Viral Load Testing in Pregnancy and the Breastfeeding Period

AIDSFree Webinar
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USAID Office of HIV/AIDS
VL/EID Webinar Series, AIDSFree
https://aidsfree.usaid.gov/

- Improving Early Infant Diagnosis (January 18, 2018)
- Managing Viral Load Results (October 31, 2017)
- Information Technology Tools to Support the Scale Up of Viral Load Testing and Early Infant Diagnosis (July 18, 2017)
- Tools for Scaling-up Viral Load Monitoring (March 22, 2017)

AIDSFree Viral Load and Early Infant Diagnosis Knowledge Base  https://aidsfree.usaid.gov/resources/vl-eid

Thank you for your attendance in past and welcome if this is your first VL related AIDSFree webinar
Today’s Presentations

- ANOVA, South Africa
  - Diana Mokoena, MBChB
  - Nozipho Maseko, BCUR

EGPAF, Rwanda

- Michelle Gill, MPH
Measuring VL in pregnancy and the breast feeding (BF) period can be difficult

Guidelines for VL assessment in pregnancy & BF period

- When to test
- Where to test

Obtaining VL and what to do with results

- Maternal considerations (i.e. when she was diagnosed and started on ART)
- Infant considerations

Research & current programming considerations
Guidelines for VL assessment in pregnancy & BF period
WHO Viral Load Guidelines (2016)

Recommendations for routine monitoring

Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting (conditional recommendation, very low-quality evidence).

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed (conditional recommendation, low-quality evidence).

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a Viral load testing should be performed early after initiating ART (within 6 months), at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible.

b WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL). For service delivery recommendations in these guidelines (see Chapter 6 "Service delivery"), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.

Source: Adapted from Consolidated Guidelines, WHO, 2016
WHO Infant postnatal prophylaxis, note definition of high risk infant

Recommendations

- Infants born to mothers with HIV who are at high risk of acquiring HIV* should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate-quality evidence).

- Breastfed infants who are at high risk of acquiring HIV,* including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality evidence).

- Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding).

* High-risk infants are defined as those:
  - born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
  - born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement available; OR
  - born to women with incident HIV infection during pregnancy or breastfeeding; OR
  - identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

WHO Viral Load Testing Strategy (all adults)

Targeted viral load monitoring (suspected clinical or immunological failure)

Routine viral load (early detection of virological failure)

Test viral load

Viral load >1000 copies/ml

Evaluate for adherence concerns

Repeat viral load testing after 3–6 months

Viral load ≤1000 copies/ml

Maintain first-line therapy

Viral load >1000 copies/ml

Switch to second-line therapy

Source: Adapted from Consolidated Guidelines, WHO, 2016
Kenya 2016 ART Guidelines

• Note advice for women already on ART vs. newly initiated
• Note VL schedule during BF period
• Note postnatal prophylaxis recommendations

Source: http://www.nascop.or.ke/?p=1060
Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2016 edition
### South Africa 2015 Viral Load Recommendations

**6.1.4 Viral load monitoring for first-line regimen in pregnant and breastfeeding women**

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<tr>
<th>Viral Load (VL)</th>
<th>Response</th>
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<tr>
<td>&lt;400 copies/mL</td>
<td>6 monthly VL monitoring and routine adherence support</td>
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<td>400-1000 copies/mL</td>
<td>Assess adherence carefully</td>
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<td>If VL≤1000 copies/mL, continue on current ART regimen</td>
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<td></td>
<td>If concerns about adherence consider doing another viral load within 6 months</td>
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<td></td>
<td>Repeat viral load at 6 months, if suppressed, return to 6 monthly VL testing</td>
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<tr>
<td>&gt;1000 copies/mL</td>
<td>Pregnant women: If VL&gt;1000 copies/mL, provide adherence counselling, repeat the VL in 1 month</td>
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<td>If second VL result is undetectable or has shown a reduction in viral load of 1 log (10-fold) or greater, continue with the existing regimen</td>
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<tr>
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<td>If the VL result is unchanged or has not shown a 1 log (10-fold) reduction or has increased, the woman should be switched to second-line therapy urgently</td>
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<td>Any woman who requires a switch to second-line therapy must receive intensive adherence counselling and support to ensure high-level adherence and rapid viral load suppression</td>
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</table>

*Always check for Hepatitis B before stopping TDF. If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. If Hepatitis B outcome is positive, TDF should be continued as a 4th drug in the second regimen.*

*If a pregnant woman is diagnosed with HBsA positive, the neonate must receive HepB immunoglobulin and HepB immunisation at birth and then continue with routine immunisations as per protocol.*

Source: [http://www.sahivsoc.org/Files/ART%20Guidelines%202015052015.pdf](http://www.sahivsoc.org/Files/ART%20Guidelines%202015052015.pdf)
1.2 WHAT IS NEW IN THESE GUIDELINES

The main changes for pregnant/breastfeeding women, paediatrics, adolescents and adults are summarised in Boxes 1-3 below.

Box 1: Changes specific to pregnant/breastfeeding women

» Immediate initiation of lifelong ART for all HIV-positive women who are pregnant, breastfeeding or within 1 year post-partum, regardless of CD4 cell count

» Use of EFV as part of the first-line regimen, regardless of the gestation of the pregnancy

» Use of maternal lifelong ART throughout pregnancy and breastfeeding to reduce MTCT

» Viral load testing for women on ART≥3 months at confirmation of pregnancy to direct management

» Repeat HIV testing for HIV-negative women 3-monthly during pregnancy, at labour/delivery, at the 6 week Expanded Programme on Immunisation (EPI) visit and 3-monthly throughout breastfeeding. This should be done during routine antenatal care, postnatal care and EPI/child health follow-up visits

» Women with contraindications to FDC should be considered high-risk pregnancies. They should be initiated on AZT immediately and referred urgently for initiation on to three single ART drugs

» Provision of birth HIV PCR for all HIV exposed neonates

» Use of extended 12 weeks NVP or dual post-exposure prophylaxis with NVP and AZT for infants where maternal viral load suppression may be inadequate

Source: http://www.sahivsoc.org/Files/ART%20Guidelines%202015052015.pdf
Obtaining VL and what to do with results
Importance of VL testing in Pregnant and Breastfeeding Women

- Several research studies have found adherence to ART during pregnancy to be suboptimal.
- It is important to diagnose HIV and initiate ART, preferably \( \geq 13 \) weeks gestation, to reduce MTCT (i.e. the sooner the woman is started, the sooner her VL will decrease).
- Follow up women postpartum so that they can be promptly initiated if they become viremic during BF period.
- Timing of when to do VL is important so that we can improve mother’s prognosis and to determine prophylaxis regimen for the infant.

Some women are not very adherent to ART postpartum

- Women who started ART under Option B+ were ~1.5 times more likely to adhere inadequately than those who were not pregnant or breastfeeding (Haas et al.)

VL for women initiating ART in pregnancy vs women conceiving already on ART

- MTCT of HIV is higher in women who initiate ART during pregnancy compared to those who were already on ART before pregnancy (5.7% vs 0.7%; p=0.01). (Hoffman et al.)
  
  - For every additional week of ART during pregnancy the chances of MTCT of HIV reduces by 8% (95% CI: 0.87-0.99, p=0.02).

- Pregnant women who have been on ART for <=4 weeks are 5.2 times more likely of MTCT of HIV compared to those who have been on ART for at least 13 weeks (95% confidence interval (CI): 2.5 –11.0) (Chibwesha at al.).

- Early and sustained control of viral load is associated with a decreasing residual risk of MTCT of HIV-1 (Tubiana et al.).
If the VL is suppressed

- There are models of care for stable infected women and their infants that can be considered if she has adequate VL suppression and support at home and in the community.

- **Child & maternal considerations:** Consider Differentiated Service Delivery (DSD) models for pregnant/BF mother and her family.
  - Synchronous & less frequent appointments
  - Offer family health services under one roof
  - Mothers to mothers (M2M) support groups and similar entities

Sources:
http://www.differentiatedcare.org
https://www.m2m.org/
If the VL is elevated (>1000 copies/mL) (Myer et al.)

Urgency of responding to elevated VL during pregnancy and breastfeeding:

- Time-limited period to reduce transmission risk from conception through delivery and breastfeeding
- A high proportion of transmissions occur in late pregnancy, during delivery, and in the early postpartum period
- Objective to achieve viral suppression before delivery and maintain it during breastfeeding
- Pregnancy and particularly postpartum period as high risk for inadequate adherence

If the VL is elevated (>1000 copies/mL)

Interventions for elevated VL during pregnancy and breastfeeding:

- Routine WHO algorithms for management of elevated VL may be inadequate for management of mothers’ HIV progression
- Protease inhibitor-based second-line treatment may be poorly tolerated during pregnancy
- Opportunity to enhance infant prophylaxis with multidrug antiretroviral (ARV) regimen if maternal VL not suppressed
- VL testing 4 weeks before delivery provides a basic approach to help target interventions from birth

— Research & current programming considerations
HIV seroconversion during late pregnancy & postpartum (Dinh et al.)

- Study offered a representative estimate of the risk of HIV-seroconversion during pregnancy (HSP) among women who had at least one HIV-negative test result during pregnancy in SA.
- Median time of HIV-seroconversion was 32.8 weeks gestation; 28.3% (19.7%-36.9%) estimated to be >36 weeks.
- Early MTCT was 10.7% (6.2%-16.8%) for HSP vs. 2.2% (1.7%-2.8%) for mothers with known HIV-positive status. Although they represent 2.2% of all mothers and 6.7% of HIV-infected mothers, HSP accounted for 26% of early MTCT.

Increased Risk of HIV Acquisition Late in Pregnancy (CROI abstract 45, see also 268, 269, 271)

- After adjustment for condom use, age, use of PrEP, and HIV viral load, the probability of HIV transmission per sex act was significantly higher in late pregnancy (aRR 2.82, p=0.01) and postpartum (aRR 3.97, p=0.01) compared to non-pregnant time.

- While further research is needed to better understand biological susceptibility, scale-up of HIV prevention and testing in antenatal and postpartum care in high HIV prevalence settings is warranted to prevent sexual transmission and identify acute maternal HIV infections (Thompson et al.).

Can we Eliminate Breast Milk Transmission of HIV? (CROI abstract 54)

- Data from several African countries, where infectious diseases are the main contributors to infant and under-five morbidity and mortality, show that breastfeeding is a key child survival strategy.

- However, maternal ART adherence is sub-optimal, few mothers receive regular viral load monitoring and where viral suppression is known, 16-78% of people living with HIV are virally suppressed. This questions the feasibility of eliminating breastmilk MTCT in real-life resource-limited settings.

- With 4.1% MTCT, the EMTCT target will only be achieved if maternal HIV prevalence is <0.12%. This massive decline in maternal HIV prevalence is unlikely; thus combination strategies of maternal ART with support for ART adherence and maternal and / or infant passive or active vaccination may be the next holy grail (Goga)

ART Detection and Resistance During Viraemic Episodes (VE) in Pregnancy and Breastfeeding (CROI abstract 140)

- The vast majority of VE in this [South African primary care] setting are explained by ART nonadherence; the frequency of early VE and rapid emergence of NNRTI Drug Resistance Mutations (DRMs) during VE have implications for long-term maternal outcomes and choice of optimal ART regimens (Myer et al.).

- “By 12m postpartum 30% of women in the cohort experienced VE after VS”.

- “In 107 cases and 124 controls, median duration on ART was 42w. Cases were younger with greater previous ARV exposure and higher pre-ART VL. At the time of VE, ARVs were detected in 17% of cases, compared to 89% of preceding samples from the same women when VS, and 94% of VS controls sampled at the corresponding time on ART (both adjusted p<0.001)”.

Does Changing ART in Early Pregnancy for Fetal Risk Destabilize Viral Suppression? (CROI Abstract 804)

- Changing ART regimens early in pregnancy to improve maternal and infant outcomes doesn’t destabilize viral suppression. However, effects will vary by patient characteristics and the ART regimen (Violaine Peyronnet et al.).

- “Treatment switches for medical strategy did not lead to poorer virological control, compared to pregnancies without such switches (19.3% vs. 16.2%, HRa: 1.0 [0.7-1.3]).”

• Young women and women who haven’t disclosed their HIV status were more likely to have a high viral load, and report difficulties with adherence and/or depression (Keshet Ronen et al.).

• “Prevalence of virologic failure was associated with clinic site (range 1%-27%, p<0.0001), continuous age (OR per year increase 0.98, 95%CI 0.97-0.99), HIV status disclosure (OR 0.31, 95%CI 0.11-0.83) and ART adherence skills score (OR 0.70 per 10% increase, 95%CI 0.53-0.93). Marital status, self-reported adherence, history of side effects, social support, history of intimate partner violence or distance to clinic were not associated with virologic failure.”

Maternal Viral Load Suppression and Vertical Transmission in Malawi’s PMTCT Program (CROI Abstract 821)

• Mothers with unsuppressed VL, mother's <19 years and non-exclusive breastfeeding were associated with vertical transmission (Ernest Nkhoma et al.)

• “Women with unsuppressed VL load were over 16 times more likely to transmit HIV to their infants (n=19/136 vs 14/988; aOR 16.7; 95% CI 6.6-41.8). Maternal age <19 years (n=4/74 vs. 11/535; aOR 6.6; 95% 1.1-39.8) and non-exclusive breastfeeding (n=6/88 vs 27/1064; aOR 4.0; 95% CI 1.2-13.8) were also associated with vertical transmission.”

Cohort of 523 women in Cape Town, South Africa (Myer et al.)

- Cohort of 523 women in Cape Town initiating ART in pregnancy and achieving VS (<50 copies/mL). Participants provided specimens through 12 months postpartum for batched viral load (VL) testing separate from routine care.

- Up to one-third of women who achieve initial viral suppression experience viremia within 1 year postpartum, and that most of these women experience VL >1000 copies/mL, often with repeated episodes over time.

- Viremia appears to occur frequently, particularly postpartum, among HIV-infected women after initial VS in this setting. More intensive VL monitoring is warranted in this population; the immediate causes and long-term implications of VE require investigation.

Why are the women poorly adherent/experiencing VL rebound?

- Could women be more adherent in pre-partum period? Motivation may wane with time.
- Prior ART defaulters had VL rebound, and could have resistant strains of HIV.

Optimal timing of viral load monitoring during pregnancy to predict viraemia at delivery in HIV-infected women initiating ART in South Africa: a simulation study (Lesosky et al.)

This is a simulation study that aimed to determine the feasibility of VL monitoring during gestation, and to predict the VL measure at birth. The results are as follows...

- “Monitoring strategies based on gestational age regardless of time on ART (sensitivity >60%) versus time on ART regardless of gestational age (sensitivity <50%) may be easier to implement in many settings, as they could coincide with routine antenatal visits.”

- “POC VL tests conducted at delivery (~36 weeks) could make VL results available for patient management within hours of specimen collection. This would theoretically have perfect sensitivity and specificity in predicting VL at delivery.”

The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy (Huntington et al.)

- Postpartum women who were initiated on ART during pregnancy had a higher chance of viral rebound compared to women who were already on ART when they conceived (27% [95% CI: 22–32%] vs 5.9% [95% CI: 4.0–7.7]).

- Overall, all postpartum women compared to their controls had an increase in viral load in the first 3 months post-delivery, but not during the 3-12 months thereafter.

Perinatal HIV Transmission: Getting to Zero (Mandelbrot et al.)

• Perinatal transmission of HIV occurred in…
  – women who started ART in the 2nd and 3rd trimester
  – women who had interrupted ART during pregnancy

• “Starting ART later in pregnancy and having a maternal viral load of >50 copies/ml were independent risk factors to perinatal HIV transmission.”

• Women who were initiated on ART before conception, were adherent to ART during pregnancy, and had a VL of < 50 copies/ml, had greatly reduced chances of perinatal transmission on HIV.

Mandelbrot L et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis 2015 Dec 1; 61:1715. (http://dx.doi.org/10.1093/cid/civ578)
Key clinical, behavioral, and health systems research questions related to viral load monitoring in pregnant and breastfeeding women

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<tr>
<th>Domain</th>
<th>Policy and programme issues</th>
<th>Specific research questions</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>When to monitor viral load (VL) in pregnant and breastfeeding women?</td>
<td>When and how frequently should VL monitoring be conducted during pregnancy and breastfeeding to maximise the detection of elevated VL, balancing clinical benefits with costs and operational complexity?</td>
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<td>When and how to intervene against elevated VL?</td>
<td>What are the implications of low-level viraemia for transmission risk and maternal outcomes, and how will that impact the threshold for virologic failure in pregnant and breastfeeding women? What are the impacts of intervening against detectable VL ≤ 1,000 copies/mL on maternal and infant outcomes?</td>
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<td>What are the relative contributions of antiretroviral resistance versus antiretroviral therapy (ART) nonadherence as immediate causes of elevated VL in pregnant and breastfeeding women?</td>
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<td>How does the epidemiology of HIV drug resistance in a given population modify the choice of interventions in response to elevated VL on routine monitoring in pregnancy?</td>
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<td>How can new antiretroviral agents alter the timing and frequency of VL monitoring, as well as responses to elevated VL, in pregnant and breastfeeding women?</td>
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<td>How can VL monitoring support adherence counselling for patients, including in response to elevated VL detected during routine monitoring?</td>
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<td>Behavioural</td>
<td>What causes elevated VL in pregnant and breastfeeding women?</td>
<td>What are the drivers of ART nonadherence during pregnancy and breastfeeding?</td>
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<td>How does knowledge or understanding of VL as a concept, and an individual’s VL result at a particular timepoint, influence adherence behaviours and retention in care?</td>
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<td>Does routine VL monitoring contribute to improved adherence and suppression outcomes during pregnancy and breastfeeding?</td>
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<td>Health systems</td>
<td>How can VL monitoring be implemented to support care for pregnant and breastfeeding women?</td>
<td>How can steps in the VL cascade be expedited to minimize delays from specimen collection to clinical action?</td>
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<td>What role may point-of-care VL monitoring technologies play in improving the detection and management of elevated VL?</td>
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<td>How can VL test results be optimally communicated across different health services providing care throughout pregnancy and breastfeeding?</td>
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<td>How do VL monitoring and feedback systems integrate into differentiated models of care?</td>
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<td>What role can VL monitoring and feedback systems play in monitoring and promoting long-term retention of postpartum women?</td>
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References


Mandelbrot L et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis 2015 Dec 1; 61:1715. (http://dx.doi.org/10.1093/cid/civ578)


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References


Consolidated Guidelines, WHO, 2016
Thank you, on to our presenters

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