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Metabolic effects of initiating lopinavir/ritonavir-based regimens among young children: 7-year follow-up of the IMPAACT P1060 trial

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Abstract

Objective: To estimate the long-term metabolic effects of initiating a lopinavir/ritonavir (LPV/r)-based regimen as first-line therapy for HIV-infected children less than three years of age in resource-limited settings.

Design: Prospective cohort study after conclusion of the P1060 randomized clinical trials (ClinicalTrials.gov Identifier: NCT00307151), with an overall follow-up of seven years.

Methods: Longitudinal total cholesterol and triglyceride measures were compared between 222 and 227 children randomized to initiate LPV/r- and NVP-based regimens respectively. Adipokines (adiponectin and leptin) and biomarkers of inflammation (C-reactive protein and IL-6), microbial translocation (LPS), and immune activation (sCD14), measured in 117 participants at a median of 45 weeks of follow-up, were also compared by randomized arm.

Results: Mean total cholesterol and the percent of participants with borderline or high total cholesterol was higher in the LPV/r arm from years 3–7 of follow-up compared to the NVP arm (adjusted relative differences ranging from 10.9–23.4 mg/dL and adjusted relative risks ranging from a 60% increased risk to a more than 4 fold increased risk for cholesterol ≥170 mg/dL at 7

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Acquisition of data: Aldrovandi, Palumbo.

Analysis and interpretation of data: Patel, Lindsey, Angelidou, Aldrovandi, Palumbo

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years of follow-up). Initiation of a LPV/r-based regimen was not associated with high triglycerides over follow-up or large differences in markers of metabolic syndrome, inflammation, microbial translocation, or immune activation.

Conclusions: Given the virologic superiority of LPV/r-based regimens in young children and open questions regarding the roll-out of dolutegravir in resource-limited settings, children are currently being maintained on LPV/r-based regimens. Our results suggest continual assessment of total cholesterol among young children initiating a LPV/r-based regimen to monitor cardiometabolic health.

Keywords

antiretroviral therapy; paediatrics; protease inhibitors; lipids; biomarkers

Introduction:

For HIV-infected children less than three years of age, the P1060 trials provided evidence of the superiority of lopinavir/ritonavir (LPV/r)-based regimens as initial therapy, over nevirapine (NVP)-based regimens, with regards to risk of treatment failure [1,2]. A LPV/r-based regimen is currently recommended as first-line therapy for HIV-infected children less than three years of age in both United States (US) and World Health Organization (WHO) treatment guidelines [3,4].

Among HIV-infected adults, cumulative exposure to LPV/r is associated with an increased risk of myocardial infarction (MI) [5,6]. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study and the French Hospital Database on HIV, cumulative exposure to LPV/r was associated with a 13% (95% CI: 5%−21%) and a 33% (95% CI: 9%−61%) increased risk of MI per year, respectively [5,6]. LPV/r is also consistently associated with established risk factors for atherosclerotic cardiovascular disease such as metabolic syndrome, hypercholesterolemia and hypertriglyceridemia [7]. Among HIV-infected children, protease inhibitors as a class have been associated with adverse lipid profiles and body fat redistribution [8–10], insulin resistance [11], and aggregate atherosclerotic risk [12]. However, individual protease inhibitors have different effects on metabolic parameters, with newer protease inhibitors (e.g. atazanavir and darunavir) having safer metabolic profiles [13–15]. LPV/r is the only protease inhibitor recommended for children less than three years of age and few studies have specifically evaluated its impact on cardiometabolic risk parameters. Three studies conducted within the NEVEREST trials of continued LPV/r use versus a NVP switch (NEVEREST 2) or an efavirenz switch at ≥3 years of age after suppression (NEVEREST 3), found continued use of LPV/r-based regimens after suppression to be associated with higher total cholesterol [16,17], LDL cholesterol [16], and triglyceride values [16–18], and lower HDL cholesterol [16,18] after approximately 31 months, 3.4 years, and 4 years of follow-up [16–18]. While the NEVEREST studies did not observe a significant difference in insulin resistance between their groups, a Thai study reported a high prevalence of insulin resistance and dyslipidemia among their LPV/r-exposed children [19].

With respect to inflammation and immune activation, there may also be differential effects of specific antiretroviral drugs, independent of viral suppression [14,20–23]. In vitro studies have shown LPV/r to increase reactive oxygen species (ROS) production in human adipocytes [22,23] as well as induction of proinflammatory cytokines such as TNF-α and IL-1β by human macrophages [23]. No studies to date have specifically evaluated the association between initial antiretroviral regimen in young HIV-infected children and biomarkers of inflammation, immune activation, or microbial translocation.

While studies are underway to evaluate alternatives to LPV/r-based regimens as initial therapy for HIV-infected children less than three years of age, children are currently being maintained on LPV/r-based regimens, particularly in settings where routine viral load monitoring is not available to consider treatment switch strategies such as those evaluated in NEVEREST. We therefore sought to evaluate the long-term implications of initiating LPV/r-based regimens on metabolic outcomes among infants and children in the IMPAACT P1060 trial through seven years post-randomization.

Methods:

The P1060 study of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network included two parallel randomized clinical trials aimed to evaluate the efficacy of initiating a LPV/r-based regimen compared to a NVP-based regimen as first-line therapy among HIV-infected, ART-eligible children aged 2–36 months of age from six African countries and India (ClinicalTrials.gov Identifier: NCT00307151). At the conclusion of the trials, participants were offered enrollment into a prospective cohort study of P1060 (Version 5.0) aimed to provide data on the long-term comparative effectiveness/safety of initiating a protease inhibitor-based (LPV/r) versus a non-nucleoside reverse transcriptase inhibitor-based (NVP) treatment at an early age. P1060 was approved by ethics review committees at each site and at each collaborating institution in the United States. Written informed consent was obtained from each participant’s parent or legal guardian.

Long-term outcomes of interest included non-fasting measures of total cholesterol and triglycerides, adipokines (adiponectin and leptin), and biomarkers of inflammation (C-reactive protein and IL-6), microbial translocation (LPS), and immune activation (sCD14). During the trial period of P1060, lipids were scheduled for measurement at baseline (i.e., entry/randomization), six months, and one year of follow-up. During the extended observational follow-up period of P1060, lipids were scheduled for measurement at entry to Version 5.0 and annually thereafter. The closest measurement within three month (for six month and one year visits) or six month windows around these time points was chosen as outcomes for analyses. Total cholesterol was evaluated as a continuous and categorical outcome. Borderline cholesterol was defined as 170–199 mg/dL and high cholesterol as ≥200 mg/dL [15–17]. Triglycerides were evaluated as a categorical outcome with high triglycerides defined as >150 mg/dL [15–17]. Biomarkers were measured on all participants with available plasma who were still on their randomized treatment at their nine month or one year (preferred) visit. Multiplex Luminex technology was used to measure adiponectin, leptin, IL-6, and CRP via a custom panel from R&D systems. The R&D systems ELISA was used to measure sCD14. LPS levels were determined by the limulus amebocyte lysate assay

(LAL) Chromogenic Endpoint assay. Biomarkers were log_{10}-transformed and evaluated as continuous outcomes.

Participants were followed to the minimum of the year they switched off of randomized treatment due to a non-protocol reason, the year of their first missing expected cholesterol or triglyceride measure, or through the year of their last clinic visit or patient contact in P1060. Protocoled reasons for switching included virologic failure, laboratory toxicities, hypersensitivity reactions, or starting treatment for tuberculosis. Potential predictors of censoring during follow-up included age at baseline (<1, 1 to <2, ≥2 years), sex (male, female), country of enrollment (India, Malawi, S Africa, Tanzania, Uganda, Zambia, Zimbabwe), breastfeeding status (yes, no), baseline WHO disease stage (1–4), and baseline and time-updated measures of CD4% (<15, 15-<25, ≥25), plasma HIV RNA (continuous in log_{10} copies/mL), WHO height for age z-score (≤−2, >−2 to −1, >−1), WHO weight for age z-score (≤−2, >−2 to −1, >−1), cholesterol (<170, 170 to <200, ≥200 mg/dL), and triglycerides (≤ 150, >150 mg/dL). This follow-up analysis only included participants with covariate information prior to or at randomization in order to appropriately adjust for differential censoring of participants over the seven-year follow-up period.

Baseline sociodemographic and clinical characteristics of the study population overall and by randomized treatment arm were summarized using descriptive statistics. For each outcome, time to being censored due to end of follow-up, missing an expected outcome measure, and switching off of randomized treatment, was compared by randomized arm. Inverse-probability of censoring weights for each type of censoring were estimated using multivariable logistic regression models including both baseline and time-varying covariates. An overall censoring weight to be applied to outcome models was calculated by multiplying the censoring weights estimated for each type of censoring. Linear regression models (unadjusted, baseline adjusted, and weighted) were used to estimate least squares mean total cholesterol by randomized arm and year of follow-up and relative differences in mean total cholesterol between LPV/r and NVP by year of follow-up. These analyses were also run separately by sex to address an *a priori* hypothesis that female children would be more sensitive to effects of LPV/r on lipid parameters compared to male children [24]. Modified Poisson regression models [25] were used to estimate relative risks for total cholesterol ≥170 mg/dL and triglycerides >150 mg/dL, comparing randomization to LPV/r versus NVP by year of follow-up. These models were not further stratified by sex due to small numbers of outcomes at specific years of follow-up affecting model convergence. Multivariable linear regression models were used to identify baseline predictors of biomarker levels. All analyses were conducted using SAS 9.4.

Results:

Study population and baseline characteristics

Of the 452 HIV-infected children enrolled in P1060, one participant who did not start their allocated treatment, and two participants who had missing baseline covariate information (1 missing CD4% and 1 missing triglycerides) were excluded. The final study population included 449 children of whom 222 were randomized to LPV/r and 227 were randomized to NVP (Figure 1). Adipokines and biomarkers of inflammation, microbial translocation, and

immune activation were measured in 117 participants (26% of total) at a median (Q1, Q3) of 45 (36, 48) weeks of follow-up. The number of participants with measured biomarkers by randomized arm is presented in Figure 1. Among the study population, median age at enrollment in P1060 was 1.2 years, 47% were male, 47% were enrolled from South Africa, and 59% were breastfed (Table 1). The median baseline CD4% and plasma HIV viral load were 16.3% and 5.8 $\log_{10}$ copies/mL respectively, and median height-for-age and weight-for-age z-scores were below WHO norms (−2.3 and −1.6 respectively). While the distributions of sociodemographic and clinical characteristics were similar between LPV/r and NVP arms at baseline, median total cholesterol and triglyceride values were higher in the LPV/r arm (cholesterol: 108 vs 100.5 mg/dL; triglycerides: 154.6 vs. 150.6 mg/dL). Seventy-nine and 76% of the participants in the LPV/r and NVP arms enrolled into the long-term follow-up version of P1060 (Version 5.0), respectively.

Censoring

For analyses of total cholesterol, 105 (23%) participants had been censored (77% remaining) by 6 months of follow-up (12% for missing an expected cholesterol measurement, 5% for switching off of randomized treatment, and 6% for end of follow-up). By one year of follow-up an additional 76 (17%) participants were censored (60% remaining), primarily for missing an expected cholesterol measurement (14%). By three, five, and seven years of follow-up, 45 (10%), 32 (7%), and 123 (27%) additional participants were censored (50%, 43%, and 16% remaining) respectively, with end of follow-up being the primary reason for censoring. Censoring for analyses of triglycerides was essentially the same.

Over the entire seven years of follow-up, participants randomized to NVP were more likely to be censored due to missing an expected total cholesterol or triglyceride measurement (23% vs. 18%) and for switching off of randomized treatment for a non-protocol defined reason (7% vs 4%). Male participants were also more likely to switch off of randomized treatment for a non-protocol defined reason. Specific regimen changes and non-protocol reasons for switching off of randomized treatment are provided in Supplemental Table 1.

Total cholesterol

In unadjusted analyses, mean total cholesterol was higher in the LPV/r arm from three to seven years of follow-up with average differences ranging from 10–24 mg/dL. Results were similar in weighted analyses including baseline adjustment of covariates (Figure 2, Supplemental Figure 1). Estimated differences in mean total cholesterol between LPV/r and NVP were higher among girls at three to six years of follow-up compared to boys (Supplemental Figure 2). The percent of participants with borderline or high total cholesterol was higher in the LPV/r arm from three to seven years of follow-up compared to the NVP arm (Supplemental Figure 3). The relative risks for borderline/high cholesterol, comparing LPV/r to NVP, ranged from a 60% increased risk at five years of follow-up (95% CI: 0.9, 2.8) to a more than four-fold increased risk at seven years of follow-up (95% CI: 1.2, 15.3) (Figure 3). In all analyses, results at two years of follow-up were more variable with wider confidence intervals due to the relatively smaller number of participants with recorded cholesterol measures during the transition between the end of the P1060 trials and enrollment into the long-term follow-up study.

Triglycerides

The percent of participants with high triglycerides in the LPV/r arm ranged from 40.5% at six months of follow-up to 13.9% at six years of follow-up compared to a range of 33.9% at six months of follow-up to 2.9% at seven years of follow-up in the NVP arm (Supplemental Figure 4). Weighted relative risks for high triglycerides over follow-up comparing the LPV/r arm to the NVP arm ranged from a 20% to a 2.9-fold increase in risk (Supplemental Figure 5). However confidence intervals around these estimates were wide.

Biomarkers

The subset of the study population with at least one biomarker measurement was less likely to be breast-fed and more likely to have been in the LPV/r arm of the study, to be enrolled from South Africa, have higher height and weight for age z-scores, and have higher baseline triglycerides (Supplemental Table 2). Being randomized to LPV/r was not a strong predictor of the biomarkers of interest (Figure 4). Significant predictors of lower adiponectin levels included age greater than or equal to two years at baseline and having been breast-fed. Age between one to two years at baseline was a significant predictor of lower leptin levels, while high triglycerides at baseline predicted having high leptin levels. There were no significant predictors of C-reactive protein or IL-6 in multivariable models. Having a weight for age less than two SD from the mean was a strong predictor of having high LPS levels.

Discussion:

Among young HIV-infected children in the P1060 trial, we found initiation of a LPV/r-based regimen to be associated with higher total cholesterol from three to seven years of follow-up compared to initiation of a NVP-based regimen. Initiation of a LPV/r-based regimen, however, was not consistently associated with high triglycerides over follow-up and was not a strong predictor of adipokines or biomarkers of inflammation, microbial translocation, or immune activation measured at approximately 45 weeks of follow-up. Our results should be interpreted together with a previous P1060 long-term follow-up study in the same population showing fewer virologic failures and deaths, but lower mean weight-for-age z-scores over five years of follow-up with initiation of a LPV/r-based regimen compared to a NVP-based regimen [26].

Our study is consistent with previous findings of high total cholesterol over extended follow-up with LPV/r initiation in young children [16–18]. The proportion of participants on LPV/r who had borderline/high total cholesterol values in our study ranged from 33.6% to 44.1% at three to seven years of follow-up. In comparison, the proportion of HIV-uninfected South African children aged 4–9 years with borderline/high total cholesterol was observed to be 23.7% [27]. The long-term effect of this cumulative exposure to high total cholesterol levels on cardiovascular health as these young children age into adolescence and young adulthood has not yet been quantified, but studies in HIV-uninfected children have shown that the atherosclerotic disease process begins at an early age with risk factors measured in childhood predicting vascular changes in young adulthood [28,29]. One recent study in Ethiopia observed higher pulse wave velocity among pediatric participants (6–17 years of age) on LPV/r-based regimens for an average of 3 years compared to participants on NVP-

based regimens [30]. Measures of total cholesterol in their LPV/r-exposed participants however, were much higher than those measured in our P1060 LPV/r study population at 7 years of follow-up (Median (IQR): 199 (173–244) versus 156 (131–184) mg/dL) [30].

To our best knowledge, our study is the first to evaluate whether initial antiretroviral regimen in young perinatally HIV-infected children predicts adipokines or biomarkers of inflammation, immune activation, and microbial translocation. The association between duration of LPV/r use and levels of leptin and adiponectin, however, was evaluated in two studies of older HIV-infected children who initiated their LPV/r-based regimen as salvage therapy after previous long-term antiretroviral therapy or after virologic failure on a non-nucleoside reverse transcriptase inhibitor-based first-line regimen [19,31]. The first study observed increasing leptin levels among their children with lipodystrophy and increasing adiponectin levels among their children without lipodystrophy over follow-up on LPV/r [31]. The second study found no correlation between duration of LPV/r use and levels of these biomarkers [19]. While their adiponectin levels were similar to those in our LPV/r study population, they observed leptin levels at approximately one year of follow-up that were a $\log_{10}$ higher than the levels we observed. This difference may reflect the comparatively older and more treatment-experienced children included in that study.

Mechanistic studies have shown LPV/r to be associated with increased ROS production and IL-6 secretion in human adipocytes as well as increased production of proinflammatory cytokines IL-1β, TNF-α, and IL-6 by human macrophages [22,23,32]. We therefore postulated that initiation of LPV/r in young children may predict higher levels of inflammation and immune activation compared to NVP. While we did not observe this association at approximately one year of follow-up, a PENPACT-1 trial analysis restricted to virologically suppressed children with a median age at treatment initiation of 6.5 years, found PI-based regimens (56% LPV/r) to be associated with higher levels of systemic inflammation as measured by IL-6 and hs-CRP compared to NNRTI-based regimens (30% NVP) at four years of follow-up [33]. Future studies in the P1060 population are warranted to determine whether we would observe similar differences in inflammatory biomarkers at later years of follow-up.

Consistent with a previous South African study evaluating lipid profiles, our study utilized non-fasting measurements of total cholesterol and triglycerides since fasting was not required in P1060. Non-fasting lipid measures have been shown to be as predictive of cardiovascular disease mortality as fasting measures [34]. Another potential limitation of our study is the lack of data on lipid subsets including non-high-density lipoprotein cholesterol (non-HDL-C) which is a significant predictor of persistent dyslipidemia and atherosclerosis in children [35]. We also observed smaller sample sizes in the later years of our study, with only 16% of our original study population still in follow-up at 7 years. The strength of our study, however, is the relatively prolonged follow-up within a randomized trial comparing initiation of first-line LPV/r- and NVP-based regimens in young children. Globally, these two regimens are the primary first-line treatment options among children<3 years of age and follow-up on these initiated regimens is still relevant as routine viral load monitoring is currently not available in many settings to consider treatment switch strategies off of LPV/r [36]. In addition to leveraging the randomization of the P1060 trials to obtain estimates of

the effect of LPV/r-based regimens on lipid parameters, we also adjusted for censoring due missing an expected outcome measure, and switching off of randomized treatment for a non-protocol reason over the long follow-up period using inverse-probability of censoring weights. Our weighted effect estimates are interpreted as the average causal effects of LPV/r compared to NVP on lipid parameters had all participants followed their assigned trial protocol over the follow-up period (i.e., staying on their assigned regimen, adhering to protocol schedules, and allowing for treatment switches due to toxicity or other protocol-defined reasons).

In summary, we sought to evaluate the long-term metabolic implications of initiating LPV/r-based regimens among infants and children in the IMPAACT P1060 trial through seven years post-randomization and found initiation of a LPV/r-based regimen to be associated with higher total cholesterol from three to seven years of follow-up compared to initiation of a NVP-based regimen. While dolutegravir is being evaluated to replace LPV/r in initial therapy for HIV-infected children, there is an ongoing debate among experts as to whether all children should be switched to dolutegravir-based regimens, suggesting that LPV/r use may still be consistent in this population. Our study suggests monitoring and management of lipid parameters among children on long-term LPV/r-based regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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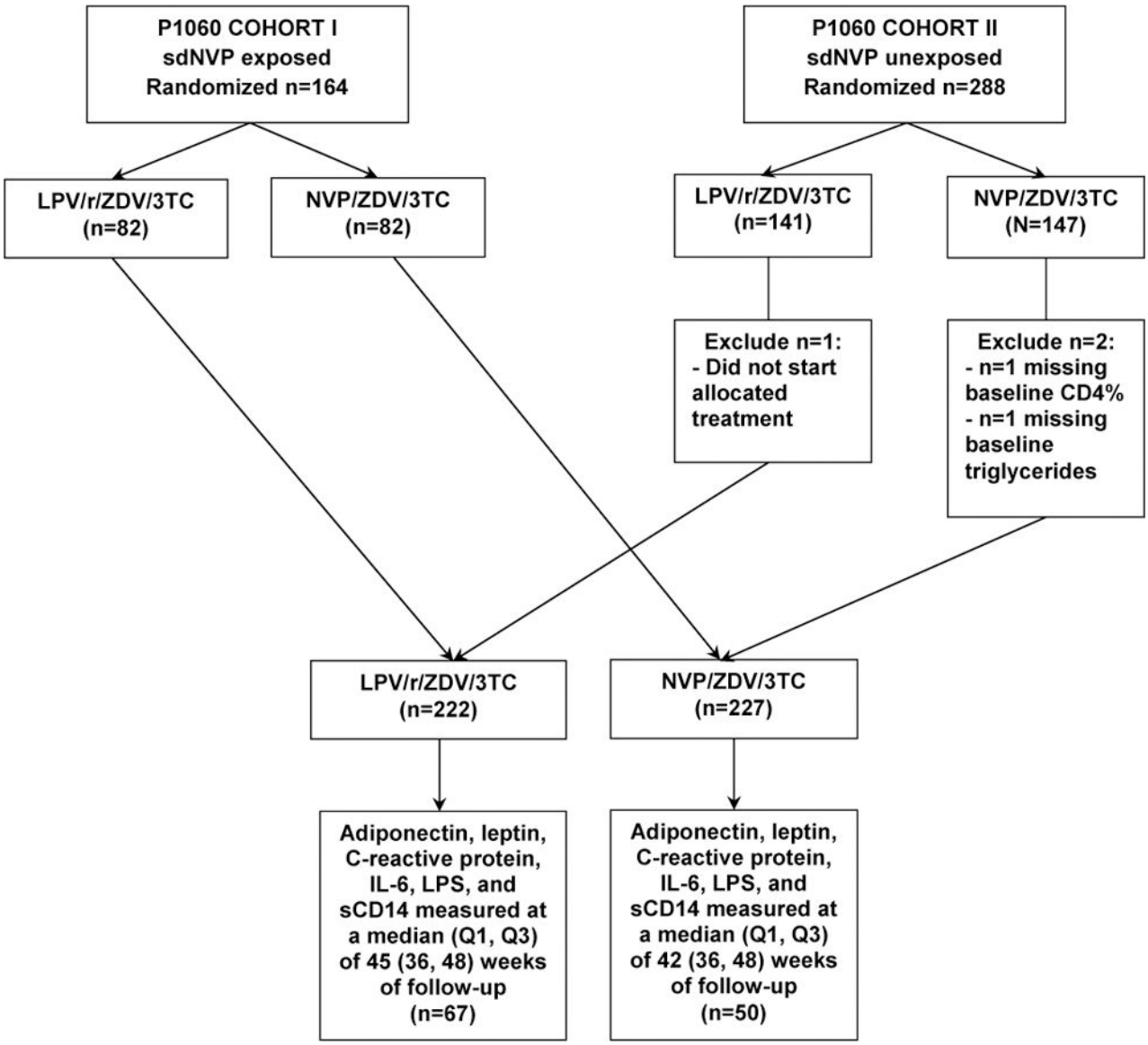

Figure 1.

Derivation of study population (sdNVP, single-dose nevirapine, LPV/r, lopinavir/ritonavir; ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine).

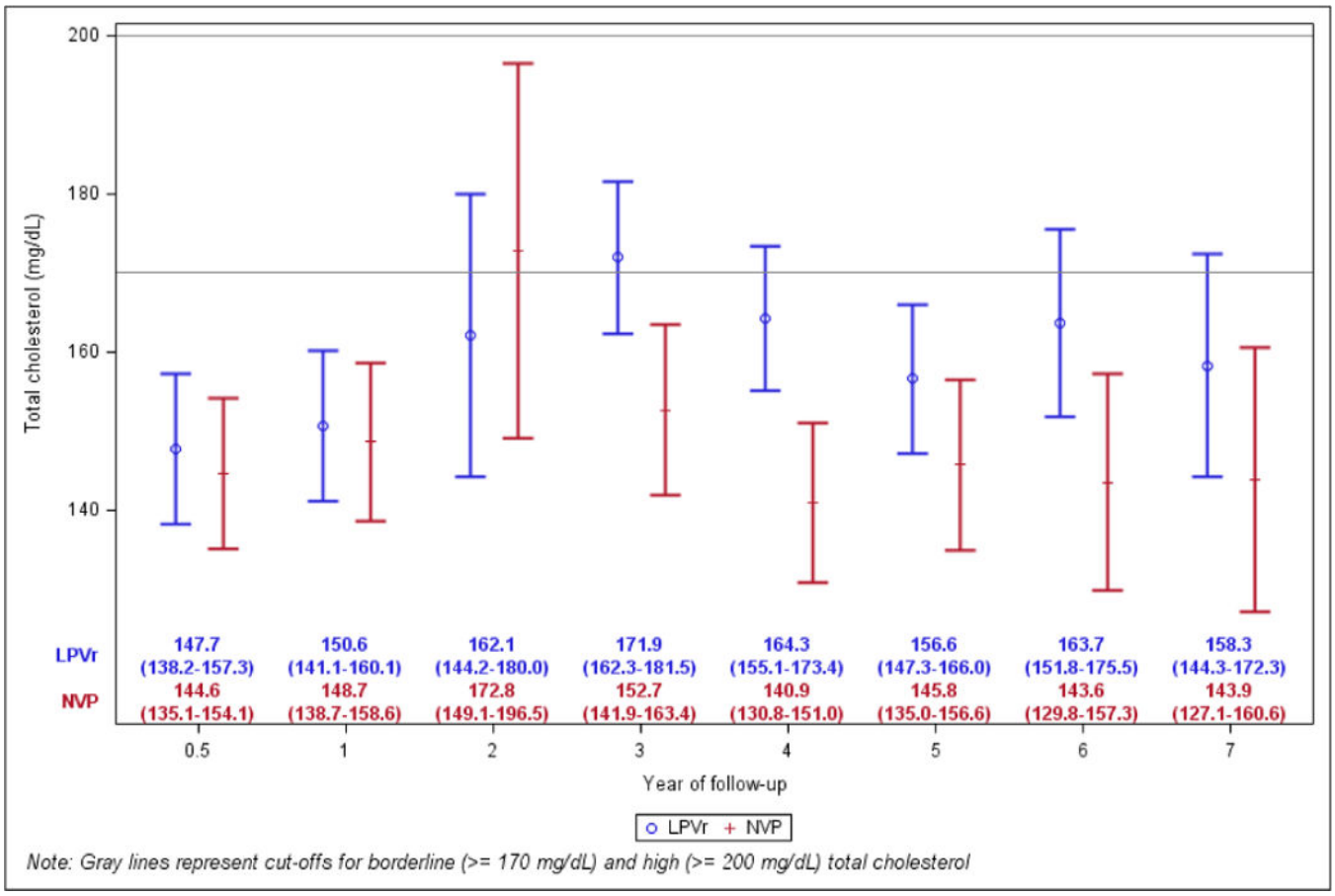

Figure 2.

Weighted least squares mean total cholesterol (95% confidence interval) by randomized treatment and follow-up year (LPVr, lopinavir/ritonavir; NVP, nevirapine).

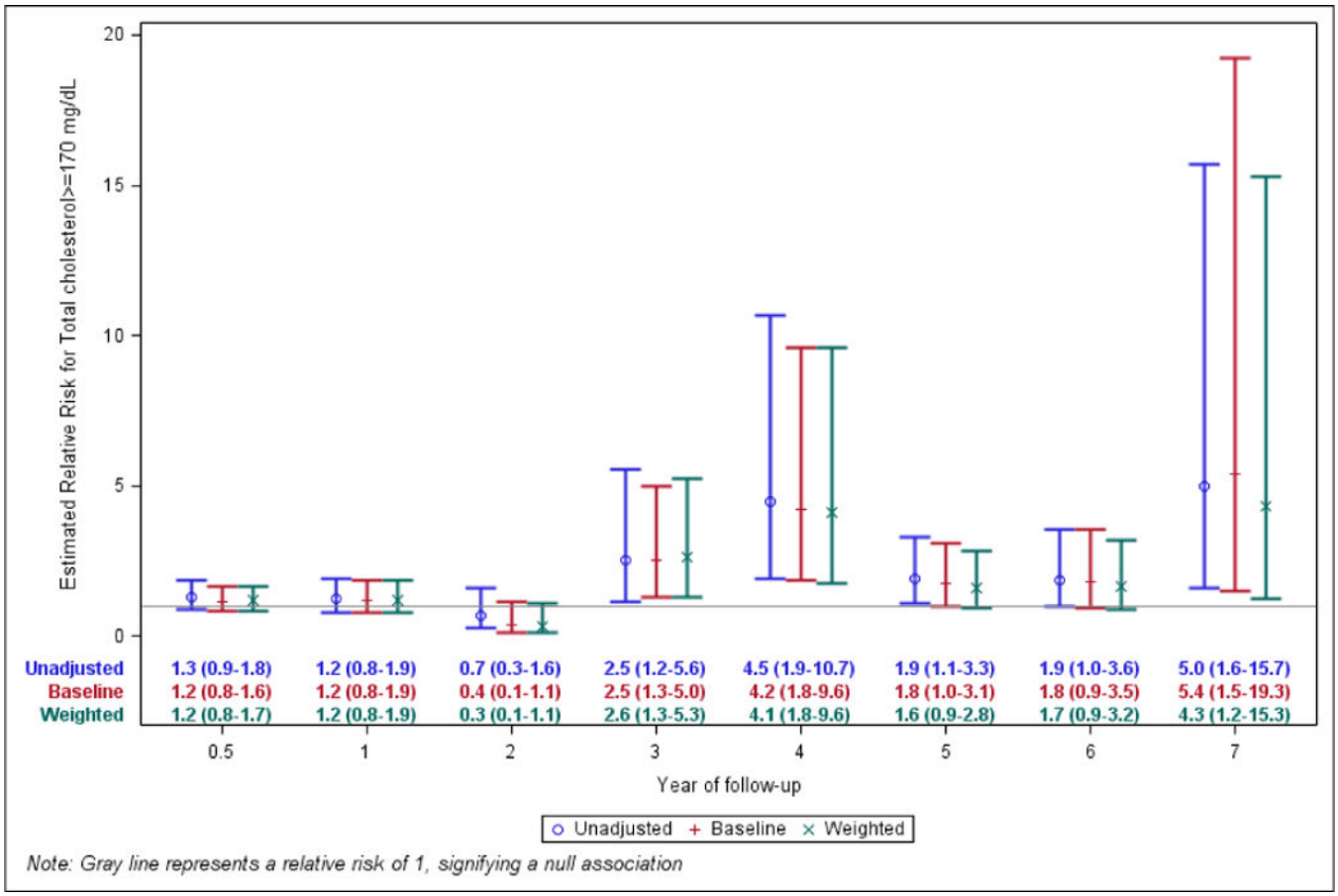

Figure 3.

Estimated relative risks (95% confidence interval) for total cholesterol ≥170 mg/dL comparing lopinavir/ritonavir- to nevirapine-based regimens by year of follow-up and model.

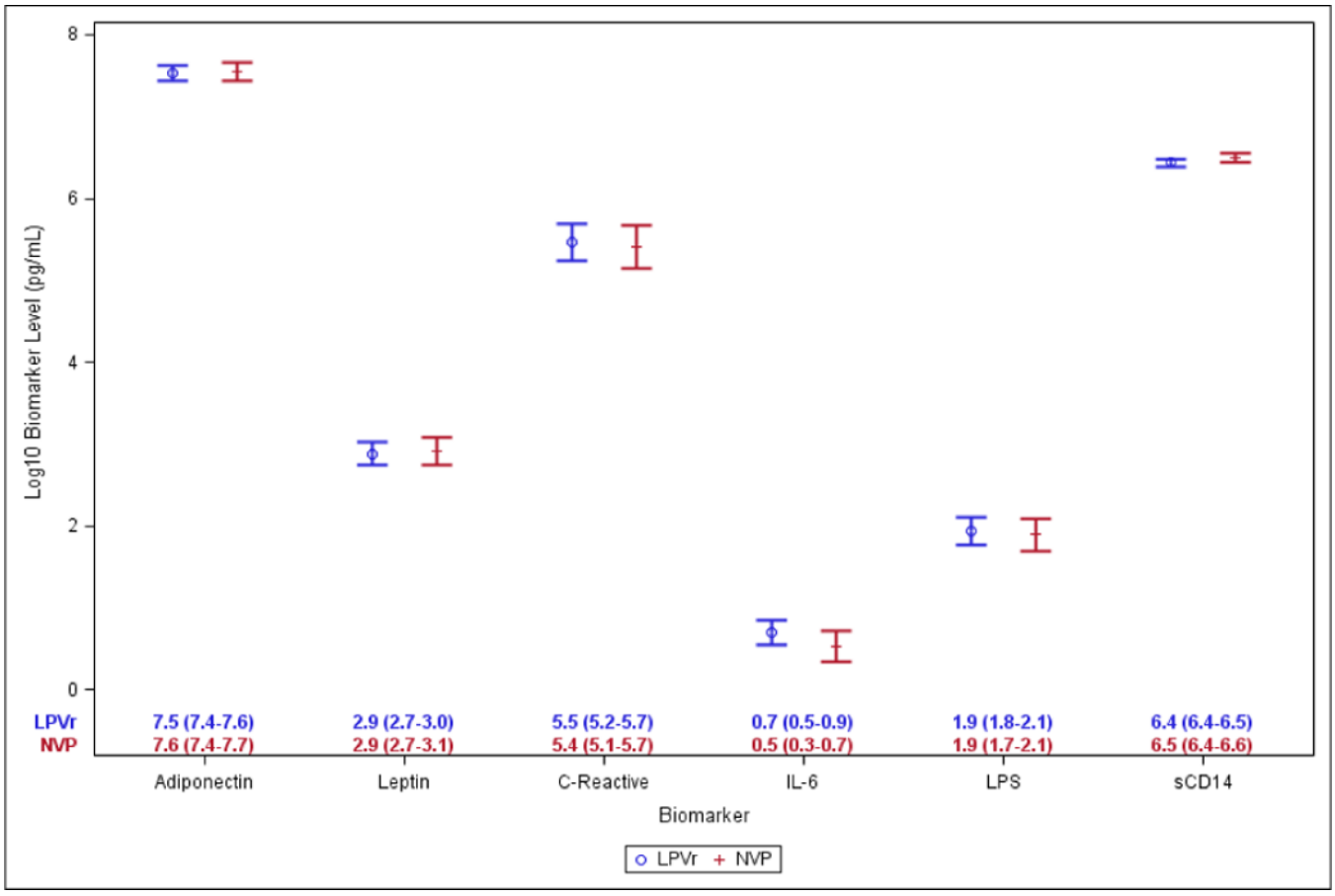

Figure 4.

Least squares mean biomarkers levels (95% confidence intervals) by randomized treatment (LPVr, lopinavir/ritonavir; NVP, nevirapine).

Table 1.

Baseline sociodemographic and clinical characteristics of study population overall and by randomized treatment arm.

Characteristic		Total (N=449)	Randomized treatment LPV/r/ZDV/3TC (N=222)	NVP/ZDV/3TC (N=227)
Age (years)	Median	1.2	1.2	1.2
	10%, 90%	0.5, 2.6	0.5, 2.5	0.5, 2.6
Male Sex		213 (47%)	110 (50%)	103 (45%)
Country	India	16 (4%)	4 (2%)	12 (5%)
	Malawi	37 (8%)	20 (9%)	17 (8%)
	S Africa	213 (47%)	101 (45%)	112 (49%)
	Tanzania	16 (4%)	7 (3%)	9 (4%)
	Uganda	45 (10%)	24 (11%)	21 (9%)
	Zambia	38 (8%)	22 (10%)	16 (7%)
	Zimbabwe	84 (19%)	44 (20%)	40 (18%)
Breast-fed		265 (59%)	134 (60%)	131 (58%)
CD4%	Median	16.3	16.6	16
	10%, 90%	9.0, 28.0	8.0, 28.1	9.1, 27.1
	<15	186 (41%)	90 (41%)	96 (42%)
	15-<25	188 (42%)	91 (41%)	97 (43%)
	≥25	75 (17%)	41 (18%)	34 (15%)
Plasma HIV RNA (log_{10} copies/mL)	Median	5.8	5.8	5.8
	10%, 90%	4.8, 6.0	4.8, 6.0	4.9, 6.0
WHO Disease Stage	1	79 (18%)	43 (19%)	36 (16%)
	2	98 (22%)	49 (22%)	49 (22%)
	3	233 (52%)	115 (52%)	118 (52%)
	4	39 (9%)	15 (7%)	24 (10%)
WHO Height-for-age z-score	Median	-2.3	-2.2	-2.4
	10%, 90%	-4.2, −0.2	-4.2, −0.3	-4.3, −0.2
WHO Weight-for-age z-score	Median	-1.6	-1.6	-1.5
	10%, 90%	-3.7, 0.3	-3.5, 0.2	-3.7, 0.4
Total cholesterol (mg/dL, non-fasting)	Median	104	108	100.5
	10%, 90%	69, 146.9	73.9, 146.9	61.9, 143.1
	<170	432 (96%)	212 (95%)	220 (97%)
	170–199	11 (2%)	4 (2%)	7 (3%)
	≥200	6 (1%)	6 (3%)	0 (0%)
Triglycerides (mg/dL, non-fasting)	Median	151	154.6	150.6

Characteristic		Total (N=449)	Randomized treatment LPV/r/ZDV/3TC (N=222)	NVP/ZDV/3TC (N=227)
	10%, 90%	80, 286.1	87.0, 309.1	74.4, 270.1
	≤150	219 (49%)	106 (48%)	113 (50%)
	>150	230 (51%)	116 (52%)	114 (50%)
In P1060 Version 5.0[1]		347 (77%)	175 (79%)	172 (76%)

LPV/r, lopinavir/ritonavir; ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; WHO, World Health Organization

[1]P1060 Version 5.0 is the prospective cohort study that followed the end of the P1060 randomized trials.