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# DIFFERENTIATED HIV RNA VIRAL LOAD MONITORING IN UGANDA: A COST-EFFECTIVENESS ANALYSIS


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## ABSTRACT

**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 HIV+ 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 (CET). 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: USD3445 (annual monitoring) to USD5393 (monthly monitoring) per patient, respectively (standard error USD3.7). The adaptive policy optimized for low-income contexts achieved 6.142 average QALYs at a cost of USD3524, similar to the fixed 12-month policy (6.135 QALY, USD3518). The adaptive policy optimized for middle-income resource settings yields 0.008 fewer QALYs per person, but saves $204 compared to monitoring every three months.

**Conclusions**: The benefits from implementing adaptive versus 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.

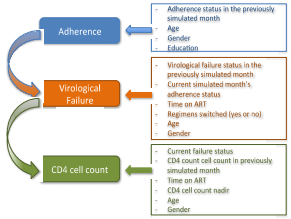

## BACKGROUND

1. Routine viral load (VL) monitoring for patients receiving antiretroviral therapy (ART) is recommended worldwide. Timely detection of loss of virologic control may improve ART choices, and reduce HIV transmission risk.
2. Costs of viral load monitoring make up 15-20% of total cost of care in low-income contexts.
3. There is limited evidence to guide viral load monitoring frequency, especially differentiated care interventions. As a result, mathematical models have been influential in addressing issues related to the benefits and cost-effectiveness of viral load monitoring.

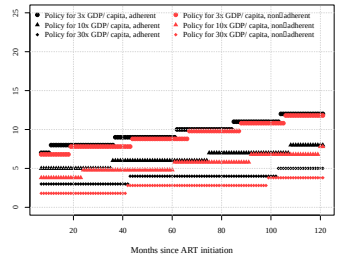
## METHODS

1. Overview: A stochastic simulation model that captures HIV disease progression, tracking patient demographics, CD4 cell counts, individual adherence and presence of virologic failure (Figure). The model was used to optimize monitoring strategies at different cost-effectiveness (CE) thresholds (CET).
2. Model Population: Simulated 100,000 individuals matching Uganda's 2011 demographic survey results over 10 years. Mean age among HIV+ individuals was 36 years old, 61% women, 25% completed primary school education; Mean initial CD4 cell count is 310 cell/mm$^3$.
3. Three parameters estimated using the Swiss HIV Cohort Study Data: Self reported adherence, Failure, and CD4 changes.
   - Parameterized using prospective cohort of 5251 ART-treated patients, 95414 data points (e.g. official cohort visits).
   - Adherence modeled as a function of previous adherence, age, sex, education, and time since last measurement.
   - Failure status was a function of current adherence status, time on ART, age, sex, and monitoring interval.
   - Quantile regression for modelling CD4 cell count changes as function of current CD4 cell count, ART, and failure.
4. Secondary infection estimation: The number of secondary HIV infections in the community is estimated as a function of the number of individuals in virologic failure in the population simulated.
5. Assumed two regimens were available. Regimens considered consisted of a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir boosted protease inhibitor (PI) and 2 nucleoside reverse transcriptase inhibitors (NRTIs).

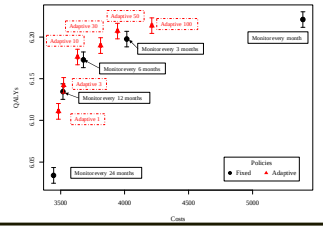
**Variables Tracked Monthly in the Simulation Model**



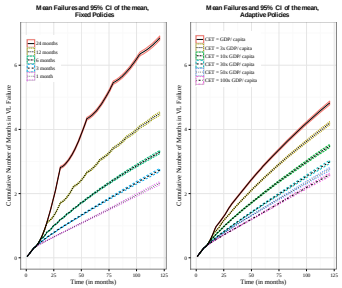

**Example of Adaptive Policy:**
**Male, Age 15 – 20 Years, Primary Education or less.**




**Cost Effectiveness Plot.** Adaptive "X" = Adaptive Policy Optimized for a CET = X Times the GDP per Capita of Uganda (US$ 572).




**Average Cumulative Number of Months Spent in Virologic Failure**




## METHODS (CONTINUED) - ADAPTIVE POLICY OPTIMIZATION

6. We use a stochastic optimization approach: 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 net monetary benefit (NMB), where NMB = QALYs × CET– costs. Here, the cost-effectiveness threshold (CET) is defined to be the dollar amount a decision maker is willing to pay per additional QALY gained.
7. We optimize VL monitoring policies for CET of 572 $ (USD)/QALY (Uganda's GDP per capita in 2013), and CETs 3, 10, 30, 50 and 100 times Uganda's per capita GDP.

## MAIN FINDINGS

1. The model was calibrated using data from a randomized clinical trial of HIV laboratory monitoring strategies conducted in Uganda and Zimbabwe. Our model closely matched several key quantities (e.g. 5-year mortality, opportunistic infection-free survival) from the trial.
2. The adaptive policies evaluated were generally on the cost-effectiveness frontier, achieving the highest QALYs at their respective costs.
3. The least costly adaptive policy that is optimized using Uganda's GDP (Adaptive 1) was cost-effective with an Incremental Cost Effectiveness Ratio (ICER) of 491 $/QALY relative to monitoring every 24 months. The next least costly adaptive policy (Adaptive 3) has an ICER of 1311$/QALY compared to Adaptive 1, which is less that a fixed 12-month interval monitoring policy (1485$/QALY compared to Adaptive 1).
   - Adaptive "X" = Adaptive Policy Optimized for a CET = X Times the Gross Domestic Product (GDP) per Capita of Uganda (US$ 572).
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 q24 months fixed interval monitoring policy. The adaptive policies for the three highest CET values (30, 50, and 100 times Uganda's GDP/capita) resulted in fewer months spent in failure than the 6-month fixed interval policy.

## CONCLUSIONS

- Adaptive policies outperform fixed interval monitoring policies, by margins that are small in low-resource settings but potentially large in high-resource settings.
- In Uganda, monitoring every twelve months is the next most efficient monitoring policy (due to its simplicity) if an adaptive policy is unavailable or infeasible.
- In higher resource contexts, adaptive monitoring policies could lead to significant cost savings. In settings with GDP per capita of $15,000 – $50,000, we estimate that $200 – $1,100 could be saved for each patient on ART by using adaptive monitoring policies instead of fixed 1-3 months monitoring policies.

## ACKNOWLEDGMENTS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