Point-of-care viral load testing for sub-Saharan Africa: informing a target product profile

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**Abstract (**100 word limit)

Point-of-care (POC) viral load tests are being developed to monitor patients on antiretroviral therapy (ART) in sub-Saharan Africa. Test design involves trade-offs between test attributes, including accuracy, complexity, robustness and cost. With use of a model of the HIV epidemic and ART programme in Zimbabwe, we find the attributes of a viral load testing approach most influential for cost-effectiveness are avoidance of a high proportion of failed tests or results not received, use of an approach that best facilitates retention on ART, and the ability to facilitate greater use of differentiated care, including through expanding coverage of testing availability.

Keywords: HIV, viral load, point-of-care, diagnostics, monitoring, economic evaluation, cost-effectiveness, model, antiretroviral therapy

**Introduction**

Since 2013, the World Health Organization (WHO) recommends viral load as the preferred approach for monitoring patients on ART(1). While in high income countries, tests are done on plasma samples obtained by venepuncture, in low income settings a more realistic option, particularly for more rural areas, is the use of dried blood spots (DBS), which are relatively easily collected and can be transported to regional laboratories in stable condition(1,2). The intent is that the result is received back at the clinic after a few weeks and acted upon at the next clinic visit. Although this approach is increasingly being adopted(3), there remains interest in development of tests which require minimal user training and can be performed in the clinic while a patient is present (i.e. at point-of-care (POC))(4-7). Several attributes need to be considered when designing such tests, including accuracy, whether the format allows easy use by lower cadres of staff and where there is not a reliable electricity supply. Developers must balance trade-offs between these attributes and with the cost at which a test can be produced. Here we use a modelling approach to explore the impacts of different test attributes on cost-effectiveness and target test costs. This builds upon previous work on POC viral load tests in relation to the use of DBS(8).

**Methods**

We use an existing individual-based stochastic model of heterosexual transmission, progression and treatment of HIV infection, which incorporates treatment adherence and acquisition and transmission of drug resistance mutations ((8); Supplementary Material). The epidemic and ART program data simulated are those from Zimbabwe (Supplementary Table S1, Figure S1). We assumed that CD4 count monitoring is used prior to 2017, but that viral load monitoring using the WHO-recommended 1000 cps/mL threshold for switching is then introduced. Measurement of viral load >1000 cps/mL prompts enhanced adherence support with a follow-up measure taken after 3 months. A measured viral load <1000 cps/mL in the past year is assumed to lead to a reduction in non-ART programmatic costs due to lowered frequency of clinic visits in people on first line ART (*viral load-informed differentiated care*(8)).

A range of attributes relating to the viral load testing approach were considered, outlined in Table 1a. We first simulated outcomes over the years 2017-2036 based on a set of viral load testing attributes that were considered to approximate the use of a DBS approach and the current situation in Zimbabwe (“base DBS scenario”; Table 1a). We then explored the effects of changes in the attribute values, one-by-one, on population health. Population health is measure using disability-adjusted life years (DALYs) incurred; a generic measure of the burden of disease in the population capturing both premature mortality and morbidity as a result of ill health.

In the DBS base scenario it is assumed that 75% of the population have access to viral load testing, while the remainder would continue to be monitored using CD4 count testing. In previous modelling results, DALY outcomes from monitoring the CD4 count using a switch criteria based on a threshold of 200 /mm3 were not appreciably different from monitoring with viral load(8). Here, so that we can capture the effects of viral load testing as intended to be used, we assume a relatively high rate of switch to second line when the failure criteria have been met with viral load monitoring (0.2 /3 months) which is greater than the 0.001 /3 months with CD4 count monitoring (based on the number of people on second line ART(9)).

*Economic considerations*

Programme costs resulting from different viral load testing attributes were also considered, enabling assessment of cost-effectiveness on the basis of *net DALYs*. This is a measure analogous to net health benefit (10) and compares the health gains from an intervention with the health losses associated with displaced or forgone intervention which can no longer be provided due to the commitment of limited healthcare resources to the evaluated intervention (i.e. it compares health gains to health opportunity costs). The cost-effectiveness threshold (CET) is central to the estimation of net DALYs – it is an estimate of the cost-per-DALY-averted of interventions displaced/foregone at the margin when a new intervention in introduced (11). Net DALYs is then calculated as DALYs + costs/CET. For most healthcare systems the CET is generally not readily apparent but a value of $500 per DALY averted is thought to be realistic for HIV programmes in low-income settings in sub-Saharan Africa because alternative HIV policy interventions (e.g. expanded ART provision) offer health gains at about this level (12). The testing policy with the lowest net DALYs is deemed the cost-effective policy from amongst those evaluated since it leads to the greatest reduction in population burden of disease (i.e. lowest DALYs).

~~burden (DALYs, plus costs divided by the cost-effectiveness threshold) associated with alternative tests. The testing policy with the lowest net DALY burden was deemed cost-effective since it leads to the lowest level of disability/ill health in the population, considering the other possible uses of the resources to enhance population health. The cost-effectiveness threshold plays an important role in determining net DALY burden and represents the opportunity costs of resources required to fund an intervention, in terms of the health gains those resources should be able to generate if used for alternative purposes in the public health care system(10). A value of $500 per DALY averted is thought to be realistic for low income settings in sub-Saharan Africa(11)~~*~~.~~*

The opportunity cost of interventions displaced at the margin, represented by the CET, also informs the price within which interventions must be delivered to offer population health improvement and be deemed cost-effective. For each value of each viral load testing attribute, the upper-bound cost that the viral load test would need to be delivered is provided. A health system perspective was adopted and costs incurred by patients were not included. Both costs and DALYs-averted were discounted to present value using a 3% per annum discount rate.

Unit costs (in $US at 2015 prices) are detailed in Supplementary Material. Costs of viral load assays were set at a base value of $22, based on costing using the DBS approach, counting all components of delivery (reagents, equipment, human resources, buildings, set up costs, etc – referred to as a “fully loaded” cost) (details in Supplementary Material). Annual programme costs for clinic visits (not including drug or viral load / CD4 count tests) are $80 per year(13) with an assumed reduction to $40 per year following measurement of viral suppression because of reduced clinical visit frequency within a differentiated care model(8). Health utilities / disability weights to calculate DALYs averted were derived from a recent comprehensive study(14).

**Results**

The status of the simulated Zimbabwean adult population in 2014 is shown in Supplementary Table S1. Figure 1a shows the effect on DALYs incurred over 20 years of differences in attribute values associated with viral load testing. The delay associated with DBS testing had a relatively modest influence on the number of DALYs incurred. The sensitivity of the test for detecting a value above 1000 cps/mL was more influential, with generally a higher sensitivity leading to a lower number of DALYs incurred; regardless of specificity, due to enhanced adherence support and switching to second-line in those who require this. When the sensitivity was approximately 90% or above then a lower specificity was associated with a lower number of DALYs incurred, reflecting that those with viral loads between 50 and 1000 copies/mL may also benefit from a switch to 2nd line. The viral load threshold used is also moderately influential, with more DALYs averted the lower the threshold. The proportion of tests which fail or the result lost was also influential, due to the inability to act on viral load failure in a timely way or at all. The probability that viral load informed differentiated care was implemented did not influence the DALYs, since we did not assume any positive or negative health effects of such a policy, only an impact on costs. The rate of switch to second-line ART in people with first-line failure is also influential on DALYs incurred. It is uncertain whether the viral load testing format (laboratory based or POC)will influence this parameter although it is plausible that if the result is available while the patient is present then a switch is more likely to be instigated compared to a laboratory result that is only available on a return visit. The extent to which a test can result in increased coverage of viral load positively influenced the DALY outcome, mostly through the assumed greater rate of switch to second line where viral load testing is used. The rate of ART interruption / loss to follow-up is highly influential although, again, it is uncertain whether the form of viral load testing will influence this parameter.

In Figure 1b we considered the influence of each factor on the net DALYs, which took into account the opportunity costs of differences in cost in addition to the DALYs incurred. The relative influence of the various factors was similar to Figure 1a, with a few exceptions. Lower specificity was associated with a higher net DALYs, due to the additional cost of second-line drugs, and a sensitivity and specificity of approximately 90% was optimal. The viral load threshold to define ART failure was less influential on net DALYs than it was on DALYs, because use of higher thresholds reduced costs. The proportion of tests that fail or are lost was even more influential on net DALYs than on DALYs, due to the cost incurred with repeated attempts to successfully measure viral load. The probability of implementing viral load informed differentiated care was also influential, due to the clinic cost savings involved. The probability of switching to second line ART once the failure criteria are met was less influential on net DALYs than on DALYs, again due to the higher costs of second line ART.

In Table 1b we provided, for each level of viral load testing attribute, the upper bound cost for a POC test to be considered cost-effective compared with the DBS base scenario. For example, if a POC test demonstrated an increase in the probability of viral load informed differentiated care from 0.8 to 0.9 then, with no other difference compared with the DBS base scenario, it could cost $24 and still be cost effective compared to the DBS base scenario with the $22 test cost. Alternatively, if a POC test demonstrated a halving of the rate of ART interruption / loss to follow-up compared with the DBS approach, with no other difference compared with the DBS base scenario, then it would be cost effective up to a cost of $41 per test. Further, if the approach resulted in 100% coverage then a test could cost up to $28 and remain cost effective. This is if the test replaced the $22 test in all - if the test were used to fill the coverage “gap” then it could cost much more and remain cost effective.

**Discussion**

Our results indicate that the attributes of a viral load testing approach most influential for cost-effectiveness are avoidance of a high proportion of failed tests or results not being received and, so far as it can be influenced by the viral load monitoring strategy, use of an approach that best facilitates retention on ART. Also of particular importance was the ability to facilitate greater use of differentiated care through expanding coverage of availability viral load testing. These attributes are most likely to be found with a robust POC viral load test that facilitates decision making while the patient is present. It is noteworthy that a three month delay in receiving a result does not result in a significant negative impact, and also that sensitivity and specificity both in the region of 90% appears acceptable. Due to the higher cost of second line drugs, the influence of the switching rate in those with first-line ART failure was not one of the most important for cost-effectiveness. Our results emphasize the need for POC viral load tests and may inform the development of tests as well as the design of future implementation studies and trials on viral load testing approaches. Our results suggest that it is important for studies to consider how POC viral load testing impacts the patient care model, such as earlier switch to 2nd line or better retention in care. Whether these factors are indeed improved with POC testing will have to be evaluated in implementation studies, and data could then be used to inform our cost-effectiveness modelling. It may prove to be important, for example, that the waiting time taken to receive a result from a POC assay is as low as possible.

Several POC viral load assays have already been developed, e.g. by Cepheid, Liat, Alere, and some pilot studies have been completed. Many of these assays already meet high levels of accuracy, but our results indicate that perhaps other parameters still need to be prioritized, such as potential coverage and assay costs.

WHO has established the ASSURED criteria for POC diagnostics (Affordable, Sensitive, Specific, User-friendly, Rapid/Robust, Equipment-free and Deliverable to end users)(15). It has been suggested that the WHO preference for equipment-free POC tests presents a potential conflict with the need to deliver high sensitivity and specificity(16). Our results suggest that the population health effects of reduced sensitivity and specificity, of an equivalent level to the DBS base scenario, for example, are modest compared to the potential benefits of increased access and ease of patient management. Weidemaier et al argue that ASSURED criteria imply that resource capacities where interventions are ultimately to be used should be taken into consideration throughout the tech­nology development process(16). This study attempts to facilitate this for POC viral load tests.

We assigned a set of attribute values to the DBS base scenario but there remains uncertainty whether these can be achieved in practice. We considered compiling one or two plausible sets of attributes that might reflect a particular POC test. We elected not to do this as any given choice of parameter sets appears extremely arbitrary as there are essentially no data yet available on real life implementation of true POC assays to inform the values. As data become available on attributes of different testing approaches, our model can be used to compare cost-effectiveness both between POC tests and with the DBS alternative.

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**Author Contributions**

All authors contributed to defining the analysis concept and design, providing critical input to the conduct of the modelling analysis, and writing the manuscript. AP, VC and FN developed the model and conducted the modelling analysis.

**Conflicts of Interests**

Dr. Phillips reports grants from BMGF, during the conduct of the study; personal fees from Gilead Sciences, personal fees from Abbvie, personal fees from GSK Biologicals, personal fees from Ashfield Communications, outside the submitted work.

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Table 1a. Key attributes of a viral load testing approach and values for attributes considered.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Attribute of viral load testing approach | Value in base scenario (using DBS) | Other values considered | | Comment |
| (i) Delay in result | 3 month delay | No delay | | By definition, any delay will be avoided with a POC test and therefore the result will be available at the same visit. |
| (ii) Sensitivity / specificity relative to plasma for 1000 copies/mL cut-off | 84% / 89% | 58/96  60/99  69/97  70/79  74/75  78/93  79/71  80/84  82/96 | 84/89  89/93  90/85  95/90  96/65  96/77  99/69  100/100 | If a plasma sample is used for a POC test then the accuracy of the test could be higher than for DBS. In calibrating any test it is useful to know whether to prioritize sensitivity or specificity |
| (iii) Viral load threshold used to define first-line ART failure (cut-off for qualitative or semi-quantitative assays) | 1000 copies/mL | 200, 500, 3000, 5000 | | WHO failure threshold is 1000 copies/mL. This choice of threshold is important if a qualitative test is being developed that reads as positive or negative rather than providing a value. |
| (iv) Proportion of tests failed or result lost | 0.15 | 0.8, 0.5, 0.3, 0 | | Likely that most tests that are done using POC will actually be used since the patient is still present when the result is received. For DBS a higher proportion of tests will not get used due to communication / linkage failures, leading to delay in informed decision-making and wasted costs. We assume if a test fails then it is attempted again after 3 months. |
| (v) Probability of differentiated care if VL < 1000 being implemented | 0.8 | 0.5, 0.6, 0.7, 0.9 | | POC test should enable viral load-informed differentiated care because the date of a person’s next clinic appointment can be set with the person present, avoiding the need to call people later on to adjust the timing of their next visit. |
| (vi) Coverage of population with viral load testing | 75% of population | 70%, 80%, 85%, 90%, 95%, 100% | | POC tests should enable greater access to (coverage of) viral load testing in a country, due to being an additional option to DBS testing. |
| (vii) Probability of switch to second-line ART per 3 months once failure definition met | 0.2 per 3 months | 0.05, 0.10, 0.15, 0.25, 0.30, 0.35, 0.40, 0.60, 1.00 | | Theoretically possible that a POC test will result in a more rapid switch, due to ability to act on viral load result while patient present. |
| (viii) Probability of ART interruption / loss to follow-up | 0.020 per 3 months | 0.030, 0.025, 0.015, 0.010, 0.005 | | Given the enabling of viral load informed differentiated care, POC tests could result in lower rates of disengagement from care, although this is uncertain and needs to be assessed in studies. |

(i) delay may be up to 3 months (ii) The sensitivity and specificity are not input parameters – they are outputs which depend on the assumed standard deviation for the measurement variability and any offset (see Supplementary Material, section 9). Values Informed by overview of various studies comparing VL values on DBS/plasma (e.g. Mavedzenge et al PLOS One 2015); World Health Organisation. Technical and operational considerations for implementing HIV viral load testing. Access to HIV diagnostics. July 2014. [www.who.int](http://www.who.int); Smit PW et al. 2014. Systematic Review of the Use of Dried Blood Spots for Monitoring HIV Viral Load and for Early Infant Diagnosis. PLoS ONE 9(3): e86461. doi:10.1371/journal.pone.0086461 (iii) WHO 2013 Treatment Guidelines, www.who.int; (iv) this is failure due to technical reasons in the lab or failure for results to be successfully returned – the value is likely to vary by setting within countries as well as between countries – the value of 0.15 is a conservative estimate of what is achieveable with a DBS transport network (e.g. Chiduo MG et al. Early infant diagnosis of HIV in three regions in Tanzania; successes and challenges. BMC Public Health 2013, 13:910; Chatterjee A, et al. Implementing services for Early Infant Diagnosis (EID) of HIV: a comparative descriptive analysis of national programs in four countries. BMC Public Health 2011, 11:553; Current EID coverage in Zimbabwe; F Cowan (personal communication, CESHHAR, Zimbabwe)) – it is not yet certain if use of DBS for viral load testing can achieve similar results, since the number of tests to be done will be much higher; (v) assumption – 0.80 may be rather high for DBS and data are required to inform this; (vi) coverage assumed to be 75% in base case – this is closely linked to (iv) above and 75% is conservative for what is feasible for EID; an assumption is made, even for base scenario DBS, that the probability of switch is higher with viral load monitoring than with CD4 count monitoring (0.001 per 3 months). (vii) Differs by setting (e.g. Johnston, V., et al. 2012. JAIDS., 61, (3) 370-380 ; Fox MP et al. JAIDS 2012. 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, (4) 428-437 available from: PM:22433846); (viii) consistent with Kranzer, K. & Ford, N. 2011. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. *Trop.Med.Int.Health*, 16, (10) 1297-1313 (see details in Supp Material). This is base rate of interruption – increased within first 2 years of ART and in those with sub-optimal lifetime tendency to adhere (see details in Supp Material).

Table 1b. Maximum cost of viral load test for net health benefit in the context of changes in values of each attribute of the viral load testing approach, changing the value of only one attribute at a time.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Attribute of viral load testing approach | Values for factor considered | | Maximum fully-loaded cost of viral load test for reduced net DALYs compared with base scenario | |
| (i) Delay in result | No delay  3 month delay\* | | $23  $22 | |
| (ii) Sensitivity / specificity relative to  plasma for 1000 copies/mL cut-off | Sensitivity / Specificity  58/96  60/99  69/97  70/79  74/75  78/93  79/71  80/84  82/96 | 84/89\*  89/93  90/85  95/90  96/65  96/77  99/69  100/100 | $21  $20  $20  $19  $17  $20  $15  $19  $21 | $22  $21  $22  $21  $15  $17  $20  $23 |
| (iii) Viral load threshold used to define  first-line ART failure (copies/mL)  (cut-off for qualitative assay) | 200  500  1000\*  3000  5000 | | $20  $23  $22  $19  $19 | |
| (iv) Proportion of tests failed or result lost  \*\* | 0.80  0.50  0.30  0.15\*  0.00 | | $5  $16  $19  $22  $24 | |
| (v) Probability of differentiated care  if VL < 1000 being implemented | 0.5  0.6  0.7  0.8\*  0.9 | | $14  $16  $19  $22  $24 | |
| (vi) Difference in coverage of population with viral load testing | 70%  75% \*  80%  85%  90%  95%  100% | | $20  $22  $23  $25  $26  $26  $28 | |
| (vii) Probability of switch to second-line  ART per 3 months once failure definition met | 0.05  0.10  0.15  0.20\*  0.25  0.30  0.40  0.60  1.00 | | $17  $20  $20  $22  $22  $23  $23  $23  $25 | |
| (viii) Probability of ART interruption / loss  to follow-up (per 3 months) | 0.030  0.025  0.020\*  0.015  0.010  0.005 | | $3  $14  $22  $29  $41  $48 | |
|  |  | |  | |

\* base scenario (VL cost $22); \*\* assumed that there is a 90% chance that the cost of the test is nevertheless incurred

Figure 1a**.** Comparison of health outcomes according to individual attributes of the viral load testing approach, shown as the difference in DALYs incurred compared with DBS base scenario. The influence of the attribute is indicated by the range in difference in DALYs incurred for plausible values of the attribute. *Note: will be combined with Figure 1b in printed version.* DALYS are per 3 months over 20 years from 2017, discounted at 3% per year.

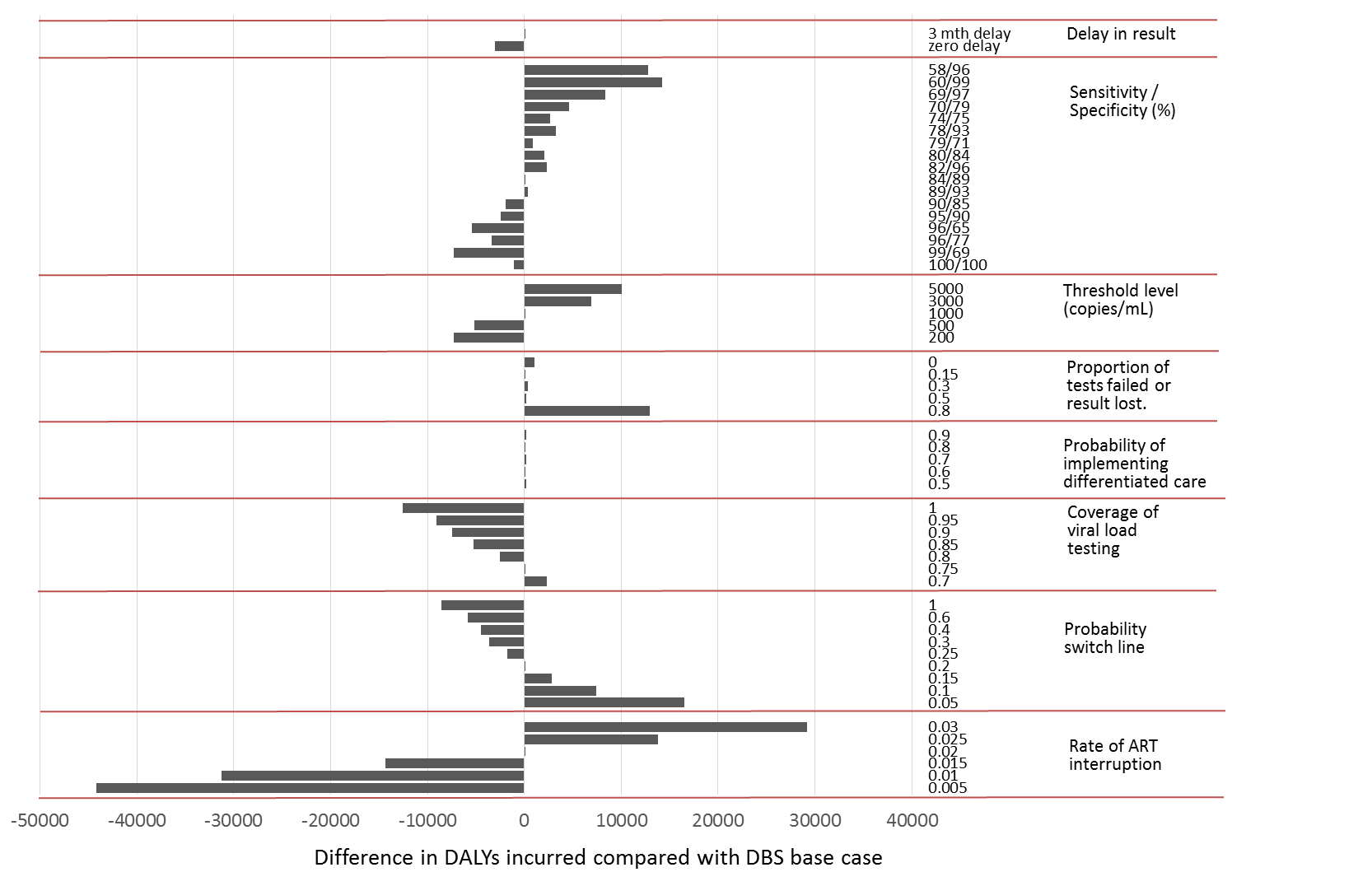


Figure 1b.Comparison of cost-effectiveness according to individual attributes of the viral load testing approach, shown as the difference in net DALYs compared with DBS base scenario. The influence of the attribute is indicated by the range in difference in net DALYs for plausible values of the attribute.

