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7	Post-Natal Anti-Retroviral Prophylaxis for Neonates Born to
8	Mothers Living with Resistant Human Immunodeficiency Virus
9	(HIV) Infection
10	*Laila S. Al Yazidi, ^{1,2} Philip N. Britton, ^{1,3,4} Nicole Gilroy, ⁵ Tony Lai, ¹
11	Alison Kesson ^{1,3,4}
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13	¹ Infectious Diseases and Microbiology, The Children's Hospital at Westmead,
14	Sydney, Australia; ² Sultan Qaboos University, College of Medicine, Muscat, Oman;
15	³ Discipline of Child and Adolescent Health, The University of Sydney, Sydney,
16	Australia; ⁴ Marie Bashir Institute for Infectious Diseases and Biosecurity, The
17	University of Sydney, Sydney, Australia; ⁵ Centre for Infectious Diseases and
18	Microbiology, Westmead Hospital NSW, Sydney, Australia.
19	Corresponding Author's email: <u>lailay@squ.edu.om</u>
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21	Abstract
22	Mother-to-child transmission (MTCT) accounts for the majority of new human
23	immunodeficiency virus (HIV) infections among children worldwide. Post-natal
24	prophylaxis along with other preventive measures have been very successful reducing
25	transmission to babies born to mothers living with HIV infection to $< 2\%$. Single-drug
26	prophylaxis with Zidovudine (ZDV) is the mainstay regimen for infants in low-risk
27	transmission settings. The optimal regimen for newborns of women with anti-
28	retroviral (ARV)-resistant HIV is unknown. We present a baby born to a young
29	mother living with highly resistant perinatally-acquired HIV and we discuss the
30	challenges with giving postnatal ARV prophylaxis to her baby given the lack of
31	dosing and safety data for many antiretroviral agents for neonates. The baby received
32	a combination of lamivudine and raltegravir for total of 6 weeks and he was not breast

- 33 fed. He had negative HIV proviral DNA PCR at 6 weeks and 3 months and a negative
- 34 HIV serology at 18 months of age.
- 35 *Keywords:* HIV, postnatal prophylaxis, neonate, antiretroviral, resistant.
- 36

37 Introduction

Mother-to-child transmission (MTCT) accounts for the majority of new HIV 38 39 infections among children.¹ Successful interventions to prevent MTCT include using a combination of antiretroviral therapy for women before and during pregnancy to 40 41 ensure adequate viral suppression. In addition, optimal infant postnatal antiviral 42 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 43 non-breast feeding infants and to < 5% in breast-feeding infants.^{1,3} As a consequence, 44 the number of HIV infection in infants have dramatically declined by 40% between 45 2003 and 2014⁴ and it has been estimated that HIV infection was prevented in 46

- 47 approximately 22,000 cases in the United States since 1994.³
- 48

49 HIV drug resistance has been a major challenge for controlling HIV and reducing its

- 50 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,
- 52 have a virus resistant to the non-nucleoside reverse-transcriptase inhibitors (NNRTIs).
- 53 In addition, they found that levels of resistance to NNRTIs ranged between 50-97% in
- 54 adults failing NNRTI-based first line ART.⁵ In this case report, we discuss the
- 55 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

57 antiretroviral agents.

58

59 Case Report

A term baby was born at 38 weeks of gestation to a perinatally-HIV infected 24-yearold mother with a highly resistant HIV strain. The mother had developed resistance

- 62 due to adherence issues during her treatment over many years. Her virus showed
- 63 intermediate to high-level resistance to all commonly used nucleoside reverse
- 64 transcriptase inhibiters (NRTI) except lamivudine which had low-level resistance,
- 65 high level resistance to nevirapine, and intermediate resistance to other non-
- 66 nucleoside reverse transcriptase inhibitors (NNRTI). The only protease inhibitor (PI)

67 that tested susceptible was darunavir. All integrase inhibitors tested were susceptible. 68 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), 69 70 etravirine dolutegravir and darunavir / ritonavir with an undetectable viral load and 71 CD4 count between 200-300/uL through the pregnancy. The baby was born by 72 elective caesarean section at term with Apgar score of 9 and 9 at 1 and 5 minutes 73 respectively. We found it challenging to provide advice on postnatal ARV 74 prophylaxis given the mother's HIV antiviral resistance and the limited dosing and 75 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 76 age, 3 mg/kg/dose twice daily from 1-4 weeks of age and then 6 mg/kg/dose twice 77 78 daily from 4-6 weeks of age) for a combined total of 6 weeks and he was not breast 79 fed. He had a normal full blood count at 6 weeks of age. Unfortunately, there was no 80 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 81 months of age and negative HIV serology at 18 months of age. Guardian consent was 82 83 obtained for publication purposes.

84

85 Discussion

The strongest individual predictor of risk of MTCT is the maternal plasma viral load 86 and the viral suppression was found to be the most effective way to minimize the risk 87 of perinatal transmission.^{2,6} All pregnant and breast feeding women living with HIV 88 infection should be given ARV to optimally suppress viral replication.^{6,7} Prevention 89 of MTCT has been a real challenge in cases with ARV resistance. Resistant virus can 90 be transmitted to the infant during pregnancy and labour and through breast feeding.⁸ 91 ARV-resistance appears to be more common in women who acquired HIV infection 92 93 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 94 95 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 96 97 98 Updated US guidelines recommend that all newborns perinatally exposed to HIV

99 should receive postpartum prophylaxis with selection of the appropriate regimen

100 guided by the level of transmission risk.^{1,6} For 'low risk' groups - mothers who

101 received ART during pregnancy with undetectable viral load at time of delivery - 4 weeks of zidovudine (ZDV) prophylaxis can be used.^{1,6} However, the additional 102 benefit of infant prophylaxis may be negligible in such cases.¹ There is no uniform 103 104 definition for a 'high-risk' group, but includes ARV naïve pregnant woman and 105 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 106 107 multidrug regimens have significantly reduced risk of HIV transmission in 'high-risk' 108 HIV-exposed infants however, 3 drug regimens were not superior to 2 drugs.^{1,6} If the neonate has high risk of transmission, the updated US guidelines recommend using 109 110 presumptive HIV therapeutic regimen with either ZDV, lamivudine (3TC) and 111 treatment doses of nevirapine (NVP) or ZDV, 3TC and RAL from birth for total of 6 weeks.⁶ 112

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The optimal post-natal prophylaxis for newborns of women living with ARV-resistant 114 115 HIV is unknown.⁶ ARV drug-resistant virus may have decreased capacity of replication and transmission but perinatal transmission of multidrug-resistant virus has 116 117 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 118 such cases consultation with a paediatric HIV specialist before delivery should be 119 done early.⁶ There is no evidence that customized prophylaxis, based on maternal 120 drug resistance patterns, are more effective than standard neonatal prophylaxis.⁶ We 121 122 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 123 124 depending on his maternal viral resistance profile. We gave him raltegravir and 125 lamivudine and he tolerated them very well and they were effective. His HIV PCR at 126 6 weeks, 3 and 6 months and 18-months serology were negative.

127

128 ZDV resistance does not affect the indications for use as a prophylaxis.^{5,9} The

129 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

131 ZDV resistance.⁹ ZDV crosses the placenta readily and it is the best for central

132 nervous system cover compared with other drugs and ZDV is beneficial at eliminating

133 a potential reservoir of HIV in the neonate.^{6,10}

135 There is limited data on pharmacodynamics/pharmacokinetic, safety, dosing regimen, and toxicity of ARV in neonates.¹¹ There is no significant difference in adverse 136 reactions between term neonates receiving combination therapy or ZDV alone.¹² 137 Transient hematologic toxicity is the most common side effect.¹² Paediatric 138 139 formulations for some protease inhibitors like lopinavir/ritonavir (LPV/r) are 140 available however their use in neonates in the first week of life is not preferred due to 141 safety concerns. LPV/r induced-cardiotoxicity in neonates has been reported previously.^{6,12} Based on post-marketing reports of cardiotoxicity of protease 142 inhibitors, the US Food and Drug Administration (FDA) recommends that LPV/r oral 143 solution not be used in term neonates < 14 days of age.⁶ Maraviroc (MVC) was recently 144 145 approved for use in infants ≥ 2 kg which may provide an additional option for treatment and 146 prophylaxis of newborns born to mothers with multidrug-resistant HIV-1infection. However, 147 the lack of data and risk of drug interactions of MVC may limit its role for routine use in 148 neonates.6

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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.¹³ 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.¹⁴

156

157 Conclusion

In conclusion, we believe that the postnatal prophylaxis regimen for newborns born to 158 159 mothers with known or suspected drug resistance should be determined with knowledge of the level of transmission risk and maternal HIV resistance profile 160 161 notwithstanding the limited therapeutic options in this vulnerable group. Such infants 162 at risk of vertical HIV acquisition should also have close monitoring, optimal follow-163 up and prompt initiation of ARV therapy where infection has occurred. Studies 164 assessing the rates of HIV resistance among neonates are highly required. In addition, 165 more studies are urgently required to assess the efficacy and the safety of more antiretroviral options that can be used for post-natal prophylaxis in babies born to mother 166 167 with HIV resistant virus.

169 Author's Contribution

- 170 PB, NG and AK conceptualized the idea. AK provided the patient's data. LSAY
- 171 drafted the manuscript and TL drafted the medication dosing. PB, NG, TL and AK
- 172 revised the manuscript. All authors approved the final version of the manuscript.
- 173

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- 216 <u>expanded-dosing-in-neonates-for-raltegravir.html</u> Last accessed July 2018.

Table 1: Mother's antiretroviral resistance profile

Image: Nucleoside RT Inhibitors Zidovudine (ZDV) mutations Db7G (2005) K219N (2015) K219N (2005) K219N (2012) L210W (2005) K219N (2012) L210W (2005) K219N (2012) L210W (2008) L21W M41L (2008) L74V (2004) M41L (2008) L74V (2004) M41L (2008) L74V (2004) M41L (2012) T215V (2004) L210W (2012) V1181 (2012) T215V (2004) L210W (2012) L210W (2012) L210W (2012) L210W (2012) L210W (2012) L210W (2012) L210W (2014) L	Drug Class	Drug	Primary	Secondary	Profile
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(2012) K219KN L74LV M41L (2004) L74V (2012) M184V (2008) L210LW T215Y (2004) L210W (2012) V118I (2012) M4IL T215C Abacavir K219KN (ABC) K219KN K219KN K219KN (2012) L210W (2004) L210LW K219KN (2012) L210W (2004) L210LW M41L (2004) L210W (2012) M184V (2008) L74LV T215Y (2004) L74LV T215Y (2004) L74LV T215Y (2004) L74LV T215Y (2004) L74V (2012) W118I (2012) M4IL T215C Tenofovir K219KN D67G (2005) High-level resistance		(DDI)	K219KN	L210W (2004)	resistance
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(2012) L210W (2004) L210LW M41L (2004) L210W (2012) M184V (2008) L74LV T215Y (2004) L74V (2012) V118I (2012) M4IL T215C Tenofovir K219KN (2012) K219KN (2012) K219KN		(ABC)	K219KN	K219KN	resistance
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L74V (2012) M4IL T215C V118I (2012) Tenofovir (TDF) K219KN D67G (2005) High-level resistance			L74LV	T215Y (2004)	
M4IL T215CM4IL High-levelTenofovir (TDF)K219KND67G (2005)High-level resistance			L74V (2012)	V118I (2012)	
T215CTenofovirK219KND67G (2005)High-level(TDF)(2012)K219KNresistance			M4IL		
TenofovirK219KND67G (2005)High-level(TDF)(2012)K219KNresistance			T215C		
(TDF) (2012) K219KN resistance		Tenofovir	K219KN	D67G (2005)	High-level
		(TDF)	(2012)	K219KN	resistance
L210LW L210W (2004)			L210LW	L210W (2004)	
L210W (2012) M41L (2004)			L210W (2012)	M41L (2004)	
M4IL T215C			M4IL	T215C	
1215C (2013) V1181 (2012)	NT.	N T · ·	1215C (2013)	V1181 (2012)	TT 1 1 1
Non- Nevirapine H2211HY V1081 (2012) High-level	Non-	Nevirapine	H2211HY	V 108I (2012)	High-level
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	nucleoside	$(\mathbf{N}\mathbf{V}\mathbf{P})$	V 1081V	V 1081V (2013)	resistance
K1 Innibitors Y181C H221HY (2013) Eferinger H221HY V1091 (2012) Ferrer	KI Inhibitors	Eferring -		$\frac{H221HY}{(2013)}$	Trada mara di ada
$\begin{array}{c c} \text{Eravirenz} & \text{H221HY} & \text{V108I}(2012) & \text{Intermediate} \\ \hline $		Elavirenz		v 1081 (2012)	register ac
$(L1^{\circ})$ $V1001V$ $V1001V$ $V1001V$ (2015) $Iesistance$ $V181C$ $H221HV$ (2013)			V1001V	V 1001V (2013) H221HV (2013)	resistance

	Rilpivirine	H221HY	V108I (2012)	Intermediate
	(RPV)	Y181C	H221HY (2013)	resistance
	Etravirine	H221HY	V108I (2012)	Intermediate
	(ETR)	Y181C	H221HY (2013)	resistance
Protease	Indinavir (IDV)	I47V (2008)	A71V (2008)	High-level
Inhibitors		I47IV (2013)	A71AV (2013)	resistance
		I54V	L10F (2013)	
		I54LV (2012)	L33I (2013)	
		L10F	M36I (2005)	
		L90M	N88G (2008)	
		M46I	N88DG (2012)	
		N88D (2005)	Q58E (2013)	
		N88DG (2013)		
		V32I (2012)		
		V32IV (2013)		
		D30DN (2012)		
		D30N (2013)	•	
	Saquinavir	I54V	A71V (2008)	High-level
	(SQV)	154LV (2012)	A71AV (2013)	resistance
		L90M	L10F (2013)	
		M46I (2013)	L33I (2013)	
		N88D (2005)	M36I (2005)	
		N88DG (2013)	M46I	
		D30DN (2012)	N88G (2008)	
		D30N (2013)	N88DG (2012)	
		V32IV (2013)	L10F (2012)	
		I47IV (2013)	(Q58E (2013)	
	Tipranavir	D30N (2013)	A71V (2013)	Intermediate
	(TPV)	D30DN (2012)	A71AV (2013)	resistance
		I47V (2013)	L10F (2013)	
		147IV (2013)	L33I (2013)	
		154V	M36I (2005)	
		154LV (2012)	M461	
		L90M (2013)	N88G (2008)	
		M461(2013)	N88DG (2012)	
		N88DG (2013)	Q58E (2013)	
		Q38E V201 (2012)		
		$V_{321}(2013)$		
		$V_{321V}(2013)$		
	Atanazavir	L_{2012} L_{2012} L_{2012}	$\Lambda 71 V (2013)$	High level
	(ΔTV)	147V(2003) 147IV(2013)	A71V(2013)	resistance
Y	(AIV)	14/1V (2013) 154V	I = 10F(2013)	resistance
		154LV (2012)	$L_{33L}(2013)$	
		190M	M36I (2005)	
		M46I	N88D	
		N88D (2005)	N88DG (2012)	
		N88DG (2013)	058E	
		V32L(2008)	250L	
		V32IV (2013)		
		D30DN(2012)		
		D30N (2013)		

	Darunavir	D30N (2013)	A71V (2013)	Susceptible
	(DRV)	D30DN(2013)	$\Lambda 71 \Lambda V (2013)$	Busceptible
	(DKV)	U_{2012}	A/1AV(2013)	
		14/1V(2013)		
		154V (2013)	L331 (2013)	
		154LV (2012)	M36I (2005)	
		L90M (2013)	N88G (2008)	
		M46I (2013)	N88DG (2012)	
		N88DG (2013)	Q58E (2013)	
		V32I (2013)		
		V32IV (2013)		
	Lopinavir	I47V (2008)	A71V (2008)	Intermediate
	(LPV)	I47IV (2013)	A71AV (2013)	resistance
		I54V	L10F	
		I54LV (2012)	L33I (2013)	
		L90M	M36I (2005)	
		M46I	N88G (2008)	
		V32I (2008)	N88DG (2012)	
		V32IV (2013)	O58E (2013)	
		D30DN (2012)		
		D30N (2013)		
		N88DG (2013)		
	Nelfinavir	D30N	A71V (2008)	High_level
	(NEV)	D300N (2012)	A71 AV (2003)	resistance
	$(111\mathbf{v})$	1/2000 (2012)	I = 10F(2013)	resistance
		147V(2000)	$L101^{\circ}(2013)$	
		14/1V(2015)	$L_{201}(2015)$	
		134 V 1541 V (2012)	N1301(2003)	
		154LV (2012)	N88G (2008)	
		LIOF	N88DG (2012)	
		L90M	Q58E	
		M461		
		N88D		
		N88DG (2013)		
		V32I (2008)		
		V32IV (2013)		
	Fosamprenavir	154V	A71V (2008)	Intermediate
	(FPV)	I54LV (2012)	A71AV (2013)	resistance
		I47V (2008)	L10F (2013)	
		I47IV (2013)	L33I (2013)	
		L10F	M36I (2005)	
		L90M	N88G (2008)	
		M46I	N88DG (2012)	
		V32I (2008)	Q58E (2013)	
		V32IV (2013)		
		D30DN (2012)		
		D30N (2013)		
		N88DG (2013)		
Integrase	Dolutegravir			Susceptible
Inhibitor	(DTG)			
	Elvitegravir			Susceptible
	(EVG)			L
	Raltegravir			Susceptible
	(RAL)			

Table 2: Antiretroviral drug dosing for neonates

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	Drug	Doses	Note
1	Zidovudine (ZDV)	 ≥ 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 > 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 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.
2	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
3	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 	-
4	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 Age 1 – 4 weeks: 6 mg/kg/dose PO twice daily Age > 4 weeks: 200 mg/m² BSA/ dose PO twice daily 	-

		 ≥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) 	
5	Raltegravir (RAL)	 ≥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.
6	Maraviroc (MVC)	 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 MVC use in infants and the risk of drug interactions will limit its routine use in neonates