

# Potential Cost-effectiveness of HIV Viral Load Sample Collection and Testing Methods in Malawi

**Joseph B. Babigumira**

University of Washington

**Solomon J. Lubinga**

University of Washington

**Mindy M. Cheng** (✉ [mindy.cheng@roche.com](mailto:mindy.cheng@roche.com))

Roche Molecular Systems Inc <https://orcid.org/0000-0003-0148-8098>

**James K. Karichu**

Roche Molecular Systems Inc

**Louis P. Garrison, Jr.**

University of Washington

---

## Research article

**Keywords:** HIV viral load testing, cost-effectiveness, dried blood spot (DBS), plasma, sample collection

**Posted Date:** August 27th, 2019

**DOI:** <https://doi.org/10.21203/rs.2.13295/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

Background HIV viral load (VL) monitoring informs antiretroviral therapy failure and helps to guide regimen changes. Typically, VL monitoring is performed using dried blood spot (DBS) samples transported and tested in a centralized laboratory. Novel sample collection technologies based on dried plasma stored on a plasma separation card (PSC) have become available. The cost-effectiveness of these different testing approaches to monitor VL is uncertain, especially in resource-limited settings. The objective of this study is to evaluate the potential cost-effectiveness of HIV VL testing approaches with PSC samples compared to DBS samples in Malawi. Methods We developed a decision-tree model to evaluate the cost-effectiveness of two different sample collection and testing methods—DBS and PSC samples transported and tested at central laboratories. The analysis used data from the published literature and was performed from the Malawi Ministry of Health perspective. We estimated costs of sample collection, transportation, and testing. The primary clinical outcome was test accuracy (proportion of patients correctly classified with or without treatment failure). Sensitivity analysis was performed to assess the robustness of results. Results The estimated test accuracy for a DBS testing approach was 87.5% compared to 97.4% for an approach with PSC. The estimated total cost per patient of a DBS testing approach was \$19.39 compared to \$17.73 for a PSC approach. Based on this, a PSC-based testing approach “dominates” a DBS-based testing approach (i.e., lower cost and higher accuracy). Conclusion The base-case analysis shows that a testing approach using PSC sample is less costly and more accurate (correctly classifies more patients with or without treatment failure) than with a DBS approach. Our study suggests that a PSC testing approach is likely an optimal strategy for routine HIV VL monitoring in Malawi. However, given the limited data regarding sample viability, additional real-world data are needed to validate the results.

## Background

Of the nearly 37 million people living with human immunodeficiency virus (HIV) infection worldwide in 2016, 25.5 million were in sub-Saharan Africa[1]. In Malawi, one million of the 18.1 million population (5.5%) are estimated to be living with HIV, and there were an estimated 36,000 new HIV infections and 24,000 acquired immunodeficiency syndrome (AIDS) related deaths in 2016[1]. Of the people living with HIV in Malawi, 70% know their infection status, 66% are on antiretroviral therapy (ART), and 59% are virally suppressed[1].

The World Health Organization (WHO) recommends viral load (VL) monitoring at six months after ART initiation and annually thereafter to assess the effectiveness of ART in maintaining viral suppression [2]. Routine VL monitoring allows for earlier detection of therapy failure, prevents accumulation of resistance mutations, and identifies patients with treatment adherence challenges [3].

HIV VL monitoring generally involves the collection of a blood specimen, which is then stored and transported to a centralized laboratory for testing. In remote and/or resource-limited settings, access to VL testing is challenging due to limited healthcare infrastructure and sample transport constraints

associated with whole blood or plasma. Dried blood spot (DBS) specimens are commonly collected for HIV VL testing. Compared to whole blood or plasma, DBS samples are easier to collect from capillary finger pricks and remain more stable over time and temperature variations. However, DBS testing yields lower testing accuracy and is associated with greater probability of both upward and downward VL misclassification compared to plasma testing because of the smaller sample volume and excessive cellular genetic material contained in whole blood [3,4]. The WHO recommends use of plasma specimens for determining virological failure at a threshold of 1,000 copies/mL [5]. To overcome the test performance limitations of DBS, novel sample collection technologies based on dried plasma spots have become available. However, the cost-effectiveness of these different testing approaches for routine VL monitoring is uncertain, especially in resource-limited settings. The objective of this study is to evaluate the potential cost-effectiveness of HIV VL testing approaches using dried plasma spot samples stored on a plasma separation card (PSC) compared to DBS samples in Malawi.

## Methods

### Analytic Overview

A cost-effectiveness model (decision tree structure) (Figure 1) was developed using Microsoft® Excel to project the costs and test accuracy of HIV VL testing approaches using PSC compared to DBS samples. The population assumed in the base-case analysis was HIV-positive patients on ART, undergoing treatment and follow-up at outlying clinics in Malawi. The reference case (the average analytic entity) was a single sample of blood collected from one of these patients for routine VL testing. The analysis was conducted from the healthcare payer perspective, assumed to be the Malawi Ministry of Health. The time horizon of analysis was from sample collection to completion of sample testing, assumed to be a maximum of thirty days. This time horizon was appropriate to capture the costs and diagnostic outcomes of using different testing approaches for routine VL testing.

### Comparators

The comparators evaluated in the analysis included: (1) capillary blood collected and transported on a DBS card to a central laboratory and tested using the Abbott m2000 RealTime System (Abbott Laboratories, Abbott Park, Illinois) (“DBS”); (2) capillary blood collected and transported on the *cobas*® Plasma Separation Card to a central laboratory and tested using the *cobas*® 6800 System (Roche Molecular Systems, Pleasanton, California) (“PSC”).

The *cobas*® Plasma Separation Card is a novel sample collection device that separates the plasma component from a whole blood spot (minimum 140µL volume) resulting in a dried plasma spot. The *cobas*® Plasma Separation Card has an integrated stabilizer that maintains sample integrity between 18-45°C and 85% humidity for up to 21 days [6].

# Decision-Tree Model

In the decision-tree model, a reference case sample could be viable or non-viable (sample optimality) after transport and upon arrival at a central laboratory. Upon testing, the reference case blood sample may have a viral load of 1,000 copies per ml or more (positive VL test) or less than 1,000 copies per ml (negative VL test). The sensitivity and specificity of the testing platforms were used to estimate the true-positive, false-negative, true-negative, and false-positive rates. We made the following simplifying assumptions: (1) non-viable samples are discarded and are by definition inaccurate, (2) sub-optimal sample collection, storage, and transportation exert an effect on VL result accuracy via sensitivity and specificity, and (3) no human or other sources of error occurred in the sample preparation and testing process at the central laboratory. The primary outcome in the analysis was test accuracy, defined as the proportion of patients correctly classified with or without treatment failure. This outcome evaluates the combined effectiveness of the sample collection approach and testing platform.

## Clinical Inputs

The estimated prevalence of ART failure in Malawi was obtained from the published literature. The test performance estimates used in the base-case analysis were derived from a head-to-head evaluation of HIV VL testing with the *cobas*<sup>®</sup> Plasma Separation Card on the *cobas*<sup>®</sup> 8800 System compared with DBS on the Abbott m2000 RealTime System using the WHO ART failure threshold of 1,000 copies/mL [7]. The *cobas*<sup>®</sup> 6800 and 8800 Systems have demonstrated equivalent test performance differing only in throughput [8]. We were not able to identify a data source to estimate the impact of transportation on sample viability upon arrival at a central laboratory (i.e., the proportion of samples optimal vs. not optimal for testing). Due to this data limitation, we assumed that all samples were viable in the base-case analysis and evaluated the impact of this parameter on results in sensitivity analysis. The clinical estimates used in the base-case analysis are described in Table 1.

## Resource Use and Cost Inputs

Data on resources and unit costs were derived from a combination of the published literature, unpublished sources, and expert opinion. The data were used to estimate the per-patient cost of sample collection, sample transportation, and sample testing. The capital costs of VL test platforms were annuitized using estimates of useful life. We summed the costs of test consumables and utilities to estimate recurrent costs. For utilities, we considered only electricity costs which were estimated based on machine electric consumption and local electricity prices in Malawi. Transportation costs per sample were estimated by calculating the per-test transport cost based on planning data[9]. Costs obtained in local currency units (Malawi kwacha) were converted into U.S. dollars (USD) using the official exchange rate of the Reserve Bank of Malawi in July 2018[10]. Cost estimates from previous years were converted

into 2018 USD using Malawi's Consumer Price Index for Health[9]. The resource inputs and unit costs used in the base-case analysis are described in Table 1.

## Sensitivity Analysis

Univariate sensitivity analysis was conducted to assess which parameters had the greatest influence on the results. All parameters were varied across plausible ranges, either 95% confidence intervals when available or +/- 20% when unavailable. We conducted probabilistic sensitivity analyses (PSA) by creating probability distributions for all parameters using beta distributions for probabilities and log-normal distributions for costs. We used base-case estimates as the mean, and standard errors were estimated assuming that ranges represented 95% confidence intervals with the range equal to four times the standard error. The PSA was conducted using 1,000 runs of Monte Carlo simulation. The parameter ranges assessed in sensitivity analyses are presented in Table 1.

## Results

### Base-case Analysis

The base-case results are shown in Table 2. The estimated test accuracy for a DBS testing approach and PSC testing approach were 87.5% and 97.4%, respectively. The cost per patient sample of a DBS testing approach was \$19.39, while the cost per patient sample of a PSC testing approach was \$17.73. Based on this, a PSC testing approach "dominates" a DBS testing approach as it is associated with lower costs and higher test accuracy.

### Sensitivity analysis

Given that a PSC testing approach dominates a DBS testing approach, we performed univariate sensitivity analysis on incremental accuracy and incremental costs separately. The univariate sensitivity analysis comparing the PSC testing approach with the DBS testing approach showed that the incremental accuracy was most affected by the proportion of samples optimal for testing (sample viability) and the test performance (sensitivity and specificity) of the test platforms (Figure 2a). The incremental cost was most affected by the cost of test consumables in the laboratory for both platforms (Figure 2b).

PSA results are presented in Figure 3 as a cost-effectiveness scatter plot which shows the parameter uncertainty surrounding the incremental accuracy and incremental cost projected in the base-case analysis. As can be seen, all 1,000 simulations suggest that a PSC testing approach would have higher accuracy with lower cost relative to a DBS testing approach, and would be considered the economically dominant strategy across the parameter ranges described in Table 1.

## Discussion And Conclusion

We developed a decision-analytic model to evaluate the costs and test accuracy of two different HIV VL sample collection and testing approaches in Malawi, a low-income country with high HIV prevalence. From a Malawi Ministry of Health perspective, our results suggest that the current practice of DBS sample transported to a central laboratory and tested on the Abbott m2000 RealTime System is not optimal and is projected to lead to approximately 10% higher misclassification rate than a testing approach using dried plasma spots collected on the *cobas*<sup>®</sup> Plasma Separation Card, transported to a central laboratory and tested on the *cobas*<sup>®</sup> 6800/8800 System. Additionally, the DBS testing approach was estimated to cost \$1.66 more per patient sample compared to the PSC testing approach. Although our study did not attempt to model the downstream impact of VL misclassification on costs and health outcomes, it is expected that false-positive results could amplify the cost impact of inaccurate testing through unnecessary switching of virally suppressed patients to more expensive second-line therapy.

For this analysis, we faced real-world data limitations for the key parameter of sample viability. We could not find adequate information about the proportion of HIV VL samples adversely affected by transportation conditions. As a result, our best analytic option was to assume all samples are viable upon arrival to a central laboratory (100% sample viability). In sensitivity analysis, the sample viability parameter was shown to be impactful on results. Therefore, our base-case estimate of DBS test accuracy may be an overestimate if, in real-world use, the DBS card has less protective effect on sample integrity over varying environmental conditions than previously assumed.

The Malawi Ministry of Health is committed to scaling up routine HIV VL testing services for patients on ART [3]. The question at hand is how best to scale-up these services to efficiently meet the increasing short-, medium-, and long-term demand for routine VL monitoring. Our analysis suggests that a testing approach utilizing the *cobas*<sup>®</sup> Plasma Separation Card with high-throughput batch testing at established central laboratories is the most economically efficient strategy. The methods and results of this model-based analysis are generalizable to other sub-Saharan African countries, particularly the test performance estimates and accuracy results. However, given the wide variety of health system organizations, country terrain, and mechanisms of sample transportation, cost estimates would need to be collected on a country-by-country basis. Further research to understand the viability and quality of samples arriving at central laboratories is warranted and would provide the necessary data to enhance model parameterization and, thus, the decision analysis.

## Abbreviations

ART = antiretroviral therapy

DBS = dried blood spot

MOH = Ministry of Health

PSA = probabilistic sensitivity analysis

PSC = plasma separation card

VL = viral load

WHO = World Health Organization

## Declarations

*Ethics approval and consent to participate:* Not applicable

*Consent for publication:* Not applicable

*Availability of data and material:* Data sharing is not applicable as no datasets were generated or analyzed in the study. Model inputs were derived from publicly available sources and were referenced accordingly.

*Competing interests:* JBB, SJL and LPG served as paid consultants to Roche Molecular Systems. JKK and MMC are employees of Roche Molecular Systems.

*Funding:* This study was sponsored by Roche Molecular Systems, manufacturer of the *cobas*<sup>®</sup> Plasma Separation Card (PSC) and the *cobas*<sup>®</sup> 6800/8800 Systems.

*Authors' contributions:* JBB, SJL and LPG led the study design, acquisition of data and analysis. JBB and MMC prepared the draft manuscript. All authors reviewed the analysis, contributed to the data interpretation and provided substantial modifications to the final manuscript.

*Acknowledgements:* No assistance in the preparation of this manuscript is to be declared.

## References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2017. Available at [http://www.unaids.org/sites/default/files/media\\_asset/20170720\\_Data\\_book\\_2017\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf).
2. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.
3. Pannus P, Claus M, Gonzalez MMP, Ford N, Fransen K: Sensitivity and specificity of dried blood spots for HIV-1 viral load quantification. *Medicine* 2016, 95:e5475.
4. Bonner K, Siemieniuk RA, Boozary A, Roberts T, Fajardo E, Cohn J: Expanding Access to HIV Viral Load Testing: A Systematic Review of RNA Stability in EDTA Tubes and PPT beyond Current Time and

Temperature Thresholds. PLoS ONE 2014, 9:e113813.

5. Government of Malawi. Ministry of Health. HIV Viral Load Scale Up Strategic and Implementation Plan 2015 - 2018. Available at: [https://aidsfree.usaid.gov/sites/default/files/malawi\\_vl\\_scaleup.pdf](https://aidsfree.usaid.gov/sites/default/files/malawi_vl_scaleup.pdf). Accessed May 17, 2018.

6. Roche Diagnostics. *cobas*<sup>®</sup> Plasma Separation Card: <https://diagnostics.roche.com/global/en/products/params/cobas-plasma-separation-card.html> Accessed: April 1, 2018.

7. Carmona S, Marins EG, Simon CO, Magubane D, Hans L, Hoppler M. Accuracy, sensitivity, and specificity of the *cobas*<sup>®</sup> Plasma Separation Card on *cobas*<sup>®</sup> 8800 System vs DBS on Abbott m2000 for the classification of HIV virological failure as compared to plasma. Poster presented at the 10<sup>th</sup> IAS Conference on HIV Science, Mexico City, 2019. Available at: <http://programme.ias2019.org/Abstract/Abstract/1922>

8. U.S. FDA. Summary of Safety and Effectiveness (SSE) of the *cobas*<sup>®</sup> HIV-1 Assay. Available at: <https://www.fda.gov/media/95275/download> Accessed August 5, 2019.

9. Government of Malawi. National Statistics Office. Consumer Price Index 2018. Available at [http://www.nsomalawi.mw/index.php?option=com\\_content&view=article&id=204%3Aconsumer-price-index-national-2014&catid=3&Itemid=37](http://www.nsomalawi.mw/index.php?option=com_content&view=article&id=204%3Aconsumer-price-index-national-2014&catid=3&Itemid=37). Accessed July 1, 2018.

10. Reserve Bank of Malawi. Exchange Rates. Available at: <https://www.rbm.mw/> Accessed July 1, 2018.

11. Mungwira RG, Divala TH, Nyirenda OM, Kanjala M, Muwalo F, Mkandawire FA, Choko A, Taylor TE, Mallewa J, van Oosterhout JJ, et al. A targeted approach for routine viral load monitoring in Malawian adults on antiretroviral therapy. *TM & IH* 2018; 23(5):526–532.

12. CAP Today, October 2018. Abbott Molecular, m2000 RealTime System (Molecular, 2018): <http://captodayonline.com/productguides/abbott-molecular-m2000-realtime-system-automated-molecular-platforms-october-2018.html> Accessed April 1, 2018.

13. Roche Diagnostics; *cobas*<sup>®</sup> 6800 Installation Manual

14. The Global Fund. HIV Viral Load and Early Infant Diagnosis Selection and Procurement Information Tool. Version 2 April 2017. Available at [https://www.theglobalfund.org/media/5765/psm\\_viralloadearlyinfantdiagnosis\\_content\\_en.pdf](https://www.theglobalfund.org/media/5765/psm_viralloadearlyinfantdiagnosis_content_en.pdf). Accessed May 17, 2018.

## Tables

Table 1. Clinical and Cost Inputs

<b>Model Input Parameters</b>	<b>Base-case</b>	<b>Low</b>	<b>High</b>	<b>Reference</b>
Sample viability: DBS	1	0.8	1	Assumption
Sample viability: PSC	1	0.8	1	Assumption
Prevalence of ART Failure	0.094	0.076	0.113	[11]
<i>Test Performance</i>				
Abbott m2000 RealTime Sensitivity (DBS)	0.906	0.855	0.956	[7]
Abbott m2000 RealTime Specificity (DBS)	0.872	0.835	0.910	[7]
<b>cobas</b> <sup>®</sup> 6800/8800 System Sensitivity (PSC)	0.969	0.931	1.000	[7]
<b>cobas</b> <sup>®</sup> 6800/8800 System Specificity (PSC)	0.974	0.950	0.998	[7]
Abbott m2000 RealTime System electric consumption (VA)	600	480	720	[12]
<b>cobas</b> <sup>®</sup> 6800 System electric consumption (VA)	2,000	1,600	2,400	[13]
Abbott m2000 RealTime - Samples run per hour	18	14	22	[14]
<b>cobas</b> <sup>®</sup> 6800 - Samples run per hour	46.5	37	56	[14]
<i>Resource Use</i>				
Capillary blood sample collection time (minutes)	5	4	6	Assumption
Malawi voltage (volts)	220	—	—	Standard
<i>Unit Costs</i>				
Nurse assistant wage (per hour)	\$1.09	\$0.87	\$1.31	Malawi MOH
Laboratory technician wage (per hour)	\$2.40	\$1.92	\$2.88	Malawi MOH
PSC and Bundle	\$4.50	\$3.60	\$5.40	Roche Diagnostics
DBS card and Bundle	\$2.60	\$2.08	\$3.12	Malawi MOH
Transportation (per sample)	\$1.87	\$1.49	\$2.24	[5]
Electricity (per unit (Kilowatt hour))	\$0.14	\$11	\$0.17	Eskom Malawi
<b>cobas</b> <sup>®</sup> 6800 System*	\$300,000	\$240,000	\$360,000	[14]
<b>cobas</b> <sup>®</sup> 6800 System consumables (per test)	\$9.40	\$7.52	\$11.28	[14]
<b>cobas</b> <sup>®</sup> 6800 System maintenance (per year)	\$30,000	\$24,000	\$36,000	[14]
Abbott m2000 machine*	\$170,000	\$136,000	\$204,000	[14]
Abbott m2000 consumables (per test)	\$13.00	\$10.40	\$15.60	[14]
Abbott m2000 maintenance (per year)	\$18,000	\$14,400	\$21,600	[14]
Machine useful life (all machines) (years)	7	5	9	Assumption
Scrap value (all machines)	\$0	—	—	Assumption
Discount rate (for annuitization)	3%	—	—	Standard

DBS = Dried blood spot; PSC = Plasma separation card; ART = antiretroviral therapy; VA = volt amperes; MOH = Ministry of Health

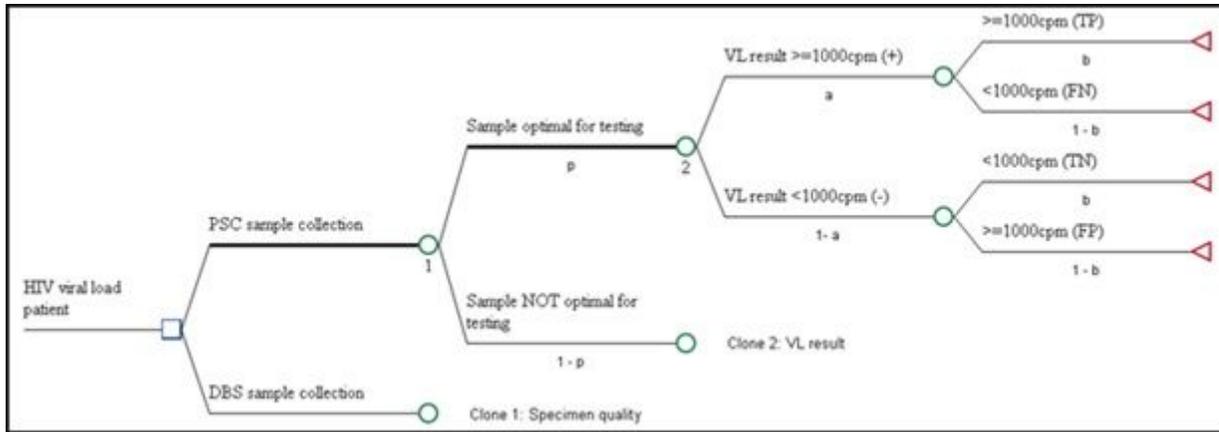
\*Includes warranty

Table 2. Base-case Results

	<b>Cost</b>	<b>Incremental cost</b>	<b>Accuracy</b>	<b>Incremental accuracy</b>	<b>ICER (\$/additional accurate test)</b>
DBS	\$19.39	\$1.66	87.5%	-9.9%	—
PSC	\$17.73	--	97.4%	--	Dominant

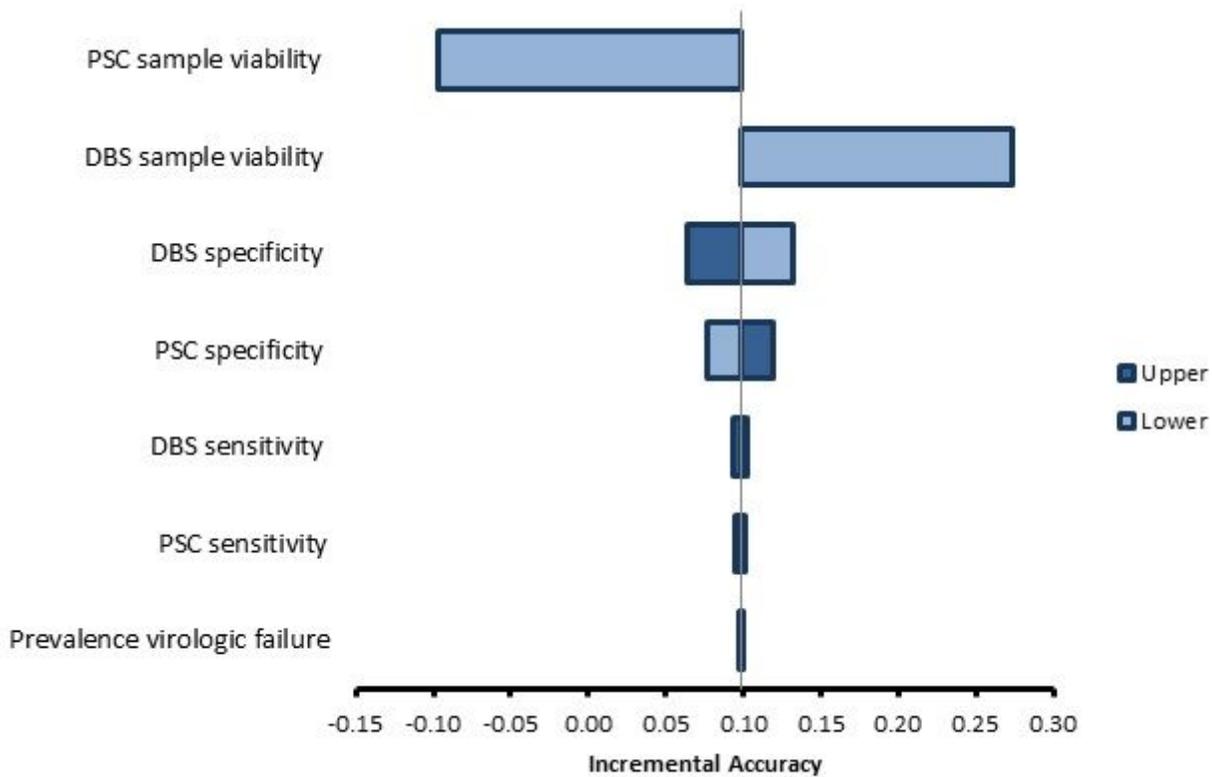
DBS = Dried blood spot; PSC = Plasma separation card; ICER = Incremental cost-effectiveness ratio

# Figures



**Figure 1**

Decision tree comparing HIV viral load testing approaches in Malawi



**Figure 2**

Univariate sensitivity analysis on incremental accuracy comparing PSC and DBS testing approaches

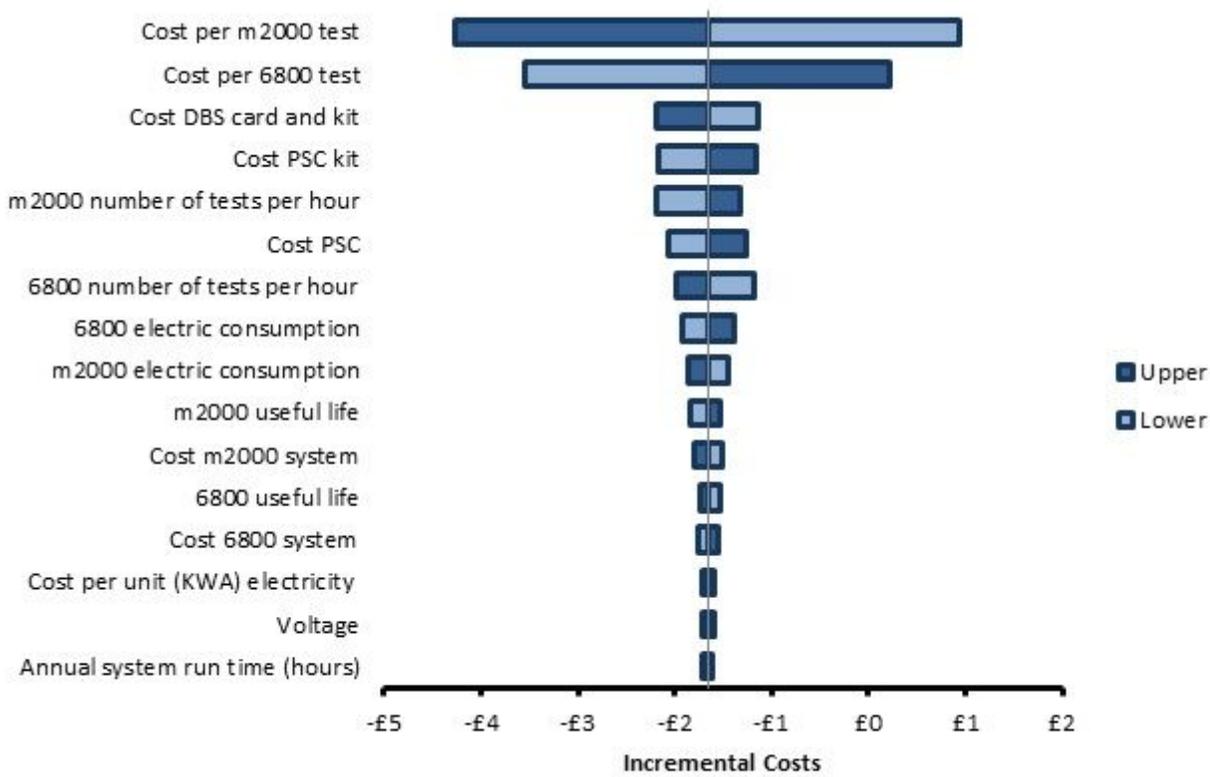


Figure 3

Univariate sensitivity analysis on incremental cost comparing PSC and DBS testing approaches

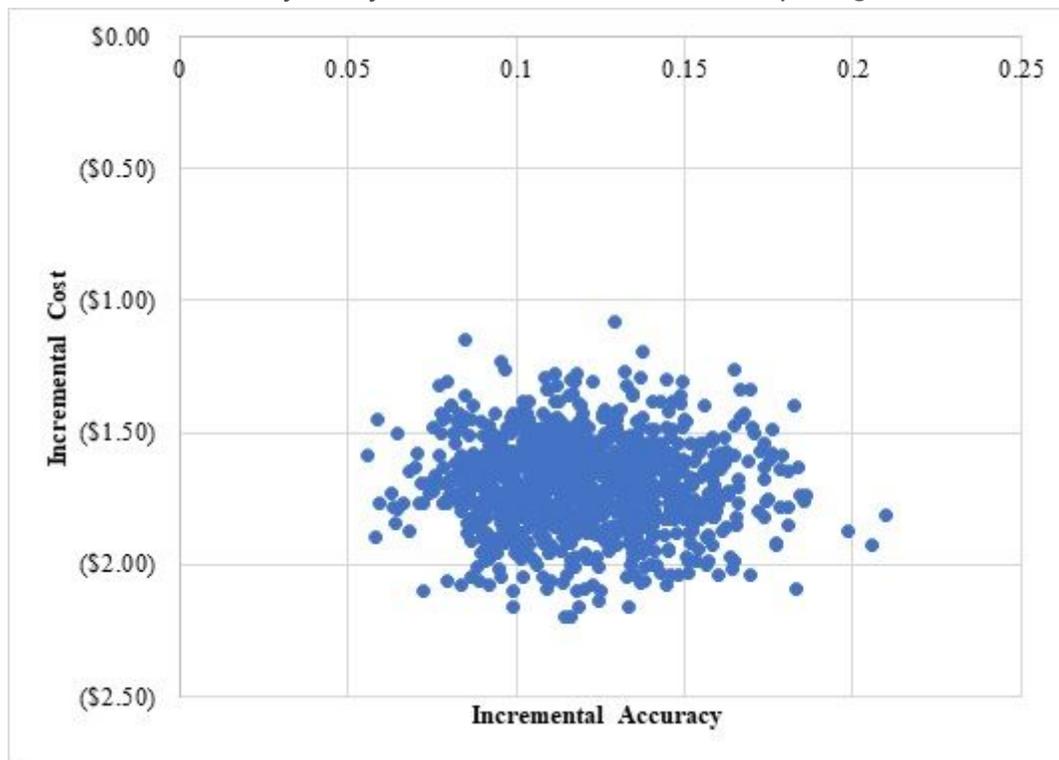


Figure 4

## Cost-effectiveness Scatter Plot