Post-Natal Anti-Retroviral Prophylaxis for Neonates Born to Mothers Living with Resistant Human Immunodeficiency Virus (HIV) Infection

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Abstract
Mother-to-child transmission (MTCT) accounts for the majority of new human immunodeficiency virus (HIV) infections among children worldwide. Post-natal prophylaxis along with other preventive measures have been very successful reducing transmission to babies born to mothers living with HIV infection to < 2%. Single-drug prophylaxis with Zidovudine (ZDV) is the mainstay regimen for infants in low-risk transmission settings. The optimal regimen for newborns of women with antiretroviral (ARV)-resistant HIV is unknown. We present a baby born to a young mother living with highly resistant perinatally-acquired HIV and we discuss the challenges with giving postnatal ARV prophylaxis to her baby given the lack of dosing and safety data for many antiretroviral agents for neonates. The baby received a combination of lamivudine and raltegravir for total of 6 weeks and he was not breast
fed. He had negative HIV proviral DNA PCR at 6 weeks and 3 months and a negative HIV serology at 18 months of age.

**Keywords:** HIV, postnatal prophylaxis, neonate, antiretroviral, resistant.

### Introduction

Mother-to-child transmission (MTCT) accounts for the majority of new HIV infections among children.\(^1\) Successful interventions to prevent MTCT include using a combination of antiretroviral therapy for women before and during pregnancy to ensure adequate viral suppression. In addition, optimal infant postnatal antiviral prophylaxis and avoidance of breast feeding play a major role in MTCT prevention.\(^2\) These interventions have significantly reduced the rates of MTCT of HIV to < 2% in non-breast feeding infants and to < 5% in breast-feeding infants.\(^1,3\) As a consequence, the number of HIV infection in infants have dramatically declined by 40% between 2003 and 2014\(^4\) and it has been estimated that HIV infection was prevented in approximately 22,000 cases in the United States since 1994.\(^3\)

HIV drug resistance has been a major challenge for controlling HIV and reducing its associated morbidity and mortality. The WHO HIV drug resistance report 2021 showed that > 10% of adults and around 50% of infants, newly diagnosed with HIV, have a virus resistant to the non-nucleoside reverse-transcriptase inhibitors (NNRTIs). In addition, they found that levels of resistance to NNRTIs ranged between 50-97% in adults failing NNRTI-based first line ART.\(^5\) In this case report, we discuss the challenges with giving postnatal ARV prophylaxis to neonates born to mothers with resistant virus given the lack of dosing and safety data for neonates for many antiretroviral agents.

### Case Report

A term baby was born at 38 weeks of gestation to a perinatally-HIV infected 24-year-old mother with a highly resistant HIV strain. The mother had developed resistance due to adherence issues during her treatment over many years. Her virus showed intermediate to high-level resistance to all commonly used nucleoside reverse transcriptase inhibitors (NRTI) except lamivudine which had low-level resistance, high level resistance to nevirapine, and intermediate resistance to other non-nucleoside reverse transcriptase inhibitors (NNRTI). The only protease inhibitor (PI)
that tested susceptible was darunavir. All integrase inhibitors tested were susceptible.

A summary of her antiretroviral resistance profile is included in table 1. When she was planning to get pregnant, she was treated with emtricitabine/tenofovir (Truvada), etravirine dolutegravir and darunavir / ritonavir with an undetectable viral load and CD4 count between 200-300/uL through the pregnancy. The baby was born by elective caesarean section at term with Apgar score of 9 and 9 at 1 and 5 minutes respectively. We found it challenging to provide advice on postnatal ARV prophylaxis given the mother’s HIV antiviral resistance and the limited dosing and safety data on many ARV agents for neonates. The baby received lamivudine 2 mg/kg/dose twice daily and raltegravir (1.5 mg/kg/dose once daily until 1 week of age, 3 mg/kg/dose twice daily from 1-4 weeks of age and then 6 mg/kg/dose twice daily from 4-6 weeks of age) for a combined total of 6 weeks and he was not breast fed. He had a normal full blood count at 6 weeks of age. Unfortunately, there was no baseline HIV PCR done at the first week of life prior to commencing the antiviral prophylaxis. He had a negative HIV proviral DNA PCR at 6 weeks, 3, 6 and 12 months of age and negative HIV serology at 18 months of age. Guardian consent was obtained for publication purposes.

**Discussion**

The strongest individual predictor of risk of MTCT is the maternal plasma viral load and the viral suppression was found to be the most effective way to minimize the risk of perinatal transmission.2,6 All pregnant and breast feeding women living with HIV infection should be given ARV to optimally suppress viral replication.6,7 Prevention of MTCT has been a real challenge in cases with ARV resistance. Resistant virus can be transmitted to the infant during pregnancy and labour and through breast feeding.8 ARV-resistance appears to be more common in women who acquired HIV infection perinatally. Despite that, a recent study from Rio de Janeiro, showed a high prevalence rate of ARV resistant HIV in 17.2% in treatment-naïve patients.6,8 So, this strongly supports the need for resistance testing in pregnant women prior to initiating ARV to optimise strategies to avoid MTCT of resistant HIV strains to the baby.8

Updated US guidelines recommend that all newborns perinatally exposed to HIV should receive postpartum prophylaxis with selection of the appropriate regimen guided by the level of transmission risk.1,6 For ‘low risk’ groups - mothers who
received ART during pregnancy with undetectable viral load at time of delivery - 4 weeks of zidovudine (ZDV) prophylaxis can be used.\textsuperscript{1,6} However, the additional benefit of infant prophylaxis may be negligible in such cases.\textsuperscript{1} There is no uniform definition for a ‘high-risk’ group, but includes ARV naïve pregnant woman and women who received insufficient ARV therapy during pregnancy resulting in a detectable viral load at the time of delivery.\textsuperscript{1} A systematic review showed that multidrug regimens have significantly reduced risk of HIV transmission in ‘high-risk’ HIV-exposed infants however, 3 drug regimens were not superior to 2 drugs.\textsuperscript{1,6} If the neonate has high risk of transmission, the updated US guidelines recommend using presumptive HIV therapeutic regimen with either ZDV, lamivudine (3TC) and treatment doses of nevirapine (NVP) or ZDV, 3TC and RAL from birth for total of 6 weeks.\textsuperscript{6}

The optimal post-natal prophylaxis for newborns of women living with ARV-resistant HIV is unknown.\textsuperscript{6} ARV drug-resistant virus may have decreased capacity of replication and transmission but perinatal transmission of multidrug-resistant virus has been reported.\textsuperscript{2,6,8} Two studies showed that ARV-resistance does not increase the risk of HIV MTCT compared with sensitive HIV strains.\textsuperscript{2,8} Guidelines recommend that in such cases consultation with a paediatric HIV specialist before delivery should be done early.\textsuperscript{6} There is no evidence that customized prophylaxis, based on maternal drug resistance patterns, are more effective than standard neonatal prophylaxis.\textsuperscript{6} We advocated for tailoring the postnatal prophylaxis to maternal resistance pattern especially if the baby is at ‘high risk’. We customized a regimen for our patient depending on his maternal viral resistance profile. We gave him raltegravir and lamivudine and he tolerated them very well and they were effective. His HIV PCR at 6 weeks, 3 and 6 months and 18-months serology were negative.

ZDV resistance does not affect the indications for use as a prophylaxis.\textsuperscript{5,9} The rationale for using ZDV is that the wild-type virus appeared to be mainly transmitted to infants born to mothers who have mixed virus populations including low-level ZDV resistance.\textsuperscript{9} ZDV crosses the placenta readily and it is the best for central nervous system cover compared with other drugs and ZDV is beneficial at eliminating a potential reservoir of HIV in the neonate.\textsuperscript{6,10}
There is limited data on pharmacodynamics/pharmacokinetic, safety, dosing regimen, and toxicity of ARV in neonates.\(^1\)\(^1\) There is no significant difference in adverse reactions between term neonates receiving combination therapy or ZDV alone.\(^1\)\(^2\) Transient hematologic toxicity is the most common side effect.\(^1\)\(^2\) Paediatric formulations for some protease inhibitors like lopinavir/ritonavir (LPV/r) are available however their use in neonates in the first week of life is not preferred due to safety concerns. LPV/r induced-cardiotoxicity in neonates has been reported previously.\(^6\)\(^1\)\(^2\) Based on post-marketing reports of cardiotoxicity of protease inhibitors, the US Food and Drug Administration (FDA) recommends that LPV/r oral solution not be used in term neonates < 14 days of age.\(^6\) Maraviroc (MVC) was recently approved for use in infants ≥2 kg which may provide an additional option for treatment and prophylaxis of newborns born to mothers with multidrug-resistant HIV-infection. However, the lack of data and risk of drug interactions of MVC may limit its role for routine use in neonates.\(^6\)

We decided to be guided by the maternal viral resistance profile for prophylaxis. We used lamivudine and raltegravir for our patient. There is some data on raltegravir dosing and safety in neonates derived from the IMPAACT P1110 study. In this trial there were no adverse effects detected in the 26 term neonates included.\(^1\)\(^3\) Our patient did not develop any skin rash or GI symptoms after receiving raltigravir. We note that in December 2017 the FDA approved expanded dosing in neonates for raltegravir.\(^1\)\(^4\)

**Conclusion**

In conclusion, we believe that the postnatal prophylaxis regimen for newborns born to mothers with known or suspected drug resistance should be determined with knowledge of the level of transmission risk and maternal HIV resistance profile notwithstanding the limited therapeutic options in this vulnerable group. Such infants at risk of vertical HIV acquisition should also have close monitoring, optimal follow-up and prompt initiation of ARV therapy where infection has occurred. Studies assessing the rates of HIV resistance among neonates are highly required. In addition, more studies are urgently required to assess the efficacy and the safety of more anti-retroviral options that can be used for post-natal prophylaxis in babies born to mother with HIV resistant virus.
Author’s Contribution
PB, NG and AK conceptualized the idea. AK provided the patient’s data. LSAY drafted the manuscript and TL drafted the medication dosing. PB, NG, TL and AK revised the manuscript. All authors approved the final version of the manuscript.

References


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  - 0 - 4 weeks of age: 4mg/kg/dose PO twice daily  
  - Age > 4 weeks: 12 mg/kg/dose PO twice daily (increase dose in cases of confirmed HIV infection only)  
• 30 - < 35 Weeks’ Gestation at Birth  
  - Age 0 – 2 weeks: 2mg/kg/dose PO twice daily  
  - Age 2 – 6 weeks: 3mg/kg/dose PO twice daily  
  - Age > 6- 8 weeks: 12 mg/kg/dose PO twice daily (increase dose in cases of confirmed HIV infection only)  
• < 30 weeks’ gestation at birth  
  - Age 0 – 4 weeks: 2mg/kg/dose PO twice daily  
  - Age 4 – 8 weeks: 3mg/kg/dose PO twice daily  
  - Age > 8 – 10 weeks: 12 mg/kg per dose PO twice daily (increase dose in cases of confirmed HIV infection only) | If the neonates does not tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval. |
| Abacavir (ABC) | • ≥ 37 Weeks’ Gestation at Birth  
  - Age 0 – 1 month: 2 mg/kg/dose PO twice daily  
  - Age 1 - < 3 months: 4 mg/kg/ dose PO twice daily | - ABC has not been approved yet by the FDA for use in neonates <1 month of age.  
- The current dosing recommendations have been modeled using PK simulation |
| Lamivudine (3TC) | • ≥32 Weeks’ Gestation at Birth  
  - Age 0 – 4 weeks: 2 mg/kg/dose PO twice daily  
  - Age > 4 weeks: 4 mg/kg/dose PO twice daily | - |
| Nevirapine (NVP) | • ≥37 Weeks’ Gestation at Birth  
  - Age 0 – 4 weeks: 6 mg/kg/dose PO twice daily  
  - Age > 4 weeks: 200 mg/m² BSA/ dose PO twice daily (increase dose in cases of confirmed HIV infection only)  
• ≥34 to <37 Weeks’ Gestation at Birth  
  - Age 0 – 1 week: 4 mg/kg/dose PO twice daily  
  - Age 1 – 4 weeks: 6 mg/kg/dose PO twice daily  
  - Age > 4 weeks: 200 mg/m² BSA/ dose PO twice daily (increase dose in cases of confirmed HIV infection only) | - |
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<td>- Age 0 – 2 weeks: 2 mg/kg/dose PO twice daily</td>
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<tr>
<td></td>
<td></td>
<td>- Age 2 – 4 weeks: 4 mg/kg/dose PO twice daily</td>
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<td>- Age 4 – 6 weeks: 6 mg/kg/dose PO twice daily</td>
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<td></td>
<td>- Age &gt; 4 weeks: 200 mg/m² BSA/dose PO twice daily (increase dose in cases of confirmed HIV infection only)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5</th>
<th>Raltegravir (RAL)</th>
<th>≥37 Weeks’ Gestation at Birth and Weighing ≥2 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Age 0 – 1 week: 1.5 mg/kg/dose PO daily</td>
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<td>- Age 1 – 4 weeks: 3 mg/kg/dose PO twice daily</td>
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<tr>
<td></td>
<td></td>
<td>- Age 4 – 6 weeks: 6 mg/kg/dose PO twice daily</td>
</tr>
</tbody>
</table>

No dosing information is available for preterm infants or infants weighing <2 kg at birth.

<table>
<thead>
<tr>
<th>6</th>
<th>Maraviroc (MVC)</th>
<th>Infants ≥2 kg:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Age 0 – 6 weeks: 8 mg/kg/ dose PO twice daily</td>
</tr>
</tbody>
</table>

- Approved recently for infants ≥2 kg
- Presence of limited data about MVC use in infants and the risk of drug interactions will limit its routine use in neonates