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Chapter 10

Second-line antiretroviral treatment successfully resuppresses drug resistant HIV-1 after first-line failure: prospective cohort in sub-Saharan Africa

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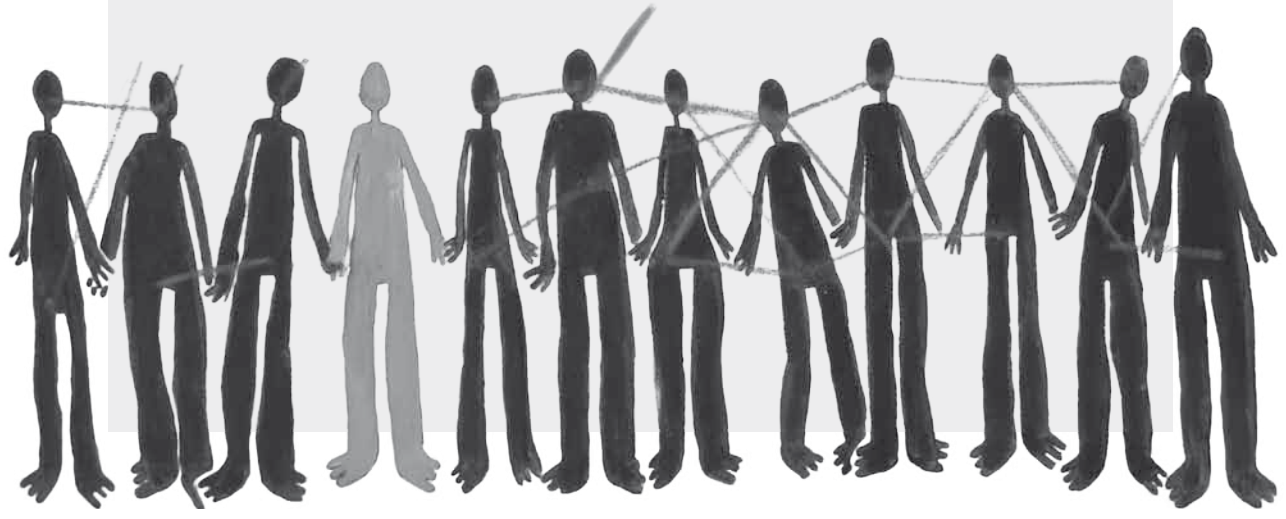

ABSTRACT

Little is known about the effect of human immunodeficiency virus type 1 (HIV-1) resistance mutations present at time of regimen switch on the response to second-line antiretroviral therapy in Africa. In adults who switched to boosted protease inhibitor-based regimens after first-line failure, HIV-RNA and genotypic resistance testing was performed at switch and after 12 months. Factors associated with treatment failure were assessed using logistic regression. Of 243 participants, 53% were predicted to receive partially active second-line regimens due to drug resistance. The risk of treatment failure was, however, not increased in these participants. In this African cohort, boosted protease inhibitors successfully resuppressed drug resistant HIV after first-line failure.

INTRODUCTION

With more human immunodeficiency virus type 1 (HIV-1) infected people receiving antiretroviral therapy (ART) in low-resource settings, treatment failure and the need to switch to second-line regimens is likely to increase. Reported regimen switching rates have been lower than expected,[1,2] due in part to actual rates of treatment success, but also because of restricted access to virological monitoring and second-line regimens. The absence of virological monitoring is associated with delayed switching and consequent accumulation of resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs).[3,4] Lack of access to genotypic resistance testing further complicates the selection of optimal second-line regimens. Few data exist on the impact of resistance mutations selected for by the first-line regimen on the response to empirically prescribed second-line ART in resource-poor settings.[5]

This study investigated the impact of acquired drug HIV-1 drug resistance mutations present at time of regimen switch on the response to second-line ART, within the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) cohort in 6 sub-Saharan African countries.

METHODS

Study design and population

PASER-M is a prospective cohort of adults infected with HIV-1 who receive ART at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe. Cohort and site characteristics have been profiled elsewhere.[6] Participants were consecutively enrolled during a median site-specific enrolment period of 12 months between March 2007 and September 2009. The present analysis included participants who were switched to second-line ART after first-line failure had been diagnosed using clinical, immunological and/or virological failure criteria.[7] We excluded participants who had received protease inhibitors (PIs) prior to switch, or who were pregnant at study screening. Human immunodeficiency virus type 2 (HIV-2) co-infection was ruled out using an HIV-2 specific antibody test in endemic countries (i.e. Nigeria). The study protocol was approved by the appropriate national research ethics committees and the Academic Medical Center of the University of Amsterdam in The Netherlands. Participants provided written informed consent at enrolment.

Procedures

Participants were treated and followed-up as per local standard of care, generally in accordance with 2006 World Health Organization guidelines.[7] Medical staff at each site completed case-report forms at 3-month intervals, which were entered into an online

database. A data monitoring team reviewed study data. Drug adherence was assessed at each follow-up visit by 2 measures of self-reported adherence. For 3-day self-reports, the number of follow-up visits at which the patients reported to have missed any pills during the previous 3 days were counted. For the 30-day visual analogue scale, the number of pills taken at all follow-up visits was averaged and classified as <95% or >95%.

Blood collection was performed prior to regimen switch and after 12 months of follow-up (window, 11-15 months). Plasma specimens were batch-shipped to either of 2 reference laboratories in South Africa and Uganda for HIV-RNA determination, and genotypic resistance testing if HIV-RNA was >1000 copies/mL, as described elsewhere.[3] Drug resistance mutations (DRMs) were scored according to the 2010 International Antiviral Society-USA list.[8] HIV-1 subtypes were determined using the STAR algorithm and confirmed with the REGA subtyping algorithm (version 2.0). All sequences have been deposited in GenBank.

Drug resistance profiles at time of switch have been reported elsewhere.[3] Drug-susceptibility was scored using the Stanford algorithm (version 6.0.9)[9] in participants who harbored at least 1 DRM. Participants with Stanford levels 3 (low-level resistance), 4 (intermediate resistance), or 5 (high-level resistance) to at least one of their prescribed drugs were considered to have received partially-active ART. Participants with Stanford levels 1 (susceptible) or 2 (potential low-level resistance) to all prescribed drugs were considered to have received fully-active ART. Participants who had HIV-RNA <1000 copies/mL, or HIV-RNA >1000 copies/mL without DRMs were also considered to have received fully-active ART.

Among participants still in follow-up after 12 months, virological failure was defined as an HIV-RNA of ≥400 copies/mL. Immunological failure was defined according to WHO guidelines as a decrease in CD4 cell count to the value before regimen switch, a decline of at least 50% from highest measurement on treatment, or a persistent CD4 cell count <100 cells/mm^3.[7] Clinical failure was defined as the presence of a new WHO clinical stage 4 event or new diagnosis of pulmonary tuberculosis.

Statistical analysis

Group comparisons for categorical data were done using chi-square or Fisher exact test, and for continuous data using 1-way analysis of variance or Kruskal-Wallis test. Logistic regression with robust standard errors, accounting for clustering of observations within sites, was used to identify risk factors for the 2 outcomes virological failure and any type of failure. Attrition was additionally considered as virological failure. Any type of failure was defined as virological, immunological or clinical failure, or attrition. Explanatory variables at time of switch to second-line ART included the activity of the second-line regimen, age, sex, WHO clinical stage, CD4 cell count, and HIV-RNA load. Prospective parameters included any single-drug substitutions,

30-day and 3-day adherence. In addition to activity of the second-line regimen, age and sex, all variables univariately associated ($p<0.05$) with the outcome were stepwise entered into the multivariate model. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CI) and two-sided p-values, with $p<0.05$ regarded statistically significant. All statistical analyses were performed using Stata version 10 (StataCorp LP, TX, USA).

RESULTS

Study population

We enrolled 243 participants who switched to a second-line PI-based regimen after first-line ART failure (figure 1). HIV-RNA and genotypic test results were available for 232 participants (95.5%), for whom the predicted activity of the second-line regimen

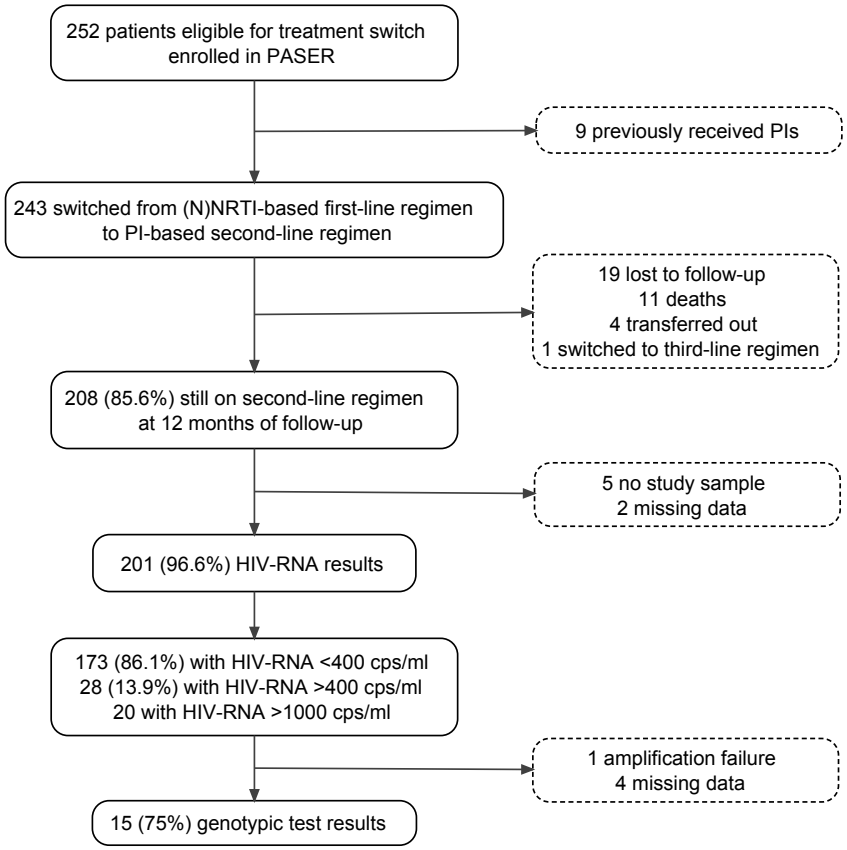

Figure 1. Study profile. PASER, PharmAccess African Studies to Evaluate Resistance; (N)NRTI, (non) nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

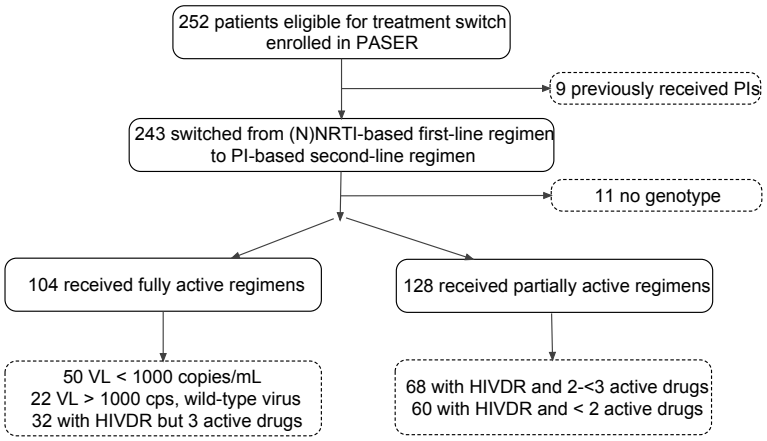

Figure 2. Predicted regimen activity at start of second-line ART. (N)NRTI, (non)nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

could be determined (figure 2). ART was predicted to be fully active for 104 participants (44.8%), comprising 50 participants (48.1%) with HIV-RNA <1000 copies/mL, 22 participants (21.2%) with HIV-RNA >1000 copies/mL and wild-type virus, and 32 participants (30.8%) with HIV-RNA >1000 copies/mL and drug resistant virus at Stanford levels 1 or 2. ART was predicted to be partially active for 128 participants (55.2%), harboring drug resistant virus with reduced predicted susceptibility to at least 1 prescribed drug. Of these, 60 (46.9%) received <2 active drugs (figure 2). Among participants with drug resistant virus, NRTI-associated DRMs were observed in 154 (96.3%), NNRTI-associated DRMs in 153 (95.6%) and dual-class resistance in 147 (91.9%).

At second-line start, WHO clinical stage 4 was diagnosed in 12 participants (11.5%) predicted to receive fully active regimens and in 25 participants (19.5%) with partially active regimens (p=0.014, Table 1). For the 2 groups, median CD4 cell count was 147 and 104 cells/mm^3 (p=0.001) and median HIV-RNA load was 3.2 and 4.7 $\log_{10}$ copies/ml (p<0.001), respectively. The median duration of first-line ART was 26.7 months; participants predicted to receive fully active regimens had shorter duration of previous ART than participants with partially active ART (22.8 versus 30.1 months, p=0.024). Subtype C was most commonly identified (n=77, 42.3%), followed by A (n=49, 26.9%), D (n=26, 14.3%), G (n=14, 7.7%), and circulating recombinant forms (CRFs) (n=16, 8.8%).

Response to second-line ART

After 12 months of follow-up, 208 participants were still on second-line ART and 201 had available HIV-RNA results (figure 1). Of these, 28 participants (13.9%) experienced virological failure. Eleven of 80 participants (13.8%) predicted to receive fully active

Table 1. Participant characteristics at second-line start, stratified by regimen activity

		Overall (n=232)	Fully active (n=104)	Partially active (n=128)	p^a
Women		116 (50)	56 (53.9)	60 (46.0)	0.291
Median age (years)		38.3 [34.1-45.1]	38.5 [34.4-44.5]	38.2 [33.8-45.9]	0.972
WHO clinical stage					0.014
Stage 1 and 2	119 (51.3)	57 (24.6)	62 (26.7)		
Stage 3	76 (32.8)	35 (33.7)	41 (32.0)		
Stage 4	37 (16.0)	12 (11.5)	25 (19.5)		
Median CD4 cell count (cells/mm^3)[b]		126 [66-205]	147 [92-230]	104 [51-185]	0.001
Median HIV-RNA (log_{10} copies/ml)		4.2 [3.3-5.0]	3.2 [1.6-4.2]	4.7 [4.1-5.2]	<0.001
Median duration of first-line regimen (months)[c]		26.7 [15.2-43.7]	22.8 [13.8-39.5]	30.1 [16.5-48.7]	0.024
ART regimen at failure[d]					0.001
ZDV, 3TC, NNRTI	102 (44.0)	39 (37.5)	63 (49.2)		
D4T, 3TC, NNRTI	95 (41.0)	59 (56.7)	36 (28.1)		
TDF, FTC, NNRTI	23 (9.9)	3 (2.9)	20 (15.6)		
NNRTI-based, other	5 (2.2)	2 (1.9)	3 (2.3)		
Triple NRTI	4 (1.7)	0	4 (3.1)		
Criteria used for switch[e]					0.006
Clinico-immunological only	60 (25.9)	36 (34.6)	24 (18.8)		
Targeted viral load testing	172 (74.1)	68 (65.4)	104 (81.3)		
Country of origin					0.002
Uganda	73 (31.5)	21 (20.2)	52 (40.6)		
South Africa	59 (25.4)	34 (32.7)	25 (19.5)		
Kenya	36 (15.5)	22 (21.2)	14 (10.9)		
Nigeria	30 (12.9)	16 (15.4)	14 (10.9)		
Zambia	24 (10.3)	9 (8.7)	15 (11.7)		
Zimbabwe		10 (4.3)	2 (1.9)	8 (6.3)	

Percentages are shown in parentheses and interquartile ranges in square brackets. ART, antiretroviral treatment; ZDV, zidovudine; 3TC, lamivudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; D4T, stavudine; TDF, tenofovir; FTC, emtricitabine.

[a]Categorical data were compared using the chi-square test; continuous were compared using the Wilcoxon rank-sum test. [b]230 observations. [c]227 observations. [d]229 observations.

[e]Clinico-immunological criteria for switch was defined as WHO clinical staging or CD4 counts only. Targeted viral load testing was defined as ART failure based on clinical and immunological information, confirmed with an HIV-RNA test.

regimens and 17 of 112 (15.2%) of those with partially active ART experienced virological failure (p=0.782). Of participants predicted to receive <2 active drugs, 7 of 51 (13.7%) experienced virological failure.

Of participants with an HIV-RNA load >1000 copies/mL after 12 months of follow-up, 15 of 20 (75%) had a valid genotype. Nine (60%) harbored ≥1 major DRMs. Detected mutations were associated with NRTIs (n=7, 46.7%), NNRTIs (n=8, 53.3%) and PIs (n=1, 6.7%). There were no significant differences in DRM patterns between participants predicted to receive a fully versus partially active second-line regimens.

CD4 cell counts were available for 173 of 208 participants still in follow-up. The median CD4 cell count gain was 146.5 cells/mm^3. Immunological failure was diagnosed in 21 participants (12.1%). Information on WHO clinical stage was available for all participants, and 13 (6.3%) experienced clinical failure. Clinical and immunological failure rates did not differ significantly for participants predicted to receive fully or partially active second-line regimens.

An HIV-related cause of death was recorded in 11 participants (4.5%). Other participants not retained in care were lost to follow-up (n=19, 7.8%) or transferred out (n=4, 1.6%). One person switched to a third-line regimen due to alleged virological failure before the 12 month visit. The attrition rates did not differ significantly for participants predicted to receive fully or partially active second-line regimens.

Risk factors for failure of second-line ART

In multivariate analyses, the predicted activity of the second-line regimen was not significantly associated with virological failure or any type of failure (Table 2). The risk of virological failure was increased for patients with 30-day adherence <95%, and reduced for increasing age. The risk of any type of failure was increased for patients with 30-day adherence <95% and for those in clinical stage 4 at second-line start.

DISCUSSION

In this assessment of routine ART programs in sub-Saharan Africa, the risk of second-line ART failure was not increased in participants who harbored virus with predicted reduced susceptibility to at least 1 prescribed second-line drug, compared to those who received ART that was predicted to be fully active. After 12 months of second-line ART, 14% of participants experienced virological failure, 5% died and 8% were lost to follow up. Our study demonstrates that empirically prescribed PI-based regimens can successfully

Table 2. Risk factors for second-line failure

	Virological failure[a]					Any type of failure[b]				
		Events (%)	Univariate	Multivariate	p	Events (%)	Univariate		Multivariate model	p
Activity of second-line regimen[c]										
Fully-active		31 (29.8)	1.0	1.0		44 (42.3)	1.0		1.0	
Partially-active		30 (23.4)	0.72 (0.38-1.36)	0.80 (0.33-1.91)	0.610	39 (30.5)	0.60 (0.37-0.99)		0.53 (0.24-1.17)	0.115
Sex										
Female	28 (23.0)	1.0	1.0			40 (32.8)	1.01.0	1.0		
Male	35 (28.9)	1.37 (0.74-2.51)	1.76 (0.65-4.72)	0.263		47 (38.8)	1.30 (0.73-2.32)	1.55 (0.57-4.27)	0.393	
Age (years)			0.98 (0.94-1.01)	0.94 (0.90-0.98)	0.006		0.99 (0.95-1.02)		0.96 (0.92-1.00)	0.083
Clinical stage at second-line start										
1-3		48 (23.5)	1.0	1.0		62 (30.4)	1.0		1.0	
4		15 (38.5)	2.03 (0.78-5.30)	2.44 (0.97-6.17)	0.059	25 (64.1)	4.09 (1.33-12.57)		5.25 (1.55-17.74)	0.008
CD4 count at second-line start										
≥100 cells/mm^3		35 (24.7)	1.0			53 (37.3)	1.0			
<100 cells/mm^3		27 (27.3)	1.15 (0.63-2.10)			33 (33.3)	0.84 (0.53-1.33)			
VL at second-line start (log_{10})			1.19 (0.97-1.45)				1.07 (0.87-1.31)			
Substitutions										
None		58 (13.2)	1.0	1.0		81 (35.4)	1.0			
Yes, ≥1		5 (33.3)	1.64 (0.78-3.46)	2.59 (0.95-7.08)	0.063	6 (42.9)	1.37 (0.64-2.95)			
3-day adherence[d]										
No pills missed	32 (16.6)	1.0				50 (25.9)	1.0			
Pills missed at ≥1 visit	12 (38.7)	3.18 (1.05-9.64)				18 (58.1)	3.96 (1.29-12.18)			
Average 30-day adherence (%)[e]										
≥95%		35 (17.2)	1.0	1.0		55 (27.0)	1.0		1.0	
<95%		7 (38.9)	3.07 (1.51-6.25)	2.90 (1.12-7.54)	0.029	11 (61.1)	4.26 (1.80-10.08)		4.08 (1.45-11.46)	0.008

(table legend on next page)

Table 2 (legend)
Multivariate logistic regression with robust standard errors. Data are given as odds ratio (95% confidence interval). VL, viral load. [a] Virological failure defined as HIV-RNA ≥ 400 copies/mL (n=28). Participants that died (n=11), were lost to follow-up (n=19), transferred out (n=4) or switched to third-line ART (n=1) were additionally considered as virological failure [b] Any type of failure defined as clinical, immunological or virological failure (n=63). Participants who were lost to follow-up, transferred out or switched to third-line ART were additionally considered as any type of failure. [c] Activity of second-line regimen for participants harboring DRMs based on the Stanford drug-susceptibility algorithm (version 6.0.9). [d] The number of follow-up visits at which the participant reported to have missed any pills during three days prior. [e] The average percentage of pills taken during 30 days prior to all follow-up visits.

resuppress HIV, even in the absence of a fully active NRTI backbone. This corroborates findings of a Malawian study among patients with extensive NRTI resistance at the time of switch.[5] Our study adds important insights to the limited available data on the effectiveness of second-line ART in resource-limited settings.[10,11]

The good immunological and virological response to partially active second-line regimens, i.e., in participants who harbored NRTI resistance, is likely explained by the high potency and genetic barrier to resistance of ritonavir-boosted PIs.[12] Our data suggest potential for the use of "simplified" PI-based regimens after failure of an NNRTI-based regimen. Preliminary results from the ACTG 5230 trial, evaluating PI monotherapy after first-line treatment failure in low-resource settings, showed promising results with 87% virological suppression after 6 months.[13] By contrast, a meta-analysis and recent trial have shown that boosted PI monotherapy is inferior to standard triple ART regimens and cannot be considered an alternative to standard treatment.[14,15] Therefore, long-term results from the ACTG 5230 and other ongoing studies, such as the EARNEST trial, are eagerly awaited.

Participants with predicted partially active second-line regimens had more advanced HIV disease, lower CD4 cell counts and higher viral loads, which is in line with the observation that prolonged ART failure leads to disease progression and drug resistance accumulation.[3,4] Starting second-line ART after the occurrence of an AIDS-defining event increased the risk of treatment failure, indicating that regimen switch should ideally occur before the onset of severe clinical symptoms. Early detection of first-line failure can be improved by implementing routine virological monitoring, which has also been shown to avert unnecessary switches in the absence of viral breakthrough.[3] Furthermore, access to affordable second-line drugs needs to be urgently improved to enable switching to second-line ART when appropriate.

Our finding that suboptimum adherence to second-line ART was associated with an increased risk of treatment failure expands on previous knowledge,[5,10] and underscores

the importance of meticulous long-term adherence. A limitation of our study is the fact that our findings apply to the first year of second-line ART. Longer term follow-up is required to determine if these early outcomes can be sustained over the following years of treatment. Secondly, there was an overrepresentation of urban sites in our cohort and therefore caution is warranted when extrapolating the results to other settings where resource constraints may be more significant.

In conclusion, our cohort study in 6 African countries showed that individuals on second-line ART achieve favorable virological outcomes after 12 months of follow-up, despite the fact that more than half were predicted to receive partially active regimens. Given that the provision of effective and safe ART requires life-long commitment, it is a global health priority to ensure access to viral load testing and to improve availability of second-line drugs.

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