Dolutegravir intensification for prevention of perinatal transmission in a vertically infected pregnant women harboring multidrug-resistant HIV-1

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Abstract

Dolutegravir (DTG) is a second generation integrase inhibitor which retains susceptibility against raltegravir and elvitegravir resistant strains. However, it´s not recommended for use in pregnancy unless the benefits outweigh the potential risks and literature of exposure to this drug in pregnancy is extremely limited. In this report, we present the case of a perinatally infected woman harboring multidrug-resistant HIV whose antiretroviral treatment was successfully intensified with DTG in the third trimester due to detectable viremia in the context of an obstetric emergency.

Perinatally infected HIV-positive pregnant women constitute an emerging therapeutic challenge for adult HIV and obstetric units. These patients have a history of long term exposure to antiretroviral therapy (ART), including suboptimal regimens. Irregular adherence, virologic failure and infection with drug-resistant HIV are prevalent in this population. In this context, perinatal transmission would likely to be by drug-resistant virus, jeopardizing infant´s therapeutic options in case infection occurs [1,2]. In some critical situations (late presenters, detectable viremia in the third trimester despite ART), several guidelines consider adding an integrase strand transfer inhibitor (InSTI) as an approach to rapidly decrease viral load (VL) being most of the cumulative experience with raltegravir (RAL) [3-6]. Dolutegravir (DTG) is a second generation InSTI. It´s US FDA pregnancy category B and not recommended during pregnancy unless benefits outweigh risks [7,8]. In this report, we present the case of a perinatally infected woman harboring multidrug-resistant HIV (including evidence of resistance to RAL) who required intensification with DTG in third trimester due to detectable viremia in the context of an obstetric emergency. This young woman was ambulatory admitted to care through the mother-to-child transmission working group in our institution at 22 weeks of gestational age in December 2015. The current was her second pregnancy as she had a previous spontaneous abortion. She had evidence of clinically advanced disease, with HIV CDC stage C due to prior multidrug-resistant pulmonary tuberculosis, lymphocytic interstitial pneumonitis, and ongoing HIV-associated neurocognitive

disorder. She had a history of exposure to multiple drug regimens (including RAL-containing ART) and multiple virologic failures with a selection of multiclass resistant HIV, including G163K, a nonpolymorphic mutation which confers low-level resistance to RAL and elvitegravir (table 1) [9].

Table 1. Antiretroviral drug exposure and drug-resistance associated mutations in a perinatally infected HIV-positive pregnant woman that required intensification with dolutegravir in late pregnancy.

Antiretroviral drug exposure	**Resistance associated mutations**
NRTIs Zidovudine, didanosine, stavudine, lamivudine, abacavir, tenofovir, emtricitabine	**41L**, **215Y**, 44D
NNRTIs Nevirapine, efavirenz	**98G**, **103N**, **188L**
PIs Nelfinavir, lopinavir/ritonavir, darunavir/ritonavir	10I, 20I, 24l, 36I, 43T, **54V**, 64V, 74S, 77I, **82L**
InSTIs Raltegravir	163K

NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; InSTIs: integrase strand transfer inhibitors.
Note: major mutations are in bold

In the previous 12 months she was prescribed ART with coformulated tenofovir-emtricitabine, ritonavir boosted darunavir and maraviroc as she had an infection by R5-tropic virus in Trofile® assay. Her VL and CD4-T cell count were 354 copies/mL and 304 cells/uL (22%), respectively, in the context of self-reported "good adherence". Low level detectable viremia could be attributed to a new virologic failure or suboptimal adherence. In this context, adherence was reinforced and supervision by her male partner was suggested. Doing a new genotypic resistance test was prevented by the low-level viremia. Proviral DNA tropism testing showed R5-tropic virus. Her current ART remained unchanged.

Patient was lost to follow-up until she is admitted to the obstetric unit due to suspected vaginal bleeding at 33 weeks of gestational age. Fetal ultrasonography and cervical examination were normal. The patient referred no missing doses of her ART following her last appointment in the infectious diseases unit. A new VL showed detectable low-level viremia (93,2 copies/mL). In this context, intensification with DTG 50 mg BID was instituted, considering the presence of G163K mutation that may affect the efficacy of RAL. Patient was discharged from the obstetric unit and scheduled weekly appointments for obstetrical and clinical evaluation, with good tolerance to DTG and the other antiretrovirals. At 36.2 weeks of gestational age the patient was readmitted to the obstetric unit due to premature rupture of membranes. An emergency cesarean section was performed with no adverse events and she delivered a male healthy newborn of 2740 gr. The intrapartum viral load was <20 copies/mL. The newborn received postnatal prophylaxis with zidovudine for 6 weeks. Mother and newborn were discharged from the hospital in healthy status. Infant had negative HIV-1 DNA PCR at birth and 4 months of age.

ART is the standard of care for the prevention of perinatal transmission. The main goal of ART is maximal suppression of HIV replication. Its implementation together with other effective interventions has led to considerable declines in the number of perinatally HIV-infected children both in resources rich and constrained settings. However, several barriers to eliminating HIV perinatal transmission persist, being absent or delayed prenatal care one of the most relevant obstacles for achieving an HIV-free generation of infants. Traditionally, a combination of two nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor were the ARTs of choice in HIV-infected pregnant women. However, InSTIs emerge as an attractive option, particularly in clinical scenarios were a rapid VL decline is needed. Despite most of the published experience is with RAL, being currently a preferred drug in US Guidelines [8], DTG may emerge as an alternative option due to its potency and once daily dosing profile for InSTI-naive population. In this context, information regarding the efficacy and safety of DTG in the mother-child binomium is urgently needed.

Considering DTG based ART in pregnancy, available information is limited to case reports. Pain et al reported the use of DTG as an intensification strategy in a 35-year-old African woman with detectable low level viremia with tenofovir/emtricitabine, atazanavir and ritonavir who delivered prematurely. No safety concerns were reported for mother and infant [10]. Rahangdale et al recently reported four cases of dolutegravir exposure in pregnancy, being two cases of initial therapy, one case of switching and one case of intensification. All 4 women experienced at least a 1-log reduction in viral load. No maternal side effects were noted; 1 neonate was small for gestational age and was diagnosed with hyperbilirubinemia [6]. All neonates exposed to DTG, including ours, were HIV-uninfected. As far as we know, this is the first report describing the use of DTG as an intensification strategy in a perinatally infected pregnant woman with an InSTI mutation. Further research is needed to determine the safety and efficacy of DTG during pregnancy in complex scenarios.

Conflict of interest

All authors, no conflicts

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