Sustainable HIV Treatment in Africa through Viral Load-Informed Differentiated Care

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

* Membership listed in Appendix

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Correspondence: Andrew Phillips, Research Department of Infection & Population Health, UCL, London. email: andrew.phillips@ucl.ac.uk

Abstract (250 words)
There are inefficiencies in current approaches to monitoring patients on antiretroviral therapy (ART) in sub-Saharan Africa. Patients typically attend clinics every 1-3 months for clinical assessment, with clinic costs being comparable with costs of drugs themselves, CD4 counts are measured every 6 months, yet patients are rarely switched to second-line therapies. To ensure sustainability of treatment programmes a transition to more cost-effective ART deliver is needed. In contrast to the CD4 count, measurement of the level of HIV RNA in plasma ("viral load") provides a direct measure of current treatment effect. *Viral load informed differentiated care* is a means of tailoring care whereby those with suppressed viral load have less frequent clinical visits and attention is paid to those with unsuppressed viral load to promote adherence and timely switching to a second-line regimen. The most feasible approach in many countries to measure viral load is by collecting dried blood spot (DBS) samples for testing in regional laboratories, although there have been concerns over the sensitivity/specificity of DBS to define treatment failure and the delay in receiving results. We use modelling to synthesize available evidence and evaluate the cost-effectiveness of *viral load-informed differentiated care*, account for limitations of DBS. We find that *viral load-informed differentiated care* using DBS is expected to be cost-effective and is recommended as the 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 future availability of point-of-care (POC) viral load tests.

Introduction

It is critical for sustainability of antiretroviral therapy (ART) programmes in sub-Saharan Africa that the approach to monitoring people on therapy is optimized with regard to effectiveness and cost. Currently, in most countries patients, are required to attend clinics every 1-3 months for clinical assessment, with the costs of providing for such clinic attendances – for personnel, infrastructure and maintenance - being comparable with costs of the antiretroviral drugs themselves (1-3). In most settings, patients are monitored with CD4 count measurement every 6 months with clinical observation at least every 3 months, but are rarely switched to second-line regimens. A reduction in visit frequency in patients who are adherent to ART and doing well would benefit programmes by reducing costs and patients by saving travel costs and time away from work, possibly leading to reduced rates of defaulting from care (4). To achieve this it is necessary to be able to identify objectively who is doing well on ART.

The biomarker which most directly measures the on-going effect of ART is the HIV ribonucleic acid (RNA) level in plasma ("viral load"). If viral load is suppressed, it indicates good adherence to drug taking and lack of drug-resistant virus. Experience in high income countries suggests that after 1-2 years on ART with viral load suppression visit frequency can be reduced. If viral load is unsuppressed this suggests the need for improved adherence and/or a switch in regimen. In most countries in sub-Saharan Africa, measurement of viral load is not so far widely available. Quantification of HIV RNA requires sophisticated facilities and skilled staff and costs have been high, although they have decreased substantially recently (5, 6). While modelling studies have indicated there is a benefit of viral load monitoring over monitoring strategies based on the CD4 count or clinical observation (7-16) viral load monitoring has not been found to be cost-effective (7, 10-14), due to the cost of viral load tests and second-line regimens. Currently, the most feasible approach in most countries to begin to measure viral load 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 services (15). 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 means such as SMS. However, presence of cells and low sample volume in DBS specimens mean that sensitivity and specificity for detecting whether the level is above the 1000 cps/mL threshold 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 - i.e. tests that enables a decision to be made about patient management at the same visit as the sample is taken - may become widely available (28), and this may facilitate scale-up and result in greater accuracy than use of DBS.

In the light of these issues, we here consider the question of how should HIV treatment programmes in low- income countries in sub-Saharan Africa monitor patients on ART in a way that is likely to lead to greatest population health gains from within limited resources available (29). Here we update a model previously used to compare monitoring strategies incorporating the 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 incorporating use of specific drugs, resistance mutations, and adherence, which has been described previously (8,32-36).

Modelling of ART programme scenario and ART monitoring strategies

We based our simulated population around that in Zimbabwe and the the underlying model is described in detail in the Supplementary Material. We assumed that up to year 2015 a CD4 count monitoring strategy has been employed. Then we considered introduction of plausible alternative monitoring strategies and predicted outcomes over 20 years to 2035. The seven main monitoring strategies compared, which are detailed in Table 1 (together with the short-hand names we use for the strategies from now on), 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 testing, 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 1000 RNA cps/mL threshold. Viral load measured < 1000 cps/mL in the past year is assumed to lead to a reduction in non-ART programme costs due to lowered frequency of clinic visits in people on first line ART. Measurement of viral load $\geq$ 1000 cps/mL is assumed to lead to a targeted adherence counselling 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 three months. In practice currently switch rates are lower than this, even in settings with viral load monitoring in place (37-39) but we chose this higher probability in order 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 >1000 cps/mL compared with measurement on a plasma sample are 86% and 92%, respectively (compared with values ranging from 81%-85% sensitivity and 88%-99% specificity in (5) for most assays); we consider other values in sensitivity analysis. We also assume there is a 3 month delay in the clinician acting on the result with the patient (i.e at the next clinical visit, even though the turn-around time of getting the result back to the clinic is generally less than this).

Sensitivity analyses were performed to consider: possible differences in population adherence profile, potential future increases in sexual behaviour, changes in effectiveness of the adherence intervention triggered by viral load being > 1000 cps/mL, a policy of initiation of ART at diagnosis, that visit frequency might be reduced in those with CD4 count > 350 /mm^3 in the past year, a zero rate of switch to second-line, 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 due to viral load being < 1000 copies/mL, a higher discount rate of 5% rather than 3%, and a 10 year time horizon instead of 20. Additionally, we considered whether whole blood or plasma is used, whether the test is done in a central laboratory and incurring the 3 month delay in acting on the result or at POC with no delay, the threshold to define failure (200, 1000 or 5000 which is only assessed in the context of plasma), and the frequency of measurement (6 monthly, annually or 2 yearly).

Lastly, 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 necessarily 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 in order to avoid a plasma separation step. Further details of how all these aspects are modelled are provided in the Supplementary Material.

Economic Analysis

Our objective is to maximize population health - the health benefits associated with the alternative monitoring strategies estimated using the metric disability-adjusted life years (DALYs) averted – from within 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 inform which is likely to represent best value from 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 those resources could generate if used for alternative purposes in the public health care system (41). As such, the threshold for a country is not readily apparent, but $500 per DALY averted is likely to be at the upper end based on the magnitude of benefit if resources were spent on other programmatic priorities such as eliminating coverage gaps for ART if these are large (42). The modelling results are intended to inform decisions in sub-Saharan African countries classified as low and low-middle income using the World Bank country classifications; which have typically struggled to scale-up viral load monitoring (31). The analyses may also be informative to higher income countries in the region (e.g. South Africa, Botswana) that have already scaled up viral load monitoring but are seeking more efficient ways to deliver ART.

Disability weights to calculate DALYs averted were derived from a recent comprehensive study (43). Unit costs (in $US at 2014 prices) are detailed in Supplementary Material. In brief, costs of viral load assays are assumed to be $22, counting all components of the cost (reagents, costs of equipment, human resources, buildings, etc) (details in Supplementary Material). Since POC VL tests are not yet available it was not possible to know the cost so we assumed a similar cost of $22 although it is likely that costs will be higher than this. The cost of measuring CD4 counts is assumed to be $10 (44). The current annual cost (including supply chain) of the first-line regimen of efavirenz, emtricitabine, tenofovir (assumed used as a fixed dose combination) is assumed to be $144 per person per year and second-line regimen of zidovudine, emtricitabine, ritonavir-boosted atazanavir $312 per person per year (44). Annual programme costs for clinic visits (not including drug or viral load / CD4 count tests) are $80 per year (1,2) with an assumed reduction to $40 per year following measurement of viral suppression because of reduced clinical visit frequency to 6-monthly from 1-3 monthly visits (with interim pharmacy-only visits depending on amount of drug that can be dispensed).

Results

The status of the simulated population in 2014 is shown in Supplementary Material (Table S1). Mean predicted outcomes over 20 years are shown in Table 2. The proportion of ART-experienced people 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 pre-ART baseline level (which can occur due to high CD4 count variability, and particularly if ART has been interrupted for a period). The proportion is intermediate for the *CD4 count monitoring (< 200)* strategy and *viral load-informed differentiated care using DBS* strategies (at 24% and 25%, 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 given in Figure 1. Programme costs for clinic visits are lowest with *viral load-informed differentiated care using DBS* due to the reduction in clinic visit frequency among virally suppressed persons. Figure 2 shows the cost effectiveness plane, indicating the total DALYs averted in the population over 20 years together with the increment in costs (both discounted), compared with *no monitoring*. Due to the higher death rate in people on

ART and higher incidence, the clinical monitoring strategies avert less DALYs than the viral load and CD4 count-based monitoring strategies. Additional costs incurred are greatest for CD4 count monitoring. *Viral load-informed differentiated care using DBS* averts a similar number of DALYs as CD4 count monitoring and is the most cost effective strategy due 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 ICER is affected by the assumed costs of viral load tests and savings in clinic visit costs in people with suppressed viral load. At our base case viral load test cost of $22, viral load-informed differentiated care is cost-effective only so long as reduced clinic visits provide at least a $30 per person per year saving offset.

In Figure 4 and Supplementary Figure 1, we consider the effect of varying model assumptions. 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 > 1000 cps/mL 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 condomless 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 in Figure 3, if no reduction in visit frequency is assumed with viral load monitoring (Supplementary Figure 1(u)) 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 due to viral load being < 1000 copies/mL (Figure 4 and Supplementary Figure 1(q and r)).

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, currently in most settings, despite CD4 counts being measured, switching rates are much lower than this. In Figure 5 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. This suggests 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 0.54m DALYs compared to *no monitoring* at a cost of $500m whereas *viral-load informed differentiated care using DBS* averts 1.12m DALYs compared to no monitoring at a cost of $361m.

In Figure 6 we consider only the viral load-informed differentiated care strategy and assess the effect of variations in various aspects; whether whole blood or plasma is used, whether the test is POC (central laboratory testing using whole blood is our DBS scenario), the threshold to define failure (200, 1000 or 5000, which is only assessed in the context of plasma), and the frequency of measurement (6 monthly, annually or 2 yearly). Monitoring 6-monthly instead of annually averts more DALYs but does not appear cost effective at the $500 threshold (ICER=$1,234). Less frequent

monitoring (e.g. 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 yearly is currently untested and potential downside health consequences are unknown so this strategy is excluded from the comparison (i.e. it is crossed out in Figure 6a). Using the 5000 cps/mL threshold also averts DALYs at a similar ICER to the 1000 cps/mL threshold, but with reduced total benefit. Use of a whole blood sample (e.g. 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 modest (6%) benefit of POC over laboratory monitoring in DALYs averted due to the fact that the 3 months 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 represents a sustainable model for providing ART. That said, the level of savings resulting from reduced clinic visits that can be realized in practice with differentiated care are as yet not certain and require monitoring. The extent of savings depends partially on the cost of viral load testing: with the fully-loaded viral load test cost of $22 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 annual non-ART programme costs averaging around $80 per year (2) in the context of patients being seen 1-3 monthly, reduction in visit frequency to 6 monthly, and perhaps in time for long term suppressed patients to 9-12 monthly, should enable such savings. There is little evidence that patients seen at sites with higher non-ART programme costs have better outcomes (2). We estimate based upon modelling Zimbabwe over 20 years, that in contrast to the current situation in many countries of CD4 count monitoring with low switch rates, introduction of viral load-informed differentiated care would more than double the number of DALYs-averted compared to no monitoring (1.12m vs 0.54m) and deliver these at reduced costs ($360m vs $500m).

Reduction in clinic visit frequency could also affect patients' adherence to ART and retention in care. There is some evidence that a reason for patients' defaulting from care is due to an inability to keep up with the intensive clinic visit schedule due to travel time and cost and loss of work time (4). Notably, retention in care was over 90% at four years among individuals enrolled in community ART clubs in Mozambique, due 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 patients may feel less connected to care with a differentiated care model, with adverse consequences for adherence and retention.

When using the CD4 count to monitor people on ART, the WHO recommended approach has been to define failure by a CD4 count < 100 /mm^3 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 infrequent for people to interrupt ART for periods of time, this latter component results in low specificity and many patients with viral suppression would be incorrectly categorized as failing and hence switched unnecessarily. The alternative approach we evaluated, similar to that used in the DART trial (48), is to define failure based on a CD4 < 100 in years 1-3 on ART, and a CD4 count < 200 thereafter. This approach performed well in our modelling in terms of the death rate in 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 overall poorer effectiveness. In settings which continue to have CD4 count capacity but not viral load capacity, this suggests 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 the 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 remains not possible to prescribe more than 1-2 months of drug, various approaches can be considered to prevent patients having to make frequent pharmacy-only visits to clinic (46,47,49-54). These include community ART groups, whereby one member picks up drug for all the members, or patients are allowed to pick up medicines in a shop or other non-clinical setting (55). 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 on-going effect of treatment means it provides an ideal means to differentiate care provision. However, given current wider availability of CD4 count tests, it might be suggested that the CD4 count could be used instead. It might be, for example, that visit frequency for people with a CD4 count above 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. 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 virologic failure is occurring (56) and, likewise, that the CD4 count can remain low despite full virologic suppression. Thus, there would be concern over the negative effects of such a strategy and, while we did model this as a potential strategy (Supplementary Figure 1(j)) it is possible that we did not fully capture the extent of those negative effects.

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

While we have argued that a DBS approach is feasible in most settings, this is not to say that the approach is working well everywhere (57). 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 evaluating viral load using DBS compared to plasma have been performed in a laboratory setting using venipuncture samples and a capillary tube to fill in the DBS card. Few studies are available to assess performance of DBS in the real world scenario where it is hot, sample transport times are long, where venipuncture is not an option, and where samples are from a finger prick rather than a capillary tube in order to measure a precise 100 µl whole blood amount per DBS, although one such study has found encouraging findings (27). Our finding of cost effectiveness of viral load informed differentiated care was robust to low levels of sensitivity or specificity using DBS (Figure 4 and Supplementary Figure 1).

We simplified consideration of types of viral load test by breaking them down according to whether 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 over-simplification in that, for example, measurement of viral load by POC testing on whole blood may not always have the same sensitivity/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 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, with plasma samples, DBS and POC, depending on settings. It should be noted that that cost we assumed for a POC assay of $22 was essentially used as a place-holder for the actual cost when this becomes known. It is uncertain whether such tests will be able to be delivered at this 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 implemented using viral load monitoring less frequently than every 12 months (e.g. 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 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 healthcare systems (with a cost-effectiveness threshold above $1400 per DALY averted) is more frequent monitoring (e.g. every 6 months) expected to be cost-effective.

We found little evidence of substantial benefits associated with moving from a cut-off to define treatment failure of viral load counts > 1000 cps/mL towards either a lower or a higher cut-off. A cut-off of 200 results in more DALYs being averted – due to identifying people with virologic failure earlier - but relies on a plasma-based test (and phlebotomy to achieve sufficient sample volume) and is not cost-effective at the $500 cost-effectiveness threshold.

Given the role of viral load testing for enabling reduced visit frequency it should have a role also in people on second-line regimens. When evaluating our monitoring strategies we assumed that CD4 count / viral load tests would only be done in patients on first-line, 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%) viral load-informed differentiated care remained cost-effective. Likewise in a scenario with high incidence rate, and scenarios with different HIV prevalence and ART coverage, suggesting our findings should hold quite broadly 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 outcome. Such trials have been characterised 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 tendency for lesser adherence. However, there may be greater reluctance to reduce visit frequency as children are growing up and constantly facing new challenges and situations. Likewise, in women in the year or so post-partum there may be reluctance to reduce visit frequency. We also considerered whether 6-monthly monitoring would be cost-effective for populations with poorer adherence profile (Supplementary Figure 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. Further, we assume continuation of HIV testing and ART availability at current trends. The profile of new POC VL tests is also 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 there are other approaches such as probabilistic sensitivity analysis and approximate Bayesian computation that we intend to pursue in further work.

This work provides insights 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 to determine how maximum health gains can be realized by patients from within the constrained resources available. We find that evidence is sufficient to recommend viral-load differentiated care using DBS but that further empirical confirmation as the approach is rolled out would be valuable.

Appendix

Working Group on Cost effectiveness of ART Monitoring Strategies in Sub-Saharan Africa

Andrew Phillips, UCL, Amir Shroufi, MSF, Lara Vojnov, CHAI, Jennifer Cohn, MSF, Teri Roberts, MSF, Tom Ellman, MSF, Kimberly Bonner, MSF, Christine Rousseau, BMGF, Geoff Garnett, BMGF, Valentina Cambiano, UCL, Fumiyo Nakagawa, UCL, Deborah Ford, UCL, Loveleen Bansi-Matharu, UCL, Alec Miners, LSHTM, Jens Lundgren, Rigshospitalet, Copenhagen, Denmark, Jeff Eaton, Imperial, Rosalind Parkes-Rotanshi, IDI Uganda, Zachary Katz, CHAI, David Maman, MSF, Nathan Ford, WHO, Marco Vitoria, WHO, Meg Doherty, WHO, David Dowdy, Brooke Nichols, Maurine Murtagh, Meghan Wareham, Kara Palamountain, Christine Chiedza Musanhu, Wendy Stevens, David Katzenstein, Andrea Ciaranello, Ruanne Barnabas, Scott Braithwaite, Eran Bendavid, Kusum J Nathoo, David van de Vijver, David Wilson, Charles Holmes, Anna Bershteyn, Simon Walker, University of York, Elliot Raizes, Ilesh Jani, Lisa Nelson, Rosanna Peeling, Fern Terris-Prestholt, Joseph Murungu MoHCC Zimbabwe, Tsitsi Mutasa-Apollo MoHCC Zimbabwe, Tim Hallett, Imperial College, Paul Revill, U of York.

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Table 1. Description of the seven main monitoring strategies modelled. The column heading is the short name given to the strategy.

	No monitoring	**Clinical monitoring**	**Clinical monitoring VL 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)	--	Check on presence of symptoms every 3m.	Check on presence of symptoms every 3m Measure viral load if WHO 4 condition diagnosed or 2 WHO 3 conditions diagnosed in 1 year.	Check on presence of symptoms every 3m Measure CD4 count if WHO 4 condition diagnosed or 2 WHO 3 conditions diagnosed in 1 year.	6 m CD4 count. If failure criteria appear to be met, re-measure to confirm (confirmatory CD4 count).	12 m CD4 count. If failure criteria appear to be met, re-measure to confirm (confirmatory CD4 count).	VL measure using DBS at 6m, 12m and every 12m thereafter. If VL > 1000 then give adherence intervention and re-measure VL 3 m later (confirmatory VL measure). No CD4 count measurments.
Failure criteria	--	WHO 4 condition diagnosed or 2 WHO 3 conditions diagnosed in 1 year.	VL > 1000 cps/mL	CD4 count <250 /mm^3.	CD4 count < pre-ART baseline or CD4 count < 100 /mm^3 in confirmatory CD4 count	CD4 count < 200 after > 3 years on ART. CD4 < 100 /mm^3 after > 1 year on ART in confirmatory CD4 count)	VL >1000 cps/mL in confirmatory VL measure.
Reduction in clinical visit frequency (and hence reduction in non-ART programme cost)*	No	No	No	No	No	No	Yes, when most recent viral load < 1000 cps/mL, measured in past year.

***** We assume 3 monthly clinical visits for all strategies except under viral load-informed differentiated care when most recent viral load < 1000 cps/mL, measured in past year. More frequent clinical visits than 3 monthly are not modelled as the model advances in 3 month periods; cps = copies; VL = viral load; WHO 4 = WHO stage 4 condition; ART = antiretroviral therapy; 3m = 3 monthly, etc.

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

	No monitoring	**Clinical monitoring**	**Clinical monitoring VL confirmation**	**Clinical monitoring CD4 count confirmation**	**CD4 count monitoring (WHO)**	**CD4 count monitoring (< 200)**	**Viral load-informed differentiated care using DBS**
Percent of ART experienced people who have fulfilled criterion for failure of first-line ART	7%	14%	10%	13%	41%	26%	27%
Percent of ART-experienced people who have started second-line ART	3%	13%	10%	13%	38%	24%	25%
Percent of people on ART who have (true) viral load < 1000 cps/mL (mean; over 20 year time horizon)	76%	79%	78%	79%	85%	82%	86%
Death rate (per 100 person years) amongst people on ART	4.43	3.63	4.06	3.67	3.02	3.07	3.18
Death rate (per 100 person-years) amongst people with HIV	5.45	4.91	5.2	4.93	4.36	4.43	4.47
Death rate (per 100 person-years) in whole adult population	1.69	1.63	1.66	1.63	1.56	1.58	1.57
Death rate (per 100 person years) amongst people on ART who have virologically failed 1st line (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

cps = copies; ART = antiretroviral therapy;

Figure 1. Overall programme costs in ($m per 3 months) according to monitoring strategy (mean over 2015-2034, discounted at 3% per annum from 2015)

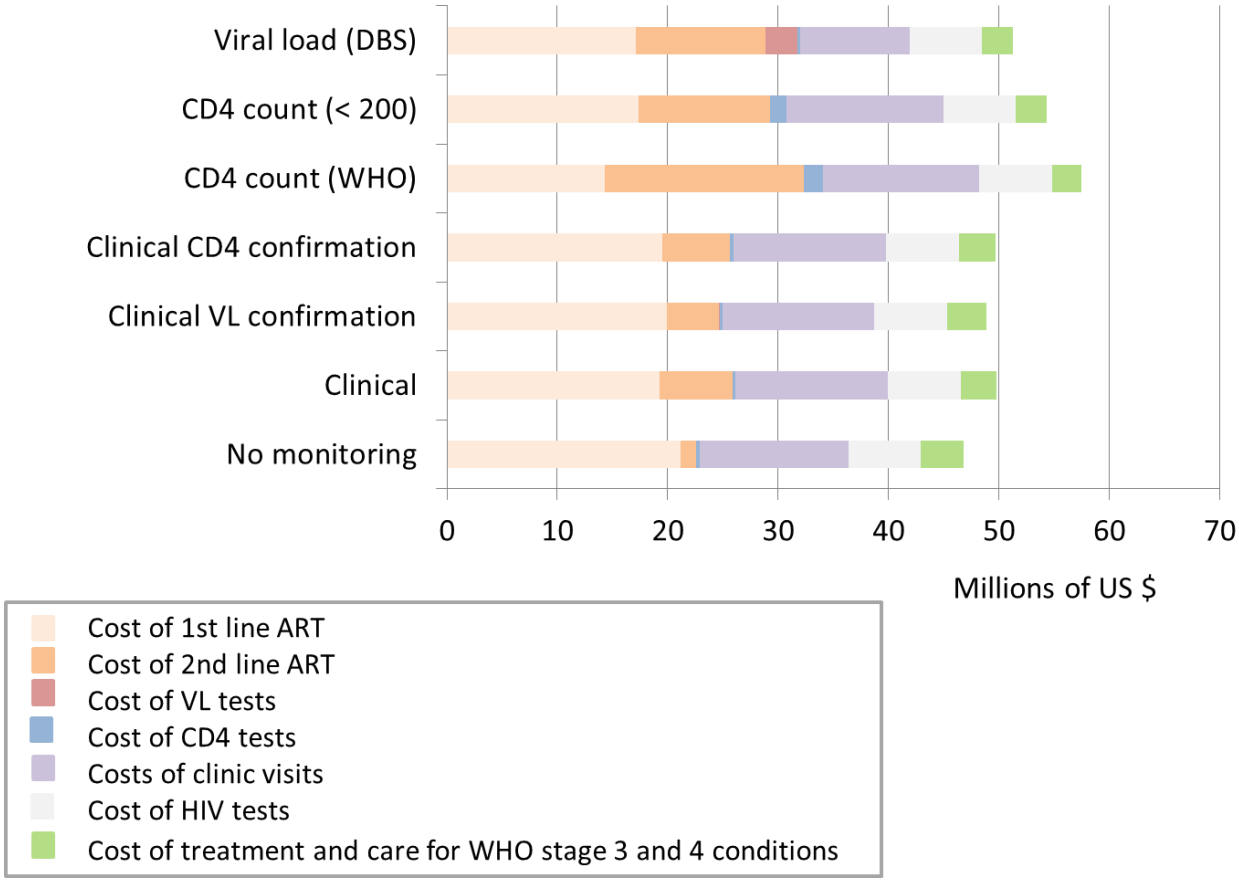


Figure 2. Cost effectiveness plane showing clinical- and CD4-based monitoring strategies along with viral load-informed differentiated care using DBS. ICER - incremental cost-effectiveness ratio

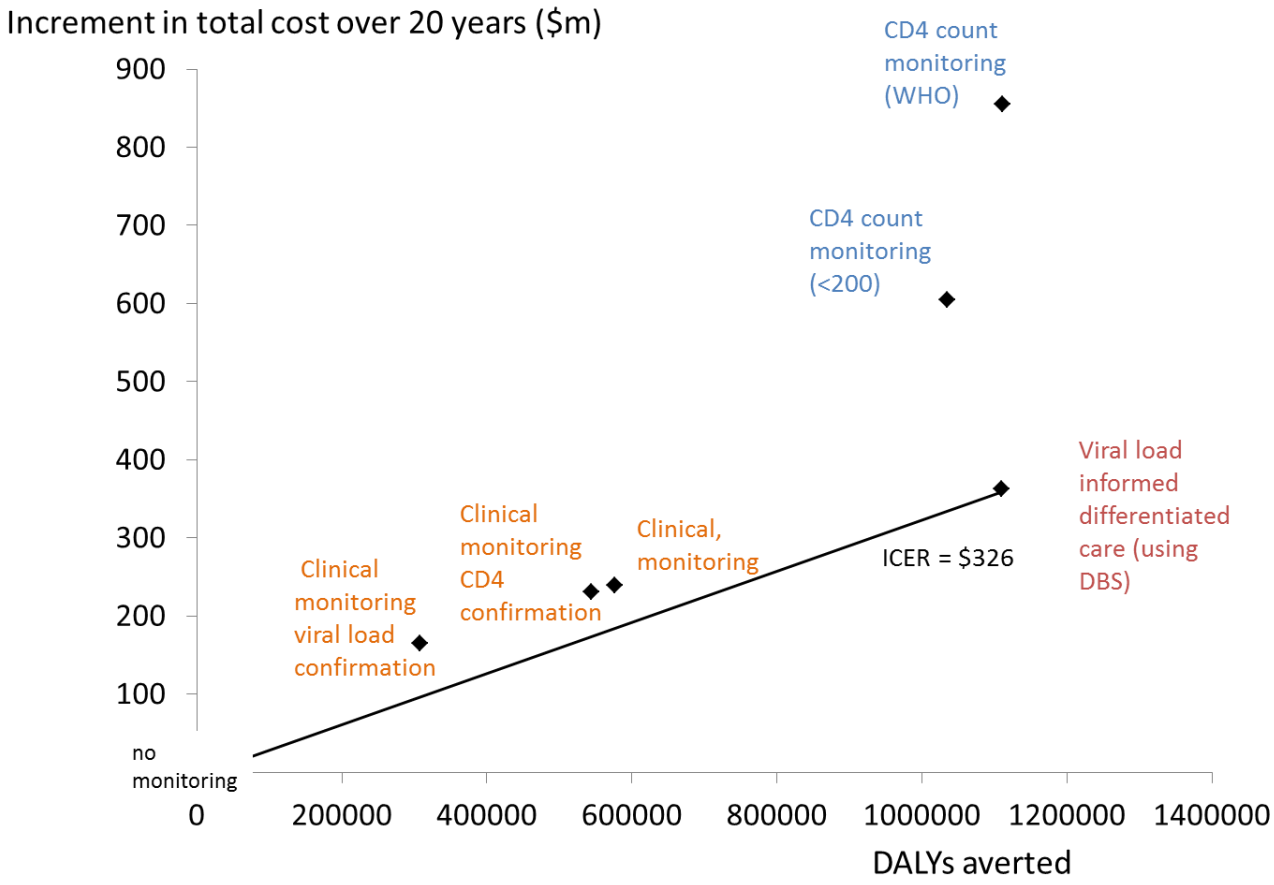


Figure 3. Indication of whether viral load-informed differentiated care is the most cost effective monitoring strategy according to (i) cost of viral load tests and (ii) reduction in non-ART programme costs in people with viral suppression. In context of cost-effectiveness threshold $500. Colours indicate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

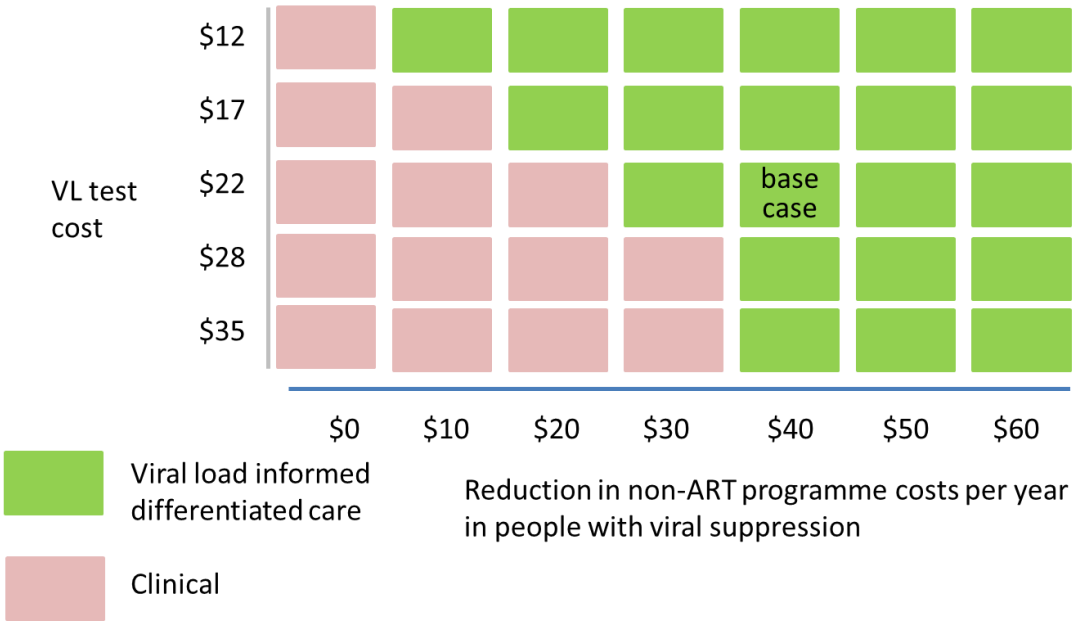
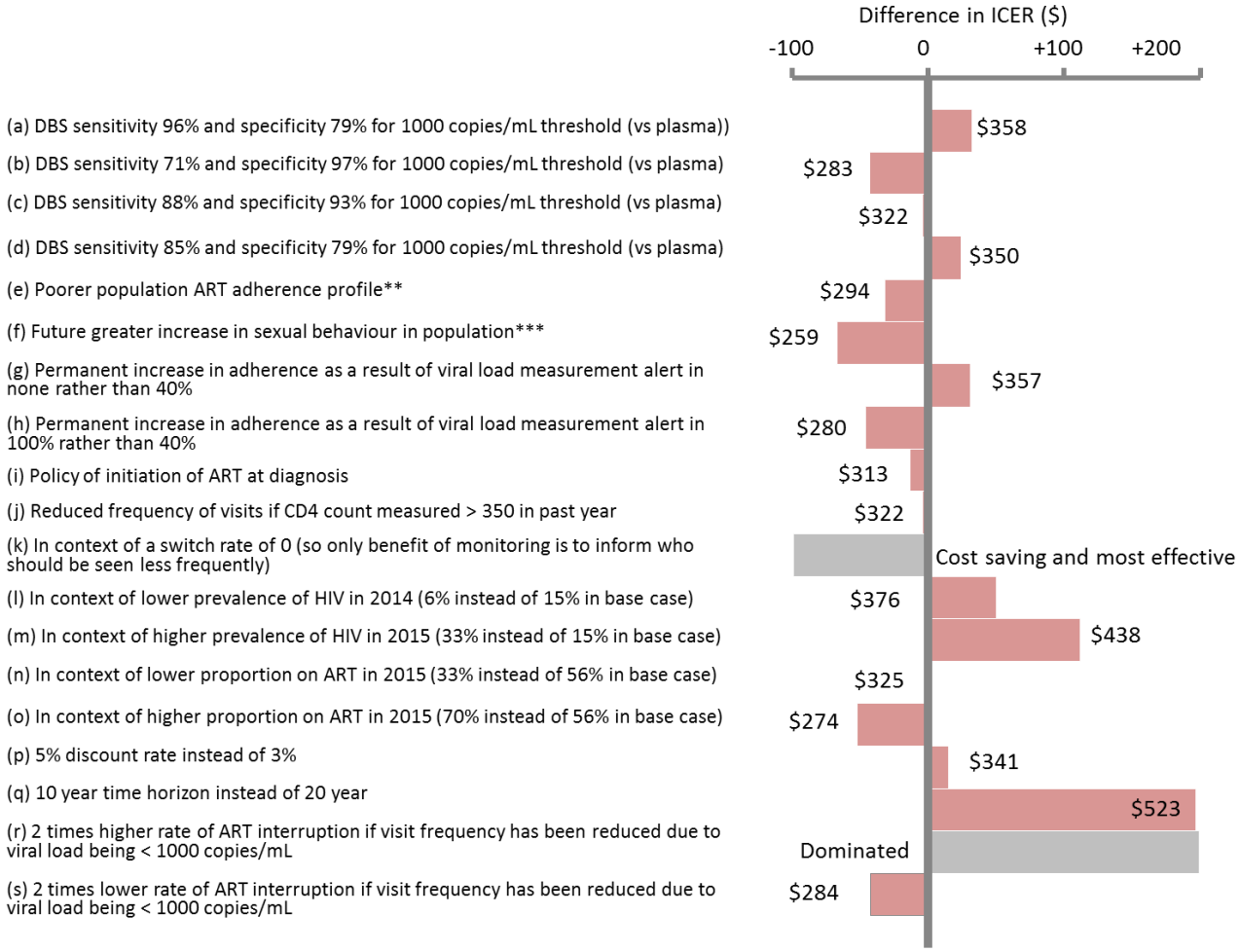


Figure 4. Incremental cost-effectiveness ratio (ICER) for viral load informed differentiated care using DBS (compared with next less effective strategy on the efficiency frontier) according to changes in assumptions. In each case, except where indicated (^),viral load informed differentiated care is the strategy with the lowest net monetary burden at the $500 threshold. See also corresponding cost effectiveness planes in Supplementary Figure 1.



+ base case: sensitivity 86% and specificity 92% * clinical monitoring with CD4 count confirmation is cost-effective; ** 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 / 100 person years compared with 0.84 in base case; *** such that HIV incidence is 1.46 / 100 person years compared with 0.84 in base case; ^ no monitoring is the most cost effective strategy; based on 200 model runs per strategy for each of (a)-(s).

Figure 5. Cost effectiveness plane showing the current sitiation - CD4 count (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)

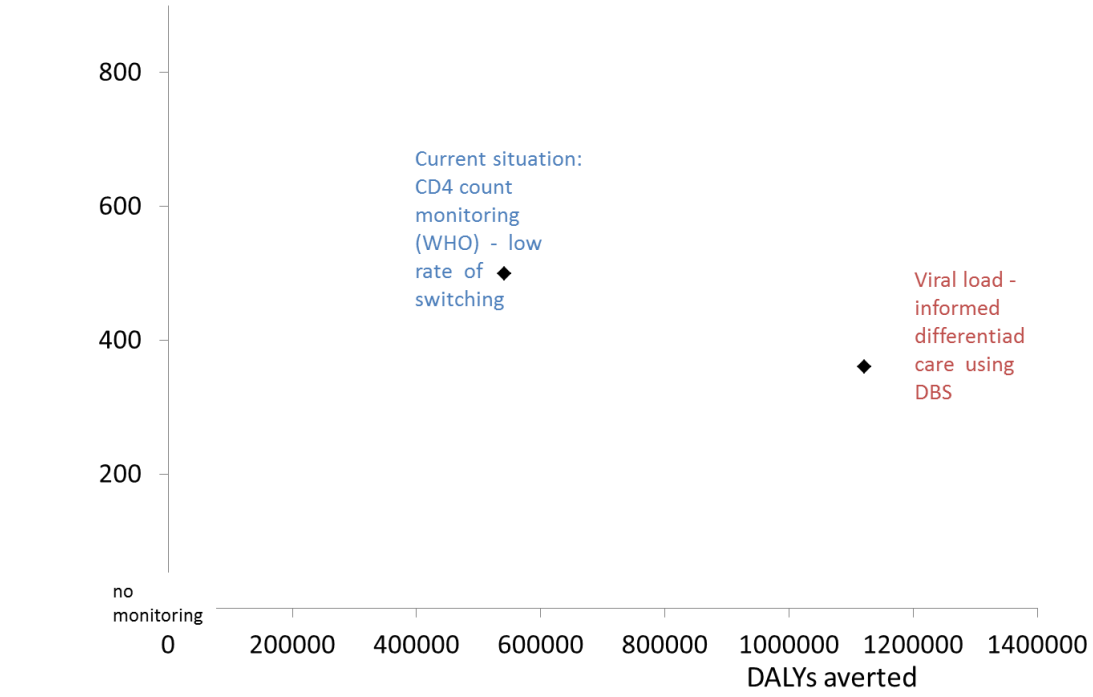
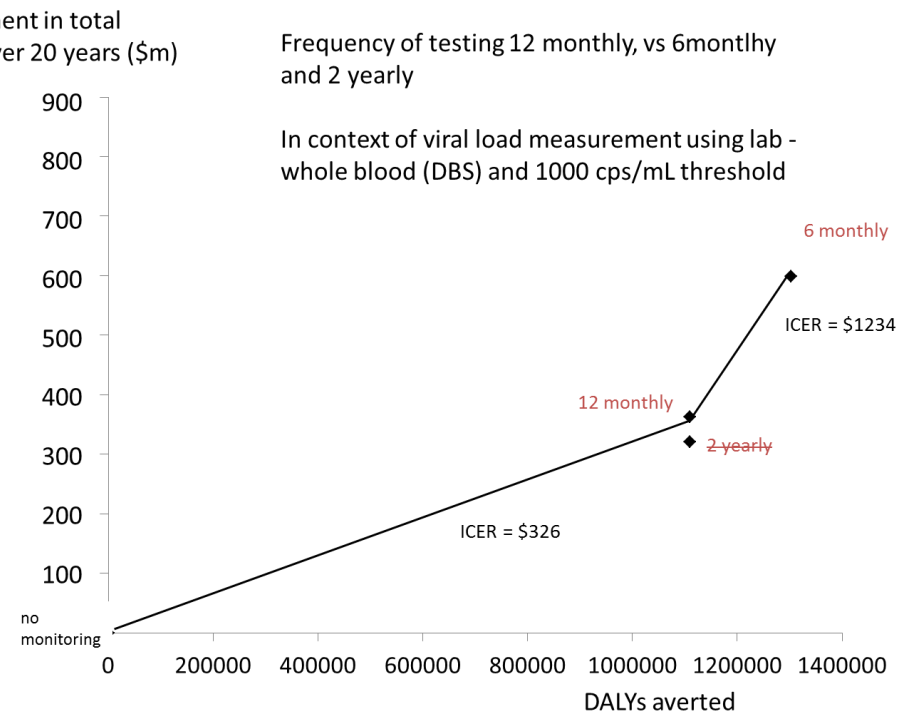
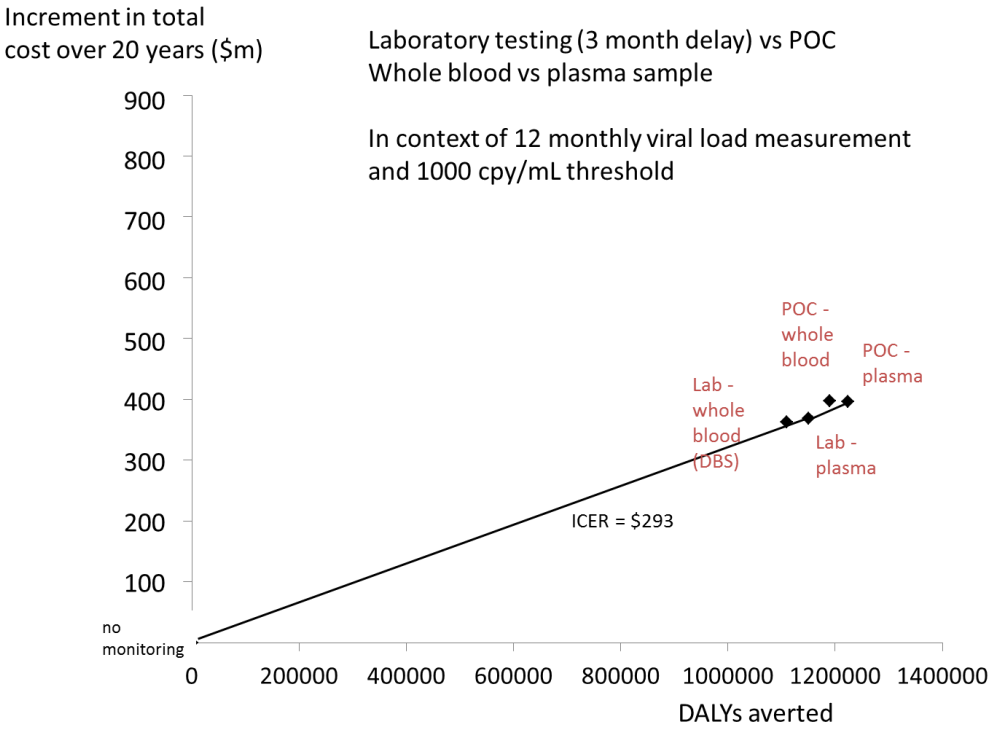


Figure 6. Cost-effectiveness planes showing the effect of viral load measurement frequency, format and threshold, all in the context of viral load-informed differentiated care. In (a), 12-monthly viral load monitoring is compared to 6 monthly (n.b. 2 yearly monitoring is excluded from the cost-effectiveness 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). In (b), laboratory whole blood corresponds to DBS. In (c), alternative thresholds to define failure (viral load cps/mL>200, >100 and >5000) are compared in the context of 12-monthly laboratory monitoring using plasma.

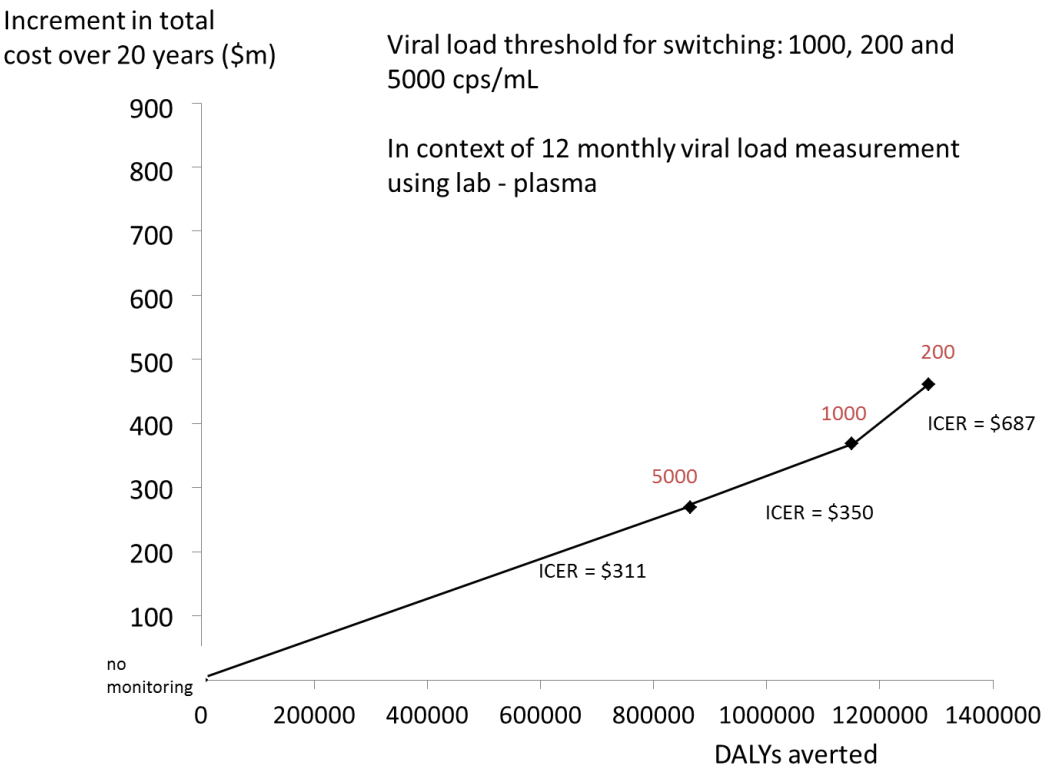
(a)



(b)


Increment in total cost over 20 years ($m)
Laboratory testing (3 month delay) vs POC
Whole blood vs plasma sample
In context of 12 monthly viral load measurement and 1000 cpy/mL threshold
900
800
700
600
500
400
300
200
100
no monitoring
0
200000
400000
600000
800000
1000000
1200000
1400000
DALYs averted
POC - whole blood
POC - plasma
Lab - whole blood (DBS)
Lab - plasma
ICER = $293

(c)


Increment in total cost over 20 years ($m)
Viral load threshold for switching: 1000, 200 and 5000 cps/mL
In context of 12 monthly viral load measurement using lab - plasma
900
800
700
600
500
400
300
200
100
no monitoring
0
200000
400000
600000
800000
1000000
1200000
1400000
DALYs averted
200
1000
5000
ICER = $687
ICER = $350
ICER = $311

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