Reuse of Nevirapine in Exposed HIV-Infected Children After Protease Inhibitor–Based Viral Suppression

A Randomized Controlled Trial

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Context Protease inhibitor (PI)–based therapy is recommended for infants infected with human immunodeficiency virus (HIV) who were exposed to nevirapine for prevention of mother-to-child HIV transmission. However, there are limitations of continuing PI-based therapy indefinitely and reuse of nevirapine has many advantages.

Objective To test whether nevirapine-exposed infants who initially achieve viral suppression with PI-based therapy can maintain viral suppression when switched to nevirapine-based therapy.

Design, Setting, and Patients Randomized trial conducted between April 2005 and May 2009 at a hospital in Johannesburg, South Africa, among 195 children who achieved viral suppression less than 400 copies/mL for 3 or more months from a cohort of 323 nevirapine-exposed children who initiated PI-based therapy before 24 months of age.

Interventions Control group children continued to receive ritonavir-boosted lopinavir, stavudine, and lamivudine (n=99). Switch group children substituted nevirapine for ritonavir-boosted lopinavir (n=96).

Main Outcome Measures Children were followed up for 52 weeks after randomization. Plasma HIV-1 RNA of greater than 50 copies/mL was the primary end point. Confirmed viremia greater than 1000 copies/mL was used as a criterion to consider regimen changes for children in either group (safety end point).

Results Plasma viremia greater than 50 copies/mL occurred less frequently in the switch group (Kaplan-Meier probability, 0.438; 95% CI, 0.334-0.537) than in the control group (0.576; 95% CI, 0.470-0.668) ($P=.02$). Confirmed viremia greater than 1000 copies/mL occurred more frequently in the switch group (0.201; 95% CI, 0.125-0.289) than in the control group (0.022; 95% CI, 0.004-0.069) ($P<.001$). CD4 cell response was better in the switch group (median CD4 percentage at 52 weeks, 34.7) vs the control group (CD4 percentage, 31.3) ($P=.004$). Older age (relative hazard [RH], 1.71; 95% CI, 1.08-2.72) was associated with viremia greater than 50 copies/mL in the control group. Inadequate adherence (RH, 4.14; 95% CI, 1.18-14.57) and drug resistance (RH, 4.04; 95% CI, 1.40-11.65) before treatment were associated with confirmed viremia greater than 1000 copies/mL in the switch group.

Conclusion Among HIV-infected children previously exposed to nevirapine, switching to nevirapine-based therapy after achieving viral suppression with a ritonavir-boosted lopinavir regimen resulted in lower rates of viremia greater than 50 copies/mL than maintaining the primary ritonavir-boosted lopinavir regimen.

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NEVIRAPINE, USED TO PREVENT mother-to-child human immunodeficiency virus (HIV) transmission, selects drug-resistant viral mutations among a large proportion of HIV-infected infants[1,2] and is associated with reduced viral suppression when nonnucleoside reverse transcriptase inhibitor (NNRTI)–based antiretroviral therapy is initiated.[3] A trial comparing nevirapine-based therapy to protease inhibitor (PI)–based therapy among nevirapine-exposed infants was terminated early when reduced viral suppression was observed in the nevirapine-based therapy group,[4] consistent with an adult study.[5] Current guidelines for nevirapine-exposed infants advise that treatment be initiated with regimens based on ritonavir-boosted lopinavir.[6]

There are many limitations of continuing to use PI-based regimens indefinitely in young children. These include its unpleasant taste, which poses adherence challenges for children too

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young to be prescribed tablets.[7,8] Refrigeration is required and dosing has to be modified for co-treatment for tuberculosis.[9] Metabolic toxicities are of concern with long-term use during critical periods of child development.[10-12] Using this PI in first-line regimens limits second-line options. The high cost of ritonavir-boosted lopinavir is a major disincentive to implementing optimal primary therapy recommendations in several sub-Saharan African countries.

We conducted a clinical trial to test the hypothesis that nevirapine-based therapy would be as effective as ritonavir-boosted lopinavir in maintaining viral suppression among nevirapine-exposed children if only initiated once viral suppression had been achieved with the initial PI-based regimen.

METHODS

We conducted a randomized, open-label trial at 1 site in Johannesburg, South Africa, among 195 children infected with HIV. The children randomized were accrued from a cohort of 323 nevirapine-exposed children who met clinical and immunologic criteria for treatment when younger than 24 months and who initiated a PI-based regimen as their first treatment regimen. Data involving the children in this study population were included in prior publications about immune reconstitution inflammatory syndrome and initial response to PI-based antiretroviral therapy, respectively.[13,14] Those who achieved and sustained plasma HIV-1 RNA of less than 400 copies/mL for at least 3 months within the first 12 months of treatment were eligible for randomization either to the switch group, who had nevirapine substituted for ritonavir-boosted lopinavir, or to the control group, who continued with the ritonavir-boosted lopinavir–based regimen. Follow-up continued to 52 weeks after randomization. The study received approval by the institutional review boards of Columbia University and the University of the Witwatersrand.

Each child's guardian provided signed informed consent. Consent was obtained for screening for study eligibility with a specific consent form only for screening. For children found to be eligible for the study, a second consent was obtained for enrollment in the trial. At this point, events prior to randomization, eligibility for randomization, and events after randomization (conditional on eligibility) were explained to the guardians.

Population

Women with HIV-infected children younger than 24 months of age who reported that nevirapine was used for prevention of mother-to-child transmission were identified and referred from inpatient wards and pediatric HIV clinics to 1 research site between April 8, 2005, and July 10, 2007. Children were evaluated for eligibility for treatment based on South African guidelines in place at the time.[15] Eligibility criteria for treatment included World Health Organization (WHO) stage III or IV disease, CD4 percentage less than 25 if younger than 12 months or less than 20 if 12 months or older, or recurrent (>2 times/year) or prolonged (>4 weeks) hospitalization for HIV-related complications. Children needing acute treatment for opportunistic infections (except tuberculosis) or tumors were excluded. These children would have been considered candidates for initiation of antiretroviral therapy but were not eligible to enroll in the trial. In practice, we did not identify any child during screening for this study who was excluded on these grounds.

For most children (n=254) enrolled, treatment was initiated under supervision of the study team. A further 69 children were enrolled after initiating PI-based therapy elsewhere (other local pediatric antiretroviral treatment services) but who otherwise met all study eligibility criteria except that pretreatment blood samples could not be stored for resistance testing. The 69 children all initially began receiving ritonavir-boosted lopinavir, stavudine, and lamivudine, but not administered by our study team. They all were nevirapine-exposed and met the same criteria for starting antiretroviral therapy as the other children. Informed consent for the trial was obtained at enrollment, which for most of the children (n=254) was soon before treatment initiation, but for the 69 children, consent for the study was obtained when they were already receiving treatment.

Procedures

Children older than 6 months received treatment with ritonavir-boosted lopinavir (230 mg/m^2), stavudine (1 mg/kg), and lamivudine (4 mg/kg) every 12 hours. Children younger than 6 months or undergoing treatment for tuberculosis received ritonavir (400-450 mg/m^2), stavudine, and lamivudine every 12 hours. After the children became older than 6 months of age, or after they completed tuberculosis treatment, ritonavir was changed to ritonavir-boosted lopinavir. At each visit, drug doses were adjusted according to growth. All medications were administered as syrups.

Caregivers were educated about their child's treatment. Comprehensive adherence counseling was provided, including by peer counselors who conducted home visits if necessary. Participants were encouraged to consult the study team for all clinical problems. Information from inpatient records was abstracted for children who were hospitalized, and the clinical circumstances of all deaths were reviewed.

Blood samples were collected before treatment began and at 4, 12, 24, 36, and 52 weeks after treatment initiation and were tested for HIV-1 RNA quantity, and CD4 percentages were determined. Weight and length were measured, and concomitant medications and other clinical conditions were recorded at each visit. Weight-for-age and height-for-age *Z* scores were calculated using WHO software.[16] Caregivers were requested to return medication bottles, which were weighed and the contents reconciled with the expected usage of each medication to determine the extent of adherence. Returning more than 20% of the expected

drug volume for any of the 3 drugs was defined as nonadherence based on expectations that more than 95% adherence is not necessarily required for suppression.[17]

Children who achieved viral suppression less than 400 copies/mL for at least 3 months within the first 12 months of treatment were eligible for randomization. The cut-off of 400 copies/mL was selected as the criterion for randomization for pragmatic reasons because an assay that only quantified to this threshold was in routine use at the time the study was designed. Other criteria for randomization included not receiving tuberculosis treatment and no abnormalities in alanine aminotransferase (ALT) greater than grade 2 (grading from Division of AIDS guidelines). Randomization was done in cohort blocks of variable size between 8 and 12. Allocations were generated by the study statistician and were concealed in opaque envelopes opened on site at the time of randomization. Once randomization criteria were met, a visit was scheduled to begin the changed regimen for the switch group or to start the postrandomization clock for the controls.

Children randomized to the switch group substituted nevirapine for ritonavir-boosted lopinavir within their treatment regimen. Nevirapine was introduced at 120 mg/m^2 once per day for the first 2 weeks and thereafter at 200 mg/m^2 every 12 hours. Children randomized to the control group continued to receive ritonavir-boosted lopinavir. Both groups received additional adherence counseling, including specific instructions concerning the lead-in schedule and possible adverse effects for the switch group.

Children in both the switch and control groups had blood samples collected for HIV-1 RNA quantification in plasma at 4, 16, 24, 36, and 52 weeks after randomization and for CD4 cell determination at 16, 24, 36, and 52 weeks. Measurements of ALT and neutrophil levels were scheduled to be taken at 2, 4, 16, 24, 36, and 52 weeks.

Laboratory Methods

Plasma HIV-1 RNA measurements (Roche Amplicor assay version 1.5; Roche, Branchburg, New Jersey), CD4 cell determinations, blood cell counts, and liver function tests were conducted by Clinical Laboratory Services in Johannesburg and reported directly to the site for use in clinical management. The Roche standard assay (quantification range, 400-750 000 copies/mL) was used on pretreatment samples and the ultrasensitive assay (quantification range, 50-150 000 copies/mL) for posttreatment samples. Available pretreatment plasma samples were tested in South Africa for mutations in the reverse transcriptase gene using bulk population sequencing at the end of the study using methods previously described.[18] Resistance data have been reported for children who experienced treatment failure before randomization (none of whom were randomized) and for the entire cohort before treatment to describe resistance after exposure to nevirapine and compare allele-specific polymerase chain reaction to sequencing.[19] Samples from children not achieving viral suppression after randomization were also tested by population sequencing.[20] Resistance was defined using the Stanford algorithm (http://hivdb.stanford.edu/pages/algs/HIVdb.html).

Study End Points

The study protocol defined any viremia greater than 50 copies/mL after randomization as the primary end point following recommendations that full viral suppression is the goal of antiretroviral treatment.[21] This was also the lowest threshold discernable with the ultrasensitive assay used during the trial. In addition, as a safety end point, all children with 2 or more HIV-1 RNA measurements greater than 1000 copies/mL were evaluated as candidates for regimen change. If poor adherence was ruled out, children in the switch group who met this safety end point were returned to the original regimen of ritonavir-boosted lopinavir, and other potential regimens were considered for children in the control group. Elevated ALT levels, neutropenia, CD4 percentage, and growth were compared between the groups as secondary end points.

Statistical Analysis

We calculated that 93 children per group were needed to detect a 20% failure rate in the switch group vs 5% in the control group using standard methods for comparing proportions[22] and allowing for a 95% follow-up rate after randomization and $\alpha = .05$ and $\beta = 0.2$. The slightly larger number randomized (n = 195) occurred because randomization was contingent on meeting eligibility after enrollment. We initially planned to enroll 234 children but expanded to 341 children when the proportion meeting eligibility criteria was lower than expected.

Modified intent-to-treat analyses were conducted excluding those children (n = 3) missing virologic outcome data. All virologic and clinical data were included through 52 weeks after randomization or up to the time of death or censoring for those who died or were lost to follow-up. Virologic end points, mortality, and loss to follow-up were analyzed using Kaplan-Meier methods and groups compared using log-rank tests.[23] Relative hazards (RHs) were calculated using Cox proportional hazards models. The proportional hazards assumption was not violated. Other outcomes were compared across groups using Wilcoxon and *t* tests for continuous variables (eg, CD4 percentage and anthropometric indicators) and χ^2 or Fisher exact tests for categorical variables (eg, ALT grades). Analyses were done using SAS version 9.1.3 (SAS Institute, Cary, North Carolina). All statistical tests were 2-sided and $P < .05$ was considered statistically significant.

RESULTS

Population

Among 323 HIV-infected children who initiated PI-based therapy during the prerandomization period, 38 (11.8%) died, 40 (12.4%) did not remain in fol-

low-up, and 50 (15.5%) did not meet criteria for randomization (FIGURE). Children who met criteria for randomization tended to be older at treatment start, had less severe disease, and were more likely to have mothers receiving treatment (eTable, available at http://www.jama.com). Children who were randomized were a median 10 months of age at treatment start and had a median CD4 percentage of 18.5 before treatment, and 55% had greater than 750 000 HIV-1 RNA copies/mL in plasma. A prior report described prerandomization characteristics of the study population in detail.[14] At randomization, a median of 9 months later, the median CD4 percentage was 29.1. The switch groups and control groups were similar in all prerandomization characteristics (TABLE 1).

Primary End Points After Randomization

Loss to follow-up and mortality were low in both groups. Four children died after randomization. Two children in the control group died: one from bacterial pneumonia and the other from unknown causes; 2 children in the switch group died: 1 from fulminant sepsis and 1 from preexisting renal pathology. None of the deaths was considered drug-related.

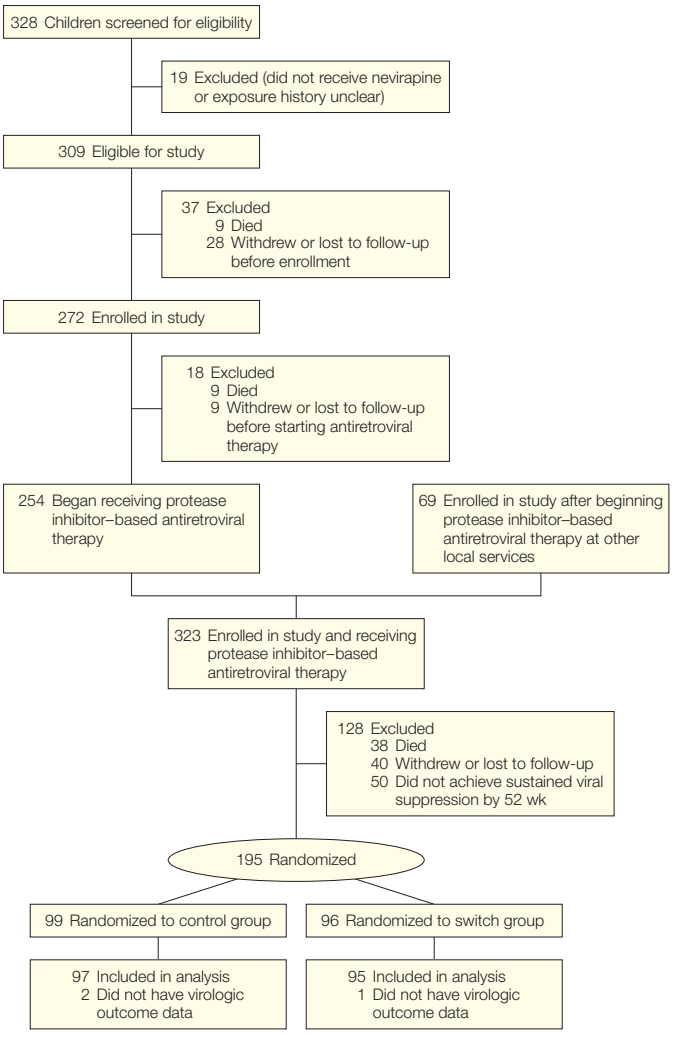
There was better virologic suppression in the switch group based on the primary end point of viremia of more than 50 copies/mL. In the control group, the Kaplan-Meier probability of having at least 1 measurement greater than 50 copies/mL was 0.576 (95% confidence interval [CI], 0.470-0.668), which was higher than in the switch group for whom the probability was 0.438 (95% CI, 0.334-0.537) ($P=.02$) (TABLE 2).

Secondary End Points

Confirmed viremia of more than 1000 copies/mL, a safety end point, was more common among children in the switch group than the control group. In the control group, the probability of confirmed viremia greater than 1000 copies/mL was 0.022 (95% CI, 0.004-0.069), whereas in the switch group, the probability was 0.201 (95% CI, 0.125-0.289) ($P<.001$) (TABLE 3). Of 18 children in the switch group with confirmed viremia greater than 1000 copies/mL, 3 achieved viral suppression again without regimen change, and 9 achieved it after being switched back to ritonavir-boosted lopinavir. Three children discontinued study participation soon after viral elevations were noted, and 3 were returned to ritonavir-boosted lopinavir but discontinued study participation before the next measurement. In all 6 cases, severe household disruption affecting adherence, including changes in caregivers, maternal illness, and relocation, were known to have occurred.

Viral RNA could be sequenced from 15 of 18 children in the switch group and 2 of 2 children in the control group with confirmed viremia greater than 1000 copies/mL to determine drug resistance genotype. Major NNRTI resistance could be detected among 13 of 15 children (86.7%) in the switch group and in neither of the 2 children in the control group. Y181C was the most common mutation occurring among 10 of 15 children (66.7%). Five of 6 children in the switch group with wild-type virus before treatment had NNRTI resistance at time of treatment failure

Figure. Flow Diagram of Study Participants



(2 had Y181C, 2 had V106A, and 1 had K101E and G190A). Nucleoside reverse transcriptase inhibitor mutations could be detected among 12 of 15 children (80.0%) in the switch group and 1 of 2 children in the control group. All were M184V/I except for one D67N.

Elevated ALT levels were common in the switch group but tended to be of low grades. Neutropenia was rare in either group. CD4 percentage increased at a significantly slower pace in the control group than in the switch group. Weight-for-age *Z* scores were similar on average, but more children in the control group than in the switch group experienced a decline in weight for age after randomization (Table 3).

Table 1. Pretreatment and Prerandomization Characteristics of 195 HIV-Infected Children Randomized to Maintain a Ritonavir-Boosted Lopinavir–Based Regimen (Control Group) or Switch to a Nevirapine-Based Regimen (Switch Group)[a]

	Control Group (n = 99)	Switch Group (n = 96)	*P* Value[b]
Male sex, No. (%)	50 (51)	54 (56)	.42
Before Treatment			
Age at treatment start, No. (%)			
<6 mo	28 (28)	26 (27)	.16
6-11 mo	29 (29)	40 (42)	
12-17 mo	25 (25)	22 (23)	
18-24 mo	17 (17)	8 (8)	
Age, median (range), mo	11 (2-24)	9 (2-22)	.09
HIV-1 RNA quantity, No. (%)			
<100 000 copies/mL	7 (8)	12 (13)	.56
100 000-750 000 copies/mL	29 (35)	29 (33)	
>750 000 copies/mL	48 (57)	48 (54)	
CD4 percentage, No. (%)			
<10	16 (17)	10 (11)	.36
10-14.9	16 (17)	21 (23)	
≥15	61 (66)	62 (67)	
CD4 percentage, median (range)	19.0 (2.2-41.8)	18.4 (1.5-39.3)	.68
WHO stage, No. (%)			
I/II	16 (21)	18 (23)	.73
III/IV	61 (79)	60 (77)	
Weight-for-age *Z* score			
Mean (SD)	−2.23 (1.84)	−2.13 (1.48)	.71
Score <2 SD below mean, No. (%)	48 (54)	43 (49)	.55
Height-for-age *Z* score			
Mean (SD)	−3.14 (1.67)	−3.10 (1.70)	.88
Score <2 SD below mean, No. (%)	70 (80)	62 (73)	.31
Time of Randomization			
Age at randomization, No. (%)			
6-11 mo	6 (6)	9 (9)	.40
12-17 mo	34 (34)	36 (38)	
18-23 mo	26 (26)	29 (30)	
≥24 mo	33 (33)	22 (23)	
Age, median (range), mo	20 (10-36)	19 (9-43)	.09
CD4 percentage, No. (%)			
<10	0	1 (1)	.70
10-14.9	4 (4)	3 (3)	
15-19.9	8 (8)	10 (11)	
≥20	84 (88)	81 (85)	
CD4 percentage, median (range)	28.9 (10.9-55.7)	29.5 (7.3-52.3)	.81
Weight-for-age *Z* score			
Mean (SD)	−0.56 (1.21)	−0.59 (1.12)	.84
Score <2 SD below mean, No. (%)	9 (9)	9 (9)	.95
Height-for-age *Z* score			
Mean (SD)	−3.19 (1.49)	−3.07 (1.65)	.60
Score <2 SD below mean, No. (%)	75 (76)	73 (76)	.96
Median time receiving therapy before randomization (range), mo	9 (4-19)	9 (5-21)	.88

Abbreviations: HIV, human immunodeficiency virus; WHO, World Health Organization.
[a] Percentages may not sum to 100 because of rounding.
[b] Categorical variables were compared across groups using χ^2 tests; median age, CD4 percentage, and time receiving therapy were compared using Wilcoxon tests; and height and weight for age were compared using *t* tests. Denominators are as shown.

Predictors of Viremia

Children who were older at the time of randomization were more likely to have viremia greater than 50 copies/mL (RH, 1.71; 95% CI, 1.08-2.72) than younger children, but this age trend was only significant in the control group (TABLE 4). Adherence ascertained by pharmacy reconciliation was not associated with viremia greater than 50 copies/mL in either group (Table 4). However, inadequate adherence was associated with viremia greater than 1000 copies/mL in the switch group (RH, 4.14; 95% CI, 1.18-14.57).

Pretreatment NNRTI resistance mutations were detected among 31 of 143 children (21.7%) tested (25 had Y181C, 4 had K103N, 1 had Y188C, and 1 had G190A). As expected, there was no association between pretreatment NNRTI resistance mutations and viremia in the control group. In the switch group, there was a nonsignificant trend toward an association using the end point of greater than 50 copies/mL. Pretreatment NNRTI mutations were strongly related to confirmed viremia greater than 1000 copies/mL in the switch group (RH, 4.04; 95% CI, 1.40-11.65). The probability of confirmed viremia greater than 1000 copies/mL was 0.447 (95% CI, 0.214-0.657) among those who had NNRTI mutations before treatment compared with 0.120 (95% CI, 0.049-0.226) among those who did not ($P = .005$). Pretreatment NNRTI mutations were more common among children 12 months or younger at the time of initiating therapy (29.0%) than among older children (8.0%), but this difference did not lead to worse outcomes in children who were

younger when starting therapy. Younger age, whether categorized at the time of starting treatment or at the time of randomization, was not associated with viremia greater than 1000 copies/mL in the switch group (Table 4).

COMMENT

A recent trial demonstrated that nevirapine-exposed, HIV-infected children should initiate therapy with a PI-based regimen,[4] but whether this regimen needs to be continued indefinitely is unclear. Our data indicate that children who switch to nevirapine-based therapy once they have achieved viral suppression after an average of 9 months of therapy based on ritonavir-boosted lopinavir are more likely to achieve viremia less than 50 copies/mL than children who kept their original regimen. However, a sizable minority (20%) experienced breakthrough viremia greater than 1000 copies/mL that required consideration for therapy change. This outcome was strongly related to pretreatment NNRTI mutations and was rare (2%) among children who maintained their original regimen. These seemingly inconsistent results highlight the promise and pitfalls of switching nevirapine-exposed infants. Switching allows treatment options to be expanded and the desirable benefits of a nevirapine-based regimen to be accrued. However, for about 20% of exposed children, the regimen is suboptimal. Therefore, switching can only be considered in situations in which adequate virologic monitoring can be conducted, both to identify who is eligible to switch and to identify as early as possible children who should be returned to the ritonavir-boosted lopinavir–based regimen.

Switching following a suppressive regimen has not, to our knowledge, been previously investigated as a strategy to overcome preexisting drug resistance in either adults or children. Several trials in adults have evaluated switching from PI-based therapy to NNRTI-based therapy for reasons of toxicity, adherence, and quality of life.[24-31] The overall conclusions are that switching can be accomplished safely while maintaining virologic suppression, improving adherence, and reducing some toxicities.[24-31] Toxicities associated with PIs may be less common

Table 2. Primary End Points Through 52 Weeks After Randomization Among 99 Children Who Continued With a Ritonavir-Boosted Lopinavir–Based Regimen (Control Group) and 96 Children Switched to a Nevirapine-Based Regimen (Switch Group)[a]

	Control Group (n = 99)	Switch Group (n = 96)	*P* Value
Probability of loss to follow-up by 52 wk (95% CI)	0.031 (0.008-0.080)	0.053 (0.020-0.110)	.46
Lost to follow-up before 52 wk, No.	3	5	
Probability of mortality by 52 wk (95% CI)	0.020 (0.004-0.065)	0.021 (0.004-0.068)	.97
No. who died	2	2	
Probability of HIV-1 RNA >50 copies/mL (95% CI)[b]	0.576 (0.470-0.668)	0.438 (0.334-0.537)	.02
No. with 1 or more measurement >50 copies/mL[b]	55	40	

Abbreviation: CI, confidence interval.
[a] Probabilities were calculated using Kaplan-Meier methods and compared across groups using log-rank tests.
[b] Three children (2 in the control group and 1 in the switch group) were missing virologic data and were excluded. Virologic data were included through 52 weeks after randomization or up to the time of death or censoring.

Table 3. Secondary End Points Through 52 Weeks After Randomization Among 99 Children Who Continued With a Ritonavir-Boosted Lopinavir–Based Regimen (Control Group) and 96 Children Switched to a Nevirapine-Based Regimen (Switch Group)

	Control Group (n = 99)	Switch Group (n = 96)	*P* Value
Confirmed viremia >1000 copies/mL, No. (probability) [95% CI][a]	2 (0.022) [0.004 to 0.069]	18 (0.201) [0.125 to 0.289]	<.001
Highest ALT measurement, No. (%)[b,c]			
Grade 1	20 (20)	35 (36)	<.001
Grade 2	2 (2)	11 (11)	
Grade 3/4	4 (4)	7 (7)	
Lowest neutropenia, No. (%)[b,c]			
Grade 1	8 (8)	15 (16)	.18
Grade 2	5 (5)	8 (8)	
Grade 3/4	3 (3)	5 (5)	
CD4 percentage, median (IQR)[d]			
Week 16	30.3 (26.2 to 35.3)	34.6 (27.6 to 39.5)	.005
Week 24	30.0 (24.3 to 34.2)	33.9 (28.9 to 41.1)	<.001
Week 36	31.8 (26.4 to 35.9)	33.2 (27.3 to 39.6)	.08
Week 52	31.3 (26.5 to 37.4)	34.7 (29.6 to 40.8)	.004
CD4 percentage declined by 10% by 52 wk, No. (%) [95% CI][c]	14 (15) [8.87 to 24.56]	3 (3) [0.84 to 9.81]	.005
Weight-for-age *Z* score, mean (SD)[d]			
Week 16	–0.39 (1.10)	–0.30 (1.04)	.59
Week 24	–0.40 (1.15)	–0.30 (1.08)	.56
Week 36	–0.43 (1.23)	–0.35 (1.07)	.63
Week 52	–0.38 (1.19)	–0.44 (1.09)	.69
Weight-for-age *Z* score declined by 1 *Z* score by 52 wk, No. (%) [95% CI][c]	13 (13) [7.45 to 21.76]	4 (4) [1.36 to 11.04]	.03

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; IQR, interquartile range.
[a] Three children (2 in the control group and 1 in the switch group) were missing virologic data and were excluded. Virologic data were included through 52 weeks after randomization or up to the time of death or censoring. Probabilities were calculated using Kaplan-Meier methods and compared across group using log-rank tests.
[b] Grading was based on Division of AIDS guidelines, available at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf.
[c] Proportions were compared across groups using χ^2 tests. No children were missing ALT data, 1 child in the switch group was missing data on neutropenia, 7 children in the control group and 3 children in the switch group were missing data on CD4 percentage, and 1 child in the switch group was missing data on weight.
[d] Groups were compared using Wilcoxon tests for CD4 percentage and *t* tests for weight for age.

in children, particularly prior to puberty, but are of concern as therapy is being given during developmentally critical periods and long-term consequences may be serious.[10-12] There are 2 nonrandomized reports of children switched from PI-based regimens to NNRTI-based regimens.[32,33] Both reported sustained viral suppression and improved lipid profiles.[32,33]

NNRTI resistance mutations detected by standard population sequencing before treatment were strongly related to confirmed viremia greater than 1000 copies/mL in the switch group. Among those without pretreatment resistance, 88% did not reach this safety end point after the switch (Table 4). These data suggest that screening for mutations before treatment would be clinically useful if the switching strategy were used. However, in practice, drug-resistance testing is likely to be difficult to accomplish in low-resource settings. Nevertheless, strategies to use targeted drug-resistance testing should be considered because the cost of resistance testing could be justified based on the potential for cost savings from the less expensive nevirapine-based regimen.

It was unexpected that younger age at treatment initiation was not associated with virologic response in the switch group. Among nevirapine-exposed women, the proportion who have detectable mutations declines with time after exposure and response to first-line NNRTI-based therapy is generally better with longer time after exposure.[3,34-36] Child response to exposure may be different from adult response to exposure, or the ritonavir-boosted lopinavir–based induction regimen may have modified the relationship.

Older age was strongly related to intermittent and low-level viremia in the control group. Low-level viremia occurred among more than half of all children (55%) and more than three-quarters of children (76.4%) older than 24 months at randomization in the control group. Few prior studies have included large numbers of children of this age treated with ritonavir-boosted lopinavir or described viral response in such detail. Ritonavir-boosted lopinavir syrup poses substantial adherence challenges among young children, given its unpleasant taste.[7,8] As children become old enough and strong enough to resist their caregivers, the taste of this drug may play a larger role in adherence. Potency could be compromised if children do not consume adequate volumes. More palatable formulations in pediatric doses are urgently needed. A limitation of our study is that blinding was not possible. Thus,

Table 4. Predictors of the Primary End Point (Viremia >50 copies/mL) and the Safety End Point (Confirmed Viremia >1000 copies/mL) in the Control Group and Switch Group Separately[a]

	Control Group			Switch Group		
	No.	Children With Viremia, No. (Probability) [95% CI]	*P* Value	No.	Children With Viremia, No. (Probability) [95% CI]	*P* Value
Primary end point: viremia >50 copies/mL						
No.	99	55		96	40	
Age at randomization, mo						
6-11	6	2 (0.333) [0.046-0.676]	.01	9	3 (0.375) [0.087-0.674]	.12
12-17	34	13 (0.408) [0.239-0.570]		36	15 (0.457) [0.280-0.618]	
18-23	26	15 (0.605) [0.386-0.767]		29	9 (0.323) [0.161-0.496]	
≥24	33	25 (0.764) [0.577-0.877]		22	13 (0.591) [0.361-0.762]	
Drug resistance results						
Major NNRTI mutations	11	7 (0.659) [0.298-0.866]	.60	20	11 (0.605) [0.342-0.791]	.16
No major NNRTI mutations	61	33 (0.570) [0.433-0.686]		51	20 (0.406) [0.269-0.539]	
Adherent	89	52 (0.595) [0.483-0.689]	.45	79	33 (0.436) [0.322-0.544]	.41
Inadequate adherence[b]	3	4 (0.667) [0.009-0.774]		6	3 (0.600) [0.126-0.882)]	
Safety end point: confirmed viremia >1000 copies/mL						
No.	99	97		96	78	
Age at treatment start, mo						
<6	28	0	.18	26	2 (0.087) [0.015-0.243]	.13
6-11	29	2 (0.074) [0.013-0.211]		40	10 (0.271) [0.140-0.419]	
12-17	25	0		22	6 (0.273) [0.111-0.464]	
18-24	17	0		8	0	
Drug resistance results						
Major NNRTI mutations	11	0	.55	20	8 (0.447) [0.214-0.657]	.005
No major NNRTI mutations	61	2 (0.036) [0.007-0.109]		51	6 (0.120) [0.049-0.226]	
Adherent	82	2 (0.026) [0.005-0.082]	.66	79	13 (0.172) [0.097-0.265]	.02
Inadequate adherence[b]	8	0		6	3 (0.600) [0.126-0.882]	

Abbreviations: CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor.
[a] Three children (2 in the control group and 1 in the switch group) were missing virologic data and were excluded. Virologic data were included through 52 weeks after randomization or up to the time of death or censoring. Probabilities were calculated using Kaplan-Meier methods and compared across groups using log-rank tests. The results presented are from univariate models.
[b] Inadequate adherence was defined as returning more than 20% of the expected drug volume for any of the 3 drugs based on pharmacy reconciliation at the time of the outcome.

we cannot distinguish pharmacologic and virologic differences between the regimens from behavioral changes that may result from poor palatability. We used standard recommended doses of ritonavir-boosted lopinavir based on body surface area, although some have questioned whether these doses are sufficient.[37] Because higher doses are thought to be necessary for younger children, inadequate dosing would not explain the observed age gradients.

CD4 cell response was weaker in the control group. Although CD4 percentages were mostly in the normal range and increased over time in both groups, the increase was larger in the switch group. Mean weight-for-age *Z* scores were similar between the groups, but a larger proportion of children in the control group dropped a *Z* score at some point after randomization. One possible explanation may be appetite suppression related to the poor palatability of ritonavir-boosted lopinavir. Similar differences have been noted in some other studies.[4]

Guidelines now recommend starting treatment among all HIV-infected infants as soon as possible after diagnosis following a trial demonstrating better outcomes if treatment is initiated immediately rather than waiting until standard prognostic indicators are reached.[38] Thus, large numbers of HIV-infected infants should be initiating ritonavir-boosted lopinavir–based treatment, but the high cost of this regimen poses a barrier in many low-resource settings. Our results suggest that a majority of nevirapine-exposed children who are successfully treated with initial regimens based on ritonavir-boosted lopinavir and achieve viral suppression could benefit from the switch strategy, which would allow reductions in costs of pediatric treatment programs. However, switching should only be undertaken with adequate virologic monitoring. Although the value of virologic monitoring in HIV treatment is strongly emphasized in well-resourced settings,[21,39] most programs in low-resource settings do not include it as part of routine services because of cost. Simple algorithms could be developed for targeted virologic testing to safely implement the switch strategy.

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Man lives consciously for himself but unconsciously he serves as an instrument for the accomplishment of historical and social ends.

—Leo Tolstoy (1835-1910)

