Published in final edited form as:
*Pediatr Infect Dis J*. 2014 August ; 33(8): 846–854. doi:10.1097/INF.0000000000000337.

# Predictors of Virologic and Clinical Response to Nevirapine versus Lopinavir/Ritonavir-Based Antiretroviral Therapy in Young Children with and without Prior Nevirapine Exposure for the Prevention of Mother-To-Child HIV Transmission

**Jane C. Lindsey, ScD**[1], **Michael D. Hughes, PhD**[1], **Avy Violari, MD**[2], **Susan H. Eshleman, MD, PhD**[3], **Elaine J. Abrams, MD**[4], **Mutsa Bwakura-Dangarembizi, MD**[5], **Linda Barlow-Mosha, MD**[6], **Portia Kamthunzi, MD**[7], **Pauline M. Sambo, MMed**[8], **Mark F. Cotton, MMed**[9], **Harry Moultrie, MD**[10], **Sandhya Khadse, MD**[11], **Werner Schimana, MD**[12], **Raziya Bobat, MD**[13], **Bonnie Zimmer, BS**[14], **Elizabeth Petzold, PhD**[15], **Lynne M. Mofenson, MD**[16], **Patrick Jean-Philippe, MD**[17], **Paul Palumbo, MD**[18], and **for the P1060 Study Team**

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA USA [2]University of Witwatersrand, Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Johannesburg, S Africa [3]Johns Hopkins University School of Medicine, Baltimore, MD USA [4]ICAP, Mailman School of Public Health and College of Physicians & Surgeons, Columbia University, NY, NY USA [5]Department of Paediatrics and Child Health, University of Zimbabwe College of Health Sciences, Harare, Zimbabwe [6]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda [7]University of North Carolina Project, Lilongwe, Malawi [8]University Teaching Hospital, Lusaka, Zambia [9]Tygerberg Children's Hospital, Stellenbosch University, Tygerberg, S Africa [10]University of the Witwatersrand Reproductive Health and HIV Institute, Faculty of Health Sciences, Johannesburg, S Africa [11]Department of Pediatrics, BJ Medical College and Sassoon General Hospital, Pune, India [12]Duke University-Kilimanjaro Christian Medical Center Collaboration, Moshi, Tanzania [13]Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, S Africa [14]Frontier Science and Technology Research Foundation, Amherst, NY, USA [15]Social and Scientific Systems, Durham, NC, USA [16]Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville MD USA [17]HJF-DAIDS, a Division of The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Contractor to NIAID, NIH, DHHS, Bethesda, MD, USA [18]Geisel School of Medicine at Dartmouth, Division of Infectious Diseases and International Health, One Medical Center Drive, Lebanon, NH 03756, USA

## Abstract

**Corresponding author and reprint requests:** Jane C Lindsey, ScD, Center for Biostatistics in AIDS Research, Harvard School of Public Health, 651 Huntington Ave, Boston, MA 02115 lindsey@sdac.harvard.edu Phone: 617 432-2812 FAX: 617 432-2843.

**Meetings where previously presented:** 19th Conference on Retroviruses and Opportunistic Infections in Seattle WA in March 2012 (Paper 25).

**P1060 ClinicalTrials.gov number:** NCT00307151

**Background—**In a randomized trial comparing nevirapine (NVP)- versus lopinavir/ritonavir (LPV/r)– based antiretroviral therapy (ART) in HIV-infected children (primary endpoint discontinuation of study treatment for any reason or virologic failure (VF) by week 24) aged two months to three years, we assessed whether clinical, virologic, immunologic and safety outcomes varied by prior single-dose NVP exposure (PrNVP) for prevention of mother-to-child HIV transmission and other covariates.

**Methods—**Efficacy was assessed by time to ART discontinuation or VF, VF/death, and death; safety by time to ART discontinuation due to a protocol-defined toxicity and first ≥grade 3 adverse event; immunology and growth by changes in CD4%, weight/height WHO z-scores from entry to week 48. Cox proportional hazards and linear regression models were used to test whether treatment differences depended on PrNVP exposure and other covariates.

**Results—**Over a median follow-up of 48 (PrNVP) and 72 (No PrNVP) weeks, there was no evidence of differential treatment effects by PrNVP exposure or any other covariates. LPV/r – based ART was superior to NVP-based ART for efficacy and safety outcomes but those on NVP had larger improvements in CD4%, weight and height z-scores. Lower pre-treatment CD4% and higher HIV-1 RNA levels were associated with reduced efficacy, lower pre-treatment CD4% with shorter time to ART discontinuation due to a protocol-defined toxicity, and no PrNVP with shorter time to first grade ≥3 adverse event.

**Conclusions—**Differences between LPV/r and NVP ART in efficacy, safety, immunologic and growth outcomes did not depend on PrNVP exposure, prior breastfeeding, sex, HIV-1 subtype, age, pre-treatment CD4%, HIV-1 RNA or WHO disease stage. This finding should be considered when selecting an ART regimen for young children.

## Keywords

pediatrics; antiretroviral therapy; clinical trials; Africa; prevention of mother-to-child transmission

---

Administration of single dose nevirapine (sdNVP) to mothers at delivery and to their newborns for prevention of mother to child HIV transmission (PMTCT) significantly decreases transmission risk.[1,2] However even a single dose of NVP can induce non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance which can persist for more than six months.[3] Recent trials therefore evaluated whether the effectiveness of NVP-based versus protease inhibitor-based antiretroviral therapy (ART) might differ according to prior single dose NVP exposure in both mothers[4, 5] and children.[6,7] Both trials included cohorts who had received sdNVP at least 6 months before enrollment (PrNVP) and who had no prior exposure (no PrNVP); both randomized participants to either NVP- or lopinavir/ritonavir (LPV/r) – based ART. ACTG 5208 demonstrated that NVP-based ART was inferior to LPV/r-based ART in mothers with PrNVP[4], but the two regimens had similar efficacy in previously unexposed mothers[5]. In contrast, IMPAACT P1060 found that NVP-based ART was inferior in young children regardless of PrNVP[6,7]. This finding in children without NVP exposure has major implications since LPV/r is more expensive, the liquid formulation requires refrigeration, and it is less palatable than NVP.[8] Our objectives were to investigate whether the differences between NVP- and LPV/r-based ART observed in children with PrNVP differed significantly from those with no PrNVP, identify other predictors of

virologic and clinical response, and determine whether treatment differences depended on these other predictors.

# METHODS

## Study design, population and intervention

The study included two parallel, randomized trials in HIV-infected children two months to three years of age who had (Cohort I) and had not (Cohort II) been exposed to sdNVP for PMTCT[6]. Children at ten sites in Africa (9) and India (1) were randomized to either NVP/ZDV/3TC or LPV/r/ZDV/3TC. Results comparing rates of treatment failure in each Cohort have been reported previously.[6,7] An additional study objective was to compare treatment failure rates between the two Cohorts and determine whether PrNVP use affected efficacy of either regimen by testing for a treatment by Cohort interaction.

The study opened to accrual in November 2006. NVP was started at a dose of 4 mg/kg once daily (observed median [$10^{th}$, $90^{th}$ percentiles] dose of 81 [62, 92] mg/$m^2$/dose) and increased after 14 days to 7 mg/kg twice daily. In September 2007 the dose of NVP was increased to conform to new World Health Organization (WHO[9]) guidelines (160–200 mg/$m^2$ once daily for 14 days, observed median of 217 [196, 237] mg/$m^2$/dose, and then increased to 160–200 mg/$m^2$ twice daily).

On the study's second full review by an independent Data Safety Monitoring Board (DSMB) (April 20, 2009), a recommendation to close Cohort I to accrual was made due to the superiority of the LPV/r -based treatment but to continue enrollment to Cohort II. This analysis uses follow-up of children with PrNVP exposure through April 20, 2009 and of unexposed children through October 27, 2010 (the date the DSMB recommended releasing the Cohort II results). Median ($10^{th}$, $90^{th}$ percentile) follow-up in the PrNVP cohort was 48 (4, 96) weeks with one third of participants having less than 24 weeks follow-up, compared to 72 (24, 156) weeks in the no PrNVP cohort. Loss-to-follow-up rates (excluding deaths) were less than 7%.

## Outcomes

Efficacy outcomes included (i) discontinuation of study treatment (NVP or LPV/r) for any reason or virologic failure (VF) by week 24 (the primary study outcome) (ii) discontinuation of study treatment for any reason or VF throughout follow-up, (iii) VF/death throughout follow-up and (iv) death throughout follow-up. VF was defined as a confirmed plasma HIV-1 RNA level <1 $\log_{10}$ copies/ml below the last pre-treatment value at 12 to 24 weeks or a confirmed HIV-1 RNA > 400 copies/ml at 24 weeks or a confirmed viral rebound to >4000 copies/ml after 24 weeks. Safety outcomes were (i) discontinuation of NVP or LPV/r due to a protocol-defined toxicity (reasons listed in Table 1, Supplemental Digital Content) and (ii) first grade ≥3 laboratory value, sign, or symptom while on NVP or LPV/r. Growth and immunologic response was assessed using changes from baseline to week 48 in weight and height WHO[10] z-scores and CD4%.

## Statistical Methods

There was intensive effort to determine whether children or their mothers had PrNVP exposure, including review of medical records and child health cards, determination of when sdNVP was first locally available, or if the child was born before the mother had been found to be HIV-infected. Only 23% of children in Cohort I and 14% in Cohort II had PrNVP exposure determined only by "verbal report deemed to be highly reliable by the study nurse". Despite this, four children were identified after randomization as being incorrectly assigned to Cohort II. This analysis uses actual PrNVP exposure rather than Cohort assignment and is restricted to children who started study treatment.

Pre-treatment characteristics were compared by PrNVP exposure using Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. HIV-1 subtype was available for 412 of the 451 children and otherwise imputed by the dominant regional subtype (not C in Tanzania and Uganda and C at other sites). Cumulative incidence of components of the primary study outcome (virologic failure, off study treatment or death by 24 weeks) were estimated using methods for competing risks[11].

Models were fit with randomized ART regimen (TRT), PrNVP and a term for their interaction. Cox proportional hazards models were used for time-to-event outcomes and linear regression for changes from baseline in growth and CD4%. A statistically significant interaction term would imply the difference between ART regimens varied by PrNVP exposure. Since PrNVP exposure versus no exposure was not a randomized comparison, the interaction of TRT and PrNVP exposure could be confounded by differences between the exposed and non-exposed children in other pre-treatment characteristics. To address this, models were fit adjusting for potential confounding variables, including prior breastfeeding (Yes/No), sex, HIV-1 subtype (C/Not C), age (years), and pre-treatment CD4%, HIV-1 RNA ($\log_{10}$ copies/ml) and WHO disease stage (I/II vs. III/IV). Separate models were fit with TRT, PrNVP and initial NVP dose, to evaluate whether any outcomes varied according to the starting NVP dose. Stepwise variable selection was used to identify predictors (main effects, two and three-way interactions) of each outcome. TRT and PrNVP were included in these models regardless of statistical significance. A model was then fit for each outcome using a common set of predictors that included any variable identified in the stepwise variable selection for at least one outcome. This was done for the safety, efficacy and CD4% outcomes as one group and the growth outcomes as a separate group. Model-predicted mean changes for children starting in each PrNVP exposure group on each treatment regimen at specified values of the covariates in the model were calculated for changes in CD4% and growth outcomes to help interpret the results of the linear regression models. Two-sided p-values are presented unadjusted for interim analyses and multiple comparisons. P1060 was designed and written by the Study Team and approved by the ethics committees at each site, the Ministries of Health, and institutional review boards of sites' partner institutions in the United States. Each child's parent or legal guardian provided written informed consent.

# RESULTS

## Baseline characteristics

Baseline characteristics by PrNVP exposure are shown in Table 1. The PrNVP group was dominated by South African children and participants were younger. Other sites started enrolling later and tended to enroll older children with more advanced HIV disease. Exposed children were also less likely to have been breastfed, and had higher median weight and height z-scores, HIV-1 RNA and CD4% (in the absence of treatment, both HIV-1 RNA and CD4%[12] decline between 6 and 18 months of age). They were more likely to have been enrolled when the study was using the lower NVP dose and had a higher prevalence of HIV-1 subtype C infection. Patterns of antiretroviral drug use in addition to sdNVP for PMTCT before study entry differed, with 44% of PrNVP exposed children receiving up to seven days of ZDV+ after birth (37% of their mothers received ZDV) compared to none (one mother) in the unexposed. Among children with resistance results, 19 of 156 (12%) PrNVP children had detectable NVP resistance at entry compared to five (2%) of the 253 children with no PrNVP (Table 2, Supplemental Digital Content).

## Treatment differences by PrNVP

Table 2 summarizes the number of primary endpoints, which component of the endpoint was met, and cumulative incidence estimates from a competing risk model (which protocol-defined toxicities were met are summarized in Table 3, Supplemental Digital Content). Rates of the composite endpoint and the virologic failure, death, and protocol-defined toxicities components were two to three times higher in the NVP arm in both exposure groups and comparable for going off study treatment for any other reason.

Figure 1 demonstrates similar separation between treatments in both exposure groups for all safety and efficacy outcomes. There was no statistically significant evidence that the differences between treatments varied by exposure (i.e. no statistically significant interactions between treatment and PrNVP exposure). Hazard ratios for treatment effects were comparable in unadjusted and adjusted models (Figure 2), despite the differences in age, history of breastfeeding, HIV-1 subtype and HIV disease status by PrNVP. For the primary study endpoint, the unadjusted hazard ratio (95% confidence interval) for failure for NVP versus LPV/r was 1.8 (1.0–3.4) in children with PrNVP and 2.6 (1.6, 4.2) in those with no PrNVP (interaction p=0.35). Hazard ratios were similar in analyses adjusted for all covariates. Across all outcomes, LPV/r-based ART was superior to NVP-based ART in both exposure groups with estimated hazard ratios for NVP versus LPV/r greater than one. Results were similar for changes to week 48 in CD4%, weight and height z-scores (Figure 3, interaction p>0.29 for all unadjusted and adjusted analyses).

To evaluate whether outcomes varied according to starting NVP dose, models were fit with TRT, PrNVP, initial NVP dose, and a TRT by NVP dose interaction, but no interactions were statistically significant. Among children randomized to the NVP arm, 45 of 84 (54%) in the PrNVP group and 31 of 145 (21%) in the no PrNVP group started at the lower NVP dose, but since the dose was increased relatively early in study conduct, only 34% of follow-

up in the PrNVP group and 10% in the no PrNVP group was under the lower NVP dose, so the power to detect other than large effects for NVP dose was low.

### Predictors of outcomes

Results for the two final models are shown in Table 3. There was no statistically significant evidence that differences between treatments varied with level of any other predictor. The final model presented for the efficacy and safety outcomes included TRT, PrNVP and pre-treatment CD4% and $\log_{10}$ HIV-1 RNA. Lower CD4% and higher viral loads increased hazards for some efficacy and safety outcomes. Notably, age was not associated with any efficacy or safety outcome so was not included in the final model. The final model for changes in weight and height z-scores included TRT, PrNVP, screening CD4%, entry age and WHO disease category.

**Efficacy—**Treatment was a significant predictor for all outcomes (except p=0.06 for time to death), with shorter times to event in the NVP arm. Lower CD4% predicted shorter time to the combined treatment discontinuation/VF outcomes and death, but not the VF/death outcome. Higher HIV-1 RNA was at least marginally significantly ($p<0.09$) associated with shorter time to all outcomes except death. PrNVP was not a significant predictor of any outcome.

There were 14 deaths in the NVP arm and six in the LPV/r arm, 13 (ten on NVP-based ART and three on LPV/r-based ART) of which occurred within 12 weeks of starting treatment. None of the deaths were assessed as related to study treatment (Table 4, Supplemental Digital Content).

**Safety—**NVP-based ART was a marginally significant predictor of shorter time to the safety outcomes ($p \leq 0.08$), but no PrNVP exposure was the strongest predictor of shorter time to a grade ≥3 abnormal lab, sign or symptom ($p<0.001$). Neutropenia (n=100), fever (n=24) and anemia (n=12) were the first grade ≥3 safety event in at least ten children. These types of events occurred at significantly higher rates in children with no PrNVP (neutropenia: 26.2% vs. 15.5%, p=0.008; anemia: 3.9% vs. 0.6%, p=0.036; fever: 8.1% vs. 0.6%, p=0.001). Because of the differences in characteristics between infants with and without PrNVP exposure (Table 1), stepwise variable selection was also performed without including PrNVP exposure to explore possible confounding of association with PrNVP exposure. Without PrNVP exposure in the model, prior breastfeeding, non-C HIV-1 subtype, female sex and locations other than S Africa were associated with shorter time to first grade ≥3 safety event. It was not possible therefore to disentangle whether lack of PrNVP exposure or these other factors were causally associated with reduced time to a grade ≥3 safety event. Lower CD4% was also a predictor of shorter time to discontinuation of NVP or LPV/r due to protocol-mandated reasons.

**Immunology—**Screening CD4% and treatment were significantly associated with changes in CD4% to week 48, with HIV-1 RNA also marginally significant. Among children with PrNVP exposure (median CD4% at entry: 19.1% and median HIV-1 RNA: >750,000 copies/ml), the model predicted a mean increase in CD4% by week 48 of 15.3 percentage points on

NVP-based ART versus 13.7 percentage points on LPV/r-based ART. With no PrNVP (starting from a lower median CD4% at entry (14.9%) and a lower median HIV-1 RNA (514,000 copies/ml)), mean increases were 16.0 percentage points on NVP-based ART versus 14.4 percentage points on LPV/r-based ART - in both cohorts treatment differences of less than 2 percentage points.

**Growth—**Screening weight and height, treatment, age and WHO disease stage were all at least marginally ($p \leq 0.05$) significant predictors of changes in growth z-scores to week 48. Using median entry age and weight or height z-score (see Table 1), the regression models predicted mean weight z-score increases of 0.57 units on NVP-based ART and 0.29 units on LPV/r-based among children with PrNVP exposure and 0.93 units on NVP-based ART compared to 0.65 units on LPV/r-based ART among those with no PrNVP. For height, the models predicted mean decreases in height z-scores of 0.11 units on the NVP arm and 0.31 units on the LPV/r arm in children with PrNVP exposure compared to increases in children with no PrNVP exposure of 0.64 units on NVP-based ART and 0.45 units among children on LPV/r-based ART. For both exposure groups, changes in growth were superior on the NVP treatment arm by about 0.3 z-score. Children with less impaired growth at study entry and less advanced HIV disease improved less after starting treatment than those with more impaired growth. Age had an opposite effect on changes in height and weight z-scores with older children having smaller increases in weight but larger increases in height.

## DISCUSSION

The results of P1060 in young children were surprising as the study team had anticipated larger differences between LPV/r and NVP in children with PrNVP compared with no PrNVP exposure based on the possibility of archived low-level NVP-resistant virus among children with PrNVP. Analyses presented here showed no evidence of statistically significant differential treatment responses by PrNVP exposure for any outcomes in unadjusted analyses. Imbalances in pre-treatment characteristics by PrNVP exposure could bias conclusions. However, after adjusting for sex, age, prior breastfeeding, HIV-1 subtype and HIV disease status at study entry, there was still no evidence of differential treatment responses by PrNVP. NVP-based ART consistently performed worse than LPV/r-based ART for efficacy and safety outcomes, but was superior to LPV/r-based ART for improving mean CD4% (by about 2 percentage points) and weight and height z-scores (by about 0.3 units) through 48 weeks. It is important to note that NVP-based ART still provided substantial benefit and was relatively safe.

Observed differences in outcomes by treatment were not associated with the presence of NVP resistance at entry since significant differences were observed among the 88% of children with prior sdNVP exposure but with no detectable resistance at entry and among the children with no PrNVP exposure (results not shown). In contrast to initial hypotheses, pre-existing resistance to NVP through sdNVP exposure at birth was not the major factor driving the superior performance of LPV/r treatment.

Pre-treatment CD4% or HIV-1 RNA were predictors of some efficacy and safety outcomes as also demonstrated in previous studies[13–15] with lower baseline CD4% and higher HIV-1

RNA levels having higher hazards of adverse outcomes. Since both CD4% and HIV-1 RNA levels decline in the absence of treatment in this young age group and since the children in P1060 had to have survived without access to antiretrovirals long enough to participate in the study, it is difficult to extend these results into making recommendations for when ART should be initiated. Age and WHO disease stage were predictors of change in weight and height z-scores over 48 weeks of follow-up, but neither were predictors of the efficacy and safety outcomes.

No PrNVP exposure was associated with higher rates of toxicity. It is possible that children with PrNVP or ZDV exposure at birth who had suffered adverse events then, would be less likely to enroll in P1060, lowering the rates of safety events in this group. In addition, the PrNVP group, known to be HIV-exposed at birth, may have been on co-trimoxazole longer and have had more regular medical follow-up than the no PrNVP group, making the latter group more susceptible to adverse events. Analyses were conducted to investigate the effect of the higher NVP dose introduced early in the study, but there was no evidence that this was related to the treatment differences for any outcomes. Analyses were also conducted adjusting for baseline characteristics that differed by PrNVP group. This showed that PrNVP exposure was highly confounded with these factors, and hence it was not possible to determine which of these factors (or possibly other unmeasured confounders) might be causally associated with differences in toxicity rates between the PrNVP exposure groups. Regardless of which factors were included in the models however, the estimates and statistical significance of the differences between NVP- and LPV/r-based treatment changed minimally, with NVP having marginally significantly shorter times to toxicity events.

These analyses have a number of limitations, including relatively low power to detect differential treatment effects in the two exposure groups even under the original study design (576 children followed at least 24 weeks). This analysis used the final DSMB review databases for each cohort, when approximately one third of the 168 PrNVP-exposed children had not yet reached 24 weeks of follow-up, further reducing power to detect interactions. When analyses were repeated using all available follow-up until October 27, 2010 for the PrNVP exposure cohort, results were qualitatively the same: there was no evidence of any interactions between treatment and PrNVP or between treatment and any covariates found to be predictive of any outcome.

One hypothesis for the disappointing performance of NVP-based ART is the very high baseline viral loads in young children combined with standard NVP dosing which employs a ramp-up approach (low dose for the initial two weeks) to minimize NVP-associated rash. This may enhance the development of NVP resistance with associated high treatment failure rates. NVP was started at full dose in young children in the CHAPAS study[16] with relative safety and similar virologic outcomes versus a ramp-up approach. Both safety and pharmacokinetics are the subject of an ongoing IMPAACT trial. It is also possible that some children had baseline NVP resistance at levels below that detectable by the ViroSeq assay which uses a population sequencing methodology. Results from deep sequencing of the PrNVP-exposed children in P1060 indicate that presence of resistance at lower levels did not explain the inferior responses to NVP-based ART.[17]

The significantly inferior performance of NVP compared with LPV/r –based ART regarding the endpoint of virologic failure and death, the frequent detection of NVP resistance at failure, and the demonstrated inability of PrNVP exposure to inform the 'What to Start' decision, all argue for reconsideration of guidelines for choice of first-line therapy in young children in resource-limited settings. LPV/r has clear advantages but is far from a perfect choice, which underscores the urgent need for identification of new drugs and treatment regimens for HIV-infected infants and young children.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank Linda Millar, who was the data manager for the first four years of the study, the children, their families, and caregivers who agreed to participate in P1060, and the site clinical study teams.

**Conflicts of interest and source of funding:** Boehringer Ingelheim, Abbott and GlaxoSmithKline provided the antiretroviral agents used in the study. MD Hughes reports having been a paid member of clinical trial data monitoring committees for Boehringer Ingelheim, Medicines Development, Pfizer and Tibotec. SH Eshleman received an honorarium from Abbott Laboratories (distributor of the ViroSeq Genotyping System) in 2009 for an invited presentation at a symposium sponsored by Abbott Diagnostics and collaborates with investigators from Abbott Diagnostics on research studies. H Moultrie has conducted clinical trials for GlaxoSmithKline, ViiV Healthcare, and Tibotec in the last three years. However these were unrelated to the current publication. A Violari received an honorarium for a lecture at Abbott in 2009. For the remaining authors none were declared.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) [U01 AI068632] and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). This project was funded in part with Federal funds from the National Institute of Allergies and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272200800014C. This work was supported by the Statistical and Data Analysis Center at Harvard School of Public Health, under the NIAID cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group. The views expressed are solely the responsibility of the authors and do not necessarily reflect the official policies of the NIH or the U.S. Government nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. Some of the authors are U.S. government employees who must comply with the NIH Public Access Policy, and the authors or NIH will deposit, or have deposited, in NIH's PubMed Central archive, an electronic version of the final, peer-reviewed manuscript upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication.

## References

1. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother to child transmission of HIV-1 in Kampala, Uganda: 18 month follow-up of the HIVNET 012 randomized trial. Lancet. 2003; 362:859–68. [PubMed: 13678973]
2. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. N Engl J Med. 2000; 343:982–991. [PubMed: 11018164]
3. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS. 2001; 15:1951–1957. [PubMed: 11600822]
4. Lockman S, Hughes MD, McIntyre J, Zheng Y, Chipato T, Conradie F, et al. Antiretroviral therapies in women after single-dose nevirapine exposure. N Engl J Med. 2010 Oct 14; 363(16): 1499–509. [PubMed: 20942666]

5. McIntyre, J.; Hughes, M.; Mellors, J.; Zheng, Y.; Hakim, J.; Asmelash, A., et al. Efficacy of ART with NVP+TDF/FTC vs LPV/r+TDF/FTC among Antiretroviral-naïve Women in Africa: OCTANE Trial 2/ACTG A5208; Conference on Retroviruses and Opportunistic Infections; San Francisco CA. 2010.
6. Palumbo P, Lindsey JC, Hughes MD, Cotton MF, Bobat R, Meyers T, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. N Engl J Med. 2010; 363(16):1510–20. [PubMed: 20942667]
7. Violari A, Lindsey JC, Hughes MD, Mujuru HA, Barlow-Mosha L, Kamthunzi P, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012; 366(25):36–45.
8. Eley BS, Meyers T. Antiretroviral therapy for children in resource-limited settings: current regimens and the role of newer agents. Paediatr Drugs. 2011; 13:303–16. [PubMed: 21888444]
9. WHO Technical Reference Group. , editor. World Health Organization. WHO Antiretroviral Therapy for Infants and Children 2008. 2008.
10. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006.
11. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine. 2007; 26:2389–2430. [PubMed: 17031868]
12. Pediatric European Network for Treatment of AIDS (PENTA). HIV-1 viral load and CD4 cell count in untreated children with vertically acquired asymptomatic or mild disease. AIDS. 1998; 12:F1–F8. [PubMed: 9520161]
13. Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. J Infect Dis. 1997; 175(5): 1029–38. [PubMed: 9129063]
14. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. JAMA. 1998; 279(10):756–61. [PubMed: 9508151]
15. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: estimates according to CD4 percent, viral load, and age. Lancet. 2003; 362(9396): 1605–11. [PubMed: 14630440]
16. Mulenga V, Cook A, Walker AS, et al. Strategies for nevirapine initiation in HIV-infected children taking pediatric fixed-dose combination “baby pills” in Zambia: a randomized controlled trial. Clin Infect Dis. 2010; 51:1081–9. [PubMed: 20868279]
17. Persaud, D.; Lindsey, J.; Ziemniak, C.; Chen, Y.; Khaki, L.; Eshleman, S., et al. Association between nevirapine-resistant HIV-variants and antiretroviral treatment outcomes in single-dose nevirapine exposed infants; Poster presentation at International AIDS Conference; DC. July 2012;

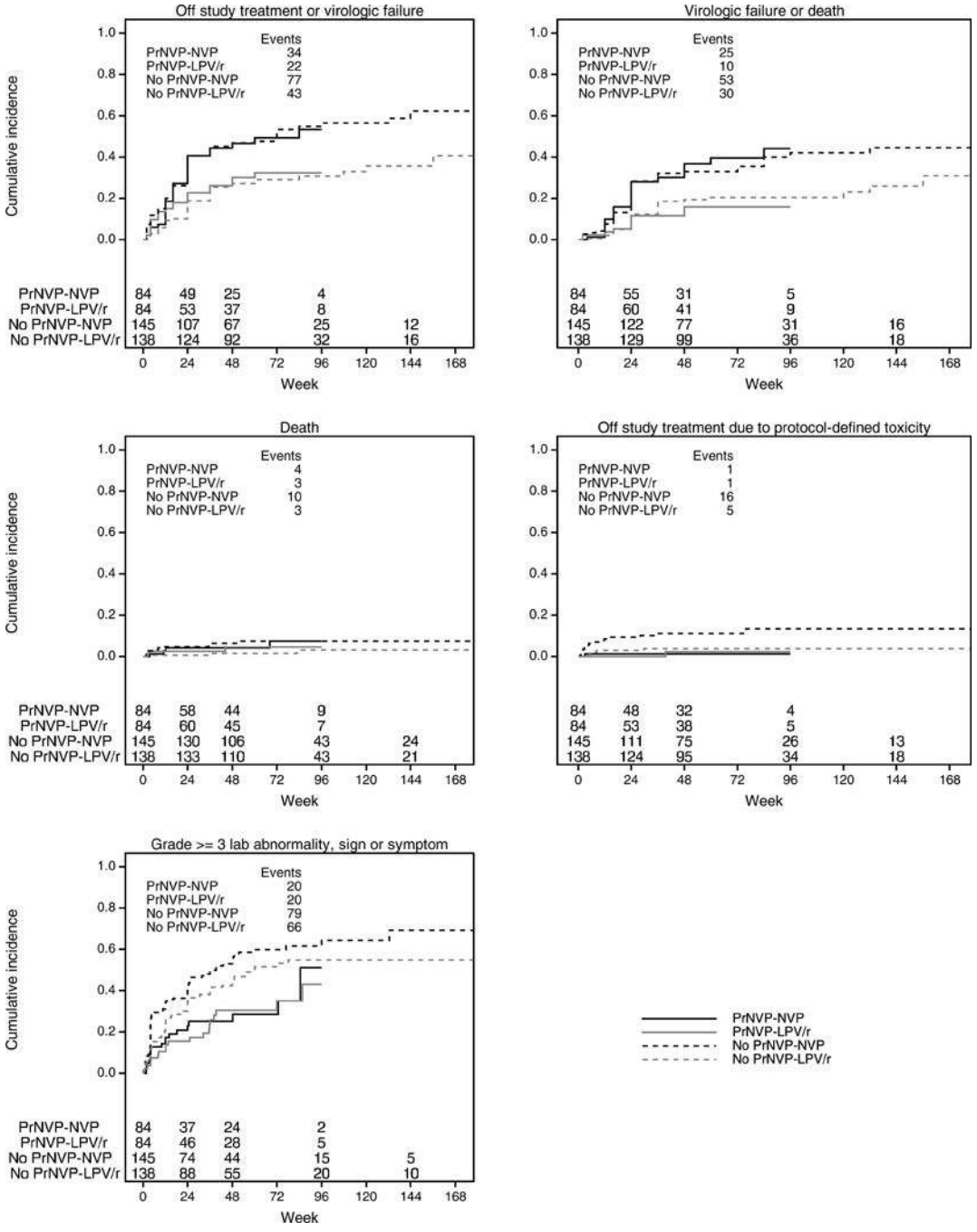


**Figure 1.**

Cumulative incidence over time of outcomes by randomized treatment for participants with and without prior single dose NVP exposure

PrNVP – trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine); LPV/r – lopinavir/ritonavir

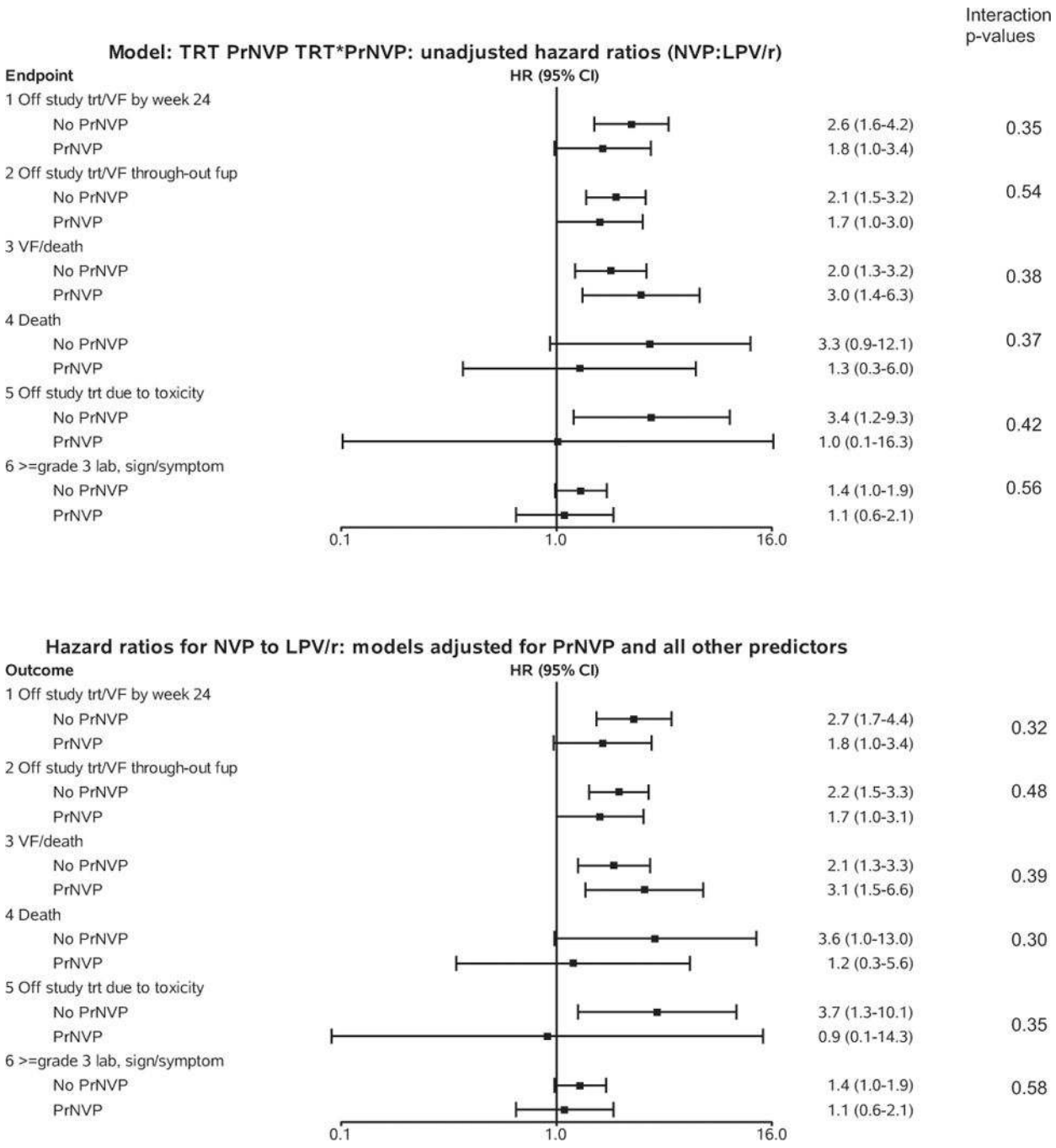


**Figure 2.**

Forest plot of hazard ratios for time to each efficacy and safety endpoint. Adjusted models included sex, HIV-1 subtype, age, prior breastfeeding, WHO category, CD4% and HIV-1 RNA at study entry

PrNVP – trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine); LPV/r – lopinavir/ritonavir; TRT – treatment; VF – virologic failure; HR – hazard ratio; CI – confidence interval

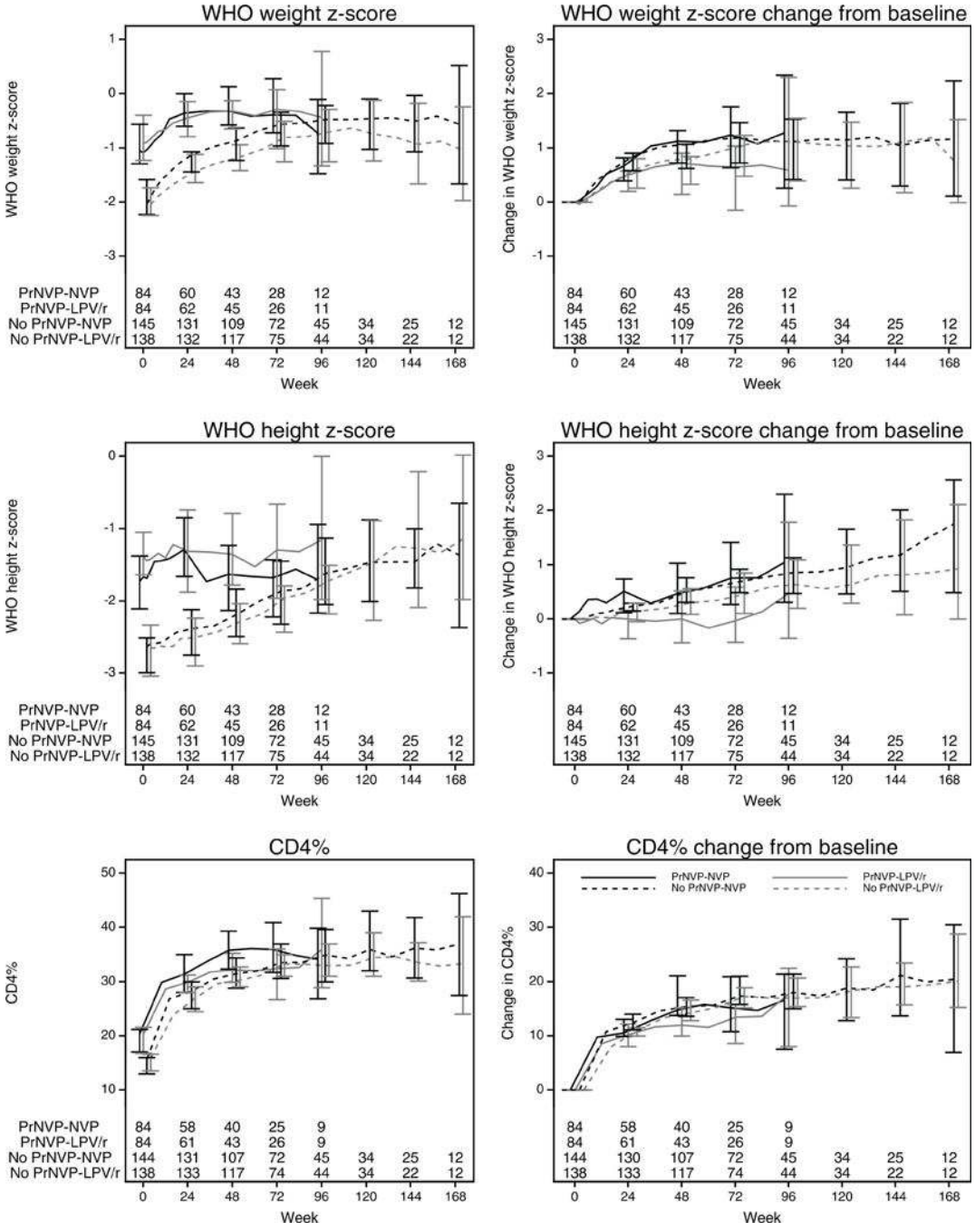


**Figure 3.**

Weight and height WHO z-scores and CD4% means (95% confidence intervals) by week (1st column) and changes from baseline (2nd column)

PrNVP – trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine); LPV/r – lopinavir/ritonavir; WHO – World Health Organization; Z – age and sex-adjusted z-score

## Table 1

Baseline characteristics by prior single dose nevirapine exposure

| | | PrNVP (n=168) | No PrNVP (n=283) | p-value[1] |
|---|---|---|---|---|
| Male | N (%) | 80 (48%) | 134 (47%) | 1.00 |
| Age (years): | Median (P10, P90) | 0.7 (0.5, 1.7) | 1.7 (0.6, 2.8) | <0.001 |
| < 1 | N (%) | 126 (75%) | 74 (26%) | <0.001 |
| 1–<2 | | 30 (18%) | 100 (35%) | |
| 2–<3 | | 12 (7%) | 109 (39%) | |
| Breastfed | N (%) | 36 (21%) | 231 (82%) | <0.001 |
| Lower NVP dose[5] | N (%) | 91 (54%) | 61 (22%) | <0.001 |
| BMI WHO Z[6] | Median (P10, P90) | −0.0 (−2.1, 1.8) | −0.3 (−2.6, 1.2) | <0.001 |
| Weight WHO Z[6] | Median (P10, P90) | −0.9 (−2.8, 0.8) | −2.0 (−3.8, −0.2) | <0.001 |
| Height WHO Z[6] | Median (P10, P90) | −1.6 (−3.3, 0.1) | −2.7 (−4.5, −0.5) | <0.001 |
| WHO Stage III/IV | N (%) | 96 (57%) | 178 (63%) | 0.23 |
| HIV-1 RNA (cp/ml) | Median (P10, P90) | >750,000 (143,000, >750,000) | 514,000 (56,500, >750,000) | <0.001 |
| <250,000 | N (%) | 29 (17%) | 92 (33%) | <0.001 |
| 250,000– ≤750,000 | | 45 (27%) | 76 (27%) | |
| >750,000[2] | | 94 (56%) | 115 (41%) | |
| CD4% (cells/mm$^3$) | Median (P10, P90)[3] | 19.1 (10.4, 30.7) | 14.9 (8.0, 25.2) | <0.001 |
| <15% | N (%) | 46 (27%) | 141 (50%) | <0.001 |
| 15–<25% | | 77 (46%) | 111 (39%) | |
| >=25% | | 45 (27%) | 30 (11%) | |
| HIV-1 Subtype C | N (%) | 160 (95%) | 227 (80%) | <0.001 |
| Country | N (%) | | | |
| S Africa | | 140 (83%) | 73 (26%) | <0.001[4] |
| Malawi | | 2 (1%) | 36 (13%) | |
| Zambia | | 6 (4%) | 32 (11%) | |
| Uganda | | 5 (3%) | 40 (14%) | |
| Zimbabwe | | 13 (8%) | 71 (25%) | |
| India | | 0 (0%) | 16 (6%) | |
| Tanzania | | 2 (1%) | 15 (5%) | |

[1] Fishers exact test for categorical and Wilcoxon for continuous characteristics

[2] Upper limit of quantification for HIV-1 RNA of 750,000 copies/ml

[3] No PrNVP: N=282

[4] S Africa vs. other countries combined

[5] Protocol version 1.0 lower NVP dose 4 mg/kg once daily increased after 14 days to 7 mg/kg twice daily. Protocol version 2.0 higher NVP dose 160–200 mg/$m^2$ once daily for 14 days increased to 160–200 mg/$m^2$ twice daily.

[6] World Health Organization (WHO) Body Mass Index (BMI), weight and height - for - age z-scores

Abbreviations:

- PrNVP - trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine)
- P10, P90 - $10^{th}$ and $90^{th}$ percentiles of distribution
- BMI -Body Mass Index
- WHO - World Health Organization
- Z - age and sex-adjusted z-score

**Table 2**

Number of primary endpoints by type (estimated cumulative incidence at week 24)

| Cohort | Treatment | Total | Endpoint | Treatment discontinuation due to toxicity as required in the protocol | Treatment discontinuation for other reasons | Virologic failure | Death |
|---|---|---|---|---|---|---|---|
| PrNVP | NVP | 84 | 29 (40.7%) | 1 (1.3%) | 12 (16.4%) | 13 (18.9%) | 3 (4.1%) |
| | LPV/r | 84 | 17 (22.6%) | 0 (0.0%) | 11 (14.2%) | 4 (6.0%) | 2 (2.4%) |
| No PrNVP | NVP | 145 | 59 (40.7%) | 12 (9.0%) | 10 (6.2%) | 30 (20.7%) | 7 (4.8%) |
| | LPV/r | 138 | 26 (18.8%) | 4 (3.6%) | 9 (5.8%) | 12 (8.7%) | 1 (0.7%) |

Abbreviations:

- PrNVP - trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine)

*Pediatr Infect Dis J*. Author manuscript; available in PMC 2015 August 01.

## Table 3

Final models from variable selection: Estimate (95% confidence interval) [p-value]

| **Time to: HR (95% CI) [p-value]** | **Treatment (NVP:LPV/r)** | **PrNVP exposure (Yes:No)** | **CD4% (per 10% increase)** | **HIV-1 RNA (per 1 $\log_{10}$ cp/ml increase)** |
|---|---|---|---|---|
| Efficacy: Primary endpoint: Off treatment or VF by week 24 | 2.33 (1.59, 3.40) [<0.001] | 1.13 (0.76, 1.68) [0.56] | 0.75 (0.57, 0.98) [0.035] | 1.49 (0.96, 2.33) [0.08] |
| Efficacy: Secondary endpoint: Off treatment or VF through-out follow-up | 2.05 (1.49, 2.82) [<0.001] | 1.09 (0.76, 1.55) [0.64] | 0.75 (0.59, 0.94) [0.015] | 1.54 (1.05, 2.26) [0.026] |
| Efficacy: Secondary endpoint: VF/Death through-out follow-up | 2.29 (1.54, 3.39) [<0.001] | 1.00 (0.65, 1.55) [0.99] | 0.80 (0.61, 1.06) [0.13] | 1.48 (0.94, 2.32) [0.09] |
| Efficacy: Death | 2.48 (0.95, 6.48) [0.06] | 1.41 (0.53, 3.75) [0.49] | 0.35 (0.16, 0.79) [0.011] | 2.50 (0.55, 11.41) [0.24] |
| Safety: Off treatment due to protocol defined toxicity | 3.17 (1.24, 8.09) [0.016] | 0.26 (0.06, 1.17) [0.08] | 0.39 (0.18, 0.83) [0.015] | 0.93 (0.43, 2.01) [0.86] |
| Safety: First grade ≥3 lab, sign or symptom on randomized treatment | 1.30 (0.97, 1.74) [0.08] | 0.51 (0.35, 0.73) [<0.001] | 1.00 (0.82, 1.22) [0.99] | 0.95 (0.73, 1.23) [0.68] |

| **Change to week 48: Estimate (95% CI) [p-value]** | | | | | **Screening value** | **Age (years)** | **WHO (I/II:III/IV)** |
|---|---|---|---|---|---|---|---|
| Immunologic: CD4% | 1.62 (−0.16, 3.40) [0.023] | 0.21 (−1.98, 2.40) [0.85] | −0.26 (−0.38, −0.14) [<0.001] | 1.49 (−0.06, 3.04) [0.06] | | | |
| Growth: Weight z-score | 0.29 (0.10, 0.47) [0.003] | 0.12 (−0.12, 0.36) [0.32] | | | −0.40 (−0.47, −0.34) [<0.001] | −0.20 (−0.34, −0.07) [0.003] | −0.40 (−0.60, −0.20) [0.001] |
| Growth: Height z-score | 0.19 (0.00, 0.38) [0.046] | 0.27 (0.03, 0.50) [0.031] | | | −0.30 (−0.36, −0.24) [<0.001] | 0.16 (0.02, 0.30) [0.022] | −0.20 (−0.40, −0.00) [0.05] |

Abbreviations:

- PrNVP - trial participants who had received single dose nevirapine (NVP) at least 6 months before enrollment to P1060 (No PrNVP had never received nevirapine)
- HR -hazard ratio
- CI -confidence interval
- NVP -nevirapine; LPV/r -lopinavir/ritonavir

- VF -virologic failure