MAJOR ARTICLE

HIV/AIDS

Nevirapine- Versus Lopinavir/Ritonavir-Based Antiretroviral Therapy in HIV-Infected Infants and Young Children: Long-term Follow-up of the IMPAACT P1060 Randomized Trial

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Background. The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1060 study demonstrated short-term superiority of lopinavir/ritonavir (LPV/r) over nevirapine (NVP) in antiretroviral therapy (ART), regardless of prior NVP exposure. However, NVP-based ART had a marginal benefit in CD4 percentage (CD4%) and growth. We compared 5-year outcomes from this clinical trial.

Methods. Human immunodeficiency virus (HIV)–infected, ART-eligible children were enrolled into 2 cohorts based on prior NVP exposure and randomized to NVP- or LPV/r-based ART. The data safety monitoring board recommended unblinding results in both cohorts due to superiority of LPV/r for the primary endpoint: stopping randomized treatment, virologic failure (VF), or death by 6 months. Participants were offered a switch in regimens (if on NVP) and continued observational follow-up. We compared time to VF or death, death, and CD4% and growth changes using intention-to-treat analyses. Additionally, inverse probability weights were used to account for treatment switching and censoring.

Results. As of September 2014, 329 of the 451 (73%) enrolled participants were still in follow-up (median, 5.3 years; interquartile range [IQR], 4.3–6.4), with 52% on NVP and 88% on LPV/r as originally randomized. NVP arm participants had significantly higher risk of VF or death (adjusted hazard ratio [aHR], 1.90; 95% confidence interval [CI], 1.37–2.65) but not death alone (aHR, 1.65; 95% CI, .72–3.76) compared with participants randomized to LPV/r. Mean CD4% was significantly higher in the NVP arm up to 1 year after ART initiation, but not beyond. Mean weight-for-age *z* scores were marginally higher in the NVP arm, but height-for-age *z* scores did not differ. Similar trends were observed in sensitivity analyses.

Conclusions. These findings support the current World Health Organization recommendation of LPV/r in first-line ART regimens for HIV-infected children.

Clinical Trials Registration. NCT00307151.

Keywords. HIV/AIDS; antiretroviral therapy; pediatrics; long-term follow-up.

Without intervention, more than half of human immunodeficiency virus (HIV)–infected children in resource-limited countries experience rapid disease progression and die by 2 years of age [1]. Early initiation of antiretroviral therapy (ART) in children reduces the risk of severe morbidity and mortality by 75% [2]. The World Health Organization (WHO) currently recommends universal ART for all HIV-infected individuals, including children <10 years of age, regardless of immunologic status [3]. Fully implemented, this simplified treatment approach will increase coverage in settings where pediatric HIV burden is highest.

Key advances in clinical research, policy, and implementation have fueled efforts toward prevention of mother-to-child HIV transmission (PMTCT) globally [4]. New pediatric HIV infections have declined dramatically; however, children who acquire HIV often do so while exposed to antiretroviral drugs. The development of antiretroviral drug resistance with failed PMTCT is well documented in the setting of "single-dose" nevirapine (NVP) for PMTCT [5–7]; however, similar complications may occur with continuous infant nevirapine prophylaxis or maternal ART [8–10]. Ongoing work is needed to optimize pediatric ART, to ensure that the regimens offered are effective and durable over time.

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The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1060 trial was designed to assess the safety and efficacy of 2 ART regimens for children <3 years of age with and without prior exposure to single-dose NVP for PMTCT. By 12 months, the lopinavir/ritonavir (LPV/r)–based regimen was associated with fewer virologic treatment failures or deaths compared with the NVP-based regimen. However, improvements in CD4 percentage (CD4%) and growth (weight-for-age and height-for-age *z* score) marginally favored NVP [11, 12]. To better understand the comparative long-term effect of these 2 ART regimens in an HIV-infected pediatric population, we present data from extended follow-up in this multicenter clinical trial.

METHODS

Study Design

IMPAACT P1060 comprised 2 parallel, randomized trials targeting children with and without documented exposure to peripartum single-dose NVP. A full description of study procedures is published elsewhere [11, 12]. In brief, infants and young children aged 2 months to 3 years were recruited once ART eligibility was established. Participants were randomized to receive either LPV/r- or NVP-based regimens, which included a nucleoside reverse transcriptase inhibitor backbone of zidovudine and lamivudine. Children were prescribed liquid formulations in the randomized trial; however, in the observational phase of the study (see below), solid formulations were permitted. The primary study endpoint was stopping randomized treatment, virologic failure (VF), or death by 6 months. Participants were considered to be off randomized treatment if they initiated tuberculosis treatment or met protocol-defined toxicity endpoints requiring regimen discontinuation. Virologic failure was defined as a confirmed plasma HIV type 1 (HIV-1) RNA level <1 $\log_{10}$ copies/mL below the study entry level at 4–6 months after starting treatment, a confirmed HIV-1 RNA level >400 copies/mL at 6 months, or 2 consecutive HIV-1 RNA levels >4000 copies/mL after 6 months. The planned sample size of 288 participants in each of the 2 cohorts, or 576 overall, provided >90% power to detect an absolute difference of 20% in the rate of the primary endpoint between treatment groups. The study opened to accrual in November 2006 and by March 2010 had enrolled 452 children at 9 sites in Africa (4 in South Africa and 1 each in Zimbabwe, Zambia, Malawi, Uganda, and Tanzania) and 1 site in India.

Study History

In April 2009, the data safety monitoring board (DSMB) closed accrual in the NVP-exposed cohort due to superiority of the LPV/r -based treatment for the primary study endpoint [11], but allowed the NVP-unexposed cohort to continue enrolling. In October 2010 the DSMB recommended results be released in the NVP-unexposed cohort, which also showed that LPV/r-based ART was superior to the NVP treatment arm for the primary study endpoint [12]. With closure of each cohort, clinicians and caregivers had the choice to switch from NVP-based ART to LPV/r-based ART. Children in both cohorts continued study follow-up every 3 months; however, site clinicians directed HIV management based on local standards of care. The observational follow-up study was implemented in a revised protocol in March 2011, when participants were offered continued follow-up. Parents/caregivers provided informed consent with the child's assent where appropriate. ART was provided through local or national HIV programs, and drug selection and toxicity management were performed according to local standard of care. Plasma HIV-1 RNA and immunologic and anthropometric assessments were conducted every 3 months. Figure 1 presents a CONSORT (Consolidated Standards of Reporting Trials) flow diagram summarizing the history of the study. Data up to 21 September 2014 were included in this analysis, as this was the last date when all sites contributed to long-term study follow-up.

Statistical Methods

Participant follow-up spanned periods when patient management was guided by the protocol (randomized clinical trial period) and, following 2 separate DSMB interventions, guided by clinician discretion (observational period). Reasons for discontinuing NVP and LPV/r-based ART thus included protocol- and non-protocol-mandated factors, which complicated the interpretation of longer-term outcomes. To address this issue, we considered participants to be "off study treatment" if they discontinued their originally allocated LPV/r or NVP for at least 30 days. In our primary analysis, we incorporated an intention-to-treat (ITT) approach. To evaluate whether differential treatment switching and censoring were influencing conclusions, we performed sensitivity analyses using inverse probability weighting [13–15]. Details of methods for the weighted models are given in the Supplementary Appendix. We pooled data from both cohorts, following analyses demonstrating that previous NVP exposure was not associated with differential treatment outcomes between the 2 randomization arms [16].

Kaplan–Meier curves were used to illustrate time to VF or death (VF/death) and death alone. Mean (95% confidence interval [CI]) CD4%, WHO weight-for-age *z* (WAZ) scores, and WHO height-for-age *z* (HAZ) scores were summarized at targeted times (entry, 6 months, and then every 12 months) [17]. Cox proportional hazards models were used to analyze time-to-event outcomes, and generalized estimating equations were used to fit models to compare CD4% and growth outcomes in children on the 2 treatment regimens. Adjusted models included sex, prior NVP exposure (cohort), age at entry (<1 years; ≥1 year), HIV-1 RNA (<750 000; ≥750 000 copies/mL), CD4% (<15%; 15% to <25%; ≥25%), HAZ score and WAZ score (by tertile of all values at entry), and WHO stage (I/II; III/IV). Two-sided *P* values unadjusted for multiple

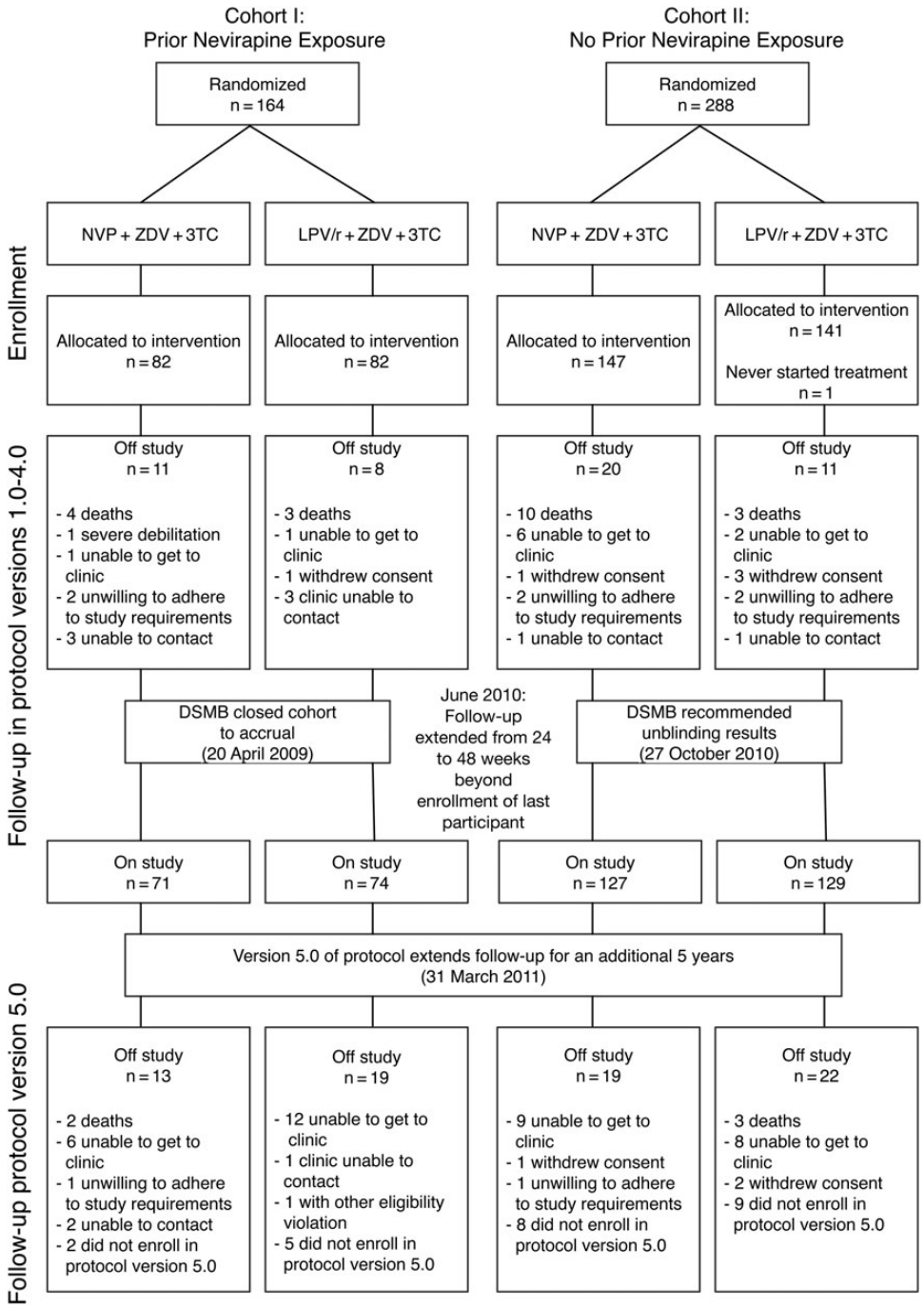

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow through the different stages of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1060 trial. Abbreviations: 3TC, lamivudine; DSMB, data safety monitoring board; LPV/r, lopinavir/ritonavir; NVP, nevirapine; ZDV, zidovudine.

comparisons were reported. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline and Current Characteristics

Overall, 452 infants and children were randomized between November 2006 and March 2010; 451 started treatment and were included in the analyses (229 in the NVP arm and 222 in the LPV/r arm). At enrollment, 44% of participants were <12 months of age. Most children had relatively advanced disease: baseline median CD4% 16% and plasma HIV-1 RNA 687 000 copies/mL; 61% were WHO stage III/IV (Table 1).

As of 21 September 2014, 329 of the 451 (73%) remained in study follow-up (Supplementary Table 1). Twenty-five

Table 1. Baseline Characteristics of Human Immunodeficiency Virus-Infected Children Initiating Antiretroviral Therapy in the International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1060 Trial, Stratified by Original Randomization Arm

	Randomization Arm		
Characteristic	NVP (n = 229)	LPV/r (n = 222)	Total (N = 451)
Prior NVP exposure			
Exposed	82 (36)	82 (37)	164 (36)
Unexposed	147 (64)	140 (63)	287 (64)
Age			
Median (Q1, Q3)	1.19 (0.71–2.10)	1.23 (0.65–1.97)	1.22 (0.68–2.07)
<12 mo	100 (44)	100 (45)	200 (44)
≥12 mo	129 (56)	122 (55)	251 (56)
Sex			
Male	105 (46)	110 (50)	215 (48)
Female	124 (54)	112 (50)	236 (52)
CD4%			
Median (Q1, Q3)	16 (12–21)	17 (12–22)	16 (12–22)
<15%	97 (43)	90 (41)	187 (42)
15% to <25%	97 (43)	91 (41)	188 (42)
≥25%	34 (15)	41 (18)	75 (17)
Missing	1	0	1
Weight-for-age *z* score[a]			
Median (Q1, Q3)	−1.54 (−2.84 to −0.65)	−1.59 (−2.54 to −0.62)	−1.57 (−2.71 to −0.63)
<−2.22	80 (35)	68 (31)	148 (33)
−2.22 to <−1.04	73 (32)	76 (34)	149 (33)
≥−1.04	76 (33)	78 (35)	154 (34)
Height-for-age *z* score [a]			
Median (Q1, Q3)	−2.40 (−3.39 to −1.34)	−2.17 (−3.14 to −1.14)	−2.31 (−3.31 to −1.24)
<−2.97	76 (33)	69 (31)	145 (32)
−2.97 to <−1.63	81 (35)	71 (32)	152 (34)
≥−1.63	72 (31)	82 (37)	154 (34)
Clinical stage (WHO)			
Stage I/II	85 (37)	92 (41)	177 (39)
Stage III/IV	144 (63)	130 (59)	274 (61)
HIV-1 RNA, copies/mL[b]			
Median (Q1, Q3)	689 000 (250 000–750 000)	680 918 (225 034–750 000)	687 000 (232 882–750 000)
<750 000	123 (54)	119 (54)	242 (54)
≥750 000	106 (46)	103 (46)	209 (46)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HIV-1, human immunodeficiency virus type 1; LPV/r, lopinavir/ritonavir; NVP, nevirapine; WHO, World Health Organization.

[a] Tertiles of entry distribution.

[b] Censored at 400 copies/mL and 750 000 copies/mL.

participants had died (16 on NVP and 9 on LPV/r), 44 were unable to continue with clinic visits (mostly because of relocation outside of the study area), and 24 declined enrollment in the observational phase. Median follow-up was 5.3 years (interquartile range [IQR], 4.3–6.4), with no differences between the 2 treatment arms (5.2 years for NVP vs 5.3 years for LPV/r; $P = .47$). Characteristics at the most recent clinic visit before the data cutoff are summarized in Supplementary Table 2. Median CD4% was 37%, and 94% had HIV-1 RNA ≤400 copies/mL.

Of participants randomized to NVP, 52% remained in follow-up on NVP and 33% had been switched to LPV/r. Of those randomized to LPV/r, 88% were in follow-up on LPV/r, and only 4% had been switched to NVP. Median time on study drug was 20.5 months (IQR, 6.4–63.7 months) for NVP and 61.2 months (IQR, 28.1–71.9 months) for LPV/r. Time to discontinuation of NVP or LPV/r is shown in Supplementary Figure 1. Of the 152 participants who stopped NVP or LPV/r, approximately two-thirds did so for protocol-mandated reasons. Fourteen were taken off NVP after the DSMB closure of enrollment to the NVP-exposed cohort. Reasons for discontinuing randomized study drugs are shown in Supplementary Table 3.

Virologic Failure and Death

An early separation by treatment arm in time to VF/death was observed by 6 months and the curves remained separated throughout follow-up, with relatively few events occurring

beyond 24 months. The proportion of participants experiencing VF/death by 6 months in the NVP arm was 17% greater than in the LPV/r arm ($P < .001$) (Figure 2). This difference persisted at 12 months (17%; $P < .001$), 36 months (19%; $P < .001$), and 60 months (19%; $P < .001$). The hazard ratio (HR) for VF/death was significantly higher among children initiating NVP compared with LPV/r, both in crude (HR, 1.87; 95% CI, 1.35–2.61) and multivariable (adjusted HR, 1.90; 95% CI, 1.37–2.65) Cox regression models. Results from the sensitivity analysis gave an estimated rate ratio of 2.90 (95% CI, 1.67–5.06) when compared to LPV/r. Time to VF/death by treatment arm and entry HIV-1 RNA level is illustrated in Figure 2, showing that differences in outcomes varied little by initial viral loads. Time to VF/death by treatment arm and prior NVP exposure is illustrated in Supplementary Figure 2. Differences in outcomes varied little regardless of NVP exposure for PMTCT.

Death was an early phenomenon, primarily in the first 3–6 months of follow-up (Figure 2). Of the 16 deaths in the NVP arm, 14 occurred during NVP-based ART. Eight of the 9 deaths in the LPV/r arm occurred while receiving LPV/r-based ART. Infants and children initiating NVP were at greater risk for death, but the difference was not statistically significant in either unadjusted (HR, 1.78; 95% CI, .79–4.04) or adjusted Cox models (adjusted HR, 1.65; 95% CI, .72–3.76). The estimated rate ratio from weighted models (1.95; 95% CI, .82–4.66) gave similar findings.

CD4 Percentage Over Time

Mean CD4% over time by randomized treatment arm overall and by entry levels is shown in Figure 3. Children with lower initial values demonstrated greater improvement than those with higher values at baseline. Mean CD4% levels at 60 months

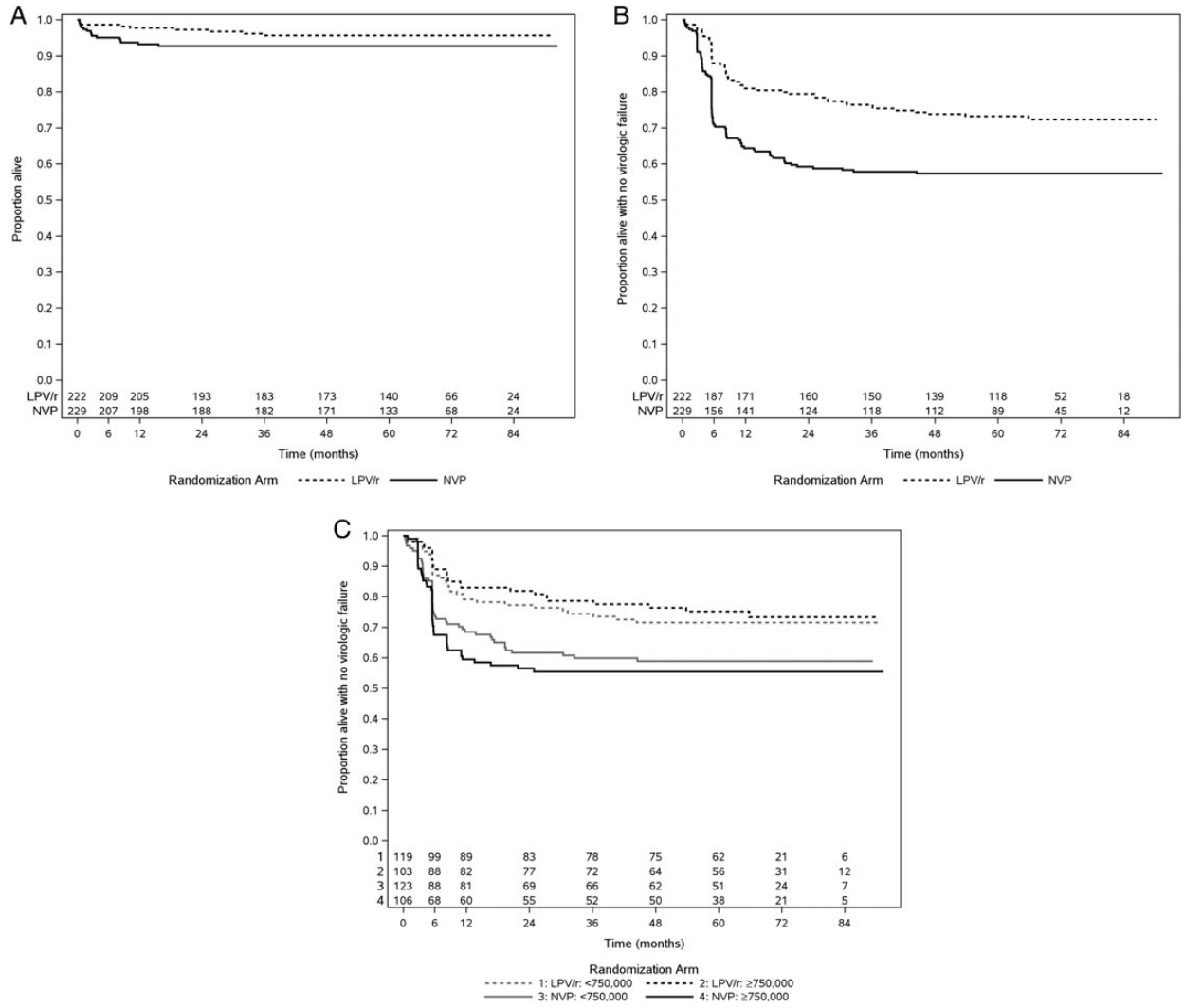

Figure 2. Kaplan–Meier analysis comparing primary outcomes in the International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1060 trial, including death only (*A*), virologic failure or death (*B*), and virologic failure or death, stratified by baseline viremia level (*C*). The figures included at the bottom of each graph represent the number of participants at risk at each time point. Abbreviations: LPV/r, lopinavir/ritonavir; NVP, nevirapine.

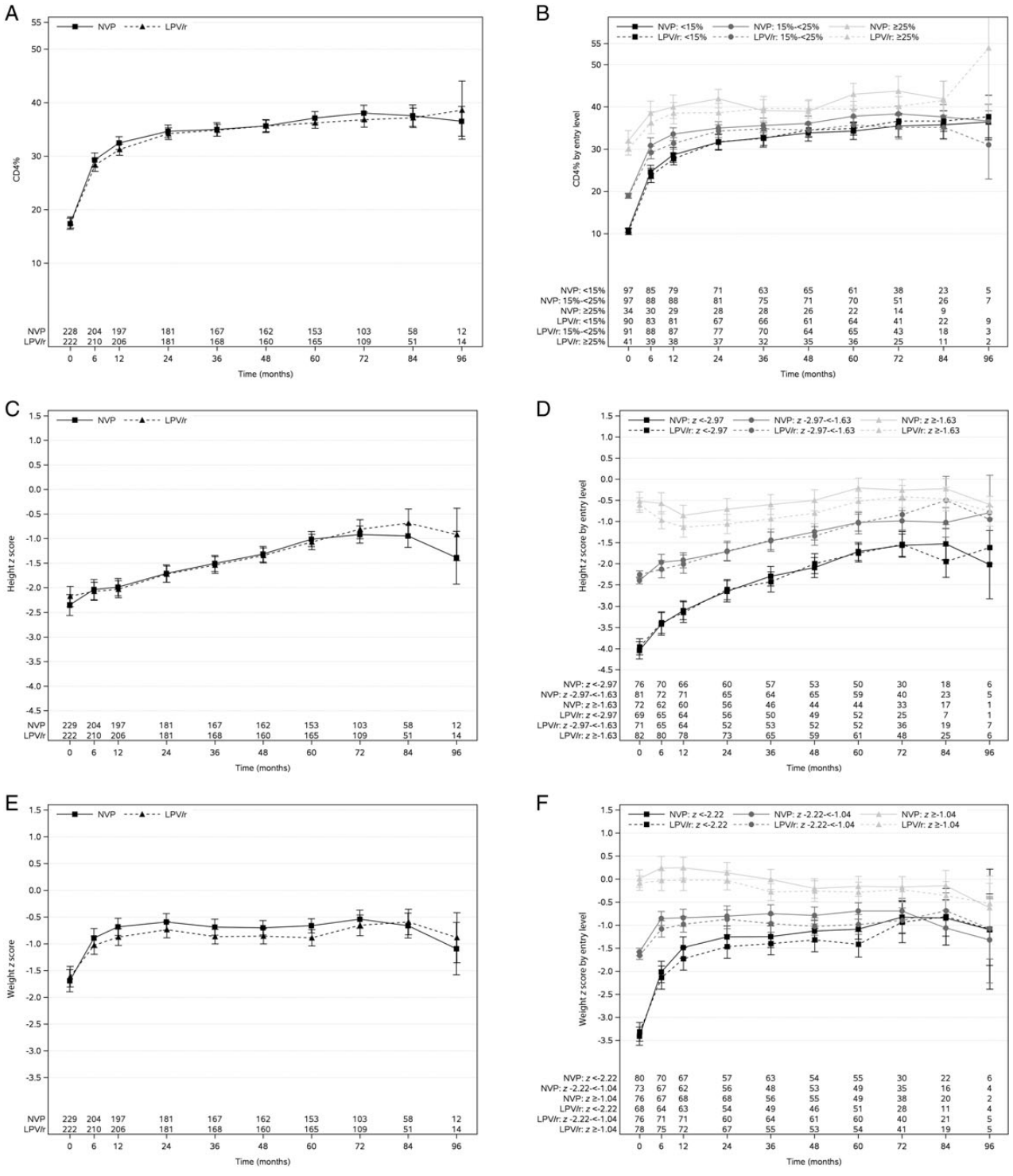

Figure 3. Trends in specific treatment outcomes (mean, 95% confidence intervals) over time for the nevirapine (NVP) and lopinavir/ritonavir (LPV/r) arms of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1060 trial, CD4 percentage (*A* and *B*), height-for-age *z* scores (*C* and *D*), and weight-for-age *z* scores (*E* and *F*). The figures included at the bottom of each graph represent the number of participants with available data at each time point.

were >25% regardless of initial level. Differences by treatment arm are shown in Table 2. In ITT unadjusted models, there were no statistically significant differences by treatment arm. In adjusted models, significantly greater CD4% gains with NVP were observed at 6 months (+1.4%; $P = .06$) and 12 months (+1.5%; $P = .03$), but differences were not significant beyond 12 months. There were no statistically significant interactions between entry levels and randomized treatment in the CD4% outcomes.

Table 2. Treatment Differences in CD4 Percentage, Weight-for-age *z* Score, and Height-for-age *z* Score Outcomes Over Time, Between the Nevirapine and Lopinavir/Ritonavir Arms of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1060 Trial

		Intention-to-Treat Unadjusted		Intention-to-Treat Adjusted[a]		Inverse Probability Weighting Model[a]	
Outcome	Time	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
CD4%	6 mo	0.94 (−.81 to 2.69)	.29	1.42 (−.06 to 2.90)	.06	1.15 (−.35 to 2.65)	.13
	12 mo	1.23 (−.36 to 2.82)	.13	1.53 (.13 to 2.93)	.03	1.24 (−.17 to 2.66)	.08
	24 mo	0.44 (−1.17 to 2.05)	.59	0.79 (−.68 to 2.26)	.29	0.01 (−1.50 to 1.51)	.99
	36 mo	0.17 (−1.51 to 1.85)	.84	0.19 (−1.39 to 1.76)	.82	0.96 (−.64 to 2.56)	.24
	48 mo	0.01 (−1.61 to 1.62)	.99	0.10 (−1.43 to 1.64)	.90	0.66 (−.90 to 2.21)	.41
	60 mo	0.91 (−.66 to 2.48)	.26	1.08 (−.41 to 2.57)	.16	1.27 (−.16 to 2.70)	.08
Weight-for-age *z* score	6 mo	0.14 (−.11 to .38)	.28	0.21 (.04 to .39)	.02	0.22 (.04 to .39)	.01
	12 mo	0.19 (−.03 to .41)	.09	0.22 (.05 to .39)	.01	0.20 (.02 to .37)	.03
	24 mo	0.14 (−.08 to .36)	.20	0.15 (−.03 to .32)	.11	0.12 (−.06 to .30)	.21
	36 mo	0.18 (−.02 to .38)	.08	0.21 (.05 to .38)	.01	0.26 (.10 to .43)	.002
	48 mo	0.16 (−.04 to .35)	.12	0.16 (−.01 to .33)	.06	0.27 (.09 to .45)	.003
	60 mo	0.23 (.02 to .43)	.03	0.25 (.08 to .43)	.01	0.42 (.24 to .60)	<.001
Height-for-age *z* score	6 mo	0.04 (−.24 to .31)	.80	0.17 (−.02 to .35)	.08	0.17 (−.01 to .35)	.07
	12 mo	0.04 (−.21 to .29)	.74	0.12 (−.06 to .30)	.18	0.11 (−.07 to .28)	.24
	24 mo	0.01 (−.23 to .25)	.93	0.08 (−.11 to .27)	.39	0.04 (−.15 to .23)	.67
	36 mo	0.03 (−.20 to .27)	.79	0.14 (−.04 to .33)	.14	0.08 (−.10 to .26)	.37
	48 mo	0.02 (−.20 to .25)	.83	0.08 (−.11 to .26)	.41	0.12 (−.06 to .29)	.19
	60 mo	0.06 (−.16 to .28)	.60	0.11 (−.08 to .29)	.26	0.16 (−.02 to .34)	.07

Differences based on values from the NVP arm minus values from the LPV/r arm.

Abbreviations: CI, confidence interval; LPV/r, lopinavir/ritonavir; NVP, nevirapine.

[a] Adjusted for entry randomized regimen, sex, cohort, age, human immunodeficiency virus type 1 RNA, CD4%, growth tertile, and World Health Organization stage.

Growth Over Time

Mean WAZ and HAZ scores over time by randomized treatment arm overall and by entry levels are shown in Figure 3. For both measures, mean values at 60 months in participants with the lowest levels at study entry remained lower than those with higher values at entry. HAZ scores continued to improve throughout follow-up. Differences in these outcomes by treatment arm are shown in Table 2. In ITT unadjusted models, no statistically significant differences between the treatment arms were detected at any time point except for WAZ scores at 5 years (mean NVP *z* score 0.23 higher, $P = .03$). In adjusted models, mean WAZ scores were marginally higher in the NVP arm at all the time points (smallest difference: month 24 by 0.15, $P = .11$; largest difference: month 60 by 0.25, $P = .01$). HAZ scores were marginally higher in the NVP arm only at 6 months (by 0.17, $P = .08$). Similar trends were observed in sensitivity analyses. There were no statistically significant interactions between entry levels and randomized treatment in the growth outcomes.

DISCUSSION

In this study of HIV-infected infants with and without prior exposure to NVP at birth, participants randomized to NVP-based ART had higher risk for virologic failure or death (primary outcome) compared with those randomized to LPV/r-based ART. These findings, reported in early analyses [11, 12], remained consistent over a median follow-up of >5 years. Separation of treatment effect by arm occurred early; thereafter, children on both treatment arms experienced relative stability. The first 4–6 months of ART appears to be an especially high-risk period for NVP-treated infants in terms of virologic failure or death. If successfully navigated, such infants are able to achieve and sustain virologic suppression at rates similar to those of LPV/r-treated infants.

These results differ from other large clinical trials. The PENPACT 1 (PENTA 9/PACTG 390) and the Prevention of Malaria and HIV disease in Tororo (PROMOTE) studies, for example, did not show significant differences in treatment outcomes between protease inhibitor (PI)– and nonnucleoside reverse transcriptase inhibitor (NNRTI)–based ART regimens in children [18, 19]. However, in both studies, the median age of enrollment was considerably older (6.5 and 3.1 years, respectively, vs 1.2 years in the current study). In addition, PI and NNRTI choices were not limited to LPV/r and NVP alone. The Optimal Combination Therapy after Nevirapine Exposure (OCTANE) study randomized adult women with and without prior NVP exposure to either NVP- or LPV/r-based ART, using a design similar to IMPAACT P1060. In women with prior NVP exposure, LPV/r was superior for the time to VF/death outcome [20]; among women without prior NVP exposure, however, the 2 regimens had similar long-term outcomes [20]. Similarly, Clumeck and colleagues in the Democratic Republic of the Congo found no differences in

therapeutic failure among adults after randomization to LPV/r- or NVP-based regimens, although overall failure rates were high (approximately 30%) [21]. The reasons for different outcomes between IMPAACT P1060 and other trials may relate to characteristics of the study participants, who were very young (44% under 12 years of age), with high baseline viremia (46% with ≥750 000 copies/mL) and advanced clinical staging (61% with stage III/IV). The high levels of viral replication among newly infected infants require a longer time on ART to achieve viral suppression. It is possible that for drugs requiring only a single mutation to confer resistance (such as NVP), there is increased risk for virologic failure during this window period. This was borne out by the high rate of NNRTI resistance detected among children failing NVP-based ART in IMPAACT P1060 [11, 12]. In addition, the ramp-up strategy commonly used at NVP initiation (half-dose prescribed for an initial 2 weeks to minimize risk for toxicity), as practiced in this study, could give suboptimal drug levels when viral replication remains high.

Previous analyses of IMPAACT P1060 suggested better growth and CD4% recovery among participants randomized to NVP-based ART at 6 and 12 months [11, 12], findings consistent with at least 1 other clinical trial [22]. We reexamined this important scientific question with the longer follow-up available in both cohorts. Differences in CD4% by treatment arm remained marginally significant at 12 months but not beyond. Mean HAZ scores were also higher in the NVP arm, but differences were not significant. Differences in WAZ scores, although significantly higher in the NVP arm, were of relatively small magnitude. For example, for a 6-year-old boy with a WAZ score of −0.78 (median at the time of database freeze), the 0.25 difference in *z* scores at year 5 predicted by adjusted ITT analyses translates to a weight difference of approximately 0.7 kg. Reasons for these findings may include the poor palatability (particularly with liquid formulations), appetite suppression, and metabolic effects associated with LPV/r and other protease inhibitors [23–25]. Interestingly, despite the reputation of liquid LPV/r formulations for challenging administration, the IMPAACT P1060 trial demonstrated remarkable acceptability and adherence among these young infants, with desirable short- and long-term outcomes.

Despite our findings from IMPAACT P1060, NVP remains an important component of a broader armamentarium for pediatric ART. When LPV/r is not available, NVP-based regimens are a viable alternative, particularly when virologic monitoring is available. The persistent gap between adult and pediatric access to ART has been well documented [26]. An approach that realistically considers availability of antiretroviral drugs across different settings is critical to reaching the millions of HIV-infected children worldwide.

Key strengths of this study were its randomized design and long follow-up. The combination of participant follow-up from both the randomized and nonrandomized time periods of the study, however, added a degree of complexity to the analysis. While we relied on an ITT approach for the primary analysis, we also performed sensitivity analyses to account for treatment switching and censoring during follow-up. That the results of the ITT analysis and the sensitivity analysis were consistent was reassuring. An alternative to the composite VF or death endpoint would have required using competing risks methodology. For consistency with prior publications on shorter-term outcomes, we used this protocol-defined composite outcome. While the primary focus of this trial was HIV-related outcomes, studies have shown unfavorable alterations in lipid profiles and body composition among infants on LPV/r [27, 28]. Longitudinal data on such outcomes are needed as, with current treatment recommendations, the duration of LPV/r-based ART exposure will only increase for perinatally infected children. Similarly, a better understanding of neurodevelopment is needed in the context of HIV infection and specific drug regimens [29]. McGrath et al found that infants on NVP-based ART demonstrated later speech attainment than those on LPV/r ART (18.1 vs 15.5 months; $P = .003$), although its long-term significance is yet unknown [30]. We are currently collecting longitudinal and neuropsychological assessment data among IMPAACT P1060 participants at several sites to address this gap. Additionally, adherence to LPV/r regimens may have varied according to the follow-up period of the study. LPV/r suspension, known for its poor palatability, was strictly used during the randomized study component. When the study moved into its observational stage, local ART programs were able to provide solid-form LPV/r to older participants.

In summary, compared with NVP-based ART, LPV/r-based ART was associated with fewer virologic failures or deaths over time in extended 5-year follow-up. The short-term superiority of the NVP arm in CD4% recovery did not persist beyond 1 year, but increased weight gains with NVP remained consistent, although minor from a clinical standpoint. These findings provide support for the continued use of LPV/r-based regimens as part of first-line treatment for pediatric HIV.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Author contributions. L. B.-M., K. A., J. L., P. P., and B. H. C. designed the analysis, interpreted the data, and wrote the manuscript. K. A., J. L., and

K. P. managed study data, conducted statistical analysis, and critically revised the manuscript. M. A., M. C., S. D., L. F., E. K., P. K., A. K., T. M., L. M., P. S., and A. V. oversaw study activities at our recruitment sites and critically revised the manuscript. L. B.-M., P. P., A. V., and M. A. served as protocol co-chairs for the study and provided oversight in its design, implementation, and dissemination. L. M., P. J. P., and E. B. served on the protocol team, assisted in data interpretation, and critically revised the manuscript. All authors have reviewed and approved the submitted version. Members of the writing team had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

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