

# Cost-effectiveness of point-of-care viral load monitoring of antiretroviral therapy in resource-limited settings: mathematical modelling study

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**Background:** Monitoring of HIV viral load in patients on combination antiretroviral therapy (ART) is not generally available in resource-limited settings. We examined the cost-effectiveness of qualitative point-of-care viral load tests (POC-VL) in sub-Saharan Africa.

**Design:** Mathematical model based on longitudinal data from the Gugulethu and Khayelitsha township ART programmes in Cape Town, South Africa.

**Methods:** Cohorts of patients on ART monitored by POC-VL, CD4 cell count or clinically were simulated. Scenario A considered the more accurate detection of treatment failure with POC-VL only, and scenario B also considered the effect on HIV transmission. Scenario C further assumed that the risk of virologic failure is halved with POC-VL due to improved adherence. We estimated the change in costs per quality-adjusted life-year gained (incremental cost-effectiveness ratios, ICERs) of POC-VL compared with CD4 and clinical monitoring.

**Results:** POC-VL tests with detection limits less than 1000 copies/ml increased costs due to unnecessary switches to second-line ART, without improving survival. Assuming POC-VL unit costs between US\$5 and US\$20 and detection limits between 1000 and 10 000 copies/ml, the ICER of POC-VL was US\$4010–US\$9230 compared with clinical and US\$5960–US\$25540 compared with CD4 cell count monitoring. In Scenario B, the corresponding ICERs were US\$2450–US\$5830 and US\$2230–US\$10380. In Scenario C, the ICER ranged between US\$960 and US\$2500 compared with clinical monitoring and between cost-saving and US\$2460 compared with CD4 monitoring.

**Conclusion:** The cost-effectiveness of POC-VL for monitoring ART is improved by a higher detection limit, by taking the reduction in new HIV infections into account and assuming that failure of first-line ART is reduced due to targeted adherence counselling.

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## Introduction

Despite the rapid scale-up of combination antiretroviral therapy (ART) in HIV-infected patients during the past decade, the capacity to monitor treatment response remains limited in many settings [1]. Routine viral load monitoring is standard to detect virologic failure and inform decisions on switching patients to second-line ART in industrialized countries. In contrast, in most resource-limited settings, these decisions are based on clinical symptoms and CD4 cell counts, which correlate poorly with viral load [2]. The main barriers for the implementation of viral load monitoring in low-income settings are the need for centralized laboratory facilities [3] and the required scale-up of expensive second-line ART [4].

A recent randomized controlled trial (RCT) evaluating the effect of routine laboratory monitoring on clinical outcomes among patients on ART in Uganda showed that compared with clinical monitoring alone, outcomes were more favourable with laboratory monitoring, but there was no significant difference between the CD4 arm and the viral load arm [5]. The setting of an RCT may not, however, reflect routine care in settings without access to viral load monitoring, in which patients may stay on failing first-line regimens for prolonged periods of time, which may increase the risk of onward transmission of HIV [6], lead to multidrug resistance [7] and increase mortality [8]. Lack of viral load monitoring hampers the detection of poor adherence to ART and the targeted counselling of patients [9]. Finally, a substantial number of patients may switch unnecessarily with suppressed viral load [10].

In sub-Saharan Africa, only South Africa [11] and Botswana [12] have implemented viral load monitoring in their national ART programmes. Point-of-care (POC) tests are being developed for monitoring both CD4 cell counts and viral load. UNITAID and the Bill & Melinda Gates Foundation are supporting the development and implementation of POC tests [13,14]. POC testing can improve the monitoring of ART by making results available rapidly and providing access to clinics in remote settings [13].

The aim of our study was to explore the cost-effectiveness of routine POC-VL monitoring in settings in sub-Saharan Africa where only CD4 cell count or clinical monitoring is currently available. We assumed that the viral load test would be qualitative and available to all patients on ART. We varied the assumptions regarding the costs and detection limits of the test, and the costs of second-line therapy.

## Materials and methods

### Data sources

The International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) is a collaboration

of ART programmes in seven countries in Southern Africa [15]. Data are collected at ART initiation (baseline) and each follow-up visit using standardized instruments. All sites have ethical approval to collect data and participate in IeDEA-SA. We restricted our analyses to the Gugulethu [16] and Khayelitsha [17] township ART programmes in Cape Town, South Africa, where viral load and CD4 cell counts are measured regularly (Table 1). All treatment-naïve patients aged at least 16 years, who had started ART with at least two nucleoside reverse transcriptase inhibitors (NRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI), were included. Second-line ART was defined as a switch from an NNRTI-based regimen to a protease inhibitor-based regimen, with at least one NRTI changed.

### Definitions of treatment failure

Criteria for clinical and immunologic failure were those of the WHO [18]. Virologic failure was defined with five alternative thresholds (125, 400, 1000, 5000 or 10 000 copies/ml). Failures had to be confirmed in a second measurement within 1 year (usually 3 months after the first measurement). True treatment failure was defined as a rebound in viral load after suppression to at least 125 copies/ml, with viral load remaining elevated until the patient switched therapy. Whereas virologic, immunologic and clinical failures are observations, true treatment failure is an underlying event that cannot be observed exactly. Detectable viral load of unknown origin (DVU) was defined as viral load above 125 copies/ml, which returns below 125 copies/ml while on the same regimen. We calculated the probabilities of observing a DVU with all five thresholds (Supplementary Table 1, <http://links.lww.com/QAD/A330>).

### Mathematical model

The IeDEA-SA mathematical model of ART has been described in detail elsewhere [6]. We adapted this model to compare quality-adjusted life-years (QALYs), costs and cost-effectiveness between different monitoring strategies in cohorts of patients receiving ART. In brief, the model simulates cohorts of patients who are followed from starting ART until death. The properties of the individual patient and the timing of events are calculated probabilistically on the basis of a series of rules and parametric distributions [6]. The model was parameterized with data from the South African township ART programmes and estimates published in the literature (Supplementary Table 2, <http://links.lww.com/QAD/A330>). For the present study, we additionally modelled viral load trajectories (Web Appendix 1, <http://links.lww.com/QAD/A330>).

Each simulated patient is at a risk of true treatment failure, clinical failure, immunologic failure and death. The observation of the failures depends on the chosen monitoring strategy. If viral load monitoring is available, virologic failure is observed if the viral load trajectory is

**Table 1. Patient characteristics in the Gugulethu and Khayelitsha programmes used to parameterize the mathematical model.**

	Unit	Value
Age at baseline <sup>a</sup> (n = 9888)	Years, median (IQR)	33 (29–39)
Sex (n = 9888)	Number (percentage)	
Male		3240 (32.8%)
Female		6648 (67.2%)
Cohort (n = 9888)	Number (percentage)	
Gugulethu		2658 (26.9%)
Khayelitsha		7230 (73.1%)
CD4 cell count at baseline <sup>a</sup> (n = 7259)	Cells/µl; median (IQR)	93 (41–158)
HIV-1 viral load at baseline <sup>a</sup> (n = 5274)	Log <sub>10</sub> copies/ml; median (IQR)	5.0 (4.5–5.5)
First-line regimens (n = 9888)	Number (percentage)	
d4T 3TC EFV		4985 (50.4%)
d4T 3TC NVP		3182 (32.2%)
ZDV 3TC NVP		1031 (10.4%)
ZDV 3TC EFV		680 (6.9%)
d4T ddI EFV		7 (0.1%)
ZDV ddI EFV		3 (0.0%)
Second-line regimens (n = 353)	Number (percentage)	
ZDV ddI LPV/r		244 (69.1%)
ZDV 3TC EFV LPV/r		34 (9.6%)
d4T ddI LPV/r		22 (6.2%)
ZDV 3TC LPV/r		9 (2.6%)
Other		44 (12.5%)
Follow-up time on ART (n = 9888)	Months, median (IQR)	17.8 (7.5–29.8)
Time from ART start to switch to second line (n = 353)	Months, median (IQR)	21.2 (13.7–30.3)

A total of 9888 patients were followed for 16 278 person-years on first-line therapy and 435 person-years on second-line therapy. 3TC, lamivudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; IQR, interquartile range; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; ZDV, zidovudine.

<sup>a</sup>Baseline variables were defined as the closest value within 3 months before up to 2 weeks after antiretroviral therapy initiation.

above the limit of detection (LOD) at the time of the measurement. Virologic failure may also be observed if the trajectory is below the LOD but DVU is present, typically due to blips [19,20] or nonadherence. After an immunologic or virologic failure is observed, another measurement is taken 3 months later. If failure is observed again, the patient switches to second-line ART. On second-line ART, the patient continues to be at risk of failure. Finally, the number of expected HIV transmissions is calculated. Each patient is assigned a frequency of partner change and sex acts. The times of virologic failures and switching determine the value of the viral load at each sex act. The expected number of new infections is calculated using a relationship between viral load and infectiousness based on the results of the Rakai study in Uganda [21,22] (Web Appendix 2, <http://links.lww.com/QAD/A330>).

### Costs, quality-adjusted life-years and incremental cost-effectiveness ratios

Costs of appointments, CD4 and viral load measurements and ART were considered (Supplementary Table 3, <http://links.lww.com/QAD/A330>). Cost estimates of the antiretroviral drugs were based on the ceiling price list of the Clinton Health Access Initiative (CHAI) [23]. We used the average of the two most common first-line (zidovudine/lamivudine/nevirapine or tenofovir/lamivudine/efavirenz, \$146.50/year) and second-line (zidovudine/lamivudine/ritonavir-boosted lopinavir or tenofovir/lamivudine/ritonavir-boosted lopinavir, \$465.50/year) regimens. On the basis of discussions

with experts and organizations developing and implementing POC-VL tests, a range of prices per test was assumed. With the currently available laboratory-based VL tests, the cost of the consumables is about US\$28 and the cost of the machine between US\$100 000 and US\$225 000 [13]. The cost-effectiveness study [24] of the Ugandan trial [5] estimated the total cost per test to be US\$29.64, but higher estimates have also been reported [25,26]. The Bill & Melinda Gates Foundation is currently funding the development of a qualitative POC-VL test costing US\$3–US\$5 per cartridge and less than US\$1000 per machine [14]. We assumed that a plausible minimum for the unit cost of the POC-VL test (including consumables and per-test costs of the machine) would be US\$5 with an LOD of 1000 copies/ml or higher. For lower thresholds, we assumed a minimum of US\$10 per test. Finally, we assumed that the cost would not exceed US\$20 per test for any LOD.

Quality of life weights were derived from the disability weights according to the Global Burden of Disease project [27]. For asymptomatic HIV, the weight was 0.865. For symptomatic HIV, we took the weight of the most common disease, tuberculosis (TB), and multiplied it with the weight of asymptomatic HIV: 0.865\*0.729 = 0.631. We used the same weights for all patients irrespective of age. We also estimated costs and lost QALYs in the partners infected by the modelled patients. We assumed that the infected partners would have a life expectancy of 40 years at the time of infection, which would be reduced to 30 years because of HIV.

We calculated incremental cost-effectiveness ratios (ICERs), which are defined as the ratio of the change in costs divided by the change in QALYs. Both QALYs and costs were discounted by 3% per year.

### Model scenarios

The following monitoring strategies were modelled: clinical monitoring, 6-monthly CD4 cell count monitoring and 6-monthly viral load monitoring with a qualitative POC-VL test with an LOD of 125, 400, 1000, 5000 or 10 000 copies/ml. We assumed that the results of the viral load test would be immediately available to the caregiver and the patient. We used the model to calculate the ICERs of viral load monitoring with different LODs compared with either CD4 cell count or clinical monitoring. We investigated three possible benefits of routine viral load monitoring: in Scenario A, we included only the more accurate detection of treatment failure and more timely and potentially more appropriate switching of patients to second-line ART. In Scenario B, we additionally considered the effect on HIV transmission. In Scenario C, we also assumed that the risk of virologic failure is twice as high with clinical or CD4 cell count monitoring than with viral load monitoring, because viral load monitoring detects nonadherence and improves adherence by making targeted interventions possible [28,29].

## Results

We present key model outcomes, including the number of unnecessary switches to second-line ART, the number of missed true treatment failures, the QALYs expected at the start of ART, the costs of patient management on ART (in total and broken down by costs of appointments, tests and ART) and outcomes related to HIV transmission (QALYs lost due to new infections and total costs due to new infections). These outcomes are given in Table 2 per lifetime of one patient or 100 patients on ART, by monitoring strategy and the five different LODs for the POC-VL test.

Five to six out of 100 true treatment failures remained unobserved over the entire lifetime with viral load monitoring strategies, compared with 37 with CD4 and 76 with clinical monitoring. The number of unnecessary switches to second-line ART per 100 patients was nine with clinical monitoring and five with CD4 cell count monitoring. With viral load monitoring, it ranged from 15 (lowest LOD, 125 copies/ml) to 5 or fewer (LODs  $\geq$ 1000 copies/ml). Despite these differences in the accuracy of monitoring and switching, only small differences in the quality-adjusted life expectancy emerged, with mean QALYs expected at the start of ART ranging from 12.78 with clinical monitoring to 12.93 with POC-VL monitoring. Expressed per 100 patients, the difference in QALYs was 15. If we

assumed that the true treatment failure rate was twice as high with clinical monitoring compared with viral load monitoring (Scenario C), this difference increased to 33 QALYs. Depending on the monitoring strategy, the number of new HIV infections ranged from around four with POC-VL monitoring to seven per 100 patients with clinical monitoring, leading to a loss of 15–23 QALYs per 100 patients (Table 2). The number of new infections was higher in viral load monitoring with LOD 125 copies/ml compared with higher LODs. This is due to the large number of unnecessary switches to second-line ART, which will move second-line failure forward in time and, in the absence of further treatment options, increase the total number of patients on failing regimens.

Total (lifetime) cost of ART ranged between US\$3037 per patient (clinical monitoring) and US\$4739 per patient (viral load monitoring, US\$20/VL test, LOD 125 copies/ml). The most important determinant of total costs was second-line ART, which increased over three-fold from US\$456 per patient (clinical monitoring) to US\$1506 per patient (viral load monitoring, LOD 125 copies/ml) (Fig. 1). The costs of tests were substantially higher in strategies with viral load monitoring than CD4 cell count monitoring even when assuming a low unit cost of US\$5 per viral load test. New HIV infections caused additional costs between US\$9400 (viral load monitoring, LOD 1000 or 5000 copies/ml) and US\$14500 (clinical monitoring) per 100 patients on ART (Table 2) but were not an important contributor to costs over the lifetime of the index patients on ART (Fig. 1). As viral load monitoring using an LOD of 125 or 400 copies/ml was more expensive, did not improve survival and caused slightly more transmissions than viral load monitoring with a higher LOD, these two strategies were excluded from the cost-effectiveness analyses.

The cost-effectiveness of POC-VL monitoring compared with CD4 cell count monitoring was poor in Scenario A (Table 3): even the most cost-effective viral load monitoring scenario (US\$5 per POC-VL test, LOD 10000 copies/ml) had an ICER of US\$5960 per QALY. Compared with clinical monitoring, CD4 cell count monitoring (ICER US\$3300/QALY) was more cost-effective than viral load monitoring (ICER US\$4010 per QALY) under the same assumptions (US\$5/test, LOD 10000 copies/ml). Including the effect on transmission (Scenario B) improved the cost-effectiveness of routine viral load monitoring. Compared with CD4 cell count monitoring, the ICER of routine viral load monitoring with the same assumptions as above decreased from US\$5960 under Scenario A to US\$2230 per QALY. Compared with clinical monitoring, POC-VL monitoring became more cost-effective than CD4 cell count monitoring (US\$2450/QALY versus US\$2590/QALY). Finally, in Scenario C, routine POC-VL monitoring became a clearly cost-effective strategy. Compared with CD4 cell count monitoring, viral load monitoring was

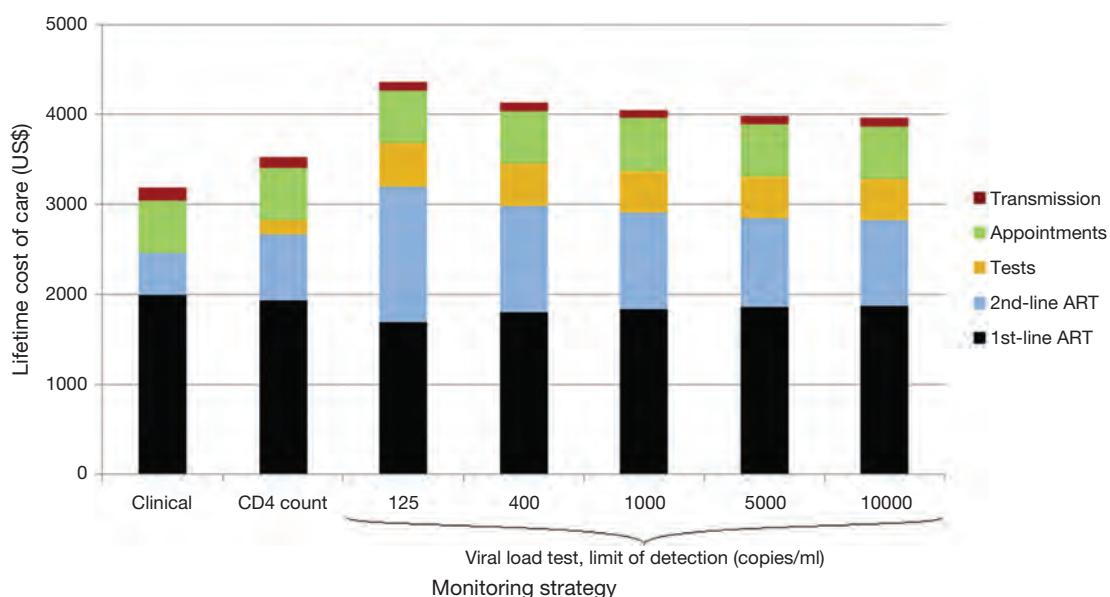
**Table 2. Key outcomes of simulated strategies.**

Outcome	Clinical monitoring			CD4 monitoring			POC viral load monitoring		
	Adherence scenario:		Adherence scenario:			LOD (copies/ml):			
A/B	C	A/B	C	125	400	1000	5000	10000	
Monitoring									
Unnecessary switches to second-line ART (per 100 patients)	9	7	5	5	15	8	5	3	2
Missed true treatment failure (per 100 failures)	76	77	37	36	5	5	5	5	6
Life expectancy at start of ART (QALYs)	12.78	12.60	12.89	12.80	12.93	12.93	12.93	12.93	12.93
Mean quality-adjusted life-years									
Costs (US\$ per person)									
Appointments	577	569	582	577	583	583	584	584	583
Diagnostic tests	0	0	159	159	476–952 <sup>a</sup>	470–941 <sup>a</sup>	234–935 <sup>b</sup>	232–928 <sup>b</sup>	231–926 <sup>b</sup>
First-line ART	2004	1952	1940	1800	1698	1799	1838	1865	1873
Second-line ART	456	527	720	1117	1506	1187	1066	977	951
Total costs of ART	3037	3047	3400	3654	4263–4739 <sup>a</sup>	4038–4510 <sup>a</sup>	3721–4422 <sup>b</sup>	3658–4354 <sup>b</sup>	3639–4334 <sup>b</sup>
HIV transmission (per 100 patients)									
New infections	7.1	11.1	5.7	9.3	4.3	4.0	3.9	3.9	4.0
QALYs lost	22.6	32.3	20.2	29.2	15.5	14.9	14.7	14.7	15.0
Costs in US\$	14500	20600	12900	18700	9900	9500	9400	9400	9600

Each simulation is based on 10 000 patients starting antiretroviral therapy, followed up until death. Adherence scenario A/B: Risk of virologic failure is equal in all monitoring strategies. Adherence scenario C: Risk of virologic failure is twice as high with clinical and CD4 monitoring than viral load monitoring. ART, antiretroviral therapy; LOD, limit of detection; POC, point-of-care; QALY, quality-adjusted life-year.

<sup>a</sup>Depending on unit cost of viral load test, ranging from \$10 to \$20.

<sup>b</sup>Depending on unit cost of viral load test, ranging from \$5 to \$20.



**Fig. 1. Breakdown of costs of antiretroviral therapy care per patient in different monitoring strategies.** Unit cost of viral load test was assumed to be US\$10. ART, antiretroviral therapy.

cost-saving if the cost of the viral load test was US\$5. The ICER compared with either CD4 cell count or clinical monitoring remained below US\$2500 per QALY with all LODs and costs of POC-VL tests.

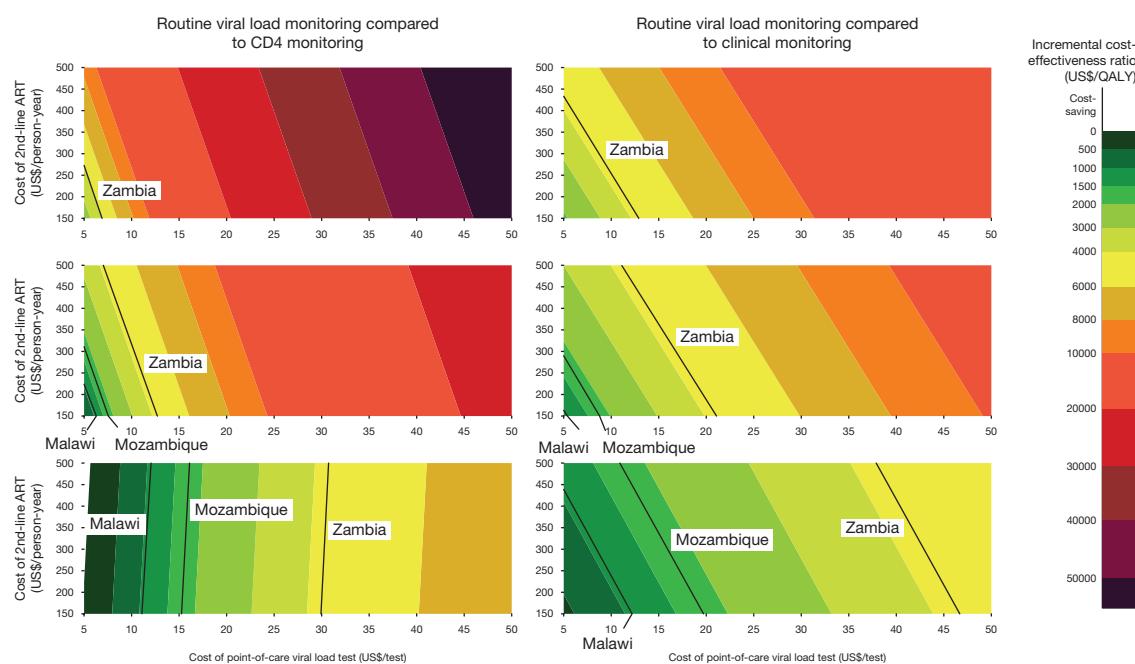
Figure 2 shows the cost-effectiveness of POC-VL monitoring compared with CD4 cell count monitoring (left panel) and clinical monitoring (right panel) for

Scenarios A, B and C. The LOD was 1000 copies/ml and the costs of POC-VL tests and of second-line ART ranged from US\$5 to US\$50 and US\$150 to US\$500, respectively. The limits for cost-effectiveness (three times per-capita gross domestic product) are shown for three sub-Saharan African countries: Zambia (US\$4242/QALY), Mozambique (US\$1749/QALY) and Malawi (US\$1053/QALY) [30]. In Scenarios A and B, the cost-effectiveness of

**Table 3. Cost-effectiveness of point-of-care routine viral load monitoring compared with CD4 or clinical monitoring in three scenarios.**

	Unit cost of viral load test (US\$)	CD4 monitoring	POC viral load monitoring LOD (copies/ml):		
			1000	5000	10 000
<b>Scenario A</b>					
Compared with CD4 monitoring	5	n/a	8010	6430	5960
	10	n/a	13 860	12 230	11 740
	20	n/a	25 540	23 830	23 340
Compared with clinical monitoring	5	3300	4560	4140	4010
	10	3300	6120	5690	5550
	20	3300	9230	8780	8650
<b>Scenario B</b>					
Compared with CD4 monitoring	5	n/a	3010	2340	2230
	10	n/a	5470	4780	4740
	20	n/a	10 380	9670	9790
Compared with clinical monitoring	5	2590	2760	2490	2450
	10	2590	3790	3500	3470
	20	2590	5830	5530	5520
<b>Scenario C</b>					
Compared with CD4 monitoring	5	n/a	c/s	c/s	c/s
	10	n/a	760	520	460
	20	n/a	2460	2210	2170
Compared with clinical monitoring	5	2540	1110	990	960
	10	2540	1570	1440	1420
	20	2540	2500	2360	2340

Cost-effectiveness is presented as incremental cost-effectiveness ratio (US\$/quality adjusted life year) with 3% annual discounting. Cost-effectiveness of CD4 versus clinical monitoring is also shown. Scenario A (equal failure rates, HIV transmission not considered), Scenario B (equal failure rates, HIV transmission considered) and Scenario C (true treatment failure rate twice as high with CD4 or clinical compared to viral load monitoring, HIV transmission considered). c/s, cost-saving; LOD, limit of detection; n/a, not applicable; POC, point-of-care.



**Fig. 2. Cost-effectiveness of point-of-care routine viral load monitoring compared with CD4 (left panel) or clinical monitoring (right panel) as a function of the unit cost of a viral load test and the annual costs of second-line antiretroviral therapy in three scenarios: A (equal failure rates, no transmission), B (equal failure rates, transmission included) and C (failure rate two times higher with clinical or CD4 monitoring compared with viral load monitoring, transmission included). Limit of detection of the viral load test was assumed to be 1000 copies/ml. The black lines show the maximum limit of cost-effectiveness (three times per-capita gross domestic product) for selected southern African countries. ART, antiretroviral therapy; QALY, quality-adjusted life-year.**

routine viral load monitoring was highly sensitive to the cost of second-line therapy: the lower the cost of the second-line therapy, the more cost-effective viral load monitoring was. In Scenario C, the cost of the POC-VL test was the most important determinant when comparing with CD4 cell count monitoring, whereas the cost of second-line ART was again the determining factor in the comparison with clinical monitoring (Fig. 2).

In Scenario A, viral load monitoring could be considered cost-effective in Zambia if both viral load and second-line costs were minimised. In Scenario B, cost-effectiveness in Mozambique could be reached under the same conditions. The pattern changed in Scenario C when viral load monitoring was compared with CD4 cell count monitoring: as viral load monitoring now decreased the need for second-line therapy, cost-effectiveness increased with higher second-line therapy costs. Assuming a fixed price of US\$500 per year for second-line therapy (corresponding to current levels), a unit cost of US\$12 per viral load test would render viral load monitoring cost-effective in Malawi. A unit cost of US\$5 would be cost-saving.

## Discussion

This mathematical modelling study found that POC-VL monitoring likely not only improves survival slightly and

prevents new HIV infections but also increases the costs of ART. Viral load monitoring more accurately detects treatment failure, but as the risk of failure is low, the resulting benefit on survival was small. The cost-effectiveness was thus poor when, in Scenario A, we only considered this benefit of POC-VL monitoring. When we also included effects on adherence and HIV transmission, our estimates of cost-effectiveness improved. Nevertheless, POC-VL monitoring remained more expensive than CD4 cell count monitoring even when reducing the costs of POC tests to US\$5, as in most scenarios, viral load monitoring increased the need for second-line ART and required additional tests to confirm failure. To minimize unnecessary switches to second-line ART, the LOD of the POC-VL test should be 1000 copies/ml or higher.

We studied the cost-effectiveness of POC-VL monitoring under a range of assumptions, with results covering a wide range of ICERs from cost-saving to over US\$25000/QALY saved. We did not highlight any particular scenario, as the key determinants, that is the unit cost of the POC-VL test and the overall benefit of viral load monitoring, remain unknown. The assumed benefits in Scenarios B and C will also vary across different settings. In particular, the effect on HIV transmission will depend on the sexual behaviour, and the effect on adherence on the type of adherence intervention in place in a given programme.

Our study consistently supports the use of viral load tests with detection limits of 1000 copies/ml or above. This is at odds with current practice: a systematic review found that out of 39 studies from sub-Saharan Africa reporting a single virologic failure threshold, only two used 10 000 copies/ml as recommended by WHO at that time [31], and 12 used a threshold of 500 copies/ml or below [32]. Since then, WHO reduced the threshold from 10 000 to 5000 copies/ml [18]. Using a threshold below 1000 copies/ml is problematic because it results in a large number of DVUs. Additional measurements are required to determine whether a detectable viral load has returned to undetectable levels before switching to second-line ART. Moreover, some patients will have two consecutive DVUs and therefore switch to second-line therapy unnecessarily.

The cost-effectiveness of routine viral load compared with CD4 cell count monitoring has been investigated in several modelling studies [25,26,33–37] as well as a RCT [5] (Supplementary Table 4, <http://links.lww.com/QAD/A330>). The results from these studies vary and are difficult to compare because monitoring frequency, failure criteria, time horizon, costs and other parameters differed substantially between studies. Only Phillips *et al.* [35] modelled adherence, and Vijayaraghavan *et al.* [34] was the only study considering HIV transmission. Moreover, our study, together with the recent analysis by Hamers *et al.* [26], were the only two studies that replaced viral load monitoring with CD4 cell count monitoring, rather than combining them. The results of Hamers *et al.* [26] were clearly in favour of viral load monitoring: the ICER was \$86 per life-year when compared with CD4 cell count monitoring. However, Hamers *et al.* [26] investigated a laboratory-based, quantitative viral load test and assumed 100% sensitivity and specificity. We found that the poor specificity with low LODs led to many unnecessary switches. We feel that a specificity of 100% is unrealistic even with a quantitative test, and that the high cost-effectiveness reported by Hamers *et al.* [26] is questionable.

Our study has several limitations. The lack of empirical data on the effect of viral load monitoring on adherence and consequently the rate of virologic failure is one of them. In the Khayelitsha and Gugulethu township cohorts less than 5% of all patients failed virologically in the first year of ART. We assumed that without viral load monitoring, failure rates would be twice as high. Some support for a higher rate of virologic failure in the absence of viral load monitoring comes from cross-sectional studies of virologic failure from settings without routine viral load monitoring. For example, in the HIV/AIDS outpatient clinic of the Central Hospital in Yaoundé, Cameroon, the percentage of patients with detectable viral load at 1 year was 16% [38]. Similarly, 26% of individuals receiving ART in Luanda, Angola, had detectable viral load after a median of 1 year of follow-up

[39]. In a rural district of Malawi, 13% of patients on ART had detectable viral load at 10 months [40]. In all three studies, virologic failure was defined as a viral load above 1000 copies/ml. However, the key question – to what extent routine viral load monitoring prevents treatment failure – remains unanswered. More research is urgently needed to address this question.

Another limitation is the lack of data on long-term outcomes: simulations were not limited to a fixed time window, but modelled costs and benefits over the entire lifespan. We thus had to extrapolate the progression of the disease from the available data, which was restricted to, at most, 10 years of follow-up. Our results may therefore be sensitive to long-term outcomes, although their influence on model outcomes was reduced by annual discounting. Also, the data on disease progression from the two township ART programmes in Cape Town, which have electronic medical records and access to routine viral load and CD4 cell count monitoring and second-line ART, may not be applicable to other settings in sub-Saharan Africa. We did not explicitly model all potential benefits of POC-VL testing, for example improved retention in care [41] or the prevention of viral resistance. The effect on adherence was modelled by varying virologic failure rates, but costs of adherence interventions were not included. Finally, our estimates of new infections do not take into account transmission dynamics at the population level or differences in risk behaviours. We will expand the present model to address these shortcomings.

## Conclusion

Our study demonstrates that the impact of POC-VL monitoring on adherence and HIV transmission remains poorly understood despite the fact that these are the key factors that determine whether or not POC-VL tests will be cost-effective. To minimize unnecessary switches, the detection limit of the test should not be less than 1000 copies/ml, which has important implications for the design of these tests. In general, lowering the cost of any POC-VL test, and of second-line ART regimens, are the most promising strategies to maximize cost-effectiveness of monitoring ART with POC-VL tests.

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J.E., M.E. and O.K. designed the study. J.E., T.H. and O.K. developed the mathematical model. J.E., N.B. and L.S. performed the statistical analyses. D.G. and R.W. were involved in data acquisition and data management. J.C. provided expertise on health economics and cost data. J.E. wrote the first version of the manuscript, which was revised by M.E. and O.K. All authors contributed to the interpretation of the results and to the final version of the manuscript.

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### Conflicts of interest

Part of the salary of J.C. is paid by grants supporting the expansion of point-of-care testing in seven countries.

### References

- Keiser O, Orrell C, Egger M, Wood R, Brinkhof M, Furrer H, et al. **Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared.** *PLoS Med* 2008; **5**:e148.
- 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.
- Médecins Sans Frontières. Undetectable – how viral load monitoring can improve HIV treatment in developing countries. Geneva, Switzerland: Médecins Sans Frontières; 2012. [http://www.msfaccess.org/sites/default/files/MSF\\_assets/HIV\\_AIDS/Docs/MSF\\_ViralLoad\\_Report\\_FINAL\\_Sept2012\\_webres.pdf](http://www.msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/MSF_ViralLoad_Report_FINAL_Sept2012_webres.pdf). [Accessed 19 December 2012].
- Walensky RP, Ciaranello AL, Park JE, Freedberg KA. **Cost-effectiveness of laboratory monitoring in sub-Saharan Africa: a review of the current literature.** *Clin Infect Dis* 2010; **51**:85–92.
- Mermin J, Ekwueme JP, Were W, Degerman R, Bunnell R, Kaharuzza F, et al. **Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial.** *BMJ* 2011; **343**:d6792.
- Estill J, Aubrière C, Egger M, Johnson L, Wood R, Garone D, et al. **Viral load monitoring of antiretroviral therapy, cohort viral load and HIV transmission in Southern Africa: a mathematical modelling analysis.** *AIDS* 2012; **26**:1403–1413.
- Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Piyavong B, Chumpathat N, Chantratita W. **Options for a second-line antiretroviral regimen for HIV type 1-infected patients whose initial regimen of a fixed-dose combination of stavudine, lamivudine, and nevirapine fails.** *Clin Infect Dis* 2007; **44**:447–452.
- Keiser O, Chi BH, Gsponer T, Boulle A, Orrell C, Phiri S, et al. **Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in Southern Africa.** *AIDS* 2011; **25**:1761–1769.
- Hoffman CJ, Charalambous S, Sim J, Ledwaba J, Schwikkard G, Chaisson RE, et al. **Viremia, resuppression, and time to resistance in human immunodeficiency virus (HIV) subtype C during first-line antiretroviral therapy in South Africa.** *Clin Infect Dis* 2009; **49**:1928–1935.
- Signaloff KCE, Hamers RL, Wallis CL, Kityo C, Siwale M, Ivey P, et al. **Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa.** *J Acquir Immune Defic Syndr* 2011; **58**:23–31.
- National Department of Health, South Africa. Clinical guidelines for the management of HIV & AIDS in adults and adolescents. Pretoria, South Africa: National Department of Health; 2010. [http://www.who.int/hiv/pub/guidelines/south\\_africa\\_art.pdf](http://www.who.int/hiv/pub/guidelines/south_africa_art.pdf). [Accessed 19 December 2012].
- Ministry of Health, Botswana. Botswana National HIV/AIDS Treatment Guidelines: 2008 Version. Botswana: Ministry of Health; 2008. [http://www.moh.gov.bw/templates/moh/File/BOTSWANA%20HIV/AIDS%20TREATMENT%20%20GUIDE\\_LINES%20\(November%20%202008\).pdf](http://www.moh.gov.bw/templates/moh/File/BOTSWANA%20HIV/AIDS%20TREATMENT%20%20GUIDE_LINES%20(November%20%202008).pdf). [Accessed 19 December 2012].
- UNITAID. *HIV/AIDS diagnostic technology landscape*. 2nd ed. Geneva, Switzerland: UNITAID; 2012.
- Rousseau C. HIV point of care viral load test development – request for applications. Diagnostics innovation in China: bringing Chinese TB and HIV molecular diagnostics to market. Shanghai; 2012. <http://mat1.gimg.com/gongyi/2012/enzhen-duandahui/16ChristineRousseau.pdf>. [Accessed 19 December 2012].
- Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braistein P, et al. **Cohort Profile: The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa.** *Int J Epidemiol* 2012; **41**:1256–1264.
- 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.
- 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.
- World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva, Switzerland: World Health Organization; 2010. [http://whqlibdoc.who.int/publications/2010/9789241599764\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf). [Accessed 19 December 2012].
- Nettles RE, Kieffer TL, Kwon P, Monie D, Han Y, Parsons T, et al. **Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART.** *JAMA* 2005; **293**:817–829.
- Gallant JE. **Making sense of blips.** *J Infect Dis* 2007; **196**:1729–1731.
- Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. **Viral load and heterosexual transmission of human immunodeficiency virus type 1.** *N Engl J Med* 2000; **342**:921–929.
- Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. **Relation between HIV viral load and infectiousness: a model-based analysis.** *Lancet* 2008; **372**:314–320.
- Clinton Health Access Initiative. Antiretroviral (ARV) ceiling price list. Clinton Health Access Initiative; 2012. [http://www.clintonhealthaccess.org/files/CHAI\\_ARV\\_Ceiling\\_Price\\_List\\_May\\_2012.pdf](http://www.clintonhealthaccess.org/files/CHAI_ARV_Ceiling_Price_List_May_2012.pdf). [Accessed 19 December 2012].
- Kahn JG, Marseille E, Moore D, Bunnell R, Were W, Degerman R, et al. **CD4 cell count and viral load monitoring in patients undergoing antiretroviral therapy in Uganda: cost effectiveness study.** *BMJ* 2011; **343**:d6884.
- Braithwaite RS, Nucifora KA, Yiannoutsos CT, Musick B, Kimaiyo S, Diero L, et al. **Alternative antiretroviral monitoring strategies for HIV-infected patients in east Africa: opportunities to save more lives?** *J Int AIDS Soc* 2011; **14**:38.
- Hamers RL, Sawyer AW, Tuohy M, Stevens WS, de Wit TFR, Hill AM, et al. **Cost-effectiveness of laboratory monitoring for management of HIV treatment in sub-Saharan Africa: a model-based analysis.** *AIDS* 2012; **26**:1663.
- World Health Organization. Global burden of disease 2004 update: disability weights for diseases and conditions. Geneva, Switzerland: World Health Organization; 2004. [http://www.who.int/healthinfo/global\\_burden\\_disease/GBD2004\\_Disability\\_Weights.pdf](http://www.who.int/healthinfo/global_burden_disease/GBD2004_Disability_Weights.pdf). [Accessed 19 December 2012].
- 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.
- Maggioli F, Airolidi M, Kleinloog HD, Callegaro A, Ravasio V, Arici C, et al. **Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients.** *HIV Clin Trials* 2007; **8**:282–292.
- International Monetary Fund. World Economic Outlook Database. International Monetary Fund; 2012. <http://www.imf.org/external/pubs/ft/weo/2012/01/weodata/index.aspx> [Accessed 19 December 2012].

31. 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, Switzerland: World Health Organization; 2006. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>. [Accessed 19 December 2012].
32. Barth RE, van der Loeff MFS, Schuurman R, Hoepelman AIM, Wensing AMJ. **Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review.** *Lancet Infect Dis* 2010; **10**:155–166.
33. Bishai D, Colchero A, Durack DT. **The cost effectiveness of antiretroviral treatment strategies in resource-limited settings.** *AIDS* 2007; **21**:1333–1340.
34. Vijayaraghavan A, Efrusy MB, Mazonson PD, Ebrahim O, Sanne IM, Santas CC. **Cost-effectiveness of alternative strategies for initiating and monitoring highly active antiretroviral therapy in the developing world.** *J Acquir Immune Defic Syndr* 2007; **46**:91–100.
35. 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.
36. Bendavid E, Young SD, Katzenstein DA, Bayoumi AM, Sanders GD, Owens DK. **Cost-effectiveness of HIV monitoring strategies in resource-limited settings: a southern African analysis.** *Arch Intern Med* 2008; **168**:1910–1918.
37. Kimmel AD, Weinstein MC, Anglaret X, Goldie SJ, Losina E, Yazdanpanah Y, et al. **Laboratory monitoring to guide switching antiretroviral therapy in resource-limited settings: clinical benefits and cost-effectiveness.** *J Acquir Immune Defic Syndr* 2010; **54**:258–268.
38. Kouanfack C, Montavon C, Laurent C, Aghokeng A, Kenfack A, Bourgeois A, et al. **Low levels of antiretroviral-resistant HIV infection in a routine clinic in Cameroon that uses the World Health Organization (WHO) public health approach to monitor antiretroviral treatment and adequacy with the WHO recommendation for second-line treatment.** *Clin Infect Dis* 2009; **48**:1318–1322.
39. Garrido C, Zahonero N, Fernández D, Serrano D, Silva AR, Ferraria N, et al. **Subtype variability, virological response and drug resistance assessed on dried blood spots collected from HIV patients on antiretroviral therapy in Angola.** *J Antimicrob Chemother* 2008; **61**:694–698.
40. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, et al. **Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment.** *Lancet* 2006; **367**:1335–1342.
41. Jani IV, Sitoe NE, Alfai ER, Chongo PL, Quevedo JI, Rocha BM, et al. **Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study.** *Lancet* 2011; **378**:1572–1579.