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MAJOR ARTICLE

Differentiated Human Immunodeficiency Virus RNA Monitoring in Resource-Limited Settings: An Economic Analysis

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Background. Viral load (VL) monitoring for patients receiving antiretroviral therapy (ART) is recommended worldwide. However, the costs of frequent monitoring are a barrier to implementation in resource-limited settings. The extent to which personalized monitoring frequencies may be cost-effective is unknown.

Methods. We created a simulation model parameterized using person-level longitudinal data to assess the benefits of flexible monitoring frequencies. Our data-driven model tracked human immunodeficiency virus (HIV)–infected individuals for 10 years following ART initiation. We optimized the interval between viral load tests as a function of patients' age, gender, education, duration since ART initiation, adherence behavior, and the cost-effectiveness threshold. We compared the cost-effectiveness of the personalized monitoring strategies to fixed monitoring intervals every 1, 3, 6, 12, and 24 months.

Results. Shorter fixed VL monitoring intervals yielded increasing benefits (6.034 to 6.221 discounted quality-adjusted life-years [QALYs] per patient with monitoring every 24 to 1 month over 10 years, respectively, standard error = 0.005 QALY), at increasing average costs: US$3445 (annual monitoring) to US$5393 (monthly monitoring) per patient, respectively (standard error = US$3.7). The adaptive policy optimized for low-income contexts achieved 6.142 average QALYs at a cost of US$3524, similar to the fixed 12-month policy (6.135 QALYs, US$3518). The adaptive policy optimized for middle-income resource settings yields 0.008 fewer QALYs per person, but saves US$204 compared to monitoring every 3 months.

Conclusions. The benefits from implementing adaptive vs fixed VL monitoring policies increase with the availability of resources. In low- and middle-income countries, adaptive policies achieve similar outcomes to simpler, fixed-interval policies.

Keywords. differentiated care; adaptive viral load monitoring.

Routine human immunodeficiency virus (HIV) RNA (viral load [VL]) monitoring is recommended for all patients receiving antiretroviral therapy (ART) by the World Health Organization (WHO) and many national HIV care guidelines [1, 2]. Using VL monitoring to improve patients' likelihood of virologic suppression benefits patients as well as individuals at risk of HIV infection [1]. Personal benefits include the timely detection of loss of virologic control, which may improve ART choices. Population benefits include the identification of HIV transmission risk, which may lead to public health interventions [3]. Due to its relatively high cost, VL testing is often foregone or conducted infrequently in patients receiving ART in low-resource settings, even though clinical and immunological monitoring are poorly predictive of virologic failure [4]. Because HIV-infected patients benefit from ART initiation even at high CD4 cell counts, routine VL monitoring is increasingly recognized as a critical part of ART programs [5]. The lifelong need for ART implies that the costs of VL monitoring make up an important portion of overall costs of care, estimated at 15%–20% of total cost of care in low-income contexts [6, 7]. However, there is limited evidence to guide VL monitoring frequency, especially differentiated care interventions [2, 8–10]. As a result, mathematical models have been influential, alongside expert opinion, in addressing issues related to the benefits and cost-effectiveness of VL monitoring [11, 12].

In this analysis we examine an understudied paradigm for VL testing: adaptive monitoring, wherein the frequency of testing depends on personal patient characteristics. We develop and implement a mathematical model that uses parameters derived from person-level data to personalize decisions for timing of VL monitoring. In identifying the optimal interval for monitoring, our analysis takes into account the patient's

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demographics, clinical history, and self-reported adherence behavior. In addition, we perform a cost-effectiveness analysis to inform the optimal monitoring interval in different resource contexts. We also develop a decision support tool that calculates the optimal monitoring interval given a few basic patient characteristics.

METHODS

Overview

We designed and developed a stochastic simulation model that captures HIV disease progression and transmission in order to evaluate alternative VL monitoring strategies. The model tracked patient demographics, CD4 cell counts, individual adherence to ART, and presence of virologic failure (a schematic is presented in Figure 1). The model was used to optimize monitoring strategies at different cost-effectiveness (CE) thresholds (CETs). We use the CET to indicate the upper bound of societal resources that are considered affordable to gain 1 quality-adjusted life-year (QALY). This threshold varies with the resource context—low-income countries have a lower CET than middle-income countries—and in this analysis we use the gross domestic product (GPD) per capita in 2013 as a benchmark.

Model Population

We simulated a population of 100 000 individuals that was age-, education-, and gender-matched to Uganda's 2011 nationally representative Demographic and Health Survey over a 10-year time horizon [13]. At baseline, the mean age among HIV-infected individuals was 36 years old, 61% were women, and 25% completed primary school education. The initial CD4 count had an average of 310 cells/μL.

Adherence, Failure, and CD4 Cell Count Modeling

We used data from the Swiss HIV Cohort Study (SHCS) to estimate the risk of virologic failure in different HIV risk groups. We used the SHCS because it contained detailed, longitudinal information on adherence, virologic failure, and CD4 cell counts. While patients in the SHCS live with HIV in a different environment from low-resource countries, we considered the use of the SHCS acceptable for our primary model population if the events under study could be considered context-independent. We used SHCS to assess the risk of virologic failure given self-reported adherence status, and the implications of failure for CD4 cell change. We analyzed longitudinal data from 5251 ART-naive SHCS patients (95 414 patient visits). Detailed information on the SHCS is provided elsewhere [14].

We used a mixed-effects logistic regression model fitted to the SHCS self-reported adherence data to model a patient's current adherence status (a binary outcome), as a logit function of previous adherence status, age, gender, education, and time since last measurement. Self-reported nonadherence was defined as having missed >2 doses in the month previous to a biannual SHCS cohort visit and was measured in the SHCS data with a 2-item questionnaire that has been shown to predict virologic failure, presence of viral resistance, and progression of HIV disease [15–17].

Virologic failure in the SHCS data was defined as (*i*) 2 consecutive measurements of a VL >200 copies/mL, (*ii*) 1 VL measurement >1000 copies/mL, or (*iii*) not reaching virologic suppression within 6 months of either ART initiation or regimen change. For patients on first-line therapy who were not in virologic failure in the previous month, we estimated the probability of failure at any month (binary outcome) as a logit function of current adherence status, time on ART, age, gender, and

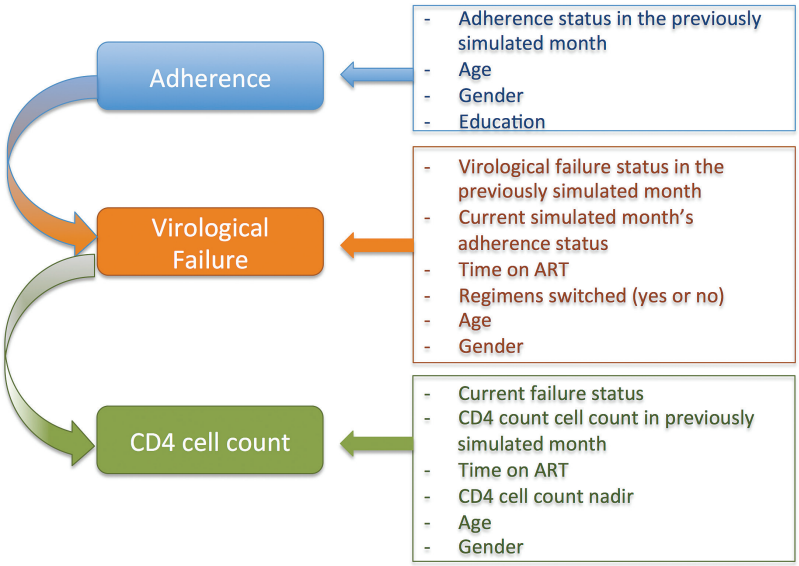

Figure 1. Variables tracked monthly and their dependencies. Abbreviation: ART, antiretroviral therapy.

time between measurements, and used the predicted probabilities to parameterize the simulation model. For patients on second-line therapy, we use a fixed monthly probability of failure, which does not depend on individual patient characteristics. We also estimated the probability of spontaneous resuppression after the first occurrence of virologic failure in the SHCS data, depending on current adherence status. We assumed that if patients do not resuppress within a month, then they remain in virologic failure until a switch in regimen occurs.

We estimated CD4 cell count changes using quantile regression models fitted to SHCS data to capture the distribution of the data, and estimated the monthly change in CD4 cell count as a function of previous CD4 cell count, time since ART initiation, CD4 cells at ART initiation, age, and gender.

HIV Disease, Treatment, and Monitoring

We used data from Uganda to estimate age- and gender-specific mortality by CD4 cell counts. Model parameters are shown in Supplementary Tables 1–5 [18, 19]. We track our simulated cohort starting at the first month of ART initiation. All patients receive 1 VL measurement at 6 months on ART [2]. Afterward, patients are monitored according to the policy we evaluate, or upon development of an AIDS-defining opportunistic infection (OI). CD4 cell–specific OI rates are adjusted in calibration to match OI rates reported in clinical data from Uganda [1, 20]. We use WHO life tables to estimate age- and gender-specific mortality.

In our simulation model, if virologic failure is detected during monitoring on first-line therapy, patients return for a follow-up VL test in the next month. If virologic failure is still present (spontaneous resuppression has not occurred), the patient is switched to second-line therapy. We did not model regimen switching for patients on second-line ART, and assumed annual VL monitoring for all patients on second-line therapy regardless of failure status.

Outcomes

Our principal outcomes are QALYs lived by patients and HIV-specific costs. We used QALY weights based on CD4 cell count [21, 22]. We tracked monthly costs based on the patient's ART regimen, administration of VL measurement, and CD4 cell count (<250 cells/μL or not; Supplementary Tables 3 and 4) [23–26].

Estimating Transmitted HIV Infections

We estimate the number of secondary HIV infections in the community as a function of the number of individuals in virologic failure in the population simulated [27]. We track the number of patient-months spent in failure during the time horizon of our simulation, and calculate the number of secondary infections as a function of the average number of partners, HIV prevalence (ie, the probability that a partner is HIV-infected), probability of HIV transmission per sex act for patients in failure, and the average number of sex acts per month, all parameterized using data from Uganda [28–31]. We then also estimate the loss in QALYs and gain in costs per secondary infection generated assuming that the newly infected individual would be placed on ART and subject to the same monitoring policy, and adjust the costs and QALYs resulting from our simulation according to these estimates. We discount costs and QALYs by 3% per year [32]. We report the average total discounted costs and QALYs per patient over the 10-year time horizon.

Monitoring Policies

We simulate fixed and adaptive VL monitoring strategies. In the 5 fixed strategies, patients are monitored every 1, 3, 6, 12, or 24 months. The adaptive strategies use the fact that patients have differing risk of failure. We use the model to search for monitoring policies that better reflect a patient's optimal monitoring frequency based on patient characteristics. As a simple example, a patient who reports being nonadherent should have VL monitoring sooner than a similar patient reporting good adherence, even if both patients appear to be currently suppressed.

We use a stochastic optimization approach where, given patient characteristics (time since ART initiation, current adherence status, age, sex, and education level), we optimize the time until the next VL test by maximizing the average net monetary benefit (NMB), where NMB = QALYs × CET– costs. A key feature in determining an adaptive policy is the CE threshold. By varying the CET value, we recover a continuum of adaptive strategies, the costs and QALYs of which should define the cost-effectiveness frontier as each adaptive policy is optimized to provide the most benefit at a given cost per QALY. For this analysis, we show findings for CET of US$572/QALY (Uganda's GDP per capita in 2013), and 3, 10, 30, 50, and 100 times Uganda's per-capita GDP, where we note that $57 200 per QALY is similar to the GDP per capita in Organisation for Economic Co-operation and Development countries.

RESULTS

Model Calibration/Validation

We calibrated our model to data from a randomized clinical trial of HIV laboratory monitoring strategies conducted in Uganda and Zimbabwe [1]. In the trial, 3321 ART-naive patients with CD4 counts <200 cells/μL at ART initiation were randomized to 2 monitoring arms: laboratory and clinical monitoring. Our model closely matches several key quantities from the trial such as 5-year mortality, OI-free survival, and percentage of patients with CD4 cell counts >200 cells/μL (for details, see Supplementary Appendix).

Adaptive Monitoring

A few themes emerge from our analysis. First, optimal VL monitoring frequency is higher in contexts with higher CE

thresholds. For example, we estimate that a 35-year-old woman who has been on ART for 2 years and who reports being adherent would optimally have her next VL test in 12 months in Uganda, and in 6 months in contexts with CE threshold similar to South Africa. Second, nonadherent patients should generally be monitored at shorter intervals than adherent patients.

Third, as time since ART initiation increases without loss of virologic control, patients should be monitored less and less frequently. Our model suggests that the 35-year-old woman in the example above should optimally be monitored in 14 months after 4 years on ART in Uganda. Figure 2 shows an example of adaptive policy where we hold gender, age, and education level constant and vary the CET and the adherence status. The figure plots the optimized VL monitoring interval vs the time since ART initiation and shows the lengthening monitoring intervals with increasing time on ART, for adherent patients, and at lower CE thresholds.

Cost-effectiveness and Sensitivity Analyses

The adaptive policies evaluated were generally on the cost-effectiveness frontier, achieving the highest QALYs at their respective costs. Monitoring at fixed intervals of 24 months is the least costly VL monitoring strategy we evaluated ($3445 on average per patient in total costs, standard error [SE] = $3.7, discounted over 10 years), but also yields the smallest number of QALYs (6.034, SE = 0.005). The adaptive policy optimized for the Ugandan resource context (CET = Ugandan GDP per capita) is cost-effective with an incremental cost-effectiveness ratio (ICER) of $491/QALY relative to monitoring every 24 months. Furthermore, monitoring every 24 months resulted in an additional 2 months average time spent in virologic failure per patient during the simulated 10-year horizon compared to the optimized adaptive policy at Uganda's GDP per capita.

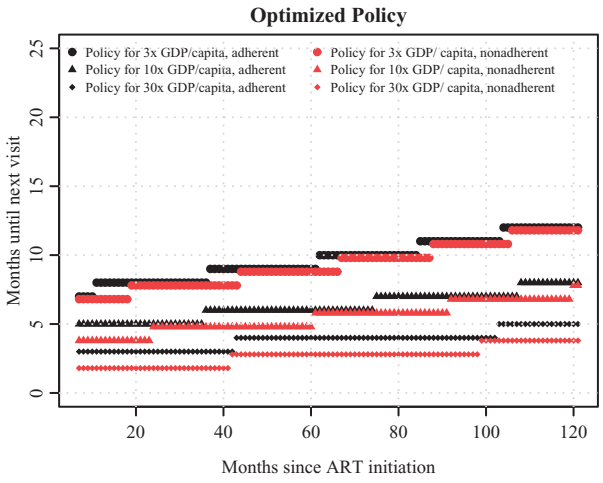

Figure 2. Example of adaptive policy: male, age 15–20 years, primary education or less. Abbreviations: ART, antiretroviral therapy; GDP, gross domestic product.

Table 1. Average Per-Person Costs and Quality-Adjusted Life-years of Fixed-Interval Monitoring Policies

Frequency	Mean QALY	Mean Cost, US$	SE QALY	SE Cost, US$
1 month	6.221	5393	0.005	4.1
3 months	6.198	4017	0.005	3.4
6 months	6.173	3678	0.005	3.5
12 months	6.135	3518	0.005	3.7
24 months	6.034	3445	0.005	3.8

Abbreviations: QALY, quality-adjusted life-years; SE, standard error; US, United States.

If decision makers are willing to spend up to 3 times Uganda's GDP per capita, then using the adaptive policy optimized for that CET provides the highest benefits (6.142 QALYs), ICER of $1311/QALY compared to the first adaptive policy. However, the fixed 12-month interval monitoring policy yields similar outcomes to the adaptive policy optimized for a CET of 3 times Ugandan GDP per capita (6.135 QALYs at a cost of $3518), ICER of 1485 ($/QALY) compared to the adaptive policy for Ugandan GDP per capita. The adaptive policies optimized for 10, 50, and 100 times Uganda's GDP per capita are on the cost-effectiveness frontier, dominating the fixed-interval monitoring policies of monitoring every 3 months and 6 months. The costs and QALYs achieved by all policies are summarized in Tables 1 and 2 and in Figure 3.

Health Outcomes—Virologic Failure and Transmission Outcomes

The average cumulative number of months that a patient spends in failure is shown in Figure 4. Compared to fixed-interval policies, adaptive policies incur similar or fewer months in virologic failure on average, and therefore generate fewer secondary infections on average per patient on ART. All 6 adaptive policies we simulated incurred fewer months in failure than the fixed-interval policy that monitors every 24 months, and the adaptive policies for the 3 highest CET values (30, 50, and 100 times Uganda's GDP per capita) resulted in fewer months spent in failure than the 6-month fixed-interval policy. Despite costing on average $204 less per patient, the adaptive policy optimized for a CET of 30 times Ugandan GDP per capita achieves similar averages of months spent in failure and secondary infections (2.7 and 0.144, respectively, over 10 years simulated)

Table 2. Average Per-Person Costs and Quality-Adjusted Life-years of Adaptive Monitoring Policies

CET, US$	Mean QALY	Mean Cost, US$	SE QALY	SE Cost, US$
572	6.111	3483	0.005	3.7
1716	6.142	3524	0.005	3.6
5720	6.176	3632	0.005	3.5
17 160	6.190	3812	0.005	3.5
28 600	6.207	3945	0.005	3.4
57 200	6.214	4213	0.005	3.4

Abbreviations: CET, cost-effectiveness threshold; QALY, quality-adjusted life-year; SE, standard error; US, United States.

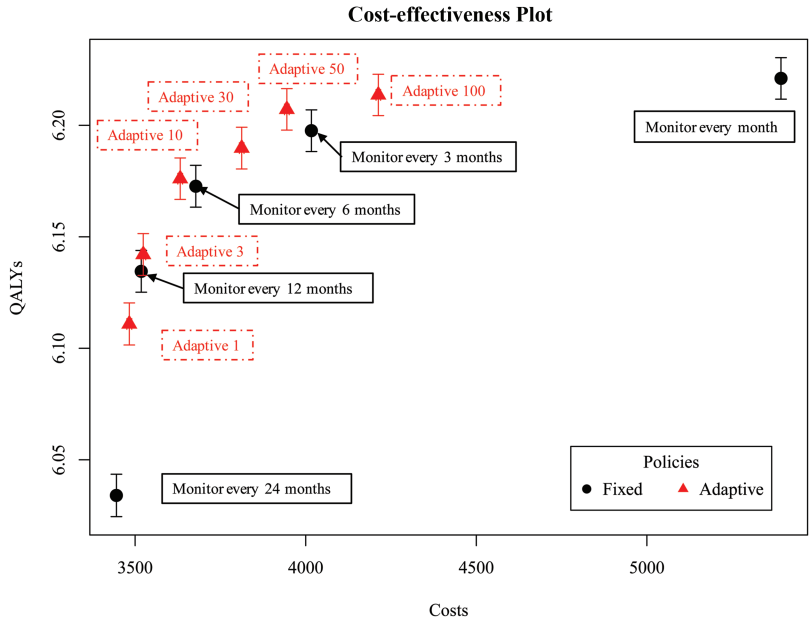

Figure 3. Cost-effectiveness plot. Adaptive "X" = adaptive policy optimized for a cost-effectiveness threshold = X times the gross domestic product per capita of Uganda (US$572). Abbreviation: QALY, quality-adjusted life-year.

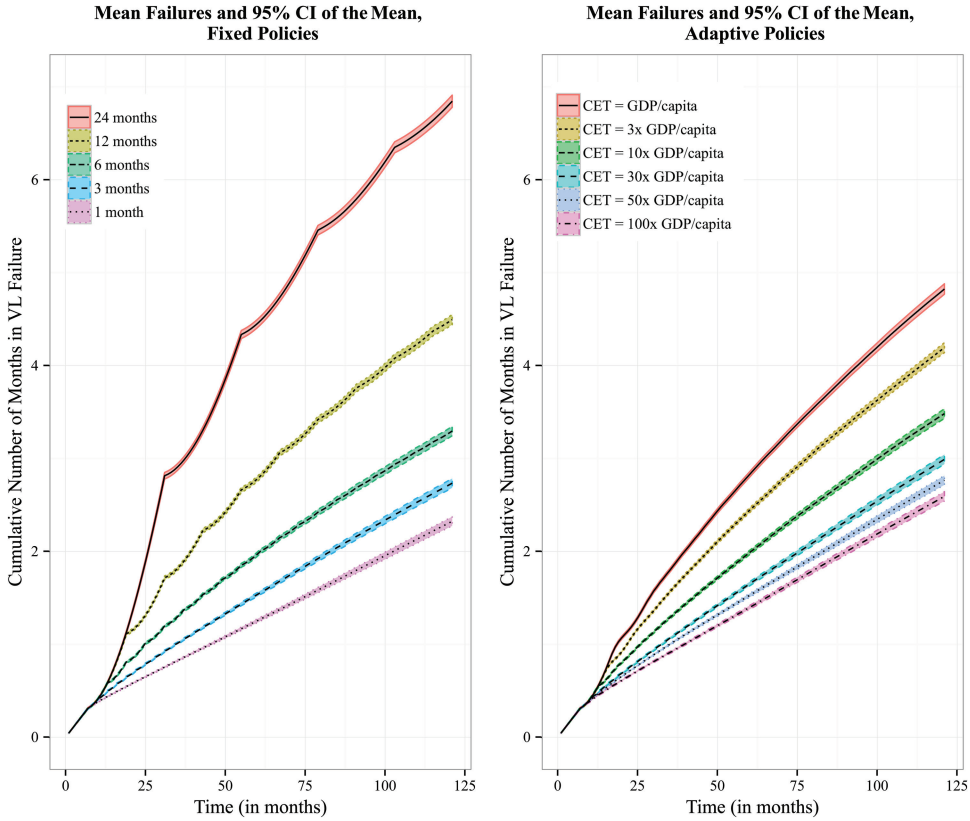

Figure 4. Average cumulative number of months spent in virologic failure. Abbreviations: CET, cost-effectiveness threshold; CI, confidence interval; GDP, gross domestic product. Abbreviation: VL, viral load

and only 0.008 QALYs fewer than the fixed-interval policy that monitors every 3 months.

DISCUSSION

We model the important clinical and public health decision [33] of how to tailor VL monitoring intervals of HIV patients on ART to individual patient characteristics, adherence behavior, and disease dynamics, and we evaluate the cost-effectiveness of such adaptive intervals relative to fixed-interval monitoring policies. We find that adaptive policies outperform fixed-interval monitoring policies, by margins that are small in low-resource settings but potentially large in high- resource settings. Our analysis suggests that in contexts such as Uganda, monitoring at fixed 12-month intervals performs closely to the adaptive monitoring policies that define the cost-effectiveness frontier. Due to its simplicity, the former policy may be a good alternative to implement in resource-limited settings. In higher-resource contexts, however, adaptive monitoring policies could lead to significant cost savings. In settings with GDP per capita of $15 000—$50 000, we estimate that $200–$1100 could be saved for each patient on ART by using adaptive monitoring policies instead of fixed 1- to 3-month monitoring policies.

The optimal monitoring frequency depends crucially on the amount of resources available in the respective setting. For this reason, we embed a CET in our algorithm when optimizing for adaptive monitoring policies, which we then vary to recover adaptive policies in a range of settings. Policies that monitor more frequently tend to achieve high QALYs but also incur more costs, and therefore perform better at high CETs. The small performance margin of adaptive policies at low CETs compared to fixed-interval policies can be explained by the fact that the long monitoring intervals imposed by the resource constraints translate to a loss in accuracy when predicting individualized risks over long time horizons. On the other hand, at higher CET values, monitoring intervals are generally smaller ,and individualized (differentiated) monitoring policies can better take advantage of short-term discrepancies in the risk of failure for different patients.

In developing our simulation model, we use SHCS data—representing a diverse population of HIV-infected individuals with low loss of follow-up [14]—to model patient self-reported adherence, VL failure, and CD4 cell dynamics. Analyzing this data also allowed us to optimize for adaptive policies that depend on patient characteristics, time on ART, and, importantly, on self-reported adherence. We find that patients who report nonadherence behaviors are at an increased risk of VL failure, in accordance with existing studies [15–17, 34–36], and therefore monitoring policies should test them more frequently. Similarly, our analysis of SHCS data found that the risk of VL failure decreases after the initial 6 months on ART, and thus adaptive monitoring intervals tend to become larger the longer the patients have been on treatment. Our study also confirms previous findings that monitoring VL every 12 months provides a reasonably cost-effective VL monitoring policy [37], but extends the analysis to find other adaptive monitoring policies that outperform fixed-interval policies at various expenditure levels.

Our analysis has several limitations. First, we use data from a resource-rich setting (Switzerland) to inform a model for resource-limited settings such as Uganda. Specifically, we use the Swiss data to estimate nonadherence given sociodemographic factors such as age and education, to estimate failure from first-line therapy given nonadherence, and CD4 chances given failure status. Generalizing the probability of nonadherence from Switzerland to resource-limited countries is the most tenuous assumption, while the others tend to be more intrinsic to HIV and thus may be similar between populations. For this reason, we test the sensitivity of our model to assumptions about nonadherence, and we simulate a clinical trial performed in Uganda [1] to check that key outcomes such as mortality and CD4 cell progression match historical values (Supplementary Appendix). Finally, our simulation model does not explicitly model HIV transmission or changes in adherence behavior arising from varying monitoring intervals. Our model does track, however, the number of months that each simulated patient spends in virologic failure, which allows estimation of the number of secondary infections from each policy using a well-known result [28].

Our study can inform decisions about when to test the VL of HIV-infected patients. We provide a decision support tool (menet.umn.edu/~negoescu/downloads.html) that returns a monitoring interval as a function of patient age, gender, education, time since ART initiation, adherence, and resource setting. Our analysis highlights the important role played by patient adherence and time since ART as well as the resource context in determining the frequency of virologic monitoring.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. M. N., E. B., and H. C. B. designed the protocol. D. M. N. developed the model with input from E. B. and H. C. B.; D. M. N., and Z. Z. implemented the simulation model in the R package. D. M. N., E. B., and H. C. B. wrote the final manuscript. H. C. B. is the guarantor.

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References

1. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet **2010**; 375:123–31.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents 2009. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 26 May 2016.
3. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med **2016**; 375:830–9.
4. Badri M, Lawn SD, Wood R. Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting. BMC Infect Dis **2008**; 8:89.
5. Babiker AG, Emery S, Fätkenheuer G, et al; INSIGHT START Study Group. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. Clin Trials **2013**; 10(1 suppl):S5–36.
6. Menzies NA, Berruti AA, Berzon R, et al. The cost of providing comprehensive HIV treatment in PEPFAR-supported programs. AIDS **2011**; 25:1753–60.
7. Orlando S, Diamond S, Palombi L, et al. Cost-effectiveness and quality of care of a comprehensive ART program in Malawi. Medicine (Baltimore) **2016**; 95:e3610.
8. Asboe D, Aitken C, Boffito M, et al; BHIVA Guidelines Subcommittee. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. HIV Med **2012**; 13:1–44.
9. Weissman S, Singh S, Dykema S, Parker RD. Randomized controlled trial: 4 month versus 6 month monitoring of HIV-infected patients on highly active antiretroviral therapy. J Community Health **2016**; 41:1044–8.
10. Kerschberger B, Boulle AM, Kranzer K, et al. Superior virologic and treatment outcomes when viral load is measured at 3 months compared to 6 months on antiretroviral therapy. J Int AIDS Soc **2015**; 18:20092.
11. Bendavid E, Young SD, Katzenstein DA, Bayoumi AM, Sanders GD, Owens DK. Cost-effectiveness of HIV monitoring strategies in resource-limited settings: a southern African analysis. Arch Intern Med **2008**; 168:1910–8.
12. Phillips AN, Cambiano V, Miners A, et al. Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naive populations beginning treatment: modelling study and economic analysis. Lancet HIV **2014**; 1:e85–93.
13. Uganda Bureau of Statistics. Uganda demographic and health survey. Kampala: Uganda Bureau of Statistics, and ICF International Inc, **2012**.
14. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al; Swiss HIV Cohort Study. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol **2010**; 39:1179–89.
15. Glass TR, Sterne JA, Schneider MP, et al; Swiss HIV Cohort Study. Self-reported nonadherence to antiretroviral therapy as a predictor of viral failure and mortality. AIDS **2015**; 29:2195–200.
16. von Wyl V, Klimkait T, Yerly S, et al; Swiss HIV Cohort Study. Adherence as a predictor of the development of class-specific resistance mutations: the Swiss HIV Cohort Study. PLoS One **2013**; 8:e77691.
17. Glass TR, De Geest S, Hirschel B, et al; Swiss HIV Cohort Study. Self-reported non-adherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients. Antivir Ther **2008**; 13:77–85.
18. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365:493–505.
19. Mermin J, Lule J, Ekwaru JP, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. Lancet **2004**; 364:1428–34.
20. Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. J Acquir Immune Defic Syndr **2006**; 42:464–9.
21. Robberstad B, Olsen JA. The health related quality of life of people living with HIV/AIDS in sub-Saharan Africa—a literature review and focus group study. Cost Eff Resour Alloc **2010**; 8:5.
22. Pitter C, Kahn JG, Marseille E, et al. Cost-effectiveness of cotrimoxazole prophylaxis among persons with HIV in Uganda. J Acquir Immune Defic Syndr **2007**; 44:336–43.
23. Besamusca J, Tijdens K, Kahyarara G, Tingum EN. Wages in Uganda—WageIndicator survey 2012. Available at: http://www.wageindicator.org/documents/publicationslist/publications-2012/AIAS_WI_countryreports_f2f_report_Uganda_final_20121211.pdf. Accessed 31 July 2016.
24. Siedner MJ, Lankowski A, Tsai AC, et al. GPS-measured distance to clinic, but not self-reported transportation factors, are associated with missed HIV clinic visits in rural Uganda. AIDS **2013**; 27:1503–8.
25. Clinton Health Access Initiative. 2015 CHAI ARV reference price list: Clinton Health Access Initiative; 2015. Available at: http://www.clintonhealthaccess.org/2015-chai-arv-reference-price-list-2/. Accessed 31 July 2016.
26. Hyle EP, Jani IV, Lehe J, et al. The clinical and economic impact of point-of-care CD4 testing in Mozambique and other resource-limited settings: a cost-effectiveness analysis. PLoS Med **2014**; 11:e1001725.
27. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet **2010**; 376:532–9.
28. Pinkerton SD, Holtgrave DR, Leviton LC, Wagstaff DA, Abramsom PR. Model-based evaluation of HIV prevention interventions. Eval Rev **1998**; 22:155–74.
29. Hughes JP, Baeten JM, Lingappa JR, et al; Partners in Prevention HSV/HIV Transmission Study Team. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis **2012**; 205:358–65.
30. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis **2005**; 191:1403–9.
31. Gray RH, Wawer MJ, Brookmeyer R, et al; Rakai Project Team. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet **2001**; 357:1149–53.
32. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA **1996**; 276:1339–41.
33. El-Sadr WM, Rabkin M, DeCock KM. Population health and individualized care in the global AIDS response: synergy or conflict? AIDS **2016**; 30:2145–8.
34. Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. J Acquir Immune Defic Syndr **2013**; 64:74–8.
35. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. Ann Intern Med **2007**; 146:564–73.
36. Bangsberg DR, Perry S, Charlebois ED, , et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS **2001**; 15:1181–3.
37. Phillips A, Shroufi A, Vojnov L, et al. Sustainable HIV treatment in Africa through viral-load-informed differentiated care. Nature **2015**; 528:S68–76.

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Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother and Child Substudy), Scherrer AU (Head of Data Center), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.