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Hamers, R.L.

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Chapter 14

Cost-effectiveness of laboratory monitoring for management of HIV treatment in sub-Saharan Africa: a model-based analysis

Raph L Hamers, A Will Sawyer, Martin Tuohy, Wendy S Stevens, Tobias F Rinke de Wit, Andrew M Hill

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ABSTRACT

Objective

To compare the cost-effectiveness of three different strategies for long-term monitoring of antiretroviral therapy (ART) failure and regimen switching in sub-Saharan Africa: a symptom-based approach, or monitoring of either CD4 cell counts or plasma viral load (pVL).

Design

Markov model

Setting and participants

Hypothetical HIV-infected adult population who began first-line ART and subsequently had up to 6 years of follow-up.

Main outcome measures

Total cost, life expectancy and incremental cost-effectiveness ratio (ICER).

Results

A symptom-based approach yielded a life expectancy of 64.0 months at a total cost of US$ 4028 per person. All laboratory-based strategies, at testing intervals of 6 or 12 months, were cost-saving and improved life expectancy, compared with a symptom based approach. The life-expectancy gain was larger for pVL than for CD4 strategies at 6-monthly (2.3 and 0.9 months, respectively) and 12-monthly testing (2.0 and 0.8 months, respectively). Cost-savings of 6-monthly pVL or CD4 testing were similar (US$ 630 and 621, respectively), whereas 12-monthly CD4 cell counts were more cost-saving than 12-monthly pVL (US$ 1132 and 880, respectively). Testing every 12 months – rather than every 6 months – decreased the ICER by 102% for CD4 cell count and 67% for pVL. These findings were robust to a wide range of deterministic sensitivity analyses, but were sensitive to the specificity and costs of diagnostic tests.

Conclusion

Additional diagnostic costs are balanced by cost-savings from avoiding unnecessary switching due to misdiagnosis of ART failure. Routine pVL monitoring may be preferred as a replacement for CD4 cell counts because of its additional public health advantages in preventing drug-resistance, supporting adherence and reducing HIV transmission.

INTRODUCTION

Combination antiretroviral therapy (ART) has been shown to dramatically improve survival especially in sub-Saharan Africa [1], a region that continues to be the most affected by the global HIV/AIDS epidemic [2]. During the past decade, ART has been scaled-up as widely and rapidly as possible to reach millions of HIV-infected people in resource-limited countries, although access is not yet universal [3]. A proportion of patients receiving ART will inevitably experience therapy failure, mainly due to poor adherence, treatment interruptions or drug interactions, putting them at increased risk of HIV-related morbidity and mortality.

In most ART programmes in resource-limited settings, management of ART effectiveness and decisions to switch from first-line to second-line therapy are based on the occurrence of new HIV-related clinical disease and, if available, CD4 cell count changes, rather than on the basis of plasma viral load (pVL) which is the standard-of-care in high-income countries [4,5]. The DART trial in Uganda and Zimbabwe – which did not assess pVL testing – demonstrated that CD4 cell count monitoring in the first 5 years of ART yielded a small but significant benefit in terms of disease progression and mortality, probably owing to earlier switching to second-line ART, compared to a clinically driven approach [6]. Real-time pVL testing can more accurately identify people who are experiencing ART failure than CD4 cell counts or clinically driven monitoring, and several studies in sub-Saharan Africa have shown that WHO-defined clinical and immunological criteria poorly predict virological failure in both adults [7–10] and children [11] receiving first-line ART. pVL monitoring additionally avoids the incremental costs associated with unnecessary switches to more expensive second-line regimens in patients without real virological failure [12], prevents drug-resistance accumulation [12–14] and subsequent resistance transmission [15] and reduces HIV transmission [16]. Previous model based evaluations of cost-effectiveness have yielded conflicting results regarding the survival gains and cost effectiveness associated with diagnostic strategies based on CD4 cell counts alone, or additive approaches that combined CD4 and pVL assessments [17–19].

Routine laboratory monitoring of CD4 cell counts or pVL requires substantial investment in laboratory infrastructure, equipment, training and arrangements for maintenance and quality control. As this could divert resources away from scaling-up access to ART, it is critical to establish whether this would be cost-effective. Our aim was therefore to develop a model to assess the total cost, life expectancy and cost-effectiveness of three diagnostic strategies for long-term ART management in sub- Saharan Africa: a symptom-based approach, or monitoring of either CD4 cell counts or pVL, with diagnostic testing at 6 or 12 months intervals.

METHODS

Procedure

From the perspective of the WHO-recommended public health model of ART delivery in resource-limited countries, which includes standard first-line, second-line and third-line regimens and limited laboratory monitoring [20], we developed a Markov model using MS Excel 2010 to estimate life expectancy and costs for a hypothetical adult population with HIV infection who began first-line ART, in accordance with 2010 WHO guidelines. Figure 1 illustrates the states in the model and all possible transitions between them during each cycle. We used a cycle of 6 or 12 months duration to correspond with the typical interval between diagnostic evaluations in current clinical practice. The first-line regimen could be switched to a second-line regimen when the criterion for therapy failure was fulfilled, dependent on the diagnostic strategy. While being treated, a patient is considered either a 'success' or a 'failure' with respect to the current treatment, meaning that their pVL is either below or above a critical threshold. The diagnostic strategies differ in their

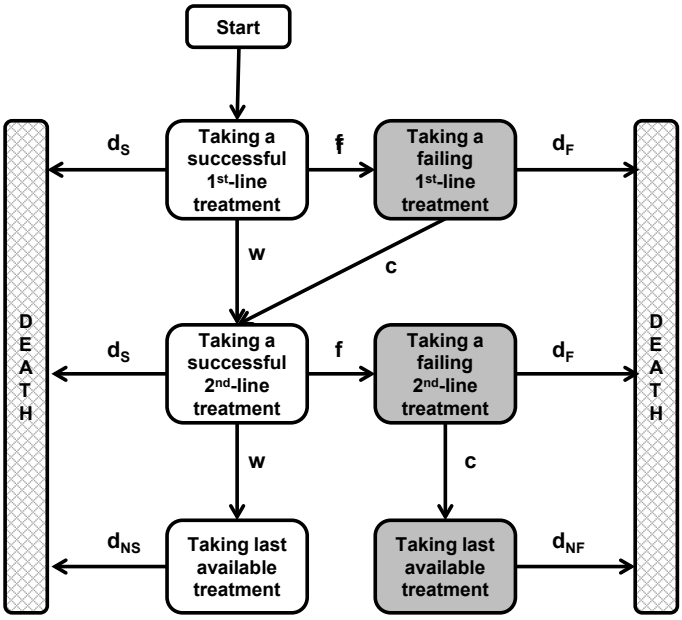

Figure 1: Markov model, a simplified transition-state diagram.
The probabilities in the model are: (f) the patient's viral load has risen above a critical threshold but this has not yet been detected and the patient is continuing on the failed therapy; (w) the patient has been wrongfully diagnosed as having failed therapy and has moved to the next line of therapy; (c) the patient's therapy failure is detected by either clinical judgment or a diagnostic test; (d_s) the patient dies while being successfully treated; (d_f) the patient dies while taking a failed therapy; (d_{NS}) the patient dies while not receiving further therapy after a false-positive diagnosis of therapy failure; and, (d_{NF}) the patient dies while not receiving further therapy after a true-positive diagnosis of therapy failure.

ability to detect treatment failures and to missclassify patients as treatment failures when they are actually responding to treatment. We ran our model to correspond to 6 years of follow-up and calculated the time spent in each health state. Attributing a cost to each health state, total costs and incremental cost-effectiveness ratios (ICERs) were estimated for each of the diagnostic strategies. We expressed our findings in terms of the total cost, life expectancy and the incremental ICER, that is incremental cost per life-year gained. In developing countries, an ICER of less than twice the per capita gross domestic product is generally thought cost-effective by policy makers (http://www.who.int/choice/en/).

For the symptom-based approach, therapy failure was defined as the occurrence of either a new or recurrent WHO-defined stage 3 or 4 clinical event at least 6 months after the start of ART [7]. For monitoring of CD4 cell count, therapy failure was defined as either a return to a CD4 cell count below the pre-therapy baseline, or a fall in CD4 cell count to less than 50% of the maximum value while on therapy [7]. Therapy failure by pVL criteria was defined as a value greater than 400 HIV RNA copies/ml, as this was the cut-off used in most published studies [21].

We assumed that the probability of treatment failure was highest during the first 3 months of ART and then declined over time. The initial probability of virological failure in the first 3 months of ART was based on a meta-analysis reported by Barth and et al. [21], computed as $1 - \sqrt{(1-22.0\%)} = 11.7\%$ (table 1). The subsequent probability of virological failure is believed to become constant with time [22]; as no data on limiting probability were available from Africa, we used the data from a UK cohort, computed as $1 - \sqrt[4]{(1-3.0\%)} = 0.76\%$ per three months [22]. Mortality in people receiving first-line ARTon data from the ART-LINC cohort was computed as $1 - \sqrt[4]{(1-2.2\%)} = 0.55\%$ per 3 months for those on a successful regimen and $1 - \sqrt[4]{(1-11.7\%)} = 3.1\%$ per 3 months for those who experienced first-line failure [23]. Mortality in people receiving second-line ART on data was estimated from the Médecins Sans Frontières ART programmes in Africa and Asia, as $1 - \sqrt[4]{(1-5.4\%)} = 1.4\%$ per 3 months [24]. We estimated mortality when no further treatment was available after a true or false diagnosis of failure as $1 - \sqrt[4]{(1-9.2\%)} = 2.4\%$ per 3 months [24] and used this same estimate for mortality if no treatment was available. We based the sensitivity and specificity of clinical judgment and CD4 cell counts for identifying virological failure on a study in South Africa by Mee et al. [7] (table 1).

Our analysis included the cost of diagnostic tests, ART and end-of-life care (table 1). The unit costs of first-line and second-line therapy were drawn from a costing study conducted at a large urban public sector site in Johannesburg, South Africa, in 2010 [25]. ART cost incorporated the cost of the most commonly used generic antiretroviral drugs

Table 1. Base-case model inputs

Variables	Data	Sources
Risk of treatment failure		
Initial probability of virological failure	11.7% per 3 months	Estimated with meta-analysis by Barth et al. (19)
Limiting probability of virological failure	0.76% per 3 months	Estimated with Benzie et al. (20)
Time to convergence	1.0 year	
Mortality		
Probability of death if successful regimen	0.55% per 3 months	Estimated with Keiser et al. (21)
Probability of death if first-line failure	3.1% per 3 months	As above
Probability of death if second-line failure	1.4% per 3 months	Estimated with Pujades-Rodriges et al. (22)
Probability of death if no treatment available, or no further treatment available after false diagnosis of failure	2.4% per 3 months	As above
Probability of death if no further treatment available after true diagnosis of failure	2.4% per 3 months	As above
Diagnosis inputs		
Clinical diagnosis		
False-positive proportion (1-specificity)	11.9%	Mee et al. (7)
False-negative proportion (1-sensitivity)	84.8%	As above
CD4 cell counts		
False-positive proportion (1-specificity)	4.2%	As above
False-negative proportion (1-sensitivity)	78.8%	As above
HIV viral load		
False-positive proportion (1-specificity)	0%	By definition
False-negative proportion (1-sensitivity)	0%	As above
Costs		
Unit cost of ART per patient per year		
First-line therapy	$ 403	Long et al. (23)
Second-line therapy	$ 1107	As above
Unit cost of laboratory test		
CD4 cell count	$ 9	Assumption based on South African public sector 2011
HIV plasma viral load	$ 36	Long et al. (23)
One-off cost of end-of-life care	$ 50	
Modelling period		
Cohort follow-up time	up to 6 years	

and other drugs, outpatient visits and infrastructure and other fixed costs and excluded inpatient care and laboratory tests. The all-in unit cost of a pVL test was drawn from the same study [25]. The all-in unit cost of a CD4 cell count was based on 2011 prices

in the public health sector in South Africa (W. Stevens, personal communication). All diagnostic costs accounted for equipment, consumables, maintenance and staff time. We assumed a one-off cost for end-of-life care, including hospitalization and illnesses. All costs are presented in US$ (November 2011).

Uncertainty

We performed deterministic sensitivity analyses to test the robustness of the model assumptions and data sources, using the point estimates of our model parameters. Sensitivity analyses considered a wide range of parameters in the model and varied therapy failure and mortality rates, sensitivity and specificity of diagnostic tests, costs of diagnostics, ART and end-of-life care and coverage of first-line, second-line and third-line ART. The sensitivity analyses included cost estimates of ART (2011) [26] and diagnostics (2009) [27] based on the latest Clinton HIV/AIDS Foundation (CHAI) prices. The lowest negotiated CHAI prices for the recommended first-line regimen of tenofovir, lamivudine, efavirenz (US$ 169 per year) and second-line regimen of atazanavir/ritonavir, tenofovir, lamivudine (US$ 395 per year) were used [26] and both estimates were increased by US$ 300 to cover for fixed costs of medical care. Both low-end and high-end CHAI estimates for diagnostic tests were considered [27].

RESULTS

Base-case analysis

In the base-case analysis, the symptom-based approach yielded a life expectancy of 64.0 months at a total cost of US$ 4028 per person. All laboratory-based diagnostic strategies, at testing intervals of either 6 or 12 months, were cost-saving and improved life expectancy, compared with a symptom-based approach (table 2 and figure 2). The gain in life expectancy was larger for pVL strategies than CD4 cell count strategies, at both 6 (2.3 and 0.9 months, respectively) and 12 months testing intervals (2.0 and 0.8 months, respectively). Cost-savings of pVL or CD4 cell counts every 6 months were similar (US$ -630 and -621, respectively), whereas CD4 testing every 12 months was more cost-saving than pVL testing every 12 months (US$ -1132 and -880, respectively). Compared with CD4 cell counts every 6 months, pVL testing every 12 months reduced costs by US$ 249. CD4 cell counts every 12 months was a more cost-effective strategy than CD4 cell counts every 6 months, or pVL testing every 6 or 12 months. For equivalent strategies, testing every 12 months rather than every 6 months was associated with a minimum life expectancy loss of 3 days for CD4 strategy and 11 days for pVL strategy, whereas the additional cost-savings were substantial (102% decrease in the ICER for CD4 cell count and 67% for pVL) (table 2).

Table 2. Base-case analysis results – cost-effectiveness

Monitoring strategy	Total life expectancy (months)	Total cost per person (US$)	Gain in life expectancy (months) *	Incremental costs per person (US$)*	ICER (US$/LYG)*
Symptom-based approach	64.0	4028	Reference	Reference	Reference
CD4-only every 6 months	64.9	3397	0.9	-630	-8024
CD4-only every 12 months	64.8	2896	0.8	-1132	-16193
pVL-only every 6 months	66.3	3407	2.3	-621	-3183
pVL-only every 12 months	66.0	3148	2.0	-880	-5319

pVL,plasma viral load; ICER, incremental cost effectiveness ratio, expressed as cost (US$) per life-years gained; na, not applicable.

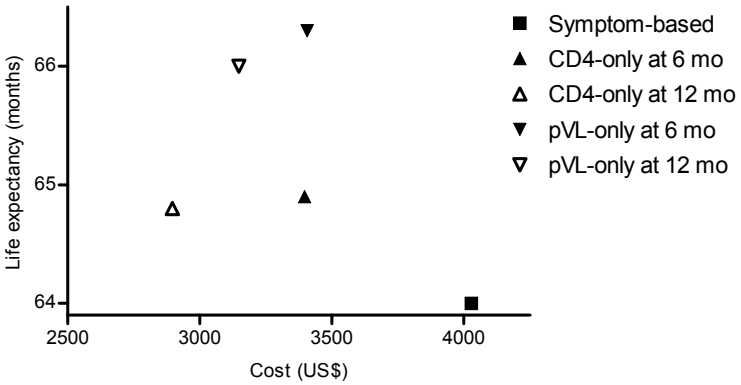

Figure 2. Base-case analysis results - cost-effectiveness.
Figure shows life-expectancy and total cost per patient over six years modeling period. All laboratory strategies were associated with higher life expectancy and reduced cost. A longer test interval substantively reduced cost. mo, months; pVL, viral load.

Sensitivity analysis

A wide range of sensitivity analyses varying the base-case assumptions and model parameters also showed that all laboratory-based diagnostic strategies were cost-saving, relative to a symptom-based approach (table 3). The superiority of laboratory-based diagnostic strategies was not sensitive to variations in mortality and failure rates.

The cost-effectiveness of laboratory-based diagnostic strategies was sensitive to the specificity, and to a lesser extent the sensitivity, of clinical judgment and the diagnostic tests. If the specificity of clinical judgement was increased to 95%, laboratory monitoring of either CD4 or pVL was cost-saving for 12-monthly intervals and cost-effective for 6-monthly intervals. Decreasing the specificity of CD4 to 90%, 6 or 12 monthly CD4 monitoring remained cost-saving. Decreasing the specificity of pVL testing to 95%, pVL

Table 3. Sensitivity analyses results

	Costs versus symptom-based approach				ICER versus symptom-based approach			
	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly
Base-case (deterministic)	-630	-1132	-621	-880	-8024	-16193	-3183	-5319
Sensitivity analyses (deterministic)								
Failure rates								
SA1: initial probability increased by 50%	-515	-1045	-352	-602	-6463	-16389	-1585	-3179
SA2: initial probability decreased by 50%	-760	-1227	-930	-1186	-10011	-16413	-5940	-8839
SA3: limiting probability increased by 20%	-623	-1127	-599	-858	-8005	-16453	-3058	-5185
SA4: limiting probability decreased by 20%	-638	-1136	-644	-902	-8042	-15939	-3314	-5455
SA5: time to convergence set to 0.5 years	-699	-1182	-789	-1057	-8808	-14859	-4421	-6825
SA6: SA1 and SA3 combined	-509	-1041	-335	-586	-6442	-16634	-1508	-3093
SA7: SA2 and SA4 combined	-770	-1233	-961	-1215	-10020	-16133	-6190	-9076
Mortality rates								
SA8: probability of death if successful regimen increased by 20%	-625	-1123	-618	-875	-8641	-17702	-3395	-5688
SA9: probability of death if successful regimen decreased by 20%	-635	-1140	-624	-884	-7484	-14907	-2994	-4990
SA10: probability of death if first-line failure increased by 20%	-633	-1137	-609	-882	-7983	-17838	-2800	-4978
SA11: probability of death if first-line failure decreased by 20%	-628	-1126	-635	-879	-8104	-14714	-3721	-5782
SA12: probability of death if second-line failure increased by 20%	-627	-1126	-615	-874	-7700	-15093	-3071	-5132
SA13: probability of death if second-line failure decreased by 20%	-634	-1137	-627	-886	-8382	-17484	-3305	-5522
SA14: probability of death if no treatment available, or no further treatment available after true or false diagnosis of failure increased by 20%	-612	-1107	-603	-857	-6583	-12352	-2877	-4646

Table 3 (continued)

	Costs versus symptom-based approach				ICER versus symptom-based approach			
	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly
SA15: probability of death if no treatment available, or no further treatment available after true or false diagnosis of failure decreased by 20%	-649	-1157	-640	-904	-10212	-23325	-3561	-6199
Sensitivity and specificity								
SA16: sensitivity and specificity CD4=VL=100%	-850	-995	-621	-880	-4358	-6013	-3183	-5319
SA17: sensitivity set to 100% for all three options	-667	-1034	-1008	-1266	-7580	-11927	-8241	-13680
SA18: clinical diagnosis specificity set to 80%	-1060	-1562	-1051	-1310	-7012	-10946	-3927	-5504
SA19: clinical diagnosis specificity set to 90%	-475	-976	-466	-724	-7707	-18400	-2614	-4880
SA20: clinical diagnosis specificity set to 95%	37	-464	47	-212	1500	-28267	331	-1894
SA21: clinical diagnosis sensitivity set to 10%	-534	-1035	-525	-784	-5699	-12156	-2496	-4339
SA22: clinical diagnosis sensitivity set to 20%	-704	-1205	-695	-954	-10617	-20874	-3803	-6230
SA23: CD4 specificity set to 90%	-17	-667	na	na	-513	-10382	na	na
SA24: CD4 specificity set to 100%	-1235	-1499	na	na	-12658	-21217	na	na
SA25: CD4 sensitivity set to 15%	-728	-1214	na	na	-12235	-20795	na	na
SA26: CD4 sensitivity set to 20%	-645	-1144	na	na	-8514	-16795	na	na
SA27: CD4 sensitivity set to 25%	-579	-1082	na	na	-6502	-14005	na	na
SA28: CD4 sensitivity set to 30%	-528	-1026	na	na	-5263	-11964	na	na
SA29: pVL specificity set to 95%	na	na	5405	-470	na	na	36	-2994
SA30: pVL sensitivity set to 95%	na	na	-628	-893	na	na	-3258	-5514
Diagnostic cost								
SA31: CD4 set to $ 2.50, VL set to $28 (CHAI low-end)	-679	-1159	-689	-914	-8633	-16558	-3531	-5525
SA32: CD4 set to $ 8, VL set to $29 (CHAI high-end)	-638	-1136	-680	-910	-8114	-16221	-3487	-5500

Table 3 (continued)

	Costs versus symptom-based approach				ICER versus symptom-based approach			
	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly	CD4 6-monthly	CD4 12-monthly	pVL-only 6-monthly	pVL-only 12-monthly
SA33: pVL set to $100	na	na	-79	-606	na	na	-406	-3664
SA34: pVL set to $25	na	na	-714	-927	na	na	-3661	-5603
ART cost								
SA35: ART cost decreased by 20%	-491	-898	-437	-674	-6251	-12822	-2239	-4073
SA36: first-line set to $169, second-line set to $395 including drugs only (CHAI prices)	-155	-337	13	-175	-1971	-4815	68	-1057
SA37: first-line set to $469, second-line set to $695 including drugs and fixed costs of medical care ($300) (CHAI prices)	-128	-328	78	-131	-1629	-4689	401	-794
SA38: SA32 and SA37 combined including diagnostics, drugs and fixed costs (CHAI prices)	-135	-333	19	-161	-1724	-4750	97	-975
Cost of end-of-life care								
SA39: cost of end-of-life care doubled	-633	-1133	-625	-884	-8052	-16220	-3205	-5342
Line of ART with laboratory monitoring								
SA40: second-line monitoring added	-606	-1123	-547	-844	-7718	-16074	-2803	-5103
ART coverage								
SA41: second-line coverage set to 50%	-584	-1043	-565	-806	-4922	-6976	-2336	-3456
SA42: second-line coverage set to 10%	-546	-973	-521	-748	-3628	-4561	-1863	-2599
SA43: first-line set to 50%, second-line set to 10%	-273	-546	-260	-433	-3628	-5056	-1863	-2986
SA44: first-line set to 30%, second-line set to 1%	-161	-371	-153	-304	-3409	-5281	-1774	-3309
SA45: third-line coverage set to 100%, combined with SA40	-660	-1199	-602	-915	-18960	-155208	-3985	-8628

ICER, incremental cost-effectiveness ratio, expressed as cost (US$) per life-years gained; SA, sensitivity analysis; CHAI, Clinton HIV/AIDS Foundation; VL, HIV viral load.

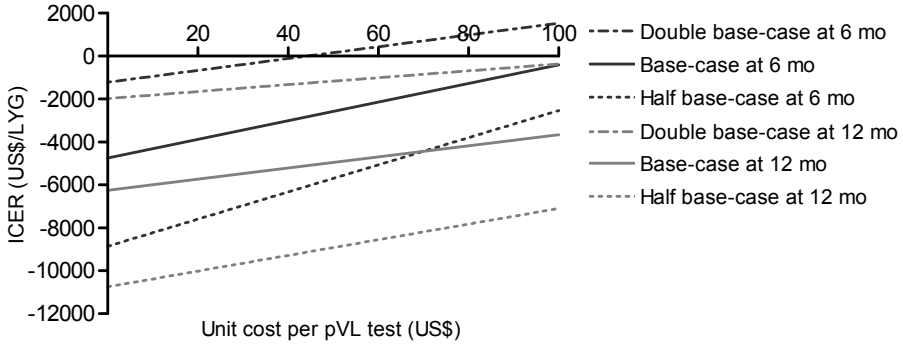

Figure 3. Sensitivity analysis of plasma viral load only monitoring strategies.
The ICER of pVL-only monitoring, compared with a symptom-based approach, is represented at the y-axis. Half or double base-case indicates half or double the rate of virologic failure, respectively, compared with the base-case. A negative ICER suggests that a strategy was cost-saving, compared with a symptom-based strategy. The ICER was sensitive to the per-test cost, the monitoring interval, and the rate of virologic failure. ICER, incremental cost-effectiveness ratio; LYG, life-year gained; pVL, plasma viral load.

monitoring was cost-saving for 12-monthly intervals and cost-effective for 6-monthly intervals.

The cost-effectiveness of laboratory-based diagnostic strategies was also somewhat sensitive to ART cost. In sensitivity analyses that used CHAI prices of ART, pVL testing every 6 months was cost-effective and all other laboratory-based strategies were cost-saving. Laboratory-based diagnostic strategies remained cost saving even if coverage of first and second line was restricted to as low as 30 and 1%, respectively. The cost-effectiveness of laboratory-based strategies was further increased if we assumed availability of third-line therapy, including diagnostic monitoring of the preceding second-line therapy.

The cost-effectiveness of pVL strategies was sensitive to diagnostic cost, monitoring interval and the rate of virological failure (figure 3). If the per test cost was increased to US$ 100, both the 6 and 12 monthly pVL strategies remained cost-saving. pVL strategies were more cost-saving than CD4 strategies if the pVL test cost was reduced. For instance, for 6-monthly test intervals, pVL was more cost-saving then CD4, at a pVL test cost of US$ 34 or less.

DISCUSSION

Our findings show that laboratory-based diagnostic monitoring, with either CD4 cell counts or pVL testing, is cost-saving for long-term ART management in sub-Saharan

Africa, compared with a symptom-based approach using WHO-defined clinical criteria. This conclusion is robust when assessed with a wide range of sensitivity analyses around the base-case. The savings with laboratory-based diagnostic strategies – despite additional diagnostic costs – were primarily because of the better performance (i.e. higher test specificity) at identifying and diagnosing those patients who have genuinely failing on their current therapy and who are eligible for regimen switch, so averting the incremental health expenditure of unnecessary switches to more expensive second-line regimens and intensified monitoring. For equivalent strategies, testing every 12 months rather than every 6 months substantially reduced cost, while not reducing life expectancy. This finding suggests that routine laboratory testing once every year may be sufficient, restricting more frequent testing to high-risk cases only.

Our findings seem robust for several reasons. First, varying diagnostic test performance, which may differ across assays, settings and populations [7–11], did not change our conclusions. Second, pVL strategies remained cost-saving even at substantially increased pVL test costs – which may be more realistic in other African countries. Third, the treatment costs we included were based on the most commonly used generic drug costs in South Africa and in the CHAI pricing list – this is a conservative assumption (i.e. it does not favour laboratory monitoring), as usual care possibly includes a wider range of more expensive drugs leading to underestimation of the benefits of more efficient diagnosis. Fourth, diagnostics can only be cost-effective when used in the context of treatment, whereas actual coverage of first-line, second-line and third-line ART differs between countries in the sub-Saharan African region [3]. Our base-case model demonstrated that laboratory-based diagnostic strategies were associated with cost-savings in settings with universal access to first-line and second-line ART. Additionally, sensitivity analyses showed that diagnostic monitoring was also cost-saving in settings where access to ART is still restricted. Therefore, our findings have value for health policymakers in countries that are close to achieving universal access (e.g. Namibia, Botswana and Rwanda), but also for countries with a less advanced ART scale-up [3]. Of note, the 2010 WHO ART guidelines recommend that national programs should develop policies for third-line therapy [20]; our model suggests that in settings where third-line coverage is assumed to be universal, diagnostic monitoring will reduce costs.

Although with current test cost estimates, 12-monthly CD4 monitoring may seem the most cost-effective strategy, there are a number of arguments that would favour pVL monitoring. First, the cost-effectiveness of pVL monitoring strongly depends on the test cost and the cost-effectiveness will further increase if the test price is reduced. Second, additional public health benefits of pVL monitoring not captured by the model might be valuable. These include fewer accumulation of drug-resistance mutations [13] and re-

duced subsequent resistance transmission [15], operational support tool for improving adherence [28], reduced incidence of opportunistic infections and mortality [29] with resultant increased economic productivity and reduced HIV transmission by limiting the number of persons with non-suppressed HIV replication [16]. Therefore, the model may underestimate the overall benefits of pVL testing. Third, challenges related to the implementation of pVL monitoring in resource-limited settings are increasingly becoming surmountable, as recent advances in pVL technology enable lower per-test cost as well as simpler machines that require less infrastructure, maintenance and technical expertise [30].

This model is the first cost-effectiveness analysis we know of that compares different diagnostic strategies for ART management that includes a pVL-only strategy – without concomitant CD4 cell counts. Previous studies in developed countries have suggested that there is limited benefit from continued measurements of CD4 cell counts in patients who have achieved full pVL suppression, which can be considered a marker for sustained high CD4 cell counts (>350 cells/μl) [31, 32]. Use of CD4 cell counts could thus be restricted to establish eligibility for ART initiation and to determine the need for prophylaxis for opportunistic infections in patients who have a detectable pVL during ART. Recently updated national ART guidelines in some countries (e.g. Malawi [33]) no longer recommend the use of CD4 cell counts for routine monitoring of patients on ART, instead they recommend routine pVL monitoring.

The feasibility and cost-effectiveness of pVL monitoring in the context of scaling-up ART in resource-limited settings have been debated [34–36], and WHO guidelines stipulate that pVL monitoring is desirable, but not essential, for a public health approach to ART [20]. Previous empirical research has suggested that routine pVL monitoring may yield limited survival benefit in the short-term [37,38]. Of note, a recent cluster randomized trial in Zambia found that routine 6-monthly pVL monitoring did not reduce all-cause mortality over the first 36 months of ART, compared with the current standard-of-care of using pVL sparingly to adjudicate discrepancies between CD4 and clinical assessments, although routine pVL monitoring resulted in earlier regimen change [39]. However, longer term follow-up data are not available. A previous modelling study, which used 2007 data from southern Africa, reported that immunological monitoring was cost-effective compared with symptom-driven strategies and that the addition of pVL monitoring led to a 2-month gain in life expectancy [17]. However, the ICER was less favourable for pVL than for CD4 cell count monitoring. Another modelling exercise also found that pVL monitoring provided a moderate long-term advantage, but the high associated costs were not deemed cost-effective for most resource-limited settings [18]. Our model, which was based on up-to-date cost data and included a pVL-only strategy – rather than

a more expensive additive diagnostic strategy – demonstrated a beneficial relative cost-effectiveness for laboratory-based diagnostic strategies.

The assumptions included in the model are a source of potential limitations. pVL testing was our reference standard for diagnosing therapy failure and was therefore apportioned 100% sensitivity and specificity. We acknowledge that very few diagnostic tests have perfect test performance. As might be expected, our conclusions based on the model were somewhat sensitive to variations in the sensitivity and specificity values. In addition, few published data were available to inform the estimates of costs related to the provision of healthcare, particularly outside of South Africa, which may limit the generalizability of the results to other settings. Publishing these costs in future studies would improve the accuracy of this and future economic analyses. Available data on second-line failure and mortality rates from resource-limited countries were somewhat limited, although the estimates we used concur with a recently published meta-analysis [40]. Finally, the current study did not assess paediatric populations; given that recent studies suggest that in children, CD4 cell counts perform even worse compared with pVL [11], it seems reasonable to assume that routine pVL monitoring will also be beneficial in children. Further research that would improve the model would include additional studies of the relative sensitivity and specificity of diagnostic testing in different subpopulations and settings, access to detailed data of healthcare costs in different countries and inclusion of the additional public-health advantages of pVL monitoring, particularly the potential impact of routine pVL monitoring in preventing secondary HIV infections [16].

In conclusion, we have identified that laboratory-based diagnostic strategies can provide substantial cost savings for long-term ART management in sub-Saharan Africa by averting the high costs of unnecessary switching to second-line therapy. pVL monitoring may be preferred over CD4 cell counts because of its important combined public-health advantages. Routine pVL monitoring, at least annually, in ART programmes should be seriously considered. As the number of persons receiving ART rises and test prices go down, the potential health benefit and cost-savings from the use of laboratory monitoring will further increase.

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Contributors

T.F.R.W., M.T. and A.M.H. conceived the study. A.W.S. designed and programmed the model, with input from R.L.H., T.F.R.W. and A.M.H. The cost-effectiveness analyses were undertaken by R.L.H. supported by A.W.S. and A.M.H. W.S. gave advice on the monitoring of HIV treatment and advised on issues particular to developing countries. R.L.H. wrote the first draft of the manuscript, with the assistance of A.W.S. and A.M.H. A.W.S., A.M.H., M.T. and T.F.R.W. helped with the interpretation of the results and critically reviewed and edited the paper. All authors read, commented on and approved the final manuscript.

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