Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa

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Objectives: To compare outcomes of antiretroviral therapy (ART) in South Africa, where viral load monitoring is routine, with those in Malawi and Zambia, where monitoring is based on CD4 cell counts.

Methods: We included 18 706 adult patients starting ART in South Africa and 80 937 patients in Zambia or Malawi. We examined CD4 responses in models for repeated measures and the probability of switching to second-line regimens, mortality and loss to follow-up in multistate models, measuring time from 6 months.

Results: In South Africa, 9.8% [95% confidence interval (CI) 9.1–10.5] had switched at 3 years, 1.3% (95% CI 0.9–1.6) remained on failing first-line regimens, 9.2% (95% CI 8.5–9.8) were lost to follow-up and 4.3% (95% CI 3.9–4.8) had died. In Malawi and Zambia, more patients were on a failing first-line regimen [3.7% (95% CI 3.6–3.9], fewer patients had switched [2.1% (95% CI 2.0–2.3)] and more patients were lost to follow-up [15.3% (95% CI 15.0–15.6)] or had died [6.3% (95% CI 6.0–6.5)]. Median CD4 cell counts were lower in South Africa at the start of ART (93 vs. 132 cells/μl; $P < 0.001$) but higher after 3 years (425 vs. 383 cells/μl; $P < 0.001$). The hazard ratio comparing South Africa with Malawi and Zambia after adjusting for age, sex, first-line regimen and CD4 cell count was 0.58 (0.50–0.66) for death and 0.53 (0.48–0.58) for loss to follow-up.

Conclusion: Over 3 years of ART mortality was lower in South Africa than in Malawi or Zambia. The more favourable outcome in South Africa might be explained by viral load monitoring leading to earlier detection of treatment failure, adherence counselling and timelier switching to second-line ART.

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Introduction

The World Health Organization (WHO) estimates that over 5 million HIV-1-infected people were receiving antiretroviral therapy (ART) in low-income and middle-income countries by the end of 2009 [1]. As access to HIV treatment continues to expand, more people are experiencing treatment failure, and switching to second-line therapy is on the increase. Viral load monitoring is typically not available in the public sector in resource-limited settings: viral load monitoring is expensive and the necessary laboratory infrastructure is difficult to implement and maintain, particularly in rural areas.

In the absence of viral load monitoring, diagnosis of treatment failure relies on immunological (i.e. CD4 cell counts) and clinical criteria [2]. The ability of CD4 cell counts to predict virological failure is, however, limited: sensitivity and positive predictive value of the immunological WHO criteria for virological treatment failure have been shown to be poor [3,4]. Use of these criteria may therefore lead to unnecessary switching to second-line ART among patients with suppressed viral replication, or cause undue delays in switching among patients with real – but undetected – virological failure.

In a recent analysis of 17 ART programmes in resource-limited settings, we found that patients with access to viral load monitoring were more likely to switch to second-line therapy earlier and at higher CD4 cell counts than those enrolled in programmes without viral load monitoring [5]. Delays in switching will increase the time on low CD4 cell counts and may promote the selection of resistant strains and thus affect long-term prognosis. In the present study, we analysed data from treatment programmes in southern Africa to compare switching to second-line ART, loss to follow-up and mortality in the Republic of South Africa (RSA), where viral load monitoring is routine with the outcomes in Zambia and Malawi, where monitoring is based on CD4 cell counts.

Methods

Antiretroviral treatment programmes

The International epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) is a collaboration of ART programmes in southern Africa [6]. Data are collected at ART initiation (baseline) and each follow-up visit, using standardized instruments, and transferred in regular intervals to data centres at the Universities of Cape Town, RSA, and Bern, Switzerland. All sites have ethical approval to collect data and participate in IeDEA-SA.

We included four public-sector ART programmes from RSA, which monitor viral load and CD4 cell counts every 3–6 months: Khayelitsha [7], Gugulethu [8] and the Tygerberg clinic [9] in Cape Town, and the Themba Lethu clinic [10] in Johannesburg. The South African programmes ('viral load sites') were compared with two treatment programmes from Malawi and Zambia, which monitor CD4 cell counts but have only limited access to viral load measurements (also referred to as 'nonviral load sites'): the Lighthouse clinic at Kamuzu Central Hospital in Lilongwe [11] and the Ministry of Health – Centre for Infectious Disease Research in Zambia (MoH-CIDRZ) programme in Lusaka [12,13]. All six programmes trace patients lost to follow-up (LTFU). In Khayelitsha, patients LTFU who could not be contacted by telephone are visited at home by a clinic nurse. In Gugulethu, patients are allocated a therapeutic counsellor who lives in the same community, visits patients at home and provides counselling and adherence support. In Themba Lethu and Tygerberg, patients are traced using mobile telephone contacts. The Lighthouse clinic and the MoH-CIDRZ programme use community health workers to trace patients.

Eligibility criteria and definitions

We included all treatment-naive patients aged 16 years and older who started ART with a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and who had at least 1 day of follow-up. 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/μl after 6 months of antiretroviral therapy [2]. Virological failure was defined as a plasma HIV viral load value above 10 000 copies/ml [2]. For both immunological and virological failure, we required two consecutive values within 12 months of each other meeting the criteria. For immunological failure, the second value had to be equal to or lower than the first.

A switch to a second-line ART regimen was defined as a change from the initial regimen to a protease inhibitor-based regimen after at least 6 months of follow-up with a simultaneous change in at least one nucleoside reverse transcriptase inhibitor (NRTI). Clinical disease stage was defined as less advanced (CDC stage A/B or WHO stage I/II) or advanced (CDC stage C or WHO stage III/IV). A patient was considered LTFU if the last visit was more than 12 months before the closure date for that site, with the closure date defined as the most recent visit date recorded in the database for that site. Only patients with at least 12 potential months of follow-up could therefore be LTFU.

Analyses of treatment outcomes

We plotted Kaplan–Meier curves to determine the probability of death from all causes, measuring time from ART initiation. Differences between viral load and nonviral load patients were compared using log-rank tests. We then built a multistate model [14] to compare

probabilities of death, loss to follow-up and switching to second-line regimens between viral load and nonviral load programmes, measuring time from ART initiation. After 6 months of ART, when treatment response is assessed, a patient may remain on a nonfailing first-line regimen or move to treatment failure (virological failure in sites with routine viral load monitoring or immunological failure in sites without routine viral load monitoring), second-line ART, loss to follow-up or death (Fig. 1). A patient failing first-line therapy may remain on the failing regimen, switch to second-line ART, be LTFU or die. A patient switching may remain on the new regimen, be LTFU or die. Death and loss to follow-up are final (absorbing) states in the model [14].

We calculated hazard ratios separately for the first 6 months of ART and from 6 months to the end of the follow-up. We present hazard ratios for death and loss to follow-up and for the second period additionally for switching to second-line ART. We compared sites with and without viral load monitoring, adjusting for age (per 10 years increase), sex, first-line regimen, CD4 cell count (per 100-cell increase) and WHO clinical stage (WHO stage III and IV vs. stage I and II) at ART initiation in the first analysis and for age, sex, first-line regimen and CD4 cell count at 6 months in the second analysis. Four

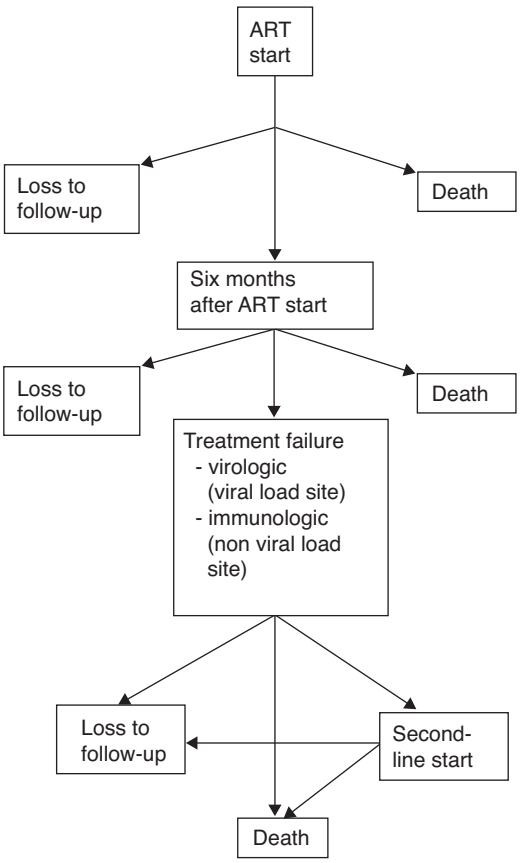

Fig. 1. States and transitions between states in the multistate model. ART, antiretroviral therapy.

categories of first-line regimens were included in the model: lamivudine, stavudine and nevirapine (3TC/d4T/NVP), lamivudine, zidovudine and nevirapine (3TC/ZDV/NVP), lamivudine, stavudine and efavirenz (3TC/d4T/EFV) and lamivudine, zidovudine and efavirenz (3TC/ZDV/EFV) or other. We imputed missing CD4 cell counts at baseline and 6 months and missing WHO clinical stage at baseline. Imputations were based on multinomial and linear regression models with disease stage and CD4 cell count as dependent variables and site, age, sex, year of starting ART, time to death and CD4 cell count (in case of missing clinical stage) or clinical stage (in case of missing CD4 cell count) as independent variables. Analyses were run on each of 20 datasets; results were combined with Rubin's rules [15]. In sensitivity analyses, we repeated the analyses dropping one cohort in turn and restricting analyses to patients with complete data (complete-case analysis).

Analysis of CD4 cell counts over time

We used models for repeated measures to compare CD4 cell count trajectories between sites with and without viral load monitoring. We constructed a multilevel model (CD4 measurements within patients) with a random intercept and slope for each patient, transforming time to the square root and the natural logarithm of time [fractional polynomial [2, (−0.5, ln)]), as described previously [16]. All patients with a baseline CD4 cell count and at least one additional CD4 cell count were included. We again examined the influence of single cohorts by repeating the analyses dropping one cohort in turn.

Non-HIV-related mortality

We explored to what extent differences in HIV-free background mortality influenced results. We obtained estimates of non-HIV-related mortality for the year 2004 (the last year for which data were available) from the Global Burden of Disease Study [17,18]. We compared the expected HIV-unrelated mortality between countries with and without viral load monitoring. Briefly, the expected number of deaths due to causes other than HIV between months 7 and 36 was calculated by multiplying the number of person-years by the corresponding sex, age-specific (in 5-year age groups) and country-specific rates of HIV-free mortality.

Data were analysed using Stata software version 11 (College Station, Texas, USA) and R version 2.10 (The R Development Core Team).

Results

Patient and programme characteristics

A total of 99 643 patients met eligibility criteria and were included: 7230 patients from Khayelitsha, 2658 patients

from Gugulethu, 7457 patients from Themba Lethu, 1361 patients from Tygerberg, 9604 patients from Lighthouse and 71 333 patients from MoH-CIDRZ. Overall, 18 706 patients were treated at sites with routine viral load monitoring in RSA (27 288 person-years of follow-up) and 80 937 patients at sites without access to viral load monitoring in Malawi and Zambia (147 876 person-years of follow-up). The proportion of patients excluded because they were only seen once and had no follow-up was similar across sites: 1.5% (range across sites 0.4–2.2%) in viral load sites and 1.3% (range 1.0–3.6%) in nonviral load sites.

Patients from viral load sites were more likely to be women (66% vs. 62%) and had lower CD4 cell counts (93 vs. 132 cells/μl) at the start of therapy (Table 1). In both settings, most patients started ART with a regimen that combined 3TC/d4T either with NVP or EFV. ZDV, didanosine (ddI) and boosted lopinavir (LPV/r) was the most common second-line regimen in viral load sites, whereas in CD4 sites, a combination of tenofovir (TDF), emtricitabine (FTC) and LPV/r was most commonly used. The South African programmes had better access to diagnostic examinations and treatments than the programmes in Malawi and Zambia, including availability of computer tomography, *Cryptococcus neoformans* antigen testing, and first-line therapy for opportunistic infections. Further details on patient characteristics and availability of diagnostic examinations are given in Web Tables 1 and 2, http://links.lww.com/QAD/A152.

Table 1. Patient characteristics in public-sector HIV treatment programmes with and without routine viral load monitoring in the International epidemiological Databases to Evaluate AIDS in Southern Africa cohort.

Variable	Viral load sites (Republic of South Africa, $n = 18\,706$)	Nonviral load sites (Zambia and Malawi, $n = 80\,937$)
Women (%)	12 291 (65.7)	50 036 (61.8)
Median age (IQR) (years)	34 (30–41)	35 (30–42)
Clinical stage (%)		
Stage available	18 359 (98.1)	77 572 (95.8)
Advanced[a]	10 601 (57.7)	54 878 (70.7)
CD4 cell count (cells/μl)		
CD4 cell count available	11 880 (63.5)	59 939 (74.1)
Median (IQR)	93 (39–159)	132 (66–203)
HIV-1 viral load (copies/ml)		
Viral load available (%)	7 183 (38.4)	839 (1.0)
Median log viral load (IQR)	5.0 (4.5–5.5)	
≤10 000	805 (11.7%)	
10 001–100 000	2626 (36.6%)	
First-line regimens (%)		
3TC d4T EFV	12 231 (65.4)	4 970 (6.1)
3TC ZDV EFV	954 (5.1)	2 756 (3.4)
3TC d4T NVP	4 204 (22.5)	46 940 (58.0)
3TC ZDV NVP	1 217 (6.5)	25 419 (31.4)
Other	100 (0.5)	852 (1.1)
Second-line regimens (%)		
TNV FTC LPV/r		817 (59.7%)
ZDV ddI LPV/r	657 (73.1%)	
ABC ddI LPV/r		231 (16.9%)
3TC ZDV LPV/r	81 (9.0%)	
3TC ZDV LPV/r TNV		59 (4.3%)
3TC ZDV EFV LPV/r	33 (3.7%)	
Other	128 (14.2%)	262 (19.1%)

Interquartile ranges (IQRs) and percentages are shown in brackets. 3TC, lamivudine; ABC, abacavir; ddI, didanosine; EFV, efavirenz; d4T, stavudine; FTC, emtricitabin; LPV, lopinavir; NVP, nevirapine; RTV, boost of ritonavir; ZDV, zidovudine.
[a]World Health Organization (WHO) stages III or IV.

Treatment outcomes

Of the eligible 99 643 patients, 3009 (3.0%) failed their first-line regimen, 1839 (1.8%) switched to a second-line regimen, 13 547 (13.6%) were LTFU and 8015 (8.0%) died during the first 3 years on ART. Figure 2 shows Kaplan–Meier curves of the all-cause mortality for programmes with and without viral load monitoring. Cumulative mortality was slightly higher in nonviral load sites in the first 6 months of ART, but curves crossed and separated thereafter, with higher mortality in nonviral load sites than in viral load sites ($P < 0.001$). When programmes were analysed separately, mortality was highest from month 6 onward in the two nonviral load sites. Figure 3 shows the results of the multistate model from 6 months after starting ART, based on 84 564 patients with at least 6 months of follow-up. At 3 years, 1.3% [95% confidence interval (CI) 0.9–1.6] of patients were on a failing first-line regimen in viral load sites, 9.8% (95% CI 9.1–10.5) had switched to second-line ART, 9.2% (95% CI 8.5–9.8) were LTFU and 4.3% (95% CI 3.9–4.8) had died. In nonviral load sites, more patients were on a failing first-line regimen (3.7%; 95% CI 3.6–3.9), fewer patients had switched (2.1%; 95% CI 2.0–2.3) and more patients were LTFU (15.3%; 95% CI 15.0–15.6) or had died (6.3%; 95% CI 6.0–6.5). Estimates for different time points are given in Web Table 3, http://links.lww.com/QAD/A152.

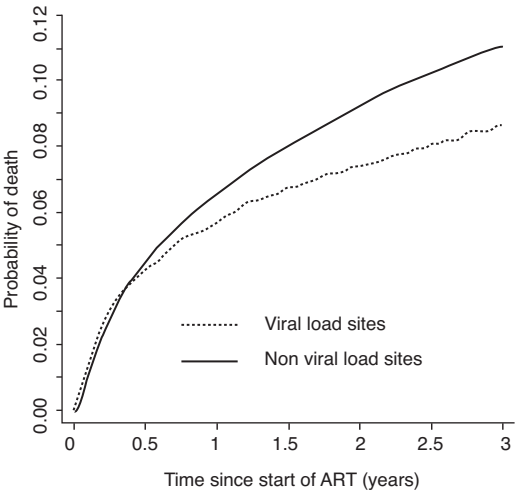

Fig. 2. Cumulative mortality of patients starting antiretroviral therapy in four sites with routine viral load monitoring from the Republic of South Africa and two sites without access to routine viral load monitoring in Malawi and Zambia.

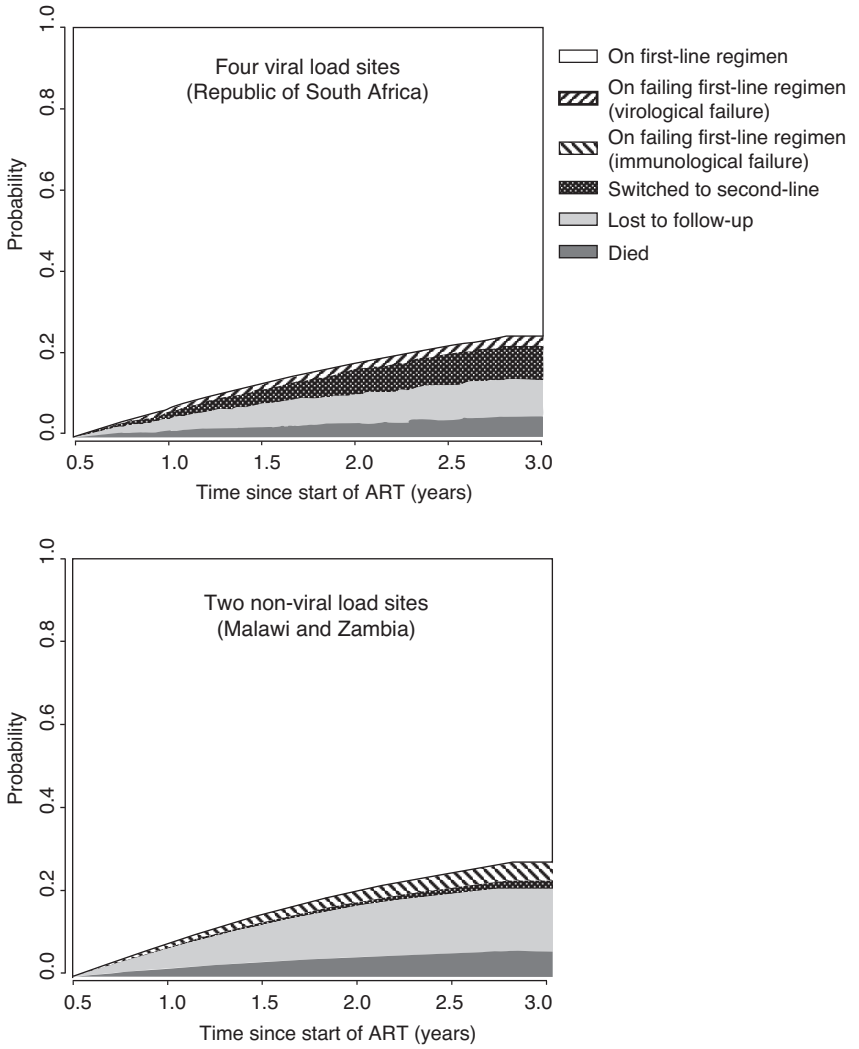

Fig. 3. Cumulative probability of treatment outcomes from 6 months after starting antiretroviral therapy in sites with and without routine viral load monitoring in the International epidemiological Databases to Evaluate AIDS in Southern Africa cohort. Failure relates to virological failure in viral load sites and immunological failure in nonviral load sites and relates to patients who met criteria for failure but have not been switched to second-line therapy. ART, antiretroviral therapy.

Table 2 shows crude and adjusted hazard ratios from multistate models measuring time from the start of ART to 6 months and from 6 months to the end of follow-up. Mortality was slightly lower in sites with viral load monitoring during the first 6 months on therapy (adjusted hazard ratio 0.83; 95% CI 0.74–0.92) and substantially lower after the first 6 months (adjusted hazard ratio 0.58; 95% CI 0.50–0.66). Loss to follow-up was similar in the first 6 months; after 6 months, however, the risk was lower in viral load sites (adjusted hazard ratio 0.53; 95% CI 0.48–0.58). Patients were more likely to switch to second-line ART in viral load compared with nonviral load sites (adjusted hazard ratio 4.16; 95% CI 3.57–4.85). Results were similar in sensitivity analyses that omitted one cohort in turn from the analysis (Web Table 4, http://links.lww.com/QAD/A152) and similar in the complete-case analysis (Web Table 5, http://links.lww.com/QAD/A152).

CD4 cell counts over time

A CD4 cell count at baseline and at least one additional CD4 cell count during follow-up were recorded for 8981 (48.0%) patients from viral load sites and 42 587 (52.6%) patients from nonviral load sites. The 51 568 patients included in the analysis contributed a total of 257 636 CD4 cell counts. The median number of CD4 measurements was four [interquartile range (IQR) 3–7] in both settings. Figure 4 shows 6-week moving averages of CD4 cell counts and modelled CD4 trajectories by CD4 cell count at ART initiation. The

Table 2. Crude and adjusted hazard ratios for HIV treatment outcomes comparing antiretroviral treatment programmes with and without (reference group) routine viral load monitoring in the International epidemiological Databases to Evaluate AIDS in Southern Africa cohort.

	Crude analysis		Adjusted analysis	
Outcome	Crude HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
From start of ART to 6 months				
All-cause mortality	0.97 (0.89–1.05)	0.43	0.83 (0.74–0.92)	0.002
Loss to follow-up	1.37 (1.28–1.48)	<0.001	1.00 (0.91–1.11)	0.39
From 6 months to end of follow-up				
All-cause mortality	0.65 (0.58–0.72)	<0.001	0.58 (0.50–0.66)	<0.001
Loss to follow-up	0.56 (0.52–0.60)	<0.001	0.53 (0.48–0.58)	<0.001
Switch to second-line ART	4.71 (4.24–5.24)	<0.001	4.16 (3.57–4.85)	<0.001

Results from multistate models based on 20 imputed datasets. ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, first-line regimen, CD4 cell count and clinical stage at start of first-line therapy and for age, sex, first-line regimen and CD4 cell count at 6 months.

trajectories crossed at 6 months, with less pronounced increases in nonviral load sites compared with viral load sites thereafter. Table 3 shows CD4 cell count and viral load data at different time points for viral load and nonviral load sites. In viral load sites, CD4 cell counts were lower initially, but higher at virological failure and at the start of second-line ART than in nonviral load sites. Three years after starting ART, median CD4 cell counts were 425 cells/μl (IQR 308–582) in viral load sites and 383 cells/μl (IQR 268–526) in nonviral load sites ($P < 0.001$). The omission of one cohort in turn did not materially alter results (Web Fig. 1, http://links.lww.com/QAD/A152).

Non-HIV-related mortality

The expected non-HIV-related mortality rate was 0.62 (95% CI 0.52–0.75) per 100 person-years for the South African sites compared with 0.80 (0.75–0.85) per 100

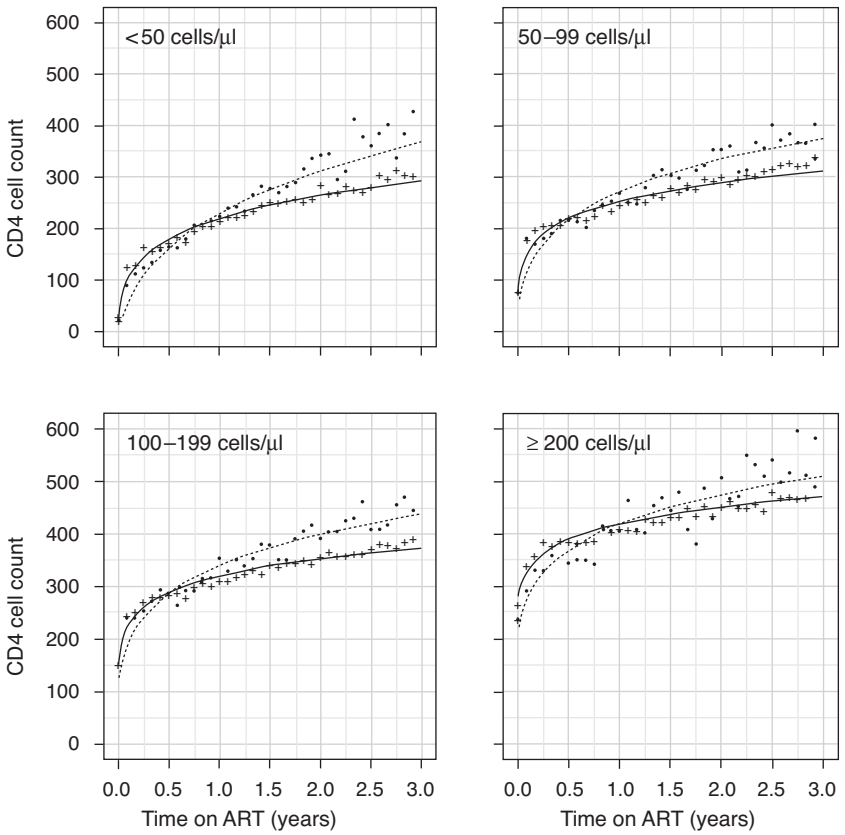

Fig. 4. Evolution of CD4 cell counts from start of antiretroviral therapy up to three years after start of antiretroviral therapy in four sites with routine viral load (Republic of South Africa) and two sites without access to viral load monitoring (Malawi and Zambia). Lines represent the mean fit of the mixed effect model and dots and crosses the moving averages of the observed data. Viral load sites are shown as broken lines and dots and nonviral load sites as solid line and crosses. ART, antiretroviral therapy.

Table 3. CD4 cell count and viral load at different time points after starting antiretroviral therapy in sites with and without routine viral load monitoring in the International epidemiological Databases to Evaluate AIDS in Southern Africa cohort.

	CD4 cell count			HIV viral load		
Variable	Viral load sites	Nonviral load sites	*P*	Viral load sites	Nonviral load sites	*P*
Start of first-line ART						
No. of patients	18 706	80 937		18 706	80 937	
Value available	11 880 (63.5%)	59 939 (74.1%)		7 183 (38.4%)	839 (1.0%)	
Median (IQR)	93 (39–159)	132 (66–203)	<0.001	5.0 (4.5–5.5)	5.2 (4.6–5.6)	0.001
Median (IQR) imputed	105 (50–165)	143 (74–217)	<0.001			
Month 6						
No. of patients	14 258	70 306		14 258	70 306	
Value available	9 263 (65.0%)	24 923 (35.5%)		8 892 (62.4%)	781 (1.1%)	
Median (IQR)	225 (151–314)	270 (178–387)	<0.001	0 (0–0)	2.6 (2.6–2.6)	<0.001
Median (IQR) imputed	234 (157–324)	295 (192–414)	<0.001			
Failure						
No. of patients	479	2758		479	2758	
Value available	397 (82.9%)	2 758 (100%)		479 (100%)	249 (9.0%)	
Median (IQR)	161 (95–242)	136 (75–222)	<0.001	4.7 (4.3–5.1)	2.6 (2.6–4.3)[a]	<0.001
Start of second-line ART						
No. of patients	899	1369		899	1369	
Value available	526 (58.5%)	805 (58.8%)		671 (74.6%)	513 (37.5%)	
Median (IQR)	214 (118–321)	154 (81–256)	<0.001	4.1 (3.6–4.7)	4.2 (3.4–5.0)	0.02
Year 3						
No. of patients	2618	19 749		2618	19 749	
Value available	1 779 (68.0%)	13 067 (66.2%)		1 319 (50.4%)	555 (2.8%)	
Median (IQR)	425 (308–582)	383 (268–526)	<0.001	0 (0–0)	2.6 (2.6–2.6)	<0.001

ART, antiretroviral therapy; IQR, interquartile range.
[a]Viral load below 400 copies/ml in 147 patients (59.0%).

person-years in Zambia and Malawi. The crude observed mortality from 6 months to 3 years was 2.12 (1.93–2.34) and 3.10 (2.99–3.20) per 100 person-years, respectively. Differences in background mortality could therefore explain about 20% of the observed mortality difference. Details of calculations are presented in Web Table 6, http://links.lww.com/QAD/A152.

Discussion

We compared long-term outcomes of ART in four scale-up programmes in RSA, where viral load is routinely monitored, with two programmes from Zambia and Malawi, where only CD4 cell counts are regularly measured. Mortality was somewhat lower initially and substantially lower after 6 months on ART in viral load compared with nonviral load sites. A similar picture was seen for loss to follow-up, with lower rates of loss to follow-up in viral load sites after 6 months. Comparisons of CD4 cell count trajectories were compatible with the findings for mortality, with less pronounced increases in counts in nonviral load sites compared with viral load sites after 6 months. Finally, switching to second-line regimens was more frequent in viral load sites. These results were robust in sensitivity analyses and not driven by a single cohort.

Our study was based on almost 100 000 adult patients from six public-sector treatment programmes in the three countries. Results should thus be applicable to many other patients in a region heavily affected by HIV. We acknowledge that the treatment programmes included in this study will not be representative for all programmes in the three countries: they are located in urban areas, equipped with electronic medical record systems and have access to regular CD4 cell determination and second-line therapy [19]. Information on stage of disease and CD4 cell counts was missing in some patients, both in settings with and without routine viral load monitoring. We used multiple imputations to account for the missing information and followed recent guidelines when building these models [20]. 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.

There is debate on the place of viral load monitoring for ART in resource-limited settings [21,22]. A modelling study of long-term ART concluded that the reduction in mortality associated with viral load monitoring is small and has poor cost-effectiveness [21]. A randomized trial [23] compared 3-monthly monitoring of CD4 cell count with viral load monitoring in Thailand and found that over 3 years, switching was somewhat more frequent with CD4 cell count monitoring compared with viral load monitoring (7.2 vs. 5.1%; $P = 0.10$) and that mortality was similar (3.4 vs. 4.3%; $P = 0.57$). Modelling studies assume that patients monitored by CD4 cell counts switch to second-line ART when meeting criteria for

immunological failure and protocols of clinical trials ensure that this is the case. The present study shows that the situation in practice is quite different: few patients switch to second-line ART in programmes relying on CD4 cell counts to monitor ART in Malawi and Zambia and many more patients remain on a failing first-line regimen compared with programmes monitoring viral load in RSA. Mortality in patients remaining on failing first-line regimens is high: in a previous study of 11 ART programmes in sub-Saharan Africa, we found that mortality at 1 year was 4.2% (95% CI 2.2–7.8) in patients who switched to a second-line regimen but 11.7% (95% CI 7.3–18.5) in patients who remained on a failing first-line regimen [5,24].

Our results support the notion that routine viral load monitoring contributed to the lower mortality in RSA. First, mortality curves and CD4 trajectories separated after 6 months, when patients start to switch to second-line therapy and when in viral load sites the first viral load data became available to identify patients for adherence interventions. Data from RSA [25] and Thailand [26] showed that many patients with low-level viraemia (<1000 copies/ml) suppress viral replication after targeted interventions to improve adherence. The monitoring of viral load may thus promote adherence and retention in care [27], in addition to detecting high-level virological failure requiring second-line therapy. In nonviral load sites, targeted viral load monitoring was used in some patients: 37% of those starting second-line therapy had a viral load measurement.

Second, the higher mortality in programmes without viral load monitoring was not explained by differences in patient characteristics at baseline. The median baseline CD4 cell count was in fact lower in viral load than in nonviral load sites. Third, switching to second-line ART occurred later and at lower CD4 cell counts in programmes without viral load monitoring, in line with a previous analysis of ART programmes in lower-income countries [5]. Switching at lower CD4 cell counts is associated with higher mortality [24,28]. Finally, at 3 years, nearly three times as many patients were on a failing first-line regimen in nonviral load sites than in viral load sites. A study of patients initiating ART in several countries in Asia also found a higher risk of disease progression in patients from sites with fewer than one annual viral load [29]. A meta-analysis of cohort studies demonstrated that in patients treated under WHO guidelines, viral load monitoring was associated with reduced probabilities of mutations conferring resistance to NNRTIs, the M184V/I mutation and thymidine analogue mutations [30].

This was an observational study and other factors than viral load monitoring could explain our results. RSA is a middle-income country with a per capita gross domestic product (GDP) of US$ 9332 in 2009, whereas Zambia and Malawi are low-income countries with a per capita GDP of US$ 1297 and 779, respectively, in the same year [31]. The ART programmes in the latter two countries lacked access to diagnostic tests and treatments to manage the complications of advanced HIV infection. In RSA, resistance testing can be done in programmes linked to an academic department, but not routinely: testing is generally done in the context of research, or in complex cases of second-line failure.

We carefully considered programme attrition: a significant proportion of those LTFU may have died, particularly over the first year of therapy [32]. Analyses of mortality were based on patients remaining in care, and uncounted deaths among patients not returning to clinics could have introduced bias. After 6 months, patient attrition was almost twice as common in nonviral sites than in viral load sites: the bias associated with loss to follow-up thus probably means that we underestimated mortality differences. This bias will, however, be modest: fewer than 10% of patients were lost in the initial 6 months and between 6 months and 3 years. In this situation, the mortality observed among patients retained in care will provide a reasonable estimate of programme-level mortality [33].

In conclusion, over the first 3 years of ART, mortality, loss to follow-up and CD4 trajectories were more favourable among patients enrolled in programmes in RSA compared with programmes in Malawi and Zambia. These differences may at least partly be explained by more timely switching to second-line ART after virological failure in RSA and better adherence counselling, where monitoring of viral load is routine.

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Conflicts of interest

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References

1. World Health Organization. **Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector**. *Progress Report 2010*. Geneva: World Health Organization; 2010. http://www.who.int/hiv/pub/2010progressreport/en/index.html. [Accessed 20 May 2011]
2. World Health Organization. **Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach**. *2010 revision*. Geneva: World Health Organization; 2010. http://www.who.int/hiv/pub/arv/adult2010/en/index.html. [Accessed 20 May 2011]
3. Keiser O, MacPhail P, Boulle A, Wood R, Schechter M, Dabis F, *et al*. **Accuracy of WHO CD4 cell count criteria for virological failure of antiretroviral therapy.** *Trop Med Int Health* 2009; **14**:1220–1225.
4. Moore DM, Mermin J, Awor A, Yip B, Hogg RS, Montaner JS. **Performance of immunologic responses in predicting viral load suppression: implications for monitoring patients in resource-limited settings.** *J Acquir Immune Defic Syndr* 2006; **43**:436–439.
5. Keiser O, Tweya H, Boulle A, Braitstein P, Schecter M, Brinkhof MW, *et al*. **Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring.** *AIDS* 2009; **23**:1867–1874.
6. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, *et al*. Cohort Profile: **The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa**. *Int J Epidemiol* 2011. doi: 10.1093/ije/dyr080. [Epub ahead of print]
7. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, *et al*. **Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa.** *AIDS* 2010; **24**:563–572.
8. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. **Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design.** *AIDS* 2005; **19**:2141–2148.
9. Eshun-Wilson I, Havers F, Nachega JB, Prozesky HW, Taljaard JJ, Zeier MD, *et al*. **Evaluation of paradoxical TB-associated IRIS with the use of standardized case definitions for resource-limited settings.** *J Int Assoc Physicians AIDS Care* 2010; **9**:104–108.
10. Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van Rie A. **Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study.** *J Int AIDS Soc* 2009; **12**:38.
11. Beadles WI, Jahn A, Weigel R, Clutterbuck D. **Peripheral neuropathy in HIV-positive patients at an antiretroviral clinic in Lilongwe.** *Malawi Trop Doct* 2009; **39**:78–80.
12. Chi BH, Cantrell RA, Mwango A, Westfall AO, Mutale W, Limbada M, *et al*. **An empirical approach to defining loss to follow-up among patients enrolled in antiretroviral treatment programs.** *Am J Epidemiol* 2010; **171**:924–931.
13. Stringer JSA, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, *et al*. **Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes.** *JAMA* 2006; **296**:782–793.
14. Putter H, Fiocco M, Geskus RB. **Tutorial in biostatistics: competing risks and multistate models.** *Stat Med* 2007; **26**:2389–2430.
15. Rubin D. *Multiple imputation for nonresponse in surveys*. New York: Wiley; 1987.
16. Nash D, Katyal M, Brinkhof MW, Keiser O, May M, Hughes R, *et al*. **Long-term immunologic response to antiretroviral therapy in low-income countries: a collaborative analysis of prospective studies.** *AIDS* 2008; **22**:2291–2302.
17. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. **Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data**. *Lancet* 2006; **367**:1747–1757.
18. Brinkhof MW, Boulle A, Weigel R, Messou E, Mathers C, Orrell C, *et al*. **Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality**. *PLoS Med* 2009; **6**:e1000066.
19. Forster M, Bailey C, Brinkhof MW, Graber C, Boulle 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.
20. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, *et al*. **Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies.** *Lancet* 2009; **373**:1352–1363.
21. 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.
22. Revell AD, Wang D, Harrigan R, Hamers RL, Wensing AM, Dewolf F, *et al*. **Modelling response to HIV therapy without a genotype: an argument for viral load monitoring in resource-limited settings.** *J Antimicrob Chemother* 2010; **65**:605–607.
23. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Traisaithit P, Barbier S, Techapornroong M, *et al*. **PHPT-3: a randomized clinical trial comparing CD4 vs viral load ART monitoring/switching strategies in Thailand**. In: *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections*, Boston, MA; 27 February to 3 March 2011.
24. Keiser O, Tweya H, Braitstein P, Dabis F, MacPhail P, Boulle A, *et al*. **Mortality after failure of antiretroviral therapy in sub-Saharan Africa.** *Trop Med Int Health* 2010; **15**:251–258.
25. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, *et al*. **Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited.** *Antivir Ther* 2007; **12**:83–88.
26. Wilson D, Keiluhu AK, Kogrum S, Reid T, Seriratana N, Ford N, *et al*. **HIV-1 viral load monitoring: an opportunity to reinforce treatment adherence in a resource-limited setting in Thailand.** *Trans R Soc Trop Med Hygiene* 2009; **103**:601–606.
27. Lawn SD, Bekker LG, Calmy A, Wood R. **Monitoring of antiretroviral therapy in low-resource settings.** *Lancet* 2008; **372**:287–288; author rely 289.
28. Pujades-Rodriguez M, Balkan S, Arnould L, Brinkhof MA, Calmy A. **Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries.** *JAMA* 2010; **304**:303–312.
29. Oyomopito R, Lee MP, Phanuphak P, Lim PL, Ditangco R, Zhou J, *et al*. **Measures of site resourcing predict virologic suppression, immunologic response and HIV disease progression following highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database (TAHOD).** *HIV Med* 2010; **11**:519–529.
30. Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von Wyl V, Yerly S, *et al*. **Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis.** *Lancet Infect Dis* 2009; **9**:409–417.
31. Hiatt RA, Fireman BH. **Serum cholesterol and the incidence of cancer in a large cohort.** *J Chronic Dis* 1986; **39**:861–870.
32. Brinkhof MW, Pujades-Rodriguez M, Egger M. **Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis.** *PLoS One* 2009; **4**:e5790.
33. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, *et al*. **Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa.** *PLoS Med* 2011; **8**:e1000390.