

# Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring

The ART-LINC of IeDEA Study Group\*

**Background:** In high-income countries, viral load is routinely measured to detect failure of antiretroviral therapy (ART) and guide switching to second-line ART. Viral load monitoring is not generally available in resource-limited settings. We examined switching from nonnucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimens to protease inhibitor-based regimens in Africa, South America and Asia.

**Design and methods:** Multicohort study of 17 ART programmes. All sites monitored CD4 cell count and had access to second-line ART and 10 sites monitored viral load. We compared times to switching, CD4 cell counts at switching and obtained adjusted hazard ratios for switching (aHRs) with 95% confidence intervals (CIs) from random-effects Weibull models.

**Results:** A total of 20 113 patients, including 6369 (31.7%) patients from 10 programmes with access to viral load monitoring, were analysed; 576 patients (2.9%) switched. Low CD4 cell counts at ART initiation were associated with switching in all programmes. Median time to switching was 16.3 months [interquartile range (IQR) 10.1–26.6] in programmes with viral load monitoring and 21.8 months (IQR 14.0–21.8) in programmes without viral load monitoring ( $P < 0.001$ ). Median CD4 cell counts at switching were 161 cells/ $\mu$ l (IQR 77–265) in programmes with viral load monitoring and 102 cells/ $\mu$ l (44–181) in programmes without viral load monitoring ( $P < 0.001$ ). Switching was more common in programmes with viral load monitoring during months 7–18 after starting ART (aHR 1.38; 95% CI 0.97–1.98), similar during months 19–30 (aHR 0.97; 95% CI 0.58–1.60) and less common during months 31–42 (aHR 0.29; 95% CI 0.11–0.79).

**Conclusion:** In resource-limited settings, switching to second-line regimens tends to occur earlier and at higher CD4 cell counts in ART programmes with viral load monitoring compared with programmes without viral load monitoring.

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**Keywords:** antiretroviral therapy, CD4 cell count, cohort studies, collaborative research, resource-limited settings, switching to second-line regimens, viral load monitoring

## Introduction

In industrialized countries, the prognosis of HIV infection has improved considerably since highly active

antiretroviral therapy (ART) was introduced in 1995 [1–3]. In low-income countries with a high burden of HIV and AIDS, ART has become more widely available in recent years. The World Health Organization (WHO)

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estimates that about 3 million people were receiving ART in low-income and middle-income countries at the end of 2007, a 7.5-fold increase during the past 4 years [4]. With increasing exposure to ART, the risk of resistance and subsequent treatment failure has become more important, and switching of patients to alternative, second-line regimens is increasingly needed.

Although HIV-1 RNA concentration (viral load) is regularly assessed to diagnose treatment failure in high-income countries [5], viral load measurements are often not available, or are only available at high cost, in resource-constrained settings. Costs of second-line drugs are also high [6]. The lack of viral load monitoring in resource-limited settings may lead to late switching of regimens, increase the risk of viral resistance and jeopardize long-term prognosis: second-line regimens are the last treatment option for many patients in these settings. Conversely, if treatment is switched unnecessarily, resources may be wasted and future treatment options reduced. Switching to second-line regimens is less common in lower-income settings than in high-income countries [7,8] but direct comparisons of switching rates between treatment programmes with and without access to viral load monitoring in resource-limited settings are lacking at present.

We studied rates of switching to second-line regimens, time to switching and determinants of switching in a collaborative network of treatment programmes in Africa, Asia and Latin America that includes both programmes that routinely monitor viral load, and programmes without access to viral load monitoring.

## Methods

### The Antiretroviral Therapy in Lower Income Countries collaboration

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) is a collaborative network of ART programmes, which has been described in detail elsewhere [9,10]. Briefly, programmes from resource-constrained settings that collect data on patient characteristics and treatment outcomes were eligible for participation in ART-LINC. In all sites, institutional review boards approved the participation in ART-LINC.

### Inclusion criteria and definitions

We included all patients aged 16 years and older with known date of starting ART, who had not previously received ART, started ART with a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and had at least 6 months of follow-up. A switch to a second-line regimen was defined as a change from the initial NNRTI-

based regimen to a protease inhibitor-based regimen after at least 6 months of follow-up, because WHO recommends switching due to treatment failure not before completion of at least 6 months of therapy [11]. In addition, at least one nucleoside reverse transcriptase inhibitor (NRTI) had to be changed. A patient was considered lost to follow-up if the time between the last visit and the closing date of the cohort was longer than 1 year.

Stage of disease was defined as less advanced [US Centers for Disease Control and Prevention (CDC) stage A/B or WHO stage I/II] or advanced (CDC stage C or WHO stage III/IV). Routine viral load monitoring was defined as at least one viral load measurement between 3 and 9 months after starting ART in at least 50% of patients treated at that site. Measurements of CD4 cell counts and RNA values closest to the starting date of ART (within 6 months before up to 1 week after the date of starting ART) were taken as the baseline levels. For CD4 cell counts below 25 cells/ $\mu\text{l}$  and HIV viral loads above 100 000 copies/ml, the time window was extended to 1 year before starting therapy. At switching, the time window was 3 months before up to 2 weeks after switching.

In patients who switched to a second-line regimen, we determined whether immunological or virological failure had occurred during the 3 months before switching and examined the reasons for switching recorded in the database. Following WHO criteria [11], we defined immunological failure as a decline in the CD4 cell count to the baseline value or below, a decline of at least 50% from the highest count on treatment or a persistent CD4 cell count below 100 cells/ $\mu\text{l}$  after 6 months of antiretroviral therapy. Virological failure was defined as a plasma HIV viral load value above 10 000 copies/ml [11].

### Statistical analysis

Patient characteristics at start of first-line and second-line ARTs were compared between sites with and without viral load monitoring using  $\chi^2$  tests and Wilcoxon rank sum tests. We calculated times to switching and rates of switching per 100 person-years and fitted random-effects Weibull models, comparing sites with and without routine viral load monitoring. We plotted Kaplan–Meier curves of the probability of switching to second-line ART therapy and obtained *P* values from log rank tests comparing programmes with and without virological monitoring. We measured time from 6 months after start of ART (baseline) to the time of switching, the time of the last follow-up visit, or 3 years after baseline, whichever came first. Hazards were not proportional over time (*P* = 0.0012 from test of proportional hazards) [12] and follow-up was, therefore, split into periods 7–18, 19–30 and 31–42 months after starting ART. Analyses were adjusted for sex, age, calendar year, CD4

cell count, clinical stage (advanced or less advanced) at baseline and the number of available antiretroviral drugs in the clinic (tertiles;  $\leq 10$ , 11–13,  $\geq 14$  drugs). We examined predictors of switching separately for programmes with and without access to viral load monitoring and used tests of interaction to determine whether programmes differed.

We compared CD4 cell counts at the time of switching in sites with and without routine viral load monitoring and used linear regression analysis to examine whether differences persisted when adjusting for age, sex, clinical stage and CD4 cell count at baseline. The square root of CD4 cell counts was used in these analyses. In sensitivity analyses, we restricted data to sites from sub-Saharan Africa. All analyses were performed using Stata version 10 (Stata Corporation, College Station, Texas, USA). Results are presented as hazard ratios with 95% confidence intervals (CIs) or medians with interquartile range (IQR).

## Results

### Sites and study populations

Seventeen treatment programmes from 14 countries were included (Table 1). All sites carried out routine CD4 monitoring and had access to second-line therapy, and 10 sites routinely monitored viral load. The database included 34 715 adult patients of whom 14 602 patients (42.1%) were excluded for the following reasons: 1403 (4.0%) died before 6 months, 11 250 (32.4%) had less than 6 months of follow-up and 1949 (5.6%) started with a

NNRTI-based ART. A total of 20 113 patients, including 6369 patients (31.7%) from programmes with routine viral load monitoring, and 16 591 (82.5%) patients from sub-Saharan Africa, were analysed. A viral load value at 6 months after ART initiation was available in 58–99% of patients at sites with routine viral load testing, and 0–7% at other sites (Table 1).

Table 2 shows patient characteristics separately for programmes with and without viral load monitoring. The characteristics of patients at start of ART were similar with respect to age and sex, but median CD4 cell counts at the start of ART were lower in programmes with viral load monitoring than in programmes without viral load monitoring (97 versus 129 cells/ $\mu\text{l}$ ,  $P < 0.001$ ). Both in sites with and without viral load monitoring, the four most common initial regimens were lamivudine (3TC) with stavudine (d4T) or zidovudine (ZDV), combined with efavirenz (EFV) or nevirapine (NVP) (Table 2).

### Rates and time to switching

A total of 576 patients (2.9%) switched to a second-line regimen. The rate of switching overall was 2.4 per 100 person-years (95% CI 2.2–2.6). It was higher in programmes with access to viral load monitoring than in programs without: 3.2 (95% CI 2.8–3.6) compared with 2.0 (95% CI 1.8–2.3) per 100 person-years ( $P < 0.001$ ). Figure 1 shows the Kaplan–Meier curves of the probability of switching to a second-line regimen separately for programmes with and without viral load monitoring. Switching occurred earlier in programmes with access to viral load monitoring. Median time to switching was 16.3 months (IQR 10.1–26.6 months) in 236 patients from programmes with viral load monitoring

**Table 1. Characteristics of antiretroviral treatment programmes included in analyses.**

Site	Site (country)	Start of programme	No. of patients switching	Rate of switching per 100 person-years (95% CI)	Routine HIV-1 viral load testing <sup>a</sup>	No. of patients with viral load (%)
CEPREF	Abidjan (Côte d'Ivoire)	1999	1941 (46)	1.6 (1.2–2.2)	No	139 (7)
1290 ANRS	Dakar (Senegal)	1998	194 (0)	0 (0–3.7)	Yes	153 (79)
AMPATH	Eldoret (Kenya)	2002	3229 (106)	5.0 (4.1–6.0)	No	0
AMU	Kampala (Uganda)	2002	84 (3)	2.7 (0.9–8.2)	Yes	83 (99)
Lighthouse	Lilongwe (Malawi)	2000	4082 (9)	0.2 (0.1–0.3)	No	0
Connaught	Harare (Zimbabwe)	2002	707 (31)	3.5 (2.5–5.0)	No	0
Gugulethu	Cape Town (South Africa)	2002	1243 (23)	1.8 (1.2–2.6)	Yes	1106 (89)
Khayelitsha	Cape Town (South Africa)	2001	1527 (45)	2.4 (1.8–3.2)	Yes	1444 (95)
Themba Lethu	Johannesburg (South Africa)	1999	1874 (97)	6.5 (5.3–7.9)	Yes	1127 (60)
PHRU	Soweto (South Africa)	2004	439 (2)	0.8 (0.2–3.3)	Yes	387 (88)
Morocco	Casablanca (Morocco)	1999	231 (8)	2.5 (1.3–5.0)	Yes	136 (59)
MTCT-Plus	Several <sup>b</sup>	2003	1455 (22)	1.7 (1.1–2.5)	No	0
PUMA	Buenos Aires (Argentina)	2003	136 (6)	5.2 (2.3–11.5)	Yes	102 (75)
SOBRHIV	Porto Alegre (Brazil)	1996	349 (7)	0.8 (0.4–1.7)	Yes	289 (83)
RIOHIV	Rio de Janeiro (Brazil)	1996	292 (45)	5.7 (4.3–7.6)	Yes	183 (63)
YRG Care	Chennai (India)	1996	2114 (122)	3.2 (2.7–3.8)	No	154 (7)
HIV-NAT	Bangkok (Thailand)	2003	216 (4)	1.0 (0.4–2.6)	No	0
Total			20 113 (576)	2.4 (2.2–2.6)	10/17	5303 (26)

See Acknowledgements section for further details on participating sites. CI, confidence interval.

<sup>a</sup>Routine viral load monitoring was defined as at least one measurement between 3 and 9 months after starting antiretroviral therapy, in at least 50% of patients.

<sup>b</sup>Network including sites in South Africa, Zambia, Kenya, Rwanda, Uganda, Ivory Coast and Thailand.

**Table 2. Patients characteristics at baseline and at switching to second-line antiretroviral regimen.**

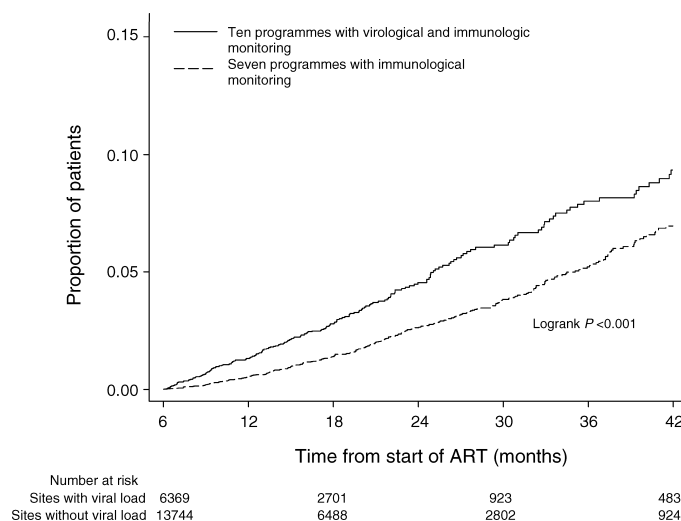
Variable	At baseline			At start of second-line regimen		
	Routine viral load monitoring (n = 6369)	No routine viral load monitoring (n = 13 744)	P	Routine viral load monitoring (n = 236)	No routine viral load monitoring (n = 340)	P
Women (%)	4101 (64.4)	8350 (60.8)	<0.001	145 (61.4)	181 (53.2)	0.05
Median age [IQR] (years)	34 [30–41]	35 [30–41]	<0.001	35 [31–41]	38 [33–44]	<0.001
Clinical stage (%)			<0.001			
Stage available	5831 (91.6)	11 588 (84.3)		0	0	
Less advanced	2591 (44.4)	3343 (28.9)				
Advanced <sup>a</sup>	3240 (55.6)	8245 (71.2)				
CD4 cell count (cells/ $\mu$ l)			<0.001			<0.001
CD4 cell count available	5462 (85.8)	10 315 (75.1)		141 (59.7)	261 (76.8)	
Median [IQR]	97 [42–163]	129 [60–195]		161 [77–265]	102 [44–181]	
HIV-1 viral load (copies/ml)						
Viral load available (%)	3750 (58.9)	271 (2.0)		143 (60.6)	14 (4.1)	
<10 000 (%)	511 (13.6)			71 (49.6%)		
10 000–100 000 (%)	1455 (38.8)			36 (25.2%)		
>100 000 (%)	1784 (47.6)			36 (25.2%)		
Median log viral load [IQR]	5.0 [4.4–5.4]			4.0 [3.4–5.0]		
First-line regimens (%)			<0.001			<0.001
3TC d4T EFV	3495 (54.9)	9717 (70.7)				
3TC ZDV EFV	1193 (18.7)	1757 (12.8)				
3TC d4T NVP	1050 (16.5)	1254 (9.1)				
3TC ZDV NVP	358 (5.6)	955 (7.0)				
Other	273 (4.3)	61 (0.4)				
Second-line regimens (%)			<0.001			<0.001
ZDV ddl LPV				114 (48.3)	58 (17.1)	
3TC ddl IDV RTV				0 (0)	60 (17.7)	
ABC ddl LPV				3 (1.3)	43 (12.7)	
d4T ddl LPV				19 (8.1)	1 (0.3)	
3TC ZDV LPV				18 (7.6)	18 (5.3)	
3TC ZDV IDV RTV				6 (2.5)	28 (8.2)	
Other				76 (32.2)	132 (38.8)	

Interquartile ranges are shown in square brackets and percentages in brackets. ABC, abacavir; ddl, didanosine; EFV, efavirenz; d4T, stavudine; IQR, interquartile range; LPV, lopinavir; NVP, nevirapine; RTV: boost of ritonavir; 3TC, lamivudine; ZDV, zidovudine.

<sup>a</sup>US Centers for Disease Control and Prevention (CDC) stage C, or World Health Organization (WHO) stages III or IV.

and 21.8 months (IQR 14.0–21.8 months) in 340 patients from programmes without viral load monitoring ( $P < 0.001$ ). The rate of switching tended to be higher in sites with virologic monitoring during months 7–18 after

starting ART, similar to during months 19–30 and lower than in programmes without viral load monitoring during months 31–42. The adjusted hazard ratios (aHRs) for the three periods were 1.38 (0.97–1.98,  $P = 0.07$ ),



**Fig. 1. Kaplan–Meier curves of the probability of switching to second-line antiretroviral regimens in 10 treatment programmes with virological monitoring and seven programmes without virological monitoring.**

0.97 (0.58–1.60,  $P=0.90$ ) and 0.29 (0.11–0.79,  $P=0.02$ ), respectively. The results were similar when, in addition, adjusting for the first-line regimen (3TC d4T NVP, 3TC d4T EFV, 3TC ZDV EFV, 3TC ZDV NVP, others).

A majority of patients who switched (316 patients; 54.9%) changed both NRTIs. The NRTI component of the new regimen consisted of zidovudine/didanosine (190 patients; 33.0%), abacavir/didanosine (65; 11.3%), other drugs combined with didanosine (102; 17.7%), other drugs combined with abacavir (12; 2.1%), combinations with tenofovir (65; 11.3%) or other combinations (142; 24.7%). Common protease inhibitors in the second-line regimen were lopinavir boosted with ritonavir (340 patients; 59.0%), indinavir boosted with ritonavir (140; 24.3%) and nelfinavir (57; 9.9%).

### CD4 cell count at the time of switching

The median CD4 cell count at the time of switching was 102 cells/ $\mu\text{l}$  (IQR 44–181 cells/ $\mu\text{l}$ ) in 261 patients from sites without viral load monitoring compared with 161 cells/ $\mu\text{l}$  (77–265 cells/ $\mu\text{l}$ ) in 141 patients from sites with routine viral load monitoring ( $P<0.001$ ). The remaining patients did not have a CD4 cell count at the time of switching. Differences persisted in the multi-variable regression analyses ( $P=0.001$ ).

### Predictors and reasons of switching

The baseline CD4 cell count, but not clinical stage, was associated with switching both in sites with and without viral load monitoring: the lower the CD4 cell count, the higher the probability of switching to a second-line regimen (Table 3). Switching was more frequent in earlier calendar periods.

Reasons for switching were available for 241 (42%) of the 576 patients who switched. Switching was due to treatment failure (179 patients; 74%), toxicity (25; 10%) and other reasons (37; 15%). At the time of switching, 399 (69.3%) of 576 patients had a CD4 cell count, 153 (26.6%) had a viral load measurement and 118 (20.5%) patients had both. Of 399 patients with available measurements, 263 patients (66%) had immunological failure, virological failure or both.

Results were similar when restricting analyses to sites from sub-Saharan Africa. For example, the median time to switching was 15.2 months (IQR 9.8–24.9 months) in 170 patients from programmes with viral load monitoring and 18.0 months (IQR 12.3–24.2 months) in 212 patients from programmes without viral load monitoring ( $P=0.04$ ). The median CD4 cell count at the time of switching was 113 cells/ $\mu\text{l}$  (IQR 44–186 cells/ $\mu\text{l}$ ) in 149 patients from sites without viral load monitoring compared with 168 cells/ $\mu\text{l}$  (85–236 cells/ $\mu\text{l}$ ) in 97 patients from

**Table 3. Predictors of switching to second-line antiretroviral therapy.**

Variable	Sites with routine viral load monitoring ( $n=5058$ )		Sites without routine viral load monitoring ( $n=8699$ )		$P$ for interaction <sup>a</sup>
	Adjusted HR (95% CI)	$P$	Adjusted HR (95% CI)	$P$	
Age (years)		0.55		0.25	0.23
16–29	1		1		
30–39	0.93 (0.62–1.39)		0.93 (0.62–1.39)		
40–49	0.69 (0.41–1.17)		1.33 (0.84–2.12)		
$\geq 50$	0.97 (0.47–1.98)		1.46 (0.73–2.91)		
Sex		0.91		0.11	0.34
Male	1		1		
Female	0.98 (0.68–1.41)		1.36 (0.94–1.98)		
Time period of starting ART		0.001		0.06	0.53
<2002	1		1		
2002–2004	0.40 (0.25–0.65)		0.58 (0.32–1.03)		
2005–2006	0.55 (0.29–1.06)		0.88 (0.45–1.72)		
Baseline CD4 cell count (cells/ $\mu\text{l}$ )		0.03		<0.001	0.87
<25	4.81 (0.64–35.94)		6.21 (1.47–26.12)		
25–49	3.59 (0.47–27.35)		5.12 (1.19–21.97)		
50–99	3.13 (0.42–23.59)		4.01 (0.95–16.82)		
100–199	2.35 (0.32–17.54)		2.55 (0.61–10.64)		
200–349	2.03 (0.26–15.92)		1.50 (0.34–6.69)		
$\geq 350$	1		1		
Clinical stage		1.00		0.91	0.67
Less advanced	1		1		
Advanced	1.00 (0.55–1.82)		1.02 (0.67–1.57)		
Number of antiretroviral drugs available in programme		0.26		0.58	0.45
$\leq 10$	1		1		
11–13	1.96 (0.36–10.82)		1.90 (0.47–7.73)		
$\geq 14$	3.56 (0.78–16.34)		1.04 (0.22–5.05)		

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.  
<sup>a</sup>Test for interaction between sites with and without routine viral load monitoring.

sites with routine viral load monitoring ( $P=0.007$ ). Again, this difference persisted in multivariable regression ( $P=0.003$ ).

## Discussion

Many ART programmes in resource-limited settings do not have access to viral load testing to monitor treatment response, identify treatment failure and inform decisions on when to switch to a second-line regimen, but they rely on clinical examinations and, where available, on CD4 cell counts. In this study of ART programmes from sub-Saharan Africa, Asia and Latin America, all sites had access to CD4 cell counts and some had access to viral load monitoring. We could thus study patterns of switching to second-line regimens in sites with and without viral load monitoring. We found that patients tended to switch earlier and at higher CD4 cell counts in programmes with, compared to programmes without, access to viral load monitoring. Low CD4 cell counts at the start of ART predicted switching both in programmes with and without viral load monitoring, and fewer patients switched in more recent calendar periods.

Our study included over 20 000 patients who started ART and almost 600 patients who switched to second-line ART. The decision to measure, or not to measure, viral load in an individual patient will often be related to prognosis and the probability of switching to a second-line regimen. By comparing sites with and without a policy of monitoring viral load, rather than comparing patients with and without available viral load measurements, such confounding by the indication to test was avoided. The definition we used for second-line ART is in accordance with WHO recommendations [11] and was used in a previous analysis of the Médecins Sans Frontières (MSF) programmes in Africa, Asia, Latin America and eastern Europe [8]. Our study includes patients who were treated in 17 programmes from 14 countries, and results should therefore be applicable to many other patients on ART in resource-limited countries. Of note, results were robust when restricting analyses to programmes from sub-Saharan Africa. However, we stress that the sites participating in the ART-LINC collaboration are not necessarily representative of all sites providing ART in these countries: they represent a sample of programmes with electronic medical record systems [13] and access to CD4 cell counts and second-line regimens.

A substantial number of patients did not have a CD4 cell count recorded at the time of switching, and this could have introduced bias in the comparison of CD4 cell counts at switching in sites with and without viral load monitoring. This is unlikely; however, the baseline CD4 cell counts were similar in patients with missing counts in

sites with and without viral load monitoring (data not shown). We did not examine clinical failure: not all sites systematically collect data on opportunistic infections and diagnostic capabilities and criteria vary between sites. Also, we had no information on adherence or drug resistance, and data about reasons for switching were available for only some patients. In a programme of a faith-based organization in three countries in sub-Saharan Africa, immunological failure was the most common reason for switching, followed by virological failure. Clinical failures were rare [14].

We only considered switching of regimens, as recommended by WHO in case of treatment failure, and not substitutions of single drugs or other changes. A recent study comparing Switzerland with the Khayelitsha and Gugulethu township programmes in South Africa showed that changes to first-line regimens of any type occurred twice as often in Switzerland than in South Africa [7]. The difference was, however, explained by a higher rate of changes due to toxicity or patient wishes in Switzerland, whereas changes due to treatment failure were infrequent in both settings [7]. In the present study, most of the patients with information on the reason for switching changed regimens because of treatment failure, and results were similar when analyses were adjusted for differences in the first-line regimens used in programmes with and without viral load monitoring.

Both in programmes with and without access to viral load monitoring, the rates of switching were substantially higher than in the MSF programmes [8]: the MSF programmes do not have access to viral load monitoring and the rate was 0.5 per 100 person-years. Rates were, however, lower than in the programme in three African countries, which includes routine viral load monitoring in all sites: the rate of switching was 4.9 per 100 person-years [14]. A multicountry survey by the WHO found highly variable rates of switching to second-line regimens [15]. It seems unlikely that this variability is explained by differences in primary resistance to NRTIs or NNRTIs. At present, viral resistance is rare in most resource-limited settings, although important levels of resistance have been reported from Nigeria and north India [16]. The availability of viral load monitoring and general differences in clinical practice are more likely explanations: practice varies across sites participating in the collaboration, even within the same country. For example, in township programmes in Cape Town, therapy is switched after two consecutive viral loads above 5000 copies/ml in Khayelitsha, whereas the threshold is 1000 copies/ml in Gugulethu.

A low CD4 cell count when starting ART was the most important predictor of switching to a second-line regimen, in line with a previous study [14]. Starting ART earlier might thus not only reduce the high

mortality during the initial months of ART [7,10,17] but also help preserve first-line regimens. The rate of switching was lower in more recent calendar years compared with the early years of the ART scale-up, again confirming previous findings [14]. Of note, this was not explained by the increase in CD4 cell counts at the start of ART, which was observed in more recent years [10]: the effect was evident in analyses adjusted for baseline CD4 cell count, and might reflect a change in practice associated with the substantial increase in patients starting ART since the early 2000s.

There is debate on the feasibility and cost-effectiveness of viral load monitoring in the context of scaling up of ART in resource-limited settings [18–22]. WHO stipulates that viral load monitoring is desirable, but not essential, for a public health approach to ART [23]. According to a recent modelling study, routine viral load monitoring has only limited benefit on survival and cost-effectiveness is poor [20]. An analysis of mortality in the first year after starting ART showed similar survival in sites with and without viral load monitoring [17], and preliminary results of a randomized trial led to similar conclusions [24]. The results from empirical research are reassuring for sites without access to routine viral load monitoring, but they are based on short-term follow-up, and the effect of viral load monitoring on long-term outcomes is unclear at present. The higher CD4 cell counts at the time of switching in sites with, compared with sites without, access to viral load monitoring indicate that treatment failure is detected earlier in programmes using viral load monitoring, and this might translate into better clinical outcomes in the long-term.

In conclusion, we found that in programmes with access to viral load monitoring, patients tended to switch earlier and at higher CD4 cell counts than in sites without viral load monitoring. Future studies should examine what the consequences of earlier or later switching are for clinical outcomes. For example, the effect of switching based on virological failure in patients monitored virologically, with switching based on immunological and clinical criteria, could be compared in a randomized trial. Alternatively, this comparison could be mimicked in longitudinal, observational studies using causal modelling [25,26]. Finally, further research is required to determine the optimal frequency of determining CD4 cell counts and of measuring viral load to maximize cost-effectiveness and optimize patient outcomes in different settings in lower income countries.

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## References

1. Egger M, Hirschel B, Francioli P, Sudre P, Wirz M, Flepp M, *et al.* **Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study.** *BMJ* 1997; **315**:1194–1199.
2. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, *et al.* **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.** *N Engl J Med* 1998; **338**:853–860.
3. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller VT, Gargalianos P, *et al.* **Changing patterns of mortality across Europe in patients infected with HIV-1.** *Lancet* 1998; **352**:1725–1730.
4. World Health Organization. *World Health Organization. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector.* Progress report 2008. Geneva: WHO; 2008. Available at [http://www.who.int/hiv/mediacenter/universal\\_access\\_progres\\_report\\_en.pdf](http://www.who.int/hiv/mediacenter/universal_access_progres_report_en.pdf). [Accessed February 2009]
5. Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, *et al.* **Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel.** *JAMA* 2008; **300**:555–570.
6. Report on WHO/UNAIDS Meeting on Forecasting ARV needs up to 2010; 7–8 November 2005. Geneva. Geneva: WHO; 2006. pp. 1–35.
7. Keiser O, Orrell C, Egger M, Wood R, Brinkhof MW, Furrer H, *et al.* **Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared.** *PLoS Med* 2008; **5**:e148.
8. Pujades-Rodriguez M, O'Brien D, Humblet P, Calmy A. **Second-line antiretroviral therapy in resource-limited settings: the experience of Medecins Sans Frontieres.** *AIDS* 2008; **22**:1305–1312.
9. Dabis F, Balestre E, Braitstein P, Miotti P, Brinkhof WGM, Schneider M, *et al.* **Antiretroviral Therapy in Lower Income Countries (ART-LINC): international collaboration of treatment cohorts.** *Int J Epidemiol* 2005; **34**:979–986.
10. Keiser O, Anastos K, Schechter M, Balestre E, Myer L, Boule A, *et al.* **Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America.** *Trop Med Int Health* 2008; **13**:870–879.
11. World Health Organization. *Antiretroviral therapy for HIV Infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach.* Geneva: WHO, 2006. Available at [http://www.who.int/hiv/mediacenter/universal\\_access\\_progres\\_report\\_en.pdf](http://www.who.int/hiv/mediacenter/universal_access_progres_report_en.pdf). [Accessed February 2009]
12. Grambsch PM, Therneau TM. **Proportional hazards tests and diagnostics based on weight residuals.** *Biometrika* 1994; **81**:515–526.
13. Forster M, Bailey C, Brinkhof MW, Graber C, Boule A, Spohr M, *et al.* **Electronic medical record systems, data quality and loss to follow-up: survey of antiretroviral therapy programmes in resource-limited settings.** *Bull World Health Organ* 2008; **86**:939–947.
14. Palombi L, Marazzi MC, Guidotti G, Germano P, Buonomo E, Scarcella P, *et al.* **Incidence and Predictors of Death, Retention, and Switch to Second-Line Regimens in Antiretroviral-Treated Patients in Sub-Saharan African Sites with Comprehensive Monitoring Availability.** *Clin Infect Dis* 2009; **48**:115–122.
15. Renaud-Thery F, Nguimfack BD, Vitoria M, Lee E, Graaff P, Samb B, *et al.* **Use of antiretroviral therapy in resource-limited countries in 2006: distribution and uptake of first- and second-line regimens.** *AIDS* 2007; **21** (Suppl 4):S89–S95.
16. Gupta RK, Pillay D. **HIV resistance and the developing world.** *Int J Antimicrob Agents* 2007; **29**:510–517.
17. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boule A, Miotti P, *et al.* **Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.** *Lancet* 2006; **367**:817–824.
18. Bagchi S, Kempf MC, Westfall AO, Maherya A, Willig J, Saag MS. **Can routine clinical markers be used longitudinally to monitor antiretroviral therapy success in resource-limited settings?** *Clin Infect Dis* 2007; **44**:135–138.
19. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E, *et al.* **HIV viral load monitoring in resource-limited regions: optional or necessary?** *Clin Infect Dis* 2007; **44**:128–134.
20. Phillips AN, Pillay D, Miners AH, Bennett DE, Gilks CF, Lundgren JD. **Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model.** *Lancet* 2008; **371**:1443–1451.
21. Schooley RT. **Viral load testing in resource-limited settings.** *Clin Infect Dis* 2007; **44**:139–140.
22. Walensky RP, Freedberg KA, Weinstein MC. **Monitoring of antiretroviral therapy in low-resource settings.** *Lancet* 2008; **372**:288.
23. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, *et al.* **The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings.** *Lancet* 2006; **368**:505–510.
24. Couthino R, Mermin J, Ekwaru J, Were W, Bunnell R, Kaharuza F, *et al.* **Utility of routine viral load, CD4 cell count, and clinical monitoring among HIV-infected adults in Uganda: a randomized trial [abstract].** In: *Proceedings of the 15th Conference on Retroviruses and Opportunistic Infections*; February 3–6 2008. Boston; 2008; abstract 125.
25. Hernan MA, McAdams M, McGrath N, Lanoy E, Costagliola D. **Observation plans in longitudinal studies with time-varying treatments.** *Stat Methods Med Res* 2009; **18**:27–52.
26. Hernan MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, *et al.* **Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease.** *Epidemiology* 2008; **19**:766–779.