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Comparison of guidelines for HIV viral load monitoring among pregnant and breastfeeding women in sub-Saharan Africa: a simulation study

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Abstract

Background: Intensified viral load (VL) monitoring for pregnant and breastfeeding women has been proposed to help address concerns around antiretroviral therapy (ART) adherence, viraemia and transmission risk, but there have been no systematic evaluations of existing policies.

Methods: We used an individual Monte Carlo simulation to describe longitudinal ART adherence and VL from conception until two years postpartum. We applied national and international guidelines for VL monitoring to the simulated data. We compared guidelines on the percentage of

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Role of authors

LM, EJA, ML conceptualised the study and simulation. ML, JR developed the analytic framework for the simulation. ALC, SE, DVH, CAK, RLS, EJA, LM provided critical input and feedback on the model framework. ML, TG wrote the simulation and analysis code. SSB, JSC, DVH, AO, RLS, EJA, LM, contributed source data for the calibration and validation of the simulation model. All authors provided input on the draft manuscript and approved submission.

Conflicts of interest

No authors report conflicts of interests.

women receiving VL monitoring and the percentage of women monitored at the time of elevated VL.

Results: Coverage of VL monitoring in pregnancy and breastfeeding varied markedly, with between 14-100% of women monitored antenatally and 38-98% monitored during breastfeeding. Specific recommendations for testing at either a fixed gestation or a short, fixed period after ART initiation achieved >95% testing in pregnancy but this was much lower (14-83%) among guidelines with no special stipulations. By the end of breastfeeding, only a small proportion of simulated episodes of elevated VL>1000 copies/mL were successfully detected by monitoring (range, 20-50%).

Discussion: While further research is needed to understand optimal VL frequency and timing in this population, these results suggest that current policies yield suboptimal detection of elevated VL in pregnant and breastfeeding women.

Keywords

HIV; antiretroviral therapy; viral load monitoring; pregnancy; mathematical model; simulation

INTRODUCTION

Lifelong antiretroviral therapy (ART) to suppress HIV viral load (VL) is the critical intervention to support the long-term health of women living with HIV while preventing both sexual and perinatal transmission. However high levels of suboptimal ART adherence, disengagement from care and elevated VL have been widely documented among pregnant and postpartum women living with HIV globally [1–3]. Because of the risks of both vertical and horizontal transmission associated with HIV viremia during pregnancy and breastfeeding (BF), raised maternal VL during these periods requires rapid detection and intervention within ART programs. For low- and middle-income countries, VL monitoring has only recently entered national policies [4,5]; several policies call for VL monitoring annually in HIV-infected adults on ART, with an additional VL test 4-6 months after ART initiation to monitor initial adherence [5]. While intensified VL monitoring for pregnant and breastfeeding women has been proposed in some recommendations [5], it has not yet been evaluated systematically. To address this gap, we evaluated a selection of available VL monitoring guidelines and estimated the percentage of women likely to be detected with raised VL during pregnancy or breastfeeding.

METHODS

We used an individual Monte Carlo simulation, based on earlier models [6,7], to describe longitudinal ART adherence, VL and vertical transmission risk from conception until two years postpartum in a hypothetical cohort of 10,000 HIV-infected women. The model simulates ART use and adherence, uses this to simulate VL and then bases *in utero*, intrapartum and breastfeeding transmission risks on VL within individual women on a weekly time step, and allows for variations in: the proportions of women conceiving on ART or initiating ART during pregnancy; gestational age at entry to antenatal care (and from this,

duration of ART before delivery among women initiating ART in pregnancy), gestation at delivery, and duration of breastfeeding.

ART use and adherence among women on ART are the primary drivers of changes in VL in the absence of drug resistance. ART adherence is modeled using a combination of population and individual level parameters: the model allows settings for the population proportion in each of three adherence classes at entry (non-adherent, partially adherent, or fully adherent), with individual adherence allowed to vary weekly depending on the class of adherence at entry, previous intra-individual adherence, gestational age or time postpartum, infant feeding practices, and additional stochastic noise. VL values change in response to weekly ART adherence levels, with both magnitude of change and additional noise depending on current VL levels. For example, decreasing levels of adherence will result in increasing VL values, with (on average) larger changes as the VL value is larger. The model was calibrated using available data from countries across sub-Saharan Africa, including MCH-ART [8,9], Mma-Bana [10], PROMISE (IMPAACT 1077BF) [11], and PROMOTE [12].

Input parameters relevant to this analysis include the distributions of: gestational age at entry into antenatal care (set at a median 22 weeks' gestation (IQR, 16-28)), gestational age at delivery (set at a median of 38 weeks (IQR, 37-40), and breastfeeding duration (set at median duration of 40 weeks (IQR, 29-49)). We assumed that 50% of women initiated ART during pregnancy (at the time of antenatal care (ANC) entry) and 50% were receiving ART prior to conception; among those on ART prior to conception, 70% had VL <50 copies/mL at entry into antenatal care. For this analysis, no lost to follow-up or maternal or fetal loss was included.

Guidelines were selected for inclusion on the basis of being representative of recent guidelines used in sub-Saharan African countries and non-overlapping in terms of monitoring strategies; US Department of Health and Human Services (DHHS) and WHO guidelines were also selected for comparison. Guidelines included in this analysis were South Africa 2015 [5], Malawi 2016 [13], Kenya 2016 [14], Zambia 2018 [15], the WHO 2016 consolidated guidelines [4] and the 2018 US DHHS guidelines [16]. The monitoring schedule in the guidelines vary from relatively low frequency (for example the Malawi guidelines with testing 6 months after ART initiation then every 2 years) to higher frequency (for example DHHS, with testing 1-3 monthly depending on VL levels). The guidelines differ slightly if a woman is initiating ART for the first time (Table 1).

VL monitoring guidelines were applied to each of 20 simulated populations of 10,000 women and the results averaged. Random seeds were specified to ensure all guidelines were applied to identical simulated data sets but seeds for each of the 20 populations were unique. The main outcome measures of interest were: the percentage of women with elevated VL at different time points, including before delivery or at any time before the end of breastfeeding; the percentage of women receiving VL monitoring during pregnancy and/or breastfeeding; the percentage of women monitored at the time of elevated VL; the time from elevated VL until monitoring; and the cumulative VL (expressed as $\log_{10}$ copies/year) experienced by women at the time of detection. Sensitivity analyses were used to examine

the robustness of findings when varying input parameters, and subsidiary analyses were carried out with the subgroup of women who achieved viral suppression during pregnancy.

RESULTS

The results (Table 2) show that the percentage of women who receive VL monitoring in pregnancy and breastfeeding varied markedly by guidelines, with between 14-100% of women monitored antenatally and 38-98% monitored during breastfeeding. Specific recommendations for testing at either a fixed gestation (WHO, DHHS, Zambia) or a short, fixed period after ART initiation (DHHS) achieved >95% testing in pregnancy; other guidelines led to 59-83% antenatal testing; and with no special stipulation, only 14% of women received an antenatal test under Malawian guidelines. Guidelines calling for monitoring during breastfeeding (SA, Kenya, Zambia) had >80% coverage compared to 30-60% among guidelines that did not (WHO, Malawi).

In the simulation, by 24 months postpartum, 92% of women initiating ART achieved VL<50 copies/mL, and 18% of these subsequently experienced transient or extended elevations in VL >1000 copies/mL. Only a small proportion of simulated episodes of elevated VL>1000 copies/mL were successfully detected by monitoring (range, 20-50%) among women who had reached viral suppression. Guidelines with more frequent testing in pregnancy and breastfeeding led to shorter delays from the onset of elevated VL (50 copies/mL) to detection (SA median weeks 10 (IQR: 5, 16) vs Kenya median weeks 17 (IQR: 9, 23)) as well as lower cumulative VL before detection (DHHS cumulative VL 0.34 $\log_{10}$ copies/mL/year (IQR: 0.26, 0.41) vs SA 0.54 (IQR: 0.34, 0.98)) (Table 2). In sensitivity analyses, higher proportions of women initiating ART during pregnancy did not alter the relative performance of guidelines appreciably (not shown). Findings across guidelines were also similar when varying other input parameters, including the median gestational age at antenatal care entry and duration of breastfeeding (not shown).

DISCUSSION

This work provides the first systematic evaluation of existing policies for VL monitoring in pregnant and breastfeeding women on ART. The key finding is that without guidance specific to pregnant and breastfeeding women, fewer than 30% of women would receive antenatal or postnatal VL monitoring. However even with specific guidance, current guidelines may lead to suboptimal detection of elevated VL, in the form of either undetected viremia and/or substantial delays from the onset of viremia to its detection during routine monitoring.

Like all findings from mathematical models, these results depend on a set of underlying assumptions; however, this model has been subject to intense calibration using multiple, diverse data sources, as well as sensitivity analyses with considerable expert input. In addition, it is important to note that this analysis did not consider the delays between time of specimen collection for VL monitoring and return of result to health care worker for review and potential intervention; accounting for these delays is likely to lead to further reductions in performance of VL monitoring in real-world settings. Health systems considerations, like

the delay in return of VL results, reduction of stigma related to HIV diagnosis, and retention and engagement of women in care, may have impacts that outweigh the use and timing of VL monitoring, however VL monitoring is one of the few objective methods we have to assess treatment adherence and development of drug resistance, and understanding how to apply this tool optimally is important.

Although vertical transmission rates have reduced dramatically with increased coverage and access to HIV testing and rapid initiation of ART, hurdles remain to eliminate mother-to-child-transmission. In order to identify episodes of viremia (and risk of vertical transmission), targeted strategies for VL monitoring, and ultimately, drug resistance testing, will be needed for the elimination of mother-to-child-transmission [17]. While further research is needed to understand the specifics of optimal VL frequency and timing, these findings underscore the need for stronger policies to support when and how VL monitoring during pregnancy and breastfeeding should occur in order to improve maternal and child health outcomes in the context of HIV infection.

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Table 1 :

Details of guidelines based monitoring.

Guideline (year) [ref]	VL monitoring time points antenatal	VL monitoring time points breastfeeding
WHO (2016) [4]	If initiating ART: 6m, 12m, then annually and at 34-36 weeks GA If continuing ART: annually from ART initiation date and at 34-36 weeks GA	Annually
USA DHHS (2018) [11]	If initiating ART: 2-4 weeks after ART initiation, then monthly until VS, then 3 monthly (if VL<50 copies/ml) plus at 34-36 weeks GA If continuing ART: 1st ANC visit and routinely every month, move to monitoring every 3 months (if VL<50 copies/ml) plus 34-36 weeks GA	BF not recommended in this population
Malawi (2016) [8]	If initiating ART: 6m, then every 24m If continuing ART: every 24m	Continue every 24m until end BF
Kenya (2016) [9]	If initiating ART: 6m, then every 6m If continuing ART: first ANC, then every 6m	Continue every 6m until end of BF
Zambia (2018) [10]	If initiating ART: 6m, then every 6m plus at 34-36 weeks GA If continuing ART: first ANC, then every 6m plus at 34-36 weeks GA	Continue every 6m until end BF
South Africa (2015) [5]	If initiating ART: 3m, 6m then every 6m If continuing ART: first ANC, every 6m	Continue every 6m until end of BF

BF: breastfeeding; ANC: antenatal care; ART: antiretroviral therapy; WHO: World Health Organisation; GA: gestational age

Table 2.

Results of simulations applying existing guidelines for viral load (VL) monitoring to populations of pregnant and breastfeeding women. All entries are median (IQR) for stated value.

Characteristics of simulated population						
Proportion of women with viral suppression <50 copies/mL before delivery					69 (68.5, 69.2)	
Proportion of women with viral suppression <50 copies/mL before end BF					88.7 (88.5, 89.0)	
Proportion of women with viral suppression <1000 copies/mL before delivery					84.3 (84.2, 84.5)	
Proportion of women with viral suppression <1000 copies/mL before end BF					95 (94.9, 95.2)	
Proportion of women with elevated viral load after viral suppression (<50 copies/mL)					11.8 (11.6, 12.0)	
Proportion of women with elevated viral load after viral suppression (<1000 copies/mL)					18.9 (18.8, 19.1)	
Characteristics of VL monitoring						
Guidelines	**WHO 2016 [4]**	**US DHHS 2018 [11] ^**	**Malawi 2016 [8]**	**Kenya 2016 [9]**	**Zambia 2018 [10]**	**SA 2015 [5]**
Number of VL tests per woman during pregnancy through end of breastfeeding	2 (2, 3)	6 (4, 7)	1 (1, 1)	2 (2, 3)	3 (3, 4)	3 (2, 3)
Weeks to first VL (among women *initiating* ART during pregnancy) from ANC entry	10 (4, 16)	0 (0, 0)	29 (14, 43)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Weeks to first VL (among women *continuing* ART into pregnancy) from ANC entry	13 (7, 18)	3 (2, 4)	31 (29, 33)	31 (29, 33)	14 (7, 20)	13 (13, 18)
Percent of women with at least one VL monitoring test during pregnancy	98.0 (97.8, 98)	100.0 (100.0, 100.0)	13.8 (13.4, 14.0)	56.3 (56, 56.8)	97.8 (97.8, 97.9)	82.8 (82.5, 83.1)
Percent of women with at least one VL monitoring test during breastfeeding	80.1 (79.5, 80.9)	37.5 (36.5, 37.9)	54.7 (54.3, 55)	91.8 (90.7, 92.5)	91.5 (90.5, 92)	92.6 (90.9, 93.4)
Proportion of women with at least one VL monitoring test among those who experienced any elevated viral load after viral suppression (<50 copies/mL)	99 (98.9, 99.2)	100 (100, 100)	83.7 (82.7, 84.9)	94.3 (93.5, 95.8)	99.3 (99.1, 99.5)	99.1 (98.9, 99.2)
Proportion of women who received VL monitoring test at the time of elevated viral load after viral suppression (<50 copies/mL)	25.1 (24.5, 25.4)	31.1 (30.8, 32)	16.6 (15.2, 17.1)	23.1 (22, 23.6)	28.6 (28.2, 29.6)	27.5 (26.8, 29.3)
Weeks elapsed from start of VL>50 copies/mL until first VL monitoring test or end of BF	10 (5, 17)	2 (1, 12)	16 (9, 23)	17 (9, 23)	10 (5, 16)	10 (5, 16)
Cumulative VL from 1st ANC until detection of VL >50 copies/mL or 2 years postpartum (if not detected) (log_{10} copies/mL * years)	0.45 (0.31, 0.89)	0.34 (0.26, 0.41)	0.61 (0.34, 1.48)	0.56 (0.34, 1.52)	0.44 (0.31, 0.90)	0.54 (0.34, 0.98)
Proportion of women who received VL monitoring test among those that experienced any elevated viral load after viral suppression (<1000 copies/mL)	98.8 (98.7, 99.2)	100 (100, 100)	85.2 (84.9, 86.7)	93.2 (92.5, 94.1)	99.1 (99, 99.2)	98.5 (98.4, 98.6)
Proportion of women who were monitored at the time of elevated viral load after viral suppression (<1000 copies/mL)	35.5 (35, 36.1)	46.6 (46.3, 47.5)	22.8 (22.5, 23.3)	29.9 (28.9, 30.5)	38.4 (37.7, 38.8)	38.5 (38.1, 39.7)

Characteristics of simulated population						
Time elapsed in weeks from start of VL>1000 copies/mL until VL monitoring or end of BF	10 (5, 17)	2 (1, 3)	21 (13, 26)	20 (13, 26)	10 (5, 16)	9 (5, 14)
Cumulative viral load from 1st ANC until detection of VL>1000 copies/mL or 2 years postpartum (if not detected) (log_{10} copies/mL * years)	0.50 (0.32, 1.08)	0.37 (0.28, 0.51)	0.62 (0.35, 1.64)	0.58 (0.34, 1.55)	0.49 (0.32, 1.09)	0.58 (0.34, 1.17)

^ US DHHS 2018 guidelines have no recommendation for VL monitoring during breastfeeding as breastfeeding is not recommended.