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Extended prophylaxis with nevirapine and cotrimoxazole among HIV-exposed uninfected infants is well tolerated

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Abstract

Objective—Nevirapine and cotrimoxazole are associated with hematologic toxicities and skin-rash. Safety of their concurrent use for prophylaxis over extended periods among HIV-exposed uninfected infants has not been previously assessed.

Design—Secondary data analysis of the 'HIV Prevention Trials Network-046 protocol' (version 2.0), a phase-III, randomized, placebo-controlled trial that assessed efficacy and safety of nevirapine prophylaxis against breast milk transmission of HIV-1.

Methods—Trial infants received 6-month study nevirapine/placebo, and standard-of-care peripartum single-dose nevirapine+/– zidovudine 'tail', and cotrimoxazole prophylaxis from 6 weeks through breastfeeding cessation. Adverse events were monitored using United States Division of AIDS Toxicity Tables (2004). Risk of neutropenia, anemia and skin-rash in the cotrimoxazole+nevirapine and the cotrimoxazole+placebo groups were compared using negative-binomial regression.

Results—Incidence of neutropenia and/or anemia, and skin-rash was highest during the first 6 weeks of life and declined, thereafter, regardless of study group. Time to first adverse event after 6 weeks was similar in cotrimoxazole+nevirapine and cotrimoxazole+placebo groups: hazard ratio (95% confidence interval) was 1.26 (0.96–1.66) for neutropenia and/or anemia (all grades), 1.27

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Conflicts of interest

None of the authors has financial, consultant, institutional or other relationships that might lead to a bias or conflict of interest.

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(0.80–2.03) for neutropenia and/or anemia (grade ≥3) and 1.16 (0.46–2.90) for skin-rash (grade ≥2). There were no statistically significant differences in immediate (6 weeks–6 months) and long-term (6–12 months) adverse event risk among infants on cotrimoxazole+nevirapine versus cotrimoxazole+placebo.

Conclusion—Extended nevirapine and cotrimoxazole prophylaxis through 6 months of age among HIV-exposed uninfected infants did not appear to increase the immediate or long-term risk of neutropenia, anemia or skin-rash. Concurrent use beyond 6 months, however, needs to be evaluated.

Keywords

anemia; cotrimoxazole; HIV-exposed uninfected infants; neutropenia; nevirapine; skin-rash

Introduction

The 2010 WHO prevention of mother-to-child (PMTCT) of HIV-1 guidelines recommend that HIV-exposed uninfected (HIV-EU) infants in resource-limited settings may receive daily nevirapine (NVP) prophylaxis for PMTCT from birth through 12 months of life or cessation of breastfeeding, whichever comes first [1,2]. This recommendation is based on recent clinical trial evidence demonstrating the benefits of extended daily infant NVP prophylaxis in reducing breast milk transmission of HIV-1 [3–6]. The WHO also recommends that HIV-EU infants should receive cotrimoxazole (CTX) prophylaxis from 4–6 weeks of age until they are no longer exposed to HIV and confirmed HIV uninfected [7]. CTX prophylaxis is highly effective against bacterial and protozoan opportunistic infections [8–11].

However, the safety of concurrent use of extended NVP and CTX prophylaxis among HIV-EU infants is not well understood. Frequently reported side-effects with CTX include skin rash, neutropenia and anemia [9–16]. Infant NVP prophylaxis over extended periods is generally well tolerated with some reports of rashes and neutropenia [3–6]. The objectives of this analysis were to assess risk of neutropenia, and/or anemia (all grades); risk of severe (grade ≥3) neutropenia and/or anemia; and risk of severe (grade ≥2b) skin-rash, among breastfeeding HIV-EU infants receiving concurrent daily NVP and CTX compared with those receiving daily CTX prophylaxis alone.

Methods

This is secondary data analysis of the HIV Prevention Trials Network (HPTN) 046 protocol, version 2.0, a phase-III, randomized, double-blind, placebo-controlled trial that assessed the efficacy and safety of NVP prophylaxis against breast milk transmission of HIV-1. This analysis was based on a fixed sample size of infants enrolled between February–August 2007. The trial registration number is NCT00074412 under clinical-trials.gov registry and protocol version 2.0 can be accessed at http://www.hptn.org/Web%20Documents/HPTN_Protocols/HPTN046/HPTN046v2.pdf.

Identification and recruitment of trial participants

HIV-1-infected women with intent to breastfeed identified by PMTCT program staff during antenatal follow-up at Mulago Hospital in Kampala, Uganda and primary care maternity clinics in Chitungwiza, Zimbabwe were referred to study staff at the same location. Study staff obtained written informed consent from interested eligible mothers for the mother and her baby's potential trial participation after confirming the following in the mother: at least 18 years old, third trimester pregnancy or before day 3 after delivery, and intent to

breastfeed. Clinical examination was conducted and blood drawn to confirm HIV status. All recruited women met the eligibility criteria. The study was reviewed and approved by Institutional Review Boards of the respective institutions in Uganda, Zimbabwe and the United States.

Study enrollment and randomization

After delivery, eligible mother–infant pairs were enrolled on or before day 3 after delivery/birth. Infants were eligible if they were born to an eligible mother: birth weight at least 2000 g; able to breastfeed and had a blood sample obtained for HIV-1 DNA PCR, complete blood count (CBC) and alanine aminotransferase (ALT). Infants were excluded if they had skin rash at least grade 2b (urticaria), at least grade 3 adverse event, confirmed or suspected clinical hepatitis and any serious condition as judged by the site clinician. Randomization was conducted by site using permutated block algorithms with randomized block size, which was coordinated by the Data Management Center at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) at the Fred Hutchinson Cancer Research Center in Seattle, USA.

At trial entry, enrolled infants were randomized to one of two study arms; 6-months NVP (SMON) or placebo in a 1 : 1 ratio stratified by maternal antiretroviral drug use during pregnancy (PMTCT, maternal treatment or neither) sequentially according to lists generated by SCHARP. Infants whose mothers received antiretroviral drugs for both treatment and PMTCT were assigned to the maternal treatment stratum.

However, after the release of the 6-weeks NVP (SWEN) trial results suggesting a 50% reduction in mother-to-child transmission risk of HIV-1 [5], the following protocol design changes were implemented starting 10 August 2007 based on guidance from the study sponsor, the United States National Institutes of Health Division of AIDS (DAIDS). First, study recruitment was stopped. Second, study participants already recruited by this date who met eligibility criteria were enrolled on or before day 3 postdelivery/birth. Enrolled infants were not randomized but started on open-label SWEN regimen. Although study infants who were enrolled and randomized prior to 10 August 2007 were followed through 18 months of life, the SWEN infant cohort was terminated earlier from further study follow-up when the subsequent version 3.0 study protocol was implemented. Third, study infants already randomized but less than 6 weeks (day 42) old on this date were unblinded and those on placebo switched to open-label NVP taken through day 42, whereas those on NVP continued as randomized.

Study scheduled assessments of enrolled participants

Infant clinical evaluations were conducted at 2, 4, 6, and 8 weeks and 3, 4, 5, 6, 9, 12, and 18 months. Blood samples for the following assays were drawn at birth (prior to enrollment), 2, 4, 6 and 8 weeks and 3, 6 and 12 months: ALT through 6 months, CBC with differential and HIV-1 DNA PCR (excluding 4 and 8 weeks). Infants with confirmed HIV infection had $CD4^+$ cell counts at 2 and 6 weeks and 3, 6, 12 and 18 months. At 9 months, blood was drawn for HIV-1 DNA PCR. At 18 months, an HIV enzyme immunoassay or rapid HIV test was performed and any positive results confirmed with western blot or immunofluorescence assay (IFA). Any infant with a positive virologic assay (either positive HIV-1 DNA PCR or western blot or IFA at 18 months) had a repeat assay drawn to confirm infection status. Infants identified as HIV infected were taken off of study treatment but remained in study follow-up. Quantitative HIV-1 RNA PCR was used as an alternative for infant diagnosis if HIV-1 DNA PCR was not available.

Enrolled mothers had clinical reviews at 2 and 6 weeks and 3, 6, 12, and 18 months. Based on 2006 WHO PMTCT guidelines [17], study mothers were encouraged to wean at 6 months. Intensive infant feeding counseling was provided by study staff during follow-up, although the timing of breastfeeding cessation was determined by the mother. Infant feeding practices and drug adherence were assessed by interview. Study staff also encouraged participants to continue attending the PMTCT program (outside the study).

Study drug dosing

Randomized infants received study product (10 mg/ml NVP suspension/placebo) once daily from day 5(±2 days) after birth through 6 months or through breastfeeding cessation, whichever came first. Breastfeeding cessation was defined as completely stopping all exposure to breast milk for at least 30 consecutive days. Daily doses were given according to age-bands as follows: 0.6 ml (6 mg) from day 5 (±2 days) to 2 weeks; 1.5 ml (15 mg) from 2 to 4 weeks; 1.8 ml (18 mg) from 4 to 6 weeks; 2.0 ml (20 mg) from 6 to 8 weeks; 2.2 ml (22 mg) from 8 weeks to 3 months; 2.4 ml (24 mg) from 3 to 4 months; 2.6 ml (26 mg) from 4 to 5 months; and 2.8 ml(28 mg) from 5 to 6 months of age.

Concomitant medications

Information on infant antiretroviral drugs and systemic medications including antimicrobial agents was collected through 8 months of life. As part of standard-of-care (SOC), study mothers and their infants received the recommended PMTCT interventions at that time by the respective local Ministry of Health in Uganda and Zimbabwe. The SOC PMTCT antiretroviral regimens evolved during the study period including maternal antenatal short-course zidovudine (ZDV), peripartum maternal and infant sdNVP and infant ZDV tail 1-week postpartum. Eligible women on the basis of their $CD4^+$ cell counts and/or symptomatic HIV disease were started on HAART for their own health according to the 2006 WHO guidelines [17]. Maternal HAART history was assessed at each infant follow-up visit to record infant breast milk exposure to antiretroviral drugs.

Cotrimoxazole prophylaxis

Study infants received SOC CTX prophylaxis from 6 weeks of life through breastfeeding cessation and HIV-1 infection was ruled out. Ugandan study infants received CTX crushed tablets once daily (400 mg/80 mg): 5.0–13.9 kg = ½ tablet; 14.0–29.9 kg = 1 tablet and 30–34.9 kg = 2 tablets. Zimbabwean study infants received CTX suspension (240 mg/5 ml) by age bands: 120 mg from 6 weeks to 6 months and 240 mg after 6 months.

Adverse event assessment

An adverse event was defined for this trial as any unfavorable or unintended symptom, sign (including an abnormal laboratory finding) or disease temporally associated with the use of the study product (onset after enrolment), regardless of relatedness. Abnormalities with onset prior to enrollment were considered pre-existing conditions, and only classified as adverse events if they worsened, or resolved and then recurred, after enrollment.

Active adverse event surveillance included a tiered safety review and reporting process as the following. First, intensive monitoring by on-site staff including clinical assessments at the study scheduled and interim/sick visits. Mothers were instructed to promptly bring their baby to the study clinic in case of illness and if reviewed elsewhere, to bring the medical records to the study team at the next study visit. Study staff also contacted the mother to bring her baby to the study clinic immediately, if an abnormal laboratory value was identified. Second, DAIDS Medical Officer review of adverse events that met protocol-defined expedited reporting. Third, ongoing review of the clinical and laboratory data by

clinical staff of the Data Management Center at SCHARP; fourth, frequent safety data reviews by the Protocol Safety Review Team; and fifth, periodic review by the Data and Safety Monitoring Board.

Management of adverse events was according to the best clinical practice available and the judgment of the site clinical management team. The decision to hold study drug temporarily or permanently as determined by the site clinician was based on adverse event severity grade (I, II, III, IV or V) and the protocol adverse event management plan. We used the DAIDS Toxicity (2004) and Supplemental Skin-Rash Tables for adverse event severity grading [18].

Statistical methods

Simple descriptive statistics were calculated to describe adverse events (neutropenia and/or anemia and skin rash) for specified intervals of age (birth-week 6, week 6–month 6 and months 6–12) comparing SMON versus placebo arms. Baseline data (at week 6) prior to initiation of CTX was summarized by randomization arms. The proportional hazards regression model was used to compare time to first adverse event between arms. A rate ratio of adverse event was calculated using a negative binomial regression. The outcome was the number of events over follow-up (prespecified age interval). Log-linear regressions with (log) duration of follow-up as the offset, negative binomial errors were used to estimate the treatment effect on adverse events. The count event of interest was neutropenia and/or anemia (all grades), and the severe (grade ≥3) forms, and severe (grade ≥2) skin-rash. For prespecified age intervals, age-specific event rates were computed and compared between the two groups of interest. The model was adjusted for baseline and time-varying covariates including the study drug group as a covariate.

Results

Three hundred and fifty infants were enrolled in this trial, 293 (83.7%) prior to 10 August 2007 and, therefore, randomized either to SMON ($n = 148$) or placebo ($n = 145$), whereas 57 (16.3%) infants enrolled, thereafter, were not randomized and received SWEN regimen. Of the randomized infants, 39 (13.3%) determined to be on placebo following unblinding performed on 10 August 2007 were switched to open-label NVP taken through day 42. Infant HIV infection during follow-up was determined in four of 146 (2.7%) versus seven of 97 (7.2%) in the SMON and placebo arms, respectively, $P = 0.12$, and three of 57 (5.3%) in SWEN group. This analysis was restricted to HIV-uninfected infants who received SMON ($n = 146$) and placebo alone ($n = 97$). Incident HIV cases were removed from further analysis upon determination of HIV infection, four (one on SMON and three on placebo) by week 6, and seven (three on SMON and four on placebo) after 6 weeks (Fig. 1). Two infants on SMON were terminated from further study follow-up prior to the 6-week visit.

Baseline characteristics of study participants at the week 6 visit prior to initiation of CTX are summarized in Table 1. Infants in the SMON compared with placebo group had a significantly higher history of antimicrobial use, 92 versus 83%, $P = 0.03$; and significantly lower hemoglobin levels, g/dl, median [inter-quartile range (IQR)], 10.7 (9.7–11.6) and 11.4 (10.5–12.1), $P < 0.0001$. Other characteristics assessed were comparable including sex, infant weight, BMI, baseline absolute neutrophil count, ALT, skin rash, infant-ZDV tail and breast milk exposure to maternal HAART. None of the trial infants received concomitant antiretroviral drugs. All 237 infants evaluated at the week six visit initiated CTX prophylaxis taken for a median (IQR) duration of 140 (121–141) days in the SMON and 139 (127–141) days in the placebo arm. The median (IQR) duration of study-drug receipt after the week six visit was 140 (127–141) and 139 (127–141) for the SMON and placebo arms, respectively.

The majority (96%) of infants had at least one episode of neutropenia and/or anemia (all grades) and about half with the more severe forms (≥ grade 3) through study follow-up, whereas skin rash (≥ grade 2) was rare (13%). These patterns were similar across randomization arms (Fig. 2). However, adverse event incidence was highest during the first 6 weeks of life, then 6 weeks to 6 months interval and lowest in the 6–12 months period, independent of study arm (Table 2).

Time to first adverse event after 6 weeks was similar in CTX + SMON and CTX + placebo study drug groups: hazard ratio (95% confidence interval) was 1.26 (0.96–1.66) for neutropenia and/or anemia (all grades), 1.27 (0.80–2.03) for neutropenia and/or anemia (grade ≥3) and 1.16 (0.46–2.90) for skin-rash (grade ≥2). We also assessed the rate ratios of adverse events in the CTX + SMON versus CTX + placebo during the 6 weeks–6 months and 6–12 months follow-up periods, respectively. After adjusting for infant hemoglobin levels at week 6, prior antimicrobial use by week 6, infant ZDV tail and maternal HAART use, there were no statistically significant differences in incidence of neutropenia and/or anemia (all grades and more than or equal to grade 3) and skin-rash (≥grade 2), during both follow-up periods (Table 3). Similarly, there were no statistically significant differences between CTX + SMON versus CTX + placebo in separate analyses of the Ugandan and Zimbabwean cohorts, respectively (results not shown).

Hepatobiliary disorders among HIV-EU infants were rare, two of 143 and two of 93 in the SMON and placebo arms, respectively, $P = 0.65$, at week 2; and one of 143 in the SMON group at week 4, and in each instance not associated with raised ALT (≥grade 1). One infant in the SMON group diagnosed with a hepatobiliary disorder at weeks 6 and 8; months 4 and 6 had associated grade 1-raised ALT through 6 months, which was deemed not related to study drug.

Discussion

In this cohort of HIV-EU trial infants followed prospectively through 18 months of life, a relatively high occurrence of neutropenia and/or anemia was observed while skin-rash was rare; adverse event rates were highest in the first 6 weeks of life and declined thereafter, regardless of randomization arm; there were no immediate (6 weeks–6 months) or long-term (6–12 months) adverse event risks associated with concurrent use over 6 months of NVP and CTX.

To the best of our knowledge, there are no previously published data assessing the safety of concurrent NVP and CTX prophylaxis use over extended periods among HIV-EU infants. Most CTX prophylaxis safety data are based on HIV-infected individuals, particularly adults. Commonly reported adverse events with CTX prophylaxis among HIV-infected adults include rash, fever and anemia [12,13], although the drug may be better tolerated in infants [14,15]. Leucopenia is a common occurrence in adult HIV-infected patients receiving CTX prophylaxis with concomitant medications [16]. Although rare, more life-threatening side-effects may occur such as hepatitis or Stevens–Johnson syndrome [15]. The lack of published risk-benefit data of CTX prophylaxis among HIV-EU infants has impeded public health implementation. Extended CTX prophylaxis could be counterproductive to effectiveness in settings of scale-up of efficacious PMTCT interventions resulting in low mother-to-child transmission risk and with widely available early-infant HIV diagnosis [19,20].

On the contrary, extended NVP prophylaxis is well tolerated among HIV-EU infants on the basis of clinical trial evidence from African and Indian infant populations with rare reports of serious rashes (0.7%), and neutropenia (10.4%), which were similar in both intervention

and control groups [3–6]. However, among older children and adults chronic use of higher NVP doses for treatment may be associated with hepatotoxicity, severe skin rash and hypersensitivity [21,22]. In children, clinically important adverse events (all causes) associated with chronic use of NVP-based therapy includes skin rash (20–24%), neutropenia (9–38%), anemia (7.3%) and hepatotoxicity (2.4%) [22–25]. More severe forms of skin rash at least grade 2 (5–33%) [24–26] and neutropenia at least grade 3 (7%) may occur, although children in these studies were also receiving ZDV, a known cause of granulocytopenia [23].

Similar to other NVP prophylaxis trials, the NVP dose used for this study targeted achievement of drug levels 10 times the in-vitro 50% inhibitory concentration of NVP for HIV, but which is much lower than the recommended standard NVP dose for treatment of HIV-infected infants (7 mg/kg twice per day) [3–6,27,28]. The age-bands for NVP dosing used in this trial are similar to NVP regimens used in more recent trials with slight modifications with only three dose changes required in the first 6 months [3,4]. Currently, the WHO recommends more simplified NVP regimens with dose escalation to coincide with well child visits at 6 weeks, 6 months and 9 months [2].

The potential for drug–drug interactions that may result in significant patient morbidity or even death has been described extensively. Coadministration of NVP can alter the concentrations of other drugs and vice-versa [29]. The potential for interactions between CTX with other antiretroviral drugs such as ZDV and lamivudine has been reported in animal studies and among human participants [30,31]. The placebo-controlled design of the HPTN 046 NVP trial in a setting of routine CTX prophylaxis provided a unique opportunity to assess the immediate and long-term adverse event risks associated with concurrent NVP and CTX use. To eliminate any confounding effects from the ZDV tail received by some trial infants and HAART by some mothers because some maternal antiretroviral drugs appear in pharmacologically active levels in breast milk [32,33], adjustments for these variables were made in the time to adverse event and adverse event risk assessments. Although these analyses were based on a fixed sample size, there was sufficient power (>80%) to assess adverse event differences between the CTX + SMON and CTX + placebo treatment groups.

The relatively high rates of asymptomatic neutropenia/ and or anemia across the study drug groups suggest a high background of neutropenia and or anemia in this study population. This, however, may be attributable to overestimation bias because the US-based DAIDS tables with primarily white-based norms for neutrophil ranges were used to assess potential toxicity in this predominantly black-African population [34–36].

These findings are reassuring and have important policy implications as they confirm the safety of using NVP and CTX concurrently for prophylaxis over extended periods among HIV-EU infants in resource-poor settings, in which monitoring of patients on chronic medication is often not optimal. The long-duration (1 month) supplies of study drug and CTX prophylaxis dispensed for the older (after 2 months of age) study infants is critical in resource-limited settings in which individuals receiving chronic treatment often have challenges with frequent clinic visits due to travelling long distances and high transport costs [37]. Policy makers in developing countries reviewing the 2010 WHO PMTCT guidelines will be better informed regarding potential safety concerns of dual NVP and CTX prophylaxis through the first 6 months of life.

Conclusion

Concurrent use of extended NVP and CTX prophylaxis through 6 months of age among HIV-EU infants did not appear to increase the immediate or longer term risk of anemia,

neutropenia and skin rash. However, the safety of concurrent use of NVP and CTX prophylaxis beyond 6 months among HIV-EU breastfed infants as currently recommended by WHO needs further evaluation.

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J.A., Uganda site study coordinator for the HPTN 046 study, developed the DACS on 'NVP and CTX safety sub-study, data analyses plan, and took the lead in writing this manuscript. H.C. (HPTN 046 protocol chair) and M.G.F., HPTN 046 investigator, contributed to the design of the overall HPTN 046 version 2.0 protocol and provided input into the development of the DACS analyses plan, data interpretation, writing and revisions to the manuscript and served as mentors to J.A., the first author. P.M., A.K.S. and L.S.C., site investigators on the HPTN 046 trial, interpreted the data, and contributed to writing and editing of the manuscript. J.W. and E.B. carried out the statistical analysis and contributed to writing this article. M.K. and S.B. monitored and reported adverse events and contributed to writing and editing of the manuscript.

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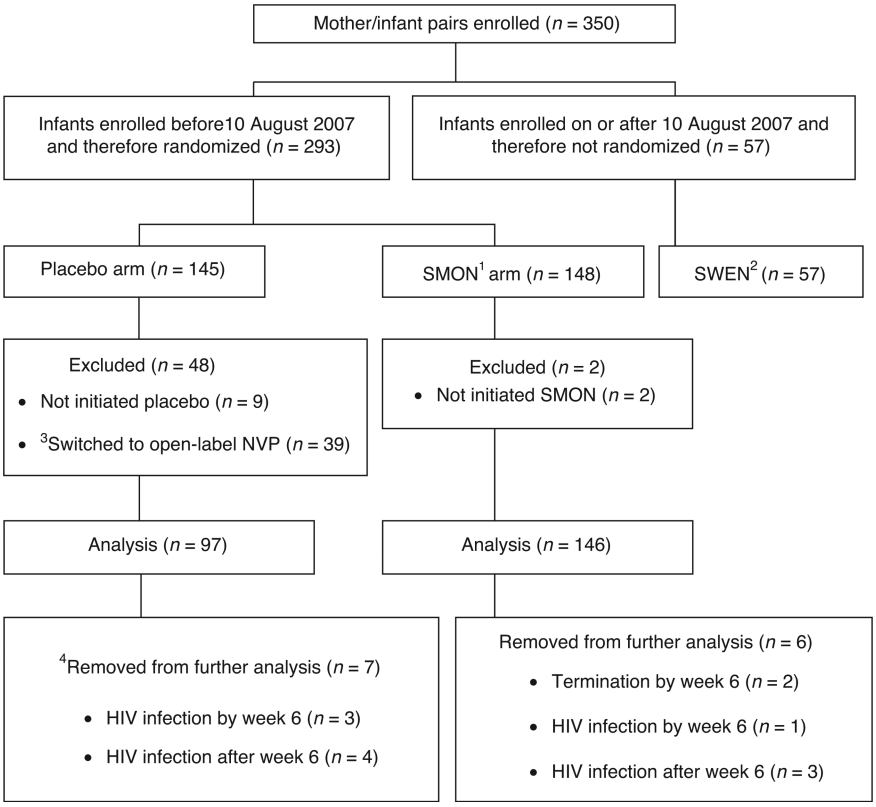

Fig. 1. Study profile

[1]SMON [6-months of Nevirapine (NVP)]; [2]SWEN (6-weeks of NVP) given as open label (active-NVP drug) to study infants enrolled after 10 August 2007 based on SWEN trial results; [3]Of the randomized infants, 39 (13.3%) determined to be on placebo following unblinding performed on 10 August 2007 were switched to open-label NVP taken through day 42; [4]Removed from further analysis upon determination of HIV infection or termination from further study participation.

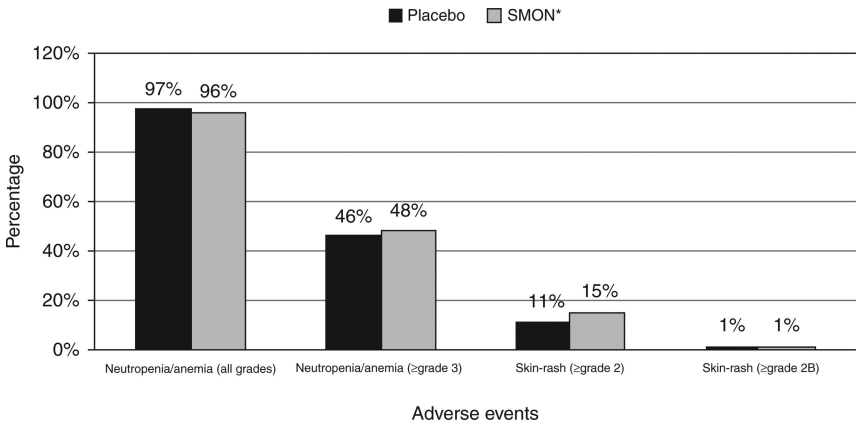

Fig. 2. Infants by randomization arm with at least one episode of neutropenia/anemia, and skin rash through study follow-up

*SMON (6-months of Nevirapine).

Table 1

Baseline characteristics of 237 infants at the week 6 visit by randomization arm.

Characteristic	Randomization arms		
	Placebo (*n* = 94)	SMON (*n* = 143)	a_P
Gender (female), [*n*(%)]	42 (45%)	74 (52%)	0.29
Weight (kg), median (IQR)	5 (4–5)	5 (4–5)	0.97
BMI (m/kg^2), median (IQR)	15.5 (14.7–16.6)	15.8 (14.8–16.9)	0.50
[b]Antimicrobial drugs [*n*(%)]	78 (83%)	132 (92%)	0.03
Hemoglobin (g/dl), median (IQR)	11.4 (10.5–12.1)	10.7 (9.7–11.6)	<0.0001
ALT(U/I), median (IQR)	15 (4–107)	15 (4–84)	0.88
ANC (cells/μl), median (IQR)	1278 (953–1890)	1360 (990–1930)	0.79
Decreased ANC (≥grade 3)	675 (568,710)	612 (585,675)	0.43
Skin rash	22 (23%)	35 (24%)	0.85
[c]Mother on antiretroviral therapy	20 (21%)	31 (22%)	0.94
Infant ZDV tail	44 (47%)	62 (43%)	0.60

ALT, alanine aminotransferase;ANC, absolute neutrophil counts;IQR, inter-quartile range;SMON, six-months of Nevirapine; ZDV, zidovudine.

[a]*P* value comparing randomization arms.

[b]Antimicrobial drugs: systemic antibiotics, antifungal and antimicrobicides.

[c]Mother on antiretroviral therapy at time of randomization.

Table 2

Adverse events incidence rates (events/infant-months) by randomization arm and infant age band.

	Randomization arms	
	Placebo	**Six-months nevirapine**
Neutropenia/anemia (all grades)		
<6 weeks	73/127 = 0.58	140/192 = 0.73
6 weeks–6 months	164/421 = 0.39	272/647 = 0.42
6–12 months	57/528 = 0.11	90/800 = 0.11
Neutropenia/anemia (≥grade 3)		
< 6 weeks	19/127 = 0.15	18/192 = 0.09
6 weeks–6 months	34/421 =0.08	73/647 = 0.11
6– 12 months	9/528=0.02	20/800 = 0.03
Skin rash (≥grade 2)		
< 6 weeks	4/127=0.03	5/192 = 0.03
6 weeks–6 months	7/421 =0.02	12/647 = 0.02
6– 12 months	2/528=0.004	8/800 = 0.01

There were no statistically significant differences between the study drug groups.

Table 3

Rate ratios of neutropenia and/or anemia, and skin rash comparing cotrimoxazole + six-months Nevirapine versus cotrimoxazole + placebo by infant age.

	Rate ratio[a] (95% confidence interval)	
Adverse event	**6 weeks–6 months**	**6–12 months**
Neutropenia and/or anemia (all grades)	1.00 (0.87–1.14)	1.01 (0.77–1.33)
Neutropenia and/or anemia (≥grade 3)	1.29 (0.82–2.03)	1.60 (0.61–4.20)
Skin-rash (≥grade 2)	1.88 (0.66–5.38)	2.23 (0.38–12.98)

[a]Adjusted for baseline (week 6) hemoglobin levels, antimicrobial use history collected at week 6 visit, infant zidovudine tail for prevention of mother-to-child and maternal use of antiretroviral therapy at time of randomization.