Strategies for viral load monitoring during pregnancy in resource-limited settings

P767

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Background

- Raised maternal viral load (VL) drives mother-to-child transmission (MTCT) *in utero*, intrapartum and postpartum and occurs frequently in HIV-infected (HIV+) pregnant and postpartum women (PPW).
- Increasing VL increases MTCT risk in a dose-response manner and labour and delivery are a period of particularly high transmission risk.
- High levels of suboptimal antiretroviral (ART) adherence and disengagement from care have been widely documented among HIV+ PPW globally.
- VL monitoring as part of routine care has entered low- and middle-income country (LMIC) national policies only recently. 2016 WHO guidelines suggest that VL monitoring during pregnancy may be used to identify infants at high risk of MTCT who may be targeted with enhanced infant prophylaxis or other interventions based on maternal VL $>$ 1000 copies/mL.
- The optimal timing and frequency of VL monitoring is unknown during pregnancy, but PPW require special attention for VL monitoring because of the time restricted period of MTCT risk.
- **We developed a pilot individual simulation model to evaluate optimal timing and frequency of viral load monitoring during pregnancy in order to predict VL at the time of delivery.**

Methods

- A Monte-carlo model was developed to simulate individual longitudinal VL trajectories (Figure 1).
- The model iterates on a weekly time step and simulates VL measures throughout pregnancy until 50 weeks post-partum, from conception to delivery, with ART initiation, time to viral suppression, viral rebound and time of delivery modeled as variable parameters.
- Input parameters estimated from an existing cohort (MCH-ART) of women initiating ART during pregnancy in South Africa, n = 522 women, 30% of women demonstrate loss of viral control post-suppression (Figure 2).

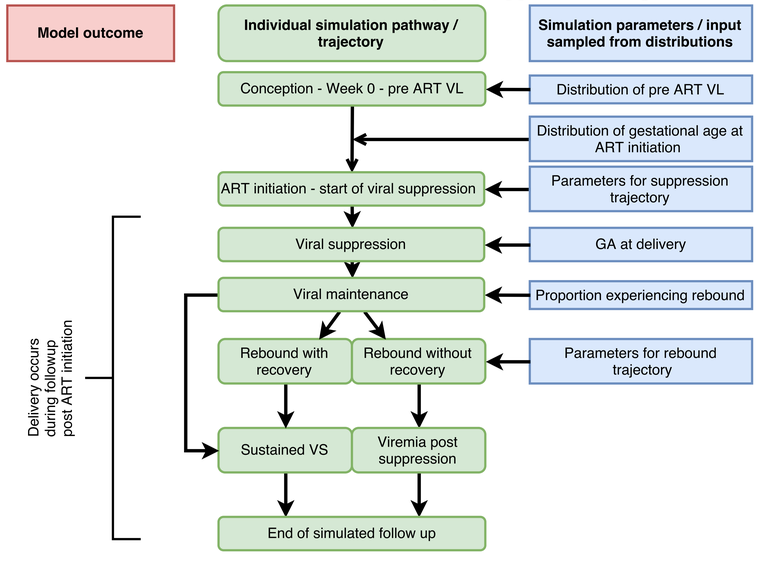


Figure 1: Simplified schematic of simulation model of model used to simulate viral loads in HIV+ pregnant women initiating ART.

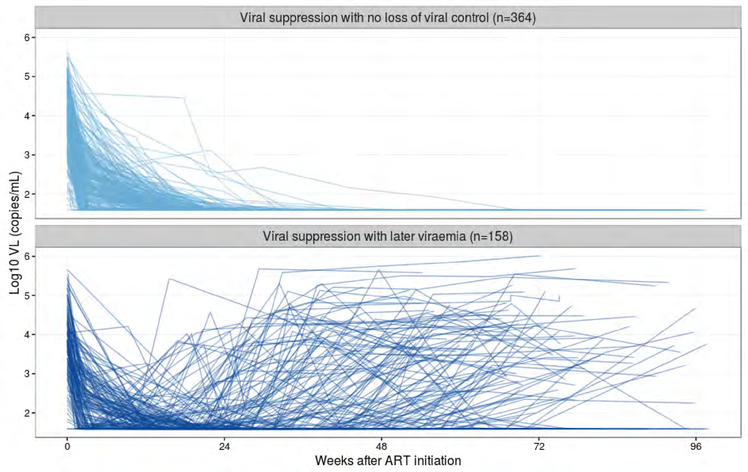


Figure 2: Individual Log_{10} VL vs weeks post ART initiation - MCH-ART data [1]

- Statistical prediction models are applied to the simulated data to predict VL at delivery using either a single VL test after ART initiation in the antenatal period or pre-ART VL with a second VL test in the antenatal period.
- All antenatal time points by gestational age (eg, 32 wks) and by time on ART (eg, 12 wks since ART initiation) were evaluated.
- Last-observation-carried forward, linear, and spline-based statistical prediction models were evaluated.
- Model predictive performance (sensitivity, specificity, positive predictive value, negative predictive value) are estimated on simulated data.

Results

- Ten runs of 10,000 individuals each were run, 5 runs used for model fitting and 5 runs used as hold out samples for model prediction.
- The simulation model produced a reasonable facsimile of VL trajectories (Figure 3).
- Statistical models were used to predict VL at delivery, and performance evaluated by correct binary classification ($\leq$ 1000 c/mL vs $>$ 1000 c/mL).

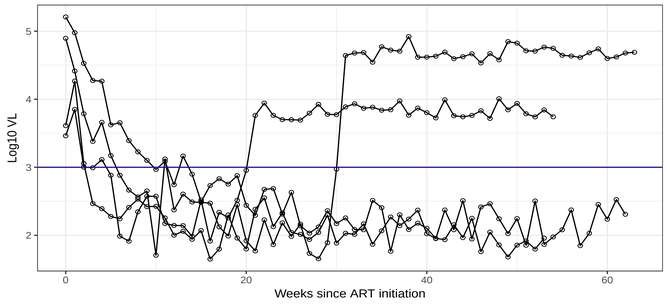


Figure 3: Plot of random sample of viral load trajectories for four individuals in the VL simulation; this sample purposefully selects 2 patients who achieve and maintain viral suppression, and two patients who experience elevated VL after initial suppression.

- Results of modeling demonstrate that:
  - Proximity to time of delivery was the major factor in determining test performance: the closer the VL test is taken to the time of delivery, the greater the predictive power in detecting viremia at delivery (Figure 4).
  - Because elevated VL after initial viral suppression can be difficult to predict, all models had poor sensitivity until approximately $<$2-4 weeks prior to delivery.
  - However, VL testing carried out after 32 weeks' gestation was only possible for $<$85% of pregnant women due to preterm deliveries.
  - In addition, pre-ART VL had limited additional predictive performance (results not shown), increasing predictive accuracy by 2-3% across models.

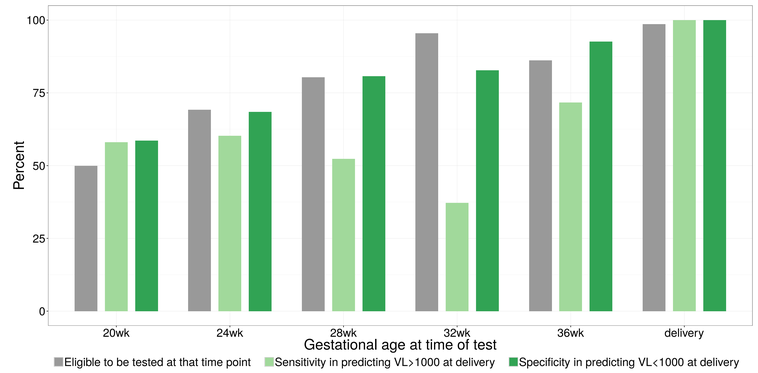


Figure 4: Sensitivity and specificity of VL monitoring at select gestations during pregnancy to detect VL $>$ 1000 cps/mL at the time of delivery.

Discussion

- If taken $>$2-4 weeks before delivery, single VL tests in the antenatal period may have limited ability to predict viremia at delivery.
- Rapid turnaround times between routine VL test and return of results are necessary for a single VL to be useful, however given the challenges in the VL "cascade" this is often difficult to achieve in many LMIC.
- These findings suggests that Point-of-Care VL monitoring late in pregnancy or at delivery may be a useful tool to identify elevated VL at delivery.
- Pre-ART VL improves predictive performance by only a small amount and may not be cost-effective in LMIC programmes.
- Additional work is required on validating and calibrating the simulation model as well as evaluating more complex monitoring schedules, and extending the modeling framework to breastfeeding and postnatal MTCT risk.

References

[1] Myer L, Dunning L, Lesosky M, Hsiao N-Y, Phillips TK, Petro G, Zerbe A, McIntyre JA, and Abrams EJ. Frequency of viremic episodes in HIV-infected women initiating antiretroviral therapy during pregnancy: a cohort study. *Clinical Infectious Diseases*, 2017.

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