Effects of Nevirapine, Compared with Lamivudine, on Lipids and Lipoproteins in HIV-1–Uninfected Newborns: The Stopping Infection from Mother-to-Child via Breast-Feeding in Africa Lipid Substudy

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Background. The objective of the present study was to assess whether the high-density lipoprotein cholesterol (HDL-c)–increasing effect of nevirapine (NVP), as observed in human immunodeficiency virus type 1 (HIV-1)–infected subjects, at least in part may relate to intrinsic properties of NVP.

Methods. At 2, 6, and 12 weeks after birth, complete lipid profiles as well as plasma apolipoproteins levels were assessed in 80 HIV-uninfected newborns, half of whom received NVP and half lamivudine (3TC), respectively. Newborns were randomly selected from a randomized trial in which NVP or 3TC had been administered to HIV-uninfected infants born to HIV-infected mothers to try and prevent HIV-1 transmission from occurring during breast-feeding.

Results. After 6 weeks of therapy, the expected physiological decline in HDL-c levels in the newborns was attenuated in infants treated with NVP, compared with levels in those treated with 3TC. Apolipoprotein A–I (apoA-I) levels were higher at all time points in the NVP arm than they were in the 3TC arm ($P = .02$), reaching peak levels at 6 weeks. The difference in HDL-c was no longer significant at 12 weeks.

Conclusions. apoA-I levels and HDL-c were elevated in HIV-1–uninfected newborns receiving NVP, compared with those receiving 3TC. These data support that NVP may indeed have intrinsic apoA-I and HDL-c elevating properties in humans.

The natural course of HIV infection has long been known to be associated with low levels of high-density lipoprotein cholesterol (HDL-c). Previous studies have shown HDL-c levels to decrease by 24%–37% after HIV seroconversion and before starting antiretroviral treatment [1, 2], with a concomitant 27% decrease in apolipoprotein A–I (apoA-I), the major apolipoprotein of HDL [2]. Because HDL-c is an inverse phase reactant [3–6], first-time suppression of HIV by combination antiretroviral therapy (cART) can be expected to be accompanied by an increase in HDL-c, indicative of successful reversal of the proinflammatory state during active HIV infection. Indeed, first-time suppression of HIV with cART is associated with a 13%–49% increase in HDL-c [7–13]. Because patients with more-advanced HIV disease are characterized by lower HDL-c levels [14], a greater rise during cART treatment is to be

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expected. Such an increase in HDL-c may in part be considered as a return toward normality.

Nonetheless, randomized clinical trials using different classes of cART regimens with similar potency for HIV suppression found that regimens including the nonnucleoside reverse-transcriptase inhibitor (NNRTI) nevirapine (NVP) were associated with greater rises in HDL-c as well as apoA-I, compared with regimens including either the protease inhibitor indinavir [8, 15] or nelfinavir [10]. Similarly, a trial comparing first-line cART regimens including either the NNRTI efavirenz or the protease inhibitor atazanavir found the former to be associated with a greater proportional rise in HDL-c, again in spite of similar antiviral efficacy [16, 17]. On the basis of these results, it has been suggested that both NVP and efavirenz may have intrinsic HDL-c–elevating properties. In a head-to-head comparison of NVP and efavirenz-based first-line cART regimens, both regimens indeed were confirmed to be associated with significant rises in HDL-c, with the rise being statistically significantly greater for NVP than efavirenz [7].

To further substantiate whether NNRTIs intrinsically increase HDL-c levels, we evaluated the impact of NVP on HDL-c levels in the Stopping Infection from Mother-to-Child via Breast-Feeding in Africa (SIMBA) study. This study examined whether daily antiretroviral prophylaxis with either lamivudine (3TC) or NVP administered to HIV-1–uninfected infants born to HIV-1–seropositive mothers could prevent postnatal mother-to-child-transmission (MTCT) of HIV-1. Although lipid profiles in neonates are fundamentally different from those in adults, this trial in HIV-uninfected individuals provided us with the unique opportunity to substantiate that the effect of NVP on HDL-c observed in HIV-infected persons receiving this drug at least in part may relate to intrinsic properties of NVP, rather than fully resulting simply from the suppression of the HIV infection. Thus, we performed a retrospective analysis of lipids and lipoproteins on stored plasma samples from a subset of uninfected newborns from the SIMBA study.

SUBJECTS, MATERIALS, AND METHODS

This was a retrospective, comparative study to evaluate the effects of NVP and 3TC on plasma lipids and lipoproteins in HIV-1–uninfected newborns. Eighty African newborns were randomly selected from the main SIMBA cohort for this analysis, 40 in each treatment arm. Only newborns that remained on the allocated treatment during the entire follow-up period were eligible for inclusion in the lipid substudy. In the main SIMBA study, 397 HIV-1–uninfected newborns ($n = 199$ in the 3TC arm and $n = 198$ in the NVP arm), born from HIV-1–infected mothers in Rwanda and Uganda, were randomized in a 1:1 ratio to receive either NVP or 3TC from birth for the duration of breast-feeding plus an additional 4 weeks after stopping breast-feeding. This was done to prevent MTCT of HIV-1 through breast-feeding. Blood samples from these newborn children were collected at baseline (i.e., 2–3 days after birth) and 2, 6, 12, and 24 weeks after commencing the allocated treatment. Regretfully, no plasma samples were stored at baseline because of the limited amount of blood that can be drawn from newborns. The week 24 samples could also not be used because of insufficient available stored plasma samples. Consequently, only samples gathered at time points 2, 6, and 12 weeks after initiation of therapy were available and used for the current analysis. From the overall cohort of 397 newborn infants, we determined the subcohort of newborns for whom both stored plasma samples were available at time points 2, 6, and 12 weeks after commencing treatment and who had been continuously exposed to study medication during this time period. Newborns who either became infected during the treatment period, died, were lost to follow up, or terminated the study on their mother's request were not included in the subcohort (figure 1). This selection resulted in a subcohort consisting of 316 newborns (157 in the NVP group and 159 in the 3TC group). The 80 newborns described in the current analysis were randomly selected from this subcohort. All assays for the present analysis were performed at the Academic Medical Center's Laboratory for Experimental Vascular Medicine on plasma samples, which had been cryopreserved at −80°C at the central laboratories.

Lipid analysis. Cholesterol concentrations in the main lipoprotein classes (very low-density lipoprotein [VLDL], LDL, and HDL) were determined using high-performance gel-filtration chromatography. The system contained a PU-980 ternary pump with an LG-980–02 linear degasser and FP-920 fluorescence and UV-975 UV/Vis detectors (Jasco). An extra P-50 pump (Pharmacia Biotech) was used for in-line cholesterol PAP enzymatic reagent (Biomerieux) addition at 0.1 mL/min. Plasma lipoprotein separations were performed with a Superose 6 HR 10/30 column (Pharmacia Biotech) with Tris-buffered saline (pH 7.4) as eluent at a flow rate of 0.31 mL/min. Computer analysis of the chromatograms for quantification of the lipoproteins was performed using Crompass Chromatographic software (version 1.7.403; Jasco). Commercially available lipid plasma standards (low, medium, and high) were used for quantitative analysis (SKZL) for total cholesterol (TC) quantification. apoA-I and apoB were both determined by nephelometric immunochemistry (Beckman).

Statistical analysis. The changes over time in the measured lipid parameters were compared between the 2 randomization arms by a repeated-measurements procedure using a generalized linear model (PROC MIXED of SAS software [version 8.02; SAS Institute]), which provides a valid statistical estimate of the mean effect. Such an analysis takes into account that

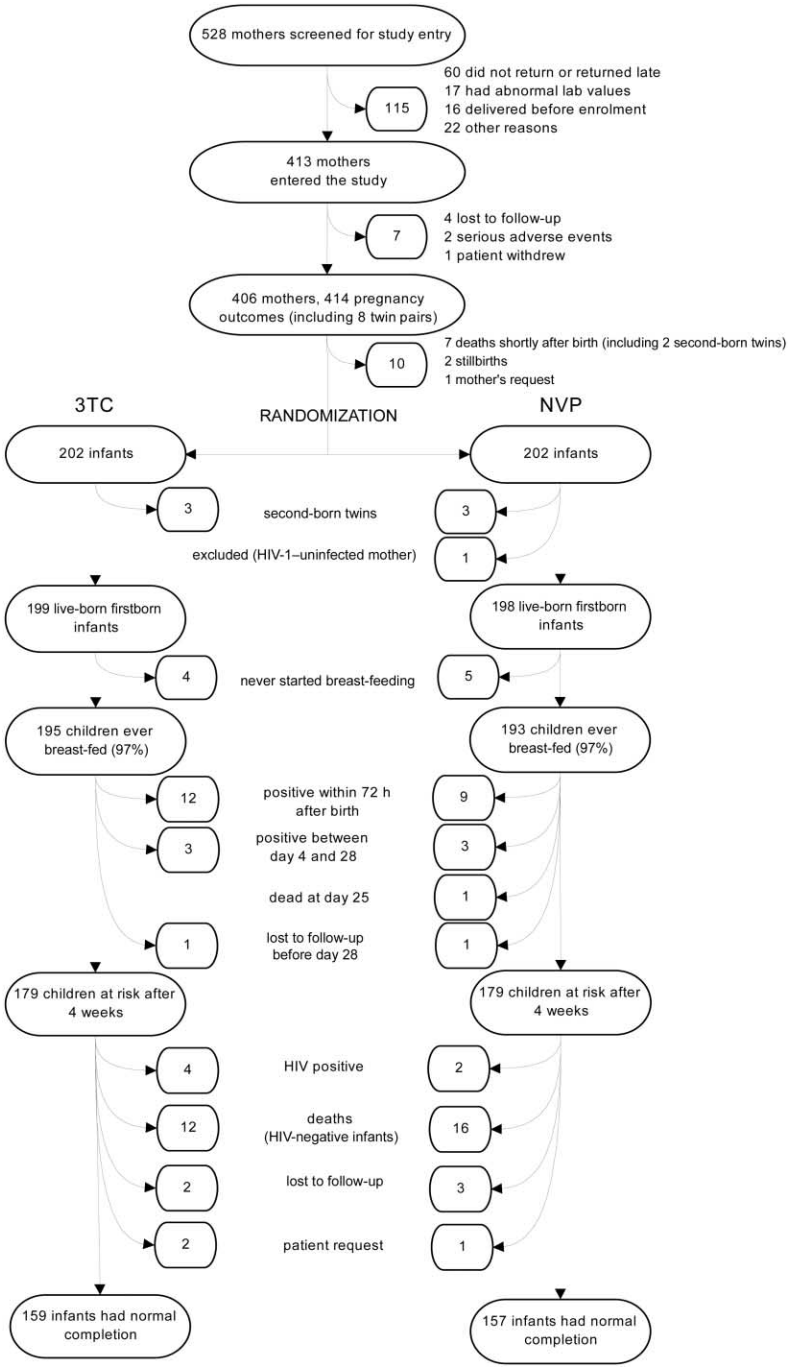

Figure 1. Stopping Infection from Mother-to-Child via Breast-Feeding in Africa trial flow chart. 3TC, lamivudine; NVP, nevirapine.

serial measurements of the outcome variable in 1 patient are correlated. An unstructured covariate structure was used to give the best fit to the models. Categorical variables were compared between randomization arms using a χ^2 test or Fisher's exact test where appropriate. Continuous variables other than the primary outcome variables were reported as medians plus interquartile range and were compared between randomization arms using the Wilcoxon 2-sample test.

RESULTS

The clinical characteristics of the newborns and their respective mothers are listed in table 1. The subset of infants randomly selected for the current analysis did not differ from the main cohort with regard to baseline characteristics. No significant differences were observed between the 2 groups of newborns in the current analysis with regard to Apgar scores, sex, and

Table 1. Clinical characteristics of newborns and their mothers at time of delivery.

Group, parameter	NVP (n = 40)	3TC (n = 40)	P
Newborns			
Gestational age, weeks	40.3 (39.3–41.3)	40.3 (39.1–41.3)	.86
Apgar score			
1′	10 (8–10)	10 (8–10)	.51
5′	10 (10–10)	10 (10–10)	.10
Length, cm	50.0 (49.0–50.5)	50.0 (48.0–51.0)	.67
Weight, kg	3.2 (2.9–3.5)	3.2 (3.0–3.4)	.60
Head circumference, cm	35 (34–36)	35 (34–36)	.63
BMI, kg/m^2	13.1 (11.6–13.7)	12.8 (11.9–13.8)	.78
Male sex, no. (%)	19 (47.5)	22 (55)	.65
Mothers			
Age, years	27 (24–30)	27 (25–31)	.48
Weight, kg	64.0 (59.2–69.5)	63.0 (59.5–67.6)	.82
Height, cm	160.0 (153.5–164.0)	159.5 (156.0–163.5)	.90
CD4$^+$ T cell count,[a] cells/mm^3	467 (380–658)	421 (294–616)	.33
Plasma HIV load,[b] $\log_{10}$ copies/mL	2.60 (2.60–2.87)	2.64 (2.60–3.29)	.13
Undetectable plasma viral load,[c] %	67.5	50	.17
CDC classification, no. (%)			1.00
A	38 (95)	39 (97.5)	
B	2 (5)	1 (2.5)	
C	0 (0)	0 (0)	

NOTE. Data are presented as median (interquartile range) unless otherwise indicated. 3TC, lamivudine; BMI, body mass index; CDC, Centers for Disease Control and Prevention; NVP, nevirapine.

[a] Collected at 36 weeks of gestation.
[b] Measured at delivery.
[c] <400 copies/mL.

measurements associated with weight and infant size. Mean gestational ages between groups were also not different from each other. Also, no significant between-group differences were observed for the mothers with regard to age, weight, height, CD4$^+$ T cell count, plasma HIV-1 RNA levels, and Centers for Disease Control and Prevention classification at the time of delivery. Nutritional intake between the 2 groups is suggested to have been comparable, as evidenced by nearly identical weight and height progression curves over the 12-week study period. At 2, 6, and 12 weeks, mean weights in the NVP arm were 3.68, 4.76, and 6.31 kg, respectively, compared with 3.64, 4.78, and 6.13 kg in the 3TC arm.

Lipids. Changes in lipids and lipoproteins in the course of the study are summarized in table 2. TC (normal values at birth: 1.86 ± 0.41 mmol/L [18]) increased from 3.20 mmol/L at week 2 to 3.83 mmol/L at week 12 in the NVP arm, whereas in the 3TC arm it increased less from 3.24 to 3.49 mmol/L (P = .025).

The net mean change in HDL-c (normal values at birth: 0.88 ± 0.23 mmol/L [18]) between week 2 and week 12 was −0.47 mmol/L in the NVP arm, compared with −0.57 mmol/L in the 3TC arm (figure 2). Overall, the HDL-c curves in the 2 arms were not statistically different (P = .17). However, there was a highly significant interaction between treatment and time (P = .0029). In the NVP arm, mean HDL-c increased initially up to 1.58 mmol/L at week 6 and decreased thereafter, whereas it decreased consistently in the 3TC arm. The net mean change in HDL-c between week 2 and week 6 was +0.11 mmol/L in the NVP arm, compared with −0.19 mmol/L in the 3TC arm. To compare the HDL-c levels between the 2 arms at week 6, we employed the "slice" option of the LSMEANS statement of PROC MIXED from SAS and found a significant difference (P = .012). There were no statistically significant differences in changes over time in LDL-c (normal values at birth: 0.75 ± 0.34 mmol/L [18]) (P = .61). LDL-c increased from 1.29 mmol/L at week 2 to 1.98 mmol/L at week 12 in the NVP arm. A similar increase was observed in the 3TC arm (from 1.35 to 1.92 mmol/L). The VLDL-c increase was significantly greater in the NVP arm, compared with the 3TC arm, between week 2 and week 12 (from 0.44 to 0.85 mmol/L vs. from 0.40 to 0.64 mmol/L, respectively; P = .006).

apoA-I and apoB. The changes over time in apoA-I (normal values at birth: 770 ± 130 mg/L [18]) were significantly different between the 2 arms (P = .02). apoA-I increased by 229 mg/L between week 2 and week 6 in the NVP arm (from 1355 to 1584 mg/L), compared with 203 mg/L in the 3TC arm

Table 2. Changes in lipids and apolipoproteins (apoA-1 and apoB) over time for nevirapine (NVP)– and lamivudine (3TC)–treated newborns.

	NVP (n = 40)			3TC (n = 40)			
Variable	Week 2	Week 6	Week 12	Week 2	Week 6	Week 12	P
Cholesterol							
Total, mmol/L	3.20 ± 0.09	3.71 ± 0.11	3.83 ± 0.11	3.24 ± 0.09	3.20 ± 0.11	3.49 ± 0.11	.03
HDL, mmol/L	1.47 ± 0.07	1.58 ± 0.07	1.00 ± 0.05	1.50 ± 0.07	1.31 ± 0.07	0.93 ± 0.05	.17
LDL, mmol/L	1.29 ± 0.06	1.61 ± 0.07	1.98 ± 0.07	1.35 ± 0.07	1.49 ± 0.07	1.92 ± 0.07	.61
VLDL, mmol/L	0.44 ± 0.03	0.52 ± 0.03	0.85 ± 0.05	0.40 ± 0.03	0.41 ± 0.03	0.64 ± 0.05	.006
apoA-I, mg/L	1355 ± 36	1584 ± 48	1408 ± 40	1265 ± 36	1468 ± 48	1278 ± 40	.02
apoB, mg/L	561 ± 27	683 ± 25	961 ± 31	517 ± 27	644 ± 25	878 ± 31	.10
apoB:apoA-I ratio	0.41	0.43	0.68	0.45	0.44	0.69	.72

NOTE. Data are mean ± SE values except for the apoB:apoA-I ratio. The reported P values are from the type 3 test of fixed effects, comparing the overall difference of the profile of the lipid parameter of interest between the NVP and 3TC arms. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

(from 1265 to 1468 mg/L). In line with the pattern of HDL-c, apoA-I levels decreased by 176 mg/L in the NVP arm and 190 mg/L in the 3TC arm between week 6 and week 12. The absolute mean change in apoA-I between week 2 and week 12 was +53 mg/L in the NVP arm, compared with +13 mg/L in the 3TC arm (figure 2). The changes over time in apoB (normal values at birth: 280 ± 90 mg/L [18]) were not significantly different between the 2 arms (P = .10). apoB increased steadily in both arms, but the net mean change in the NVP arm was not different from that of the 3TC arm (+400 vs. +361 mg/L, respectively). In agreement with these findings, the calculated apoB:apoA-I ratio increased over the course of the study in both treatment arms.

DISCUSSION

In the present study, we show that infants, in the absence of HIV-1 infection, after exposure to NVP, compared with 3TC, had higher HDL-c and apoA-1 levels after 6 weeks of treatment. These results imply that NVP may indeed exert an intrinsic effect on apoA-I and HDL metabolism, which concurs with earlier studies in HIV-1–infected adults [7, 8, 10, 15].

NVP and apoA-I/HDL-c increase. At first glance, it is apparent that the HDL-c increase in these infants is modest, compared with increases up to 49% reported on initiation of NVP in HIV-1–infected adults [8]. The latter increase most likely reflects the fact that resolution of the proinflammatory state on NVP initiation in HIV-1–infected adults provides a potent stimulus for HDL-c increase, which is obviously absent in HIV-1 negative newborns. In support, studies in HIV-1–infected adults switching to NVP after HIV-1 infection had first been suppressed with other antiretroviral regimens also reported lower HDL-c increases than studies in ART-naive patients starting NVP-containing ART [19, 20].

On interpreting HDL-c changes after birth, it is mandatory to take into account the physiological changes of HDL-c in healthy babies. At the time of birth, HDL-c levels are ~60% of adult levels (i.e., 0.80 mmol/L) [21–25]. Within the first month of life, HDL-c levels show a strong increase [26], which is followed by a steady decrease in the second and third months [27, 28]. This decrease is predominantly due to increasing triglyceride levels, which induce the transfer of cholesterol ester from HDL-c to VLDL-c via the enzyme cholesteryl ester transfer protein (CETP), resulting in lower HDL-c levels [29]. Unfortunately, HDL-c levels at the time of birth were not available in our cohort. Nonetheless, there was a significant increase in HDL-c in the NVP group between week 2 and 6, whereas HDL-c levels already declined in the 3TC group. In line with HDL-c levels, apoA-I increase was also higher in the NVP group than in the 3TC group. Whereas the difference in HDL-c levels was no longer significant at week 12, apoA-I levels remained significantly higher in infants exposed to NVP at week 12. A potential explanation contributing to loss of HDL-c but not apoA-I increase at week 12 could relate to a shift from mature α-HDL particles to smaller nascent pre-β HDL particles in the NVP group. Given the presumed greater free cholesterol acceptor capacity of pre-β HDL, this change might be beneficial. However, given the limited data available, we can only speculate on the nature of this observation. The underlying mechanism for the increase in apoA-I could either be the effect of an increased production or decreased catabolism of apoA-I under the influence of NVP. However, because the present study did not set out to investigate this, we cannot substantiate either option here. Theoretically, there are 2 options explaining the HDL-c patterns observed. On the one hand, NVP may have intrinsic HDL-c increasing capacity; on the other hand, 3TC may have detrimental effects on HDL-c, with the HDL profile in the NVP-treated newborns merely following the natural course of HDL-c after birth. With respect to the latter option,

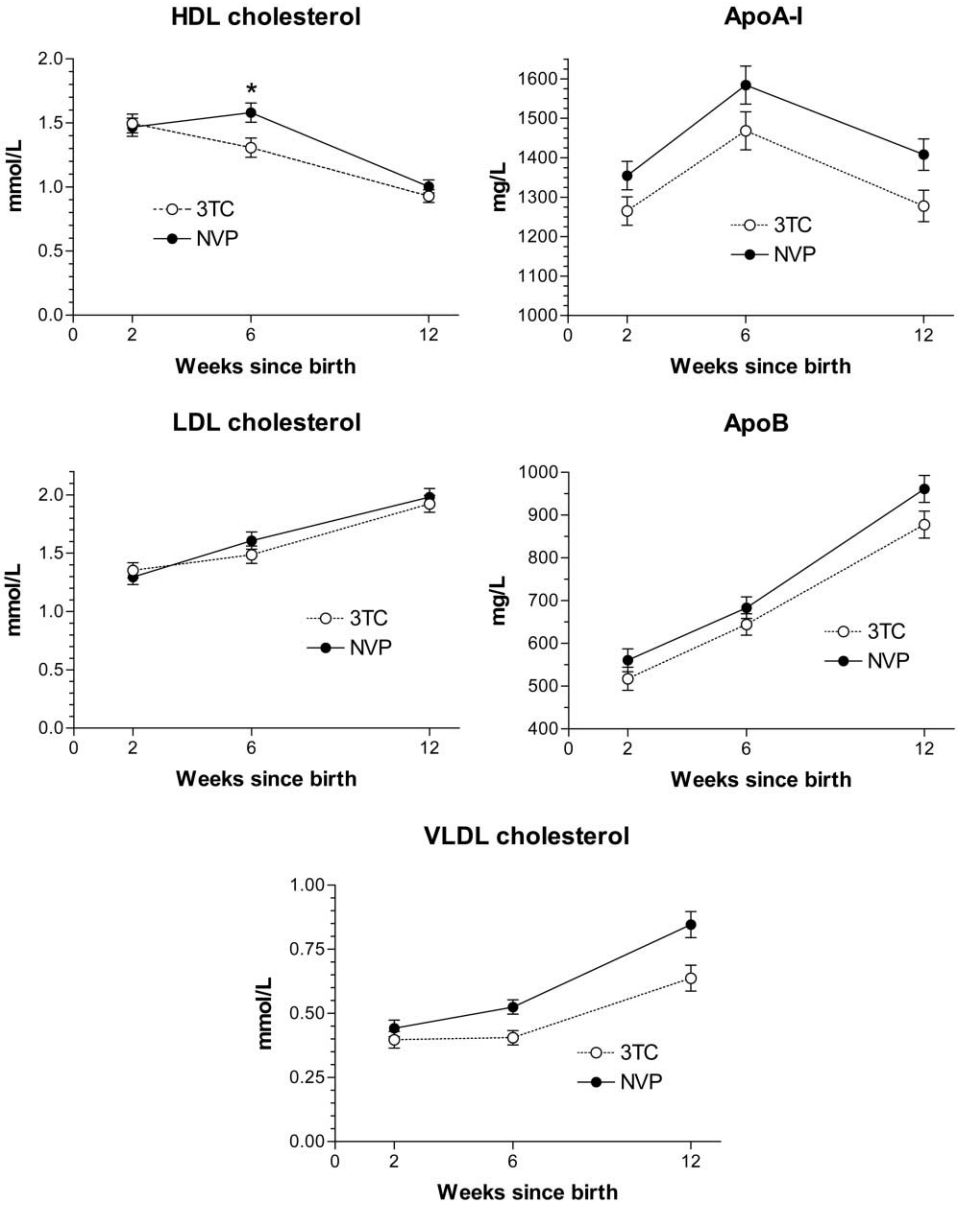

Figure 2. Course of cholesterol and apolipoproteins (apoA-1 and apoB). Weeks indicate the duration of therapy from birth onward. Black circles represent newborns treated with nevirapine (NVP); white circles represent lamivudine (3TC)–treated newborns. *The difference between NVP and 3TC is significant at the week 6 time point in the HDL graph ($P = .011$). HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

increased catabolism of HDL-c on 3TC treatment most likely pertains to the concomitant increase in VLDL-c, which induces exchange of cholesterol from HDLc via the CETP pathway [29]. In the present cohort, however, VLDL-c levels were actually lower in the 3TC group than they were in the NVP group, rendering this a less likely explanation for the differences observed between the 2 treatment groups.

With respect to NVP having intrinsic HDL-c increasing capacity, potential underlying mechanisms include changes in the activity of HDL-modifying enzymes, such as lipoprotein lipase, lecithin:cholesterol acyl transferase, or cholesteryl ester transfer protein, as well as increased apoA-1 synthesis. Whereas the present study does not provide us with mechanistical clues, such studies are currently ongoing in HIV-1–infected adults.

NVP and VLDL-c increase. In line with expectation, a rise in triglyceride-rich lipoproteins (VLDL-c) was observed in both treatment groups. This reflects increased capacity to absorb dietary fatty acids, which are secreted at the level of the liver as VLDLs. In parallel to VLDL-c increase, its structural protein apoB also increases progressively. The increase in VLDL-c was higher in the NVP arm than it was in the 3TC arm. Several explanations can be envisaged for this phenomenon. Increased

VLDL-c levels can be caused by either increased production of VLDL-c or by decreased removal of VLDL-c by lipoprotein lipase (i.e., the principal enzyme-mediating enzymatic VLDL metabolism). Whereas we cannot distinguish between increased VLDL synthesis or decreased VLDL clearance associated with NVP use, studies in adult HIV patients have not substantiated VLDL-c increases during NVP use [20]. Another option is attenuation of the physiological VLDL-c increase in the 3TC group as a consequence of decreased uptake of dietary fats due to adverse gastrointestinal effects of 3TC. However, the latter is not substantiated by identical weight curves in time for both treatment arms. Notably, the larger VLDL-c increase in the NVP arm will stimulate CETP-mediated transfer of cholesterol esters from HDL-c to VLDL-c [30]. Hence, this may have contributed to attenuation of the HDL-c increase in the NVP group at 12 weeks. LDL-c levels showed a physiological increase that was similar in both treatment groups.

Study limitations. Our study has several limitations, including the lack of lipid measurements at birth. In view of the absence of baseline measurements, it could be postulated that the observed differences between the treatment arms merely reflect differences that were already present at birth. However, this is unlikely, because treatment was successfully allocated in a random fashion as illustrated by good comparability of baseline characteristics between the 2 treatment groups. Furthermore, interpretation of the lipid changes with time is hampered by the absence of an untreated control arm. However, the inclusion of an untreated control group was deemed unethical at the time the trial was designed from the point of view of the primary aim of the trial, which was to prevent MTCT of HIV-1 during breast-feeding. Thus, we had to refer to historical control values for lipid changes after birth, which we derived from published cohorts.

In conclusion, the results of the present study on infants exposed to NVP in the absence of HIV-1 infection suggest that rises in HDL-c and apoA-I that were previously reported in HIV-1 infected adults treated with NVP-containing ART result, at least in part, from an intrinsic property of this drug. Whether this property of NVP may modify the risk of cardiovascular events in HIV-1–infected individuals treated with cART remains to be determined.

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