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Longer-term effectiveness of protease-inhibitor-based second line antiretroviral therapy in four large sub-Saharan African clinics

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SUMMARY

Objectives: Data on the longer-term effectiveness of second line combination antiretroviral therapy (ART) in sub-Saharan Africa (SSA) are lacking. We sought to assess the probability and determinants of 2nd line ART failure in SSA.

Methods: A retrospective, multi-center study of 2nd line ART initiated between 2005 and 2017 at four ART centers in Ethiopia, Ghana and Uganda. Main outcome measure was virologic failure (VF) defined as VL>1000 copies/ml after >6 months on 2nd line therapy. Predictors of VF and virologic re-suppression on 2nd line were evaluated using Cox Proportional Hazards and multivariable logistic regression models, respectively.

Results: 2191 subjects started 2nd line therapy, 61.5% females. Switching from 1st line (56.4% NVP-based, 70.3% including thymidine-analogues) to 2nd line therapy occurred after mean of 4.1 years. 98.9% of patients started boosted PI with NRTI backbone (TDF+3TC/FTC 67.3%, AZT+3TC 18.5%, others 14.2%). There were 267 (12.0%) VF with a 5-year estimated probability of 15.0% (95% CI 13.2–16.9). Key determinants of VF were concomitant rifampicin use (aHR 2.50 [95% CI 1.54–4.05]) and clinical/immunological failure versus virologic failure as reason for switching therapy (aHR, 0.53 [0.33–0.86]). 138 of 267 (51.7%) subsequently achieved virologic re-suppression and predictors included HIV RNA levels at 2nd-line failure: +1 log higher aOR 0.59 [0.43–0.80], experiencing change within 2nd line ART before VF: aOR 0.17 [0.05–0.56], and more recent calendar year of 2nd line initiation: aOR 0.85 [0.75–0.94].

Conclusions: The effectiveness of current 2nd line ART regimens in SSA is good but challenged by interactions with TB therapy.

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Introduction

Of the 37 million people living with HIV globally by 2016, 70% were resident in sub-Saharan Africa (SSA) where a massive roll-out of anti-retroviral therapy has ensued since 2003.[1] First line therapy comprising of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) is delivered using a public health approach recommended by the World Health Organization (WHO) and has been reportedly effective with outcomes comparable to those in high-income country settings.[2–4] However, failure on first line therapy is often detected late due to unavailability of routine viral load monitoring and reliance on less sensitive indicators such as clinical and immunological failure often culminating in prolonged exposure to failing first line regimens.[5,6] As a result, second line therapy which comprises of a dual backbone of NRTIs and a boosted protease inhibitor (PI) is potentially challenged by extensive cross-resistance to the second line NRTIs, lack of resistance testing before switching to an

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individualized and optimized NRTI backbone, drug interactions between PIs and rifampin used to treat tuberculosis and generally a limited repertoire of potential options for second line therapy.

The landmark EARNEST trial in sub-Saharan Africa reported between 55% and 64% probability of good HIV replication control on the three arms of PI-based second line therapy at 96 weeks[7] and these favorable outcomes were sustained at 144 weeks.[8] Systematic reviews and meta-analytic data of clinical trials have confirmed the efficacy of second-line therapy among Africans.[9–11] Outside the pristine settings of clinical trials, short-to-medium term outcomes on second line therapy have been reported to be good.[12–18] There is however very limited data on the longer-term virological effectiveness of second line therapy in resource-limited settings in SSA. As most ART programs in SSA mature into their second and third decades, the longer term effectiveness and durability of second line therapy assumes greater importance due to the predicted increasing numbers of patients failing first line therapy in the coming years and the unavailability of third line therapy for patients who fail second line therapy. In fact, a recent simulation model study has estimated that up to 25.6 million people are expected to receive ART in 2020, of whom 0.5 to 3.0 million will be receiving second-line ART.[19] Furthermore, there is a gap in knowledge on the probability and determinants of virological failure on second line therapy administered under routine treatment settings from a multi-center and multi-national perspective across the African continent. Such information is crucial for strategic planning in developing alternative second line therapies as well as preparations for third line therapies. We sought to narrow the existing gap in knowledge by conducting a retrospective, multicenter study of second line ART initiated between 2005 and 2017 at four ART centers in Ethiopia, Ghana and Uganda. Our objectives were to assess the probability and determinants of second ART failure in SSA over the longer term.

Methods

Study design and settings

This is a retrospective, multi-center cohort study of second line PI-based ART after failure of first line NNRTI-based regimen. Participants were recruited from four ART centers in Ethiopia (Asella and Adama), Ghana (Kumasi) and Uganda (Kampala). The two Ethiopian sites Asella and Adama situated in the Oromia Region serve a combined total of 30,214 HIV patients registered under care since 2005 out of whom 11,004 received ART (7284 patients in Adama and 3720 patients in Asella). The study site in Ghana is the Komfo Anokye Teaching Hospital which is located in the metropolitan city of Kumasi with an HIV clinic that has 6500 active HIV-infected patients and 4500 receiving on ART since 2003. The Ugandan study site in Kampala is the Infectious Diseases Institute which has 31,852 patients registered under care of whom 15,121 ever started ART since 2003. Ethical permission for this retrospective study was obtained from the Institutional Review Boards of each study site.

Patients and monitoring

For this study, all patients who initiated standard public sector PI-based second-line therapy at the four study sites at least 12 months prior to data extraction (between 2005 and the first quarter of 2017) were eligible for inclusion. All patients had been previously treated with the WHO-recommended NNRTI-based first-line ART regimen and had experienced treatment failure determined either virologically, immunologically or clinically according to WHO guidelines or had been switched from the NNRTI to a PI due to treatment-limiting toxicity on NNRTI.

Data extraction

A standardized study questionnaire was designed to collect data from medical charts and was used across the study sites for the present analysis to ensure uniformity and harmonization of data collection. Demographic data collected include age, gender, first line ART information collected included date of initiation, drugs in the regimen, duration on treatment, CD4 counts at initiation and failure, viral load at initiation and failure where available. Indications for switching to second line therapy namely virological, immunological or clinical failure, treatment limiting toxicity on an NNRTI-based first line therapy were also collected. A drug switch within the NRTI class because of adverse drug events was not considered to be a switch to second-line treatment. We also collected data on use of anti-tubercular therapy whilst on second line ART and virologic re-suppression after virologic failure.

Immunological failure was defined using the World Health Organization criteria[2] either the return of CD4 counts to pre-therapy baseline, or below and/or more than 50% fall from on-therapy CD4 peak-level (and/or more than 50% fall in CD4), or persistent low CD4 of less than 100 cells/μl after one year of therapy without other concomitant infection to explain the low CD4.

Clinical failure was defined using the WHO criteria[2] as having an AIDS-defining clinical event as the occurrence of any opportunistic infections or malignancy while on cART.

Outcome measures

The primary end-point was virologic failure (VF) defined as a confirmed VL>1000 copies/ml after >6 months on 2nd line therapy. A plasma HIV-1 viral load >1000 copies/ml confirmed by a subsequent measurement was used to define virological failure. However, if no subsequent measurements were available, and the last plasma HIV-1 RNA was above 1000 copies/ml, patients were also considered to have experienced virological failure. Virological re-suppression was defined as VL<1000 copies/ml after VF. Data were analyzed by an intention-to-treat approach ignoring treatment changes. For those reaching the virological failure outcome, the end of follow-up for was defined as the most recent date with available results on plasma HIV-1 RNA before the time of data extraction, death, transfer out or being lost to follow-up. A patient was considered lost to follow-up if he or she had not shown up at the clinic for six months or longer before the moment of data extraction and if there was no available information on death or transfer out to another clinic.

Statistical analysis

Parametric and non-parametric methods were used to compare baseline characteristics of continuous data across the 4 study sites. An analysis of variance (ANOVA) or Kruskal Wallis tests was used where appropriate whilst Chi-squared or Fisher's exact test was employed for comparisons of dichotomous data. Kaplan–Meier survival analyses were used to estimate the time from switch to second-line ART to VF. To define predictors of VF, univariate analyses were performed with the following determinants: age, gender, calendar year of second line start, WHO stage at 1st line ART initiation and at 2nd line ART initiation, time from 1st line ART, reason for switch to 2nd line (clinical or immunological failure, virological with or without clinical/immunological failure, or toxicity/other/unknown), type of 1st line and 2nd line regimen, HIV RNA at start of 2nd line ART, and rifampicin use in 2nd line. Cox proportional hazards regression was used to model the individual and simultaneous effects of potential predictors of time to second line VF. Any predictor having significant association with the outcome measure at 10% level in unadjusted analysis was included in

Table 1
Characteristics of study participants on second line Antiretroviral therapy according to study site.

Characteristic	Adama, Ethiopia $N=220$	Asella, Ethiopia $N=161$	Kumasi, Ghana $N=279$	Kampala, Uganda $n=1531$	Total n (%) $N=2191$
Female	109 (49.6)	79 (49.1)	196 (70.2)	964 (63.0)	1348 (61.5)
Age, mean ± SD	35.6 ± 9.0	38.1 ± 9.6	37.9 ± 11.0	34.0 ± 9.2	34.9 ± 9.6
Initial first line ART					
AZT or D4T+3TC+NVP	114 (51.8)	75 (46.6)	117 (44.3)	902 (59.0)	1208 (55.5)
TDF + 3TC or FTC+NVP	44 (20.0)	44 (27.3)	18 (6.8)	204 (13.3)	92 (4.2)
TDF + 3TC or FTC+EFV	31 (14.1)	10 (6.2)	5 (1.9)	46 (3.0)	310 (14.3)
AZT or D4T+3TC+EFV	31 (14.1)	32 (19.9)	123 (46.6)	325 (21.2)	511 (23.5)
Other	0 (0.0)	0 (0.0)	1 (0.4)	53 (3.5)	54 (2.5)
Indications for switch to second line					
Virological failure	155 (70.5)	104 (64.7)	99 (35.5)	1263 (82.5)	1621 (74.0)
Clinical or immunological failure	35 (15.9)	52 (32.3)	92 (33.0)	125 (8.2)	304 (13.9)
Toxicity or intolerance	27 (12.3)	1 (0.6)	8 (2.9)	43 (2.8)	79 (3.6)
Other	2 (0.9)	0 (0.0)	15 (5.4)	7 (0.5)	24 (1.1)
Unknown	1 (0.5)	4 (2.5)	65 (23.3)	93 (6.1)	163 (7.4)
Duration on 1st line before switch, mean ± SD (years)	4.4 ± 3.0	5.0 ± 2.4	4.3 ± 7.4	3.9 ± 2.6	4.1 ± 3.6
Initial second line ART regimens					
TDF+3TC or FTC+PI/r	108 (49.1)	85 (52.8)	151 (54.1)	912 (59.6)	1256 (57.3)
2 NRTI + unboosted PI	0 (0.0)	2 (1.2)	22 (7.9)	0 (0.0)	24 (1.1)
3 NRTI + PI/r	0 (0.0)	0 (0.0)	6 (2.2)	26 (1.7)	32 (1.5)
AZT + 3TC+PI/r	73 (33.2)	56 (34.8)	26 (9.3)	250 (16.3)	405 (18.5)
Lopinavir monotherapy	0 (0.0)	0 (0.0)	0 (0.0)	93 (6.1)	93 (4.2)
NRTI+NNRTI+PI/r	0 (0.0)	0 (0.0)	0 (0.0)	39 (2.6)	39 (1.8)
PI/r + 1 NRTI or 1 NNRTI	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)	5 (0.2)
Other 2NRTI + PI/r	39 (17.7)	18 (11.2)	74 (26.5)	206 (13.5)	337 (15.4)
Any changes within 2nd line ART, $n=2096$					
Yes, n (%)	128 (100)	161 (100)	154 (55.8)	458 (29.9)	901 (43.0)
Rifampicin use during 2nd line	5 (2.3)	7 (4.4)	6 (2.8)	44 (2.9)	62 (2.9)

adjusted analysis. Furthermore, a multivariable logistic regression model using the same predictors as above was used to assess the determinants of virologic re-suppression on 2nd line ART. In multivariable analysis, statistical significance was attained if $p<0.05$. All p-values were two-tailed. Data was processed and statistical analyses conducted using Stata statistical software (version 15).

Results

Demographic and clinical characteristics of study participants

Two thousand, one hundred and ninety-one (2191) subjects initiated second line therapy at the 4 study sites comprising of 220 (10.0%) at Adama, Ethiopia, 161 (7.3%) at Asella, Ethiopia, 279 (12.7%) in Kumasi, Ghana and 1531 (69.9%) in Kampala, Uganda. The baseline demographic and clinical characteristics of study participants overall and per site are depicted in Table 1. Briefly, 61.5% of study subjects were females and the mean ± SD age at enrollment into care for ART initiation was 34.9 ± 9.6 years. Overall, 11.0% of the patients were at WHO clinical stage 1, 27.2% at stage 2, 40.9% at stage 3 and 20.9% at stage 4. First line ART comprised mainly zidovudine or stavudine plus lamivudine plus nevirapine (55.5%), zidovudine or stavudine plus lamivudine plus efavirenz (23.5%), tenofovir plus lamivudine or emtricitabine plus efavirenz (14.3%), tenofovir plus lamivudine or emtricitabine plus nevirapine (4.2%) and others 2.5%. The mean (±SD) duration on 1st line therapy before switch to 2nd line therapy was 4.1 ± 3.6 years and the indications for switching were virological failure (74.0%), clinical or immunological failure (13.9%), toxicity or intolerance mainly on NNRTI (3.6%), and other/unknown (8.5%). Second line regimens initiated comprised of tenofovir plus lamivudine or emtricitabine plus ritonavir boosted PI (57.3%), zidovudine plus lamivudine plus ritonavir boosted PI (18.5%), other dual NRTI plus ritonavir boosted PI (15.4%), ritonavir boosted lopinavir monotherapy (4.2%) and others (Table 1). Among those starting a boosted PI (98.9%), 60.2% were initiated on ritonavir-boosted lopinavir, 39.8% on boosted atazanavir.

Outcomes on second line therapy

The median (IQR) duration on second line therapy at close of data for analysis was 3.7 (1.9–6.7) years. As many as 901 (43.0%) out of 2096 with available data had changes made to initial second line therapy. The regimen changes included an increase from 57% on TDF+3TC or FTC+PI/r to 68%, a decline from 1.1% on 2 NRTI plus unboosted PI to 0.4%, a decline in lopinavir monotherapy use from 4.2% to 0.6% whilst the proportion on AZT+3TC+PI/r of 19% decreased slightly to 18%. Overall, LPV/r use declined from 60.2% to 53.6% whilst ATV/r increased from 39.8% to 46.4%. 62 (2.9%) of patients on 2nd line therapy used rifampicin as a component of anti-tubercular therapy. Treatment failure was experienced by 298 (14.3%) patients, broken down into 125 (5.7%) with clinical failure, 43 (2.0%) with immunological failure and 267 (12.2%) with virological failure, with some overlaps.

Predictors of virological failure on 2nd line therapy

The Kaplan Meier curve of time to virological failure on 2nd line ART among 267 of 2191 by intention-to-treat analysis gave an estimated proportion without VF at 2-years of 92.0% (95% CI of 90.7–93.2%) and at 5-years of 85.0% (95% CI of 83.1–86.8%) as depicted in Fig. 1. Factors independently associated with virological failure on 2nd therapy upon adjustment for confounders in a Cox proportional hazards regression model were concomitant rifampicin use: aHR 2.50 [95% CI 1.54–4.05], and reasons for switching to 2nd line therapy with virological failure compared to clinical or immunological failure associated with higher hazard of virological failure: aHR, 0.53 [0.33–0.86] (Table 2).

Re-suppression on 2nd line therapy and its predictors

Of 267 patients with virological failure, 138 (51.7%) achieved VL <1000 copies/mL while still on 2nd line therapy (114, 42.7% <200 copies/mL). In a parsimonious model with adjustment for confounders, the factors independently associated with a reduced odds

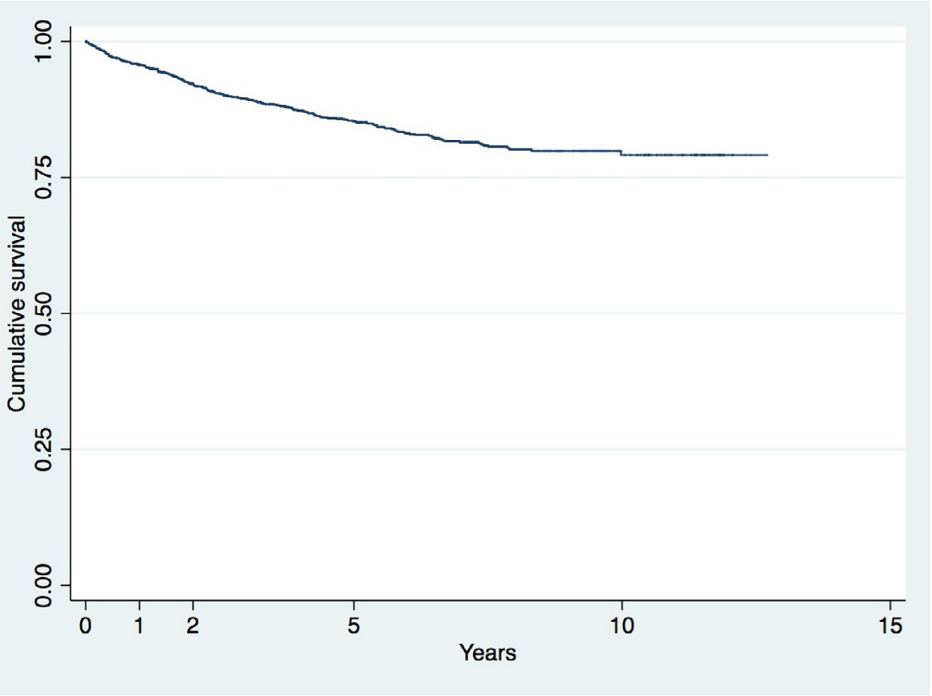

Fig. 1. Proportion surviving on 2nd line without virologic failure. Kaplan–Meier estimates.

Table 2
Predictors of virological failure on second line therapy in sub-Saharan Africa.

Predictor	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Age, each 10 years older	0.77 (0.64–0.90)	0.88 (0.74–1.02)
Calendar year of second line start	1.06 (1.02–1.12)	
Rifampicin use in second line	2.41 (1.49–3.88)	2.50 (1.54–4.05)
WHO stage at ART initiation		
4	1.00	1.00
3	0.50 (0.29–0.86)	0.66 (0.38–1.13)
2	0.77 (0.56–1.08)	0.85 (0.62–1.18)
1	0.62 (0.48–0.83)	0.79 (0.59–1.07)
HIV RNA at start of 2nd line (copies/ml)		
<1000	1.00	
1000–9999	1.41 (0.60–3.27)	
10,000–99,999	1.86 (0.87–4.00)	
>100,000	1.99 (0.92–4.29)	
Reason for switch to 2nd line		
Virological failure	1.00	1.00
Clinical or immunological failure	0.31 (0.19–0.49)	0.53 (0.33–0.86)
Toxicity/intolerance	0.30 (0.12–0.73)	0.48 (0.19–1.18)
Other	0.36 (0.09–1.45)	1.02 (0.25–4.12)
unknown	0.53 (0.32–0.91)	0.75 (0.44–1.30)
Ever changed within second line	0.71 (0.56–0.92)	
Female gender	1.09 (0.85–1.39)	
Time from first line ART initiation	1.00 (0.97–1.04)	
Initial first line ART regimen		
AZT or D4T+3TC+NVP	1.00	
TDF+3TC/FTC+ EFV	1.03 (0.65–1.61)	
TDF+3TC/FTC+ NVP	0.53 (0.22–1.29)	
D4T or AZT+3TC+ EFV	1.00 (0.75–1.33)	
Other	0.53 (0.22–1.29)	
Initial second line ART regimen		
TDF+3TC/FTC+PI/r	1.00	
2 NRTI + unboosted PI	n.e.	
3 NRTI + PI/r	0.55 (0.17–1.73)	
AZT + 3TC+PI/r	0.91 (0.63–1.32)	
Lopinavir monotherapy	1.09 (0.68–1.75)	
NRTI+NNRTI+PI/r	0.62 (0.25–1.51)	
PI/r + 1 NRTI or 1 NNRTI	n.e.	
Other 2NRTI + PI/r	0.71 (0.51–0.98)	

[a] in the multivariable model, variables are all mutually adjusted and adjusted by site. N.e. = not estimable.

Table 3
Factors associated with re-suppression of virological failure on second line therapy in sub-Saharan Africa ($n = 144$ events in 167 individuals).

Predictor	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Age, each 10 years older	1.27 (1.10–1.53)	
Female sex	0.63 (0.39–1.03)	
Initial 1st line		
AZT/d4T+3TC+EFV	1.00	
TDF+3TC/FTC+EFV	0.22 (0.07–0.60)	
AZT/d4T+3TC+EFV	0.72 (0.41–1.27)	
Initial 2nd line		
TDF+3TC/FTC+PI/r	1.00	
Other 2NRTI+PI/r	4.03 (1.93–8.43)	
AZT+3TC+PI/r	0.33 (0.14–0.78)	
Viral load at 2nd line start (+1 log higher)	0.75 (0.54–1.04)	
Rifampicin use during 2nd line	0.44 (0.16–1.22)	0.40 (0.14–1.18)
Ever changed within 2nd line	2.22 (1.36–3.64)	
HIV RNA at 2nd line failure (+1 log higher)	0.60 (0.45–0.80)	0.59 (0.43–0.80)
Change within 2nd line before VF	0.10 (0.04–0.31)	0.17 (0.05–0.56)
Calendar year of 2nd line start (+1 year more recent)	0.82 (0.76–0.89)	0.85 (0.75–0.94)
Time in years from 1st line initiation	0.97 (0.88–1.07)	
WHO stage at 1st line ART initiation		
1	1.00	–
2	1.03 (0.35–3.03)	–
3	1.00 (0.35–2.88)	–
4	1.17 (0.40–3.42)	–
WHO stage at 2nd line ART initiation		
1	1.00	
2	0.82 (0.10–6.40)	
3	0.93 (0.13–6.93)	
4	1.53 (0.21–11.23)	
Ever changed within 1st line ART	1.16 (0.72–1.88)	
Reason for switch to 2nd line		
Virological failure	1.00	–
Clinical or immunological failure	1.14 (0.45–2.85)	–
Toxicity/intolerance	0.62 (0.10–3.79)	–
Other	0.93 (0.06–15.08)	–
unknown	0.93 (0.32–2.74)	–

[a] Mutually adjusted.

ratio of virologic re-suppression were a treatment change within 2nd line therapy: aOR 0.17 [0.05–0.56], a higher viral load at 2nd-line failure: +1 log higher aOR 0.59 [0.43–0.80] and more recent calendar year of 2nd line initiation: aOR 0.85 [0.75-0.94] (Table 3).

Discussion

We have evaluated the longer-term treatment outcomes of second line ART in one of the largest multi-center cohorts in sub-Saharan Africa to date. Our principal finding is that second line ART has very good effectiveness with an estimated probability of virological failure of approximately 15% at 5 years. Switching to 2nd line therapy on account of confirmed virological failure and concomitant use of rifampin therapy for TB were significantly associated with risk of virological failure. Interestingly, 53% of patients with confirmed virological failure on 2nd line achieved virological re-suppression with VL<1000 copies/ml while still on the 2nd line therapy probably highlighting the potential contribution of adherence issues on 2nd line failure. Whilst increasing age and alterations within the initial 2nd line regimen were associated with a higher odds of virological re-suppression, use of AZT+3TC backbone in 2nd line ART, higher viral load at 2nd line failure, change within 2nd line before VF and more recent calendar year of 2nd line ART initiation were conversely associated lower odds of virological re-suppression in a univariate logistic regression model. However upon further adjustment for confounders in a parsimonious logistic regression model, we identified changes within the 2nd line regimen before VF, viral load at 2nd line failure, and more recent calendar year of initiation to be independently associated with lower odds of achieving virological re-suppression following confirmed virological failure.

Taken together, our findings demonstrate an acceptable durability of the WHO recommended boosted PI-based second line ART administered within the challenging public health approach programs in SSA. However, the very good longer term effectiveness of 2nd line reported in our present study contrasts with data from a meta-analysis of 2035 patients across low-and middle-income countries from 19 studies where the cumulative pooled proportion of virological failure by adults on 2nd line ART was 21.8% at month 6, 23.1% at month 12, 26.7% at month 24 and 38.0% at month 36.[11] A more recent meta-analysis of protease inhibitor (PI)-based second-line ART in sub-Saharan Africa showed better outcomes: virological suppression occurred in 69.3% of 4558 participants at week 48 and 61.5% of 2145 at week 96.[9] Although these outcomes are worse than those observed in the present study, the improved outcomes in our study perhaps suggest that second-line therapy may have significantly improved with the use of more effective and tolerable regimens. Interestingly, we found no differences in the probability of virological failure using distinct PI-based regimens in routine use across Africa. In line with this, a network meta-analysis comparing the outcomes of the different second line strategies as compared to lopinavir/r+2 NRTIs failed to detect any more effective regimen.[10] In the EARNEST trial, 86% of subjects on 2 NRTIs + LPV/r, 81% on raltegravir + LPV/r and 78% on LPV/r monotherapy had viral load <400 copies/ml at 144 weeks of follow-up.[8] The 96-week outcomes of the same study showed success rates of 86–87%,[7] which is comparable to our 24 month estimated probability of virological success of 92%. Also findings from the "second-line" trial, with 81% and 83% of first-line failing individuals, randomly assigned to receive LPV/r + 2 NRTIs or raltegravir, achieved a viral load <200 copies/mL at 48 weeks, respectively, are comparable with our observations.[20] We note with interest

though that outcomes from the immaculate settings of randomized controlled trial are usually better than the real world settings. However, we used a higher viral load cut-off of 1000 copies/ml for virological failure in agreement with WHO guidelines.

The findings of our study have significant implications for the future of second line ART in resource-limited settings. Firstly, the low frequencies of documented virological, immunological and clinical failures observed overall support the continual utilization of the affordable, heat-stable formulations of LPV/r or ATV/r combined with dual NRTIs.[2] Secondly, consideration should be given to the wider availability and use of rifabutin for the treatment of tuberculosis in LMICs particularly among patients on 2nd line ART given the adverse pharmacokinetic interactions of rifampicin on exposure to boosted PI,[21,22] the high burden of tuberculosis in LMICs[23] and the demonstrable favorable PK interactions between rifabutin and LPV/r in both adults and children.[24,25] Alternatively, second-line ART regimens based on dolutegravir, with manageable interaction with rifampin, should be considered.[26] Thirdly, although measures of medication adherence were not available in the present study to assess its effect on risk of virologic failure on PI/r therapy, there is ample evidence from literature to suggest that virologic failure with boosted protease inhibitor regimens is often due to poor adherence not emergence of new or major protease inhibitor mutations.[17,27–29] A South African study intriguingly showed improvements upon 1st line ART adherence rates among patients initiating 2nd line ART and dose-dependent relationship between adherence and probability of virologic failure after 24 months follow-up.[30] Of interest, older subjects who have been shown in studies to be more adherent to ART[31,32] were slightly less likely to fail virologically in our study lending indirect evidence to the possible contribution of poor adherence to adverse virological outcomes.

Over 50% of patients with documented virological failure later achieved virological re-suppression upon continuing 2nd line therapy suggesting that adherence support and frequent virological monitoring on 2nd line ART in resource-limited settings may be worthwhile investments in preserving the effectiveness of 2nd line therapy. As expected, the higher the viral load at 2nd-line failure, the lower the probability to achieve subsequent re-suppression while remaining on a 2nd-linre regimen. Of note, individuals modifying their 2nd-line regimen were less likely to achieve re-suppression, potentially suggesting a category of patients experiencing more difficulties with their regimen, although we could not collect information on their nature (e.g. toxicity or procurement issues). Finally, the association of more recent calendar year of 2nd-line start with a lower probability of re-suppression may indicate a selection of individuals with higher resistance levels or a "saturation" of the sites with consequent reduced ability to support medication adherence. Based on our findings, a reasonable management strategy could be to test for drug resistance among individuals not achieving virologic re-suppression after adherence implementation, identify the need of third-line therapy and the type of drugs needed based on the detected HIV-1 drug resistance profile. This strategy however requires a prospective validation in future studies.

There are some limitations to our study to note. Firstly, due to the retrospective observational study design, there may be unmeasured underlying determinants which could influence virological outcomes, notably the absence of adherence data and toxicity data such as renal impairment from use of tenofovir.[33–35] Adherence was however not systematically measured and documented in standardized fashion in patient charts across the study sites. Secondly, we cannot exclude the potential impact of survivorship bias. A major strength of our study is the robust virological follow-up data enabling us to use the most sensitive method for assessment of ART efficacy over the long-term which is a topical issue as treatment programs in SSA mature with more patients needing second line therapy. With increasing numbers of patients anticipated to use protease-inhibitor based second line cART in the coming decades, further considerations should be given to increased cardiovascular risk posed by these regimens given the high and growing burden of cardiovascular diseases in SSA.[36–40]

In conclusion, while the effectiveness of 2nd line ART regimens in these SSA programs was good, it was challenged by adherence-related issues and interaction with TB therapy. Strategic priorities may include increasing the repertoire of 2nd line therapy in settings with high TB endemicity, improving regimens convenience and tolerability in order to favor medication adherence, and setting 3rd line strategies for those failing existing 2nd line therapy despite adherence support and showing resistance to the current regimen.

Transparency declaration

None to declare.

Conflict of interest

None.

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