HHS Public Access

Author manuscript

Value Health Reg Issues. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Value Health Reg Issues. 2023 May ; 35: 42–47. doi:10.1016/j.vhri.2022.12.006.

Seemingly Unrelated Regression analysis of the Cost and Health-Related Quality of Life Outcomes of the REVAMP randomised clinical trial

Tamlyn A. Rautenberg, PhD,
Centre for Applied Health Economics, Griffith University, Brisbane, Queensland, Australia

Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia

Allied Health Services, Metro North Hospital and Health Service, Brisbane, Queensland, Australia

Shu Kay Ng, PhD,
Centre for Applied Health Economics, Griffith University, Brisbane, Queensland, Australia

Gavin George, PhD,
Health Economics and HIV Research Division, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Division of Social Medicine and Global Health, Lund University, Lund, Sweden

Mahomed-Yunus S. Moosa, MBChB,
School of Clinical Medicine, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Suzanne M. McCluskey, MD,
Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States

Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Rebecca F. Gilbert, BA,
Department of Medicine, Massachusetts General Hospital Boston, Massachusetts, United States

Contact information for corresponding author: Dr. Tamlyn Rautenberg, Contact No: +61439303766, tamlynr@yahoo.co.uk, Griffith University, 170 Kessels Road, Brisbane, Australia.

Author contributions

Conception and design TR, SN, GG, SM, KA, WM, PM, VM, MS, MB
Acquisition of data TR, SM, RG, SP, IA, WM, GM, MP, PM, JB, MS, MB
Analysis and interpretation of data TR, SN, BJ, VM, MS
Drafting of manuscript TR, SN, RG, PM, JB, BJ
Critical revision of paper for important intellectual content TR, SN, GG, SM, KA, MP, PM, BJ, VM, MS
Statistical analysis TR, SN
Provision of study materials or patients SP, IA, PM, JB, MB
Obtaining funding TR, PM, MS, MB
Administrative, technical or logistic support RG, SP, IA, WM, GM, MP, PM, VM, MB
Supervision TR, GG, IA, WM, GM, PM
Other KA (created the resistance management manual for clinicians in the study).

Conflict of interest disclosure

Nothing to disclose: TR, SN, GG, MM, SP, IA, KA, WM, NM, GM, MP, PM, JB, RG, BJ, HS, MB, MS

Dr. McCluskey reports grants from National Institutes of Health, grants from Gilead Sciences, grants from ViiV Healthcare, grants from Massachusetts General Hospital, personal fees from US Centers for Disease Control (through Potentia Namibia Recruitment), outside the submitted work.

Dr. Marconi reports grants from NIH, during the conduct of the study; grants from NIH, grants from VA, grants from CDC, grants, personal fees, non-financial support and other from Lilly, grants from Gilead, grants and personal fees from ViiV, non-financial support from Bayer, outside the submitted work.

Selvan Pillay, MSc,
School of Medicine, University of KwaZulu-Natal, Durban, South Africa

Isaac Aturinda, MBA,
Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Kevin L. Ard, MD,
Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States

Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Winnie Muyindike, MMed,
Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Nicholas Musinguzi, MS,
Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Godfrey Masette, BSc,
Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Melendhran Pillay, MSc,
Department of Virology, National Health Laboratory Service, Durban, South Africa

Pravi Moodley, MMed,
Department of Virology, University of KwaZulu-Natal, Durban, South Africa

Department of Virology, National Health Laboratory Service, Durban, South Africa

Jaysingh Brijkumar, MBBS,
Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

Rajesh T. Gandhi, MD,
Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States

Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Brent Johnson, PhD,
Department of Biostatistics and Computation Biology, University of Rochester, Rochester, New York, United States

Henry Sunpath, MBChB,
Department of Medicine, University of KwaZulu-Natal, Durban, South Africa

Mwebesa B. Bwana, MBChB,
Mbarara University of Science and Technology, Mbarara, Uganda

Vincent C. Marconi, MD,
Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, United States

Department of Global Health, Rollins School of Public Health, Atlanta, Georgia, United States

Mark J. Siedner, MD
Department of Medicine, University of KwaZulu-Natal, Durban, South Africa

Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States

Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Africa Health Research Institute, KwaZulu-Natal, South Africa

Abstract

Objective—To evaluate the nine-month cost and health-related quality of life outcomes of resistance versus viral load testing strategies to manage virological failure in low-middle income countries.

Methods—We analysed secondary outcomes from the REVAMP clinical trial: a pragmatic, open label, parallel-arm randomised trial investigating resistance versus viral load testing for individuals failing first-line treatment in South Africa and Uganda. We collected resource data, valued according to local cost data and used the EQ-5D-3L to measure health-related quality of life at baseline and nine-months. We applied Seemingly Unrelated Regression Equations to account for the correlation between cost and health-related quality of life. We conducted intention to treat analyses with multiple imputation using chained equations for missing data and performed sensitivity analyses using complete cases.

Results—For South Africa, resistance testing and opportunistic infections were associated with statistically significantly higher total costs andvirological suppression was associated with lower total cost. Higher baseline utility, higher CD4 count and virological suppression were associated with better health-related quality of life. For Uganda, resistance testing and switching to second-line treatment were associated with higher total cost and higher CD4 was associated with lower total cost. Higher baseline utility, higher CD4 count and virological suppression were associated with better health-related quality of life. Sensitivity analyses of the complete-case analysis confirmed the overall results.

Conclusion—Resistance testing showed no cost or health-related quality of life advantage in South Africa or Uganda over the nine-month REVAMP clinical trial.

Précis

This was a comparison of 9 month outcomes for the REVAMP clinical trial: an open label, parallel-arm randomised trial evaluating Genotype Resistance Testing versus Standard Of Care adherence support for management of patients failing first line AntiRetroviral Therapy in South Africa and Uganda. Seemingly Unrelated Regression was used for joint modelling of cost and health-related quality of life outcomes using two regression equations, with accounting for correlation between the random errors associated with cost and effect. Analysis was conducted on the intention-to-treat population.

INTRODUCTION

A substantial proportion of individuals with human immunodeficiency virus (HIV) who are on first-line treatment experience virological failure[1–5]. Virological failure is associated with loss of treatment effect resulting in symptomatic HIV and opportunistic infections which impact health-related quality of life (HRQOL)[6]. The main causes of virological failure are sub-optimal treatment adherence and drug resistance[7–10].

There are different approaches to managing virological failure. In the United States and Europe, resistance testing has been widely used for monitoring treatment and only individuals with drug resistance switch to second-line treatment[11–13]. The practice is supported by early cost effectiveness models that showed resistance testing to be cost effective[14–18]. In contrast, due to limited availability of resistance testing in sub-Saharan Africa, viral load testing alone is standard practice in accordance with World Health Organization (WHO) guidelines[19]. According to these recommendations, individuals meeting the criteria of persistent virological failure (with unknown resistance status) are recommended to switch to second-line treatment[19].

In resource-constrained countries this has a significant economic impact, because second-line treatment remains approximately 2–3 times as costly as first-line treatment[20]. If one in three individuals on first-line has virological failure within two years, treatment programs in the region will be charged with supplying second-line treatment to more than 5 million individuals[23]. One report estimated that switching to second-line therapy in Africa was unnecessary in approximately one third of cases (i.e., done in the presence of wild-type virus)[24]. It is questionable whether viral load testing strategy to define treatment failure may result in unnecessary switches to costlier second-line therapy, potentially imperilling the financial sustainability of HIV treatment programs[21,22]. Preventing unnecessary regimen switches through routine resistance testing could potentially prove cost saving, however further evidence is required to make this determination. Furthermore, studies assessing cost-effectiveness of resistance testing in resource-limited settings show contrasting results, supporting the need for well-designed pragmatic trials and contextual cost effectiveness analyses in sub-Saharan Africa[25].

The **Re**sistance Testing **V**ersus **A**dherence Support for **M**anagement of **P**atients with virological failure on first-line antiretroviral treatment in sub-Saharan Africa (REVAMP) study was a randomized controlled trial to evaluate resistance testing in public sector settings in South Africa and Uganda. The trial was designed to detect superiority of resistance testing versus standard care and an economic evaluation alongside the clinical trial was planned from the outset, and included in the study design. The primary clinical outcome was absence of virological failure (i.e., higher rates of virological suppression) after nine-months of enrolment. The economic hypothesis was that resistance testing would be cost effective because the cost of the resistance test would be offset by downstream cost savings through reduced use of second-line therapy. It was also anticipated that switching from a treatment with compromised to optimised efficacy would favourably impact their HRQOL.

The primary results showed a marginal, non-significant reduction in virological failure for resistance testing versus standard care (37% vs 39%). From a clinical perspective, these findings were not sufficient to support the implementation of resistance testing for clinical practice in South Africa and Uganda[26]. From a health economics perspective, it remained important to analyse the individual patient level cost and utility data at nine-months since interventions with equivalent clinical effectiveness may result in HRQOL gains and economic advantages[27,28]. This approach is supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Cost- Effectiveness Analysis Randomized Clinical Trial (CEA-RCT) taskforce, methods literature and published studies[29–32]. We performed *ex-ante* within-trial analyses of the secondary study outcomes to evaluate the joint estimation of cost and HRQOL effect differences in accordance with Briggs and O'Brien[27] and based on the methods described by Brand et al and applied by Maas et al[30,33].

METHODS

Study Design

The REVAMP clinical trial was an open, parallel-arm randomised trial evaluating resistance testing versus standard care for managing first-line treatment failure in South Africa and Uganda. The study was registered with clinicaltrials.gov (NCT02787499) and approved by the institutional review committees at the Mbarara University of Science and Technology, Ugandan National Council of Science and Technology, University of KwaZulu-Natal Biomedical Research Ethics Committee, Mass General Brigham, and Griffith University. The study design and primary results have been published[26,34,35].

Study population

Individuals were recruited from four public-sector HIV clinics in South Africa and one public-sector clinic in Uganda. Adults remaining on first-line treatment for longer than five months, to which they were not responding, were eligible for the study. Individuals with known drug resistance and patients taking protease inhibitors were excluded. Randomization was stratified by treatment duration, clinic, and pregnancy status with a randomization sequence created by the statistician prior to study start and locked into the database.

Intervention and Comparator

The intervention was genotype resistance testing to inform treatment decisions[11]. Results of resistance testing were used to inform whether individuals with no resistance remained on first-line and those with resistance switched to second-line. In the ReVAMP study, first-line treatments were non-nucleoside reverse transcriptase inhibitors and second-line treatments were protease inhibitors. The comparator was standard of care consisting defined as viral load testing and adherence counselling with repeat viral load testing in accordance with World Health Organisation and National HIV guidelines in Uganda and South Africa at the time of the study[19,36].

Outcomes

HRQOL was measured at baseline and nine-months study completion using the EuroQol 5D Health Questionnaire 3-level version (EQ-5D-3L). Population norms for the three-level EQ-5D are not available for South Africa or Uganda therefore population norms from Zimbabwe were used to value the dataset[37]. Healthcare resource use, side effects, comorbidities, and opportunistic infection data were measured at baseline and nine-months. Treatment regimen, treatment duration and CD4+ T-cell counts were abstracted from medical records. Resource use was valued according to best available data in local currency (South Africa rand, Uganda shilling) and converted to United States Dollars using the rate of 0.068 and 0.00028 for South Africa and Uganda, respectively. Detailed direct cost data are tabulated in Supplement Table 2. Total cost was the total cost of resource use incurred during the 9-month study period shown in Supplement Table 2. A public healthcare payer perspective was adopted for valuation of resources, and patient costs were not measured. The study was powered for the primary outcome, ensuring that the sample sizes were sufficient for estimation of the model parameters described below[38].

Seemingly Unrelated Regression

We used Seemingly Unrelated Regression (SUR) (joint modelling of two regression equations) to account for the correlation between random errors associated with cost and utility based on the method used by Maas et al[30]. We conducted analysis by intention-to-treat (ITT) for South Africa and Uganda. We used Multiple Imputation by Chained Equations (MICE) to compute missing values and create M=10 separate datasets, and applied 5,000 replications of Bias Corrected and Accelerated (BCA) bootstrapping to evaluate the uncertainty around the estimates of cost and effect. We used Rubin's rule to combine the ten SUR estimates (and 95% CIs) to obtain the final pooled SUR estimates and their 95% CI[30].

Predictor variables were age, gender, opportunistic infection, EQ-5D-3L utility at baseline, adherence, side effects, resistance status, comorbidities, second-line treatment regimen, viral load and CD4 count. Predictor variables and definitions are listed in Supplement Table 1. Resistance testing was included as a mandatory variable, all other variables without a statistically significant co-efficient were dropped from the model. We used the outcome variable logarithm of cost to account for the heavily right skewed data, the back transformation of estimated model coefficients to cost estimates is presented in this paper.

We performed sensitivity analyses on the complete dataset consisting of individuals for which there were no missing data for the variables of interest. Statistical analyses were performed using STATA (V16, Stata Corp, College Station, TX). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

RESULTS

Baseline characteristics are shown in Table 1. Comparing South Africa and Uganda respectively, there were between-country differences in male gender (51%–58% vs 41%–

44%, p=0.002), duration of ART treatment (1,613–1,745 vs 2,759–2,825 days, p<0.001), co-morbidities (36–43% vs 23–27%, p<0.001) and opportunistic infections (48–53% vs 12–19%, p<0.001).

Table 2 reports the results of the SUR models of total cost and HRQOL at nine-months for intention to treat and complete dataset analyses. For South Africa, resistance testing ($268; 95% confidence interval (CI): $49, $1009) and opportunistic infection (indicating poorer health) ($172; 95% CI: $18, $720) were associated with statistically significantly higher total cost whereas achievement of virological suppression (indicating better health) (-$149; 95% CI: -$111, -$75) was associated with statistically significantly lower total cost. Better HRQOL at baseline (indicating better health) (0.20; 95% CI: 0.03, 0.37), higher CD4 (indicating better health) (0.02 per unit increase in log scale; 95% CI: 0.01, 0.04) and virological suppression (indicating better health) (0.11; 95% CI: 0.08, 0.15) were associated with better HRQOL. For Uganda, resistance testing ($177; 95% CI: $71, $430) and switching to second-line ($91; 95% CI: $27, $265) were associated with statistically significantly higher total cost while higher CD4 (indicating better health) was associated with lower total cost (-$13; 95% CI: -$12 to -$2). Better HRQOL at baseline (indicating better health) (0.17; 95% CI: 0.08, 0.26), higher CD4 (indicating better health) (0.04 per unit increase in log scale; 95% CI: 0.01, 0.06) and virological suppression (indicating better health) (0.09; 95% CI: 0.01, 0.18) were associated with better HRQOL.

Post estimation tests using Breusch-Pagan test of independence were statistically significant at the 5%-level for both SUR models justifying the use of SUR models to account for correlation between the random errors of cost and utility[39]. Sensitivity analyses of the complete dataset confirmed the general direction and magnitude of findings shown in Supplement Table 3.

DISCUSSION

In contrast to our hypothesis, a marginal non-significant improvement in virological suppression for resistance testing failed to offset the cost of resistance testing and costlier second-line over the nine-month study duration. SUR proved extremely useful for quantifying the direction and magnitude of the association between the predictor and outcome variables. The correlation was confirmed by the post Breusch-Pagan test of independence which was statistically significant at 5%, justifying the SUR methods.

SUR was useful for confirming the direction of association between determinants and cost. In South Africa, resistance testing and opportunistic infection were associated with higher total cost and achieving virological suppression (indicating response to treatment) was associated with lower total cost. In Uganda, resistance testing and switching to second-line treatment were associated with higher total cost whereas a higher CD4 (indicating better health) was associated with lower total cost.

SUR was also valuable for confirming the direction of association between determinants and HRQOL (measured with the EQ-5D-3L). In both countries, higher baseline utility, higher CD4 (indicating better health) and achievement of virological suppression (indicating

treatment response) were associated with better HRQOL. Our results support the evidence to control for baseline utility. Overall, the direction of results confirm the internal validity of SUR. Sensitivity analyses on the complete dataset confirmed the primary findings.

SUR was also important for quantifying the magnitude of difference in effect. There are no reported minimal clinically important differences (MCID) for EQ-5D-3L for patients with HIV. However, MCID for other conditions ranges from 0.03 – 0.52 for musculoskeletal, 0.08 – 0.12 for oncology and 0.05 – 0.20 for other conditions[40]. The magnitude of change in our utility ranged from 0.02 to 0.20 indicating the potential for the determinants to have a meaningful clinical impact on HRQOL.

The results of our analysis should be considered in the context of the strengths and weaknesses of the study. The pragmatic clinical trial design and high-quality individual patient level primary data are notable strengths. A further strength is the use of SUR to analyse the nine-month cost and HRQOL outcomes, a methodologically sound approach to account for correlation between cost and HRQOL.

However, although our study results are generalizable to individuals failing non-nucleoside reverse transcriptase inhibitor-based first-line treatment in sub-Saharan Africa, they should not be extrapolated to other ART regimens or geographical regions. The EQ-5D-3L raw scores were valued using the general population dataset from Zimbabwe because no datasets are available for South Africa or Uganda. Zimbabwe datasets were considered a suitable proxy for South Africa and Uganda based on similarities in geographic factors, healthcare challenges and socio-demographic profiles. The well-documented ceiling effect of the EQ-5D-3L was confirmed in our study and may have been improved with the use of the five-level EQ-5D-5L[41]. Study variables measured at the final visit refer to the nine-month study duration and were self-reported by individuals and validated by medical records. Due to the nine-month analysis period, patient recall bias is expected to be minimised and not significantly impact on the study results. CD4 count was abstracted from medical records at study enrolment and since participants were on treatment, their CD4 count was not expected to change substantially between measurement and study enrolment. The median duration from abstracted CD4 to study enrolment was 14 months, interquartile range 23 months. The total cost and HRQOL correspond to nine-month study duration.

A question remains whether resistance testing is cost effective over a lifetime horizon. Resistance testing potentially reduces the need for more costly second-line treatment, however our analysis does not capture cost and outcomes beyond nine-months. If there is evidence to support a differential rate of virological suppression beyond nine-months, then lifetime cost effectiveness analysis is warranted. If virological suppression is equivalent beyond nine-months, then evidence to support differential mortality and/or HRQOL would be required to warrant lifetime analysis. In the REVAMP study, over the nine-month duration we found no difference in overall mortality, however literature suggests that drug resistance does negatively impact on mortality[42,43]. We did find lower rates of drug resistance in individuals at the end of the study in the resistance arm[26]. Considering these findings, lifetime analysis of the cost effectiveness of resistance testing in Sub-Saharan Africa may be informative.

CONCLUSION

Resistance testing after first-line antiretroviral failure showed no cost or utility advantage in South Africa or Uganda over the nine-month REVAMP clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The authors thank the following study, laboratory, and clinical staff for their tireless commitment and support of this study: Ntwenhle Makhaza, Nikiwe Ntanzi, Crisanne Dhevar, Sultana Abdool, Ansuri Singh, Dr. Eseza Monica Okunga Nambassi, Sabelo DlaDla, Agumenaitwe Patrick, Tumwesigyire Jonan, Kusingura Caroline, Komujuni Adah, Baryahikwa Hassan, and Agaba Edson. They also thank the study participants for their interest, partnership, and contributions to the REVAMP study. Thank you to Clifford Afoakwah, Martin Downes and Joshua Byrnes for informal discussion and guidance on the evaluation and SUR.

Funding support

This study is funded by the National Institute of Allergy and Infectious Diseases with support from the President's Emergency Plain for AIDS Relief (NIH R01 AI124718).

Role of funder/sponsor

The funding body had no role in the design of the study nor any role during its execution, analyses, interpretation of the data, or decision to submit results.

REFERENCES

1. Fox MP, Cutsem GV, Giddy J, et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. J Acquir Immune Defic Syndr. 2012;60(4):428–437. [PubMed: 22433846]
2. Boulle A, Van Cutsem G, Hilderbrand K, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. Aids. 2010;24(4):563–572. [PubMed: 20057311]
3. Brijkumar J, Edwards JA, Johnson BA, et al. Comparing effectiveness of first-line antiretroviral therapy between peri-urban and rural clinics in KwaZulu-Natal, South Africa. HIV Med. 2022;23(7):727–737. [PubMed: 35023287]
4. Ssemwanga D, Asio J, Watera C, et al. Prevalence of viral load suppression, predictors of virological failure and patterns of HIV drug resistance after 12 and 48 months on first-line antiretroviral therapy: a national cross-sectional survey in Uganda. J Antimicrob Chemother. 2020;75(5):1280–1289. [PubMed: 32025714]
5. Bulage L, Ssewanyana I, Nankabirwa V, et al. Factors Associated with Virological Non-suppression among HIV-Positive Patients on Antiretroviral Therapy in Uganda, August 2014-July 2015.BMC Infect Dis. 2017;17(1):326. [PubMed: 28468608]
6. Mutabazi-Mwesigire D, Katamba A, Martin F, Seeley J, Wu AW. Factors That Affect Quality of Life among People Living with HIV Attending an Urban Clinic in Uganda: A Cohort Study. PloS one. 2015;10(6):e0126810. [PubMed: 26039733]
7. McCluskey SM, Siedner MJ, Marconi VC. Management of Virologic Failure and HIV Drug Resistance. Infectious disease clinics of North America. 2019;33(3):707–742. [PubMed: 31255384]
8. Lailulo Y, Kitenge M, Jaffer S, Aluko O, Nyasulu PS. Factors associated with antiretroviral treatment failure among people living with HIV on antiretroviral therapy in resource-poor settings: a systematic review and metaanalysis. Systematic reviews. 2020;9(1):292. [PubMed: 33308294]

9. Meshesha HM, Nigussie ZM, Asrat A, Mulatu K. Determinants of virological failure among adults on first-line highly active antiretroviral therapy at public health facilities in Kombolcha town, Northeast, Ethiopia: a case-control study. BMJ open. 2020;10(7):e036223.
10. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. https://www.who.int/publications/i/item/9789241549684 Accessed November 30, 2022.
11. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf. Accessed November 30, 2022.
12. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 30, 2022.
13. European HIV Drug European HIV Drug Resistance Guidelines Resistance Guidelines 2009 https://rega.kuleuven.be/cev/avd/files/publications/guidelines/2009GuidelinesPocket.pdf. Accessed November 30, 2022.
14. Guidelines for surveillance of HIV Drug Resistance. https://www.who.int/3by5/publications/guidelines/en/resisguide.pdf. Accessed November 30, 2022.
15. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. January 28, 2000. HIV clinical trials. 2000;1(1):60–110. [PubMed: 11590490]
16. Antiretroviral Guidelines US Department of Health and Human Services. Guidelines with Australian commentary. https://arv.ashm.org.au/drug-resistance-testing/. Accessed November 30, 2022.
17. Weinstein MC, Goldie SJ, Losina E, et al. Use of genotypic resistance testing to guide hiv therapy: clinical impact and cost-effectiveness. Annals of internal medicine. 2001;134(6):440–450. [PubMed: 11255519]
18. Corzillius M, Muhlberger N, Sroczynski G, Jaeger H, Wasem J, Siebert U. Cost effectiveness analysis of routine use of genotypic antiretroviral resistance testing after failure of antiretroviral treatment for HIV. Antiviral therapy. 2004;9(1):27–36. [PubMed: 15040534]
19. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1&isAllowed=y. Accessed November 30, 2022.
20. Haberer JE, Kahane J, Kigozi I, et al. Real-time adherence monitoring for HIV antiretroviral therapy. AIDS and behavior. 2010;14(6):1340–1346. [PubMed: 20809380]
21. Landmark HIV diagnostic access program will save $150m and help achieve new global goals on HIV. https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2014/september/20140925prviralload. Accessed November 30, 2022.
22. Mermin J, Ekwaru JP, Were W, et al. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. BMJ (Clinical research ed). 2011;343:d6792.
23. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. The Lancet Infectious diseases. 2010;10(3):155–166. [PubMed: 20185094]
24. Boender ST HB, Sigaloff KC, Wellington M, Siwale M, Kityo CM, et al. Pretreatment HIV Drug Resistance Increases Regimen Switch in sub-Saharan Africa. Conference on Retroviruses and Opportunistic Infections; 2015.
25. Rautenberg TA, George G, Bwana MB, et al. Comparative analyses of published cost effectiveness models highlight critical considerations which are useful to inform development of new models. J Med Econ. 2020:1–7. [PubMed: 31589081]
26. Siedner MJ, Moosa MS, McCluskey S, et al. Resistance Testing for Management of HIV Virologic Failure in Sub-Saharan Africa: An Unblinded Randomized Controlled Trial. Annals of internal medicine. 2021; 174(12):1683–1692. [PubMed: 34698502]
27. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ. 2001;10(2):179–184. [PubMed: 11252048]

28. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101(11):1297–1302. [PubMed: 10725290]
29. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(2):161–172. [PubMed: 25773551]
30. Maas ET, Juch JNS, Ostelo R, et al. Cost-Effectiveness of Radiofrequency Denervation for Patients With Chronic Low Back Pain: The MINT Randomized Clinical Trials. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2020;23(5):585–594. [PubMed: 32389224]
31. Due OT, Thakkinstian A, Thavorncharoensap M, et al. Cost-Utility Analysis of Direct-Acting Antivirals for Treatment of Chronic Hepatitis C Genotype 1 and 6 in Vietnam. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2020;23(9):1180–1190. [PubMed: 32940236]
32. Zeevat F, Crépey P, Dolk FCK, Postma AJ, Breeveld-Dwarkasing VNA, Postma MJ. Cost-Effectiveness of Quadrivalent Versus Trivalent Influenza Vaccination in the Dutch National Influenza Prevention Program. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2021;24(1):3–10. [PubMed: 33431150]
33. Brand J, van Buuren S, le Cessie S, van den Hout W. Combining multiple imputation and bootstrap in the analysis of cost-effectiveness trial data. Stat Med. 2019;38(2):210–220. [PubMed: 30207407]
34. Siedner MJ, Bwana MB, Moosa MS, et al. The REVAMP trial to evaluate HIV resistance testing in sub-Saharan Africa: a case study in clinical trial design in resource limited settings to optimize effectiveness and cost effectiveness estimates. HIV clinical trials. 2017;18(4):149–155. [PubMed: 28720039]
35. Reynolds Z, McCluskey SM, Moosa MYS, et al. Who's slipping through the cracks? A comprehensive individual, clinical and health system characterization of people with virological failure on first-line HIV treatment in Uganda and South Africa. HIV medicine. 2021;23(5):474–484. [PubMed: 34755438]
36. Nel J, Dlamini S, Meintjes G, et al. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2020 update. Southern African journal of HIV medicine. 2020;21(1):1115. [PubMed: 33101723]
37. Jelsma J, Hansen K, De Weerdt W, De Cock P, Kind P. How do Zimbabweans value health states? Population health metrics. 2003;1(1):11. [PubMed: 14678566]
38. Yahya WA SB.; Jolayemi, ET.; Oyejola, BA.; Sanni, OOM. Effects of non-orthogonality on the efficiency of seemingly unrelated regression (SUR) models. InterStat Journal. 2008:29.
39. Breusch TS, Pagan A. The Lagrange Multiplier Test and its Applications to Model Specification in Econometrics. Review of Economic Studies. 1980;47(1):239–253.
40. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. Expert review of pharmacoeconomics & outcomes research. 2014;14(2):221–233. [PubMed: 24625040]
41. Ferreira LN, Ferreira PL, Ribeiro FP, Pereira LN. Comparing the performance of the EQ-5D-3L and the EQ-5D-5L in young Portuguese adults. Health and quality of life outcomes. 2016;14:89. [PubMed: 27267761]
42. Zhang T, Liao L, Shao Y, Feng Y, Ruan Y, Xing H. Relationship Between Drug Resistance and Death in HIV-Infected Patients Receiving Antiretroviral Therapy - 7 PLADs, China, 2010–2019. China CDC weekly. 2021;3(14):291–297. [PubMed: 34594868]
43. Nyandiko W, Holland S, Vreeman R, et al. HIV-1 Treatment Failure, Drug Resistance, and Clinical Outcomes in Perinatally Infected Children and Adolescents Failing First-Line Antiretroviral Therapy in Western Kenya. Journal of acquired immune deficiency syndromes (1999). 2022;89(2):231–239. [PubMed: 34723922]

Highlights:

- We analysed cost and health-related quality of life data using Seemingly Unrelated Regression Equations to account for joint correlation: this method is not widely published.
- We undertook analysis in the context of a marginal, non-significant benefit in clinical primary outcome, proceeding based on strong economic hypotheses suggesting cost and health-related quality of life benefits for resistance testing.
- Our study benefits from rich, primary, individual patient-level data to compare baseline and nine-month cost and health-related quality of life.
- Notably, in contrast to high-income countries, resistance testing showed no nine-month cost or health-related quality of life advantage compared to viral load testing in low-middle income countries.
- Results are key to informing multinational partners, non-government organizations and public health policy makers about the use of resistance testing in clinical practice.
- They are also important for informing the lifetime cost effectiveness analysis of resistance testing in the era of new resistance testing methods and treatment regimens.

Table 1:

Baseline Characteristics for South Africa and Uganda

Variable	South Africa		Uganda	
Study arm	Resistance testing	Standard care	Resistance testing	Standard care
Sample (n)	207	213	210	210
Age (years)	37 (36–38)	38 (37–39)	38 (36–39)	38 (36–39)
Males (%) *	51%	58%	41%	44%
ART (days) *	1,613	1,745	2,759	2,825
Treatment side effects	35 (17%)	17 (8%)	35 (17%)	29 (14%)
Co-morbidities				
Any *	91 (43%)	78 (36%)	57 (27%)	49 (23%)
Cardiac	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diabetes	3 (1%)	4 (1%)	2 (1%)	3 (1%)
Hypertension	17 (8%)	16 (7%)	9 (4%)	2 (1%)
Renal	14 (7%)	9 (4%)	0 (0%)	0 (0%)
Respiratory	28 (14%)	32 (15%)	13 (6%)	5 (2%)
Gastrointestinal	27 (13%)	22 (10%)	40 (19%)	43 (20%)
Mental health	28 (13%)	19 (9%)	0 (0%)	2 (1%)
Not elsewhere classified	12 (5%)	11 (5%)	6 (2%)	6 (2%)
Self-reported history of opportunistic infections				
Any *	110 (53%)	104 (48%)	27 (12%)	40 (19%)
Tuberculosis	93 (44%)	93 (44%)	23 (11%)	32 (15%)
Extrapulmonary tuberculosis	2 (1%)	4 (1%)	0 (0%)	0 (0%)
Cryptococcal meningitis	11 (5%)	6 (2%)	3 (1%)	5 (2%)
Pneumonia	35 (16%)	34 (16%)	0 (0%)	2 (1%)
Kaposi sarcoma	0 (0%)	0 (0%)	1 (0%)	3 (1%)
Esophagitis	11 (5%)	9 (4%)	2 (1%)	2 (1%)

ART=antiretroviral therapy; n= number

* significant difference between South Africa and Uganda ($p<0.05$)

Table 2:

Seemingly Unrelated Regression for intention to treat and complete datasets for South Africa and Uganda at nine-months.

Variable	Intention to Treat Dataset (n=840)		Complete Dataset (n=697)	
	Co-efficient cost (USD) (95% CI)	Co-efficient utility (95% CI)	Co-efficient cost (USD) (95% CI)	Co-efficient utility (95% CI)
South Africa				
Resistance	**268 (49, 1009)**	0.01 (−0.04, 0.04)	**260 (85, 706)**	0.01 (−0.02, 0.03)
Opportunistic infection	**172 (18, 720)**	−0.03 (−0.07, 0.01)	**115 (16, 399)**	−0.01 (−0.03, 0.02)
Baseline utility	−301 (−236, 227)	**0.20 (0.03, 0.37)**	**−287 (−232, −59)**	0.02 (−0.05, 0.08)
Log CD4 *	−39 (−43,49)	**0.02 (0.01,0.04)**	−30 (−36, 23)	0.01 (−0.01, 0.02)
Virological suppression	**−149 (−111, −75)**	**0.11 (0.08,0.15)**	−25 (−50, 102)	**0.05 (0.03, 0.07)**
Uganda				
Resistance	**177 (71, 430)**	−0.03 (−0.06, 0.01)	**115 (57, 230)**	−0.01 (−0.03, 0.02)
Baseline utility	−30 (−35, 43)	**0.17 (0.08, 0.26)**	−8 (−18, 32)	**0.12 (0.06, 0.18)**
Log CD4 *	**−13 (−12, −2)**	**0.04 (0.01, 0.06)**	−6 (−7, 2)	0.01 (−0.02, 0.03)
Second line	**91 (27, 265)**	0.01 (−0.04, 0.05)	**65 (28, 144)**	0.01 (−0.03, 0.03)
Virological suppression	−41 (−40, 22)	**0.09 (0.01, 0.18)**	−7 (−14, 19)	**−0.01 (−0.04, 0.04)**

CI = Confidence interval; CD4= Cluster of Differentiation 4; log CD4 = logarithm of CD4; n= number; USD = United States Dollars. Bolded values are statistically significant.

* Log-transformed CD4 count was used in SUR models and the interpretation is that the outcome variable increases by the value of the co-efficient for one unit increase of CD4 in log scale (i.e., when CD4 count is multiplied by 2.72).