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Preventing HIV mother-to-child transmission in a vertically infected pregnant woman with multiclass drug resistance, role of bis-in-die dolutegravir and neonatal AZT prophylaxis: A case report

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ABSTRACT

A suppressive antiretroviral therapy (ART) is necessary to prevent mother-to-child transmission (MTCT) of HIV during pregnancy. During this period, it is recommended to continue an ongoing safe and suppressive regimen, but history of multiclass drug-resistance (MDR) might need tailored, uncommon approaches posing tolerability and toxicity issues. This is the case of a 33 years of age, vertically infected woman with MDR HIV infection suppressed on a darunavir/cobicistat + atazanavir regimen switched during pregnancy to lamivudine + darunavir/ritonavir + dolutegravir 50 mg bis-in-die, maintaining complete viral suppression and delivering via caesarian section and without zidovudine (AZT) intrapartum prophylaxis a healthy HIV-negative newborn who received AZT post-exposure prophylaxis and showed regular growth patterns up to 2 years. Our case shows how archived MDR might complicate the preservation of HIV RNA suppression and highlights the importance of a tailored, multidisciplinary approach for pregnant women with MDR HIV and their newborns.

1. Introduction

A suppressive antiretroviral therapy (ART) is paramount to prevent mother-to-child transmission (MTCT) of HIV during pregnancy and breastfeeding; during these periods of time, it is generally recommended to continue an ongoing tolerated, safe, and suppressive

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regimen, due to the risk of viral rebound after switching [1]. If switches are necessary, an array of drug choices is available, and the choice of a new regimen should be individualized considering patient's history of treatment, tolerability, and adherence [2]. However, history of multiclass drug-resistance (MDR) might compromise the efficacy of first line, and even alternative, regimens. Tailored, uncommon approaches might be needed, posing toxicity and tolerability issues. Moreover, the optimal post-natal prophylaxis for newborns born to mothers with drug-resistant virus is unknown [1]. These aspects often push clinicians towards the "safe" side for the delivery with cesarean section and peripartum zidovudine (AZT) prophylaxis, even though guidelines report concerns over its efficacy for newborns to mothers with MDR [1–3].

Herein, we present the case of a 33 years of age, vertically infected woman with MDR HIV infection, suppressed on a suboptimal ART regimen, switched during pregnancy to lamivudine (3TC) + darunavir/ritonavir (DRV/r) + dolutegravir (DTG) 50 mg bis-in-die (bid), maintaining complete viral suppression and delivering a healthy HIV-negative newborn who received AZT prophylaxis. We believe the case might help guiding the choices of clinicians and patients facing the same challenges.

2. Case presentation

Vertically infected, the patient was diagnosed at four years of age in 1991 and immediately started ART. She was subsequently exposed to numerous ART regimens, experiencing many virologic failures, the last one in 2014 due to poor adherence while on a tenofovir/emtricitabine + raltegravir regimen. Genotypic resistance testing (GRT) was then performed, retrieving high level drug-resistance to reverse transcriptase inhibitors (RTI; M41L, D67 N, M184V, Y188L, L210W, T215Y mutations) and to integrase strand-transfer inhibitors (INSTI; G140S and Q148H mutations); genotyping remained wild-type for protease inhibitors (PI). She was subsequently prescribed off-label therapy with darunavir/cobicistat (DRV/c) + atazanavir (ATV), achieving full ART adherence and persistent suppression from then on. Still on this regimen, in 2020 she got pregnant, and she was transferred to our tertiary hospital in November, at twelve weeks of gestation. At transferal, $CD4^+$ T cells count was 567 cells/μL (47 %) and plasma HIV RNA was undetectable. No coinfection was detected including HBV, Treponema, Toxoplasma, CMV, and Herpes serology. ART was promptly changed, discontinuing ATV, and switching DRV/c back to DRV/r (600/100 mg bid), adding DTG 50 mg bid (due to G140S and Q148H mutations) and 3TC 300 mg/day (despite M184V mutation). Folic acid supplements were also prescribed. The switch was well tolerated and the patient maintained optimal adherence. During the whole gestation, monthly visits and laboratory tests were scheduled, and HIV RNA was persistently undetectable. Fetal development was physiologic.

In April 2021, a multidisciplinary evaluation between infectious diseases specialists, gynecologists and pediatricians occurred to plan delivery and newborn treatment.

While natural delivery was deemed possible, cesarean section was decided after obstetric-patient counselling, and was performed at week 38. At delivery, neonatal weight was 3935 g, 94th centile according to Italian Neonatal Study charts (INeS charts), length was 50 cm (50th centile according to INeS charts), and head circumference was 35 cm (70th centile according to INeS chart) [4]. After discussion, intravenous AZT *peri*-partum prophylaxis was not administered, according to guidelines indication for mothers with undetectable viral loads [1–3]. A classic four-week AZT prophylaxis was prescribed to the newborn to prevent perinatal transmission. The newborn, a healthy male, tested negative for HIV RNA and DNA at week 0, 2, 4, 24 and 48. At week 24 he showed a $CD8^+$ deficit (178 cells/μL, previously normal) while $CD4^+$, haemoglobin level, and platelet count remained normal; no additional immunologic findings were retrieved and $CD8^+$ count spontaneously increased at week 28 (380/μL) and remained normal. He started attending kindergarten at the age of 6 months, reporting a normal rate of infections for his age. Up to two years of age, the baby showed a normal growth pattern and a cognitive development in line with his age, despite mild weaknesses in social and language domains, according to the Griffith Mental Development Scales (GMDS) [5].

3. Discussion

As described in literature, achieving, or preserving HIV RNA suppression through ART during pregnancy is paramount to prevent MTCT; our case highlights how archived MDR might complicate this challenge.

Despite viral suppression and the inherent risk posed by drug switches during pregnancy, an ART regimen switch was decided upon for the patient, in light of the insufficient data available on off-label double PI regimens and the limited number of drug targets covered. As protease was the only drug target without documented archived resistance, a boosted PI was maintained: darunavir was preferred over atazanavir due the possibility of bis-in-die administration during pregnancy, and booster was switched from cobicistat to ritonavir given the lower plasmatic cobicistat concentrations known to occur during the second and third trimester [1,6].

Second-generation INSTI DTG is now a preferred antiretroviral during pregnancy despite early unconfirmed reports of higher risk for neural tube defects [1,7–9]. Due to its high genetic barrier, bis-in-die DTG has been shown to achieve suppression in case of highly treatment-experienced patients with major INSTI resistance and limited treatment options [10,11]. For this reason, we chose to prescribe bid DTG to our patient. However, extremely limited data are available on the safety of this choice during pregnancy [12]. Despite archived resistance, lamivudine was added as a safe option to exert drug pressure on RT, to comply with guideline-based indication to administer a three-drug regimen in pregnancy [3,13].

In this vertically infected young woman with MDR HIV infection, ART-suppressed on PI "functional" monotherapy during the first trimester, MTCT transmission was effectively prevented with a PI and bid DTG-based regimen, and no major adverse event was observed.

In different studies, systematic intravenous AZT appears to be unnecessary for MTCT in women with low viral loads at delivery and current recommendations in the United States do not require intrapartum AZT for women adherent to ART whose viral load is below

50 copies/mL within four weeks of delivery [1,14]. However, in a recent Italian large cohort study on pregnant women living with HIV, intrapartum AZT appeared to be widely used even in undetectable women, without any benefits, pointing out that unnecessary medicalization of delivery might generate insecurity and fear [15].

In the WITS cohort, increased risk of MTCT was observed for women with resistance mutations to AZT, but several participants had detectable viral loads at delivery, while data from the Swiss cohort demonstrated no transmission among infants born to suppressed women with high-level AZT-resistance [16,17]. While suggesting that MDR might dictate need for a different neonatal regimen, Italian guidelines also mention the possibility to avoid prophylaxis in newborns with ART-suppressed mothers [3]. Our multidisciplinary group considered both approaches. Ultimately, despite history of resistance to all reverse transcriptase inhibitors, standard neonatal AZT post-exposure prophylaxis was chosen, considering international recommendations to adopt prophylaxis for all newborns (guidelines from the British HIV Association specifically advise against regimes different than AZT for newborns to mothers with AZT resistance) [1–3,18].

Evidence is accumulating regarding HIV exposed uninfected (HEU) children. A 2006 study has shown significantly lower $CD8^+$ T cell counts in ART-exposed, uninfected infants than in uninfected infants not exposed to ART, up to 24 months [19]. In the French Perinatal Cohort Study, HIV-uninfected infants with ART perinatal exposure had significantly lower hemoglobin, platelets, neutrophils, lymphocytes, $CD4^+$, and $CD8^+$ cell counts than HIV-exposed infants without perinatal exposure to ARV drugs [20]. However, clinical correlates to immunologic features of HEU children are to be established. In our case, the HIV-exposed, uninfected boy, having also been exposed to in-utero bid DTG treatment, did not show permanent laboratory anomalies, any particular tendency towards infections, or major irregularities in growth patterns and cognitive development.

Our case highlights the importance of a tailored, multidisciplinary approach for pregnant women with MDR HIV and their newborns.

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Ethical approval statement

Written informed consent was obtained from the patient for publication of her clinical details. Notification was sent to the local ethics committee according to the Italian low.

Data availability statement

No data was used for the research described in the article as this is a case report.

CRediT authorship contribution statement

Paola Saltini: Writing - original draft. **Beatrice Tassis:** Conceptualization, Writing - review & editing. **Alice Ronchi:** Conceptualization, Writing - review & editing. **Claudia Tagliabue:** Conceptualization, Writing - review & editing. **Giada Di Pietro:** Conceptualization, Writing - review & editing. **Rosa Maria Dellepiane:** Conceptualization, Writing - review & editing. **Antonio Muscatello:** Conceptualization, Writing - review & editing. **Andrea Giacomelli:** Conceptualization, Writing - review & editing. **Lorenza Pugni:** Conceptualization, Writing - review & editing. **Enrico Ferrazzi:** Conceptualization, Writing - review & editing. **Alessandra Bandera:** Conceptualization, Writing - review & editing. **Giorgio Bozzi:** Conceptualization, Writing - original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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