Is There Any Potential for First-Line Etravirine Use? Analysis From a Large Data Set of Antiretroviral Therapy–Naive HIV-Infected Patients Undergoing Resistance Test

To the Editors:

Nonnucleoside reverse transcriptase inhibitors (NNRTIs), mainly efavirenz, are a first choice in first-line therapy. However, because of their low genetic barrier, complete class resistance is believed to take place after the appearance of a single NNRTI-associated mutation and is frequently observed.[1] Possibly, because of the large use of NNRTI-based therapies, NNRTI-associated mutations are the most common primary resistance mutations detected in antiretroviral therapy (ART)–naive patients worldwide in recent years,[2] suggesting that there is room for new NNRTI with different mutation pattern.

Therefore, we investigated the potential for use of etravirine (ETR), a new NNRTI with high genetic barrier, as part of first-line therapy, by estimating its predicted activity in ART-naive patients by means of 4 currently available interpretation systems.[3,4]

All ART-naive patients in the Icona Foundation cohort (the national cohort including patients from 65 clinical centers) and the "Lazzaro Spallanzani" National Institute for Infectious Diseases, for whom at least 1 genotypic test was performed before the initiation of ART, were included in this analysis (Appendix 1).

The Icona Foundation Study is supported by unrestricted educational grants of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Pfizer, and Janssen-Cilag.

The Spallanzani cohort is supported by a grant for current research of the Ministry of Health.

To predict the ETR activity 4 different methods were used. First of all, the most recent score was derived from the analysis of the data from DUET-1 and DUET-2 trials, including 17 reverse transcriptase mutations with given different weights, based on virological response and in vitro resistance.[5] Specifically, a score of 3 was given to mutations Y181I/V; 2.5 to L100I, K101P, Y181C, M230L; 1.5 to E138A, V106I, G190S, and V179F; and a score of 1 to V90I, V179D/T, K101E/H, A98G and G190A mutations. A sequence was predicted to be fully resistant to ETR if such score was $\geq$4 and intermediate resistant if between 2.5 and 3.5.

Alternatively, the Monogram score, obtained from assessing genotype–phenotype concordance, included 30 mutations also with different weights. Four mutations merited a weighting score of 4, L100I, K101P, and Y181C/I; a score of 3 were assigned to E138A/G, V179E, G190Q, M230L, and K238N; a score of 2 to K101E, V106A, E138K, V179L, and Y188L; and a score of 1 was assigned to V90I, K101H, V106M, E138Q, V179D/F/M, Y181F, V189I, G190E/T, H221Y, P225H, and K238T. A cumulative score $\geq$4 defines resistance.[6]

Finally, the most recent versions of the REGA (V7.1.1, http://www.rega.kuleuven.be/cev/) and ANRS (V17, http://www.hivfrenchresistance.org) interpretation systems were also used, and concordance between all these described interpretation systems was assessed in a descriptive fashion.

Independent factors associated with the risk of having predicted ETR resistance were identified using a multivariable logistic regression, including, as patients covariates, demographic information, and virological, immunological and clinical data.

Overall, 1792 patients, who underwent resistance test between 1999 and 2008, were included. The main characteristics of the patients were as follows: 75% males; median age 37 (range 18–74) years; 16% intravenous drug users, 26% homosexuals, 34% heterosexuals, 24% not reported; 15% Centers for Disease Control and Prevention C (CDC-C) stage; median CD4 count 299 (range 1–1562) cells per cubic millimeter of blood; median log HIV RNA 4.9 (range 1.7–7.0); non-B subtypes 15%; and median time from first HIV test before genotypic resistance test 3 months (range 0–16 years).

Major International AIDS Society–USA mutations (http://www.iasusa.org/resistance_mutations) for efavirenz and NVP were detected in 51 patients (2.9%) as follows: the K103N mutation was the most frequent with 30 patients (2%); L100I, 7 (0.4%); G190A/S, 11 (1%); V108I, 6 (0.3%); Y181C, 5 (0.3%), P225H, 2 (0.1%); V106A, 1 (0.1%); and no patient harbored V106M, Y181I, or Y188C/L/H.

The predicted ETR susceptibility in all patients and in patients harboring NNRTI mutations at genotype is reported in Table 1. As observed, the prevalence of predicted full resistance to ETR was low ranging from 0.05% (ANRS V17) to 1% (Monogram) in the whole sample and from 2% to 4%, in those for whom major NNRTI mutations were also detected, regardless of the interpretation system used excluding Monogram score that indicated a prevalence of 25%.

The prevalence of predicted intermediate resistance to ETR was also generally low: 0.05%–3% in the whole sample population and 2% among patients with major NNRTI mutations, with the exception of the Rega interpretation system (41%), the only including the K103N among mutations that can partially reduce ETR susceptibility.

Full or intermediate ETR resistance according to any score was found in 59 of 1792 patients (3.3%). At multivariable analysis, it was associated with log HIV RNA > 5 at baseline [OR: 3.8 vs. $\leq$4 logs; 95% confidence interval (CI): 0.98–14.4, $P = 0.05$], detection of $\geq$1 thymidine analogous mutation (TAM) (OR: 4.5 vs. no TAM; 95% CI: 1.2–11.7; $P < 0.001$), and $\geq$1 NNRTI IAS mutation (OR: 38.5 vs. no mutation; 95% CI: 17.7–84.0; $P < 0.0001$), whereas CD4 count >350 per cubic millimeter of blood was inversely associated to ETR resistance (OR: 0.4 vs. CD4 $\leq$ 200; 95% CI: 0.2–0.96; $P = 0.04$).

In conclusion, the detection of mutations predictive of full or intermediate ETR resistance is infrequent in ART-naive patients and, therefore, provided that ETR will be considered in the future as a candidate in first-line therapy, even in

TABLE 1. Predicted ETR Susceptibility in the Study Population (N = 1792) and in Patients With Concomitant Detection of Major IAS NNRTI Mutations (n = 51)

	Duet I/II, n (%)	Monogram, n (%)	ANRS V17, n (%)	REGA V7.1.1, n (%)
At N = 1792				
Susceptible	1771 (98.9)	1768 (99)	1790 (98.9)	1740 (96.9)
Intermediate	19 (1)	/	1 (0.05)	51 (3)
Resistant	2 (0.1)	24 (1)	1 (0.05)	1 (0.1)
At n = 51				
Susceptible	37 (72)	38 (75)	49 (96)	29 (57)
Intermediate	12 (2)	/	1 (2)	21 (41)
Resistant	2 (4)	13 (25)	1 (2)	1 (2)

patients with primary resistance to previous NNRTI. Nevertheless, a formulation of ETR with a reduced number of pills and daily administrations seems desirable to make it become an attractive alternative to currently recommended NNRTI.

Patients with high viral load and low CD4 count were more likely to have an ETR resistant virus, but the risk of ETR resistance was also related to the detection of TAMs and NNRTI mutations, suggesting that ETR resistance may have been transmitted from patients who have accumulated mutations during prolonged failure of NNRTI-containing regimen.

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APPENDIX 1

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Friedewald Equation Underestimates Low-Denisty Lipoprotein Elevations for Patients With High Triglyceride Levels in the ARTEMIS and TITAN Trials

To the Editors:

The standard method of indirectly calculating low density lipoprotein (LDL)

levels, using the Friedewald equation, may underestimate the number of patients with grade 3 elevations of LDL in the ARTEMIS (TMC114-C211) and TITAN (TMC114-C214) trials. This was a particular problem for patients treated with lopinavir/ritonavir, which raises triglycerides above levels, where the Friedewald equation can normally be used.

LDL is an important marker of cardiovascular risk and can be measured either directly or indirectly. Current National Cholesterol Education Program (NCEP) treatment guidelines recommend maintaining LDL levels at least below 130 mg/dL (<3.4 mmol/L), and preferably below 100 mg/dL (<2.6 mmol/L), for those with a high risk of cardiovascular disease.[1] In HIV clinical trials, LDL elevations are normally reported by the AIDS Clinical Trials Group grading scale.[2] Grade 3 elevations of LDL (above 190 mg/dL or 4.9 mmol/L) are considered high enough to justify starting cholesterol lowering drugs, even for patients with a low (<1%) 10-year risk of cardiovascular disease.[1]

Direct measurement of LDL cholesterol, using ultracentrifugation and precipitation, (known as "beta quantification") is cumbersome and time consuming and requires expensive instrumentation and trained personnel.[3] LDL cholesterol can also be calculated indirectly using the Friedewald equation[4]:

$$\begin{aligned}\text{LDL} &= \text{total cholesterol} \\ &\quad - \text{high densitylipoprotein} \\ &\quad - \text{triglycerides}/5\end{aligned}$$

This equation assumes that virtually all plasma triglyceride is carried on VLDL and that the cholesterol to triglyceride ratio of VLDL is constant at around 5:1. The Friedewald equation is not valid if triglyceride levels are above 400 mg/dL (>4.52 mmol/L). For patient samples with these high triglyceride levels, the LDL value is not normally reported.[4] Therefore, if drugs raise triglyceride levels, use of the Friedewald equation may miss important elevations in LDL cholesterol. In previous clinical trials, lopinavir/ritonavir has been shown to elevate triglyceride levels more than other antiretrovirals.[5–8]

The ARTEMIS trial evaluated lopinavir/ritonavir versus darunavir/ritonavir 800/100 mg OD in treatment-naive patients, in combination with tenofovir/emtricitabine.[7] The TITAN trial evaluated lopinavir/ritonavir versus darunavir/ritonavir 600/100 mg twice a day in treatment-experienced patients with HIV-1 RNA >1000 copies per milliliter, in combination with optimized nucleoside reverse transcriptase inhibitor/nonnucleoside reverse transcriptase inhibitor combinations.[8] In both trials, fasting lipid data were collected at baseline and through 48–96 weeks of randomized treatment. LDL was calculated using the Friedewald equation, and then either (1) excluding LDL data from patients with triglyceride levels above 400 mg/dL or (2) setting triglycerides equal to 400 mg/dL for those with higher levels.

Results from this analysis are shown in Table 1: the percentage of patients with grade 3 elevations in LDL was analyzed by treatment arm and time in the ARTEMIS and TITAN trials.

In ARTEMIS, the darunavir/ritonavir arm led to significantly lower mean triglyceride levels at week 48 (142 mg/dL or 1.6 mmol/L) and remained below the NCEP guidelines for intervention. In the lopinavir/ritonavir arm, mean triglycerides rose to 195 mg/dL (2.2 mmol/L) at Week 48, which was above the NCEP levels for intervention. There were 179 patient visits in the lopinavir/ritonavir arm with no LDL calculated owing to high triglycerides versus 48 such patient visits in the darunavir/ritonavir arm. In the lopinavir/ritonavir arm, patients with missing LDL levels at week 48 had mean total cholesterol of 6.0 mmol/L, versus 4.8 mmol/L for those with available LDL levels.

In the TITAN trial, the darunavir/ritonavir arm also led to significantly lower triglyceride levels at week 48 (221 mg/dL or 2.5 mmol/L) versus lopinavir/ritonavir (283 mg/dL or 3.2 mmol/L).

In both the ARTEMIS and TITAN trial, imputing triglycerides of 400 mg/dL (4.51 mmol/L) for patients with higher triglyceride levels resulted in more grade 3 elevations in LDL being identified compared with using the normal Friedewald equation (Table 1). The percentage of patients with grade 3 elevations in LDL was higher in both arms when calculated with the modified method but particularly in the lopinavir/ritonavir arm.

In summary, the Friedewald equation, used to calculate LDL in the ARTEMIS and TITAN trials, underestimated the number of patients with LDL elevations because LDL was not reported for patient samples with triglyceride levels above 400 mg/dL. A significant percentage of these patients may have LDL levels high enough to need intervention with lipid-lowering drugs. Analysis of the AIDS Clinical Trials

TABLE 1. Percentage of Patients With Grade 3 Elevations in LDL Cholesterol, Calculated by Friedewald Equation in the ARTEMIS and TITAN Trials

	Darunavir/Ritonavir		Lopinavir/Ritonavir	
	TG >400 mg/dL Excluded*	Set to 400 mg/dL†	>TG >400 mg/dL Excluded*	Set to 400 mg/dL†
ARTEMIS trial				
Week 0	0/338 (0.0%)	0/347 (0.0%)	1/350 (0.3%)	1/353 (0.3%)
Week 12	2/327 (0.6%)	0/330 (0.0%)	5/308 (1.6%)	6/333 (1.8%)
Week 24	0/316 (0.0%)	0/324 (0.0%)	7/296 (2.4%)	8/322 (2.5%)
Week 36	0/306 (0.0%)	0/324 (0.0%)	6/288 (2.1%)	8/313 (2.6%)
Week 48	1/304 (0.3%)	2/309 (0.6%)	7/288 (2.4%)	8/310 (2.6%)
TITAN trial				
Week 0	4/286 (1.4%)	4/297 (1.3%)	1/274 (0.4%)	2/294 (0.7%)
Week 12	6/228 (2.6%)	8/269 (3.0%)	8/227 (3.5%)	14/277 (6.2%)
Week 24	7/240 (2.9%)	9/271 (3.3%)	4/226 (1.8%)	11/281 (3.9%)
Week 36	6/228 (2.6%)	9/260 (3.5%)	5/211 (2.4%)	13/252 (5.2%)
Week 48	5/226 (2.2%)	7/253 (2.8%)	2/190 (1.1%)	6/232 (2.6%)

*For this analysis, LDL was not calculated for patient samples with triglyceride levels above 400 mg/dL.
†For this analysis, the triglyceride level was set at 400 mg/dL for samples with triglyceride levels above this limit.
TG, triglyceride.

Group 5087 trial has also showed that the Friedewald equation underestimates the actual levels of LDL for HIV-infected individuals with high triglyceride levels.[9] In both the TITAN and ARTEMIS trials, the Friedewald equation missed fewer grade 3 LDL elevations for the darunavir/ritonavir arm, which raised triglycerides less. Assuming a value of 400 mg/dL for triglyceride levels above this level allows the identification of more patients with LDL grade 3 elevations. This is an approximation, and probably overestimates the LDL level, because the triglyceride fraction of the Friedewald equation has been set to a lower level than is measured. For patients with triglycerides above 400 mg/dL (4.51 mmol/L), the best alternative is direct measurement of LDL using beta quantification.

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Avoid a Different Standard of Care When Applying Results of Development of Antiretroviral Therapy in Africa (DART) Study

To the Editors:

Recently released results of the Development of Antiretroviral Therapy in Africa (DART) study,[1] which found that little survival benefit was attained with laboratory monitoring as opposed to clinical monitoring alone in the care of HIV-infected patients, have generated a great deal of interest, particularly because it may herald far-reaching changes in the standard of care in resource-poor settings. The potential implications are appealing. DART results not only suggest that a high level of health may be attained and sustained without routine laboratory monitoring, but also that up to one-third more HIV-infected people could be treated with the money saved. Although we unequivocally support any research that can translate into more lives saved, we offer a few notes of caution as the momentum gathers to reshape the standard of care in resource-poor settings based on the DART study.

First, we believe that the DART team's provision of free medical care and free diagnostic tests for episodes of illness throughout the trial directly contributed to the presence of high adherence rates, low loss-to-follow-up (LTFU) rates, and relatively high survival rates. In this regard, the importance of developing financing mechanisms that avoid requiring any financial contributions from poor patients cannot be overstated. As policymakers and clinicians adopt nonlaboratory-based treatment guidelines based on DART and expand the number of patients in care, patients' access to ART and other related aspects of medical care must be free.[2]

Second, the DART study reported high adherence to antiretrovirals (ARVs) and low LTFU rates of only 7% for greater than 3000 patients.[1] According to a report in 2008 by the World Health Organization, more than 20% of patients were LTFU in ART programs throughout Africa, Asia, and South America.[3] Data from a South London clinic in the United Kingdom showed that the clinic had a 40% LTFU rate.[4] These reports show that achieving high adherence and low LTFU rate is not easily achievable except for populations that have access to early support, ARV adherence counseling, and outreach, which is usually the case in study populations such as those enrolled in DART.

Third, the quality of clinical monitoring in study-type settings such as DART is generally excellent, given the amount of support and supervision provided. We believe that this quality care is what mainly contributed to the minimal difference in survival between the laboratory and clinical monitoring groups. However, in many resource-constrained settings, access to excellent clinical care is limited. If the DART study does influence policy to shift away from laboratory monitoring to clinical monitoring alone, more resources should be allocated to clinical mentoring of healthcare providers in resource-limited settings to ensure quality clinical assessments.

Lastly, although DART focused on projected cost savings without laboratory monitoring and the corresponding

increase in the number of patients who could receive ARVs, the standard of care in the developed world remains clinical and laboratory monitoring. It can be argued that a lot of unnecessary laboratory tests are done in developed countries, and studies to evaluate their true benefit must be conducted. However, until that is done, we cannot disregard the potential lives saved with routine laboratory monitoring when done appropriately. Three percent more people in the laboratory monitoring arm of the study survived than people in the clinical monitoring-only arm.[1] If DART-inspired clinical guidelines are adopted more broadly, the absolute numbers of patients who will comprise that 3% gap in outcomes will increase, and 2 different standards of care between resource-rich and resource-poor settings will persist.

We are optimistic that the results of the DART study will lower barriers and lead to greater access to care for more patients, particularly if the concerns we describe above are addressed as part of revised treatment policies and programs.

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Potential Confounding of the Association Between Exposure to Nucleoside Analogues and Mitochondrial Dysfunction in HIV-Uninfected and Indeterminate Infants

To the Editors:

Animal[1,2] and human[3] laboratory studies have suggested a possible etiologic association between in utero nucleoside analogue (NA) exposure and mitochondrial toxicity in HIV-uninfected children born to HIV-infected women. However, epidemiologic studies of children with clinical signs of mitochondrial dysfunction (MD) are limited, and confounding of an etiologic association cannot be disregarded.[4,5] We conducted a study to estimate the association of in utero NA exposure and potential confounders and MD in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group protocol P1025, a multisite US cohort of HIV-infected women and their infants.

The study population included HIV-uninfected or indeterminate infants born on or before November 1, 2006. This date restriction was used to allow 6 months of follow-up to evaluate the persistence or resolution of possible signs of MD at the time data were frozen for review. P1025 visits were conducted during routine prenatal and pediatric visits. Infant visits were scheduled at birth, 2, and 6 weeks of age, and at 4, 6, 9, and 12 months of age. Data were primarily abstracted from medical records of routine clinical care, and were supplemented by certain focused assessments including infant physical and neurological examinations, and Bayley neuropsychological testing. To identify possible or established cases of early MD according to the Enquête Perinatale Française (EPF) screening definition, a retrospective review of clinical data recorded on protocol case report forms were performed by clinicians blinded to in utero exposures.[4]

The Fisher and Wilcoxon exact tests were used to assess differences in characteristics of cases and noncases. The Jonckheere–Terpstra test was used to estimate changes in maternal HIV viral loads by year of birth. *A priori* potential confounders of the association between in utero NA exposure and MD included timing of maternal prenatal care initiation, year of birth, preterm birth, neonatal zidovudine (ZDV) prophylaxis, maternal HIV viral load, and in utero alcohol, tobacco, cocaine, heroin, and prescription methadone exposure. Maternal HIV viral loads were defined as the highest recorded measurement in each trimester and overall during pregnancy. In utero NA exposure was categorized as exposure to any NA, to individual NAs, and to lamivudine/ZDV (3TC/ZDV); we only considered NAs that an infant with possible MD was exposed to.

As of November 1, 2006, 989 live born infants were delivered by 939 women in protocol P1025; 34 women enrolled for more than one pregnancy and there were 16 sets of twins. Five infants were HIV infected and excluded; 936 HIV uninfected and 48 indeterminate infants comprised the study population. Infants were followed to a median of 43 weeks of age (interquartile range [IQR]: 27, 51) in protocol P1025; 231 infants who subsequently enrolled in another study, Pediatric AIDS Clinical Trials Group protocol 219C, were followed to a median of 105 weeks (IQR: 57, 155).

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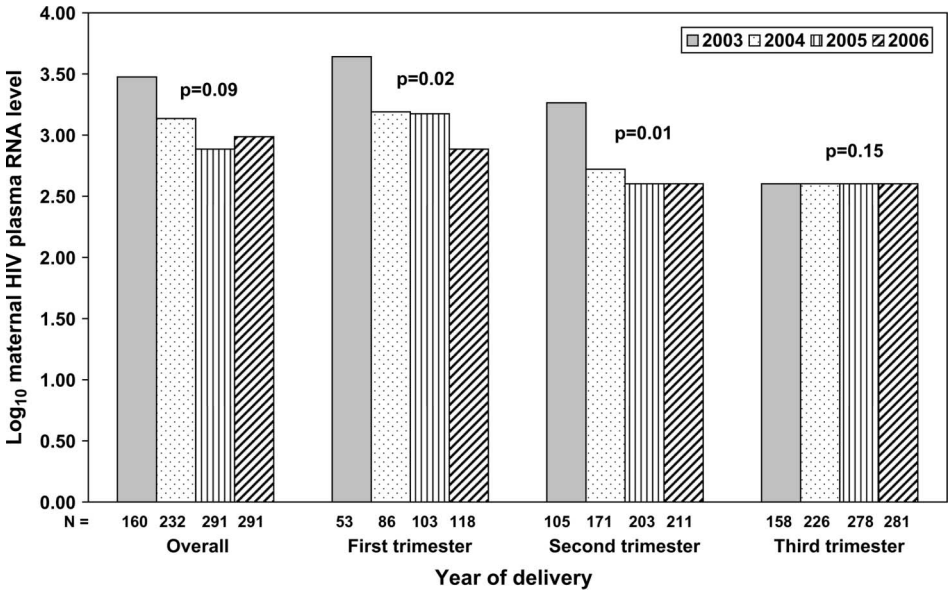

FIGURE 1. Median maternal $\log_{10}$ plasma HIV viral load by year of delivery of 974 infants in protocol P1025*. *Includes the highest maternal HIV RNA measure available per pregnancy period.

Of the 984 infants in the study population, 125 were identified through computerized database screening as having a sign of MD. Upon clinical review of the medical histories of the 125 infants, 111 were classified as having clinical signs inconsistent with MD. Four infants were classified as having sudden infant death syndrome, and 7 were classified as having mental developmental delay only. Although these latter 2 groups of infants met the EPF screening criteria,

TABLE 1. In Utero NA Exposure of Cases and Noncases*

	Cases (N = 3)		Noncases (N = 979)			Cases	Noncases	
In Utero Exposure	N	%	N	%	*P*†	Median Days of Exposure (IQR)	Median Days of Exposure (IQR)	*P*‡
Any antiretroviral								
Exposed	3	100	970	99.1	1.00	161 (29, 197)	165 (120, 254)	0.49
Unexposed	0	0	9§	0.9	—	—	—	—
Any NA								
Exposed	3	100	968	98.9	1.00	161 (29, 197)	165 (119, 253)	0.51
Unexposed	0	0	11	1.1	—	—	—	—
3TC								
Exposed	2	66.7	882	90.1	0.27	96.5 (30, 163)	158 (115, 235)	0.31
Unexposed	1	33.3	97	9.9	—	—	—	—
Abacavir								
Exposed	1	33.3	260	26.6	1.00	163	155 (99, 222)	0.88
Unexposed	2	66.7	719	73.4	—	—	—	—
Stavudine								
Exposed	1	33.3	69	7.0	0.20	31	161 (81, 266)	0.14
Unexposed	2	66.7	910	93.0	—	—	—	—
Didanosine								
Exposed	1	33.3	75	7.7	0.21	169	153 (79, 250)	0.82
Unexposed	2	66.7	904	92.3	—	—	—	—
Tenofovir								
Exposed	2	66.7	189	19.3	0.10	30 (29, 31)	142 (61, 245)	0.06
Unexposed	1	33.3	790	80.7	—	—	—	—
ZDV								
Exposed	3	100	825	84.3	1.00	163 (30, 169)	152 (109, 199)	0.61
Unexposed	0	0	154	15.7	—	—	—	—
ZDV/3TC								
Exposed	2	66.7	804	82.1	0.45	96.5 (30, 163)	152 (109, 200)	0.37
Unexposed	1	33.3	175	17.9	—	—	—	—

*Two noncases with unknown exposure excluded.
†*P* value from Fisher's exact test.
‡*P* value from Wilcoxon exact test.
§Eight of 9 infants unexposed to ARV during gestation were exposed to maternal intravenous ZDV during labor and delivery.

the reviewing clinicians did not judge the infants as having possible MD without additional clinical manifestations given the higher background rate of sudden infant death syndrome and of cognitive delay in high-risk, low socioeconomic populations.[6–9] Two infants were possible cases, one with motor and mental developmental delay and a later diagnosis of autism, and one with truncal hypotonia and repeated hospitalization for epilepsy, and one case was established through mitochondrial studies.[10] The prevalence of possible MD was 0.30% (95% confidence interval: 0.06% to 0.89%).

Possible and established cases (N = 3) were significantly more likely to be born in earlier years (all born in 2003) than noncases (N = 979, born in 2002–2006), $P = 0.02$. Among infants with maternal HIV viral loads recorded, the log median maternal HIV viral load during the first trimester was significantly higher among cases [N = 2, 5.2 (IQR: 4.6, 5.7)] than noncases [N = 355, 3.2 (IQR $\leq$ 2.6, 4.1), $P = 0.01$]. The maternal HIV viral load of the established case was 187 copies/mL at the time of the maternal HIV diagnosis early in the second trimester]. No significant difference in the distribution of other potential confounders was detected. Overall, peak maternal HIV viral loads in the first and second trimesters significantly decreased with increasing year of delivery (Fig. 1). No significant difference was observed in peak maternal HIV viral load in the third trimester by year of delivery: half of all women were below the limit of detection of 400 copies/mL in 2003 through 2006. We did not detect any significant differences in the in utero NA exposure of possible cases and noncases (Table 1).

Few infants in our study had confirmed MD, although the prevalence of 0.30% was higher than that of 0.01% in the general pediatric population.[4] Unadjusted results from the EPF suggested that this increase might be due to combination NA exposure, and findings from the Pediatric AIDS Clinical Trials Group 219/219C study suggested that it might be due to first 3TC or 3TC/ZDV exposure in the third trimester.[5] In this latter study, confounding from year of birth was evident, and possible confounding from maternal drug use and HIV viral loads was suggested. Our study also provides evidence of confounding of the association between NA exposure and MD: possible cases were significantly more likely to be born in earlier years than noncases, and median maternal HIV viral load—which is associated with antiretroviral use that has changed over time[11]—in the first trimester was significantly higher among cases than noncases. Further, first and second trimester maternal HIV viral loads decreased with increasing year of delivery overall. Laboratory studies have shown HIV-uninfected infants have depletions in mtDNA without in utero ARV exposure.[12]

Our study was limited by a small number of cases, which precluded a multivariate analysis of the association between in utero NA exposure and MD. Further, our findings could substantially change if additional cases with different profiles were identified. Screening for MD in our cohort was difficult due to the high background rate of related clinical conditions, and infants with transient abnormalities were not considered cases. Future studies should use a rigorous case definition and control of potential confounders identified in our study.

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Errata

Highly Sensitive C-Reactive Protein, Body Mass Index, and Serum Lipids in HIV-Infected Persons Receiving Antiretroviral Therapy: A Longitudinal Study: Erratum.

In the article by Boger et al., appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 52, No. 4, pp. 514–521, entitled "Highly Sensitive C-Reactive Protein, Body Mass Index, and Serum Lipids in HIV-Infected Persons Receiving Antiretroviral Therapy: A Longitudinal Study," the units for hsCRP throughout the article should be mg/L not mg/dL.

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1. Boger MS, Shintani A, Redhage LA, et al. Highly sensitive c-reactive protein, body mass index, and serum lipids in HIV-infected persons receiving antiretroviral therapy: a longitudinal study. *J Acquir Immune Defic Syndr*. 2009;52:514–521.

Tenofovir Coadministration Is Not Associated With Lower Plasma Exposure in the Clinical Setting: Erratum.

In the article by Calcagno, et al., appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 52, No. 3, pp. 431–432, entitled "Tenofovir Coadministration Is Not Associated With Lower Unboosted Atazanavir Plasma Exposure in the Clinical Setting," Giovanni Di Perri should be listed as the senior author.

This error has been noted in the online version of the article available at www.jaids.com.

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1. Calcagno A, Bonora S, Tettoni MC, et al. Tenofovir coadministration is not associated with lower unboosted atazanavir plasma exposure in the clinical setting. *J Acquir Immune Defic Syndr*. 2009;52:431–432.

Malnutrition Associated With Increased Risk of Peripheral Neuropathy in Peruvian Children With HIV Infection: Erratum.

In the letter by Esteban et al, appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 52, No. 5, pp. 656–658, entitled "Malnutrition Associated With Increased Risk of Peripheral Neuropathy in Peruvian Children With HIV Infection," the second author's name was misspelled as "Ton G. Thahn." The correct spelling is "Thanh G.N. Ton." The complete list of author names should appear as: Peggy C. Martinez, MD; Thanh G.N. Ton, MPH, PhD; Julio C. Bravo, MD; Lenka Kolevic-Roca, MD, MPH; Nicanor Mori, MD; Silvia M. Montano, MD, MPH; Joseph R. Zunt, MD, MPH.

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