## Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy

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| Panel's Recommendations |
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| • Because a pregnant person's antenatal viral load correlates with the risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible (AII).<br>• For pregnant people who have not achieved viral suppression (after an adequate period of treatment):<br>o Assess medication adherence, tolerability, dosing, potential problems with drug absorption, adherence to food requirements, and possible drug interactions. (see Adherence to the Continuum of Care in the Adult and Adolescent Guidelines.<br>o Perform HIV drug resistance testing if HIV RNA level is above the threshold for resistance testing (>500 to 1,000 copies/mL (AII).<br>o Consult an HIV treatment expert and consider possible antiretroviral regimen modification (AIII).<br>• Please see Intrapartum Care for People with HIV for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for pregnant people who have not achieved viral suppression on antiretroviral therapy (AII). |
| *Rating of Recommendations: A = Strong; B = Moderate; C = Optional*<br>*Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion* |

Virologic suppression is defined as a confirmed HIV RNA level that is below the lower limits of detection of an ultrasensitive assay. Virologic failure is the inability to achieve or maintain an HIV RNA level of <200 copies/mL. Baseline HIV RNA levels have been shown to affect the time to viral suppression in both pregnant and nonpregnant individuals, and no difference in time to viral response has been observed between pregnant and nonpregnant women.[1,2] In women with HIV who participated in three prospective studies from seven African countries and who became pregnant after initiating antiretroviral therapy (ART), incident pregnancy did not affect time to viral suppression or time to virologic failure.[3]

HIV RNA levels should be assessed 2 to 4 weeks after an antiretroviral (ARV) drug regimen is initiated or changed to provide an initial assessment of the regimen's effectiveness.[4] With use of integrase strand transfer inhibitors (INSTIs) as part of an ARV regimen, a decrease of approximately one hundred–fold in HIV RNA levels can be expected by Week 2 of therapy.[4,5] In the United Kingdom, a multicenter, retrospective observational study of women initiating ART during pregnancy found that higher baseline viral load was the only independent factor associated with faster first-phase HIV RNA half-life decay, and that lower viral load on Day 14 after starting ART was associated with an increased likelihood of achieving an undetectable plasma viral load by 36 weeks gestation.[6]

Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible in pregnancy, because maternal antenatal HIV RNA level correlates with the risk of perinatal transmission, as well as maternal HIV progression. In addition, an analysis from the Women's Interagency HIV Study cohort found that higher viral loads were associated with an increased risk of pregnancy loss through miscarriage or stillbirth.[7] However, a report from the HIV Outpatient Study noted that among 119 pregnancies that were analyzed between 2005 and 2015, 33 women (27.7%) were not virally suppressed (HIV RNA >500 copies/mL) at the end of pregnancy. Failure to achieve virologic suppression remains a common problem for pregnant people in the United States.[8]

## *Causes of Detectable Viremia*

Lack of virologic suppression is frequently associated with inadequate adherence; barriers to adherence should be addressed when the viral load does not decline as expected. (See Adherence to the Continuum of Care in the Adult and Adolescent Guidelines.) A systematic review and meta-analysis of ART adherence during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that only 73.5% of pregnant women achieved adequate (>80%) ART adherence.[9] Factors that can contribute to suboptimal adherence in pregnancy include depression, a lack of HIV seropositive status disclosure, adverse drug reactions, a history of intimate partner violence, a lack of prior experience with taking ART, and a lack of knowledge about the role of ART in preventing perinatal transmission.[10–12] Other factors that have been associated with lack of viral suppression in pregnancy, and likely associated with difficulties with adherence, include unintended pregnancy and social and economic vulnerabilities (e.g., living in the U.S. for less than 5 years with no family/friends' support, neighborhood exposures to crime), as well as poor engagement in prenatal care.[13–15] Other potential causes of detectable viremia include drug-drug interactions and lack of attention to food requirements with some ARV agents (e.g., rilpivirine, darunavir) that affect adequate drug absorption.

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART. In a retrospective multicenter cohort of 378 pregnant women, 77.2% of women achieved HIV RNA <50 copies/mL by delivery; success in achieving viral suppression varied by baseline HIV RNA level. In women with baseline HIV RNA levels <10,000 copies/mL, the gestational age of their infants at ART initiation did not affect the likelihood of achieving viral suppression up to 26.3 weeks gestation. In women with baseline HIV RNA levels >10,000 copies/mL, however, delaying ART initiation past 20.4 weeks significantly reduced the likelihood of achieving maximal suppression at delivery.[1] Among 1,070 ART-naive pregnant women with HIV who participated in the prospective cohort study IMPAACT P1025, initiating ART at >32 weeks gestation also was associated with a significantly higher risk of having a viral load >400 copies/mL at delivery.[16] A report from the French Perinatal Cohort found no perinatal transmission of HIV among 2,651 infants born to women who received ART before conception, continued ART throughout pregnancy, and delivered with a plasma HIV RNA <50 copies/mL (with an upper limit for the 95% confidence interval [CI] of 0.1%). In the entire cohort of 8,075 mother-infant pairs that were followed from 2000 through 2011, HIV RNA level and timing of ART initiation were independently associated with perinatal transmission of HIV in a logistic regression analysis.[17] A recent cross-sectional analysis of 10,052 pregnant women with HIV receiving antenatal care (ANC) in public facilities in South Africa reported that failure to achieve viral suppression (HIV RNA <50 copies/mL) was associated primarily with late registration for ANC and late initiation of ART.[18]

The response to ART also may be affected by other factors. Pregnant people with acute HIV generally have high viral loads and strategies to accelerate viral decline may be considered in these patients, though these strategies should be discussed with HIV treatment experts (see Acute HIV Infection). In a population-based surveillance study in the United Kingdom and Ireland that compared 70 pregnancies in 45 women with perinatally acquired HIV and 184 pregnancies in 118 women with non-perinatally-acquired HIV, perinatally-acquired HIV in the mother was a risk factor for detectable viral load near delivery; this finding reflects complex clinical, psychosocial, adherence, and resistance issues.[19] Among 2,123 births that occurred between 2007 and 2015 and were reported in the Surveillance Monitoring of ART Toxicities Study, as part of the Pediatric HIV/AIDS Cohort Study, women with perinatally-acquired HIV had a higher perinatal transmission rate (1.1%; 95% CI, 0.3% to 4.3% vs. 0.4%; 95% CI, 0.2% to 1.0%) and higher likelihood of having HIV RNA >1,000 copies/mL close to delivery than women with non-perinatally acquired HIV.[20] If needed, ARV regimens should be optimized in consultation with HIV treatment experts, and other possible contributing factors should be considered (see Prenatal Care, Antiretroviral Therapy, and HIV Management in People with Perinatal-Acquired HIV Infection).

## *Managing Lack of Viral Suppression*

A three-pronged approach is indicated for evaluating and managing pregnant people on ARV regimens who have lack of suppression of HIV RNA, taking time on treatment into account. The three approaches are—

- Assessing adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, use of gastroesophageal reflux disease medications, coadministration of prenatal vitamins and iron with INSTIs,[21,22] lack of attention to food requirements);
- Ordering ARV drug resistance tests if plasma HIV RNA is above the threshold for resistance testing (generally >500 copies/mL); *and*
- Considering modifying the ARV regimen (see Pregnant People with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 5).

Evaluation of and support for adherence during pregnancy are critical to achieving and maintaining maximal viral suppression. Access to and promotion of pre-pregnancy counseling and family planning services to reduce unintended pregnancy and help those with HIV achieve their childbearing aspirations, as well as early attention to the special need for adherence support among immigrant communities affected by HIV and others with adverse neighborhood exposures, are critical to achieving and maintaining maximal viral suppression. In a retrospective cohort, group prenatal care for pregnant women living with HIV as compared to individual care showed promise in achieving viral suppression by the time of delivery (adjusted odds ratio [aOR] = 2.29; 95% CI, 0.94-5.55; $P = 0.068$).[23]

Before modifying an ARV regimen, consult an expert in clinical care for ARV-experienced adults. This is particularly important in cases where a drug regimen must be modified due to resistance or adverse effects. Regimen simplification may be considered to promote better adherence. Other possible interventions include adherence education, treating problems that may interfere with drug absorption (e.g., vomiting), ensuring that a patient is taking ART in accordance with food requirements, and directly observing drug administration in the home or hospital setting (see Table 10).[24]

In a study from the French Perinatal cohort among 1,797 women with HIV RNA level <50 copies/mL before 14 weeks gestation, change in ARV regimen in 411 women due to safety concerns based on existing guidelines at the time of pregnancy did not result in loss of virologic control.[25] However, among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with HIV RNA level >400 copies/mL in late pregnancy (aOR 1.66; 95% CI, 1.07–2.57; *P* = 0.024). This highlights the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[26] The findings also highlight the importance of not changing effective ARV regimens in people who become pregnant while taking ART (see Pregnant People with HIV Who Are Currently Receiving Antiretroviral Therapy).

## *The Role of INSTIs in People with Detectable HIV RNA Levels During Pregnancy*

The INSTI class of drugs has been associated with rapid viral load reduction. Both raltegravir (RAL) and dolutegravir (DTG) are now *Preferred* ARV drugs in people trying to conceive and for use throughout pregnancy, and should be strongly considered in people who present late in pregnancy and, specifically, in those who present with high viral loads (see Table 4).The use of RAL or DTG also has been suggested as a fourth ARV drug in ART-naive people with high viral loads, but there is limited evidence of a benefit in this situation (see Pregnant People with HIV Who Have Never Received Antiretroviral Drugs, Table 4, and Table 5). Adding RAL or another INSTI to a three-drug ARV regimen also has been suggested in the setting of lack of viral suppression due to known or suspected drug-resistant mutations or nonadherence.[27] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials. The available data come from case series and two retrospective cohorts, and most of these data focus on the use of RAL.[5,28,29] A recent prospective cohort study from Thailand enrolled 154 pregnant women with HIV. These women had either started ART at ≥32 weeks gestation (73% of women) or were receiving ART and had plasma HIV RNA levels >1,000 copies/mL at 32 to 38 weeks gestation (27% of women). These women received a standard, three-drug ARV regimen plus RAL intensification until delivery. The median gestational age at entry was 34 weeks (interquartile range [IQR] 33–36 weeks) and median duration of treatment was 21 days (IQR 8–34 days). The proportion of women with HIV RNA levels of <50 copies/mL and <1,000 copies/mL at delivery was 45% and 76%, respectively; 83% of those who were ART-naive had HIV RNA <1,000 copies/mL at delivery compared with 60% of those who were already on ART but who had not achieved virologic suppression. The overall perinatal transmission rate in this high-risk group of women was 3.9% (95% CI, 1.4% to 8.2%). Six instances of perinatal transmission occurred in this group; three of those instances occurred *in utero*.[30]

In cases where treatment failure is attributed to nonadherence and/or drug resistance, concerns exist that the addition of a single agent may further increase the risk of resistance and lead to the potential loss of future effectiveness of this agent. In addition, when poor adherence is the reason that the patient has not achieved or maintained virologic suppression, it is unclear that adding a new drug to the existing regimen will improve adherence. Currently, data are insufficient to recommend adding an INSTI to a failing ARV regimen for people in late pregnancy. However, after reviewing a patient's full treatment history and drug resistance results, a clinician may consider using an INSTI as part of a new regimen for pregnant people who are experiencing virologic failure on a non-INSTI ARV regimen.

## *Viral Rebound in Late Pregnancy*

A recent retrospective study of 318 pregnant women addressed the risk of viral rebound in pregnancy among women who received ART for ≥4 weeks and who had had ≥1 prior undetectable viral load. Nineteen women (6%) had viral rebound (HIV RNA >50 copies/mL) within 1 month before delivery; six of these 19 women had viral loads above 1,000 copies/mL. Significant predictors of viral rebound included cocaine use and testing positive for hepatitis C virus RNA.[31] Viral load testing is currently recommended at 34 to 36 weeks gestation for delivery planning; providers may consider repeat testing subsequently in selected patients who are at increased risk for viral rebound.

## *Intrapartum Management of People with a Lack of Viral Suppression*

Please see Intrapartum Care for People with HIV for guidance about the use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for pregnant persons who have not achieved viral suppression on ART.

## References


1. Read PJ, Mandalia S, Khan P, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26(9):1095-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22441248.

2. Rachas A, Warszawski J, Le Chenadec J, et al. Does pregnancy affect the early response to cART? *AIDS*. 2013;27(3):357-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23079802.

3. Kourtis AP, Wiener J, King CC, et al. Effect of pregnancy on response to antiretroviral therapy in HIV-infected African women. *J Acquir Immune Defic Syndr*. 2017;74(1):38-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27787340.

4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2021. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.

5. Rahangdale L, Cates J, Potter J, et al. Integrase inhibitors in late pregnancy and rapid HIV viral load reduction. *Am J Obstet Gynecol*. 2016;214(3):385 e381-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26928154.

6. Alagaratnam J, Peters H, Francis K, et al. An observational study of initial HIV RNA decay following initiation of combination antiretroviral treatment during pregnancy. *AIDS Res Ther*. 2020;17(1):41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32660502.

7. Cates JE, Westreich D, Edmonds A, et al. The effects of viral load burden on pregnancy loss among HIV-infected women in the United States. *Infect Dis Obstet Gynecol*. 2015;2015:362357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26582966.

8. Patel M, Tedaldi E, Armon C, et al. HIV RNA suppression during and after pregnancy among women in the HIV outpatient study, 1996 to 2015. *J Int Assoc Provid AIDS Care*. 2018;17:2325957417752259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29357772.

9. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS*. 2012;26(16):2039-2052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22951634.

10. Yee LM, Crisham Janik M, Dorman RM, Chong PS, Garcia PM, Miller ES. Relationship between intimate partner violence and antiretroviral adherence and viral suppression in pregnancy. *Sex Reprod Healthc*. 2018;17:7-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30193723.

11. Mills JC, Pence BW, Edmonds A, et al. The impact of cumulative depression along the HIV care continuum in women living with HIV during the era of universal antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2019;82(3):225-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31335585.

12. Brittain K, Mellins CA, Remien RH, et al. Impact of HIV-status disclosure on HIV viral load in pregnant and postpartum women on antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2019;81(4):379-386. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30939530.

13. Dude AM, Miller ES, Garcia PM, Yee LM. Unintended pregnancy and viral suppression in pregnant women living with HIV. *Am J Obstet Gynecol MFM*. 2021;3(2):100300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33359637.

14. Momplaisir FM, Nassau T, Moore K, et al. Association of adverse neighborhood exposures with HIV viral load in pregnant women at delivery. *JAMA Netw Open*. 2020;3(11):e2024577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33156348.

15. Premkumar A, Yee LM, Benes L, Miller ES. Social vulnerability among foreign-born pregnant women and maternal virologic control of HIV. *Am J Perinatol*. 2020;38(8)):753-758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368072.

16. Katz IT, Leister E, Kacanek D, et al. Factors associated with lack of viral suppression at delivery among highly active antiretroviral therapy–naive women with HIV: a cohort study. *Ann Intern Med*. 2015;162(2):90-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25599347.

17. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):1715-1725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26197844.

18. Woldesenbet SA, Kufa T, Barron P, et al. Viral suppression and factors associated with failure to achieve viral suppression among pregnant women in South Africa. *AIDS*. 2020;34(4):589-597. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31821189.

19. Byrne L, Sconza R, Foster C, Tookey PA, Cortina-Borja M, Thorne C. Pregnancy incidence and outcomes in women with perinatal HIV infection. *AIDS*. 2017;31(12):1745-1754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28590327.

20. Goodenough CJ, Patel K, Van Dyke RB, Pediatric HIV AIDS Cohort Study. Is there a higher risk of mother-to-child transmission of HIV among pregnant women with perinatal HIV infection? *Pediatr Infect Dis J*. 2018;37(12):1267-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29742647.

21. Bordes C, Leguelinel-Blache G, Lavigne JP, et al. Interactions between antiretroviral therapy and complementary and alternative medicine: a narrative review. *Clin Microbiol Infect*. 2020;26(9):1161-1170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32360208.

22. Federspiel J, Bukhari MJ, Hamill MM. Interactions between highly active antiretroviral therapy and over-the-counter agents: a cautionary note. *BMJ Case Rep*. 2021;14(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33408101.

23. McKinney J, Jackson J, Sangi-Haghpeykar H, et al. HIV-adapted group prenatal care: assessing viral suppression and postpartum retention in care. *AIDS Patient Care STDS*. 2021;35(2):39-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33571047.

24. McCabe CJ, Goldie SJ, Fisman DN. The cost-effectiveness of directly observed highly-active antiretroviral therapy in the third trimester in HIV-infected pregnant women. *PLoS One*. 2010;5(4):e10154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20405011.

25. Peyronnet V, Warszawski J, Sibiude J, et al. Does changing antiretroviral therapy in the first trimester of pregnancy for safety concerns have an impact on viral suppression? *J Acquir Immune Defic Syndr*. 2019;80(5):574-584. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30649033.

26. Floridia M, Ravizza M, Pinnetti C, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. *HIV Clin Trials*. 2010;11(6):303-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239358.

27. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet*. 2007;369(9569):1261-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17434401.

28. Boucoiran I, Tulloch K, Pick N, et al. A case series of third-trimester raltegravir initiation: Impact on maternal HIV-1 viral load and obstetrical outcomes. *Can J Infect Dis Med Microbiol*. 2015;26(3):145-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26236356.

29. Cecchini DM, Martinez MG, Morganti LM, Rodriguez CG. Antiretroviral therapy containing raltegravir to prevent mother-to-child transmission of HIV in infected pregnant women. *Infect Dis Rep*. 2017;9(2):7017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28663779.

30. Puthanakit T, Thepnarong N, Chaithongwongwatthana S, et al. Intensification of antiretroviral treatment with raltegravir for pregnant women living with HIV at high risk of vertical transmission. *J Virus Erad*. 2018;4(2):61-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29682296.

31. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. *Obstet Gynecol*. 2017;130(3):497-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28796673.