART for treatment failure is essential to ensure that their treatment remains potent and to enable timely switches from first- to second-line therapy. In South Africa, where routine viral-load monitoring is performed, the proportion of persons switching by 3-5 years after treatment initiation was ~10% (3,4), whereas in settings without routine viral-load monitoring, such as Malawi and Zambia prior to 2011, switching rates were much lower (~2% by 3 years) (4). Delayed switching increases the risk of drug resistance (5,6) and subsequent higher viral load (7–9) and hence impairs clinical outcomes (2), while early, unnecessary switching may reduce treatment options and increase costs. The World Health Organization (WHO) recommends routine viral load monitoring for persons on ART (2), but this remains too expensive for resource-limited countries such as Tanzania. In the absence of viral-load monitoring, treatment failure is diagnosed using immunological and clinical criteria (2), as implemented in Tanzanian policy (10–12). To date, there is a paucity of data on the rates and predictors of first-line treatment failure, and the use of second-line therapy, within national programs using immunological and/or clinical criteria.

Tanzania had an estimated 1.3 million HIV-infected adults in 2011 (13). Of these, ~370,000 adults (28%) were enrolled in care, and ~260,000 were receiving ART, representing 65% in need of treatment (13). Our aim was to investigate the rate and predictors of immunological treatment

failure (ITF), and subsequent switch to second-line therapy, among HIV-infected adults receiving therapy through the Tanzania government program.

METHODS

HIV care and treatment in Tanzania

The Tanzanian National AIDS Control Program (NACP) provides HIV prevention, care and treatment services. In late 2003, the first HIV/AIDS Care and Treatment Plan was launched, and free ART was rolled out from 2004. By the end of 2011, >1100 facilities were approved to provide care and treatment services, estimated to enable >1 million persons potentially to access ART (13).

HIV-positive persons enrolling in care and treatment clinics are assessed for ART eligibility, defined pre-2012 (data collection period) as CD4 count <200 cells/mm^3, or CD4 count <350 cells/mm^3 and WHO stage III, or WHO stage IV regardless of CD4 count (10,11). Persons not yet eligible for ART are encouraged to attend clinics six-monthly for pre-treatment monitoring, while those on treatment attend monthly. First-line treatment consists of 2 nucleoside/nucleotide--reverse transcriptase inhibitors (NRTIs) and a non-NRTI, while second-line therapy included 2 NRTIs plus a protease inhibitor. Individual paper-based records, including unique, nationally-attributed patient identifiers, are maintained at each facility, and subsequently electronically-entered by data entry clerks before being regularly submitted to the national database.

Study population

We included data from clinics reporting electronic, individual-level data to the end of 2011. We included persons who initiated first-line ART in 2004-2011 aged ≥15 years with a pre-ART CD4 count available, and who completed ≥6 months of follow-up.

Definition of ITF

The Tanzanian 2005 National Guidelines for the Clinical Management of HIV and AIDS defined ITF as CD4 count <30% of peak on-treatment value or <pre-treatment levels (10); this definition was revised in 2009 to CD4 count <50% of peak value within 6 months or <pre-treatment levels (11). This resembles the WHO 2010 Antiretroviral Therapy for HIV Infection in Adults and Adolescents guidelines which defined ITF as CD4 count <50% of peak value or <pre-treatment levels, or persistently <100 cells/mm^3 (14); the WHO guidelines were revised in 2013 to remove the criterion of a 50% drop (2). For this analysis, we used the WHO 2010 guidelines, with a second consecutive confirmatory CD4 count for the definition of ITF, to rule out transient drops in CD4 counts due to other infections or measurement error. ITF was only defined ≥6 months after treatment initiation (2). We also considered a less strict definition of ITF, which did not require a confirmatory CD4 count (except for the criterion of CD4 count <100 cells/mm^3, since the WHO guidelines explicitly define ITF among individuals with CD4 counts "persistently" <100 cells/mm^3).

Statistical methods

We assessed ITF and death rates and predictors using competing risks methods to account for deaths. Death is a competing risk for IFT because its occurrence prevents us from observing ITF. In such situations, standard Cox proportional-hazards models are not appropriate, and instead competing risks models are required. Such models yield sub-hazards ratios which, although statistically-speaking are different, may be interpreted in the same way as hazard ratios derived from Cox models (15,16)~~(15);~~ ~~loss to follow-up was considered uninformative~~. Among those with ITF, we assessed switch to second-line therapy, using similar methods. Loss to follow up was considered uninformative. Body mass index (BMI) was not included in multivariable models, as it was missing for ~70% of visits, mainly due to missing height.

Data were censored at 31 December 2011. If a CD4 count was not recorded for >12 months, then follow-up was censored at 12 months after the last CD4 count, but that person could re-enter the

risk set if another CD4 count was subsequently recorded. If the person reappeared with ITF, then he/she was considered to have immunologically-failed at 12 months after the last CD4 count recorded before the gap. Time-dependent variables at ART initiation or switch were defined as the closest up to 3 months earlier, and if none then up to 2 weeks after (except for CD4 count at treatment initiation, which permitted up to 4 weeks after, to allow for delayed reporting of CD4 counts). ~~When modelling time-dependent data, we carried forward the last observation for up to 12 months.~~We performed a sensitivity analysis using 6 instead of 12 months for censoring follow-up. We performed a second sensitivity analysis including only data from 2009 or later (due to concerns about the changes in ART provision, with more being provided by health centres and dispensaries in later years).

For the analysis of switch to second-line therapy, individuals who changed to an unknown ART regimen were censored at that time; those with missing ART information were considered to still be continuing on their first-line regimen. Intermittent regimens of duration ≤14 days were ignored. Individuals with missing ART information from the date when they were last known to be on first-line therapy until the date they switched to second-line therapy were assumed to have switched at the mid-point between these dates. Participants who changed therapy on the day of ITF were given one day of follow-up. Analyses were conducted using Stata version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP). P-values are 2-sided.

Ethical considerations

This analysis was conducted on routinely-collected data under the auspices of the NACP and approved by the London School of Hygiene & Tropical Medicine ethics committee. Unique patient identifiers were used to preserve anonymity, and all names and personal identifiers were removed before analysis.

RESULTS

In 348 clinics, 243,844 adults initiated first-line ART. Of these, 71,285 (29%) participants did not have a pre-treatment CD4 count recorded: 23,038 (32%) were WHO stage IV (among whom treatment should have been initiated regardless of CD4 count as per treatment guidelines (10,11)), but 5,608 (8%) did not have WHO stage recorded, and 26,599 (37%), 11,180 (16%) and 4,860 (7%) were WHO stages I, II and III, respectively (perhaps suggesting missing CD4 count data). Of the remaining 172,559 participants, 11,397 (7%) died within the first six months after treatment initiation, 13,625 (8%) initiated treatment in the last six months of 2011 and therefore had <6 months of follow-up, and 26,229 (15%) were lost to follow-up within six months; these participants are excluded.

Of the remaining 121,308 participants (representing all 348 clinics), 73% initiated ART in hospitals and 67% initiated in government-run facilities (Table 1). Two-thirds of participants were female, 55% were married or cohabiting, and 89% were working. 26% of participants initiated ART with low BMI (<18.5 kg/m^2), 16% with WHO stage IV and 73% with low CD4 count (<200 cells/mm^3). The most common first-line ART regime was stavudine-based (61%), mainly driven by data from earlier years. The use of zidovudine, lamivudine and nevirapine or efavirenz increased from 8% and 10% respectively in 2008, to 36% and 40% respectively in 2011, following the elimination of stavudine in 2010 (Supplementary Table 1).

Nearly two-thirds of participants (65%) did not have any gaps in their follow-up due to CD4 counts not being recorded for >12 months; 28%, 6%, <1% and <1% of participants had one, two, three or four such gaps in their follow-up, respectively. Across all gaps, the median gap length was 7 months, with an interquartile range of 3-13 months.

Immunological failure

Subsequent to the first six months on ART, 8,384 (7%) participants experienced ITF and 2,486 (2%) died without ITF being observed, over a median of 1.7 years (maximum eight years). Of those experiencing ITF, 1,995 (24%) participants had CD4 counts <pre-treatment levels, 1,400 (17%) <50% of on-treatment peak, 2,625 (31%) <100 cells/mm^3, and 2,364 (28%) had a combination of these components (Supplementary Table 2). The cumulative probability of ITF by six years (to when we had sufficient data for reliable estimation) was 19.0% (95% CI: 18.5,19.7) and of death (without ITF) was 5.1% (4.8,5.4; Figure 1).

Under the less strict ITF definition, 19,380 (16.0%) participants would have been considered to have experienced ITF, with cumulative probability of 23.8% (23.5,24.2) by three years and 40.6% (39.8,41.5) by six years.

Predictors of ITF

Using the definition of IFT with confirmatory CD4 count, ~~i~~In adjusted analyses, higher risk of ITF was found among those who initiated treatment in lower-level facilities and in "other" facilities, which predominantly included institutional facilities with restricted access (*P*<0.001; Table 2). However, those in "other" facilities had lowest death rate (0.6 versus 1.1/100 person-years in hospitals). The ITF risk was ~~higher among those in faith-based versus government facilities (sub-hazard ratio, SHR=1.11 [95% confidence interval, CI: 1.07,1.15]), and~~ lower in private versus government facilities facilities (sub-hazard ratio, SHR=0.5~~6~~9 [95% confidence interval, CI: 0.50~~62~~,0.~~7~~69]), with no difference for faith-based facilities (SHR=1.01 [0.95,1.07]). ~~Compared to those who initiated treatment pre-2006, t~~There was lower ITF risk with later year of treatment initiation (*P*<0.001), and death rates decreased from 1.2/100 to 0.5/100 person-years among those who initiated treatment pre-2006 and in 2011, respectively. Females had lower ITF risk than men (SHR=0.7~~8~~9 [0.7~~8~~5,0.8~~492~~]). Compared to persons who were married or cohabiting at treatment initiation, single ~~and divorced or widowed~~ separated persons were at higher ITF risk (SHR=1.12~~09~~ [1.05,1.20~~14~~] ~~and~~

~~1.06 [1.00,1.12], respectively~~), but there was no evidence of a difference for those divorced or separated, or widowed.

Persons initiating treatment with lower weight were at somewhat higher risk of ITF (SHR=1.07 [0.99,1.16] and 1.08 [1.02,1.14] for <45 and 45-<55 versus ≥55 kg, respectively). There was some ~~a~~ difference in ITF risk by WHO stage at treatment initiation (p=0.0~~0~~3), although no clear trend across the stages. Of note, ~~with lower stage associated with higher risk, likely attributable to~~ the competing risk of death varied by stage (0.5 versus 1.5/100 person-years for WHO stage I and IV, respectively). Persons who initiated with the lowest CD4 counts were at higher risk of ITF (SHR=1.78 [1.65,1.92] for <50 versus 200-349 cells/mm^3). However, persons initiating with high CD4 counts were also at higher ITF risk (SHR=2.51 [2.20,2.86] and 5.33 [4.65,6.10] for 350-499 and ≥500 versus 200-349 cells/mm^3, respectively). In the unadjusted model, persons who initiated on zidovudine-based regimens had a lower ITF risk versus stavudine-based regimens; this relationship was reversed once we adjusted for confounders (SHR=1.1~~3~~4 [1.0~~8~~6,1.2~~1~~7]). Persons who initiated treatment with other regimens had much higher ITF risk (SHR=6.12~~3.21~~ [4.90,7.65~~2.67,3.85~~] versus stavudine-based). There was no evidence of a difference in ITF risk by age (*P*=0.58) or functional status (*P*=0.21~~85~~) ~~or weight at treatment initiation (*P*=0.79)~~.

~~Perhaps counterintuitively, higher CD4 count at treatment initiation was associated with higher ITF risk (*P*<0.001), but, as expected, lower current CD4 count was associated with higher risk (*P*<0.001; for example, SHR=1.67 [1.53,1.83] for <50 versus 200-349 cells/mm^3). There was higher ITF risk with lower current weight (*P*<0.001; for example, SHR=1.32 [1.23,1.42] for <45 versus ≥55 kg). There was lower ITF risk among those who had had a gap in CD4 counts of >12 months (SHR=0.66 [0.62,0.70]).~~ Variable selection to obtain a parsimonious model (removing variables in a stepwise fashion with *P*~~<~~>0.05) yielded similar results to the full model. Sensitivity analyses censoring follow-up after 6

rather than 12 months, or including only participants who initiated in 2009 or later, yielded broadly similar results.

Switch to second-line therapy

Of 8,384 persons who immunologically-failed on first-line therapy, 135 (2%) had previously used second-line therapy, 276 (3%) had previously taken an unknown regimen and 591 (7%) had an ITF date estimated at 12 months after the last CD4 count before a gap of >12 months; these persons are excluded from the following analyses. Of the remaining 7,382 (88%) participants, 40% had been on first-line ART for <1 year, 34% for 1-<2 years and 27% for ≥2 years (Table 1). The distribution of participant characteristics at the time of ITF broadly reflected those at ART initiation. The proportions of participants with CD4 counts of <50, 50-199, 200-349, 350-499 and ≥500 cells/mm^3 at ITF were 25%, 50%, 18%, 5% and 2%, respectively.

Overall, 416 (6%) persons were observed to subsequently switch to second-line therapy, while 355 (5%) died before switching. By four years after ITF, the cumulative probability of switching was 7.3% (95% CI: 6.6,8.0) and of death 6.8% (6.0,7.6; Figure 2).

The most common second-line regimen to which people switched was abacavir, didanosine and ritonavir-boosted lopinavir (n=343; 82%), followed by tenofovir, emtricitabine and ritonavir-boosted lopinavir (43; 10%). The reasons for switch were not reported for 162 (39%) individuals; of those given, the most common reasons were ITF (184; 72%) or clinical treatment failure (20; 8%).

Predictors of switch to second-line therapy

In adjusted analyses, there were large differences in the switching rates by facility level and type, with those who immunologically-failed in health centers and dispensaries being less likely to switch than those in hospitals (SHR=0.43 [95% CI: 0.26,0.71] and 0.50 [0.27,0.93], respectively), and those

in “other” facilities more likely to switch (SHR=2.27 [1.52,3.39]). People who experienced ITF in faith-based facilities were much more likely to switch than those in government facilities (SHR=2.29 [1.79,2.91]). We observed less frequent switching with later year of ITF (*P*<0.001). Women were less likely to switch than men (SHR=0.77 [0.60,0.97]). Persons at lower WHO stage at treatment initiation were more likely to switch (*P*<0.001; for example, SHR=1.64 [1.18,2.28] for WHO stage I versus III). Persons with lower CD4 count at ITF were much more likely to switch (*P*<0.001; for example, SHR=6.33 [4.03,9.95] for <50 versus 200-349 cells/mm^3). Persons who had initiated ART on zidovudine-based therapy were more likely to switch than those on stavudine-based regimens (SHR=1.76 [1.36,2.29]). There was increasing probability of switch with increasing time on therapy (*P*<0.001). There was no evidence of a difference in switching rates by age (*P*=0.76), marital status (*P*=0.35), functional status (*P*=0.34) or weight (*P*=0.54).

DISCUSSION

In this study of >120,000 HIV-infected adults initiating first-line therapy in Tanzania, the need for second-line therapy was high, with ITF rates of 19% by 6 years after treatment initiation. The analysis was restricted to persons with ≥6 months of follow-up, excluding the 7% of people who died within 6 months; nonetheless, over the following 6 years, there was a 5% cumulative probability of death without observed ITF. Following ITF, the cumulative probability over 4 years of switching to second-line therapy was 7%, which was approximately the same as that of death (7%).

To our knowledge, this is the first study to assess ITF rates and switches to second-line therapy among adults on first-line ART using national routinely-collected data. In a recent study from Nigeria, which used the same WHO criteria for ITF but without a confirmatory CD4 count, the cumulative probability of ITF was ~35% by 3 years, similar to our estimation of 24% under the less strict ITF definition ~~compared to 11% in our study~~ (17)~~(16)~~. ~~However, while the~~ When ~~the Nigerian study used the same WHO criteria for ITF, they did not require a confirmatory CD4 count; when they~~

~~incorporated~~ a confirmatory CD4 count was incorporated in the Nigerian analysis, the overall proportion of participants experiencing ITF reduced from 32% to 10% and therefore the cumulative ITF probability when incorporating a confirmatory CD4 count (not directly reported) is likely to be similar to that observed under the main IFT definition in our study. The differences in the estimated IFT rates between definitions requiring and not requiring a confirmatory CD4 count are large. CD4 count measurement is known to have large variability and CD4 count trajectories may display transient changes, thus we believe that it is unlikely that the IFT rates are as high as suggested by the unconfirmed criteria, hence reinforcing the importance of a confirmatory CD4 count, which is typically what clinicians seek in practice.

Encouragingly, ITF rates ~~have~~ dropped with later calendar year of ART initiation, with 72~~49~~% lower risk among those who initiated in 2011 versus 2008, which may be attributable to improvements in care and drug efficacy. Switching rates also decreased over time, with 59% lower "risk" of switching among those who immunologically-failed in 2011 versus 2008, perhaps suggesting that the national program in Tanzania has not yet organized itself for widespread second-line therapy use. ~~Indeed, our results~~ The overall low switching rates observed in this study indicate that there is a large unmet need for second-line therapy, and so this should be a future priority for the ART program if excess morbidity and mortality among persons on ART are to be minimized. Our results likely reflect what clinicians are doing in practice, regardless of national policies, due to barriers in accessing second-line therapy such as lack of availability and higher cost. Approaches to increase coverage to ART, such as decentralization, could be harnessed to increase access to second-line therapy.

We found important differences in the rates of both ITF and switching by the types of facilities participants were attending. The Tanzanian HIV program has successfully devolved care to lower-level clinics, and there are calls for similar initiatives for the management of other chronic diseases (18)~~(17)~~. However, the higher ITF rates and lower switching rates in lower-level and particularly

government-owned facilities highlights that adequate training and support is required for front-line health-care workers, along with a stable drug supply chain and adequate equipment, to ensure that consistent services are provided.

We have identified key sub-groups of the population who may be at higher ITF risk, including men, single ~~and divorced or separated~~ persons, and those with lower ~~current~~ weight at ART initiation. Men typically have poorer healthcare-seeking behaviors than women, as illustrated by mean lower CD4 counts at enrolment to HIV care (5,13), poorer ART uptake (19)~~(18)~~, and the higher ITF risk observed in this study. In contrast, we found that women were less likely to switch to second-line therapy than men; the reasons for this are unclear and this finding warrants further investigation.

~~Persons who had gaps in CD4 measurements had lower ITF risk. Although other studies have found that gaps in care are associated with higher ITF risk (3), it may be that CD4 measurement frequency is not a good proxy for remaining in care: for example, persons with high CD4 counts and absence of clinical symptoms may have less frequent CD4 measurements than persons with lower CD4 counts or clinical symptoms. If people at risk of dropping out of care can be identified, then they can be targeted for services such as adherence counselling, which may result in virological suppression without the need for switching . Even in the presence of virological failure, it is necessary to address non-adherence before switching to minimize the failure risk on second-line therapy .~~

The drivers behind the higher ITF risk with zidovudine-based and other first-line regimens, compared to stavudine-based therapy, are unclear. Stavudine has been phased out since 2010, and tenofovir-based regimens are now recommended. Although only a small percentage of participants initiated tenofovir in this cohort, its use is increasing.

Both low and high CD4 count at ART initiation were associated with higher ITF risk. Participants starting treatment with CD4 counts <100 cells/mm^3 would have met the definition for ITF if they had two subsequent CD4 counts <100 cells/mm^3, even if higher than their baseline value. Individuals initiating treatment at high CD4 counts were likely to be different in some way; for example, they may be presenting for care due to an opportunistic infection. While we have controlled for the confounders routinely captured in the national data, such as WHO stage, there may remain residual confounding.

Lower CD4 count at ITF was strongly associated with switching; nonetheless, our results indicate that there remains a large need for second-line therapy which is not being met, with the probability of switch among those who have immunologically-failed being only 7% by 4 years. The poor predictive ability of ITF for virological failure is well-known (17,22–26)~~(16,21–25)~~, meaning that persons with a low CD4 count may not necessarily have virologically-failed. However, in a setting without routine or targeted viral-load monitoring, switching decisions must be made based on the immunological evidence (2), and this is the situation in many countries across sub-Saharan Africa. New and cheaper viral load tests, using dried blood spots, w~~c~~ould ideally be used to perform targeted monitoring of persons with ITF in order to minimize unnecessary switches to second-line treatment, as recommended by the WHO (27)~~(26)~~. Switching persons who have ITF but not virological failure has individual and economic implications, and such persons would be unlikely to benefit from second-line therapy, therefore it would be important to assess viral load before switch.

A strength of this study is the use of appropriate statistical methodology, namely competing risks analysis, to take into account the correlation between death and ITF. A naïve approach would be to use proportional hazards regression, ignoring the competing risk of death for ITF. Such an approach underestimates the ITF rate, due to deaths occurring in those with unobserved ITF. This under-

estimation may be greater in a resource-poor setting with less-intensive CD4 monitoring. In addition, our results were robust to sensitivity analyses.

While we included over 120,000 persons in this analysis, the 348 clinics included do not represent every region in Tanzania, as the analysis was restricted to clinics who submitted electronic data in 2011. Due to the definition of ITF, we were not able to include nearly a third of registered participants since they did not have a baseline CD4 count; it is difficult to know whether this selection has led to bias in our results. Attrition rates from care and treatment clinics in Tanzania are high (28)~~(27)(26)~~, and it is likely that many deaths remain unreported, therefore our mortality rates will be underestimates. While we attempted to address incompleteness of immunological data by censoring follow-up when no CD4 count had been recorded for >12 months, it may be that incomplete data contributes to the deaths without ITF. Information on causes of death might help inform this question further, but these data are not currently captured. We used the WHO 2010 ITF criteria, covering the majority of the data collection period (14); application of the WHO 2013 guidelines would yield lower ITF rates (2). The implications of different definitions could be explored, including the incorporation of persons who initiated at WHO stage IV without CD4 measurements recorded. Further, interpretations of ITF were required for analysis, for example related to "persistent" CD4 count <100 cells/mm^3. This raises questions about how the guidelines are interpreted~~ations~~ in clinical practice. The guidelines state that transient drops in CD4 count should be ignored and we attempted to address this by requiring a confirmatory CD4 count for ITF, but we may therefore have underestimated the ITF rate. However, the IFT rates indicated by our less strict definition, which did not require a confirmatory CD4 count, were implausibly high. Detailed information on clinical treatment failure was not captured, although the number of persons switching to second-line therapy in the absence of ITF was low, suggesting perhaps that clinical failure – which may be more complex to diagnose – may not be adequately assessed in clinics. This study does not attempt to address the optimal time to switch to second-line therapy to minimize

adverse outcomes, which is of importance and should be considered for future work. As second-line therapy use increases, work should address outcomes after switch, particularly as a substantial proportion of persons may be expected not to achieve virological suppression (7,29)~~(7,28)~~~~(7,27)~~.

In summary, we have used national routinely-collected data to investigate ITF rates in Tanzania; such rates are high, and the need for second-line treatment is not currently being met. The Tanzanian national control program has successfully focused on ART roll-out, and this remains crucial, particularly with new WHO guidelines recommending earlier initiation (2). In order to sustain the benefits of increased coverage, there is a priority to address the need for second-line therapy, and (targeted) virological monitoring is required to minimize unnecessary switches to second-line therapy.

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TABLES

Table 1. Participant characteristics at ART initiation and immunological treatment failure.

		At ART initiation [1]		At immunological failure [1,2]	
		N=121,308		N=7,382	
Health facility level	Hospital	87,770	(72.7%)	4,712	(64.3%)
	Health center	16,798	(13.9%)	1,189	(16.2%)
	Dispensary	13,131	(10.9%)	1,027	(14.0%)
	Other [3]	2,995	(2.5 %)	397	(5.4 %)
Health facility type	Government	74,789	(66.7%)	4,696	(68.8%)
	Faith-based	28,343	(25.3%)	1,712	(25.1%)
	Private	8,947	(8.0 %)	413	(6.1 %)
Year	Up to end 2005	5,951	(4.9 %)	42	(0.6 %)
	2006	12,181	(10.0%)	471	(6.4 %)
	2007	19,770	(16.3%)	954	(12.9%)
	2008	26,158	(21.6%)	1,396	(18.9%)
	2009	25,726	(21.2%)	1,559	(21.1%)
	2010	22,121	(18.2%)	1,581	(21.4%)
	2011	9,401	(7.7 %)	1,379	(18.7%)
Sex	Male	40,055	(33.0%)	2,630	(35.6%)
	Female	81,250	(67.0%)	4,752	(64.4%)
Age, years	15-29	23,412	(19.3%)	953	(12.9%)
	30-39	50,750	(41.8%)	3,063	(41.5%)
	40-49	31,848	(26.3%)	2,263	(30.7%)
	≥50	15,278	(12.6%)	1,099	(14.9%)
Marital status [4]	Single	24,757	(22.2%)	1,648	(25.2%)
	Married or cohabiting	61,586	(55.3%)	3,493	(53.4%)
	Divorced or separated	11,866	(10.7%)	635	(9.7 %)
	Widowed	13,156	(11.8%)	765	(11.7%)
Functional status	Working	102,301	(88.7%)	6,980	(96.9%)
	Ambulatory	11,866	(10.3%)	177	(2.5 %)
	Bed-ridden	1,177	(1.0 %)	49	(0.7 %)
Weight, kg	<45	21,754	(18.1%)	690	(9.4 %)
	45-<55	47,019	(39.1%)	2,292	(31.2%)
	≥55	51,633	(42.9%)	4,365	(59.4%)
BMI [5]	Underweight	11,035	(26.2%)	427	(13.4%)
	Normal	25,097	(59.6%)	2,030	(63.7%)
	Overweight	6,002	(14.2%)	732	(23.0%)
WHO stage [4]	I	11,586	(10.4%)	562	(9.0 %)
	II	27,636	(24.9%)	1,445	(23.0%)
	III	53,603	(48.3%)	3,169	(50.5%)
	IV	18,158	(16.4%)	1,102	(17.6%)
CD4 count, cells/mm^3	<50	24,339	(20.1%)	1,822	(24.7%)
	50-199	64,753	(53.4%)	3,684	(49.9%)
	200-349	27,375	(22.6%)	1,333	(18.1%)
	350-499	3,250	(2.7 %)	383	(5.2 %)
	≥500	1,591	(1.3 %)	158	(2.1 %)
First ART regimen [4]	Stavudine-based	73,402	(60.5%)	5,287	(71.6%)
	Zidovudine-based	46,739	(38.5%)	2,008	(27.2%)
	Other first-line	1,167	(1.0 %)	87	(1.2 %)
Time on first-line ART, years	<1			2,950	(40.0%)
	1-<2			2,475	(33.5%)
	≥2			1,957	(26.5%)

ART=antiretroviral therapy. BMI=body mass index. [1] Values are number (% of those with non-missing data). [2] Restricted to those included in the switching analysis (see main text). [3] "Other" facilities predominantly included institutional facilities with restricted access. [4] At ART initiation (not updated at immunological failure; marital status only recorded at enrolment into care). [5] BMI categorized as underweight (<18.5 kg/m^2), normal (18.5-<25.0 kg/m^2) or overweight (≥25 kg/m^2).

Table 2. Associations of participant characteristics at ART initiation with immunological treatment failure and death, after first-line treatment initiation.

	Immunological failure			Death (before immunological failure)			Sub-hazard ratio (95% confidence interval) for immunological failure			
	Rate per 100 person-years	N events	Person-years	Rate per 100 person-years	N events	Person-years	Univariable models		Full multivariable model	
~~AT ART INITIATION~~										
Health facility level							*P*<0.001		*P*<0.001	
Hospital	3.2	5,776	179,186	1.1	1,911	179,186	1		1	
Health center	3.3	966	28,865	1.0	302	28,865	1.05	0.98, 1.12	1.1906	1.010,1.2911
Dispensary	4.8	1,133	23,735	0.9	214	23,735	1.51	1.41, 1.61	2.231.46	2.03,2.451.36,1.56
Other [1]	5.8	448	7,763	0.6	50	7,763	1.75	1.59, 1.93	1.7320	1.5409,1.9531
Health facility type							*P*=0.01		*P*<0.001	
Government	3.5	5,169	147,962	1.0	1,455	147,962	1		1	
Faith-based	3.3	1,996	59,877	1.2	714	59,877	0.94	0.89, 0.99	1.01	0.95,1.071.07,1.15
Private	3.1	540	17,209	0.8	145	17,209	0.91	0.83, 0.99	0.569	0.5062,0.769
Year							*P*<0.001		*P*<0.001	
Up to end 2005	5.2	1,029	19,724	1.2	228	19,724	2.06	1.90, 2.24	2.471.93	2.22,2.731.80,2.07
2006	4.8	1,732	35,781	1.2	421	35,781	1.86	1.74, 1.99	1.9057	1.7548,2.071.66
2007	3.9	1,986	50,880	1.1	553	50,880	1.42	1.33, 1.52	1.4126	1.3120,1.352
2008	2.8	1,610	56,696	1.1	597	56,696	1		1	
2009	3.2	1,376	43,500	1.0	423	43,500	1.1	1.02, 1.18	0.889	0.8481,0.947
2010	2.3	612	27,165	0.8	230	27,165	0.84	0.76, 0.92	0.609	0.654,0.6874
2011	0.6	39	6,875	0.5	34	6,875	0.39	0.28, 0.54	0.2851	0.2043,0.640
Sex							*P*<0.001		*P*<0.001	
Male	4	3,017	76,151	1.4	1,065	76,151	1		1	
Female	3.3	5,367	164,463	0.9	1,421	164,463	0.82	0.79, 0.86	0.789	0.875,0.8492
Age, years							*P*=0.60		*P*=0.538	
15-29	3.4	1,537	44,600	0.9	411	44,600	0.98	0.93, 1.04	0.957	0.892,1.013
30-39	3.5	3,587	101,822	0.9	932	101,822	1		1	
40-49	3.5	2,254	64,512	1.0	669	64,512	0.99	0.94, 1.04	1.010.98	0.94,1.027
≥50	3.4	1,002	29,648	1.6	474	29,648	0.95	0.89, 1.02	0.981.01	0.950,1.067
Marital status							*P*<0.001		*P*=0.004<0.001	
Single	3.8	1,888	49,109	1.1	517	49,109	1.14	1.08, 1.21	1.1209	1.05,1.2014
Married or cohabiting	3.3	3,955	118,396	1.0	1,155	118,396	1		1	
Divorced or separated	3.2	736	22,679	1.1	239	22,679	0.97	0.90, 1.05	1.06	0.971.00,1.126
Widowed	3.2	860	26,536	0.9	252	26,536	0.97	0.90, 1.04	1.053	0.968,1.1409
Functional status							*P*=0.83		*P*=0.2185	
Working	3.4	6,774	196,437	0.9	1,852	196,437	1		1	
Ambulatory	3.4	863	25,060	1.6	394	25,060	0.98	0.91, 1.05	0.921.02	0.8596,1.071
Bed-ridden	3.4	80	2,335	1.9	45	2,335	0.97	0.78, 1.21	0.991.02	0.787,1.205
Weight, kg							*P*<0.001		*P*=0.0379	
<45	3.8	1,600	42,615	1.4	615	42,615	1.14	1.08, 1.21	1.070.98	0.992,1.1604

45-<55	3.6	3,258	91,619	1.0	961	91,619	1.09	1.04, 1.14	1.080	1.020.96,1.1404
≥55	3.3	3,430	104,635	0.8	887	104,635	1		1	
BMI [2]							*P*=0.001			
Underweight	4.2	1,022	24,193	0.9	227	24,193	1.12	1.04, 1.20		
Normal	3.8	2,095	55,456	0.6	338	55,456	1			
Overweight	3.5	474	13,516	0.5	63	13,516	0.93	0.84, 1.03		
WHO stage							*P*<0.001		*P*=0.003	
I	2.8	638	22,513	0.5	119	22,513	0.83	0.76, 0.90	0.921.01	0.8495,1.071
II	3.2	1,630	51,678	0.8	431	51,678	0.93	0.87, 0.98	1.046	0.981.02,1.11
III	3.4	3,589	104577	1.1	1,122	104,577	1		1	
IV	3.7	1,288	34,879	1.5	529	34,879	1.07	1.01, 1.14	0.946	0.8891,1.012
CD4 count, cells/mm^3							*P*<0.001		*P*<0.001	
<50	5.8	2,741	47,534	1.4	649	47,534	1.95	1.83, 2.08	1.780.65	1.65,1.920.61,0.69
50-199	2.5	3,402	133,708	1.0	1,330	133,708	0.86	0.80, 0.91	0.7859	0.7256,0.8462
200-349	2.9	1,496	51,208	0.8	411	51,208	1		1	
350-499	6.8	382	5,623	1.0	58	5,623	2.36	2.11, 2.64	2.5102	2.20,2.861.85,2.21
≥500	14.2	363	2,548	1.5	38	2,548	4.96	4.44, 5.55	5.334.10	4.65,6.103.69,4.55
First ART regimen							*P*<0.001		*P*<0.001	
Stavudine-based	3.6	6,059	167,123	1.1	1,840	167,123	1		1	
Zidovudine-based	3.1	2,233	72,418	0.9	637	72,418	0.9	0.85, 0.94	1.143	1.068,1.217
Other first-line	8.5	92	1,080	0.8	9	1,080	3.36	2.73, 4.13	6.123.21	4.90,7.652.67,3.85
TIME-DEPENDENT VARIABLES										
Current weight, kg							*P*=0.07		*P*<0.001	
<45	4.0	796	19,995	2.8	567	19,995	1.43	1.32, 1.54	1.32	1.23,1.42
45-<55	3.5	2,605	74,847	1.2	909	74,847	1.12	1.07, 1.17	1.09	1.04,1.14
≥55	3.4	4,941	145,284	0.7	993	145,284	1		1	
Current CD4 count, cells/mm^3							*P*<0.001		*P*<0.001	
<50	9.8	2,043	20,879	1.9	394	20,879	10.97	10.21, 11.79	1.67	1.53,1.83
50-199	5.5	4,252	76,943	1.2	958	76,943	4.09	3.85, 4.35	1.47	1.40,1.54
200-349	2.1	1,484	69,317	0.9	629	69,317	1		1	
≥350	0.8	605	73,482	0.7	505	73,482	0.29	0.26, 0.31	0.98	0.93,1.03
Previously had a gap between CD4 counts of >12 months							*P*=0.04		*P*<0.001	
No	3.5	6,843	197,294	1.0	2,068	197,294	1		1	
Yes	3.6	1,541	43,327	1.0	418	43,327	0.93	0.87, 1.00	0.66	0.62,0.70

ART=antiretroviral therapy. BMI=body mass index. "1" indicates the reference category. [1] "Other" facilities predominantly included institutional facilities with restricted access. [2] BMI categorized as underweight (<18.5 kg/m^2), normal (18.5-<25.0 kg/m^2) or overweight (≥25 kg/m^2).

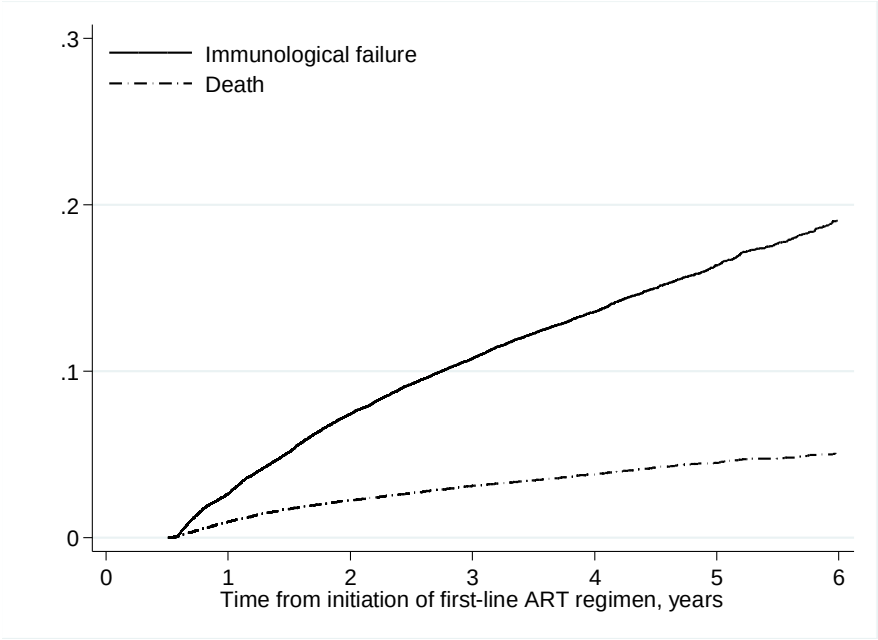
Table 3. Rates and predictors of switching, after immunological treatment failure.

	Rate per 100 person-years	N events	Person-years	Sub-hazard ratio (95% confidence interval) Univariable models		Full multivariable model	
Health facility level				*P*<0.001		*P*<0.001	
Hospital	2.7	315	11,462	1		1	
Health center	1.3	27	2,075	0.42	0.29, 0.63	0.43	0.26,0.71
Dispensary	1.1	21	1,964	0.31	0.20, 0.48	0.50	0.27,0.93
Other [1]	5.9	53	900	2.02	1.50, 2.71	2.27	1.52,3.39
Health facility type				*P*<0.001		*P*<0.001	
Government	2.1	226	10,917	1		1	
Faith-based	4.8	176	3,667	2.26	1.86, 2.75	2.29	1.79,2.91
Private	1.2	10	825	0.53	0.28, 0.99	[2]	[2]
Year				*P*=0.004		*P*<0.001	
Up to end 2005	3.6	8	223	1.70	0.83, 3.49	1.08	0.35,3.32
2006	1.8	39	2,211	0.87	0.61, 1.26	1.21	0.76,1.90
2007	2.0	75	3,676	0.90	0.67, 1.21	1.25	0.88,1.77
2008	2.7	111	4,184	1		1	
2009	3.0	100	3,339	0.90	0.69, 1.19	0.86	0.62,1.19
2010	2.4	52	2,186	0.55	0.39, 0.76	0.47	0.31,0.70
2011	4.7	31	666	0.65	0.43, 0.97	0.41	0.25,0.65
Sex				*P*=0.005		*P*=0.03	
Male	3.1	174	5,668	1		1	
Female	2.2	242	10,818	0.76	0.62, 0.92	0.77	0.60,0.97
Age, years				*P*=0.23		*P*=0.76	
15-29	3.0	67	2,253	1.32	1.00, 1.76	1.07	0.75,1.52
30-39	2.3	160	7,003	1		1	
40-49	2.5	123	4,984	1.06	0.84, 1.34	0.94	0.72,1.23
≥50	2.9	65	2,231	1.19	0.89, 1.58	0.86	0.61,1.23
Marital status [3]				*P*=0.21		*P*=0.35	
Single	2.9	102	3,483	1.20	0.94, 1.53	1.21	0.93,1.59
Married or cohabiting	2.4	180	7,442	1		1	
Divorced or separated	2.0	27	1,349	0.83	0.55, 1.25	0.92	0.60,1.42
Widowed	2.8	48	1,698	1.20	0.87, 1.65	1.24	0.87,1.75
Functional status				*P*=0.43		*P*=0.34	
Working	2.6	394	15,126	1		1	
Ambulatory	1.6	7	439	0.64	0.30, 1.35	0.50	0.20,1.26
Bed-ridden	1.6	2	123	0.67	0.16, 2.74	0.94	0.22,4.08
Weight, kg				*P*=0.92		*P*=0.54	
<45	2.7	39	1,446	0.99	0.71, 1.39	1.05	0.70,1.59
45-<55	2.5	124	4,939	0.96	0.77, 1.19	0.87	0.67,1.14
≥55	2.5	253	10,058	1		1	
WHO stage [3]				*P*<0.001		*P*<0.001	
I	4.2	51	1,201	1.73	1.27, 2.37	1.64	1.18,2.28
II	3.0	86	2,867	1.16	0.89, 1.50	1.11	0.84,1.47
III	2.5	171	6,882	1		1	
IV	1.6	37	2,288	0.63	0.44, 0.89	0.56	0.38,0.81
CD4 count, cells/mm^3				*P*<0.001		*P*<0.001	
<50	2.9	115	3,975	2.16	1.51, 3.11	6.33	4.03,9.95
50-199	3.0	255	8,543	2.31	1.65, 3.23	3.70	2.42,5.67
200-349	1.3	39	2,927	1		1	
≥350	0.7	7	1,041	0.48	0.21, 1.06	0.52	0.20,1.36
First ART regimen [3]				*P*=0.07		*P*<0.001	
Stavudine-based	2.3	301	13,018	1		1	
Zidovudine-based	3.4	115	3,414	1.22	0.99, 1.52	1.76	1.36,2.29
Other first line	0	0	55	[4]		[4]	
Time on first-line ART, years				*P*<0.001		*P*<0.001	
<1	1.2	101	8,378	1		1	
1-<2	2.9	155	5,433	2.12	1.65, 2.72	2.34	1.72,3.17
≥2	6.0	160	2,674	3.58	2.80, 4,58	5.34	3.84,7.44

ART=antiretroviral therapy. "1" indicates the reference category. [1] "Other" facilities predominantly included institutional facilities with restricted access. [2] Not reliably estimable since few switches to second-line therapy, therefore omitted this category from the model. [3] At ART initiation rather than immunological failure (marital status only recorded at CTC enrolment). [4] Omitted from the model since no-one in this category was observed to switch to second-line therapy.

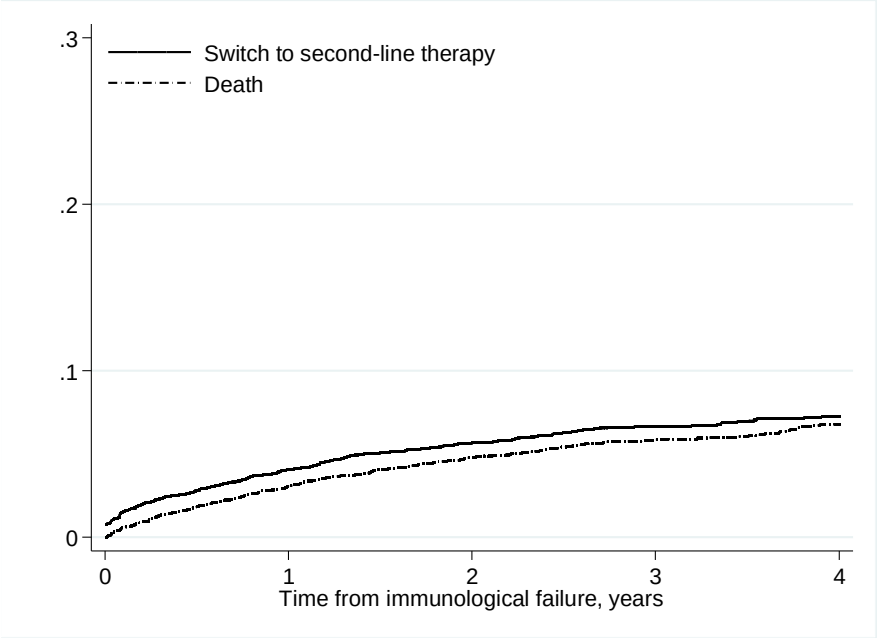
FIGURES

Figure 1. Probability of immunological treatment failure or death, following initiation of first-line ART.



ART=antiretroviral therapy. Y-axis truncated at 0.3. Persons with <6 months of follow-up (including due to death) were excluded from the analyses. Immunological failure was not defined until at least 6 months after treatment initiation.

Figure 2. Probability of switch from first- to second-line ART or death, following immunological treatment failure.



ART=antiretroviral therapy. Y-axis truncated at 0.3. Participants who changed therapy on the day of immunological failure were given 1 day of follow-up, so that they were included in the time-to-event analyses.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. First-line ART regimen by year of treatment initiation.

	Up to end 2005	2006	2007	2008	2009	2010	2011
	N=5,951	N=12,181	N=19,770	N=26,158	N=25,726	N=22,121	N=9,401
Stavudine, lamivudine, nevirapine	5,081 (85%)	10,251 (84%)	15,422 (78%)	20,290 (78%)	11,938 (46%)	4,411 (20%)	1,497 (16%)
Stavudine, lamivudine, efavirenz	191 (3%)	712 (6%)	1,122 (6%)	1,162 (4%)	834 (3%)	382 (2%)	109 (1%)
Zidovudine, lamivudine, nevirapine	428 (7%)	547 (4%)	1,190 (6%)	2,149 (8%)	4,104 (16%)	6,382 (29%)	3,351 (36%)
Zidovudine, lamivudine, efavirenz	251 (4%)	671 (6%)	2,035 (10%)	2,555 (10%)	8,767 (34%)	10,533 (48%)	3,776 (40%)
Tenofovir-based first line	0 (0%)	0 (0%)	1 (0%)	2 (0%)	80 (0%)	401 (2%)	616 (7%)
Other first line	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	12 (0%)	52 (1%)

ART=antiretroviral therapy.

Supplementary Table 2. Immunological criteria met, for the 8,384 persons who were observed to have immunological treatment failure, by CD4 count at treatment initiation.

CD4 count at treatment initiation, cells/mm^3	Criterion				Total
	CD4 count <CD4 count at treatment initiation	CD4 count <50% of on-treatment peak CD4 count	CD4 count <100 cells/mm^3	Combination of criteria	
<50	0 (0%)	362 (13%)	1,792 (65%)	587 (21%)	2,741 (100%)
50-199	583 (17%)	854 (25%)	833 (24%)	1,132 (33%)	3,402 (100%)
200-349	931 (62%)	173 (12%)	0 (0%)	392 (26%)	1,496 (100%)
349-499	263 (69%)	10 (3%)	0 (0%)	109 (29%)	382 (100%)
≥500	218 (60%)	1 (<1%)	0 (0%)	144 (40%)	363 (100%)
Total	1,995 (24%)	1,400 (17%)	2,625 (31%)	2,364 (28%)	8,384 (100%)

Some cells are zero by design. For example, if a person initiated treatment with a CD4 count <100 cells/mm^3 and subsequently had two consecutive CD4 counts below the value at treatment initiation, then that person would be considered as having immunologically-failed with CD4 count both (a) below the CD4 count at treatment initiation and (b) <100 cells/mm^3, i.e. that person could not fall solely into the category of <CD4 count at treatment initiation.

Author statement

Manuscript title:

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I have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
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