From 3/30/03
Remonitoring Report

Safety Evaluation Of Nevirapine In HIVNET 012

Safety Data – HIVNET 012 Database

Prior to re-monitoring of the study the HIVNET 012 study team compiled the safety data in their study database from birth through 18 months of follow-up for infants and for 6 weeks after delivery for mothers in the cohort. Some of these data, presented below, have not yet been published pending the results of this audit. The data are presented below to put the activities of the HIVNET 012 Re-Monitoring Safety Review Panel in context and elucidate the safety profile of Nevirapine in a resource poor setting. In addition, background health information for Uganda has been provided earlier in this document to put the safety observations into an appropriate context.

In this report, the terms Adverse Event (AE) and Serious Adverse Event (SAE) refer to any illnesses or symptoms experienced by study participants while they were enrolled in the study and are not necessarily due to the study drugs. Serious events generally were those that led to hospitalization.

Clinical Follow-up During the Study

During the study, research personnel provided additional care during labor and delivery. All infants were immunized and mothers were encouraged to bring their infants to the clinic when they were ill in order to track these events. Throughout the study, health visitors maintained contact with the participants at their homes, encouraging the mothers to come in for missed visits and enquiring about illnesses that occurred but were not reported to the research clinic. These health visitors knew each patient individually and used culturally sensitive methods of making the contact. As a result of their efforts, maternal and infant follow-up overall for the first six weeks of the study was 97.4% for those who received ZDV and 98% for those in the NVP group. The 18 months follow-up of the study was also high, 93.8% for the ZDV group and 96.1% for the NVP group.

Deaths during the study period

Six hundred forty-five mothers were enrolled in the study. Of these, 19 were randomized to receive placebo and are excluded from this analysis. Six-hundred nineteen (619) mothers gave birth to 629 live infants. Among these there were 11 twin and 1 triplet births. Four infants were stillborn; 2 in the ZDV group, 1 in the NVP group and 1 in the placebo arm. The number of deaths in mothers (619) who gave birth and were randomized to ZDV or NVP over 6 weeks following delivery and their living infants (632) over their first 18 months are listed in Table 1.

Table 1. Maternal and Infant Deaths up to 6 weeks and Infant Deaths up to 18 months after delivery (excluding the 19 who were randomized to placebo)

	ZDV	NVP	Total
Mothers	308	311	619
Infants (all) *	312	320	632
Infant deaths > 6weeks to 18 months	32	30	62

*excluding 3 stillborn infants, 2 in ZDV arm and 1 in NVP arm

These rates are low compared to the background rates of Maternal and Infant Mortality in Uganda and at Mulago Hospital. The Ugandan Maternal Mortality Rate is 505 per 100,000 live births. There were no maternal deaths associated with delivery during the study and 3 maternal deaths during the first 6 weeks post delivery. The Ugandan Infant Mortality Rate was reported to be 88.4 per 1,000 live births in 2000. The rate of infant deaths in the first 6 weeks in the study was well below this.

Adverse Event Reports During the Study

Mothers were followed for 6 weeks after delivery and infants were followed for 18 months after their birth. An additional long-term follow-up period from 18 months to 5 years is ongoing and the results will not be available until 2004. All maternal and infant AEs were reported for 6 – 8 weeks after receiving study drug . Subsequently, only infant SAEs and deaths were reported through 18 months. Maternal and infant AEs and SAEs are listed in Tables 2, 3 and 4.

The maternal toxicity analysis included 302 mothers who took ZDV and 306 who took NVP during labor. A small and equal number of mothers in each study arm experienced a mild maculo-papular rash. Only 3 SAEs were thought to possibly be related to one of the study drugs (NVP,ZDV or placebo). The mother who experienced severe anemia received placebo. Two other mothers who received ZDV experienced hypertension (1) and pre-eclampsia (1). Hepatomegaly and jaundice occurred in less than 1% of mothers and were equally distributed in both groups.

Table 2. Maternal SAEs and AEs within 6 weeks after study drug

	ZDV	Nevirapine
Number of mothers who delivered	(N=302)	(N=306)
Reported SAEs	3.6% (11)	4.9% (15)
At least 1 AE	85.8% (259)	85.9% (263)
Infection	22.2% (67)	25.8% (80)
Malaria	13.9% (42)	15.7% (49)
Lymphadenopathy	12.6% (38)	14.4% (45)
Anemia	10.9% (33)	13.7% (42)
Hypertension	11.9% (36)	7.5% (23)
Rash	8.8% (20)	6.9% (21)
Maculopapular rash	1.7% (5)	1.6% (5)

The infant toxicity analysis included all infants who received study product (directly dosed) or whose mother received study product (indirectly dosed). SAEs occurred in 11.3% infants who received ZDV and 9.1% of those dosed with Nevirapine. Only 9 of these SAEs were thought to be possibly related to study drug, primarily due to temporal association (Table 3).

Table 3. Infant SAEs through 6 weeks of age

	ZDV	Nevirapine
Number of infants receiving drug	(N=309)	(N=320)
SAEs within 6 weeks	11.3% (35)	9.1% (29)
SAEs within 6 weeks – possibly related to drug	2.2% (7)	0.6% (2)
SAEs within 18 months	31.4% (97)	34.1% (109)

The most frequently reported SAEs were sepsis, pneumonia, asphyxia, dyspnea, fever and meningitis. Anemia was reported as an SAE infrequently and only between 6 weeks and 18 months. Most cases of anemia were secondary to malaria. Among the 9 SAEs reported as possibly due to study drug, 7 occurred in infants receiving AZT and 2 in those on nevirapine. These reports were as follows: 1) AZT – neonatal death of unknown cause, respiratory distress and cephalomata, grunting respiration, birth asphyxia, hemorrhagic disease of the newborn, neonatal sepsis and vomiting and infectious dermatitis and 2) NVP – fresh stillbirth and transient tachypnea of the newborn.

Most infants experienced at least one AE during the first 6 weeks after birth. The most frequent AEs reported are listed in Table 4. Infant AEs in the first 6 weeks after birth were much less frequent than during the follow-up period through 18 months. Most infants experienced at least one AE and most were due to expected childhood illnesses or associated with HIV infection such as oral thrush (Table 4).

Table 4. Infant AEs through 6 weeks of age

	ZDV	Nevirapine
Number of infants receiving drug	(N=309)	(N=320)
> or 1 AE	95% (293)	81.3% (260)
Infection	27.2% (84)	25.9% (83)
Conjunctivitis	17.5% (54)	19.1% (61)
Skin Infection	17.5% (54)	9.7% (31)
Jaundice	18.4% (57)	5.6% (18)
Oral thrush	12.0% (37)	11.9% (38)

A higher number of infants who received ZDV experienced jaundice than those who received NVP. Skin infection was also higher in ZDV treated infants.

Skin rashes in infants were common and more frequently reported overall in infants receiving AZT. The types of skin conditions reported are listed below in Table 5.

Table 5. Skin conditions in infants through 6 weeks of age

	ZDV	Nevirapine
Number of infants receiving drug	(n=309)	(n=320)
Rash	26.2% (81)	18.4% (59)
Maculopapular rash	3.9% (12)	2.8% (9)
Pustular rash	4.5% (14)	0.6% (2)
Dermal exfoliation	4.9% (15)	8.4% (27)
- "normal peeling skin of the newborn"	14	24
- Exfoliative dermatitis	1	3
- Stevens-Johnson Syndrome	0	0

Infants who received NVP had a higher incidence of dermal exfoliation that was reported to be mild and described primarily as "normal peeling skin of the newborn." All of these reactions were mild and self-limited. No serious reactions such as Stevens-Johnson syndrome occurred in any infant.

Safety Observations During 2/02 NIAID Site Visit

During the February 2002 NIAID site visit, issues related to Adverse Event (AE)/ Serious Adverse Event (SAE) reporting were identified by the team. These included the following concerns:

a. The audit report noted that there was potentially under-reporting of a large number of additional serious adverse events in infants. The protocol required full reporting of all AEs and SAEs in infants up to 6 weeks after birth and SAEs from 6 weeks through 18 months of follow-up. One of the criteria for defining an SAE is hospitalization. The auditor noted that the children in the study had thousands of clinical events between 6 weeks and 18 months that he would consider serious, such as pneumonia, malaria, and malnutrition. However, because the children were not

hospitalized these were not reported as SAEs and were not considered by study staff to be serious events.

Note: During the Advance Team visit prior to the Stage 1 re-monitoring, the full clinic files of 12 infants were reviewed for all clinical events by the three physicians on the team to try determining the basis for the concerns of the original team.

For these 12 infants, the AEs that occurred in the first 6 weeks were accurately recorded in the CRFs with the exception of one HIV positive infant who experienced approximately 30 AEs. Of these, 7 events were correctly reported and 23 less serious events, such as URI, were documented in the source file and infant follow-up forms in the CRFs, but not listed on separate AE forms in the CRF. After 6 weeks, the source files contained all the clinical events for the infants, recorded on unscheduled and regular study infant follow-up forms. Some infants had numerous events, over 100, and others had a smaller number of intercurrent illnesses. All events that resulted in hospitalization were listed as SAEs and only those clinical events that were reported or ascertained at regular study follow-up visits were recorded in the CRFs. Those that were recorded as unscheduled visits were not entered in the CRFs because they were not considered SAEs by the study team.

The Advance Team noted that there were no events after 6 weeks of age that were attributed to study medication and that the illnesses were due either to HIV disease progression or the expected illnesses of childhood commonly seen in infants, in Western Africa. These included malaria, URTI, pneumonia, and gastrointestinal illnesses, most frequently. These illnesses were more frequent in HIV-positive infants.

b. There was some concern expressed by one of the American physician monitors about the adequacy of standards of clinical care in Uganda.

c. The rate of anemia among pregnant women who were eligible for and enrolled was noted to be very high. The inclusion criteria specified that hemoglobin was > 7.5 g/dL. The investigators had adapted the DAIDS toxicity scale for anemia to provide a wider graded scale for assessing anemia because 50% of the enrolled subjects had Grade 1 and 2 toxicities at enrollment.

Results of AE and SAE Re-Monitoring

The review of safety reporting and information was conducted in two phases. During Stage 1, all AEs and SAEs of 80 mother-infant pairs were reviewed and the database was compared to the source documentation to evaluate completeness and accuracy of reporting. During Stage 2, additional safety parameters were reviewed for all subjects. Any discrepancies noted during the re-monitoring were referred to the Safety Review Panel who also separately evaluated all the dermatological conditions reported and the safety reporting process.

Stage 1 Re-Monitoring

During the full review of 80 mother-infant charts, the reporting of AEs was found to be generally complete. The discrepancies that were found between the database and the source documentation were due to some missing information in the adverse event report. These are listed in the table below. These primarily included an incorrect or missing date of onset and date of contact, outcome, and incorrect date of resolution of these events. The discrepancies in severity were due to the grading of anemia using the DAIDS toxicity grading rather than the scale used by the study team that had been adjusted to reflect the high rate of chronic anemia in the eligible mothers.

Data Item Discrepant	Maternal AEs (n=131)	Infant AEs (n=202)
Contact Date	2.3 % (3)	1.5 % (3)
Onset Date	5.3 % (7)	2.0 % (4)
Onset Time	0 % (0)	2.0 % (4)
Time Unknown	0 % (0)	1.5 % (3)
Severity (see text above)	3.8 % (5)	0.5 % (1)
Verbatim reporting of event	0 % (0)	0.5 % (1)
Prescription medication given	0.8 % (1)	2.0 % (2)
Action taken on/off study medication	0.8 % (1)	3.0 % (5)
No action taken	0.8 % (1)	0.5 % (1)
Outcome	1.5 % (2)	0.5 % (1)
Date Resolved	1.5 % (2)	2.5% (5)
Relationship to Study Drug	0 % (0)	0.5 % (1)

Twenty additional maternal AEs and 13 infant AEs were found in the source documents in the study files during the first 6 weeks after delivery. None of the new maternal AEs were found to be due to study drug and no additional safety reports were required. These events included 4 new reports of anemia due to applying the DAIDS toxicity grading for anemia rather than the modified scale used by the study team, lymphadenopathy noted on physical exam (7), upper respiratory infection (3), atrophy of the right pinna (1), hypertension (1), pedal edema (1), low platelets (1), puerperal sepsis (1), and wasting (1).

The infant events included 3 new reports of anemia due to applying the DAIDS toxicity grading for anemia rather than the modified scale used by the study team, fever (1), gynecomastia (1), erythema toxicum (1), milia, forehead (1), upper respiratory infections (3), and extra digit (1). Two of the infant AEs was thought to be possibly related to study drug by the Safety Review Board. These were vomiting of study drug and skin peeling. A congenital anomaly (extra digit) was also reported to the FDA as that is a requirement of the IND.

Stage 2 Re-Monitoring

During Stage 2, the review of infant life status was completed and the reporting of deaths was investigated. The life status of 16 infants was changed following review of the source documentation from "deceased" to "unknown" (1), "unknown" to "living"(6), and "living" to "unknown" (9). Fourteen infant deaths were not in the database (cut-off 3/8/02) reviewed by EMMES, which included observations made during the long-term follow-up portion of the study (18 months to 5 years after birth). None of these deaths occurred during the 18-months of follow-up after birth. Ten deaths that occurred before 3/8/02 had been reported to the current study database after a lengthy delay and 4 occurred after the cut-off date of the database used by EMMES for their comparison of database to source documentation. Therefore, all deaths are included in the current study database.

During the Stage 2 re-monitoring, 23 unreported maternal AEs were found during the first 6 weeks after delivery. All were reviewed by the Safety Review Panel and found to be unrelated to the study medication or unable to judge the relationship. Eight of these had an unknown severity and 15 were Grade 3 or greater. Those not related to study medication included the following: decreased platelets (2), helminthiasis (1), anemia (3), non-specific dermatitis (1), bilateral axillary adenopathy (1), urticaria (1), and enteritis (1) in the ZDV group and decreased platelets (4), anemia (3), bilateral axillary adenopathy (1), chronic gastritis (1), and vaginal candidiasis (1) in the NVP group. In addition, decreased platelets (2) and both anemia and thrombocytopenia (1) were found in NVP treated mothers and the relationship to study medication could not be determined for these events.

Thirty unreported infant AEs were found during the first 6 weeks after delivery, 16 in the ZDV group and 14 in infants who received NVP. In the ZDV group, one episode of anemia (Hb 7.1 g/dL) at day 45 was judged by the panel to be probably related to ZDV. Two AEs were deemed to be possibly related (1 anemia and 1 anemia with thrombocytopenia). The 9 unrelated events included decreased platelets (2), milia (1), constipation and scabies (1), clavicular fracture (1), urticaria (1), skin peeling (1), skin lesions face (1), and small for gestational age (1). The Safety Review Panel were unable to judge the relationship of 4 rashes: heat rash, blistering rash, rash on back, and mild rash on shoulder. Among the infants who received NVP unreported AEs included anemia (3), thrombocytopenia (2), nappy rash (1), cough/cold (2), vomiting (2), impetigo (1), subconjunctival bleeding (1), and contact dermatitis (1). The panel was unable to judge the relationship of one episode of maculo-papular fine rash on forehead.

Safety Monitoring and Reporting

The re-monitoring and review process undertaken by the safety review panel has shown that there was a consistent attempt throughout the study to document AEs and SAEs as evidenced by the large numbers of such reports in the database and CRFs and the small numbers of missed events discovered in the re-monitoring process.

The study team did not report minor congenital anomalies such as extra digit as SAEs. They did not use the HIVNET 012 protocol defined grading scales for hemoglobin and skin rashes during the study. Because of the high prevalence of anemia (chronic, especially in pregnant women and acute, due to malaria) and skin rashes (particularly in infants) in the subjects, the team revised the DAIDS toxicity table grading for both anemia and skin rashes to create a more realistic scale of severity grading for their patient cohort. For example, the indication for transfusion is a hemoglobin level of 4.5 as most severe and acute anemia is effectively treated with anti-malarial medications. These revised grading scales were adopted early in the trial and used consistently but were never formally approved by DAIDS or submitted to the IND file due to communication problems between the site, the site management team and DAIDS. The re-monitoring using the DAIDS toxicity table grading scales did not elucidate any clinically significant safety signals for either hemoglobin or skin rashes.

The study team defined SAEs as those clinical events leading to hospitalization or death. This was consistent with the management of illnesses in the community and the research setting. This definition for SAEs was used consistently but was never formally approved by DAIDS or submitted to the IND file.. In a number of cases, the study team provided enhanced treatment at the research clinic to avoid potential delays in management by referral to the Acute Care Unit. In addition, several mothers refused to take their children to the hospital for hospitalization after evaluation at the research clinic. The investigators, in retrospect, realize that these events should have been considered SAEs. However, this applied to a small number of events none of which were related to study drug.

The clinical information provided by the site investigators for AEs and SAEs was not always complete and medical terminology was not used consistently or at times correctly. Required timeframes for reporting SAEs and deaths were not consistently met and there was no QA/QC process for monitoring the quality of safety reporting during the study.

Conclusion

HIVNET 012 has demonstrated the safety of single dose nevirapine for the prevention of maternal to child transmission of HIV infection. Although discrepancies were found in the database and some unreported AEs were discovered during the re-monitoring process, these were not clinically important in determining the safety profile of ZDV and NVP in this study. All infant deaths are included in the current study database. Issues with AE and SAE reporting in this study pertain to reporting requirements of IND studies, particularly timeliness of reports. The findings confirm the need for better DAIDS oversight, standard training in AE and SAE reporting, more rigorous and ongoing evaluation of safety monitoring, and more appropriate grading scales for selected safety parameters in resource-poor settings.