Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Integrase Inhibitors

**Glossary of Terms for Supplement**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Carcinogenic</td>
<td>Producing or tending to produce cancer</td>
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<tr>
<td>Clastogenic</td>
<td>Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td>Genotoxic</td>
<td>Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Inducing or capable of inducing genetic mutation</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Interfering with fetal development and resulting in birth defects</td>
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</table>

This class of antiretroviral (ARV) drugs inhibits integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final “strand transfer” step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step in the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects reverse transcription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

**Dolutegravir (Tivicay, DTG)**

**(Last updated November 14, 2017; last reviewed November 14, 2017)**

Preliminary human data suggest that use of dolutegravir during pregnancy is not associated with an increased risk of birth defects and miscarriage.

**Animal Carcinogenicity Studies**

Dolutegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

**Reproduction/Fertility**

Dolutegravir did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

**Animal Teratogenicity/Developmental Toxicity**

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity or effect on reproductive function with dolutegravir.

**Placental and Breast Milk Passage**

Studies in rats have demonstrated that dolutegravir crosses the placenta in animal studies and is excreted into breast milk in rats.

**Human Studies in Pregnancy**

**Pharmacokinetics**

Reports of dolutegravir pharmacokinetics (PK) in human pregnancy are limited to two studies and a series of case reports. In a safety and PK study of 21 pregnant women, dolutegravir plasma concentrations were lower during pregnancy than postpartum, but HIV-1 RNA in the third trimester was below 50 copies/mL in all 15 women for whom third-trimester data were available. Dolutegravir was well tolerated by these women.
pregnant women. In a study of five European pregnant women, dolutegravir was well tolerated and plasma exposures during pregnancy were similar to that postpartum. In the case reports, dolutegravir was used safely and effectively in pregnancy and plasma exposures were adequate.

Placental and Breast Milk Passage

Placental transfer of dolutegravir in an ex vivo perfusion model was high, with a fetal-to-maternal ratio of 60%. High placental transfer of dolutegravir has been confirmed in several of the case reports. In a report from one breast feeding mother receiving dolutegravir and her infant, the dolutegravir breast milk-to-maternal-plasma-concentration ratio was 0.02 and the plasma dolutegravir concentration in the infant was 0.10 mg/L, equal to the dolutegravir target trough plasma concentration in treatment-naive patients.

Teratogenicity Data

As of January 31, 2017, the overall birth defect rate was 3.0% (4 infants) in 133 live births from 142 pregnancies with exposure to dolutegravir reported to the Antiretroviral Pregnancy Registry. In the larger PK study in pregnant women, discussed above, birth abnormalities were reported in 4 of 18 infants: total anomalous pulmonary venous return; cystic fibrosis and polycystic right kidney; congenital chin tremor; sacral dimple with filum terminale fibrolipoma. In 2 reviews of clinical experience with pregnant women receiving dolutegravir, birth defects were noted in 3 infants born to 42 European women and in no infants born to 116 women from Botswana receiving dolutegravir during the first trimester.

Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir (DTG)</td>
<td>Tivicay</td>
<td>DTG Tablets: • 50 mg</td>
<td>Standard Adult Dose ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)</td>
<td>High placental transfer to fetus. No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest no increased risk of teratogenicity in humans.</td>
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<tr>
<td>(DTG/ABC/3TC)</td>
<td>Triumeq</td>
<td>Triumeq: • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet</td>
<td>DTG (Tivicay): • 1 tablet once daily, without regard to food. DTG/ABC/3TC (Triumeq): • 1 tablet once daily, without regard to food. ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced DTG (Tivicay): • 1 tablet twice daily, without regard to food. PK in Pregnancy: • AUC may be increased during the third trimester compared with postpartum, but good viral suppression in third trimester recipients. Dosing in Pregnancy: • No change in dose indicated.</td>
<td></td>
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</tbody>
</table>

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; FPV/r = fosamprenavir/ritonavir; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

References


