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Antiretroviral Treatment of HIV/AIDS During Pregnancy

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HIV infection in people who are pregnant remains a significant public health challenge. For all individuals with HIV, antiretroviral therapy (ART) should be initiated at HIV diagnosis and continued indefinitely. In 2021, approximately 19.7 million of the 38.4 million people worldwide living with HIV were females older than 15 years, and approximately 79% were of childbearing age. Each year, about 1.3 million people with HIV worldwide (and about 5000 in the US) give birth.

For pregnant people with HIV, ART is essential for preserving maternal health and preventing perinatal and sexual HIV transmission. Without ART, approximately 15% to 40% of pregnant or breastfeeding people with HIV will have a child who acquires HIV. However, the risk of perinatal and postpartum transmission is less than 2% if ART is used from early in pregnancy with sustained viral suppression (defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay). Currently, approximately 81% of pregnant people with HIV are receiving ART worldwide. Increased ART use has resulted in a 50% reduction in new perinatal infections globally, from approximately 320 000 in 2010 to 160 000 in 2021. Approximately 48% of the 160 000 new perinatal infections in 2021 occurred in infants born to people who did not receive ART during pregnancy, often because they did not know their HIV status; 22% in infants born to people who first acquired HIV during pregnancy or breastfeeding; 22% in infants born to people who stopped treatment during pregnancy or breastfeeding; and 8% in infants born to pregnant people taking ART without adequate viral suppression.

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Timing of ART Initiation

Ideally, ART should be started at first diagnosis of HIV and, therefore, people diagnosed with HIV prior to conception should be taking ART when they learn of their pregnancy. In a French study of more than 5400 pregnant people with HIV who were receiving suppressive ART before conception and had an HIV viral load lower than 50 copies/mL near delivery, zero HIV perinatal transmissions occurred.[1] In a clinical trial in which postpartum people with HIV were randomized to either maternal ART alone or prophylaxis of the infant with nevirapine during breastfeeding, postnatal transmission at age 18 months was low with both interventions: 0.7% with maternal ART and 0.9% with infant nevirapine.[2]

Antiretroviral Pharmacokinetics During Pregnancy

The physiologic changes of pregnancy, such as reduced intestinal motility, increased hepatic enzyme activity, and increased glomerular filtration rate, can affect antiretroviral pharmacokinetics. Six to 8 years is typically required between antiretroviral approval and availability of pregnancy-specific pharmacokinetic data.[3] The importance of pregnancy pharmacokinetic data is illustrated by cobicistat, which acts as a pharmacoenhancer by inhibiting some antiretroviral metabolic enzymes to boost antiretroviral concentrations to therapeutic levels. Pregnancy-related physiologic changes reduce this boosting activity. Several years after initial approval, elvitegravir/cobicistat and darunavir/cobicistat concentrations were demonstrated to be 50% to 60% and 80% to 90% lower, respectively, in later pregnancy than postpartum.[4] Cobicistat-based regimens are therefore not recommended as initial treatment during pregnancy.

Although blood levels of most antiretrovirals are usually slightly lower in pregnant (particularly the third trimester) than nonpregnant people, dose adjustment is not typically required. However, twice-daily dosing of darunavir/ritonavir or raltegravir is recommended in pregnant people because trough drug concentrations (concentrations present just prior to the next dose) with once-daily administration can be below the desired therapeutic range (eTable in the Supplement).

ART Regimen Selection in Pregnancy

Selection of ART regimen should be individualized, based on ART history, drug resistance testing results, comorbidities, and available data on pharmacokinetics and safety in pregnancy. The choice of ART is generally similar for people who are pregnant and those who are not pregnant, as long as pharmacokinetic data show that drug concentrations during pregnancy are within the therapeutic range and no concerning safety data exist.[5] Shared decision-making between the clinician and patient is recommended, including discussion of benefits and risks to the patient and fetus, while acknowledging that limited pregnancy safety data exist for many antiretrovirals. Pregnant people with HIV who are already taking fully suppressive ART when pregnancy occurs should generally continue their regimen because the rates of viral resistance or perinatal HIV transmission are higher if ART is interrupted or changed during pregnancy.[6]

Current guidelines for ART initiated during pregnancy recommend two nucleoside reverse-transcriptase inhibitors plus a third drug from another class. Available evidence supports the use of tenofovir disoproxil fumarate (or tenofovir alafenamide) plus emtricitabine (or lamivudine) in combination with either the integrase inhibitor dolutegravir or with the protease inhibitor darunavir/ritonavir as preferred therapy when ART is first being started in pregnancy (eTable in the Supplement). Because pharmacokinetic and safety data are limited for newer drugs including bictegravir, doravirine, and injectable long-acting cabotegravir/rilpivirine, and there is only limited experience in pregnancy with dual therapies such as dolutegravir/lamivudine, these drugs and regimens are not currently recommended for ART initiation in pregnant people with HIV.[5]

ART Risks During Pregnancy

Adverse events such as preterm birth, small-for-gestational-age, and stillbirth are more common in pregnant people with HIV who are not receiving ART, compared with pregnant people without HIV. While maternal ART reduces the risk of these adverse pregnancy outcomes, some older ART regimens (eg, nevirapine- or lopinavir/ritonavir-based)were associated with a 1.2- to 1.3-adjusted relative risk of adverse fetal outcomes compared with subsequent (efavirenz-based) regimens (eg, risk of any adverse pregnancy outcome was 42%-47% for nevirapine-based ART,depending on nucleoside backbone, and 48% for lopinavir/ritonavir-based ART compared with 36% for efavirenz-based ART), demonstrating the importance of gathering pregnancy safety data.[7] In a clinical trial of 643 pregnant people with HIV randomized after the first trimester to dolutegravir (with either tenofovir alafenamide or tenofovir disoproxil fumarate plus emtricitabine) vs efavirenz/tenofovir disoproxil fumarate/emtricitabine, the combination of dolutegravir/tenofovir and alafenamide/emtricitabine was associated with significantly lower rates of composite adverse birth outcomes compared with efavirenz (24.1% vs 32.7%).[8]

With the success of ART in reducing perinatal transmission, an increasing number of children are born after being HIV exposed in utero but remain uninfected.[9] Most pregnant people with HIV now conceive while receiving antiretrovirals, and continued surveillance for short- and long-term safety is needed. Initial data from the Botswana Tsepamo birth surveillance study suggested a potential neural tube defect safety signal among infants of 494 women who were taking dolutegravir at conception; however, more recent accumulated data including 9460 women taking dolutegravir at conception showed no significant difference between neural tube defect rates from pregnant people with HIV taking other ART at conception or women without HIV.[10] As new ART regimens become available, it is critical to ensure continued surveillance of outcomes of children with in utero ART exposure.

The benefits of ART during pregnancy for people living with HIV include improved maternal and infant health and pregnancy outcomes and reduced perinatal and sexual HIV transmission. With fully suppressive ART initiation prior to pregnancy and maintenance of ART during pregnancy, the risk of perinatal transmission is near zero. Dolutegravir-based ART is among the safest and most effective therapies. Continued long-term surveillance of

pregnancy and maternal and child outcomes with use of new antiretrovirals in pregnancy is important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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