The HIVNET 012 Safety Review: Findings and Summary
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Safety Review Background

The Remonitoring Protocol for HIVNET 012 was designed to look at critical sections of clinical trial conduct and adherence to the original HIVNET 012 protocol. This monitoring process was not designed to address missing information or bias in reporting results. The following section covers the safety review of the reported data for HIVNET 012 , a small number of additional adverse events (AE's) and Serious Adverse Events (SAE's), toxicity grading used by the study team, laboratory toxicity review by study arm and observations on subject study management such as medical records, study screening for eligibility and adverse event management, all part of the safety management of the HIVNET 012 trial. New AE's were submitted by the PPD monitors to the Safety Review Panel to determine the need for any additional safety reports for the FDA . Safety was reviewed during both Phase I and Phase II of the remonitoring process.

The HIVNET 012 Safety Review Panel (SRP)

The SRP was 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 was 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 Requirements

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 first 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

Due to the vulnerability of the study populations in perinatal treatment trials it is uncommon to follow standard safety reporting requirements. In addition the study treatments are frequently new or untested or not labeled for a specific use in the perinatal population, either pregnant women or their unborn /newborn infants. Thus some studies are also under consideration as pivotol or registrational studies where safety is still a major study objective. Intensive reporting requirements are usually followed for the mothers and neonatal reporting requirements followed for their infants. In the mid nineties this was certainly the case in DAIDS perinatal protocols and most protocols described this type of safety reporting.

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 12-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, whether or not they result in a hospitalization, 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 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. AE's become SAE's if they are of a certain toxicity grade or the treating physician feels it is of a serious nature, they are unexpected and they have a relationship to study drug. Safety reports are generated for SAE's after the SAE is reviewed.

Reference Materials for the Safety Review

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 were 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."

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 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 . There were rare occasions when the SRP referred also to the DAIDS TRP Reporting Manual (dated 6/1997) because the VPRP manual did not apply to subjects with underlying HIV/AIDS. 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) during the first six weeks after study drug administration not listed in the original HIVNET 012 database maintained by the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). Rashes of any grade, found in either the source documents or in line listings from the HIVNET SCHARP 012 database, which occurred within 14 days after delivery (the day of study drug dosing for the mother) were also reviewed. The PPD monitors submitted any previously unreported grade 3 or 4 AE's on mothers and grade 1 or higher AE's for infants during the six week timeframe. 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 reported it to the SRP for final determination. Abnormal laboratory values (hemoglobin, platelets, SGPT, bilirubin) from the HIVNET 012 database were reviewed from the first six weeks after study drug dosing for mothers and infants.

It should be noted that the SRP only had access to the SCHARP HIVNET 012 database of line listings for AE's. There remains an additional HIVNET 012 AE database at Family Health International (FHI) which was the database source for safety reports to the FDA, and which was not available to the SRP. The FHI and SCHARP HIVNET 012 databases are not reconciled according to a review done by PAREXEL.

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.

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 from the HIVNET 012 Database

The SRP reviewed the line listings in the SCHARP HIVNET 012 study database of maternal and infant AE's 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

Failure to thrive (FTT) was a diagnosis more common in the HIVNET 012 study population than in either European or US perinatal study populations. Therefore an SRP physician member individually reviewed the FTT diagnosis while on site during the Stage I remonitoring visit to evaluate its relationship to study drugs using all possible source documents. Monitors and the DAIDS' team leader on site compiled a listing of 13 FTT's found during the review of the Stage I random sample of 80 infants for the SRP member. An additional three reports of failure to thrive were made to the database in the group of 80, however these were not individually reviewed. The 13 FTT reports were reviewed by looking into additional source documents and when needed, by conferring with site investigators who had seen the subjects or knew the cases.

Safety Review Results

Site safety reporting methods

The timeframe for reporting AE's and SAE's , including deaths, was highly variable. The HIVNET 012 method of reusing the AE report forms repeatedly and refaxing them to the PI in the US and then faxing them to FHI made it difficult to follow the evaluation and resolution of AE's. Dates stamped on the reverse of the CRF for the AE were not visible to the HIVNET 012 study team during the repeated faxes, thus tracking, QA/QC and timeframes would have been extremely difficult for the study team to monitor as well. Often source documentation for identification, management or resolution of AE's and SAE's was difficult to identify and follow due to organization of site records. Subject notes were commonly unsigned and undated making it difficult to follow AE's in clinical notes for HIVNET 012.

Grading of clinical event AE's was simplified and events and laboratory values were more mildly graded by the HIVNET 012 team as compared to the DAIDS toxicity grading tables. DAIDS toxicity grading tables were not followed consistently for laboratory AE's. Hemoglobin grading in the DAIDS toxicity tables was not followed for the mothers at all.

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

Additional AE's: Stage II There were an additional 27 AE's for mothers and 33 AE's for infants submitted during the Stage II (less intensive review covering fewer variables) remonitoring visit. For the mothers there were 13 AE's (all judged by the SRP to be not related) 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. Eight of 18 unreported AE's on ZDV were either possibly related or had a possible relationship which could not be further determined. One of the 15 unreported AE's on the infant NVP arm was possibly related to study drug or had a relationship that could not be ruled out. Additional information would have been helpful to the SRP in making decisions on these AE's and during assessments made in the course of the trial it would be normal to ask additional questions about an AE in order to clarify a relationship. This review process has been terminated by the Division of AIDS at this time and no further information will be obtained.

Untimely Reporting of Deaths: There were delays in reporting some of the deaths during the follow up beyond the first 18 months of the study, sometimes taking over a year for the death to be registered in the study database. 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 noted by PAREXEL during the site visit of SCHARP conducted in September 2002, but this subject was not found to be dead by the PPD monitors or the SCHARP database. There were an additional four deaths which were reported by the PPD monitors which have occurred during this remonitoring process since March 8, 2002. Information on subjects' deaths was not always available and might 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. No deaths appeared to be directly related to the study treatments though the onset of the causes of death were not traced back to their origination and only the information supplied from the source documents by the PPD monitors was available to the SRP.

There was a notable increase in number of death reports to the database during March 2002. March 8, 2002 the database was requested to be frozen by DAIDS and a sample database was transferred to EMMES in early July 2002. After the four-day database transfer, it was discovered the database was not electronically frozen and the ability to over-write the database remains as noted during the data review during the remonitoring process. The inability to carry out the DAIDS request was also noted during the PAREXEL review and no explanation was given. The

SCHARP contract is managed by the Prevention Sciences Branch of the Vaccine and Prevention Research Program at DAIDS.

Vital Status Discrepancies: During the Stage II remonitoring visit the remonitoring tools for 5 subjects incorrectly reported their vital status as unknown, and after additional review of AE and death reports in the database 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 their 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 monitors experienced in those source documents. There were an additional 47 subjects with unknown vital statuses within the first 6 weeks of the trial, 41 of which were verified by the PPD monitors as unknown and 6 changed to "living" 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 maternal rashes were reported by the PPD monitors.

Additional Laboratory AE Review: Review of required lab results for HIVNET 012 was done by the SRP as the laboratory requirements for a drug study are chosen for safety monitoring purposes during the study. Hemoglobin and platelet (thrombocytes) abnormalities are expected adverse events for both study drugs. Bilirubin abnormalities are noted in the current package insert (PI) of NVP for both adults and children > 2 months of age (NVP is not yet FDA approved for dosing in newborns and thus newborn bilirubin elevations as well as other newborn lab abnormalities would not have been studied previously). Bilirubin abnormalities are noted in the PI (appears to be a single case report or a very limited number of reports) in adults on ZDV but not newborns on ZDV and therefore bilirubin abnormalities due to ZDV would not be expected in infants. Bilirubin elevations can be common in the first weeks of life, thus the HIVNET 012 specified bilirubin in infants were compared between the two study drugs to discern if there were differences in bilirubin elevations possibly due to a specific study drug during the study. SGPT was also required for HIVNET 012 and is an expected adverse event for mothers on either study drug and for infants (> 2 months on NVP) on either study drug and is listed in the PI's for both study drugs.

The results of the bilirubin review by treatment, approximately 310 infants on each treatment arm, show that on day 7 post treatment, the number of infants on ZDV with grade 3 was 132 (44 with other concurrent, AE's reported, 88 without) and grade 4 was 64 (24 with additional concurrent AE's, 40 without). The number of infants on NVP with grade 3 was 125 (35 with additional concurrent AE's and 90 without) and with grade 4 was 28 (9 with additional Concurrent AE's and 19 without). There was a limited number of infants who received placebo before the placebo arm of HIVNET 012 was dropped, 19, and there were 7 of grade 3 and 4 of grade 4 .

The risk for infants for a grade 4 bilirubin elevation appears to have been significantly higher if the infant was on ZDV. The difference in grade 4 bilirubin levels between the treatment arms was significant to the P<.0001 level showing the difference was very unlikely due to chance alone. The bilirubin elevations were not different between the treatment arms at birth, became different at 7 days post treatment and had returned to a baseline at least by the 6 weeks visit. The infants who had the grade 4 bilirubins have not been followed up to determine if any difference in morbidity or mortality was conferred by the difference in the risk of grade 4 bilirubin levels.

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 the study data base or underestimated according to DAIDS toxicity grading tables. A review of age-adjusted hemoglobin grades for infants on NVP with no additional reported AE's showed a total of 118: 89 had grade 1 (13 were < /= 8.9), 17 had 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. [Note that when another AE was submitted on a subject, it was not always related to hemoglobin, so these numbers are underestimated if on subjects with existing AE's, no grading of an accompanying hemoglobin laboratory abnormality was entered by the site.]

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 44 grade 3 and 4 grade 4. A number of women enrolled on the study with hemoglobin of 7.5 as this grade 3 hemoglobin was allowable at entry onto the HIVNET 012 study. A grade 3 value would be considered unrelated to study treatment if the entry value were the same or a higher toxicity grade(pre-existing), but not if the entry value were a lower toxicity grade.

A review of infant thrombocytopenia on the ZDV treatment arm showed 10 infants with no other AE's : 3 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.

A review of abnormal maternal platelets of grade 3 or higher grade within the first week of study treatment in women with no other AE's reported, showed 12 on the NVP arm: 6 grade 3 and 6 grade 4. There were 8 on the ZDV arm: 3 grade 3, 3 grade 4 and 2 grade 5/life threatening/deaths.

AE reports would be required for these grade 4 events.

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 the 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	ZDV
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. Investigators at the site appear to have received incomplete or inadequate safety reporting instructions, training or substantive monitoring of SAE reporting during the protocol and records of who received training were variable. The process of initiation, write up, follow up and review of SAE's was not clear, however, the site appeared earnest in its safety reporting attempts and willing to follow those procedures which were apparently condoned by all involved in the day to day operations of the protocol. DAIDS toxicity tables, rash supplemental grading tables or protocol derivations were not uniformly followed by investigators writing up AE's and SAE's. Review of SAE reports shows common, FDA-defined time frames for reporting were not adhered to, and possibly not clarified by the site management contractor, FHI, in charge of safety monitoring during the study. The HIVNET 012 team, including PI and co-PI's, used less stringent toxicity grading scales and created a team-defined reporting algorithm for study with the admitted goal to report fewer AE's and SAE's. The team derived toxicity grading and SAE reporting plans were not part of the protocol, or 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 other areas of DAIDS. Conversations with HIVNET 012 team members reinforce the often repeated fact that they all worked very closely together and decided most things by consensus with the FHI and DAIDS team members. In fact, all served as authors on the Lancet Article published after the interim review for HIVNET 012. Further evaluation of the safety monitoring in place by the HIVNET 012 team would require a more thorough review of

FHI and the individual levels of the monitoring process by the remonitoring protocol team, which is not planned.

Subject records on site were of poor quality and below expected standards of clinical research considered at the forefront of medical research. 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 physical exam pertinent negative findings were often absent from a visit note. Follow up of abnormal findings in a physical exam or in a laboratory value from previous visits was not routinely done 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. Known or expected adverse events 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. During 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 as well as monitors. 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. Hospital records were not consistently known about or kept in any organized format, making them generally inaccessible to clinical site staff. The source documents for deaths were often unknown. A review of subjects' hospital records to determine missed SAE's and deaths was found to be feasible (actually a common practice by experienced contractors involved in African research protocols), and was recommended by consultants to the protocol. However, further inquiry was put on "hold" by the DAIDS team leaders after "consultation" with the FDA.

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, headed up by the Clinical Research Monitoring Branch, and the Vaccine and Prevention Research Program with special emphasis on trial and safety monitoring and activities during the trial, including submissions to the FDA and IRB's on safety, has met with numerous delays and down-sizing. DAIDS pharmacy and regulatory personnel who were identified by the protocol team to give needed input into a review at FHI have been excluded. To date, the safety review at FHI has not occurred.

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 followed and no QA/QC process for monitoring this data during the study was noted. There is no evidence that either FHI or DAIDS staff ever gave instructions for changes in the safety monitoring to the site and the archives from FHI for HIVNET 012 have not been reviewed to determine how this was managed by the site and the protocol team. 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. The re-grading of AE's in the laboratory values is resulting in new tables for the IND.

The review of laboratory AE's resulted in an observed difference between the treatment arms in the infants. Bilirubin elevation is not an expected adverse event for either study drug, however since bilirubin elevation shortly after birth is generally common in newborns and not harmful unless it reaches a very high level, hyperbilirubinemia would not have been noted as unusual were there not the difference between the treatment arms. The question of the ability to treat hyperbilirubinemia in the study setting or whether additional monitoring should be in place for future trials to ascertain the impact of the risk of hyperbilirubinemia in infants in this population should be considered for future DAIDS sponsored trials. There may be a genetic basis for the increased risk of hyperbilirubinemia in the ZDV arm, which may impact the metabolism of ARV's in the population. Alternatively, there may have been some effect on breakdown products in the ZDV due to its non-traditional storage temperature or storage methods and product monitoring. An additional observation is that the small number of placebo treated infants had similar percentages of grade 3 and 4 bilirubin elevations to the infants in the ZDV treatment arm, so the possibility of whether NVP provided a moderating effect on bilirubin cannot be adequately addressed due to the very small numbers. Other perinatal trials using ZDV with or without NVP have not reported this finding, though additional trials were not reviewed for this report. A literature review did not show the hyperbilirubinemia as a risk for ZDV or NVP, though most literature derives from clinical trials in other populations.This will result in the need for a 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 cases in Stage I. FTT was not further 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 will be important for the long term follow-up study.