Betsy Smith

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The HIVNET 012 Safety Review Panel : Primary Objectives, Approach, Findings and Summary to Date

Prepared by:
Betsy Smith, M.D.
Pediatric Medicine Branch, TRP
Division of AIDS, NIAID, NIH, DHHS

The Remonitoring Protocol for HIVNET 012 was designed to look at critical sections of clinical trial conduct and acherence to the original HIVNET 012 protocol. This remonitoring process was not designed to address negligence or bias in reporting results. The following section covers the safety review of the reported data for HIVNET 012 and a small number of additional adverse events (AE's) which were found during the extensive remonitoring process. This process covered many areas of clinical site management and was not solely designed for a safety review. New AE's were submitted to the Safety Review Panel which was designated to look at safety management in the HIVNET 012 trial.

The HIVNET 012 Safety Review Panel (SRP) is comprised of two physicians who serve as DAIDS Medical Officers in the Treatment Research Program Pediatrics Section, one physician who serves as a Medical Officer in the HIVNET program, two data managers from the EMMES Corporation, the DAIDS Safety Specialist, and the Safety Coordinator of the Regulatory Operations Center Serious Adverse Event (SAE) Reporting Office. Each member has had extensive experience in safety monitoring for both government and industry sponsored HIV clinical research treatment or prevention trials, including grading events using DAIDS toxicity tables and safety reporting for IND studies using DAIDS reporting guidelines. The charge of the SRP is to ensure the correct and complete dispensation of adverse events which occurred during the implementation of the study, including those adverse events identified at the time of site remonitoring. In addition the SRP has evaluated the safety monitoring and reporting which occurred during the conduct of HIVNET 012 to determine its quality and suitability in the context of a perinatal trial.

DAIDS Serious Adverse Event (SAE) Reporting Levels

In order to describe the methods employed by the SRP to determine whether adverse events identified at the time of remonitoring should have been reported, FDA and DAIDS SAE reporting requirements must be discussed.

An adverse event is any harmful event associated with the use of a drug in humans, whether or not it is considered related to the study drug. Adverse events must be recorded on the appropriate case report forms (CRFs) to ensure that all adverse event data are entered into the study's database and evaluated according to the protocol's monitoring plan.

To determine whether an adverse event is considered serious, the SAE reporting must first be considered. There are three levels of reporting requirements for DAIDS research protocols. This

designation is determined by the Protocol Team during protocol development and is indicated in the protocol document. The SAE reporting levels are as follows:

Neonate/Infants (N) - Events at ALL toxicity Grades (1-4)
Intensive (I) - Events at toxicity Grade 3 and 4
Standard (S) - Events at toxicity Grade 4

Perinatal prevention trials usually follow neonatal reporting requirements for infants and intensive requirements for the mothers due to the vulnerability and fragility of the populations, the fact that the treatment is usually new/untested or not indicated for the study objectives and often under consideration for registrational purposes either during the trial or retrospectively.

The Vaccine and Prevention Research Programs (VPRP) utilize a modified version of intensive reporting requirements. Adverse events occurring in VPRP-sponsored studies must be reported to DAIDS if: 1) they occur any time after the first dose of study drug is taken through the twelve week period after the last dose is taken, and 2) they are deemed possibly or definitely related to the study drug, or if the relationship to the study drug cannot be determined. During this time period, the following events must also be reported to the SAE office at DAIDS regardless of the relationship to the study drug: deaths, permanent disabilities/incapacities, cancers, and congenital anomalies. Adverse events which are AIDS-related do not meet DAIDS' SAE reporting requirements but should be recorded as adverse events on the appropriate CRF.

In summary, to determine whether an adverse event meets DAIDS SAE reporting requirements, the severity (or toxicity grade) of the event, the relationship of the event to the study drug, and the timeframe during which the event occurred must be taken into consideration.

Reference Materials

Standard SAE reporting requirements are described in Section 7.3, "Adverse Experience Reporting" (pages 22 – 23) of the HIVNET 012 protocol document, Version 1.0 (dated June 5, 1997). Instructions to refer to the Manual of Operations for detailed SAE reporting procedures were also included in this section. The clinical site and Principal Investigator are again instructed to use standard SAE reporting guidelines in the Manual of Operations, Study Specific Procedures (dated November, 1997) in the section entitled "Adverse Experience Definitions and Reporting."

In contrast to the current SAE reporting requirements for perinatal studies, which utilize neonatal reporting requirements for infants, HIVNET 012 made no distinction between the SAE reporting requirements for infants and mothers (i.e., standard reporting requirements were listed for both mothers and infants in the HIVNET 012 protocol, with a grade of 4 or "serious" determined by whether or not a hospitalization occurred). During this review, the DAIDS Medical Officers and PPD monitors were instructed to use the SAE Reporting Manual for VPRP (dated 4/1/97 and developed for vaccine trials which can include normal volunteers) as the reference for SAE reporting requirements.For the review of the AE's either already reported during the trial or reported by PPD monitors during the remonitoring of the site records, the SRP followed

intensive SAE reporting requirements for the remonitoring of maternal adverse events and neonatal SAE reporting requirements for infant adverse events.

Methods Used in Adverse Event/ Serious Adverse Event Determination

The SRP reviewed a compilation of monitors' findings of potential adverse events (AE's) not listed in the SCHARP data base which occurred within the first six weeks of delivery as well as previously reported rashes which occurred within 14 days after delivery (the day of study drug dosing for the mother). The PPD monitors instructions regarding potential new AE's were to report to the SRP any previously unreported grade 3 or 4 AE's on mothers and unreported AE's of grade 1 or higher for infants during the same timeframe. In addition, unreported rashes of any grade were to be reported to the SRP by the PPD monitors. The PPD monitors were also given a listing of AIDS-related events that did not require reporting. If there was any question regarding whether something was potentially reportable, the monitors were given instructions to report it to the SRP for final determination.

The DAIDS Adult and Pediatric Tables for Grading the Severity of Adverse Events, were used to determine the severity grades of potential AE's by the SRP. The severity of rashes was graded according to the DAIDS' Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Experiences. Though listed in the protocol document, these grading tables were not followed by the protocol team during the trial according to the co-PI.

The clinical site laboratory chemistry reference ranges found in Appendix M of the HIVNET 012, Version 1.0 protocol document were used by the SRP in conjunction with the severity grading tables and local laboratory ranges to ascertain the correct severity grade of laboratory abnormalities when appropriate.

Review of Rashes Including Line Listings

The SRP reviewed the line listings (abstracted from the EMMES database) of maternal and infant adverse events which identified "rash" as the primary reaction (i.e., the "verbatim") or in which the following terms were found in the narrative of the event: ulcer, rash, dermatitis and "vesic", short for vesicular or vesicle. The SRP also reviewed any previously unreported rashes within the first two weeks after study drug exposure which were reported as potential AE's by the PPD monitors. The SRP evaluated each event with respect to relationship to study drugs and severity grade and whether it would meet criteria for an SAE as described in the reference materials.

The SRP focused on cutaneous reactions with onset occurring within two weeks after exposure to study drug (and having a blistering, pruritic, erythematous, vesicular, papular, ulcerative, or macular component, with or without and/or desquamation), as this time frame would suggest a possible relationship to study drug. Such events were considered by the SRP as potentially related to the study drug if no other diagnosis or explanation was given in source documents. Cutaneous reactions associated with systemic symptoms (such as angioedema, liver function abnormalities, serum sickness-like reaction, fever and lymphadenopathy) were considered potentially severe or life-threatening. Cutaneous reactions with onset beyond two weeks after

study drug exposure or clearly had another etiology (such as infection) were ruled out as potential study drug-associated rashes.

Failure to Thrive Review

An SRP member individually reviewed the diagnosis, failure to thrive (FTT), while on site during the Stage I remonitoring visit. Monitors and the DAIDS' team leader on site compiled a listing of 13 FTT's found during the review of the random sample of 80 infants for the SRP member. An additional 3 reports of failure to thrive were made to the database in the group of 80, however these were not individually reviewed. The 13 were reviewed by looking into additional source documents and when needed, by conferring with site investigators.

Safety Review Results
Additional AE's ,Unreported Deaths and Vital Status Found on Site by PPD Monitors

Additional AE's: For Stage I, possible adverse events noted by the Stage I monitoring team during the review of the random sample of 80 mother-infant pairs which were not thought to be contained in the SCHARP database were submitted to the SRP for review. 54 events from the first 6 weeks post treatment were submitted, 13 across both arms in the stage I remonitoring visit were determined by the SRP to be adverse events needing a case report form or CRF. 11 were determined to be unrelated to study drug and 2 were possibly related making them SAE's with a required report to DAIDS. Grading of 4 events was mild or moderate. The SRP was unable to judge the severity based on the existent information for 8.

There were an additional 27AE's for mothers and 33 AE's for infants submitted during the stage II remonitoring visit. For the mothers there were 13 AE's (all judged to be not related) which were unreported on the ZDV arm and 14 (3 with a possible relationship to study drug which could not be further determined) on the NVP arm. For infants there were 18 AE's on the ZDV arm and 15 on the NVP arm submitted to the SRP by the PPD monitors during the Stage II visit to the site. 8 of 18 unreported AE's on ZDV were either possibly related or had a possible relationship which could not be further determined. 1 of the 15 unreported AE's on the infant NVP arm had a relationship, which was possibly related to study drug since the relationship could not be further ruled out. Based on the information submitted by the PPD monitors to the SRP, additional information would have been helpful to the SRP in making decisions on these AE's and during the course of the trial it would be normal to be able to ask additional questions about an AE in order to clarify a relationship. However this review process has been terminated at this time and no further information will be obtained.

Untimely Reporting of Deaths: There were 10 deaths in infants found by the PPD monitors not previously listed in the SCHARP database prior to the DAIDS, WESTAT and BI visits to the clinical site in January and February 2002. There was also an additional "death" listed in the FHI database and found by Parexel during the review of SCHARP but this subject was not found to be dead by the PPD monitors or the SCHARP database. There were an additional 4 deaths which were reported by the PPD monitors which have occurred during this remonitoring process since March 8, 2002. In general, information on subjects' deaths is not reported in a consistent fashion

and may not reach the source documents available to the clinical site staff. The deaths noted here occurred in infants aged greater than 18 months and up to 42 months of age.

For deaths that occurred during the study, without any additional information, none appeared to be directly related to the study treatments given at onset of labor or during the first week of life. Observations show there was a delay in reporting deaths in general, sometimes taking over a year for the death to be registered in the study database. There was a flurry of death reports to the database at SCHARP just prior to and after March 8, 2002. This was the date requested for the database to be frozen. The increased reporting may have been in response to the need to update data entry due to these pending reviews. The database was not actually frozen on March 8, 2002, however, and thus the ability to over write the database remains. Although queried by the Remonitoring Protocol Team, this failure to carry out the DAIDS request has not been followed up by the DAIDS project officer.

Vital Status Discrepancies: During the Stage II remonitoring visit the remonitoring tools for 5 subjects incorrectly reported their vital status as unknown, and afetr additional review by EMMES it was determined that the vital status was known for these 5 women within the first 6 weeks of the study. The PPD monitors however were unable to determine the correct vital status of these women from the PPD review of the source documents on site. This raises a concern about the integrity of the source documents at the site and underscores the difficulty of finding information by the monitors utilizing the site source documents from the first 6 weeks after study treatment, a problem which is sure to affect the health care givers at the site as well. There were an additional approximately 57 subjects with unknown vital statuses within the first 6 weeks of the trial which were verified by the PPD monitors as unknown based on their review of the site source documents. The above noted discrepancy in vital status listing in the source documents at the site has not been further evaluated.

Rash Review Results :Rashes previously reported during the study within 15 days after dosing have been reviewed for all study subjects (626 Mother infant pairs) using the methods noted above. 163 infant rashes were reviewed. Four of the total of seven which were possibly related might have been graded a higher toxicity grading(two grade 2's, a grade 3B and a grade 4) based on only the information available to the SRP, without the benefit of further query. Four of the 156 which were unrelated to study treatment might have been graded a higher toxicity grade based on the information available to the SRP. Thirty-five maternal rashes were reviewed and none was re-graded by the SRP. One of the 2 listed as possibly related by the HIVNET investigators was thought not related to study treatment due to its clinical course and the information available to the SRP.

Six additional infant rashes possibly related to study treatment were reported to the SRP during the remonitoring process. Of these, 4 were on the ZDV treatment arm, within the first two weeks of infant dosing. None was a grade 3 or life threatening in severity. No additional rashes were reported by the PPD monitors for women.

Additional Laboratory AE Review: Hemoglobin and platelet values for all study subjects in the 6 weeks after dosing have been reviewed for all subjects. The grading by the HIVNET 012 team was often left off of crf's or underestimated according to DAIDS toxicity grading tables. A

review of age-adjusted hemoglobin grades for infants on NVP with no reported AE's showed a total of 118: 89 had varying degrees of grade 1 (13 were < /= 8.9), 17 had degrees of grade 2 (8 were </= to 8.9),and 11 had grade 3 hemoglobin levels. The review of age-adjusted hemoglobins for infants on ZDV and no reported AE's showed a total of 123 : 77 of grade 1, 39 of grade 2 and 7 of grade 3.

A review of all maternal hemoglobin grades of grade 3 or higher showed on the NVP arm, 25 of grade 3 and 7 of grade 4. On the ZDV arm, there were 43 grade 3 and 4 grade 4. A small number of women may have been enrolled on the study with hemoglobin of 7.5 as this grade 3 hemoglobin was allowed at entry onto the HIVNET 012 study. A pre-exisisting grade 3 value would be unrelated to study treatment unless the grade worsened.

A review of thrombocytopenia showed on the ZDV treatment arm showed 10 infants : 3 infants with grade 2, 6 with grade 3 and 1 with grade 4, not reported on AE forms. On the NVP arm there were 13 infants in the first 6 weeks after study treatment with decreased platelets: 7 infants showed a grade 2, 4 a grade 3, 2 a grade 4.

Maternal platelets review showed 12 on the NVP arm : 6 with grade 3 and 6 with grade 4. On the ZDV arm there were 8: 3 grade 3, 3 grade 4 and 2 grade 5/life threatening/deaths.
AE reports would be required for these grades.

Results of Failure to Thrive(FTT) Review: FTT in the random sample of 80 infant subjects in Stage I showed with few exceptions, most FTT occurred in setting of underlying illnesses, especially complications of advanced HIV infection and conditions common in population from developing countries with low economic status. FTT occurred long after exposure to study agent except in one case (which had an onset within approximately 9 weeks of study drug exposure) and was assessed as extremely unlikely to be related to study agent in all cases.

Table: FTT by treatment and HIV status:

	NVP	AZT
HIV+	4	3
HIV-	4	2

Median time to diagnosis of FTT (all treatment): 9 months. None before 2 months and 85% (11 of 13) after 3 months of age.
Median time to diagnosis of FTT by HIV status: HIV+ = 3.5 months (2.5 – 9), HIV- = 12 months (9 – 18).
Median time to diagnosis of FTT by treatment: NVP = 9 months, AZT = 3 months.

Site Management of Subject Study Visit Records and Safety Monitoring: Not withstanding the protocol designated reporting requirements or the intensive or neonatal reporting requirements chosen by the SRP for the safety re-monitoring process, visiting the clinical site in Uganda has shown that site personnel did not refer to either VPRP or other DAIDS reporting requirements referred to in the protocol. No reporting guidelines were on file at the site. Investigators at the site appear to have received no specific safety reporting instructions, training or substantive

monitoring of SAE reporting during the protocol and can not describe having received such in retrospective interviews with DAIDS' staff. DAIDS toxicity tables, rash supplemental grading tables or protocol derivations were not uniformly followed by the study chairs. The protocol document was inconsistently followed. Review of SAE reports shows common, FDA-defined time frames for reporting were not adhered to, nor monitored by the site management contractor, FHI, in charge of safety monitoring during the study. The HIVNET 012 team, including PI and co-PI's, has acknowledged using less stringent toxicity grading scales and creating a team-defined, reporting algorithm for study with the goal to report fewer AE's and SAE's. This was not found to be present in a SOP anywhere, including on site, in February 2002. The team derived toxicity grading and SAE reporting plans were never part of the protocol, were not submitted to FDA, IRB's or DAIDS Regulatory Branch. It is not possible to tell if notification of the changes in the toxicity grading, SAE reporting, and loose adherence to reporting requirements for time frames were sent to the Prevention Sciences Branch or its 1997/1998 equivalent, the then Branch Chief, or the DAIDS medical officer, however conversations with HIVNET 012 team members reinforce the fact they all worked very closely together and decided most things by consensus with the FHI representatives. Further evaluation of the safety monitoring in place by the HIVNET 012 team would require review of the FHI site and more thorough review of the FHI.

Subject records on site were of poor quality and below expected standards of clinical research considered at the forefront of medical research. During active enrollment and during the majority of the HIVNET 012 study, clinical site patient visit records documenting study visits were scattered across several areas of the charts and the clinic site making visit chronology, clinical follow up and study laboratory results difficult to follow for clinical staff at the site,monitors, site supervisors. Hospital records were not kept in any organized format, making them generally inaccessible to clinical site staff, however, in the SCHARP database "hospital" records were sited as source documents for some deaths. This problem was never apparently addressed by the study team or site staff. A review of subjects' hospital records to determine missed SAE's and deaths was found to be quite feasible and actually a common practice by contractors involved in South African research protocols (not DAIDS projects), and although requested by the Remonitoring Protocol Chair and recommended by consultants to the protocol, such a review was never allowed to be submitted for consideration by the hospital or the site IRB and was put on permanent hold by the director of DAIDS and the two team leaders after reported consultation with the FDA. Notes, including visit notes, and changes to the patients' study files appeared most often to be routinely undated and unsigned. Descriptions of health status, interim history and abnormal physical exam pertinent negative findings were often absent at each study. Follow up of abnormal findings in a physical exam or in a laboratory value from previous visits was not routinely done in a timely fashion during the study and was very difficult to do during the remonitoring process. Abnormal laboratory values were not consistently followed to resolution. Abnormal findings, signs or symptoms on physical exam were rarely followed consistently, but were sometimes "rediscovered" as if they were new events with the same differential diagnosis questions re-expressed, though not worked up, ruled in or ruled out. AE/SAE reports on subjects were not tracked to verify submission to the SCHARP or FHI databases. Changes to AE/SAE reports were not routinely dated and resubmission to the databases was not tracked at the site. No reconciliation process was in place to verify consistent AE/SAE records between the site or the FHI and SCHARP databases.

Monitoring reports which should have covered safety reporting during the trial were done by FHI and distributed in an unknown manner by FHI. Those records and distribution lists reside at FHI. A review of FHI with special emphasis on safety monitoring plans and activities during the trial, which should have included submissions to the FDA and both IRB's on safety, has been repeatedly requested by the Remonitoring Protocol Team and has met with inexplicable delays. DAIDS pharmacy and regulatory personnel who were identified by the protocol team to give needed input into a review at FHI were not contacted to help plan a site visit to FHI. To date, the safety review at FHI has not occurred and the Remonitoring Protocol Team has not been involved.

HIVNET 012 Safety Monitoring Quality and Safety Review Summary Comments

The review process (involving the first six weeks after study treatment) has shown that there was a consistent attempt during the first weeks of the trial to document AE's and SAE's, although reporting requirements and toxicity grading were not followed correctly. There was a general lack of recognition of minor, common, or inherited congenital deformities as SAE's. Grading for rashes and decreased hemoglobin did not follow the grading tables as described in the HIVNET 012 protocol and in general were graded more mildly than commonly seen in perinatal trials sponsored by DAIDS. Information included by the site when reporting AE's or SAE's was generally sketchy with a few notable exceptions among the health care providers who were only temporarily at the site. There is no listing of the temporary or transient health care providers, what their training was, what their duration of residence at the site was or what their designated responsibilities were. Confusion between a symptom and a diagnosis and correct medical terminology (sepsis appeared to be used indiscriminately) appears to exist when writing up AE's and SAE's on site. Acceptable or required timeframes for reporting SAE's and deaths were not adhered to and no evidence for a QA/QC process for monitoring this data during the study was noted. Instructions for reporting SAE's and grading toxicities were either not given to site personnel at study initiation or not reviewed during the study. Thus the safety reporting quality for the HIVNET 012 study does not meet levels expected in perinatal trials sponsored by DAIDS. There is also evidence of a lack of reconciliation between the safety data bases at the study data center, SCHARP, and the operations site management center, FHI. This is based in part on inconsistent vital status information of one of twelve randomly selected PID's submitted to PAREXEL by EMMES, to assist with the PAREXEL review of SCHARP.

The re-grading of AE's in the laboratory values is resulting in new tables for the IND. These discrepancies in reporting may result in the need for new safety reports for the FDA.

FTT was not usually attributed to study treatment in the cases reviewed, and it appeared that the decision was reasonable upon reviewing the 13 out of 16 cases from the Stage I review. FTT was not further specifically followed up in Stage II.

The monitors used for the remonitoring will be requested to help clarify some additional missing information on several of the previously unreported or incorrectly reported deaths for additional reporting to the IND. The deaths to date however appear to have occurred both in close proximity to the original 18 month part of the study (2) as well as during the 5 year extension

which was added to the study to verify long term safety of the short term treatments. The additional death clarifications may impact the long term follow up of study.

The supervision of all aspects of safety, including subject information regarding treatment risks, fulfillment of eligibility criteria for mothers and infants as well as safety reporting does not appear to have been in place. The monitoring of safety reporting at the site does not appear to have occurred during the trial. Site safety reporting appears strongest in the first week visit of the study. However, known or expected adverse events specific for the study drugs did not appear to be specifically queried at study visits and AE's were determined to be absent if no mention of those possible AE's was made. Reporting AE's to the study staff in a timely fashion in the first days or weeks after drug administration appeared to be difficult, making attribution of rashes, etc., a challenge when noted retrospectively. Safety follow-up becomes less clear after the first 6 weeks of the study even for infants. The lack of monitoring of the site safety reporting as well as the reliance of the site investigators on the key role of the US investigator (who did not see the subjects) in decision making raises concerns about the conduct of the trial from the safety perspective. SOP's for safety reporting , including death reporting, and monitoring of safety reporting as well as reporting guidelines must be put into place at the site immediately if the HIVNET 012 trial should continue to remain open. Clearly the investigators, including PI and co-PI's and health care staff, need additional mentoring and re-instruction (e.g. on how to follow reporting requirements and toxicity grading tables, clinic visit note writing, correct medical terminology, appropriate management of source documentation, proper supervision of clinical research involving human subject volunteers) in this area for a minimum time to be determined by the JHU and MU institutions, e.g. 3 years mentoring before being granted supervisory status as PI/co-PI's, if they continue to do clinical research.

There are many known challenges, advantages and opportunities which exist when doing research in new drug applications in populations with unique social and health care practices. It can be helpful in the future if investigators writing a protocol for such a setting consider acknowledging more fully (even in the protocol document) the unique aspects of the study setting and population or the possible innovations which would need to be instituted to properly conduct high quality clinical research according to GCP standards.

Abbreviated Summary

-Safety reporting did not follow DAIDS reporting requirements during the conduct of HIVNET 012. Safety conclusions from this trial should be very conservative.

-Site records for safety monitoring and subject visits were of poor quality and make safety statements very difficult from the perspective of a review process. Changes should be instituted immediately as HIVNET 012 remains open with subjects.

-Monitoring during the trial for safety or clinical trial management was not in evidence.

-New grading of adverse events including unreported deaths will result in amended tables for the IND record.