Second-line antiretroviral therapy in resource-limited settings: the experience of Médecins Sans Frontières

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Objectives: To describe the use of second-line protease-inhibitor regimens in Médecins Sans Frontières HIV programmes, and determine switch rates, clinical outcomes, and factors associated with survival.

Design/Methods: We used patient data from 62 Médecins Sans Frontières programmes and included all antiretroviral therapy-naive adults (>15 years) at the start of antiretroviral therapy and switched to a protease inhibitor-containing regimen with at least one nucleoside reverse transcriptase inhibitor change after more than 6 months of nonnucleoside reverse transcriptase inhibitor first-line use. Cumulative switch rates and survival curves were estimated using Kaplan–Meier methods, and mortality predictors were investigated using Poisson regression.

Results: Of 48 338 adults followed on antiretroviral therapy, 370 switched to a second-line regimen after a median of 20 months (switch rate 4.8/1000 person-years). Median CD4 cell count at switch was 99 cells/μl (interquartile ratio 39–200; $n = 244$). A lopinavir/ritonavir-based regimen was given to 51% of patients and nelfinavir-based regimen to 43%; 29% changed one nucleoside reverse transcriptase inhibitor and 71% changed two nucleoside reverse transcriptase inhibitors. Median follow-up on second-line antiretroviral therapy was 8 months, and probability of remaining in care at 12 months was 0.86. Median CD4 gains were 90 at 6 months and 135 at 12 months. Death rates were higher in patients in World Health Organization stage 4 at antiretroviral therapy initiation and in those with CD4 nadir count less than 50 cells/μl.

Conclusion: The rate of switch to second-line treatment in antiretroviral therapy-naive adults on non-nucleoside reverse transcriptase inhibitor-based first-line antiretroviral therapy was relatively low, with good early outcomes observed in protease inhibitor-based second-line regimens. Severe immunosuppression was associated with increased mortality on second-line treatment.

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Introduction

Since 2001, Médecins Sans Frontières (MSF) has provided antiretroviral therapy (ART) to more than 100 000 people in resource-limited settings (RLS), using World Health Organization (WHO)-recommended first-line regimens involving two nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral drugs. Satisfactory short-term outcomes in such settings have been described by MSF and others [1–4], and this contributed to the rapid scaling up of ART. As access to and time on ART increases, the need for second-line regimens in RLS becomes a priority due to the development of drug resistance [5,6]. Clinical programme data are urgently needed to help design longer-term treatment strategies, and to allow programme

managers, governments, donors, and pharmaceutical manufacturers to more accurately forecast antiretroviral drug first-line and second-line requirements [7].

Detection of first-line ART failure in most RLS relies on immunological or clinical criteria, as routine viral load monitoring is frequently not available due to financial and technical constraints. Thus, diagnosis of failure is often delayed [8], and might favour not only clinical disease progression [9], but also development of antiretroviral resistance due to concurrent antiretroviral drug exposure and high viral replication. The appearance of resistance mutations [e.g. thymidine analogue mutations (TAMs)] may thus jeopardize the effectiveness of second-line ART regimens in settings where few treatment options are available [10]. Additional constraints regarding second-line ART in RLS include availability of less robust second-line ART regimens (e.g., nonboosted protease inhibitors); difficulty in ensuring long-term adherence due to increased pill burden or meal restrictions; and high price of drugs (up to ten times more expensive than first-line regimens) [11]. Therefore, concerns about the effectiveness of second-line ART in RLS have been raised, but few data on this exist [12,13].

We report here the rate of switch from first-line to second-line ART in MSF programmes; survival and clinico-immunological outcomes of patients on second-line ART; and factors contributing to death when on second-line ART.

Methods

Study design
We used routinely collected individual patient data (FUCHIA software, Epicentre, Paris) from 62 MSF-supported HIV programmes in 26 countries between October 2001 and December 2006. Data collected included sex; age; treatment history; ART prescription date and regimen; dates of visit, appointment, or death; WHO clinical stage; and CD4 cell count and viral load, when available.

All programmes provided free care, including antiretroviral drugs and laboratory investigations, with clinical consultation performed by doctors, clinical officers, or nurses. Eligibility criteria for ART were based on the 2003 WHO recommendations [14] and generic antiretroviral drugs used, mainly in the form of NNRTI-containing fixed-dose combinations. Adherence counseling was provided to all patients both prior to and during ART. Programmes routinely provided prophylaxis and treatment of opportunistic infections and often nutritional support for malnourished individuals. CD4 cell counts were measured using either automated or manual methods (Partec, Dynabeads, Beckton Dickinson).

Although virological monitoring was not routinely performed, viral load was occasionally determined when clinicians suspected treatment failure and adequate laboratory facilities were available.

Study population
We analysed information from all ART-naive adults (> 15 years) at MSF programme inclusion and who received an NNRTI first-line regimen for more than 6 months. Missing age data was the only reason for exclusion from this study. To exclude antiretroviral drug substitutions for toxicity, we defined second-line therapy as a concomitant initiation of a protease inhibitor-containing regimen and a change in at least one NRTI drug in patients who had received NNRTI first-line therapy for more than 6 months. Women who had received prevention of mother-to-child transmission (PMTCT) prophylaxis were considered naive. Reasons for switch to second line were not prospectively collected. Treatment failure was defined as CD4 at switch less than CD4 cell count at ART initiation; CD4 cell count at switch less than 100 cells; new WHO stage 3 or 4 event within 3 months before switch; and/or viral load more than 1000 copies/ml, when available [15].

Statistical analyses
We estimated the probabilities of remaining on first-line ART, rate of switch to second-line ART, and probabilities of remaining alive and in care after first-line and second-line therapy initiation using Kaplan–Meier and censoring-naive methods. For patients on ART for more than 19.8 months (the median time of follow-up on ART before the switch to second line), we compared the probabilities of remaining alive and in care in patients started or not on second-line therapy with the log-rank test. We then described patient characteristics at the start of ART and at switch, and BMI and CD4 gains at 6, 12, and 24 months after switch, using medians, interquartile ranges (IQR), and percentages, as appropriate. Finally, we investigated factors associated with death or lost to follow-up (LFU; a missed appointment for > 2 months) using Poisson regression. To control for the heterogeneity of the data, as information from several projects was included (and access to CD4 testing and/or to diagnostic facilities for opportunistic infections vary in different contexts), all the models were adjusted for geography (sub-Saharan Africa, Asia, and Latin America) and for factors significantly associated with the outcomes (P value from likelihood ratio tests < 0.05).

Results

Description of the global Médecins Sans Frontières cohort
After excluding 856 (1.7%) patients with unknown age, we analysed data from 48 338 naive adults on ART for more than 6 months, 78% treated in MSF-supported projects in

Africa, 18% in Asia, 4% in Latin America, and 0.2% in Eastern Europe (Table 1). At the start of ART, patient median age was 35 years (IQR 30–42), and 62% were women. The median CD4 cell count was 110 cells/μl (IQR 46–178; $n = 34\,799$), and 84% were classified as WHO clinical stage 3 or 4. The first-line ART regimen most frequently prescribed was stavudine/lamivudine/nelfinavir (d4T/3TC/NVP) (86%), and median duration of ART was 18 months (IQR 11–25), with 13 871 (29%) patients on treatment for more than 2 years. For patients on regular follow-up, the probability of remaining on first-line ART after 36 months was 0.98 (95% CI 0.97–0.98). The probability of remaining alive and in care at 24 months was 0.87.

Description of patients on second-line antiretroviral therapy

A total of 370 (0.8%) patients began a second-line regimen after a median of 20 months (IQR 14–27), corresponding to a switch rate from first to second line of 4.8/1000 person-years (95% CI 4.3–5.3) (Fig. 1) (Table 2). Switch rates ranged from 4.2/1000 person-years in sub-Saharan projects to 6.5/1000 in Asia, 7.4/1000 in Latin America, and 14.5/1000 in Eastern Europe. At the start of first-line ART, 334 (90%) patients were in cumulative WHO clinical stage 3 or 4, and had a median BMI of 20 kg/m^2 (IQR 18–22; $n = 321$) and median CD4 cell count of 52 cells/μl (IQR 18–131; $n = 304$). Median CD4 nadir was 39 cells/μl (IQR 13–86; $n = 368$).

At the time of switch, median CD4 cell count was 99 cells/μl (IQR 39–200; $n = 244$), 32% having less than 50 cells/μl, 50% had less than 100 cells/μl, and 75% had less than 200 cells/μl. Median viral load was 43 188 copies/ml (IQR 16 406–166 197; $n = 75$), and median BMI was 21 kg/m^2 (IQR 19–24; $n = 320$) with 45 (14%) patients having less than 17 kg/m^2.

Table 1. Demographic and clinico-immunological characteristics of patients treatment-naïve at the start of antiretroviral treatment (ART), Médecins Sans Frontières (MSF) HIV cohort 2001–2006, 26 countries.

Patient characteristics	All MSF ART patients ($n = 48\,338$)	Second-line patients ($n = 370$)
Women (%)	29 794 (61.7)	217 (58.7)
Median age [IQR] (years)	35.0 [29.6–41.6]	35.1 [29.3–40.8]
Continent (%)		
Sub-Saharan Africa	37 918 (78.4)	250 (67.6)
Asia	8459 (17.5)	93 (25.1)
Latin America	1864 (3.9)	25 (6.8)
Eastern Europe	97 (0.2)	2 (0.5)
Median months of follow-up on ART [IQR]		
Before switch[a]	17.5 [11.2–25.4]	19.8 [13.9–27.3]
After switch		7.8 [2.4–18.4]
Median CD4 nadir [IQR] (cells/μl)	117 [51–187], $n = 45\,319$	39 [13–86], $n = 368$
Characteristics at the start of ART		
Cumulative WHO stage at ART start (%)		
Stage 3	27 353 (56.6)	208 (56.2)
Stage 4	13 067 (27.0)	126 (34.1)
Median BMI [IQR] (kg/m^2)	19.7 [17.8–21.9], $n = 37\,780$	20.1 [18.1–22.1], $n = 321$
Median CD4 cell count [IQR] (cells/μl)	110 [46–178], $n = 34\,799$	52 [18–131], $n = 304$
ART regimen (%)		
3TC-d4T-NVP	41 557 (86.0)	265 (71.6)
3TC-d4T-EFV	4167 (8.6)	45 (12.2)
3TC-ZDV-NVP	1292 (2.7)	33 (8.9)
Other	1322 (2.7)	27 (7.3)
Characteristics at switch		
Median CD4 cell count [IQR] (cells/μl)	–	99 [39–200], $n = 244$
Median VL [IQR] (copies/ml)	–	43 188 [16 406–166 197], $n = 75$
Second-line regimen (%)		
Type of PI	–	
LPV based		188 (50.8)
NFV based		160 (43.2)
Other		22 (5.9)
Boosted PI	–	207 (56.0)
NRTI class	–	
ZDV+ddI		125 (33.8)
ABC+ddI		80 (21.6)
TDF based		56 (15.1)
ZDV+3TC only		44 (11.9)
Other ddI based		50 (13.5)
Other		15 (4.1)

IQR are shown in square brackets and percentages in brackets. ABC, abacavir; BMI, body mass index; ddI, didanosine; EFV, efavirenz; d4T, stavudine; IQR, interquartile range; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; 3TC, lamivudine; VL, viral load; ZDV, zidovudine.
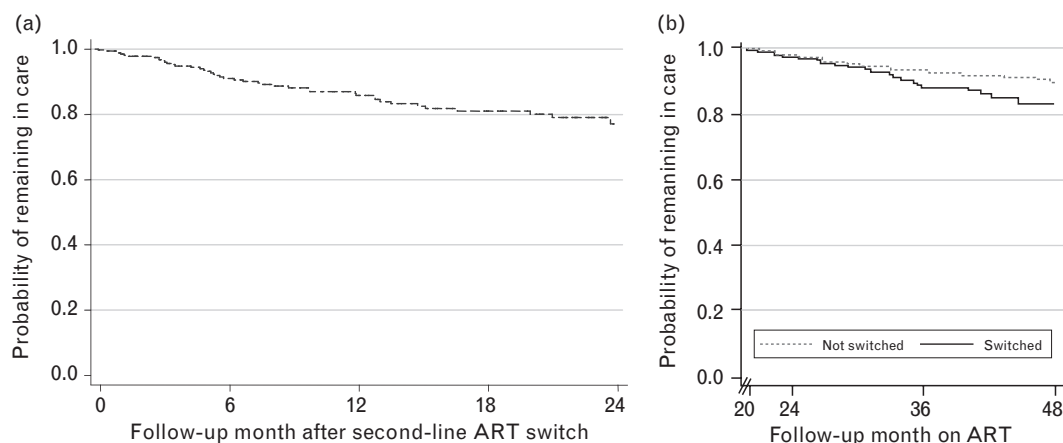[a]Median months on ART (first line or second line).
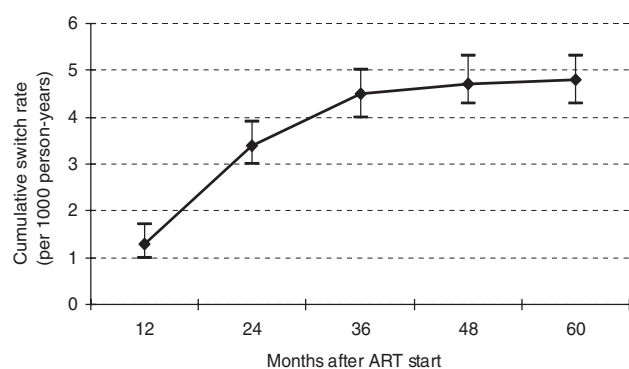
Fig. 1. Cumulative switch rates from first-line to second-line antiretroviral treatment (ART) and 95% confidence intervals among naïve patients at the start of ART, Médecins Sans Frontières HIV cohort 2001–2006, 26 countries.

During the 3 months before the switch, a new WHO clinical stage 3 or 4 condition had been recorded for 111 (30%) patients and a CD4 value of less than or equal to CD4 cell count at the start of ART for 69 (34%). Among patients who were switched to second line, 230 (62%) had at least one of the criteria of treatment failure according to the 2006 WHO criteria. A total of 139 patients had no CD4 data collected and thus could not be evaluated with regard to immunological treatment failure criteria.

The protease inhibitor component of the second-line regimen was lopinavir/ritonavir (LPV/r) for 188 (51%) patients and nelfinavir (NFV) for 160 (43%); 56% received a boosted protease inhibitor. The most frequently administered NRTI combinations were zidovudine-didanosine (ZDV-ddI; 34%) and abacavir (ABC)-ddI (22%). Only one NRTI drug had been changed instead of two for 115 (31%) patients, and only 12% received ZDV-lamivudine (ZDV-3TC) in combination with a protease inhibitor.

Table 2. Number of patients, cumulative person-years of follow-up and cumulative incidence of switches to second-line therapy, Médecins Sans Frontières, HIV cohort 2001–2006, 26 countries.

Time (months)	12	24	36	48	60
Number of patients	34 630	13 771	3202	434	29
Cumulative					
Person-years	44 696	68 179	75 694	77 120	77 272
Switches to second-line ART	57	232	340	366	370

ART, antiretroviral treatment.

Second-line treatment outcomes

Median follow-up on second-line ART was 8 months (IQR 2–18), with 138 (37%) patients on treatment for more than 12 months. Twenty-eight (8%) patients died after a median of 5 months (IQR 3–8), and 18 (5%) were LFU after a median of 9 months (IQR 3–14). Recorded causes of death were Kaposi sarcoma ($n = 7$), tuberculosis ($n = 4$), wasting syndrome ($n = 3$), and one suspicion of cerebral mass. The probabilities of remaining alive and in care at 12 and 24 months were 0.86 (95% CI: 0.81–0.90) and 0.77 (95% CI: 0.69–0.83), respectively (Fig. 2a)(Table 3). These figures did not differ by the number of NRTI drugs changed ($P = 0.99$) and were slightly, but not significantly, higher for patients on LPV/r-second-line therapy (unadjusted $P = 0.06$, compared with NFV-based therapy). The probability of remaining alive and in-care for patients with a follow-up of at least 19.8 months was similar in patients switched and not switched to second-line therapy at 20 months of ART, but it was lower for patients on second line after that (log-rank test P value 0.03; Fig. 2b and Table 4). However, latter estimates were based on data from few patients.

Median CD4 cell count was 184 cells/µl (IQR 128–306; $n = 106$) and 247 cells/µl (IQR 132–302; $n = 78$) at 6 and 12 months, respectively. Median CD4 increase was 90 (37–141; $n = 73$) and 135 (50–198; $n = 55$) at 6 and

Fig. 2. Probabilities of remaining in care, Médecins Sans Frontières, HIV cohort 2001–2006, 26 countries. (a) Kaplan–Meier estimates of remaining in care after switch from first-line to second-line treatment in antiretroviral treatment (ART)-naive patients. (b) Kaplan–Meier estimates of remaining in care after the start of ART in ART-naive patients for patients switched or not switched to second-line ART with a follow-up on ART of at least 19.8 months.

Table 3. Number of patients and incidence of deaths or lost to follow-up, Médecins Sans Frontières, HIV cohort 2001–2006, 26 countries.

Time (months)	6	12	18	24
Patients at risk	209	144	95	38
Deaths or lost to follow-up	14	4	7	10

12 months, respectively (Fig. 3). One year after switch, six (10.9%) patients had a CD4 cell count of less than 50 cells/μl, 14 (25.5%) had less than 100 cells/μl, and 30 (54.5%) had less than 200 cells/μl. Furthermore, median weight gains at 6 and 12 months after switch were 0.5 kg (IQR −2 to 3; $n = 205$) and 1 kg (IQR −2 to 4; $n = 139$), respectively. Only eight (6%; $n = 127$) patients had a BMI of less than 17 kg/m^2 1 year after the switch. After 6 months of treatment, 46 (12.4%) patients developed a WHO condition stage 3 or 4 (14 at stage 4 condition), and the CD4 cell count was equal or below the value recorded at switch for 11% (8/75).

Antiretroviral drug-related toxicity leading to cessation or change of the antiretroviral drug regimen was recorded for only three (1%) patients: two on ZDV-ddI-NFV (neuropathy WHO grades 1 to 2 and lactic acidosis) and one on ZDV-ddI-IDV/r (hepatoxicity grade 4).

Factors associated with death and lost to follow-up

In multivariable analyses, death and LFU rates were higher in patients classified as WHO stage 4 at first-line ART initiation [incidence rate ratio (IRR) 2.35, 95% CI 1.29–4.31; $P = 0.006$], and in those with CD4 cell count nadir less than 50 cells/μl (IRR 1.73, 95% CI 0.91–3.29; $P = 0.09$) (Table 5). Interestingly, the number of NRTI drugs changed ($P = 0.39$), level of CD4 cell count at switch ($P = 0.26$), and type of protease inhibitor (boosted versus nonboosted; $P = 0.31$) were not significant predictors of survival in this analysis.

Discussion

In this first published study of second-line ART in RLS, we have shown encouraging early treatment outcomes, with clinical and immunological outcomes similar to those published for first-line regimens in RLS [1,3,16].

Table 4. Number of patients and incidence of deaths or lost to follow-up by switch status, Médecins Sans Frontières, HIV cohort 2001–2006, 26 countries.

Time (months)	24	36	48
Not switched to second-line ART			
Patients at risk	13633	3172	430
Deaths or lost to follow-up	372	403	47
Switched to second-line ART			
Patients at risk	281	140	26
Deaths or lost to follow-up	9	18	4

ART, antiretroviral treatment.
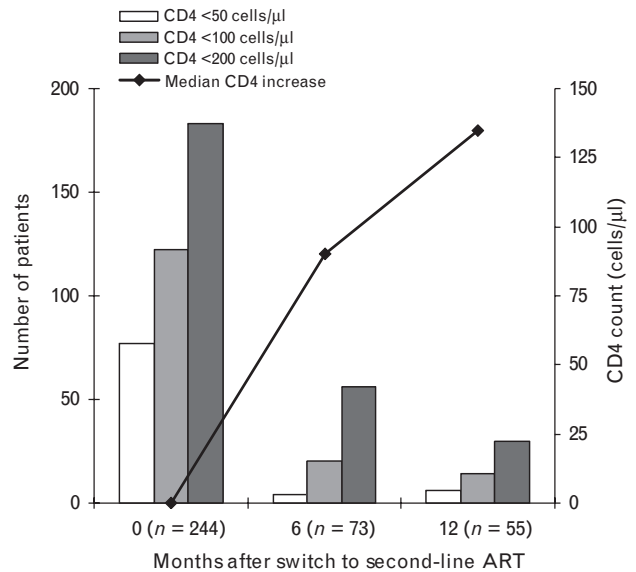
Fig. 3. Immunological response on second-line antiretroviral treatment (ART), Médecins Sans Frontières HIV cohort 2001–2006, 26 countries. Bars denote number of patients (primary Y axis). Line graph denotes CD4 cell count (secondary Y axis).

Nine out of ten patients were still alive after 12 months of treatment, and few patients were diagnosed with new severe AIDS-related illnesses. However, over half of the patients were still at a significant risk of life-threatening opportunistic infections (CD4 < 200 cells/μl) after 12 months of treatment, showing that room for improvement exists even for second-line therapy.

We found that overall a relatively small proportion of patients, after at least 6 months on ART in MSF programmes, switched to a second-line regimen for treatment failure (switch rate 4.8/1000 person-years; 6% of cohort at 48 months). Switch rates to second-line therapy were lowest in sub-Saharan patients and highest in Eastern Europeans, probably reflecting differences in access to viral load and CD4 testing in those contexts (many MSF projects in Africa are based in rural areas). Our observed switch rate probably reflects only the most obvious cases of treatment failure, due to our inability to accurately diagnose when a first-line regimen should be changed to second line. This is also suggested by our finding of lower survival in patients switched to second-line therapy compared with those who did not, suggesting that late diagnosis of failure would increase the risk of death in patients started on second-line ART. In the absence of routine virological monitoring in our programmes, diagnosis of failure is usually based on either the occurrence of a clinical event, or on immunological criteria as per WHO guidelines [14].

These data from a large number of RLS highlight the increased need for second-line therapy in similar settings.

Table 5. Factors and incidence of death or lost to follow-up of patients achieving early immunological success on second-line antiretroviral treatment (ART), Médecins Sans Frontières HIV cohort 2001–2006, 26 countries.

Patients characteristics	Lost to follow-up or death				
	n (N = 45)	Person-years	Rate/100 (95% CI)	IRR (95% CI)	IRRa (95% CI)
Sex					
Men	23	132	17.46 (11.60–26.27)	1, P = 0.09	1, P = 0. 50
Women	22	202	10.90 (7.18–16.55)	0.59 (0.32–1.07)	0.81 (0.43–1.52)
Age group					
>35 years	19	180	10.58 (6.75–16.59)	1, P = 0.09	1, P = 0.11
≤35 years	26	154	16.88 (11.49–24.78)	1.69 (0.92–3.08)	1.62 (0.89–2.97)
BMI group at ART start					
≥17 kg/m^2	28	240	11.68 (8.06–16.91)	1, P = 0.46	1, P = 0.12
<17 kg/m^2	5	60	8.32 (3.46–19.99)	0.71 (0.27–1.83)	0.49 (0.19–1.30)
WHO stage 4 at ART start					
No	22	224	9.81 (6.46–14.90)	1, P = 0.003	1, P = 0.006
Yes	23	109	21.03 (13.98–31.65)	2.53 (1.39–4.60)	2.35 (1.29–4.31)
CD4 cell count nadir					
≥50 cells/μl	15	159	9.41 (5.67–15.61)	1, P = 0.04	1, P = 0.09
<50 cells/μl	29	173	16.74 (11.63–24.09)	1.93 (1.03–3.65)	1.73 (0.91–3.29)
CD4 cell count at switch					
≥50 cells/μl	14	161	8.72 (5.16–14.72)	1, P = 0.08	1, P = 0.26
<50 cells/μl	12	58	20.72 (11.77–36.48)	2.35 (1.08–5.09)	1.86 (0.77–4.46)
Second-line regimen					
Number of changes in NRTI component					
One	15	107	14.06 (8.48–23.32)	1, P = 0.56	1, P = 0.39
Two	30	227	13.22 (9.24–18.91)	0.83 (0.44–1.56)	0.75 (0.39–1.43)
Use of boosted PI					
Yes	31	201	15.45 (10.87–21.97)	1, P = 0.36	1, P = 0.31
No	14	133	10.53 (6.24–17.78)	0.67 (0.27–1.65)	0.63 (0.25–1.59)

CI, confidence interval; IRR, incidence rate ratio from Poisson regression adjusted for geography (sub-Saharan Africa, Asia, Latin America); IRRa, incidence rate ratio from Poisson regression adjusted for geography, CD4 nadir counts, and WHO stage 4 at ART start; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. P value from likelihood ratio test.

Evidence of the efficacy of rescue regimens has been shown in studies conducted in resource-rich settings, where median CD4 cell count at second-line initiation is higher, viral load monitoring routinely performed, and treatment options readily available. In a European study [17] conducted before the widespread availability of genotyping, patients initiating a second protease inhibitor regimen at lower viral load with higher CD4 cell counts, or receiving additional nucleosides, were more likely to achieve undetectable viral loads. Studies in South Africa [18,19], where viral load is routinely measured and treatment failure is defined as two consecutive viral load measurements more than 5000 copies/ml, reported that after 36 months of NNRTI-based first-line therapy, 5.6 to 11.9% of patients switched to a second-line regimen.

Although the number of initially naive patients switched to second line in our study was small, in RLS there is an increasing need for second-line ART regimens as ART cohorts mature and access to virological monitoring increases [20]. Detection of early treatment failure will ensure that patients are able to switch regimens before the occurrence of severe clinical events and will prevent unnecessary early switches. One major strategy for improving the diagnosis of first-line treatment failure in RLS is to increase viral load monitoring. In the absence of regular viral load monitoring, diagnosis of treatment failure might be delayed due to reliance on less sensitive

immunological or clinical methods [8]. Although not a RLS, our ART programme in Khayelitsha, South Africa, routinely measures patient viral load (and CD4 cell count) at baseline and 3 and 6 months after the start of treatment, as well as every 6 months thereafter [18]. As costs and technological limitations decrease for viral load testing [21], its use in RLS could beneficially increase switching to second-line therapy while optimizing the duration of first-line regimens. Ideally, treatment-failure algorithms [22] could be designed based on diagnostic parameters, such as viral load, CD4 cell count, or haemoglobin levels, and incorporated into HIV treatment guidelines in the field.

In RLS, constraints at the treatment level also negatively affect therapy outcomes. Even in the presence of virological failure, clinicians working in RLS may be reluctant to change to second-line regimens, as shown in one of the before-mentioned South African studies [19]. Evidence shows that clinical and immunological benefits can be obtained on a virologically failing regimen, but this effect has been demonstrated only in patients on a protease inhibitor-based regimen [23]. Prices of second-line drugs have been reported to be about ten times higher than first-line agents [24]. Also, concerns exist about the limited efficacy of available second-line regimens involving boosted and nonboosted protease inhibitors or the addition of a single new NRTI. Clinicians often also doubt the immediate benefit of second-line therapy because of the

difficulties in ensuring patient treatment adherence due to the high pill burden of protease inhibitor-containing regimens, absence of fixed-dose drug combinations, need for refrigeration, and necessary meal restrictions. Finally, the fear that no further treatment options will be available if subsequent failure on second-line regimens occurs might also delay therapy switching [25].

In our study [26], more than half of the patients were put on NFV-based regimens, due to a lack of refrigeration systems and heat-stable boosted protease inhibitors, which are less effective than a regimen containing a ritonavir-boosted protease inhibitor. Also, the choices for replacing the NRTI drugs were limited due to a restricted formulary of drugs. Despite these constraints, our results showed that rescue following the failure of WHO-recommended first-line treatment (including the regimen d4T/3TC/NVP) is feasible and efficient in RLS, at least in MSF programmes. Therefore, in addition to improving the diagnosis of treatment failure, the obstacles to second-line drug access and usage must be addressed by reducing costs, increasing the availability of newer, more potent molecules (including heat-stable formulations of boosted protease inhibitors), and facilitating adherence through fixed-dose formulations that do not require food restrictions.

Less than 2% of patients eligible for the study were excluded from the analyses because of unknown age, and this percentage was similar across continents. We recognize, however, several limitations in our study. First, it was based on monitoring data from a multicentric observational cohort, and the reason for switch to second line was not recorded prospectively. Therefore, we cannot completely exclude that some of the switches in therapy were in fact antiretroviral drug replacements due to reasons other than treatment failure, such as drug toxicity. We are, however, confident that the majority of patients eligible for this analysis were true treatment failures, as 62% had at least one of the WHO criteria for treatment failure recorded, and our definition of second-line therapy (changes of both antiretroviral drug class and NRTI drug after more than 6 months of NNRTI therapy) is likely to have excluded most of the patients with antiretroviral drug replacements due to toxicity in the MSF context. Data on CD4 cell counts were not collected for the remaining patients. Second, clinico-immunological failure can occur in the presence of virological control [5], and, although clinical and immunological failure was confirmed by a viral load level in about 20% of our patients, we cannot exclude that some of our patients were not. Third, the length of follow-up was relatively short, and long-term monitoring of these patients is warranted. Despite these favourable early clinical and immunological outcomes, the absence of viral load measurements did not allow exclusion of suboptimal virological suppression that would lead to less satisfactory long-term outcomes. Finally, as we have included ART-naive patients in the analysis, the outcomes cannot be extrapolated to patients who might have received first-line regimens prior to entry in the MSF cohort.

Unsurprisingly, we showed that severe immunosuppression at baseline for first-line ART, and the history of a severe clinical event (WHO stage 3 or 4), increased the risk of mortality on second-line treatment. Our findings thus stress the need to enable access to first-line ART before severe immunosuppression has developed, reinforcing the need to scale up early access to HIV testing and treatment for those in RLS.

In summary, we report a relatively low rate of switch to second-line HIV treatment in ART-naive adults in MSF programmes in RLS, but good early outcomes on second-line therapy. Severe immunosuppression at first-line ART initiation increased mortality on second-line treatment. Considering the success of patients put on a second-line regimen, improving the tools to efficiently diagnose first-line treatment failure, and clearing the hurdles of access and adherence to more effective drug regimens, are critical actions that should be taken to allow more patients in RLS to benefit from second-line HIV therapy.

Acknowledgements

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