

ARTICLE **OPEN**

Sustainable HIV treatment in Africa through viral-load-informed differentiated care

Working Group on Modelling of Antiretroviral Therapy Monitoring Strategies in Sub-Saharan Africa*

There are inefficiencies in current approaches to monitoring patients on antiretroviral therapy in sub-Saharan Africa. Patients typically attend clinics every 1 to 3 months for clinical assessment. The clinic costs are comparable with the costs of the drugs themselves and CD4 counts are measured every 6 months, but patients are rarely switched to second-line therapies. To ensure sustainability of treatment programmes, a transition to more cost-effective delivery of antiretroviral therapy is needed. In contrast to the CD4 count, measurement of the level of HIV RNA in plasma (the viral load) provides a direct measure of the current treatment effect. Viral-load-informed differentiated care is a means of tailoring care so that those with suppressed viral load visit the clinic less frequently and attention is focussed on those with unsuppressed viral load to promote adherence and timely switching to a second-line regimen. The most feasible approach to measuring viral load in many countries is to collect dried blood spot samples for testing in regional laboratories; however, there have been concerns over the sensitivity and specificity of this approach to define treatment failure and the delay in returning results to the clinic. We use modelling to synthesize evidence and evaluate the cost-effectiveness of viral-load-informed differentiated care, accounting for limitations of dried blood sample testing. We find that viral-load-informed differentiated care using dried blood sample testing is cost-effective and is a recommended strategy for patient monitoring, although further empirical evidence as the approach is rolled out would be of value. We also explore the potential benefits of point-of-care viral load tests that may become available in the future.

Nature 528, S68–S76 (3 December 2015), DOI: 10.1038/nature16046

This article has not been written or reviewed by *Nature* editors. *Nature* accepts no responsibility for the accuracy of the information provided.

Monitoring people on antiretroviral therapy (ART) cost-effectively is crucial for the sustainability of ART programmes in sub-Saharan Africa. In most countries, patients are required to attend clinics every 1 to 3 months for clinical assessment. The cost of which — for personnel, infrastructure and maintenance — is comparable with costs of the antiretroviral drugs themselves^{1–3}. In most settings, patients are monitored by a CD4 count measurement every 6 months with clinical observation at least every 3 months, but they are rarely switched to second-line regimens. A reduction in visit frequency for patients who do not require an adherence intervention or a switch to second-line ART would benefit programmes by reducing costs and benefit patients by saving travel costs and time away from work, possibly lowering the rate of default from care⁴.

The biomarker that most directly measures the ongoing effect of ART is the HIV RNA level in plasma (the viral load). If viral load is suppressed, this indicates that the patient is adhering to the drug regimen and does not carry drug-resistant virus. Data from high-income countries suggest that after 1–2 years of ART with viral-load suppression the visit frequency can be reduced. If the viral load is not suppressed this suggests that there is a need for improved adherence and/or a switch in regimen. In most countries in sub-Saharan Africa, measurement of viral load is not widely available. Quantification of HIV RNA requires sophisticated facilities and skilled staff and the costs have been high, although costs have substantially decreased in the past 5 years^{5,6}. Modelling studies have indicated that there is a benefit to viral-load monitoring compared with monitoring strategies based on the CD4 count or clinical observation^{7–16}, but viral-load monitoring has not been found to be cost-effective^{7,10–14}, owing to the cost of viral-load tests and second-line regimens. Currently, the most feasible approach to begin to measure viral load in many

countries is to collect samples as dried blood spots (DBS). DBS are stable at ambient temperature and can be prepared from capillary whole blood, eliminating the need for phlebotomy services¹⁵. Using existing networks for early infant HIV diagnosis, they can be transported to a regional or national laboratory with results subsequently returned to the clinic by, for example, mobile phone text messaging. However, the presence of cells and low sample volume in DBS specimens means that sensitivity and specificity for detecting whether the level is above the 1,000 copies per millilitre threshold that is used to define viral suppression are imperfect and it is unclear if the approach is adequate^{5,16–27}. Looking to the future, it is anticipated that point-of-care (POC) tests — tests that enable a decision to be made about patient management during the same visit that the sample is taken — may become widely available²⁸, and this may result in greater accuracy than the use of DBS, as well as facilitating rapid action based on the test result.

In the light of these issues, we consider how HIV treatment programmes in low-income countries in sub-Saharan Africa should monitor patients on ART in a way that is likely to lead to the greatest population health gains from the limited resources available²⁹. We update a model previously used to compare monitoring strategies, incorporating new lower costs and the potential for viral-load-informed 'differentiated care' based on reducing clinic visit costs by reducing visit frequency among virally-suppressed individuals^{30,31}.

METHODS

The HIV Synthesis transmission model is an individual-based stochastic model of heterosexual transmission, natural history, clinical disease and treatment of HIV infection that incorporates use of specific drugs, resistance mutations and adherence^{8,32–36}.

*List of working group members and their affiliations appear at the end of the paper. Correspondence should be addressed to: A. P. e-mail: andrew.phillips@ucl.ac.uk.

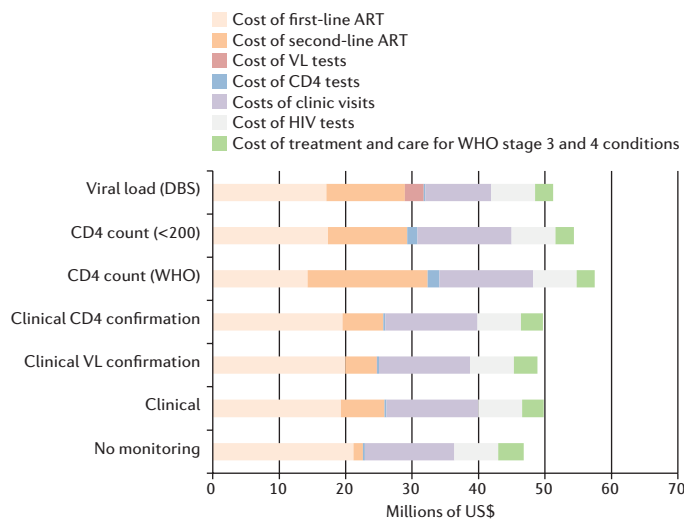


Figure 1 | Overall programme costs. Costs in US\$m per 3 months, according to monitoring strategy (mean 2015–2034, discounted at 3% per annum from 2015). ART, antiretroviral therapy; VL, viral load; WHO, World Health Organization.

ART programme and monitoring strategy modelling

We based our simulated population around that of Zimbabwe and the underlying model is described in detail in the Supplementary Information. We assumed that up to 2015 a CD4 count monitoring strategy has been used. Then we considered the introduction of plausible alternative monitoring strategies and predicted outcomes over 20 years to 2035. The seven main monitoring strategies compared (Table 1) cluster into three main types: clinical observation (with or without targeted CD4 count or viral-load testing in those with clinical disease), regular CD4 count monitoring or regular viral-load monitoring. In the case of viral-load monitoring, we simulate a strategy consisting of off-site laboratory-based testing of DBS using the World Health Organization (WHO) recommended 1,000 RNA copies (cps) ml⁻¹ threshold. Viral load measured as <1,000 cps ml⁻¹ in the past year is assumed to lead to a reduction in non-ART programme costs owing to fewer clinic visits by people on first-line ART. Measurement of viral load 1,000 cps ml⁻¹ or more is assumed to lead to a targeted adherence intervention, which increases adherence in some people. We refer to this strategy as viral-load-informed differentiated care. Regardless of the monitoring strategy used, once strategy-specific failure criteria are met we assume a probability of switching to a second-line regimen of 0.5 per 3 months. In practice, current switch rates are lower than this, even in settings with viral-load monitoring in place^{37–39}; we chose this higher probability, however, to be able to discern differences in effects between strategies. In sensitivity analyses we consider a situation in which switch rates are zero. Throughout, we assume monitoring is performed only for people on first-line ART.

We model decreased precision of DBS for measuring viral load by considering the presence of HIV RNA in cells and the small sample volume^{5,25,40}, such that the sensitivity and specificity of the measure for detecting viral load of >1,000 cps ml⁻¹ compared with measurement on a plasma sample are 86% and 92%, respectively (compared with values ranging from 81% to 85% sensitivity and 88% to 99% specificity⁵ for most assays); we consider other values in sensitivity analysis. We also assume that there is a 3-month delay in the clinician acting on the result, even though results are generally returned to the clinic quicker than this.

Sensitivity analyses were performed to consider: possible differences in population adherence profile, potential increases in sexual behaviour, changes in effectiveness of the adherence intervention triggered by viral load being >1,000 cps ml⁻¹, a policy of initiation of ART at diagnosis, that visit frequency might be reduced in those with a CD4 count of >350 per mm³ in the past year, a zero rate of switch to second-line regimens, differences in the baseline prevalence of HIV, differences in the proportion on ART, differences in the rate of ART interruption if visit frequency has been reduced owing to viral load being <1,000 cps ml⁻¹, a higher discount rate of 5% rather than 3%, and a 10-year

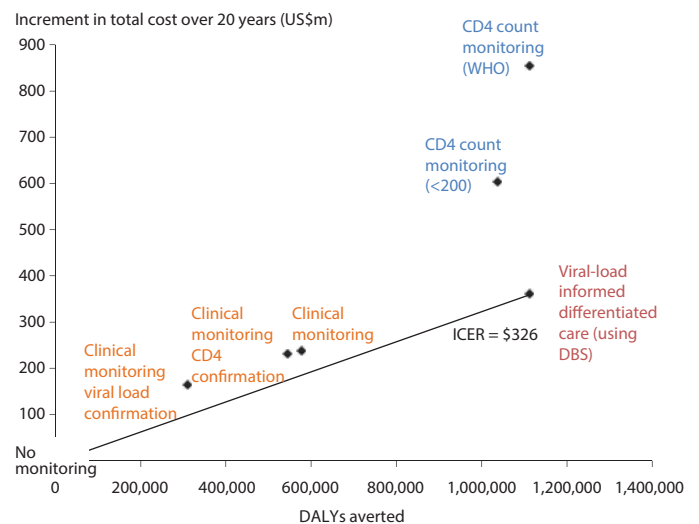


Figure 2 | Cost-effectiveness. Cost-effectiveness plane showing clinical- and CD4-based monitoring strategies along with viral-load-informed differentiated care using dried blood spots. DALYs, disability-adjusted life years; ICER, incremental cost-effectiveness ratio.

rather than a 20-year time horizon. In addition, we considered the effects of whether whole blood or plasma is used, whether the test is done in a central laboratory and incurs the 3-month delay in action or is done at POC with no delay, the threshold to define failure (200, 1,000 or 5,000 cps ml⁻¹, which is only assessed in the context of plasma), and the frequency of measurement (every 6 months, annually or every 2 years).

Last, we focussed on the specific comparison between viral load using DBS and using a plasma-based POC test to quantify the extent of various potential advantageous features of a POC test on its cost-effectiveness in relation to use of DBS. It is important to note that we are considering potential features of a POC test — it is not clear that such features can be delivered, so this analysis is directed mainly towards developers and should not be interpreted as indicating that POC tests will prove to have any of these advantageous features. This is why we chose to consider a plasma-based POC test, although in reality it may be more likely that a whole-blood-based test is used for many POC tests, to avoid a plasma separation step. Further details of how all these aspects are modelled are provided in the Supplementary Information.

Economic analysis

Our objective is to maximize population health — the health benefits associated with the alternative monitoring strategies are estimated using the metric disability-adjusted life years (DALYs) averted — with the available resources. A health sector perspective has therefore been adopted for the analysis. Direct and indirect costs incurred by the patients are excluded. Both costs and health benefits were discounted to present value using a 3% per annum discount rate in our base case. The expected costs and health outcomes associated with each monitoring strategy can be compared to indicate which is likely to represent the best value from the available resources. The cost-effectiveness threshold for a country represents the opportunity costs of resources required to fund the intervention, in terms of the health gains that those resources could generate if used for alternative purposes in the public health-care system⁴¹. As such, the threshold for a country is not readily apparent, but US\$500 per DALY averted is likely to be at the upper end based on the magnitude of benefit if the resources were spent on other programmatic priorities such as eliminating coverage gaps for ART if these are large⁴². The modelling results are intended to inform decisions in sub-Saharan African countries such as Zimbabwe classified as low and low-middle income using the World Bank country classifications that have typically struggled to scale-up viral-load monitoring³¹. The analyses may also be informative for higher income countries in the region (such as South Africa and Botswana) that have already scaled up viral-load monitoring, but are seeking more efficient ways to deliver ART.

Table 1 | The seven main monitoring strategies modelled listed by the short name given to the strategy.

	No monitoring	Clinical monitoring	Clinical monitoring viral load confirmation	Clinical monitoring CD4 count confirmation	CD4 count monitoring (WHO)	CD4 count monitoring (<200)	Viral-load-informed differentiated care using DBS
What the monitoring strategy entails for people on first-line ART	NA	Check on presence of symptoms every 3 months	Check on presence of symptoms every 3 months Measure viral load if WHO 4 condition diagnosed or two WHO 3 conditions diagnosed in 1 year	Check on presence of symptoms every 3 months Measure CD4 count if WHO 4 condition diagnosed or two WHO 3 conditions diagnosed in 1 year.	6-month CD4 count If failure criteria seem to be met, re-measure to confirm (confirmatory CD4 count)	12-month CD4 count If failure criteria seem to be met, re-measure to confirm (confirmatory CD4 count)	Viral load measure using DBS at 6 months, 12 months and every 12 months thereafter If viral load is >1,000 cps ml ⁻¹ then provide adherence intervention and re-measure viral load 3 months later (confirmatory viral load measure) No CD4 count measurements
Failure criteria	NA	WHO 4 condition diagnosed or two WHO 3 conditions diagnosed in 1 year	Viral load >1,000 cps ml ⁻¹	CD4 count <250 mm ⁻³	CD4 count less than pre-ART baseline or CD4 count <100 mm ⁻³ in confirmatory CD4 count	CD4 count <200 mm ⁻³ after more than 3 years on ART. CD4 <100 mm ⁻³ after more than 1 year on ART in confirmatory CD4 count	Viral load >1,000 cps ml ⁻¹ in confirmatory viral load measure
Reduction in clinical visit frequency and hence reduction in non-ART programme cost*	None	None	None	None	None	None	Yes, when most recent viral load <1,000 cps ml ⁻¹ , measured in the past year

*Assuming 3-monthly clinical visits for all strategies except under viral-load-informed differentiated care when the most recent viral load <1,000 cps ml⁻¹, measured in past year. More frequent clinical visits than once every 3 months are not modelled as the model advances in 3-month periods. ART, antiretroviral therapy; Cps, copies; DBS, dried blood spot; WHO 4, World Health Organization stage 4 condition.

Disability weights to calculate DALYs averted were derived from a recent comprehensive study⁴³. Unit costs (in US\$ at 2014 prices) are detailed in the Supplementary Information. In brief, costs of viral-load assays are assumed to be \$22. This is a fully-loaded cost, counting all components such as reagents, costs of equipment, human resources, buildings, and so on (see Supplementary Information). Because POC viral-load tests are not yet available it was not possible to calculate the cost so we assumed a similar cost of \$22, although it is likely that the fully-loaded cost will be higher than this. The cost of measuring CD4 counts is assumed to be \$10 (ref. 44). The current annual cost (including supply chain) of the first-line regimen of efavirenz, emtricitabine and tenofovir (assumed to be used as a fixed-dose combination) is assumed to be \$144 per person per year and for the second-line regimen of zidovudine, emtricitabine and ritonavir-boosted atazanavir to be \$312 per person per year⁴⁵. Annual programme costs for clinic visits (not including drug, or viral load or CD4 count tests) are \$80 per year^{1,2}, with an assumed reduction to \$40 per year, after measurement of viral suppression because of reduced clinical visit frequency of every 6 months from every 1 to 3 months (with interim pharmacy-only visits, depending on the amount of drug that can be dispensed).

RESULTS

The status of the simulated population in 2014 is shown in Table S1 in Modelling Methods in the Supplementary Information. Mean predicted outcomes over 20 years are shown in Table 2. The proportion of people who are taking or have taken ART (ART-experienced), who have fulfilled the criteria for failure of first-line ART is lowest with no monitoring and is below 15% for each of the clinical monitoring strategies. It is highest for the CD4 count monitoring (WHO) strategy (41%) because the failure definition is fulfilled if the CD4 count is below the pre-ART baseline level (which can occur due to high CD4 count variability, and particularly if ART has been interrupted). The proportion is intermediate for the CD4 count monitoring (<200) strategy and viral-load-informed differentiated care using DBS strategies (at 26% and 27%, respectively). The proportion of all people on ART who have viral suppression is highest with the viral-load-informed differentiated care using DBS strategy (86%) and lowest with no monitoring (76%), with the small range of 10% reflecting the generally high levels of adherence (although we consider in sensitivity analyses a situation in which adherence levels are lower and the proportion with viral suppression is accordingly lower). The death rate is markedly lower for the CD4 count and viral-load monitoring strategies than for the other strategies, and this is particularly evident in

those among whom viral-load failure has occurred. Notably, there is also a benefit of viral-load-informed differentiated care using DBS on HIV incidence over all the other strategies.

Costs and their components by monitoring strategy are shown in Figure 1. Programme costs for clinic visits are lowest with viral-load-informed differentiated care using DBS owing to the reduction in clinic visit frequency among virally-suppressed people. Figure 2 shows the cost-effectiveness plane, showing the total incremental DALYs averted in the population over 20 years, together with the incremental costs (both discounted), compared with no monitoring. Owing to the higher death rate of people on ART and higher HIV incidence, the clinical monitoring strategies avert fewer DALYs than the viral load and CD4-count-based monitoring strategies. Additional costs incurred are highest for CD4-count monitoring, particularly the CD4 count monitoring (WHO) strategy. Viral-load-informed differentiated care using DBS averts a similar number of DALYs as CD4-count monitoring and is the most cost-effective strategy owing to the reduction in non-ART programme costs in people with viral suppression, with an incremental cost-effectiveness ratio (ICER) of \$326 per DALY averted. Figure 3 depicts how the cost-effectiveness is affected by the assumed costs of viral-load tests and savings in clinic visit costs in people with suppressed viral load. In our base case viral-load test cost of \$22, viral-load-informed differentiated care is cost-effective only if reduced clinic visits provide at least a \$30 per person per year saving offset.

The effect of varying model assumptions are shown in Figure 4 and Supplementary Figure 1. Changes in the sensitivity and specificity of viral-load measurement using whole blood (as used for DBS) did not markedly influence the ICER, nor did the extent of the assumed effect of viral-load measurement >1,000 cps ml⁻¹ on adherence. The ICER for viral-load-informed differentiated care was lower when we assumed lower population adherence and when we assumed higher population levels of unprotected sex, resulting in higher HIV incidence. In a scenario with a switch rate of zero, viral-load-informed differentiated care was cost saving. Confirming the results shown in Figure 3, if no reduction in visit frequency is assumed with viral-load monitoring (Supplementary Fig. 1u) then it is not cost-effective. The only other scenarios in which viral-load-informed differentiated care was not cost-effective was when we considered a 10-year time horizon instead of 20 years and when we considered a doubling of rate of ART interruption in people with a reduced visit frequency owing to viral load being <1,000 cps ml⁻¹ (Figure 4 and Supplementary Fig. 1q and r).

Table 2 | Outcomes over 20 years (2015–2035) in people with HIV (age 15–65), according to monitoring strategy.

	No monitoring	Clinical monitoring	Clinical monitoring viral load confirmation	Clinical monitoring CD4 count confirmation	CD4 count monitoring (WHO)	CD4 count monitoring (<200)	Viral-load-informed differentiated care using DBS
Percentage of ART-experienced people who have fulfilled criterion for failure of first-line ART	7%	14%	10%	13%	41%	26%	27%
Percentage of ART-experienced people who have started second-line ART	3%	13%	10%	13%	38%	24%	25%
Percentage of people on ART who have (true) viral load <1,000 cps ml ⁻¹ (mean; over 20-year time horizon)	76%	79%	78%	79%	85%	82%	86%
Death rate (per 100 person years) among people on ART	4.43	3.63	4.06	3.67	3.02	3.07	3.18
Death rate (per 100 person years) among people with HIV	5.45	4.91	5.2	4.93	4.36	4.43	4.47
Death rate (per 100 person years) in the whole adult population	1.69	1.63	1.66	1.63	1.56	1.58	1.57
Death rate (per 100 person years) among people on ART who have virologically failed first-line ART (regardless of whether monitoring strategy has detected it)	9.94	7.5	8.66	7.62	5.53	5.79	5.85
Incidence of HIV (per 100 person years)	0.84	0.81	0.83	0.81	0.76	0.79	0.73

For each model run for each strategy, the outcome of interest (as listed in the first column) is output for each 3-month period between 2015–2035. Over 500 model runs are done for each strategy, then means are taken over 3-month periods and model runs. ART, antiretroviral therapy; Cps, copies; DBS, dried blood spot; WHO, World Health Organization.

In the base case we have considered there to be a switch rate of 0.5 per 3 months after the strategy-specific failure criteria have been met. In practice, in most settings, despite CD4 counts being measured, switching rates are much lower than this. We compared use of the CD4 count monitoring (WHO) strategy with a low switch rate of 0.05 per 3 months (the current situation in many countries) with viral-load-informed differentiated care with a switch rate of 0.5 per 3 months (Fig. 5). The results suggest that introduction of the viral-load-informed differentiated care using DBS accompanied by a high switch rate would lead to a substantial improvement in DALYs averted with a potential reduction in cost, compared with the current situation. In the simulated model population of Zimbabwe, over 20 years the CD4 count monitoring (WHO) strategy averts 540,000 DALYs compared with no monitoring at a cost of \$500 million, whereas viral-load-informed differentiated care using DBS averts 1.12 million DALYs compared with no monitoring at a cost of \$361 million.

We also consider only the viral-load-informed differentiated care strategy and assess the effect of variations in various aspects (Fig. 6); whether whole blood or plasma is used, whether the test is POC (central laboratory testing using whole blood is our DBS scenario above), the threshold to define failure (200, 1,000 or 5,000 cps ml⁻¹, which is only assessed in the context of plasma), and the frequency of measurement (every 6 months, annually or every 2 years). Monitoring every 6 months instead of annually averts more DALYs, but does not seem to be cost-effective at the \$500 threshold (ICER = \$1,234). Less frequent monitoring (such as every 2 years) would be cost-effective if it were to avert a similar number of DALYs to monitoring every year. However, implementing differentiated care based on viral-load monitoring as infrequently as every 2 years is currently untested and the potential health consequences are unknown, so this strategy is excluded from the comparison (Fig. 6a). Using the 5,000 cps ml⁻¹ threshold also averts DALYs at a similar ICER to the 1,000 cps ml⁻¹ threshold, but with reduced total benefit. Use of a whole blood sample (for example, DBS) instead of a

plasma sample is not predicted to result in a marked difference in cost incurred (assuming the same unit cost per test) and a modest (4%) benefit in DALYs averted. There is a small (6%) predicted benefit of POC testing over laboratory monitoring in DALYs averted owing to the fact that the 3-month delay is avoided.

DISCUSSION

Our results suggest that viral-load-informed differentiated ART care, using DBS sampling if necessary, is likely to be cost-effective in low-income settings in sub-Saharan Africa and is a sustainable model for providing ART. That said, the level of savings that result from reduced clinic visits and that can be realized in practice with differentiated care are, so far, uncertain and require monitoring. The level of savings required depends partially on the cost of viral-load testing. With the viral-load test cost of \$22 as used in our base case, an annual saving of at least \$30 per year in those with viral suppression is required for viral-load-informed differentiated ART care to be cost-effective. Given that annual non-ART-programme costs average around \$80 per year² if patients are being seen every 1 to 3 months, a reduction in visit frequency to once every 6 months, and perhaps for long-term suppressed patients to every 9 to 12 months, should enable such savings. There is little evidence that patients seen at sites with higher non-ART-programme costs have better outcomes². We estimate, based on modelling of Zimbabwe over 20 years, that in contrast to the current situation in many countries (CD4 count monitoring with low switch rates), introduction of viral-load-informed differentiated care would more than double the number of DALYs averted compared with no monitoring (1.12 million compared with 0.54 million) and deliver these at reduced costs (\$360 million compared with \$500 million).

A reduction in the frequency of clinic visits could also affect patients' adherence to ART and retention in care. There is evidence that some patients default from care because they are unable to keep up with the intensive clinic visit schedule owing to travel time and cost, and loss of work time⁴.

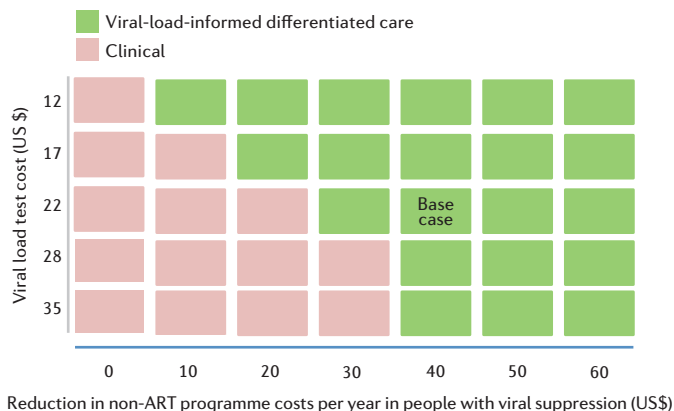


Figure 3 | Viral load cost-effectiveness. Indication of whether viral-load-informed differentiated care is the most cost-effective monitoring strategy according to cost of viral load tests and reduction in non-antiretroviral (ART) programme costs in people with viral suppression. In the context of cost-effectiveness threshold US\$500. Colours indicate which monitoring strategy is economically preferred.

Notably, retention in care was more than 90% at 4 years among individuals enrolled in community ART clubs in Mozambique, owing, in part, to community-based adherence support, decreased travel requirements and patient preference^{46,47}. We did not include in our model any such adherence or retention benefits associated with differentiated care. There is also the possibility that patients may feel less connected to care with a differentiated care model, and this might have adverse consequences for adherence and retention, although so far there is little evidence to suggest this.

When using the CD4 count to monitor people on ART, the WHO-recommended approach has been to define failure by a CD4 count of <100 cells mm⁻³ of blood or a decline from pre-ART baseline. Our modelling suggests that, given the high variability in CD4 count and the fact that it is not uncommon for people to interrupt ART for periods of time, this latter component results in low specificity and in many patients with viral suppression being incorrectly categorized as failing and hence switched unnecessarily. The alternative approach we evaluated, similar to that used in the DART trial⁴⁸, is to define failure based on a CD4 count of <100 mm⁻³ in years 1-3 on ART, and a CD4 count <200 mm⁻³ thereafter. This approach performed well in our modelling in terms of the death rate of people on ART (as it did in the trial itself), although it still resulted in a lower rate of viral suppression and hence a higher HIV incidence than with viral-load monitoring, resulting in poorer overall effectiveness. In settings that continue to have a CD4 count capacity, but not viral-load capacity, this suggests that the CD4 count monitoring (<200) strategy should be used until viral-load-informed differentiated care is introduced.

The requirement for frequent clinic visits is partially driven by shortages of ART supplies at a national level, resulting in clinic level rationing of ART quantities dispensed to patients at each visit. Increasing country buffer stocks, as well as improving forecasting of need, could enable longer drug supplies to be prescribed. However, even if it is not possible to prescribe more than a 1-2 months supply of drugs, various approaches can be considered to prevent patients from having to make frequent pharmacy-only visits to clinic^{46,47,49-54}. These include community ART groups, whereby one person picks up the drugs for all the members or situations in which patients can pick up medicines in a shop or other non-clinical setting⁵⁵. Other hurdles to overcome in adopting viral-load-driven reductions in frequency of clinical visits include obtaining buy-in from Ministries of Health for any required task shifting, and provision of human resources for dedicated adherence support for people with high viral load. In addition, support from professional associations of clinical, nursing and pharmacy staff will be important.

The fact that the viral load is a direct measure of the ongoing effect of treatment means it provides an ideal means to differentiate care provision. However, given the wider availability of CD4 count tests, it might be

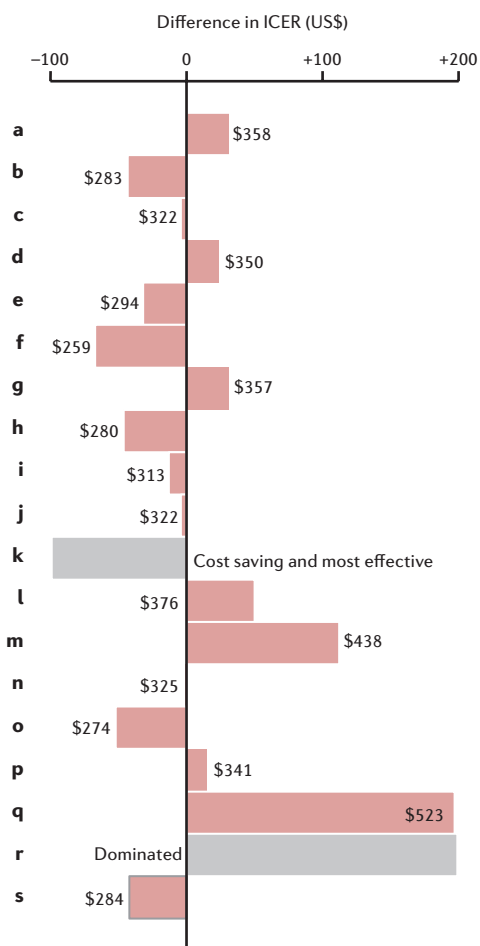


Figure 4 | Incremental cost-effectiveness ratio (ICER) for viral-load-informed differentiated care using dried blood spot (DBS) (compared with next less effective strategy on the efficiency frontier) according to changes in assumptions (see Supplementary Figure 1). **a**, DBS sensitivity 96% and specificity 79% for 1,000 copies per millilitre threshold (versus plasma). **b**, DBS sensitivity 71% and specificity 97% for 1,000 cps ml⁻¹ threshold (versus plasma). **c**, DBS sensitivity 88% and specificity 93% for 1,000 cps ml⁻¹ threshold (versus plasma). **d**, DBS sensitivity 85% and specificity 79% for 1,000 cps ml⁻¹ threshold (versus plasma). **e**, Poorer population antiretroviral therapy (ART) adherence profile such that proportion with viral suppression with no monitoring/no second-line ART is 68% compared with 76% in base case and HIV incidence is 0.96 per 100 person years compared with 0.84 in base case. **f**, Future greater increase in sexual behaviour in population such that HIV incidence is 1.46 per 100 person years compared with 0.84 in base case. **g**, Permanent increase in adherence as a result of viral load measurement alert in none rather than 40%. **h**, Permanent increase in adherence as a result of viral load measurement alert in 100% rather than 40%. **i**, Policy of initiation of ART at diagnosis. **j**, Reduced frequency of visits if CD4 count measured >350 in past year. **k**, Switch rate of 0 (so only benefit of monitoring is to inform who should be seen less frequently). **l**, Lower prevalence of HIV in 2014 (6% instead of 15% in base case). **m**, Higher prevalence of HIV in 2015 (33% instead of 15% in base case). **n**, Lower proportion on ART in 2015 (33% instead of 56% in base case). **o**, Higher proportion on ART in 2015 (70% instead of 56% in base case). **p**, 5% discount rate instead of 3%. **q**, Ten year time horizon instead of 20 year. **r**, Two times higher rate of ART interruption if visit frequency has been reduced due to viral load being <1,000 cps ml⁻¹. **s**, Two times lower rate of ART interruption. Based on 200 model runs per strategy for each of **a-s**.

suggested that the CD4 count could be used instead. For example, visit frequency for people with a CD4 count of more than 350 mm⁻³ could be reduced. This would result in a similar reduction in clinic visit costs to

viral-load-informed differentiated care. The effectiveness of such an approach is unknown, however, and it would lead to some people in whom adherence is low and/or resistance is present, and viral load is high, being asked to visit clinic less frequently. It is well established that CD4 counts can remain high when virological failure is occurring⁵⁶ and, likewise, that the CD4 count can remain low despite full virologic suppression. Thus, the negative effects of such a strategy would be a concern and, although we did model this as a potential strategy (Supplementary Fig. 1j) it is possible that we did not fully capture the extent of these negative effects.

We have largely focussed on use of DBS rather than plasma collection as an approach. Although plasma samples from a venepuncture and sample separation are an ideal sample, for transport of more than 6–24 hours this requires cold temperatures and so the approach is only likely to be applicable in areas for which samples can reach the laboratory in that time.

Although we have argued that a DBS approach is feasible in most settings, this is not to say that the approach is working well everywhere⁵⁷. It is important that there is investment in improvements to existing systems, including diagnostics laboratories and logistics of specimen distribution, and we have endeavoured to capture these costs as part of our overall costs of delivering viral-load testing using DBS. It is notable that most studies that have evaluated viral load using DBS compared with plasma have been performed in a laboratory setting using venepuncture samples and a capillary tube (which measures a precise 100 μ l whole blood) to fill in the DBS card. Few studies are available to assess the performance of DBS in the real-world scenario — where it is hot, where sample-transport times are long, where venepuncture is not an option, and where samples are from a finger prick rather than a capillary tube — although one such study has found encouraging findings²⁷. Our finding that viral-load-informed differentiated care is cost-effective was robust to low levels of sensitivity or specificity using DBS (Fig. 4, Supplementary Fig. 1).

We simplified the comparison of types of viral-load test by breaking them down according to whether they are done at POC or in a laboratory and whether the sample consisted of whole blood or plasma. We recognise that this is something of an oversimplification in that, for example, measurement of viral load by POC testing on whole blood may not always have the same sensitivity or specificity as using whole blood in the form of DBS. Improved sensitivity and specificity compared with DBS offers a modest, but real benefit, as does the ability to measure the viral-load level such that it can be acted on in the same day, avoiding a delay until the next visit or the need to contact and recall the patient. Even if a POC viral-load test with the desirable properties we considered does become available it is likely that countries would use a mix of approaches (plasma samples, DBS and POC) depending on settings. It should be noted that the cost we assumed for a POC assay of \$22 was used as a placeholder for the actual cost when this is known. It is uncertain whether such tests will be able to be delivered at this cost, as a fully-loaded cost, which takes account of staff operator time, and our results should be interpreted in the light of this.

If differentiated care can be successfully implemented using viral-load monitoring less frequently than every 12 months (for example, every 24 months) our modelling suggests that less frequent monitoring would be expected to be cost-effective. However, the health risks of differentiated care with such infrequent viral-load monitoring are not well understood and may not have been fully captured in our model. Further evidence on whether this approach is feasible, and the health consequences of its implementation, is required. Only in highly resourced health-care systems (with a cost-effectiveness threshold of more than \$1,400 per DALY averted) is more-frequent monitoring (for example, every 6 months) expected to be cost-effective.

We found little evidence to support substantial benefits associated with increasing or decreasing the cut-off (viral-load counts $>1,000$ cps ml^{-1}) at which treatment is considered to have failed. A cut-off of 200 cps ml^{-1} results in more DALYs being averted — due to identifying people with virological failure earlier — but relies on a plasma-based test (and phlebotomy to achieve sufficient sample volume) and does not meet the \$500 cost-effectiveness threshold.

Given the role of viral-load testing for enabling reduced visit frequency, it should also have a role in people on second-line regimens. When evaluating

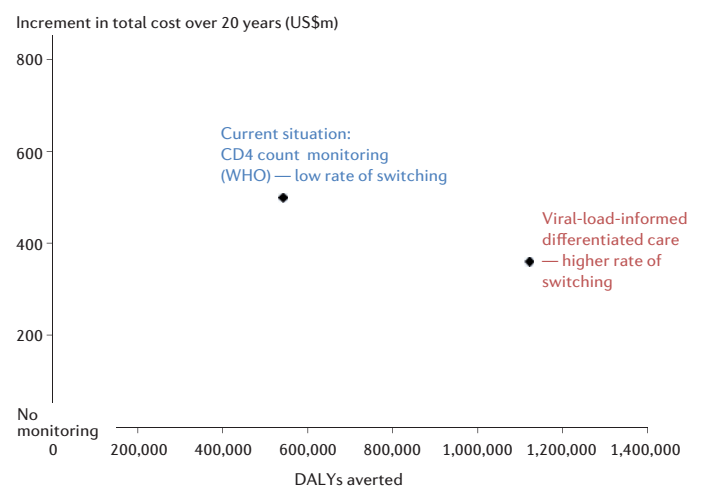


Figure 5 | Comparison with the current situation. The current situation, CD4 count (World Health Organization, WHO) monitoring with a low rate of switching in those meeting the failure criteria (0.05 per 3 months), and viral-load-informed differentiated care with switch rate as in our base case (0.5 per 3 months). DBS, dried blood spot.

our monitoring strategies we assumed that CD4 count or viral-load tests would only be done in patients on first-line treatment, so we may have understated the benefits of viral-load-informed differentiated care.

We considered whether our base case results would still hold with various alterations in assumptions and settings. In a scenario in which the pattern of adherence was generally poorer than in our base case (leading to 68% of people on ART with viral suppression compared with 82% in our base case) viral-load-informed differentiated care remained cost-effective. This was also true in a scenario with high HIV incidence rate, and scenarios with different HIV prevalence and ART coverage, suggesting that our findings should hold in various settings in the region.

Randomized trials have been performed to compare outcomes from CD4 count and viral-load monitoring, and these have not identified significant differences in outcomes. Such trials have been characterized by relatively short follow-up and low implementation of switching to second-line therapy^{58–64}, leading to low power to detect differences.

We focussed on monitoring for adults. In children and, more likely, adolescents levels of adherence may be lower than in adults. We did find that our main findings hold in populations with a tendency for lower adherence. However, there may be a greater reluctance to reduce visit frequency as children are growing up and constantly facing new challenges and situations and clinic staff may wish for regular contact to ensure that these new challenges have not led to a drop in adherence. Likewise, there may be a reluctance to reduce visit frequency for women in the year or so post-partum. We also considered whether monitoring more-intensively — every 6 months rather than every 12 months — would be cost-effective for populations with a poorer adherence profile (Supplementary Fig. 1t), but this was not the case. Other limitations of this work include the fact that we considered a hypothetical cohort with simulated outcomes, and future trends are uncertain — particularly in sexual behaviour, levels of male circumcision and adherence to ART. Furthermore, we assume continuation of HIV testing and ART availability at current trends. The profile of new POC viral-load tests is as yet uncertain, as is their cost. However, new diagnostic technologies, including POC viral-load testing and beyond, have great potential to enhance delivery of HIV care. We have investigated uncertainty through a series of one-way and multi-way sensitivity analyses and recognize that there are other approaches, such as probabilistic sensitivity analysis and approximate Bayesian computation that we intend to pursue in further work.

This work provides insight into how to deliver ART monitoring so that it is both effective and cost-effective. As well as providing some specific guidance to programmes, it highlights the need to research this area further to enable us to continue to understand the attributes of programmes and

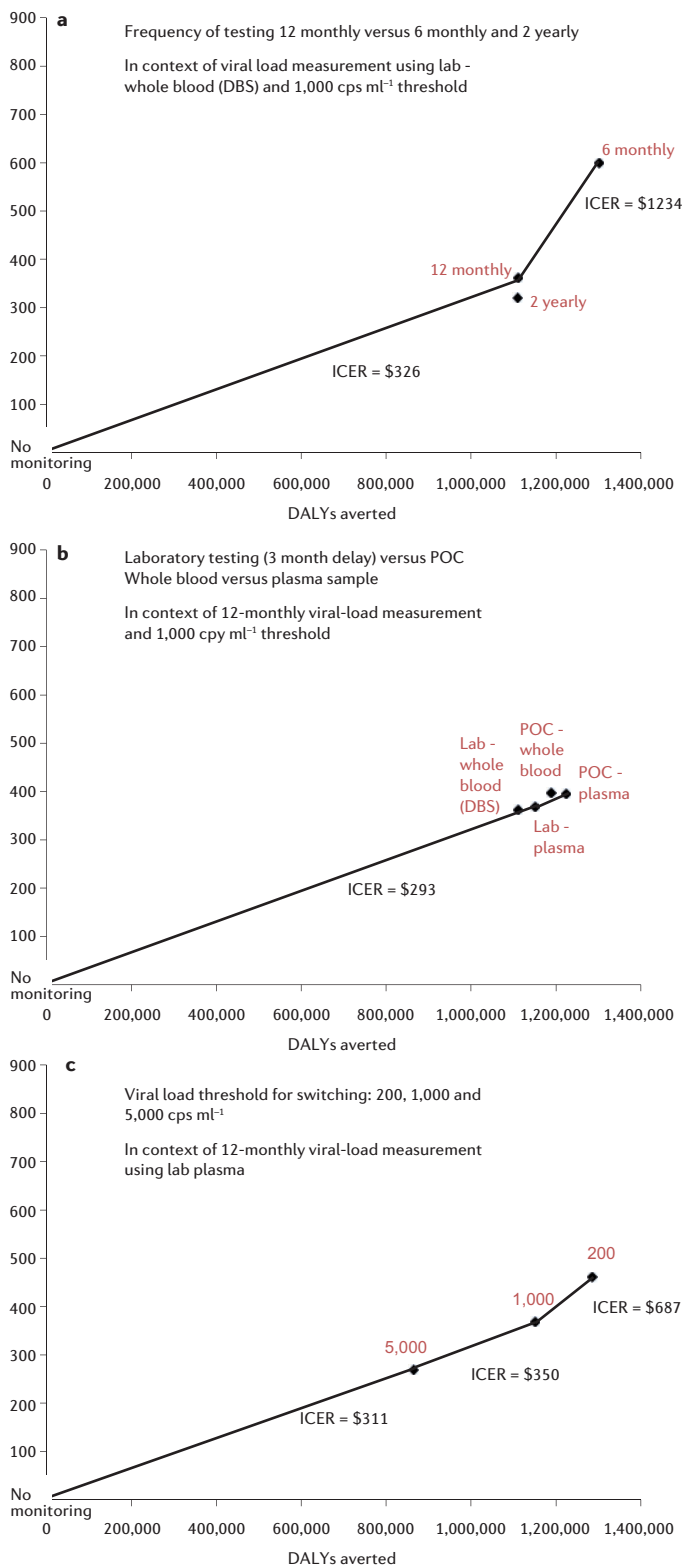


Figure 6 | Cost-effectiveness planes showing the effect of viral load measurement frequency, format and threshold, all in the context of viral-load-informed differentiated care. **a**, Viral load monitoring every 12-months is compared with every 6 months (every 2-year monitoring is excluded from the cost-effectiveness frontier due to unproven ability to base differentiated care on a 2-yearly value; however, if less frequent monitoring could be implemented without adverse health outcomes this would be cost-effective). **b**, Laboratory whole blood corresponds to dried blood spot (DBS). **c**, Alternative thresholds to define failure (viral load >200, >1,000 and >5,000 cps ml⁻¹) are compared in the context of laboratory monitoring every 12 months using plasma.

to determine how maximum health gains can be realized for patients with the resources available. We find that evidence is sufficient to recommend viral-load-informed differentiated care that uses DBS, but that further empirical confirmation as the approach is rolled out would be valuable.

- Siapka, M., Remme, M., Dayo Obure, C., Maier, C., Dehne, K. L. & Vassall A. Is there scope for cost savings and efficiency gains in HIV services? A systematic review of the evidence from low- and middle-income countries. *Bull. World Health Organ.* **92**, 499–511 (2014).
- Tagar, E. et al. Multi-country analysis of treatment costs for HIV/AIDS (MATCH): facility-level ART unit cost analysis in Ethiopia, Malawi, Rwanda, South Africa and Zambia. *PLoS ONE* **9**, e108304 (2014).
- Menzies, N. A. et al. The cost of providing comprehensive HIV treatment in PEP-FAR-supported programs. *AIDS* **25**, 1753–1760 (2011).
- Ware, N. C. et al. Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: a qualitative study. *PLoS Med.* **10**, e1001369 (2013).
- World Health Organisation. *Technical and Operational Considerations for Implementing HIV Viral Load Testing. Access to HIV diagnostics* (WHO, 2014).
- UNAIDS. *Landmark HIV Diagnostic Access Program will Save \$150m and Help Achieve New Global Goals on HIV* <http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2014/september/20140925prviralload> (UNAIDS, 2014)
- Phillips, A. N., Pillay, D., Miners, A. H., Bennett, D. E., Gilks, C. F. & Lundgren, J. D. 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* **371**, 1443–1451 (2008).
- Estill, J. et al. Viral load monitoring of antiretroviral therapy, cohort viral load and HIV transmission in Southern Africa: a mathematical modelling analysis. *AIDS* **26**, 1403–1413 (2012).
- Braithwaite, R.S. et al. Alternative antiretroviral monitoring strategies for HIV-infected patients in east Africa: opportunities to save more lives? *J. Intl AIDS Soc.* **14**, 38 (2011).
- Kimmel, A.D. et al. Laboratory monitoring to guide switching antiretroviral therapy in resource-limited settings: clinical benefits and cost-effectiveness. *J. Acquir. Immune Defic. Syndr.* **54**, 258–268 (2010).
- Braithwaite, R. S. et al. How do different eligibility guidelines for antiretroviral therapy affect the cost-effectiveness of routine viral load testing in sub-Saharan Africa? *AIDS* **28** (Suppl 1), S73–S83 (2013).
- Estill, J. et al. Monitoring of antiretroviral therapy programmes in Malawi, South Africa and Zambia: Mathematical Modelling Study. *PLoS ONE* **8**, e57611.15 (2013).
- Keebler, D. et al. Cost-effectiveness of different strategies to monitor adults on antiretroviral treatment: a combined analysis of three mathematical models. *Lancet Glob. Health* **2**, e35–e43 (2013).
- Bendavid, E. et al. Cost-effectiveness of HIV monitoring strategies in resource-limited settings: a southern African analysis. *Arch. Int. Med.* **17**, 168 (2008).
- Hamers, R. L., Sawyer, A. W., Tuohy, M., Stevens, W.S., Rinke de Wit, T. F & Hill, A. M. Cost-effectiveness of laboratory monitoring for management of HIV treatment in sub-Saharan Africa: a model-based analysis. *AIDS* **26**, 1663–1672 (2012).
- Rutstein, S. E. et al. Dried blood spots for viral load monitoring in Malawi: feasible and effective. *PLoS ONE* **10**, e0124748 (2015).
- Andreotti, M. et al. Correlation between HIV-1 viral load quantification in plasma, dried blood spots, and dried plasma spots using the Roche COBAS Taqman assay. *J. Clin. Virol.* **47**, 4–7 (2010).
- Garrido, C. et al. Correlation between human immunodeficiency virus type 1 (HIV-1) RNA measurements obtained with dried blood spots and those obtained with plasma by use of Nuclisens EasyQ HIV-1 and Abbott RealTime HIV load tests. *J. Clin. Microbiol.* **47**, 1031–1036 (2009).
- Johannessen, A. et al. Dried blood spots perform well in viral load monitoring of patients who receive antiretroviral treatment in rural Tanzania. *Clin. Infect. Dis.* **49**, 976–981 (2009).
- Marconi, A. et al. Evaluation of the Abbott Real-Time HIV-1 quantitative assay with dried blood spot specimens. *Clin. Microbiol. Infect.* **15**, 93–97 (2009).
- Arredondo, M. et al. Comparison of HIV-1 RNA measurements using plasma and dried blood spots (DBS) in the Automated Abbott Real Time Viral Load Assay. *J. Clin. Microbiol.* **50**, 569–572 (2011).
- Pirillo MF-Pinson, P. et al. Quantification of HIV-RNA from dried blood spots using Siemens VERSANT® HIV-1 RNA (kPCR) assay. *J. Antimicrob. Chemother.* **66**, 2823–2826 (2011).
- Ondoa, P. et al. Performance and logistical challenges of alternative HIV-1 virological monitoring options in a clinical setting of Harare, Zimbabwe. *BioMed Res. Int.* **2014**, 102598 (2014).
- Fajardo, E. et al. Prospective evaluation of diagnostic accuracy of dried blood spots from finger prick samples for determination of HIV-1 Load with the NuclISENS Easy-Q HIV-1 version 2.0 Assay in Malawi. *J. Clinical Microbiol.* **52**, 1343–1351 (2014).
- Smit, P. W. et al. Systematic review of the use of dried blood spots for monitoring HIV viral load and for early infant diagnosis. *PLoS ONE* **9**, e86461 (2014).
- Rutstein, E. et al. Measures of viral load using Abbott RealTime HIV-1 Assay on venous and dried blood spots from provider-collected specimens in Malawian District Hospitals. *J. Clin. Virol.* **60**, 392–398 (2014).
- Mavedzenge, S. N. et al. Finger prick dried blood spots for HIV viral load measurement in field conditions in Zimbabwe. *PLoS ONE* **10**, e0126878 (2015).

28. UNAIDS. *HIV/AIDS Diagnostics Technology Landscape. Semi Annual Update*. www.unaids.org (UNAIDS, 2015).
29. World Bank. *Country and Lending Data* http://data.worldbank.org/about/country-and-lending-groups#Sub-Saharan_Africa (World Bank, 2015).
30. Duncombe, C. et al. Reframing HIV care: putting people at the centre of antiretroviral delivery. *Trop. Med. Int. Health* **20**, 430–447 (2015).
31. Roberts, T., Bygrave, H., Fajardo, E. & Ford, N. Challenges and opportunities for the implementation of virological testing in resource-limited settings. *J. Int. AIDS Soc.* **15**, 17324 (2012).
32. Cambiano, V. et al. Transmission of drug resistant HIV and its potential impact on mortality and treatment outcomes in resource-limited settings. *J. Infect. Dis.* **207**, S57–S62 (2013).
33. Cambiano, V. et al. Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation. *AIDS* **28**, S15–S23 (2014).
34. Phillips, A. N. et al. Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naïve populations beginning treatment: modelling study and economic analysis. *Lancet HIV* **1**, e85–e93 (2014).
35. Cambiano, V. et al. Assessment of the potential impact and cost-effectiveness of self-testing for HIV in low-income countries. *J. Infect. Dis.* <http://dx.doi.org/10.1093/infdis/jiv040> (2015).
36. Phillips, A. N. et al. Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second-line regimens in resource-limited settings. *AIDS* **25**, 843–850 (2011).
37. Madec, Y., Leroy, S., Rey-Cuille, M.-A., Huber, F. & Calmy, A. Persistent difficulties in switching to second-line ART in sub-Saharan Africa — a systematic review and meta-analysis. *PLoS ONE* **8**, e82724 (2013).
38. Fox, M. P. et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. *J. Acquir. Immune Defic. Syndr.* **60**, 428–437 (2012).
39. Johnston, V., Fielding, K. L., Charalambous, S., Churchyard, G., Phillips, A. & Grant, A. D. Outcomes following virological failure and predictors of switching to second-line antiretroviral therapy in a South African treatment program. *J. Acquir. Immune Defic. Syndr.* **1**, 370–380 (2012).
40. Parkin, N. Measurement of HIV-1 viral load for drug resistance surveillance using dried blood spots: literature review and modelling of contribution of DNA and RNA. *AIDS Rev.* **16**, 160–171 (2014).
41. Claxton, K., Walker, S., Palmer, S. & Sculpher, M. *Appropriate Perspectives for Health Care Decisions, Centre for Health Economics Research Paper 54* (Univ. York, 2010).
42. Woods, E., Revill, P., Sculpher, M. & Claxton, K. *Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research*. https://www.york.ac.uk/media/che/documents/papers/researchpapers/CHERP109_cost-effectiveness_threshold_LMICs.pdf (Univ. York, 2015).
43. Salomon, J. A. et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* **380**, 2129–4310 (2012).
44. Hyle, E. P. et al. The clinical and economic impact of point-of-care CD4 testing in Mozambique and other resource-limited settings: a cost-effectiveness analysis. *PLoS Med.* **11**, e1001725 (2014).
45. MSF. *Untangling the Web of Antiretroviral Price Reductions* <http://www.msfaaccess.org/content/untangling-web-antiretroviral-price-reductions> (MSF, 2014).
46. Decroo, T. et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. *Trop. Med. Int. Health.* **19**, 514–521 (2014).
47. Rasschaert, F. et al. Sustainability of a community-based anti-retroviral care delivery model — a qualitative research study in Tete, Mozambique. *J. Int. AIDS Soc.* **17**, 18910 (2014).
48. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* **375**, 123–131 (2010).
49. MSF. *ART Adherence Club Report and Toolkit* http://www.msf.org/sites/msf.org/files/cag_toolkit.pdf
50. MSF. *Community ART Group Toolkit. How to Implement the CAG Model. Bringing Treatment Closer to Home and Empowering Patients* <http://samumsf.org/resources/toolkit-cag/> (MSF, 2015)
51. Simons, S. et al. *Ways to Reduce Costs and Improve Quality in Patient Monitoring: Barriers to Improvement, Buhera & Gutu District Experience, Zimbabwe. Consultation on Implementation Issues for Monitoring People on ART in Low-Income Settings in Sub-Saharan Africa* (MSF, 2015).
52. Babigumira, J. B. et al. Cost-effectiveness of a pharmacy-only refill program in a large urban HIV/AIDS clinic in Uganda. *PLoS ONE* **6**, e18193 (2011).
53. UNAIDS and MSF. *Community Based ART Delivery* (UNAIDS, 2015).
54. Grimsrud, A. et al. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. *J. Int. AIDS Soc.* **18**, 19984 (2015).
55. MSF and UNAIDS. *Closer to Home* http://www.msfaaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/AIDS_report_ClosetoHome_ENG_2012.pdf (MSF, 2012).
56. Ledergerber, B. et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* **364**, 51–62 (2004).
57. Terris-Prestholt F. First-line antiretroviral therapy for HIV-infected children. *AIDS* **29**, 1261–1262 (2015).
58. Mermin, J. et al. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. *Br. Med. J.* **343**, d6792 (2011).
59. Kahn, J. G. et al. CD4 cell count and viral load monitoring in patients undergoing antiretroviral therapy in Uganda: cost effectiveness study. *Br. Med. J.* **343**, d6884 (2011).
60. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* **375**, 123–131 (2010).
61. Jourdain, G. et al. Switching HIV treatment in adults based on CD4 count versus viral load monitoring: a randomized, non-inferiority trial in Thailand. *PLoS Med* **10**, e1001494 (2013).
62. Saag, M. et al. Cluster randomized trial of routine vs discretionary viral load monitoring among adults starting ART: Zambia. *19th Conf. Retroviruses and Opportunistic Infections* (2012).
63. Laurent, C. et al. Monitoring of HIV viral loads, CD4 cell counts, and clinical assessments versus clinical monitoring alone for antiretroviral therapy in rural district hospitals in Cameroon (Stratall ANRS 12110/ESTHER): a randomised non-inferiority trial. *Lancet Infect. Dis.* **11**, 825–833 (2011).
64. Boyer, S. et al. Monitoring of HIV viral load, CD4 cell count, and clinical assessment versus clinical monitoring alone for antiretroviral therapy in low-resource settings (Stratall ANRS 12110/ESTHER): a cost-effectiveness analysis. *Lancet Infect. Dis.* **13**, 577–586 (2013).

SUPPLEMENTARY MATERIAL

Is linked to the online version of this paper at: <http://dx.doi.org/10.1038/nature16046>

ACKNOWLEDGEMENTS

Funding for the study was received from the HIV Modelling Consortium, the Bill and Melinda Gates Foundation, the World Health Organization and the HIV Diagnostics Modelling Consortium. We are grateful for the use of cluster computing facilities at UCL, Legion@UCL, without which this work would not have been possible. J. L. is supported by the Danish National Research Foundation (DNRF:126).

APPENDIX

Andrew Phillips¹, Amir Shroufi², Lara Vojnov³, Jennifer Cohn⁴, Teri Roberts⁴, Tom Ellman², Kimberly Bonner⁵, Christine Rousseau⁶, Geoff Garnett⁶, Valentina Cambiano¹, Fumiyo Nakagawa¹, Deborah Ford⁷, Loveleen Banshi-Matharu¹, Alec Miners⁸, Jens D. Lundgren⁹, Jeffrey W. Eaton¹⁰, Rosalind Parkes-Ratanshi¹¹, Zachary Katz², David Maman², Nathan Ford¹², Marco Vitoria¹², Meg Doherty¹², David Dowdy¹³, Brooke Nichols¹⁴, Maurine Murtagh¹⁵, Meghan Wareham³, Kara M. Palamoutain¹⁶, Christine Chakanyuka Musanhu¹⁷, Wendy Stevens¹⁸, David Katzenstein¹⁹, Andrea Ciaranello²⁰, Ruanne Barnabas²¹, R. Scott Braithwaite²², Eran Bendavid²³, Kusum J. Nathoo²⁴, David van de Vijver¹⁴, David P. Wilson²⁵, Charles Holmes²⁶, Anna Bershteyn²⁷, Simon Walker²⁸, Elliot Raizes²⁹, Ilesh Jani³⁰, Lisa J. Nelson³¹, Rosanna Peeling³², Fern Terris-Prestholt³³, Joseph Murungu³⁴, Tsitsi Mutasa-Apollo³⁴, Timothy B. Hallett¹⁰ & Paul Revill¹⁸.

¹Department of Infection and Population Health, University College London, Rowland Hill Street, London NW3 2PF, UK. ²Southern Africa Medical Unit (SAMU), Medecins sans Frontieres (MSF) SA, Waverley Business Park, Waverley Croft Rd, Mowbray 7700, Cape Town, South Africa. ³Clinton Health Access Initiative, 383 Dorchester Avenue, Boston, Massachusetts 02127, USA. ⁴Médecins Sans Frontières, Access Campaign, rue du Lausanne 82, 1202 Geneva Switzerland. ⁵Médecins Sans Frontières, 78 rue de Lausanne, Case Postale 116, 1211 Geneva 21, Switzerland. ⁶Bill and Melinda Gates Foundation, PO Box 23350, Seattle, Washington 98199, USA. ⁷MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, Aviation House, 125 Kingsway, London WC2B 6NH, UK. ⁸Health Services Research & Policy, London School of Hygiene and Tropical Medicine, Room 134, 15–17 Tavistock Place, London WC1H 9SY, UK. ⁹CHIP, Department of infectious diseases, Rigshospitalet, University of Copenhagen, Blegdamsvej 92100 Copenhagen, Denmark. ¹⁰Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK. ¹¹Infectious Diseases Institute (IDI), College of Health Sciences, Makerere University, PO Box 22418, Kampala, Uganda. ¹²HIV/AIDS and Global Hepatitis Programme, World Health Organization, 20 Ave Appia 1211, Geneva, Switzerland. ¹³Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street E6531, Baltimore, Maryland 21205, USA. ¹⁴Department of Viroscience, Erasmus Medical Center, PO Box 2040300CA Rotterdam, the Netherlands. ¹⁵International Diagnostics Centre, London School of Hygiene & Tropical, Medicine, Keppel Street, London WC1E 7HT, UK. ¹⁶Kellogg School of Management, Northwestern University, 2001 Sheridan Road Evanston, Illinois 60208, USA. ¹⁷WHO Country Office 86 Enterprise Road Cnr, Glenara PO Box CY 348, Causeway Harare, Zimbabwe. ¹⁸Department of Molecular Medicine and Haematology, University of the Witwatersrand, South Africa. ¹⁹Division of Infectious Disease, Laboratory Grant Building S-146, Office Lane 154, Stanford University Medical Center, 300 Pasteur Drive, Stanford, California 94305-5107, USA. ²⁰Massachusetts General Hospital Division of Infectious Diseases, 50 Staniford Street, 936 Boston, Massachusetts 02114, USA. ²¹Medicine, Global Health and Epidemiology, University of Washington (UW), 325 9th Avenue, Seattle, Washington 98104, USA. ²²Department of Population Health, New York University School of Medicine, 227 East 30th Street Office 615, New York, New York 10016, USA. ²³Division of General Medical Disciplines, Department of Medicine Stanford University, MSOB 1265 Welch Road x332 Stanford,

California 94305, USA. ²⁴University of Zimbabwe, College of Health Sciences, Department of Paediatrics and Child Health, PO Box A178, Avondale, Harare, Zimbabwe. ²⁵University of New South Wales, Level 6, Wallace Wurth Building, UNSW Campus, Sydney, New South Wales 2052, Australia. ²⁶Centre for Infectious Disease Research in Zambia, 5032 Great North Road, Lusaka, Zambia. ²⁷Institute for Disease Modeling, 3150 139th Avenue SE, Bellevue, Washington 98005, USA. ²⁸Centre for Health Economics, University of York, Heslington, York YO10 5DD, UK. ²⁹Care and Treatment Branch Center for Global Health, Division of Global HIV/AIDS (GAP), CDC, MS-E04, 1600 Clifton Road NE, Atlanta, Georgia 30333, USA. ³⁰Instituto Nacional de Saúde (INS), Ministry of Health, PO Box 264, Maputo, Mozambique. ³¹The Office of the US Global AIDS Coordinator and Health Diplomacy (S/GAC), U.S. Department of State, SA-22, Suite 10300, 2201 C Street, Washington DC 20520, USA. ³²Clinical Research Department, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK. ³³Department of Global Health and Development, London School

of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK. ³⁴Ministry of Health and Child Care, P. O. CY 1122, Causeway, Harare, Zimbabwe.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests. Financial support for this publication has been provided by the Bill & Melinda Gates Foundation.

ADDITIONAL INFORMATION



This work is licensed under the Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0>