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Human Immunodeficiency Virus Antiretroviral Resistance and Transmission in Mother-Infant Pairs Enrolled in a Large Perinatal Study

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Background. The presence of antiretroviral drug-associated resistance mutations (DRMs) may be particularly problematic in human immunodeficiency virus (HIV)–infected pregnant women as it can lead to mother-to-child transmission (MTCT) of resistant HIV strains. This study evaluated the prevalence and the effect of antiretroviral DRMs in previously untreated mother-infant pairs.

Methods. A case-control design of 1:4 (1 transmitter to 4 nontransmitters) was utilized to evaluate DRMs as a predictor of HIV MTCT in specimens obtained from mother-infant pairs. ViroSeq HIV-1 genotyping was performed on mother-infant specimens to assess for clinically relevant DRMs.

Results. One hundred forty infants acquired HIV infection; of these, 123 mother-infant pairs (88%) had specimens successfully amplified using ViroSeq and assessed for drug resistance genotyping. Additionally, 483 of 560 (86%) women who did not transmit HIV to infants also had samples evaluated for DRMs. Sixty-three of 606 (10%) women had clinically relevant DRMs; 12 (2%) had DRMs against >1 drug class. Among 123 HIV-infected infants, 13 (11%) had clinically relevant DRMs, with 3 (2%) harboring DRMs against >1 drug class. In univariate and multivariate analyses, DRMs in mothers were not associated with increased HIV MTCT (adjusted odds ratio, 0.8 [95% confidence interval, .4–1.5]). Presence of DRMs in transmitting mothers was strongly associated with DRM presence in their infants ($P < .001$).

Conclusions. Preexisting DRMs were common in untreated HIV-infected pregnant women, but did not increase the risk of HIV MTCT. However, if women with DRMs are not virologically suppressed, they may transmit resistant mutations, thus complicating infant management.

Keywords. drug resistance mutations; mother-to-child transmission; HIV.

Eliminating new human immunodeficiency virus (HIV) infections in infants born to HIV-infected mothers while improving maternal health remains a high priority on the Joint United Nations Programme on HIV/AIDS (UNAIDS) list of achievable goals [1]. HIV elimination depends largely on using combinations of antiretroviral (ARV) drugs to block HIV replication in HIV-infected individuals, thus serving the dual purpose of improving the infected individuals' health while preventing transmission to others [2, 3]. However, HIV can develop ARV drug-associated resistance mutations (DRMs), which can decrease the efficacy of ARV treatment (ART). DRMs can be acquired following receipt of ARV drugs but can also be transmitted during primary infection in individuals without prior ARV exposure. In the case of pregnant women, ARV DRMs can be transmitted to the infant if the woman is not on effective ART that suppresses viral replication [4]. Antiretroviral resistance can thus impair the efficacy of future ART in mothers and in HIV-infected infants if the presence of DRMs is not promptly diagnosed and treatment is not appropriately adjusted [5, 6]. On the other hand, DRM are associated with fitness costs, possibly decreasing the likelihood of mother to child transmission (MTCT) [7]. The experience with single-dose nevirapine (NVP) administered to mothers before birth and to infants at birth demonstrated the rapid development of DRMs in both mothers and infants because of the long half-life of NVP and because a single mutation can result in high-level NVP drug resistance [8]. It has been demonstrated that resistant virus can be transmitted from mother to infant during pregnancy/

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labor or through breast milk [9]. DRMs can remain detectable for extended periods in an individual's viral population and indefinitely in viral reservoirs, rapidly reemerging in the setting of reexposure to the specific drug(s) [10]. Viral evolution in the setting of DRMs can compromise the treatment of HIV-infected infants and postpartum women [11, 12].

To evaluate the effect of maternal DRMs on HIV MTCT, we reviewed the prevalence of DRMs in a subset of treatment-naive mother-infant pairs enrolled in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)/HIV Prevention Trials Network (HPTN) 040 (P1043) perinatal clinical trial [13] (see Appendix). We also evaluated risk factors potentially associated with DRMs in both mothers and HIV-infected infants.

METHODS

Study Population

This was a secondary analysis evaluating the presence of DRMs in plasma specimens collected from participants who were enrolled and followed between April 2004 through January 2011 in the NICHD/HPTN 040 (P1043) study at sites in South Africa, Brazil, and Argentina. Subjects in this study had not received ART during current pregnancy prior to labor because of late presentation to medical care and/or lack of prenatal care. Women were enrolled during labor or immediately after delivery. The aim of the parent study was to evaluate optimal infant ARV prophylaxis to prevent intrapartum HIV transmission. Infants in group A received 6 weeks of zidovudine (ZDV) alone, infants randomized to group B received 6 weeks of ZDV plus 3 doses of NVP during the first week of life, and infants in group C received 6 weeks of ZDV plus nelfinavir and lamivudine for the first 2 weeks of life. Infants enrolled in 040 were formula fed as breastfeeding was an exclusion criterion [13].

For this analysis, our primary endpoint was whether DRMs resulted in an increase in HIV mother-to-child transmission (MTCT). We performed a case-control study of 140 mothers whose infants were HIV infected, matching each case to 4 randomly selected controls, ultimately including 560 women whose infants were HIV uninfected at 6 months of age (end of the study period). We also performed a second evaluation on blood specimens collected from all 140 HIV-infected infants to evaluate the presence of DRMs in infants. All infants were followed for development of any serious adverse outcomes during the first 6 months of life. Infant HIV infection was diagnosed with 2 positive HIV DNA polymerase chain reaction (PCR) results. Infants with positive DNA PCR within 48 hours of birth and confirmatory results on repeat testing were classified as having in utero HIV infection. Infants with a negative result at birth and positive results on subsequent testing were classified as acquiring HIV infection through the intrapartum route. For mothers, blood specimens used for resistance testing were collected during their baseline study visit during labor prior to any study medications. The time point for infant ART resistance testing varied from birth to 6 months; however, most specimens were obtained from study visits after infants had completed receiving study-related ARVs (eg, after the 6-week ARV prophylaxis regimen was completed). The majority of infants were tested for the presence of DRMs at the 3-month visit (81%). The study was approved by local and collaborating institutional review boards.

Genotypic Drug Resistance

ViroSeq testing (ViroSeq HIV-1 Genotyping System, Celera Diagnostics, Alameda, California) [14] was performed on all available mother-infant specimens to assess the presence of clinically relevant DRMs. Plasma was isolated from ethylenediaminetetraacetic acid–anticoagulated whole blood within 6 hours of sample collection. Specimens with HIV-1 RNA levels (viral load) >750 000 copies/mL were analyzed following 1:100 dilution. Plasma samples were stored frozen at –70°C prior to genotypic analysis. Specimens were analyzed at 3 laboratories including the Fiocruz reference laboratory for the 040 study in Brazil, the University of California, Los Angeles, and Clinical Laboratory Services in Johannesburg, South Africa. All laboratories were Clinical Laboratory Improvement Amendments certified and certified by the National Institute of Allergy and Infectious Diseases (NIAID) for the performance of ViroSeq assay testing. HIV-1 genotyping was performed using the ViroSeq HIV-1 Genotyping System according to the manufacturer's instructions, with the following exception: Where limited volume was available, <0.5 mL of plasma was used for analysis. In this system, HIV-1 RNA is extracted from plasma samples, and one-fifth of the extracted RNA is reverse transcribed with murine Moloney virus reverse transcriptase. A 1.8-kb DNA fragment is then amplified in the same tube in a single 40-cycle PCR with AmpliTaq gold polymerase and uracil *N*-deglycosylase decontamination control. PCR products are purified using spin columns and analyzed by agarose gel electrophoresis. The PCR products are sequenced with premixed BigDye sequencing reagents in 7 separate reactions. BigDye terminator chemistry provides 98% accuracy at 550 bases for the ABI Prism 377 DNA Sequencer and 98.5% accuracy at 600 bases for the ABI Prism 310 Genetic Analyzer according to product bulletins issued by the manufacturer. The limit for ViroSeq testing was 1000 copies/mL of viral load. Samples from subtypes B, F1, CF1, and C were properly amplified. There was mandatory amplification of the 2 positive controls; its sequencing with the 7 primers generated an electropherogram with the 2 polymorphisms and 1 nucleotide insertion at the specific positions. No resistance mutations or mixed bases were accepted.

For analytical samples and controls, sizes of the sequenced fragments were around 600 bp, and at least 6 of 7 primers generating readable sequences, which were overlapped to cover the total fragment. Once edited, the batch of analytical samples (generally 10–20/day) was submitted to a website containing

other laboratory sequences previously analyzed to check for contamination. The presence of hypermutation indicated in the Stanford University HIV Drug Resistance Database did not eliminate the sample from the study. The resulting sequences were assembled and analyzed using HIV-1 Genotyping System software. Clinical relevance was assigned by the investigator (K. N.-S. and Y. B.) based on the Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu/DR).

Analysis

For the primary endpoint, univariate and multivariate logistic regression analyses were performed to evaluate whether HIV-1 log viral load, race, infant prophylaxis arm, country of origin, maternal CD4 count, maternal age, and presence of maternal DRMs were associated with an increased odds of MTCT. Our final model included the following predictors: HIV-1 log viral load, race, infant prophylaxis arm, and maternal DRMs. We then performed another multivariate analysis evaluating whether DRMs against each drug in infant's neonatal prophylaxis resulted in increased MTCT. In this analysis, we calculated genotypic susceptibility scores against infant postexposure prophylaxis regimens. A discrete value of 1 or 0 was given if the Stanford score was <30 (susceptible) vs ≥30 (resistant) using the current Stanford University HIV Drug Resistance Database.

We then used univariate and multivariate logistic regression to evaluate the association between 5 types of maternal DRMs (nonnucleoside reverse transcriptase inhibitor [NNRTI], nucleoside reverse transcriptase inhibitor [NRTI], protease inhibitor [PI], multidrug class mutation, and any mutation) with predictors including ethnicity, maternal age, maternal $CD4^+$ T-cell counts, country of origin, log scale of maternal viral load category, infant HIV status, ZDV use during labor, and parity category.

For HIV-infected infants with DRM, Fisher exact test was used to evaluate the association between each of 4 infant DRM types (NNRTI, NRTI, PI, and multidrug class mutation) and presence of maternal DRMs. The *P* values that were calculated in this analysis were all 2-sided and statistical significance was set at $P < .05$. R version 3.3.3 statistical package was used to perform analyses.

RESULTS

A total of 700 women had plasma specimens selected for resistance testing. Ninety-four women (17 transmitters and 77 nontransmitters) with a mean viral load of 362 copies/mL (standard deviation, 344.6) were excluded from the analysis because nucleic acid was unable to be amplified due to a low viral load. Similarly, 17 of 140 (12%) HIV-infected infants did not have sufficient HIV nucleic acid to perform ViroSeq testing because of a low viral burden. As shown in Figure 1, 63 of 606 (10.4%) HIV-infected women who had resistance testing performed had evidence of clinically relevant DRMs, with 12 women (2%) having DRMs against >1 class of ARV drugs. The DRMs observed

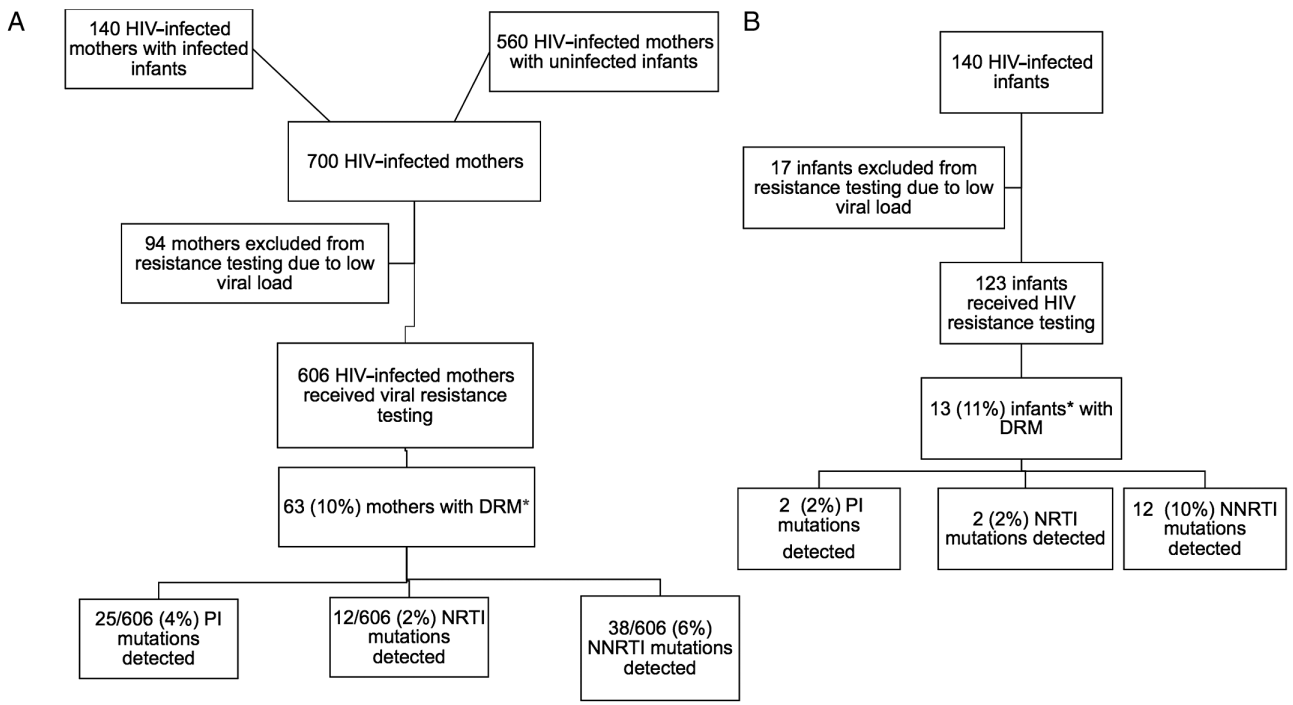

Figure 1. Flowchart of human immunodeficiency virus–infected mothers (*A*) and infants (*B*) included in this study. *Twelve mothers and 3 infants with drug-associated resistance mutations against >1 class of antiviral. Abbreviations: DRM, drug-associated resistance mutation; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

included 25 (4%) mutations conferring resistance to PIs, 38 (6%) with mutations conferring resistance to NNRTIs, and 12 (2%) mutations conferring resistance to NRTIs.

In the 123 HIV-infected infants, clinically relevant DRMs were found in 13 infants (11%), with 3 infants (2%) having DRM against >1 class of ARV drugs. Two infants (2%) had mutations conferring resistance to PIs, 12 (10%) had mutations conferring resistance to NNRTIs, and 2 (2%) had mutations conferring resistance to NRTI medications.

As seen in Table 1, mothers enrolled in this analysis were relatively young (mean age, 26.7 years), majority nonwhite, with 45.5% self-identified as black, and 31.5% self-identified as mixed, and mostly recruited in South America (78.9%). Only 12.7% had $CD4^+$ count <200 cells/μL and most (65.7%) had HIV-1 viral loads >10 000 copies/mL at the time of labor and delivery when the study enrolled subjects. Among the 606 mothers selected for this analysis, 131 (21.7%) transmitted HIV to their infants, with 87 of 131 (66%) transmissions occurring in utero and 44 of 131 (34%) intrapartum. Consistent with the study results demonstrating superiority of 2- and 3-drug infant prophylaxis to ZDV alone, infected infants were most commonly in the ZDV prophylaxis arm (n = 59 [44.7%]), followed by 36 (27.6%) each in the double ART arm (ZDV + NVP) and triple ART arm (ZDV + nelfinavir + lamivudine). Of the 123 HIV-infected infants included in the DRM analysis, 81 (65.9%) were determined to be infected in utero, and 42 (34.1%) were infected during the intrapartum period.

Table 1. Demographics and Characteristics of Human Immunodeficiency Virus–Infected Mothers and Infants

Characteristic	No.	(%)
Mothers (n = 606)		
Age, y		
13–24	241	(39.8)
25–29	167	(27.6)
≥30	198	(32.7)
Ethnicity		
Black	276	(45.5)
Mixed	191	(31.5)
White	139	(22.9)
Region		
Americas	478	(78.9)
South Africa	128	(21.1)
Viral load, copies/mL		
≤10 000	208	(34.3)
10 001–100 000	304	(50.2)
>100 000	94	(15.5)
CD4 count, cells/μL		
<200	77	(12.7)
200–500	283	(46.7)
>500	239	(39.4)
Missing	7	(1.2)
Infant status		
In utero	87	(14.4)
Intrapartum	44	(7.3)
Uninfected	475	(78.4)
Parity		
1	114	(18.8)
>1	491	(81.0)
Infants (n = 123)		
Age testing performed		
<3 mo	23	(18.7)
≥3 mo	100	(81.3)
Infant prophylaxis medications		
Zidovudine only	55	(44.7)
Zidovudine and nevirapine	34	(27.6)
Zidovudine, nelfinavir, and lamivudine	34	(27.6)
Infant HIV transmission route		
In utero	81	(65.9)
Intrapartum	42	(34.1)
Intrapartum zidovudine exposure	58	(47.2)

Abbreviation: HIV, human immunodeficiency virus.

In the univariate and multivariate analyses, the presence of DRMs in mothers was not associated with increased risk of HIV MTCT (adjusted odds ratio [OR], 0.8 [95% confidence interval {CI}, .4–1.5]). High log viral load and infant prophylaxis with ZDV alone were the only predictors of HIV MTCT (log viral load: OR, 1.4 [95% CI, 1.2–1.6]; infant prophylaxis with ZDV vs ZDV + NVP: OR, 1.6 [95% CI, 1.03–2.6]). A separate analysis was performed where only maternal DRMs that had a genotypic susceptibility score of <1 to drugs given for the infant prophylaxis regimen were included. In this more directed analysis with a lower sample size, we still found that DRM did not affect odds of MTCT (adjusted OR, 0.83 [95% CI, .3–1.9]), although the CI was increased. As seen in Table 2, our univariate analysis suggests that age, CD4 T-cell count, log maternal viral load, and parity did not appear to predict the presence of DRMs in mothers. However, as compared to living in the Americas, being from South Africa was protective against having any DRMs in our analysis (OR, 0.4 [95% CI, .2–.9]) as well as for DRMs associated with PI resistance (OR, 0.2 [95% CI, .01–.7]). Furthermore, being of mixed ethnicity was found to be associated with having NRTI DRM as compared to being black, but with a large CI (OR, 11.9 [95% CI, 2.2–222]).

As seen in Figure 2, there was a diversity of mutations detected in mothers enrolled into the trial with 59 mutations against NNRTIs, 55 mutations against NRTIs, and 106 mutations against PIs. Mutations with asterisks (Figure 2) were included in the analyses as they were considered clinically relevant by the investigators designing the study. In mothers, the most common clinically relevant mutation was the NNRTI mutation K103N, found in 15 participants.

Table 3 details information about the 13 HIV-infected infants with DRMs. Presence of any DRMs in the mother was strongly associated with presence of any DRMs in infants ($P < .001$). All infants had at least 1 of the mothers' DRM mutations, except in 3 cases (infants 9, 12, 13) where infants developed resistance to NNRTIs even though there was no evidence of any NNRTI DRMs in the mother, and in 1 case (infant 2) where the

infant developed a different NNRTI mutation than the mother (Y181C in infant vs K103N in mother). All 4 of these infants were infected in utero, and 3 of them were in the ZDV + NVP prophylaxis arm. None of the infants with resistant mutations died during the study period; significant health events are listed in Table 3.

DISCUSSION

Our study's results reveal that DRMs can commonly affect HIV-infected individuals despite the lack of prior ARV exposure, with DRMs affecting >10% of treatment-naive pregnant women and their infants. In Brazil, a 10.4% rate of DRMs in pregnancy found in this study agrees with most other studies evaluating ARV drug resistance in pregnant women, with rates ranging from 9% to 13% [15–17]. More recent reports are showing a trend toward higher rates of DRMs in pregnant women in Rio de Janeiro, with a prevalence rate of 17.2% in treatment-naive patients [18]. In other cities of Brazil, such as Belo Horizonte, a DRM rate of 9.8% in infants is consistent with published reports [19]. In contrast, since our study's completion, reported rates of DRMs are much higher in South Africa with studies demonstrating that >50% of HIV-infected infants are infected with NNRTI-resistant strains, and emphasizing the need for PI therapy for perinatally infected infants [20, 21]. Therefore, our findings support the growing literature highlighting the importance of performing resistance testing on newly diagnosed and/or treatment-naive individuals with HIV prior to initiating ARTs, especially if they are pregnant, to optimize all MTCT strategies to avoid transmission of resistant HIV strains to the infant.

It has been hypothesized that infant postexposure ARV prophylaxis may be less effective in the presence of drug-resistant maternal virus exposure, increasing the potential for intrapartum HIV MTCT. In our analysis, consistent with another published study looking at DRMs in pregnant women in Brazil, maternal ARV DRM did not appear to increase the risk of HIV MTCT [17]. Viral load and infant postexposure prophylaxis remain the most significant predictors of HIV transmission. Living in an area with high levels of ARV use seems to be the strongest predictor of having and transmitting ARV DRMs. We surmise that the association between living in South America and higher risk of maternal DRMs, especially against PI medications, is secondary to more widely available ART use in Brazil,

Table 2. Possible Predictors for Drug-Associated Resistance Mutations in 606 Human Immunodeficiency Virus–Infected Pregnant Women

Predictor	Resistance to >1 Class of Drugs (Yes)	Presence of NNRTI-Resistant Mutation (Yes)	Presence of NRTI-Resistant Mutation (Yes)	Presence of PI-Resistant Mutation (Yes)	Presence of Any Drug-Associated Resistant Mutation	No Clinically Relevant Mutations	OR[a] (95% CI)
Total No. (%)	9 (1.5)	38 (6.3)	12 (2.0)	25 (4.1)	63 (10.4)	543 (89.6)	
Age, y, mean ± SD	30.3 ± 6.9	26.7 ± 6.4	25.8 ± 5.4	25.2 ± 6.7	35.5 ± 6.1	26.8 ± 6.2	0.97 (.9–1)
Ethnicity							
Black (n = 276)	2 (0.7)	16 (5.8)	1 (0.4)	7 (2.5)	22 (8)	254 (92)	Reference
Mixed (n = 191)	6 (3.1)	13 (6.8)	8 (4.2)[b]	11 (5.8)	23 (12)	168 (88)	1.6 (.9–2.9)
White (n = 139)	1 (0.7)	9 (6.5)	3 (2.2)	7 (5)	18 (13)	121 (87)	1.7 (.9–3.3)
Region							
Americas (n = 478)	9 (1.9)	32 (6.7)	12 (2.5)	24 (5.0)	56 (11.7)	422 (88.3)	Reference
South Africa (n = 128)	0	6 (4.7)	0	1 (0.8)[c]	7 (5.5)	121 (94.5)	0.4 (.2–.9)*
Log viral load, cells/mL, mean ± SD	10.8 ± 1.6	9.8 ± 1.8	10.6 ± 1.7	10.1 ± 1.4	9.8 ± 1.6	9.9 ± 1.6	0.95 (.8–1.1)
CD4 count, cells/μL, mean ± SD	456.2 ± 278	463.7 ± 210	472.5 ± 308	553.4 ± 295	497.6 ± 248	481.2 ± 283	1
Infant status							
In utero (n = 87)	2 (2.3)	6 (6.9)	2 (2.3)	2 (2.3)	7 (8)	80 (92)	0.7 (.3–1.5)
Intrapartum (n = 44)	1 (2.3)	3 (6.8)	0	2 (4.5)	4 (9.1)	40 (91)	0.8 (.2–2.1)
Uninfected (n = 475)	6 (1.3)	29 (6.1)	10 (2.1)	21 (4.4)	52 (10.9)	423 (89)	Reference
Parity							
1 (n = 114)	3 (2.6)	9 (7.9)	3 (2.6)	8 (7)	15 (13.2)	99 (87)	Reference
≥2 (n = 491)	5 (1)	28 (5.7)	8 (1.6)	16 (3.3)	47 (9.6)	444 (90.4)	0.7 (.4–1.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; SD, standard deviation.

[a]Odds ratio evaluating predictors of having any drug-associated resistance mutations vs not having clinically relevant mutations.

[b]Being of mixed ethnicity was found to be associated with having a mutation conferring resistance to NRTI as compared to being black ($P = .01$; OR, 11.9 [95% CI, 2.2–222]).

[c]Being of South African descent was protective for acquiring a mutation against PI as compared to being from the Americas ($P = .04$; OR, 0.2 [95% CI, .01–.7]).

*$P < .05$.

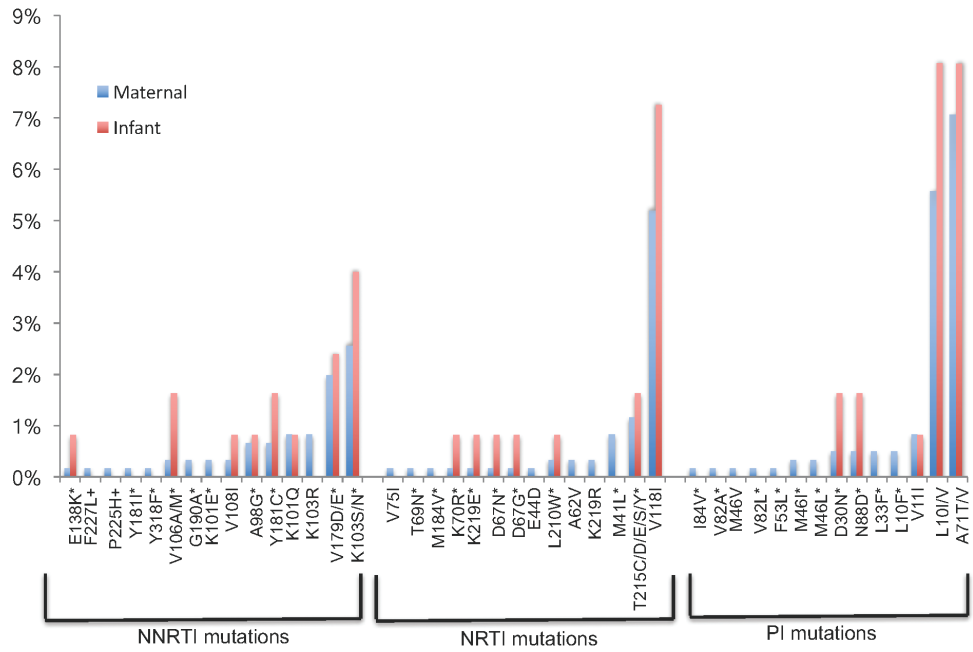

Figure 2. Graphs showing percentage of mutations found in samples collected from human immunodeficiency virus (HIV)–infected mothers (blue, n = 606) and in infants (red, n = 123). Asterisk (*) marks mutations included in our analysis as clinically relevant mutations, and plus signs (+) refer to mutations that in conjunction with another mutation were clinically relevant. These were assigned by study investigators based on the Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu/DR) at the time the study was conducted. Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 3. Specific Mutation Types and Outcomes for 13 Human Immunodeficiency Virus–Infected Infants With Drug-Associated Resistance Mutations

	Maternal DRM	Infant DRM	Age When DRM Detected	Drugs Affected by DRM	Neonatal Arm for ppx	HIV Transmission Type	Adverse Infant Outcome up to 6 mo
Infant 1	D67N, T215Y, K103N, D30N, N88D	D67N, T215Y, K103N, D30N, N88D	3 mo	NRTI, PI, NNRTI	C	In utero	Abnormal liver function tests (increasing AST), possible congenital syphilis (mother with positive VDRL, not adequately treated), thrombocytopenia
Infant 2	K103N	Y181C	6 mo	NNRTI	C	In utero	
Infant 3	K103N	K103N, V108I	3 mo	NNRTI	B	In utero	Sepsis ear infections
Infant 4	V179E	V179E	3 mo	NNRTI	A	Intrapartum	
Infant 5	A98G	A98G	4–6 wk	NNRTI	B	In utero	
Infant 6	K103N	K103N	3 mo	NNRTI	B	Intrapartum	
Infant 7	V179E, L10F	V179E	3 mo	NNRTI	C	Intrapartum	
Infant 8	V179D	V179D	3 mo	NNRTI	A	In utero	Neutropenia
Infant 9	None	K103N	3 mo	NNRTI	B	In utero	Neutropenia
Infant 10	D67G, L210W, T215S, K219E, D30N, N88D	D67G, L210W, T215S, K219E, D30N, N88D	3 mo	NRTI, PI	C	In utero	Pneumonia
Infant 11	E138K	E138K	3 mo	NNRTI	A	In utero	
Infant 12	None	V118I, K103N, V106A, V106M	4–6 wk	NNRTI	B	In utero	
Infant 13	None	Y181C	3 mo	NNRTI	B	In utero	

Infant postexposure prophylaxis study arm: group A, 6 weeks of zidovudine alone; group B, 6 weeks of zidovudine plus 3 doses of nevirapine during the first 8 days of life (2-drug group); group C, 6 weeks of zidovudine plus 2 weeks of nelfinavir and lamivudine (3-drug group).

Abbreviations: AST, aspartate aminotransferase; DRM, drug-associated resistance mutation, HIV, human immunodeficiency virus; NNRTI, nonnucleoside transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ppx, prophylaxis; VDRL, Venereal Disease Research Laboratory.

where most of the study recruitment occurred, as compared to South Africa during the study period. In Brazil, by the end of 2006, 100% of all registered AIDS cases in Brazil were receiving combination ART, including PIs [22, 23]. whereas in South Africa, it is estimated that only 5.1% of ART-eligible individuals were on ART in 2004, rising to 79% by the end of 2011, with less frequent PI use [24–26].

The most frequent ARV DRMs identified in both mothers and infants likely reflected the first-line NNRTI ART therapy recommended in both countries [27]. Brazil had notably higher frequency of NRTI mutations, probably secondary to the use of ZDV prophylaxis during pregnancy for PMTCT prior to implementation of widespread use of combination ART [28]. Infant DRMs largely mirrored those of their mothers, except in 3 cases where infants were infected in utero. These 3 infants developed resistance to NNRTIs following exposure to a prophylaxis regimen that included 3 doses of NVP, which is well known to result in resistance after minimal exposure, due to this drug's low genetic barrier to resistance [20, 29]. We hypothesize that these 3 infants acquired this DRM because their infant prophylaxis included nevirapine.

Studies have demonstrated that as the virus replicates and resistance mutations arise to circumvent selective ART pressure, viral fitness may be sacrificed, rendering the virus less likely to be efficiently transmitted [7, 30–32]. It is important to note that in high-risk situations such as detectable maternal viremia throughout pregnancy, caution should be exercised when providing ARV prophylaxis with drugs that have a low genetic barrier to development of DRM as this may compromise future HIV treatment management of these children. The benefit of reduced intrapartum transmission with combination prophylaxis must be balanced against the risk of DRM development if in utero transmission has already occurred.

The present study has some limitations. Although most patients were ART naive, having been first diagnosed at delivery, the exact number of ARV-experienced women enrolling in the study is not available, as that information was not collected. However, parity was evaluated as a potential predictor for presence of DRMs, and a higher rate of DRMs in women with prior pregnancies was not detected. Another limitation is that the number of cases where infants harbored resistance mutations was small, and so the analyses might not have had enough power to detect possible predictors of DRMs in infants.

Our results strongly support the recommendation that all pregnant women and HIV-infected infants undergo HIV genotypic resistance testing prior to initiation of ART, especially if nevirapine was used for postexposure prophylaxis regimens for the neonate. Infants at high risk of HIV acquisition should receive combination ARV regimens for prophylaxis, with attention given to early diagnosis and prompt initiation of ARV treatment in case of infection, to circumvent further development of DRMs and compromise of HIV ART management.

Notes

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APPENDIX

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