Atherosclerosis in the HIV and non-HIV setting: detecting and modifying cardiovascular risk

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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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Abstract

Objective: To assess whether the high-density lipoprotein cholesterol (HDL-c)-increasing effect of nevirapine (NVP), as observed in 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 in order to try and prevent HIV-1 transmission from occurring during breastfeeding.

Results: Following six weeks of therapy the expected physiological decline in HDL-c levels in the newborns was attenuated in infants treated with NVP when compared to in those treated with lamivudine. Apolipoprotein A-I levels were higher at all time points in the NVP-arm as compared to the 3TC-arm (p=0.02) 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 as compared to 3TC. These data support that NVP may indeed have intrinsic ApoA-I and HDL-c elevating properties in humans.
Introduction

The natural course of HIV infection has long been known to be associated with low levels of HDL-c. Previous studies have shown HDL-c levels to decrease by 24 to 37% after HIV seroconversion and prior to starting antiretroviral treatment [1,2], with a concomitant 27% decrease in apolipoprotein AI (ApoA-I), i.e. the major apolipoprotein of HDL [2]. Since 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 pro-inflammatory state during active HIV infection. Indeed, first-time suppression of HIV with cART is associated with a 13% to 49% increase in HDL-c [7-13]. Since patients with more advanced HIV disease are characterized by lower HDL-c levels [14], a greater rise upon cART treatment is to be expected. Such an increase in HDL-c may in part be considered as a return towards normality.

Nonetheless, randomized clinical trials using different classes of cART regimens with similar potency for HIV suppression, found that regimens including the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine were associated with greater rises in HDL-c as well as apolipoprotein A-1 (apo-A1) compared to 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]. Based on these results it has been suggested that both nevirapine and efavirenz may have intrinsic HDL-c elevating properties. In a head-to-head comparison of nevirapine 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 nevirapine than efavirenz [7].

To further substantiate whether NNRTI’s intrinsically increase HDL-c levels, we evaluated the impact of nevirapine on HDL-c levels in the Stopping Infection from Mother-to-child via Breastfeeding in Africa (SIMBA) study. This study examined whether daily antiretroviral prophylaxis with either lamivudine (3TC) or nevirapine (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 adults, this trial in HIV-uninfected individuals provided us with the unique opportunity to substantiate that the effect of nevirapine on HDL-c observed in HIV-infected persons receiving this drug at least in part may relate to intrinsic properties of nevirapine, rather than fully results 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.
Chapter 7

Figure 1  Simba trial flow chart

528 mothers screened for study entry

413 mothers entered the study

406 mothers, 414 pregnancy outcomes (including 8 twinpairs)

202 infants

3TC

202 infants

RANDOMISATION

NVP

202 infants

199 liveborn firstborn infants

198 liveborn firstborn infants

195 children ever breastfed (97%)

193 children ever breastfed (97%)

199 infants had normal completion

157 infants had normal completion

60 did not return or returned late
17 had abnormal lab values
16 delivered before enrolment
22 other reasons

4 lost to follow up
2 serious adverse events (SAE)
1 patient withdrew

7 deaths shortly after birth (incl. 2 second born twins)
2 stillbirths
1 mothers' request

3TC

second born twins

excluded (HIV-1 uninfected mother)

NVP

never started breastfeeding

positive within 72 hours after birth
positive between day 4 and day 28
dead at day 25
lost to follow up before day 28

HIV positive

deaths (HIV negative infants)
lost to follow up
patient request

413 mothers entered the study

413 mothers entered the study

4 lost to follow up
2 serious adverse events (SAE)
1 patient withdrew

7 deaths shortly after birth (incl. 2 second born twins)
2 stillbirths
1 mothers' request
Methods

This is a retrospective, comparative study to evaluate the effects of nevirapine and lamivudine 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 3TC, n=198 NVP), 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 breastfeeding plus an additional 4 weeks after stopping breastfeeding. This was done in order to prevent MTCT of HIV-1 through breastfeeding. Blood-samples from these newborn children were collected at baseline (that is, 2 to 3 days after birth) and 2, 6, 12 and 24 weeks after commenced the allocated treatment. Regrettfully, no plasma samples were stored at baseline due to 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 post 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 (see 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 current 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 (HPGC). The system contained a PU-980 ternary pump with an LG-980-02 linear degasser, FP-920 fluorescence and UV-975 UV/VIS detectors (Jasco, Tokyo, Japan). An extra P-50 pump (Pharmacia Biotech, Uppsala, Sweden) was used for in-line cholesterol PAP enzymatic reagent (Biomerieux, Marcy l’Etoile, France) addition at 0.1 ml/min. Plasma lipoprotein separations were performed with a Superose 6 HR 10/30 column (Pharmacia Biotech, Uppsala Sweden) with TBS 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 carried out using Crompass Chromatographic software, version 1.7.403 (Jasco, Tokyo, Japan).
Commercially available lipid plasma standards (low, medium and high) were used for quantitative analysis (SKZL, Nijmegen, the Netherlands) for TC quantification. Apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) were both determined by nephelometric immunochemistry (Beckman, USA).

**Statistical analysis**
The changes over time in the measured lipid parameters were compared between the two randomization arms by a repeated measurements procedure using a generalized linear model (PROC MIXED of SAS software [SAS version 8.02, SAS Institute Inc, Cary, NC, USA]), which provides a valid statistical estimate of the mean effect. Such an analysis takes into account that serial measurements of the outcome variable in one 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 chi-square 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 two-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 two groups of newborns in the current analysis with regard to Apgar scores, gender, and 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 CDC classification at the time of delivery. Nutritional intake between the two 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 kg, 4.76 kg and 6.31 kg respectively, compared to 3.64 kg, 4.78 kg 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. Total cholesterol (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=0.025).
Table 1  Clinical characteristics of newborns and their mothers at time of delivery

<table>
<thead>
<tr>
<th></th>
<th>NVP (n=40)</th>
<th>3TC (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40.3 (39.3-41.3)</td>
<td>40.3 (39.1-41.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Apgar score 1'</td>
<td>10 (8-10)</td>
<td>10 (8-10)</td>
<td>0.51</td>
</tr>
<tr>
<td>Apgar score 5'</td>
<td>10 (10-10)</td>
<td>10 (10-10)</td>
<td>0.10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>50.0 (49.0-50.5)</td>
<td>50.0 (48.0-51.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.2 (2.9-3.5)</td>
<td>3.2 (3.0-3.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>35 (34-36)</td>
<td>35 (34-36)</td>
<td>0.63</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.1 (11.6-13.7)</td>
<td>12.8 (11.9-13.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>Male gender (n [%])</td>
<td>19 (47.5)</td>
<td>22 (55)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Maternal parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>27 (24-30)</td>
<td>27 (25-31)</td>
<td>0.48</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.0 (59.2-69.5)</td>
<td>63.0 (59.5-67.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>160.0 (153.5-164.0)</td>
<td>159.5 (156.0-163.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>CD4+ T-cell count (cells/mm³)*</td>
<td>467 (380-658)</td>
<td>421 (294-616)</td>
<td>0.33</td>
</tr>
<tr>
<td>Plasma HIV viral load (log10 copies/mL)§</td>
<td>2.60 (2.60-2.87)</td>
<td>2.64 (2.60-3.29)</td>
<td>0.13</td>
</tr>
<tr>
<td>Undetectable plasma viral load (%)†</td>
<td>67.5</td>
<td>50</td>
<td>0.17</td>
</tr>
<tr>
<td>CDC classification (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>38 (95)</td>
<td>39 (97.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>B</td>
<td>2 (5)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median [interquartile range] unless indicated otherwise. BMI indicates body mass index.

* Maternal CD4+ T-cell count collected at 36 weeks of gestation.
§ Maternal HIV viral load measured at delivery.
† Plasma HIV viral load < 400 copies per milliliter.

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 to -0.57 mmol/L in the 3TC-arm (Fig. 2). Overall, the HDL-c curves in the two arms were not statistically different (p=0.17). However, there was a highly significant interaction between treatment and time (p=0.0029). 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 to -0.19 mmol/L in the 3TC arm. To compare the HDL-c levels between the two arms at week 6, we employed the 'slice' option of the LSMEANS statement of PROC MIXED from SAS, and found a significant difference (p=0.012). 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=0.61). 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). VLDL-c increase was significantly greater in the NVP-arm compared to the 3TC-arm between week 2 and week 12 (0.44 mmol/L to 0.85 mmol/L vs. 0.40 mmol/L to 0.64 mmol/L, respectively; p=0.006).
Apolipoproteins
The changes over time in ApoA-I (normal values at birth: 770±130 mg/L [18]) were significantly different between the two arms (p=0.02). ApoA-I increased by 229 mg/L between week 2 and week 6 in the NVP-arm (from 1355 mg/L to 1584 mg/L) compared to 203 mg/L in the 3TC-arm (from 1265 mg/L 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 as compared to +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 two arms (p=0.10). 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 mg/L 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.

Table 2  Changes of lipids and lipoproteins over time for NVP and 3TC-treated newborns

<table>
<thead>
<tr>
<th>Variable</th>
<th>NVP (n=40)</th>
<th>3TC (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 2</td>
<td>Wk 6</td>
<td>Wk 12</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.20±0.09</td>
<td>3.71±0.11</td>
<td>3.83±0.11</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.47±0.07</td>
<td>1.58±0.07</td>
<td>1.00±0.05</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>1.29±0.06</td>
<td>1.61±0.07</td>
<td>1.98±0.07</td>
</tr>
<tr>
<td>VLDL-c (mmol/L)</td>
<td>0.44±0.03</td>
<td>0.52±0.03</td>
<td>0.85±0.05</td>
</tr>
<tr>
<td>ApoA-I (mg/L)</td>
<td>1355±36</td>
<td>1584±48</td>
<td>1408±40</td>
</tr>
<tr>
<td>ApoB (mg/L)</td>
<td>561±27</td>
<td>683±25</td>
<td>961±31</td>
</tr>
<tr>
<td>ApoB/ApoA-I ratio</td>
<td>0.41</td>
<td>0.43</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data are presented as modeled means ± the standard error of the mean except for the ApoB/ApoA-I ratio. The reported p-value is 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 arm. Wk indicates week; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; TG, triglycerides; ApoA-I, apolipoprotein A-I and apoB, apolipoprotein B.

Discussion
In the present study we show that infants, in the absence of HIV-1 infection, following exposure to NVP as compared to 3TC, had higher HDL-c and apo-A1 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 to increases up to 49% reported upon initiation of NVP in HIV-1 infected adults [8]. The latter most likely reflects the fact that resolution of the pro-inflammatory state upon 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 compared to studies in ART-naïve patients starting nevirapine-containing ART [19,20].

Upon 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 approximately 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 compared to the 3TC group. Whereas the difference in HDL-c levels was no longer significant at week 12, apo-A-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 $\alpha$-HDL particles to smaller nascent pre-\(\beta\) HDL particles in the NVP group. Given the presumed greater free cholesterol acceptor capacity of pre-\(\beta\) 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, since our 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, increased catabolism of HDL-c upon 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 compared to the NVP group, rendering this a less likely explanation for the differences observed between the two 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.
Figure 2  Course of cholesterol and apolipoproteins

Weeks indicates the duration of therapy from birth onwards. Solid circles represent newborns treated with nevirapine, open circles represent 3TC-treated newborns.

* The difference between NVP and 3TC is significant at the week 6 time point in the HDL graph (p=0.011).
**NVP and VLDL-c increase**

In line with expectation, a rise in triglyceride-rich lipoproteins (VLDL-c) was observed in both treatment groups. The latter 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 as compared to 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 gastrointestinal side-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 which was similar in both treatment groups.

**Study limitations**

Our study has several limitations, which includes 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 which were already present at birth. However, the latter is unlikely since treatment was successfully allocated in a random fashion as illustrated by good comparability of baseline characteristics between the two 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 breastfeeding. Thus, we had to refer to historical control values for lipid changes after birth which we derived from published cohorts.

In conclusion, the results from our study in infants exposed to NVP in the absence of HIV-1 infection suggest that rises in HDL-c and apoA-I which 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.
Acknowledgements

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Reference List


