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CASE REPORT

Post-Natal Anti-Retroviral Prophylaxis for Neonates Born to Mothers Living with Resistant HIV Infection

*Laila S. Al Yazidi,[1,2] Philip N. Britton,[1,3,4] Nicole Gilroy,[5] Tony Lai,[1] Alison Kesson[1,3,4]

ABSTRACT: Mother-to-child transmission accounts for the majority of new HIV infections among children worldwide. Post-natal prophylaxis, in addition to other preventive measures, have been very successful in reducing transmission to babies born to mothers living with HIV infection to <2%. Single-drug prophylaxis with zidovudine is the mainstay regimen for infants in low-risk transmission settings. The optimal regimen for newborns of women with anti-retroviral (ARV)-resistant HIV is unknown. We report a baby born to a young mother living with highly resistant perinatally-acquired HIV at a tertiary care centre in Sydney, Australia, in 2018. Furthermore, the challenges with giving postnatal ARV prophylaxis to her baby, in light of the lack of dosing and safety data for many antiretroviral agents for neonates, is discussed. The baby received a combination of lamivudine and raltegravir for a total of six weeks and he was not breast-fed. He had negative HIV proviral DNA polymerase chain reaction at six weeks and three months and a negative HIV serology at 18 months of age.

Keywords: HIV; Prophylaxis; Neonate; Antiretroviral; Case Report; Australia.

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 infections in infants have dramatically declined by 40% between 2003 and 2014;[4] it has been estimated that HIV infection was prevented in approximately 22,000 cases in the USA since 1994.[3]

HIV drug resistance has been a major challenge for controlling HIV and reducing its associated morbidity and mortality. The World Health Organization HIV drug resistance report 2021 showed that >10 % of adults and approximately 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 antiretroviral therapy (ART).[5] In this case report, we discuss the challenges with giving postnatal anti-retroviral (ARV) prophylaxis to neonates born to mothers with a resistant virus in light of 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 at a tertiary hospital in Sydney, Australia, in 2018. 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 inhibiters (NRTI) except lamivudine which had low-level resistance, high level resistance to nevirapine, and intermediate resistance to other NNRTI. The only protease inhibitor that tested susceptible was darunavir. All integrase inhibitors tested were susceptible [Table 1].

When she was planning to get pregnant, she was treated with emtricitabine/tenofovir, etravirine dolutegravir and darunavir/ritonavir with an undetectable viral load and CD4 count between 200–300/μL through the pregnancy. The baby was born by elective caesarean section at term with an 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

[1]*Infectious Diseases and Microbiology, The Children's Hospital at Westmead, Sydney, Australia;* [2]*Department of Child Health, College of Medicine, Sultan Qaboos University, Muscat, Oman;* [3]*Discipline of Child and Adolescent Health, The University of Sydney, Sydney, Australia;* [4]*Marie Bashir Institute for Infectious Diseases and Biosecurity, The University of Sydney, Sydney, Australia;* [5]*Centre for Infectious Diseases and Microbiology, Westmead Hospital NSW, Sydney, Australia*

Corresponding Author's email: lailay@squ.edu.om

Table 1: Mother's antiretroviral resistance profile

Drug class	Drug	Primary mutations	Secondary mutations	Profile
Nucleoside reverse transcriptase inhibitors	Zidovudine	D67G (2005) K219KN K219N (2012) L210LW M41L T215C	D67G (2004) K219N (2005) L210W (2012) V118I (2012)	High-level resistance
	Lamivudine	M184V (2008) M41L (2012) L210W (2012)	M41L L210LW V118I (2012)	Potential low-level resistance
	Stavudine	D67G (2005) K219KN K219N (2012) L21W L74V (2004) M4IL T210W (2012 T215C	D67G (2004) K219N (2005) L210W (2008) M41L (2008) T215Y (2004) V118I (2012)	High-level esistance
	Emtricitabine	M184V (2008) M41L (2012) L210W (2012)	L210LW M4IL V118I (2012)	Potential low-level resistance
	Didanosine	K219V (2008) K219KN (2012) L74LV L74V (2012) L210LW L210W (2012) M4IL T215C	D67G (2005) L210W (2004) K219KN M41L (2004) M184V (2008) T215Y (2004) V118I (2012)	High-level resistance
	Abacavir	K219N (2008) K219KN (2012) L210LW L210W (2012) L74LV L74V (2012) M4IL T215C	D67G (2005) K219KN L210W (2004) M41L (2004) M184V (2008) T215Y (2004) V118I (2012)	High-level resistance
	Tenofovir	K219KN (2012) L210LW L210W (2012) M4IL T215C (2013)	D67G (2005) K219KN L210W (2004) M41L (2004) T215C V118I (2012)	High-level resistance
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	H2211HY V108IV Y181C	V108I (2012) V108IV (2013) H221HY (2013)	High-level resistance
	Efavirenz	H221HY V108IV Y181C	V108I (2012) V108IV (2013) H221HY (2013)	Intermediate resistance
	Rilpivirine	H221HY Y181C	V108I (2012) H221HY (2013)	Intermediate resistance
	Etravirine	H221HY Y181C	V108I (2012) H221HY (2013)	Intermediate resistance
Protease inhibitors	Indinavir	I47V (2008) I47IV (2013) I54V I54LV (2012) L10F L90M M46I N88D (2005) N88DG (2013) V32I (2012) V32IV (2013) D30DN (2012) D30N (2013)	A71V (2008) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) N88G (2008) N88DG (2012) Q58E (2013)	High-level resistance
	Saquinavir	I54V 154LV (2012) L90M M46I(2013) N88D (2005) N88DG (2013) D30DN (2012) D30N (2013) V32IV (2013) I47IV (2013)	A71V (2008) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) M46I N88G (2008) N88DG (2012) L10F (2012) Q58E (2013)	High-level resistance

Table 1 (cont'd.): Mother's antiretroviral resistance profile

Drug class	Drug	Primary mutations	Secondary mutations	Profile
Protease inhibitors	Tipranavir	D30N (2013) D30DN (2012) I47V (2013) I47IV (2013) I54V I54LV (2012) L90M (2013) M46I (2013) N88DG (2013) Q58E V32I (2013) V32IV (2013) L90M (2012)	A71V (2013) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) M46I N88G (2008) N88DG (2012) Q58E (2013)	Intermediate resistance
	Atanazavir	I47V (2008) I47IV (2013) I54V I54LV (2012) L90M M46I N88D (2005) N88DG (2013) V32I (2008) V32IV (2013) D30DN (2012) D30N (2013)	A71V (2013) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) N88D N88DG (2012) Q58E	High-level resistance
	Darunavir	D30N (2013) D30DN (2012) I47IV (2013) I54V (2013) I54LV (2012) L90M (2013) M46I (2013) N88DG (2013) V32I (2013) V32IV (2013)	A71V (2013) A71AV (2013) L10F L33I (2013) M36I (2005) N88G (2008) N88DG (2012) Q58E (2013)	Susceptible
	Lopinavir	I47V (2008) I47IV (2013) I54V I54LV (2012) L90M M46I V32I (2008) V32IV (2013) D30DN (2012) D30N (2013) N88DG (2013)	A71V (2008) A71AV (2013) L10F L33I (2013) M36I (2005) N88G (2008) N88DG (2012) Q58E (2013)	Intermediate resistance
	Nelfinavir	D30N D30DN (2012) I47V (2008) I47IV (2013) I54V I54LV (2012) L10F L90M M46I N88D N88DG (2013) V32I (2008) V32IV (2013)	A71V (2008) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) N88G (2008) N88DG (2012) Q58E	High-level resistance
	Fosamprenavir	I54V I54LV (2012) I47V (2008) I47IV (2013) L10F L90M M46I V32I (2008) V32IV (2013) D30DN (2012) D30N (2013) N88DG (2013)	A71V (2008) A71AV (2013) L10F (2013) L33I (2013) M36I (2005) N88G (2008) N88DG (2012) Q58E (2013)	Intermediate resistance
Integrase inhibitor	Dolutegravir			Susceptible
	Elvitegravir			Susceptible
	Raltegravir			Susceptible

lamivudine 2 mg/kg/dose twice daily and raltegravir (1.5 mg/kg/dose once daily until one 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 six weeks and he was not breast-fed. He had a normal full blood count at six weeks of age. Unfortunately, there was no baseline HIV polymerase chain reaction (PCR) done at the first week of life prior to commencing the antiviral prophylaxis. He had a negative HIV proviral DNA PCR at six weeks, three, six 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 viral suppression was found to be the most effective way to minimise 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

Table 2: Antiretroviral drug dosing for neonates

Drug	Doses	Note
Zidovudine	•≥35 weeks' gestation at birth: -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 neonate does not tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval.
Abacavir	•≥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	-Abacavir has not been approved yet by the FDA for use in neonates <1 month of age. -The current dosing recommendations have been modeled using pharmacokinetic simulation
Lamivudine	•≥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	•≥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) •≥32 to <34 weeks' gestation at birth -Age 0 – 2 weeks: 2 mg/kg/dose PO twice daily -Age 2 – 4 weeks: 4 mg/kg/dose PO twice daily -Age 4 – 6 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)	
Raltegravir	•≥37 weeks' gestation at birth and weighing ≥2 kg -Age 0–1 week: 1.5 mg/kg/dose PO daily -Age 1–4 weeks: 3 mg/kg/dose PO twice daily -Age 4–6 weeks: 6 mg/kg/dose PO twice daily	No dosing information is available for preterm infants or infants weighing <2 kg at birth.
Maraviroc	•Infants ≥2 kg: -Age 0–6 weeks: 8 mg/kg/dose PO twice daily	-Approved recently for infants ≥2 kg -Presence of limited data about maraviroc use in infants and the risk of drug interactions will limit its routine use in neonates

PO = per oral; IV = intravenous; FDA = Food and Drug Administration; BSA = body surface area.

cases with ARV resistance. The 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 this, a recent study from Rio de Janeiro, Brazil, showed a high prevalence

rate of ARV resistant HIV in 17.2% in treatment-naïve patients.[6,8] 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 USA 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 - four weeks of zidovudine (ZDV) prophylaxis can be used.[1,6] However, the additional benefit of infant prophylaxis may be negligible in such cases.[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.[1] A systematic review showed that multidrug regimens have significantly reduced risk of HIV transmission in 'high-risk' HIV-exposed infants however, three drug regimens were not superior to two drugs.[1,6] If the neonate has high risk of transmission, the updated USA 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 six weeks.[6]

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

ZDV resistance does not affect the indications for use as a prophylaxis.[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.[9] ZDV crosses the placenta readily and it is the best for the central nervous system compared with other drugs; ZDV is also beneficial at eliminating a potential reservoir of HIV in the neonate.[6,10]

There is limited data on pharmacodynamics/pharmacokinetic, safety, dosing regimen and toxicity of ARV in neonates.[11] There is no significant difference in adverse reactions between term neonates receiving combination therapy or ZDV alone.[12]

Transient haematologic toxicity is the most common side-effect.[12] Paediatric formulations for some protease inhibitors such as 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.[6,12] 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-1 infection. However, the lack of data and risk of drug interactions of MVC may limit its role for routine use in neonates.[6]

The current case was guided by the maternal viral resistance profile for prophylaxis. Lamivudine and raltegravir was used for the 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.[13] The current patient did not develop any skin rash or gastrintestinal symptoms after receiving raltigravir. It should be noted that in December 2017, the FDA approved expanded dosing in neonates for raltegravir.[14]

Conclusion

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 be closely monitoring, have optimal follow-up and prompt initiation of ARV therapy when infection has occurred. Studies assessing the rates of HIV resistance among neonates are needed. 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.

AUTHORS' CONTRIBUTION

PB, NG and AK conceptualised 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.

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