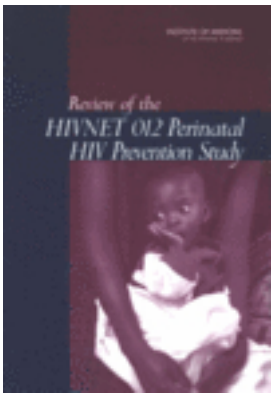

Review of the HIVNET 012 Perinatal HIV Prevention Study

Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study, Board on Population Health and Public Health Practice

ISBN: 0-309-55012-2, 150 pages, 6 x 9, (2005)

Review of the HIVNET 012 Perinatal HIV Prevention Study

Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. N01-OD-4-2139, Task Order No. 146 between the National Academy of Sciences and the National Institutes of Health. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); http://www.nap.edu.

International Standard Book Number 0-309-09651-0

Library of Congres Control Number 2005931056

For more information about the Institute of Medicine, visit the IOM home page at **www.iom.edu.**

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Adviser to the Nation to Improve Health

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON REVIEWING THE HIVNET 012 PERINATAL HIV PREVENTION STUDY

JAMES H. WARE, Ph.D. (Chair), Dean for Academic Affairs and Frederick Mosteller Professor of Biostatistics, Harvard School of Public Health, Boston, MA

R. ALTA CHARO, J.D., Elizabeth S. Wilson Professor of Law and Medical Ethics and Associate Dean, School of Law, University of Wisconsin-Madison

EZRA C. DAVIDSON, Jr., M.D., Associate Dean, Primary Care and Professor and Past Chairman, Department of Obstetrics & Gynecology, Charles R. Drew University of Medicine and Science, Los Angeles, CA

WAFAA EL-SADR, M.D., M.P.H., M.P.A., Professor of Clinical Medicine and Epidemiology, Mailman School of Public Health, Columbia University, and Chief, Division of Infectious Diseases, Harlem Hospital Center, New York, NY

MARK W. KLINE, M.D., Professor of Pediatrics, Chief of Retrovirology; Director of the AIDS International Training and Research Program; Director of the Baylor-CDC Global AIDS Technical Assistance Project; and Associate Director of the General Clinical Research Center, Baylor College of Medicine, Houston, TX

STEPHEN W. LAGAKOS, Ph.D., Henry Pickering Walcott Professor and Chair, Department of Biostatistics, Harvard School of Public Health, Boston, MA

J. RICHARD LANDIS, Ph.D., Professor of Biostatistics and Director, Division of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine

GEORGE W. RUTHERFORD, III, M.D., Professor and Director, Institute for Global Health, University of California, San Francisco School of Medicine

CHARLES van der HORST, M.D., Professor of Medicine, University of North Carolina-Chapel Hill

Staff

ALICIA R. GABLE, M.P.H., Study Director

ALINA BACIU, M.P.H., Program Officer

RUTH KANTHULA, M.P.H., Senior Program Assistant

SANDRA HACKMAN, Copy Editor

ROSE MARIE MARTINEZ, Sc.D., Director, Board on Population Health and Public Health Practice

Consultants

NANCY CALLES, B.S.N., R.N., A.C.R.N., Baylor International Pediatric AIDS Initiative, Baylor College of Medicine, Houston, TX
TOMMY CLARK, Ph.D., University of California, San Francisco
DAVID W. FEIGAL, M.D., M.P.H., Arizona Biodesign Institute, Phoenix, AZ
MARGARET G. FERRIS, M.P.H., Baylor International Pediatric AIDS Initiative, Baylor College of Medicine, Houston, TX
VALERIE FLAHERMAN, M.D., M.P.H., University of California, San Francisco
THOMAS NEWMAN, M.D., M.P.H., University of California, San Francisco
LAURA SMEATON, M.S., Harvard School of Public Health, Boston, MA

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

SOLOMON BENATAR, M.D., University of Cape Town, South Africa
EDMUND V. CAPPARELLI, Pharm.D., University of California, San Diego
HOOSEN COOVADIA, M.D., University of Kwazulu/Natal
SCOTT M. HAMMER, M.D., Columbia University, New York, NY
CAREL IJSSELMUIDEN, M.D., Council on Health Research for Development, Switzerland
KYUNGMANN KIM, Ph.D., University of Wisconsin, Madison
DEBRA LAPPIN, J.D., B&D Sagamore, Washington, DC
LISA RARICK, M.D., Gaithersburg, MD
PAUL VOLBERDING, M.D., University of California, San Francisco

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **CHARLES C.J. CARPENTER, M.D.,** Brown University and **GIL OMENN, M.D., Ph.D.,** University of Michigan. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Mother-to-child transmission of HIV-1 afflicts hundreds of thousands of children every year, especially in parts of the world such as sub-Saharan Africa, where HIV infection is prevalent and resources are limited. This tragic reality has spurred researchers to search for an effective, safe, and inexpensive treatment that could reduce the risk of perinatal HIV transmission.

At a time when many countries had no affordable, easy-to-use options for preventing perinatal HIV transmission, the 1999 publication of preliminary results from the HIVNET 012 trial offered great hope. This study found that a short-course of oral nevirapine given to the mother during delivery and to the child after birth could substantially reduce the risk of mother-to-child transmission of HIV-1 infection. A number of countries in Africa and elsewhere subsequently adopted the HIVNET 012 regimen as the standard of care in their national perinatal HIV prevention programs.

Since the original publication and a second publication with more complete findings from HIVNET 012, questions have arisen in the scientific and medical communities and have been reported by the media about the conduct of the HIVNET 012 study. It was in this context that the Institute of Medicine was approached by the National Institutes of Health (NIH) to conduct an independent review of the HIVNET 012 trial.

The Institute of Medicine convened a panel of nine members who possess significant breadth and depth of expertise in pertinent fields, including clinical trials methodology, law, ethics and regulation, pediatric HIV/AIDS care, biostatistics, epidemiology, clinical treatment of HIV, and pre-

vention. The committee members were selected because they are leading authorities who could conduct an independent, rigorous assessment of the evidence. The committee's charge was to assess the scientific validity of the findings and conclusions of the HIVNET 012 trial, including a review of methodological and data interpretation questions, and aspects of protocol design, data collection, recordkeeping, quality control, and analysis.

The committee's report does not contain an evaluation of the National Institutes of Health, nor does it examine either NIH's handling of the HIVNET 012 trial or the process of research oversight at NIH. These important matters were never part of the task assigned to this committee. Simply put, their report presents the committee's best, evidence-based judgment about the scientific validity of the HIVNET 012 study findings and conclusions.

By conducting this independent scientific assessment of a controversial and consequential clinical trial, the committee and its staff have performed a valuable public service. Their report deserves to be read carefully by anyone who seeks to understand the scientific validity of the HIVNET 012 trial. More generally, the systematic approach taken by the committee serves as a model for critical, scientific review of any clinical trial.

Harvey V. Fineberg
President, Institute of Medicine

Contents

TABLES AND BOX

Tables

Box

Executive Summary

In November 1997, investigators from Johns Hopkins University and Makerere University in Uganda began the HIVNET 012 clinical trial to evaluate the efficacy and safety of single-dose nevirapine (NVP) and short-course zidovudine (ZDV) regimens for preventing mother-to-child transmission of HIV infection. The trial was initially designed as a randomized, double-blind, placebo-controlled trial, but the placebo arms were dropped after results from a study in Thailand found short-course zidovudine to be effective in reducing mother-to-child transmission of HIV. Enrollment in the trial was concluded in April 1999. The trial was sponsored by the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

Preliminary trial results were published in the journal *Lancet* in 1999 (Guay et al., 1999). Given the encouraging evidence that single-dose nevirapine reduced the risk of mother-to-child transmission of HIV, Boehringer Ingelheim (BI), the manufacturer of nevirapine, decided to pursue a U.S. Food and Drug Administration (FDA) labeling change for the drug using HIVNET 012 as a registrational trial for its application in the United States. The decision to use the HIVNET 012 study as support for the labeling change made the trial subject to reviews that were conducted in a manner that was far more in-depth than would ordinarily occur for a clinical trial that, like HIVNET 012, was not originally intended to generate data to support a submission to FDA for approval of a new drug or new indication for an old drug.

Following BI's own review of the HIVNET 012 study, DAIDS con-

tracted with the Westat Corporation to conduct a pre-FDA inspection audit in February 2002 (Chamberlin et al., 2002). Westat's report cited some deficiencies in the conduct of the trial, which in turn prompted a comprehensive and lengthy remonitoring effort by DAIDS. BI subsequently withdrew its application to the FDA for a supplemental indication for the use of NVP in preventing mother-to-child transmission, stating that the "NIAID and Boehringer Ingelheim review could not be completed within the remaining timeline for FDA action for the supplement" (Boehringer Ingelheim, 2002). The investigators, the contract research organization monitoring the study (Family Health International, FHI), and staff of the HIVNET statistical center (SCHARP) responded to the Westat Site Visit Report, providing additional information that explained or resolved some negative audit findings (FHI, 2002; HIVNET 012 Investigators, 2002; SCHARP, 2002). The investigators and FHI also took steps to strengthen study procedures in response to findings with which the investigators concurred (HIVNET 012 Investigators, 2003).

Despite the series of evaluations of and subsequent correspondence about HIVNET 012, no definitive document in the public domain critically and objectively evaluates the study's design, conduct, results, and validity. This has led to uncertainty among public health and medical professionals—as well as those in political circles and the broader HIV-1-affected communities—about whether single-dose NVP is efficacious and safe as a regimen for prevention of mother-to-child transmission of HIV (Cohen, 2004).

In August 2004, in response to a request from NIH, the Institute of Medicine (IOM) convened a committee to review the HIVNET 012 trial and provide an independent assessment of the validity of the study's results. The committee's charge was as follows:

"The IOM committee will address methodological and data interpretation questions related to protocol design, data collection, record keeping, quality control, and analysis. The committee will assess the impact of these issues on the validity of the overall findings and conclusions of the trial. The IOM committee is charged with addressing the following questions related to HIVNET 012:

1. Was the protocol design appropriate?
2. Does the fact that, in many cases, there were no informed-consent forms from the fathers cause enough significant concern to invalidate the conclusions?
3. Are there results available (published or unpublished) of assays of drug levels and should consideration be given to what, if any, impact they might have on the conclusions?

4. Was the protocol followed sufficiently to conclude that the data are sustainable?

5. Was the quality control sufficient to uphold the conclusions?

6. A certain number of documents were destroyed by a natural disaster. Is this a significant deterrent to drawing conclusions?

7. Can the integrity of the data be sustained in view of the deficiencies of the data collection, and the consistency of its recording?

8. Are the conclusions supportable by the data?

9. Is there any reason to suggest the need to retract the publications or to revise the conclusions?"

The IOM Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study met three times and held numerous meetings by conference call between September 2004 and March 2005, and its work led to the present report. Early in its deliberations, the committee concluded that the validity of the trial's findings ultimately rested on the following elements: (1) the integrity of the study design, treatment assignment, and treatment adherence, addressed in Chapter 3; (2) the completeness and accuracy of efficacy and safety data, addressed in Chapter 4; and (3) the study's adherence to ethical principles for conducting clinical research, addressed in Chapter 5.

The committee reviewed relevant materials provided by NIH, by the investigators, previous auditors, and from a variety of other sources. In addition, the committee obtained copies of a subset of primary source documents from Uganda, as well as information from the study database maintained for HIVNET 012 by the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). After its review of these materials, the committee reached its findings about the key aspects of study design and implementation. In its work, the committee was aware of one important aspect of the broader context in which the HIVNET 012 study occurred and was audited: the procedural guidelines and standards for clinical research are always evolving, and the Westat site visit occurred more than 4 years after the initiation of the HIVNET 012 trial. This report describing the committee's analysis and findings contains six chapters and three appendixes.

In Chapter 1, the report provides background information about prevention of mother-to-child transmission of HIV in Africa, a concise summary of the study milestones, and the committee's approach to its charge. Chapter 2 provides an overview of the published findings of the HIVNET 012 trial.

Chapter 3 discusses the committee's assessment of the appropriateness of the HIVNET 012 study design (choice of site and treatment regimens, randomization, and statistical methods) and specific aspects of its imple-

mentation (randomization, drug management, and participant adherence to study regimens). Overall the committee found that the protocol designs for HIVNET 012—both before and after the discontinuation of the placebo arms—were appropriate. The committee also made the following specific findings:

The committee finds that Uganda was a reasonable setting for evaluation of short-course regimens for preventing mother-to-child transmission of HIV-1. Moreover, the regimens chosen for study were reasonable in the context of knowledge about prevention of mother-to-child transmission at that time. The decision to stop the placebo arms of the trial and continue with the originally designed active arms was reviewed and approved appropriately.[1]

The committee finds that the inclusion and exclusion criteria employed in HIVNET 012 were reasonable.

The committee finds that the designs of the original and modified randomization procedures in HIVNET 012 were scientifically sound and appropriate for the research setting.

The committee finds that the HIVNET 012 randomization procedures were implemented with a high level of accuracy, achieving the scientific goal of creating two comparable treatment groups.

The committee finds that the original and revised sample size targets for the HIVNET 012 trial were sufficient to achieve the study goals.

The committe finds that the statistical methods employed in HIVNET 012 and described in the publications were appropriate. The results obtained from the analyses of HIV infection and HIV-1 free survival[2] **were properly interpreted by the study authors. Additional analyses of efficacy in the Results and Discussion sections of Guay et al. (1999) and Jackson et al. (2003) were presented in a balanced manner and with appropriate qualifications.**

The committee finds that the HIVNET 012 investigators used appropriate practices for packaging and distributing study drugs, so that the assigned drug was consistently provided to the appropriate mothers and their infants. Evidence from cord blood specimens indicates that

[1]The trial was continued as a two-arm trial comparing NVP to ZDV and designed to select NVP as the preferred regimen if the difference in rates of mother-to-child transmission of HIV between the NVP and ZDV arms was 3% or less.

[2]HIV-1 free survival refers to absence of HIV-1 infection or death from any cause.

participants achieved a high level of adherence to the NVP regimen. Though no direct evidence is available on blood levels of ZDV, the maternal reports of high levels of adherence to the treatment regimen, the fact that hospital personnel administered a substantial fraction of the ZDV regimen, and the absence of detectable levels of NVP in the blood of participants in the ZDV arm suggest that high levels of adherence were also achieved in the ZDV arm. The high level of adherence to study regimens indicates that the treatment arms formed an appropriate basis for assessing the efficacy and safety of the study regimens.

In Chapter 4, the committee provides its assessment of the validity of study data related to the safety and efficacy endpoints. The committee reviewed the definitions of the safety and efficacy endpoints and their implementation. The committee also obtained copies of primary source documents and case report forms from the study site in Uganda for a sample of mother/infant pairs and compared those documents with HIVNET 012 database information provided by SCHARP. Using these data, the committee conducted its own evaluation of the accuracy, completeness, and timeliness in reporting of adverse events and serious adverse events, survival status, and HIV infection status of infants in the sample. Based on its detailed examination of study data, the committee found no evidence of misrepresentation of the study results. Finally, the committee reviewed other aspects of safety such as incidence of hyperbilirubinemia. The committee's findings include:

The committee finds that the testing schedule and assays used in HIVNET 012 to diagnose HIV-1 infection in infants were appropriate. Use of HIV-1 positivity and HIV-1-free survival at 6–8 weeks, 14–16 weeks, and 18 months of age as the primary efficacy endpoints also was appropriate.

The committee finds that the definitions of adverse events (AEs) and serious adverse events (SAEs) specified in the protocol were reasonable. The committee finds that the follow-up periods and schedule of evaluations established for mothers and infants participating in HIVNET 012 were reasonable and were sufficient to capture relevant information about adverse events.

The committee finds no issues of concern regarding the reliability and validity of laboratory test results obtained in HIVNET 012, or the completeness and accuracy of study laboratory records.

The committee finds that the HIVNET 012 investigators interpreted definitions contained in the 1996 and 1997 Code of Federal Regulations and the protocol so as to use hospitalization as the primary, but

not sole, determinant of seriousness for capture of serious adverse events. Although this well may have been a practical and appropriate interpretation of the definition of serious adverse events, it means that the safety results, while meaningful in a Ugandan context and other similar settings, may not be entirely generalizable to settings in which the definition of seriousness is interpreted differently and where thresholds for hospitalization vary.

The committee finds that participation of HIVNET 012 infants in the vitamin A study had no impact on the HIVNET 012 efficacy endpoints or AEs, and finds no evidence that such participation might have biased the comparative SAE rates in HIVNET 012 in favor of NVP.

The committee finds that the record keeping system implemented in HIVNET 012 was reasonable and appropriate. While there were some documentation and procedural deficiencies reported by auditors, none appeared to have affected the results of the study. There is no evidence that flooding or any other natural phenomenon significantly impacted the completeness of study records.

In its review of HIVNET 012 records, the committee finds no evidence of and only a very limited opportunity for either unreported deaths or erroneous reports of deaths.

The committee finds that source document information regarding survival status was accurately transferred to the SCHARP database in a timely manner.

The committee finds that in the subset of 49 infants whose charts it reviewed, HIV-1 RNA polymerase chain reaction (PCR) and HIV-1 enzyme immunoassay (EIA) information in the source documents used to assess HIV-1 infection status was accurately transferred to the SCHARP database, and done so in a timely manner so that all results available at the time of the data freeze for study publications were included in the analyses.

The committee finds that infant deaths, hospitalizations and visits where an infant experienced an SAE were accurately reported to the SCHARP database, although, in some instances, not all concomitant SAEs were reported. The committee also finds that some (non-serious) AEs noted in the source documents were not reported on the case report forms. The underreporting of some (non-serious) AEs and some concomitant SAEs that accompanied a reported SAE may limit the generalizability of absolute AE rates and counts to other settings. However, the committee finds no reason to believe that the rates of unreported adverse events varied by treatment group, suggesting that

the comparative safety analyses reported by the HIVNET 012 investigators are valid.

The committee concurs with the HIVNET 012 investigators' determination that 1.2 mg/dL, as suggested in the April 8, 2003, Investigational New Drug (IND) Safety Report, was not an appropriate upper limit of normal value for bilirubin in newborns, whose bilirubin levels change rapidly over the first few days after birth and are normally substantially higher than those in adults. The committee also concurs with DAIDS' decision to withdraw its initial IND safety report finding of excess hyperbilirubinemia because it was derived from the application of an incorrect criterion to study data.

The committee finds no evidence in HIVNET 012 of an increased risk of clinically significant hyperbilirubinemia in the infants who received NVP compared to the infants who received ZDV.

In Chapter 5, the committee assesses the design and conduct of the study from the perspective of protection of human subjects, including HIVNET 012 compliance with requirements for independent Institutional Review Board (IRB) oversight, the inclusion of placebo arms in the original trial design, the circumstances that made the placebo control no longer appropriate, and the informed-consent process. The Westat Site Visit Report stated that HIVNET 012 investigators were found to lack training in and awareness of Good Clinical Practice Guidelines (Chamberlin et al., 2002). In this chapter, the committee explains that the HIVNET 012 trial was not subject to these "GCP" Guidelines, which are a voluntary set of international guidelines that inform but do not constitute the FDA regulations to which HIVNET 012 was subject (ICH, 1996). Further, the committee explains that the FDA regulations that did apply to HIVNET 012 were in some important respects more stringent than the international GCP Guidelines. Finally, the committee distinguishes between compliance with the voluntary international GCP Guidelines and actual good clinical practice, which refers to good clinical management and medical care in the course of a trial. The committee also noted that conducting good, ethical clinical research does not solely consist of following procedures, but rather consists of ensuring independent oversight, a reasonable balance between risks and benefits, assurance that subjects give free and informed consent, and that subjects are protected. The committee's findings include:

The committee finds that HIVNET 012 was conducted under an IND as a matter of DAIDS policy, and that the study was not originally intended to provide data for later submission to FDA to support a labeling change for NVP, an already approved drug. The decision by

Boehringer Ingelheim to use the findings to support such a submission led to evaluating the documentation of regulatory compliance by the trial in light of a standard that did not apply when the trial began.

The committee finds that the HIVNET 012 investigators met their ethical obligation to design and conduct the study in accordance with international standards for the ethical conduct of research and ethical management of patient care. The HIVNET 012 investigators also complied with their legal obligation to design and conduct the study in accordance with FDA regulations and under the oversight of IRBs in both Uganda and the United States. The HIVNET 012 trial was not required to comply with specific procedural rules outlined in the voluntary GCP Guidelines published by the International Conference on Harmonisation, and an ethical evaluation of HIVNET 012 should not rest directly or indirectly on the degree to which it conformed to GCP Guidelines, but rather on the degree to which it conformed to FDA, IRB, and general medical ethics standards to which it was subject. The validity of the study's findings is sustained by the fact that the trial was conducted in accordance with FDA requirements and met international standards for the ethical management of clinical trials.

The committee finds no evidence that the definitions used for adverse events and serious adverse events in HIVNET 012 placed human subjects at increased risk.

The committee finds no evidence that the failures identified by the Office for Human Research Protections (OHRP) with respect to ARC's[3] continuing review procedures resulted in a loss of information that would, had it been obtained at the time, have altered the risk-benefit balance in a way that would have triggered either a change in the protocol or a change in the information given to human subjects.

The committee finds that the initial design of the HIVNET 012 trial, which incorporated two placebo arms, was properly reviewed and approved by the relevant Johns Hopkins University and Ugandan IRBs, and that justifications for the use of placebo arms were adequately presented.

The committee finds that the HIVNET 012 trial was promptly and properly reevaluated and the placebo arms discontinued when new data emerged from other studies.

[3]ARC (AIDS Research Committee) is the Ugandan Institutional Review Board.

The committee finds that the initial study design incorporated all relevant protections relating to the need for voluntary informed consent, the acceptability of placebo control, the discontinuation of placebo control, and overall compliance with IRB reviews.

The committee finds that the investigators correctly identified appropriate guardians to consent to extended 5-year follow-up in situations where the original consenting parent had died, but that the investigators failed to do this in situations where the consenting parent died while the child was still enrolled in the original, 18-month follow-up.

The committee finds that requesting additional consent from the fathers before enrolling the pregnant women or their infants in the study was not necessarily required by U.S. federal regulations but was required per DAIDS policy and was therefore incorporated into the IRB-approved protocol.

The committee finds that the failure to obtain such additional paternal consent was based on the practical unavailability of the fathers and the ethical constraints that prevented the research staff from contacting fathers in the absence of the mother's support and consent.

The committee finds that while auditors reported procedural lapses by the Ugandan IRB, there was evidence of rapid and appropriate response by the IRB in approving modification of the design of HIVNET 012 and discontinuation of placebo arms. There was also no evidence that a participant signed the wrong[4] version of the consent form.

Despite some lapses in documentation, the committee finds no evidence that study subjects failed to give voluntary informed consent.

The committee finds that HIVNET 012 met the substantive standards for ethical conduct of research and was implemented in substantial compliance with regulations governing protection of human subjects, especially independent review of risks and benefits to them.

The committee finds that there is no reason based in ethical concerns about the design or implementation of the study that would justify excluding its findings from use in scientific and policy deliberations.

Chapter 6 is a concluding narrative that provides a discussion of the committee's response to each item of the charge, based on the findings of earlier chapters.

[4]E.g., copy stamped "sample."

Based on its review, the committee finds no reason to retract the publications or alter the conclusions of the HIVNET 012 study. The committee concludes that data and findings presented in Guay et al. (1999) and Jackson et al. (2003) are sound, presented in a balanced manner, and can be relied upon for scientific and policy-making purposes.

REFERENCES

Boehringer Ingelheim. 2002. *Boehringer Ingelheim Comments on HIVNET 012 Trial.* [Online] Available at http://www.boehringer-ingelheim.com/corporate/asp/news/ndetail.asp?ID+224. Accessed June 24, 2004.

Chamberlin J, Gustavson SA, Hensley M, Lander S. 2002. Site Visit Report, Kampala, Uganda, February 18-28, 2002. Westat Corporation, MD.

Cohen J. 2004. HIV transmission. Allegations raise fears of backlash against AIDS prevention strategy. *Science* 306(5705):2168-2169.

FHI (Family Health International). 2002. Response to DAIDS by FHI on Westat Inspection Report for HIVNET 012-Kampala, Uganda-Conducted February 18-28, 2002.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181):795-802.

HIVNET 012 Investigators. 2003. Makerere University–Johns Hopkins University Quality Management Plan.

HIVNET 012 Investigators. 2002. Summary Sheet of Major Inaccuracies in the Westat Report.

ICH (International Conference on Harmonisation). 1996. Guideline for Good Clinical Practice. [Online] Available at http://www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB. Accessed March 14, 2005.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

SCHARP (Statistical Center for HIV/AIDS Research and Prevention). 2002. Response to Westat Site Visit Report. Questions Responding to Major Concerns.

1

Introduction

In sub-Saharan Africa, 10 to 30% or more of pregnant women are infected with human immunodeficiency virus type 1 (HIV-1). Mother-to-child transmission is the dominant mode by which infants and children become infected with HIV-1. In 2004 alone, about 640,000 infants and children under 15 years of age worldwide were newly infected with HIV-1, and about 510,000 died of acquired immune deficiency syndrome (AIDS). An estimated 1,700 children are born with HIV-1 infection every day owing to mother-to-child transmission. Most new infections and deaths occur in sub-Saharan Africa (UNAIDS and WHO, 2004).

A variety of interventions can reduce rates of mother-to-child transmission of HIV, from more than 20% to 2% or less. These interventions include antiretroviral treatment of pregnant women and their infants, the selective use of elective cesarean delivery, and complete avoidance of breastfeeding (UNAIDS and WHO, 2004). In a study completed in 1994, U.S. researchers showed for the first time that a three-part regimen of zidovudine (ZDV)—given to women during pregnancy and labor and delivery, and to newborns during the first 6 weeks of life—could reduce mother-to-child transmission by about two-thirds, from 25 to 8% (Connor et al., 1994). This intervention was promptly adopted programmatically in the United States and other resource-rich settings. However, the complexity and expense of this approach, which entails both oral and intravenous dosing, made it impractical for use in most developing countries and unlikely that it would be adopted in those settings. Barriers to broader availability of this and other options for reducing mother-to-child transmission

include poor public health and health care infrastructure, the complexity and expense of treatment, and the lack of suitable and acceptable alternatives to breastfeeding.

The urgent need in sub-Saharan Africa and throughout the developing world for practical, affordable approaches to preventing mother-to-child transmission of HIV-1 has spurred studies to identify inexpensive, simple, easy-to-implement new antiretroviral regimens. HIVNET 012 was one such study. Initiated in Uganda in 1997, HIVNET 012 was designed to provide preliminary information on the comparative safety and efficacy of two relatively simple and inexpensive short courses of oral antiretroviral treatment—one involving ZDV, and the other nevirapine (NVP)—likely to be feasible in resource-limited settings. The trial was sponsored by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The study was performed at Mulago Hospital, Makerere University, Kampala, Uganda, by investigators from the Johns Hopkins University School of Medicine and Makerere University, under the auspices of the NIAID-sponsored HIV Prevention Trials Network (HPTN, formerly HIVNET).

The U.S. Food and Drug Administration (FDA) had already approved both NVP and ZDV for treating HIV in adults, and HIVNET 012 was not initially intended to collect data for formal presentation to FDA for approval of new indications for NVP. However, as a matter of policy, DAIDS required that the study be conducted under an investigational new drug application, held by DAIDS. Enrollment of pregnant women in the trial was completed in 1999, but infants continued to be followed until 5 years of age (HIVNET 012 Investigators, 2000).

Two widely cited papers published in *The Lancet* in 1999 and 2003 reported striking results from HIVNET 012 (Guay et al., 1999; Jackson et al., 2003). The trial showed that a single dose of NVP—given to the mother at the onset of labor and to the infant within 72 hours of birth—reduced the risk of HIV-1 transmission by nearly 50% measured at 14 to 16 weeks postpartum, compared with the short-course ZDV regimen. These results catalyzed efforts to implement the single-dose NVP-based regimen for preventing mother-to-child transmission in resource-limited settings in Africa and throughout the world in an effort to stem the global pediatric HIV epidemic.

Based on these published results, Boehringer Ingelheim (BI), the pharmaceutical company that manufactures NVP, decided in 2001 to submit a supplemental new drug application to FDA for preventing mother-to-child transmission.[1] FDA approval of a new indication required compliance with

[1]Such an application is used to add a new indication to the label of an already approved drug. While drugs may legally be used for indications not on their labels (known as "off-label

a more stringent set of research procedures and an audit of the study site. Following a visit by BI to the Mulago Hospital study site in Kampala in November 2001, DAIDS contracted with Westat Corporation to visit the site and help HIVNET 012 staff prepare for the FDA audit, expected to occur in March 2002. In February 2002, a team from Westat visited the study site and reviewed regulatory compliance, laboratory facilities, pharmacy facilities and processes, and trial records. The Westat team reported finding multiple problems with HIVNET 012, including procedural irregularities and issues with how investigators had defined, graded, and reported serious adverse events. The Westat team also raised the possibility that the trial had not recorded some deaths that had occurred during the study, although the Westat team reported that the tests of infants' HIV-1 status were verifiable (Chamberlin et al., 2002).

Westat submitted its preliminary report to DAIDS on March 8, 2002. Based on debriefing discussions with the Westat team and FDA (although not with the investigators), DAIDS concluded that the Westat report did not contain conclusive evidence that deaths had gone unreported to the study database or to FDA (DAIDS, NIAID, 2002). The HIVNET 012 investigators, the statistical center supporting the data management and analysis of HIVNET 012 (Statistical Center for HIV/AIDS Research and Prevention, SCHARP, at the Fred Hutchinson Cancer Center in Seattle), and the contract research organization assigned to conduct regular monitoring visits to the HIVNET 012 study site (Family Health International [FHI]) developed a response to the Westat report, which they submitted to DAIDS (FHI, 2002; HIVNET 012 Investigators, 2002; SCHARP, 2002). Those responses to the Westat report clarified and corrected some of the assertions and criticisms made by Westat. Based on the findings in the Westat report, DAIDS decided to conduct its own comprehensive audit—or remonitoring—of the study to clarify the issues. BI later withdrew its application to the FDA for a supplemental indication for the use of NVP in preventing mother-to-child transmission, stating that the "NIAID and Boehringer Ingelheim review could not be completed within the remaining timeline for FDA action for the supplement" (Boehringer Ingelheim, 2002).

Between July and December 2002, DAIDS conducted a comprehensive remonitoring evaluation of the HIVNET 012 site and records at Mulago Hospital. Stage I of this assessment included laboratory, pharmacy, and regulatory audits; a review of study procedures and processes; and random selection of 80 mother/infant pairs, for which DAIDS compared reporting on informed consent, birth and delivery, virology, and adverse events with

use"), drugs may be advertised and marketed only for the indications reviewed by the FDA and approved for their labels.

source documents.[2,3] Stage II included a review of source documents for the remaining 565 mothers and 567 infants. The remonitoring team also examined the completeness of reporting on adverse events and information on study safety. In its resulting report, DAIDS identified some problems with procedures and documentation, but concluded that these issues did not compromise the results of the study. Thus, the report indicated that the HIVNET 012 trial's conclusions regarding safety and efficacy were supported (DAIDS, NIAID, 2003).

In 2003, after the DAIDS review and publication by the investigators of 18-month results from the trial which supported earlier findings (Jackson et al., 2003), DAIDS hired a director for its new Office of Policy in Research Operations, an office responsible for monitoring the quality and conduct of all DAIDS-sponsored clinical trials. This individual criticized the remonitoring of HIVNET 012 in his presentation to this committee, and his concerns have received media attention (Associated Press, 2004a; Associated Press, 2004b).

Although the trial has been the subject of several reviews, as noted, no definitive document in the public domain critically and objectively evaluates the study's design, conduct, results, and validity. This has led to uncertainty among public health and medical professionals—as well as political circles and the broader HIV-1-affected communities—regarding the use of NVP for preventing mother-to-child transmission (Cohen, 2004). Given continuing controversy surrounding the trial, NIH asked the Institute of Medicine (IOM) to conduct an independent review of the trial.

CHARGE TO THE COMMITTEE

The IOM Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study convened to address a number of questions related to the trial. Box 1-1 contains the full charge to the committee.

Some of these questions (such as numbers 2 and 6) ask the committee to render a finding on a specific issue. Overall, however, the questions focus on whether the scientific validity and results of the HIVNET 012 trial as reported in the scientific literature can be upheld.

[2]Source documents included all clinical forms completed for each participant at the time of scheduled and unscheduled visits to the study clinic, and staff abstractions developed based on hospital admissions forms, before those became available to study staff.

[3]The audit reviewed 25,000 data points from the study database on a random sample of 80 mother/infant pairs stratified by location (including Old Mulago and New Mulago enrollees—see Chapter 3) and infant mortality status.

BOX 1.1
Charge to the Committee

The IOM committee will address methodological and data interpretation questions related to protocol design, data collection, record keeping, quality control, and analysis. The committee will assess the impact of these issues on the validity of the overall findings and conclusions of the trial. The IOM committee is charged with addressing the following questions related to HIVNET 012:

1. Was the protocol design appropriate?
2. Does the fact that, in many cases, there were no informed-consent forms from the fathers cause enough significant concern to invalidate the conclusions?
3. Are there results available (published or unpublished) of assays of drug levels and should consideration be given to what, if any, impact they might have on the conclusions?
4. Was the protocol followed sufficiently to conclude that the data are sustainable?
5. Was the quality control sufficient to uphold the conclusions?
6. A certain number of documents were destroyed by a natural disaster. Is this a significant deterrent to drawing conclusions?
7. Can the integrity of the data be sustained in view of the deficiencies of the data collection, and the consistency of its recording?
8. Are the conclusions supportable by the data?
9. Is there any reason to suggest the need to retract the publications or to revise the conclusions?[a]

[a]NIH initially asked the committee to examine resistance to NVP and the implications for its use. At the time of the trial, little was known about NVP resistance. Although a number of studies have since examined the issue, the committee considered a review of NVP resistance outside its mandate, which focused on the HIVNET 012 trial. NIH therefore withdrew this question from the committee's charge.

STUDY PROCESS

The committee relied on a variety of means to gather information to address its charge. It held two information-gathering meetings that were open to the public. The first—held September 30 and October 1, 2004—focused on an overview of the HIVNET 012 trial, the NIH remonitoring effort, and information on the safety and efficacy of other clinical trials involving the use of NVP to prevent mother-to-child transmission. (See Appendix A for the agenda of that meeting.) The second information-gathering meeting, held January 4–5, 2005, focused on the quality of record keeping and other processes used during the study. (See Appendix A for the agenda of that meeting.) The committee also held a closed session November 4–5, 2004. The committee also had numerous conference call meetings after the January meeting.

Committee members and staff also obtained information from NIH, DAIDS, Johns Hopkins and Ugandan investigators, Westat, FHI, SCHARP, and others. The committee reviewed study protocols, manuals on operating procedures, key reports on audits and site visits, informed-consent forms, and documents on the randomization procedures used in the study. The committee also undertook a limited review of source records, case report forms, and the analytic database for a sample of study participants.

FRAMING OF THE COMMITTEE'S DELIBERATION

Early in its deliberations, the committee concluded that the validity of the trial's findings ultimately rested on the following elements: (1) the integrity of the study design, treatment assignment, and treatment adherence; (2) the completeness and accuracy of efficacy and safety data; and (3) the study's adherence to ethical principles for conducting clinical research. The first element encompasses the soundness of the scientific design, including the treatment setting, treatment regimen, eligibility criteria, randomization procedures, sample size, and drug delivery and adherence. The second element includes information on HIV-1 infection, the survival of infants, and adverse events (serious and non-serious). The third element focuses on the integrity of the procedures used to protect human subjects. The committee's approach was informed by the recognition that study design and conduct must be assessed from the perspective of scientific validity and global standards for protecting human subjects.

In Chapter 2, the committee provides more detail on how researchers conducted HIVNET 012 and a brief overview of the key events that occurred during and after the trial. In Chapters 3, 4, and 5, the committee evaluates the three critical elements of the study and offers its findings. In Chapter 6, the committee provides its overall assessment of the validity of the trial.

Readers familiar with the controversy surrounding HIVNET 012 should be aware that the committee's review was limited to an assessment of whether the integrity of the data from the trial is sufficient to support its findings. The committee was not involved in any investigation of NIH personnel, nor in allegations and litigation regarding cover-up of study deficiencies. The executive branch and Congress are investigating these matters. The committee's charge also does not include a review of recent reports concerning the potential toxicity of NVP as part of a long-course triple-drug therapy used to treat adult patients.

REFERENCES

Associated Press. 2004a. *NIH Researcher Seeks Whistleblower Protection: Fishbein Reported Concerns About AIDS Research*. [Online] Available at http://www.msnbc.com/id/6707616/. Accessed December 14, 2004.

Associated Press. 2004b. *NIH Dismissed Concerns About AIDS Treatment: White House Stands by US Decision to Send Drug to Africa*. [Online] Available at: http://www.msnbc.msn.com/id/6707600/. Accessed December 14, 2004.

Boehringer Ingelheim. 2002. *Boehringer Ingelheim Comments on HIVNET 012 Trial*. [Online] Available at http://www.boehringer-ingelheim.com/corporate/asp/news/ndetail.asp?ID+224. Accessed June 24, 2004.

Chamberlin J, Gustavson SA, Hensley M, Lander S. 2002. Site Visit Report, Kampala, Uganda, February 18-28, 2002. Westat Corporation, MD.

Cohen J. 2004. HIV transmission. Allegations raise fears of backlash against AIDS prevention strategy. *Science* 306(5705):2168-2169.

Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, JimenezE,O'Neill E, Bazin B, Delfraissy J, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J, for The Pediatric AIDS Clinical Trials Gropu Protocol 076 Study Group. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 331(18): 1173-1180.

DAIDS, NIAID (Division of AIDS, National Institute of Allergy and Infectious Diseases). 2003. *HIVNET 012 Monitoring Report*.

DAIDS, NIAID. 2002. *DAIDS Summary of March 19 Westat Debriefing*.

FHI (Family Health International). 2002. Response to DAIDS by FHI on Westat Inspection Report for HIVNET 012—Kampala, Uganda—Conducted February 18-28, 2002.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181): 795-802.

HIVNET 012 Investigators. 2002. Summary Sheet of Major Inaccuracies in the Westat Report.

HIVNET 012 Investigators. 2000. Protocol HIVNET 012: Amendment II. Extended Mother and Child Follow-Up.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

SCHARP (Statistical Center for HIV/AIDS Research and Prevention). 2002. Response to Westat Site Visit Report.

UNAIDS (Joint United Nations Programme on HIV/AIDS) and WHO (World Health Organization). 2004. *AIDS Epidemic Update*. [Online] Available at http://www.unaids.org/wad.2004/report.html. Accessed March 4, 2005.

2

Overview of HIVNET 012

HIVNET 012 initially was a randomized, double-blind, placebo-controlled Phase III clinical trial designed to compare the safety and efficacy of short-course oral nevirapine (NVP) and zidovudine (ZDV) for preventing mother-to-child transmission of HIV-1. The original target enrollment was 1,500 mother/infant pairs. Pregnant HIV-infected women were randomized to four treatment arms: oral ZDV (n=500), ZDV placebo (n=250), single-dose NVP (n=500), and NVP placebo (n=250) (Jackson et al., 1997). The study included placebo arms because the efficacy of short-course oral antiretroviral regimens for preventing mother-to-child transmission—whether of ZDV or NVP—for preventing mother-to-child transmission had not yet been proven. Enrollment in HIVNET 012 began in November 1997, under a protocol approved by institutional review boards in Uganda and the United States (Jackson et al., 2003).

In February 1998, a randomized, double-blind, placebo-controlled trial sponsored by the U.S. Centers for Disease Control and Prevention in Thailand of 393 mother/infant pairs showed that a short course of oral ZDV could reduce HIV-1 transmission by about 50% over a placebo—to an overall rate of 10%—in a non-breastfeeding population (CDC, UNAIDS, NIH, and NRS, 1998; Shaffer et al., 1999).[1] As a result, HIVNET 012 researchers formally dropped the placebo arms in a letter of amendment

[1]The target sample size of 392 women had the ability to detect a 50% reduction in transmission risk—from 24% to 12%—with 80% power and a Type I error rate of 5% (Shaffer et al., 1999).

(known as Amendment I) to the protocol, and stopped enrollment on February 18, 1998.

HIVNET 012 was redesigned and reopened on April 6, 1998—with approval of the Ugandan and U.S. institutional review boards—as a randomized, open-label, Phase IIB clinical trial.[2] In this newly approved protocol, the target enrollment was 400 to 600 mother/infant pairs randomized in a 1:1 ratio. Women in the NVP arm of the trial would receive a single, oral 200-milligram dose of NVP at the onset of labor. Their infants would receive a single, oral 2-milligram-per-kilogram-of-body-weight dose of NVP suspension within 72 hours of birth. Women in the ZDV arm would receive 600 milligrams of oral ZDV at the onset of labor, followed by 300-milligram doses every 3 hours during labor. Their infants would receive oral 4-milligram-per-kilogram-of-body-weight doses of ZDV twice daily for the first 7 days of life. Boehringer Ingelheim Pharmaceuticals and GlaxoWellcome, respectively, donated the study drugs.

The HIVNET 012 protocol specified follow-up of mothers for adverse events for 6 weeks after delivery. Infants were followed for adverse events until 6 weeks of age, and for serious adverse events until 18 months of age. Researchers graded such events based on toxicity tables from the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) for neonates, children, and adults, ranging from grade 1 (mild) to grade 4 (life-threatening). The 1997 *Study Specific Procedures* manual included the DAIDS toxicity tables, as well as a special grading system for adverse experiences related to skin rashes and dermatitis and hemoglobin in mothers (Jackson et al., 1997). As the medications were given for a week or less, the study did not modify drug doses for toxicity.

The primary endpoints for evaluating the efficacy of the drug regimens were HIV infection and HIV-1-free survival (the absence of HIV-1 infection or death from any cause) of infants at 6–8 weeks, 14–16 weeks, and 18 months of age. Researchers used a qualitative RNA polymerase chain reaction (PCR) assay to determine the infants' HIV-1 status. Positive test results were confirmed by a quantitative HIV-1 RNA PCR assay[3] or HIV-1 culture on a second blood sample. For infants who tested positive for HIV-1, the quantitative HIV-1 RNA PCR assay was performed at each scheduled

[2]A Phase IIb trial is sometimes viewed as an intermediate safety and efficacy trial. In this case the trial was designed to provide preliminary comparisons of the efficacy and safety of the two treatments.

[3]Both quantitative and qualitative plasma HIV-1 RNA measurements were assessed with Roche AMPLICOR MONITOR (Roche Diagnostics, Indianapolis, IN) with 1.0 version kit with additional primers if tested prior to November 1998, and with the 1.5 version primers after that (Guay et al., 1999).

blood draw, including at 12 and 18 months of age. Investigators used enzyme immunoassay to test for HIV-1 antibodies at 18 months of age. Positive test results were confirmed by an HIV-1 Western blot assay (Cambridge Biotech, Rockville, MD).

Researchers amended the study protocol in February 2000 (Amendment II) in response to findings in other studies that some women could develop viral resistance to NVP, and that some children treated with various antiretroviral drugs in utero or perinatally could possibly experience mitochondrial toxicity. The modification entailed extending follow-up of women in the NVP arm and all children in the 18-month study to 5 years, with yearly evaluations for NVP resistance in women who had received NVP (HIVNET 012 Investigators, 2000).

RESULTS

HIVNET 012 enrolled 645 pregnant women between November 1997 and April 1999, when the study reached its target enrollment. The analysis of the study did not include 19 women randomized to placebo before February 18, 1998.

The first of two papers, published in *The Lancet* in 1999, reported safety and efficacy data through 14–16 weeks of follow-up of the infants (Guay et al., 1999). This paper reported that the study had randomized 313 pregnant women to ZDV, 313 to NVP, and 19 to placebo. Of infants exposed to ZDV and NVP, 307 and 309, respectively, could be evaluated for HIV-1-free survival. The relative risk of HIV-1 infection was 0.53 in the NVP as compared to the ZDV arm (a 47% reduction) (see Table 2.1).[4]

The 1999 *Lancet* paper also analyzed adverse events and toxic effects based on the first 556 mother/infant pairs assigned to treatment with ZDV (279 pairs) and NVP (277 pairs). The authors reported that "the rates of maternal serious adverse events were similar in the two groups (4.4% in the ZDV group and 4.7% in the NVP group)," and that "the occurrence of clinical or laboratory abnormalities in mothers was similar in the two groups." The authors also reported that for infants, "the rate of occurrence of serious adverse events in the two groups was similar up to the 18-month visit (19.8% in the ZDV group and 20.5% in the NVP group)." The "frequency and severity of laboratory-detected toxic effects . . . were similar in the two groups."

[4]The authors report the "efficacy" of NVP compared with ZDV as 47%, which is actually 100*(1-RR)—that is, the percentage reduction in risk. Standard relative risks are reported above.

TABLE 2.1 Numbers (percentages) of Infants with HIV-1 Infection and HIV-1 Infection or Death at Ages 1–3 Days, 6–8 Weeks, and 14–16 Weeks, by Study Arm

	Zidovudine Arm (total number of infants=307)		Nevirapine Arm (total number of infants=309)		
	HIV-1 Infection		HIV-1 Infection		P value
Day 1–3	31	(10.4%)	25	(8.2%)	0.35
Week 6–8	59	(21.3%)	35	(11.9%)	0.0027
Week 14–16	65	(25.1%)	37	(13.1%)	0.0006
	HIV-1 Infection or Death		HIV-1 Infection or Death		P value
Day 1–3	37	(12.2%)	27	(8.8%)	0.17
Week 6–8	66	(23.1%)	38	(12.8%)	0.0012
Week 14–16	74	(27.6%)	41	(14.4%)	0.0002

SOURCE: Adapted from Guay et al. (1999). Used with permission from the authors and from Elsevier.
NOTE: A "p value" represents the probability that an event as extreme or more extreme than the observed result would have occurred by chance if the specified null hypothesis is true.

The second *Lancet* paper (Jackson et al., 2003), reported that infants assigned to the NVP arm continued to have a significantly lower rate of HIV-1 infection and a significantly greater likelihood of HIV-1-free survival through 18 months of age (Table 2.2). Specifically, the efficacy of NVP compared with ZDV was 41%.

This paper analyzed adverse events and serious adverse events more completely, reporting that both types of events among mothers up to 56 days were balanced between the study arms. Three deaths occurred among women assigned to the ZDV arm, but all were judged related to complications of HIV-1 infection.

Among infants, reported rates of serious adverse events during the first 56 days after birth and through 18 months of age were similarly balanced between the ZDV and NVP arms. However, all adverse events[5] were significantly more frequent in infants in the ZDV arm versus the NVP arm during the first 56 days. Jaundice (18.4% versus 5.6%), skin infections (17.5% versus 9.7%) and pustular rash (4.5% versus 0.6%) all occurred more often among infants in the ZDV arm. Only one condition—dermal exfoliation—occurred more often among infants in the NVP arm (4.9% versus 8.4%). All cases of dermal exfoliation were graded mild or moderate. Researchers reported no cases of Stevens-Johnson syndrome.[6] They further reported no significant differences between the treatment arms with respect to grade 3 or 4 laboratory toxicities[7], and no grade 3 or 4 abnormalities in serum liver enzymes in either study arm (see Table 2-3). The infant death rates reported after 18-month follow-up (13.6% in the ZDV arm and 10.6% in the NVP arm) should be considered in the context of infant mortality for children under 5 years of age in Uganda, which in 1998 was 134 per 1,000 births (UNICEF, 2000).

KEY EVENTS DURING HIVNET 012

The HIVNET 012 trial and its aftermath were marked by a complicated series of events involving the study sponsors (DAIDS, NIAID, NIH), various contract organizations, the U.S. Food and Drug Administration, study investigators, the pharmaceutical company Boehringer Ingelheim, and institutional review boards in Uganda and the United States. Table 2.4 outlines some of these events.

[5]This refers to both serious and non-serious adverse events.

[6]Stevens-Johnson syndrome is a rare disorder characterized by inflammation of the mucous membranes of the mouth, throat, anogenital region, intestinal tract, and membrane lining the eyelids (conjunctiva).

[7]DAIDS pediatric and adult toxicity tables are available at: http://rcc.tech-res-intl.com/tox_tables.htm.

TABLE 2.2 Numbers (percentages) of Infants with HIV-1 Infection and HIV-1 Infection or Death at Ages 12 and 18 Months, by Study Arm

	Zidovudine (total number of infants=302)		Nevirapine (total number of infants=308)		
	HIV-1 Infection		HIV-1 Infection		P value
Month 12	70	(23.9%)	46	(15.3%)	0.0083
Month 18	75	(25.8%)	47	(15.7%)	0.0023
	HIV-1 Infection or Death		HIV-1 Infection or Death		P value
Month 12	86	(28.6%)	59	(19.4%)	0.0076
Month 18	92	(30.7%)	63	(20.7%)	0.0048

SOURCE: Adapted from Jackson et al. (2003). Used with permission from the authors and from Elsevier.

TABLE 2.3 Numbers (percentages) of Women and Infants with Adverse Events, by Study Arm

	Zidovudine	Nevirapine	P value
Women			
Total	302	306	
First 8 weeks			
All adverse events (AEs)	259 (85.8%)	263 (85.9%)	0.95
Rash	20 (6.6%)	21 (6.9%)	0.91
Hepatic related	5 (1.7%)	2 (0.7%)	0.25
Serious AEs	11 (3.6%)	15 (5.9%)	0.44
Deaths	3 (1.0%)	0 (0.0%)	0.08
Infants			
Total	309	320	
First 8 weeks			
All adverse events	288 (93.2%)	260 (81.3%)	< 0.0001
Infection	84 (27.2%)	83 (25.9%)	0.72
Rash	81 (26.2%)	59 (18.4%)	0.02
Conjunctivitis	54 (17.6%)	61 (19.1%)	0.61
Hepatic related	67 (21.7%)	30 (9.4%)	< 0.0001
Skin infection	54 (17.5%)	31 (9.7%)	0.004
Oral thrush	37 (12.0%)	38 (11.9%)	0.97
Serious AEs	35 (11.3%)	29 (9.1%)	0.35
Deaths	3 (1.0%)	4 (1.3%)	0.09
18 months			
Serious AEs	97 (31.4%)	109 (34.1%)	0.48
Deaths	42 (13.6%)	34 (10.6%)	0.25

SOURCE: Adapted from Jackson et al. (2003). Used with permission from the authors and from Elsevier.

TABLE 2.4 HIVNET 012 Timeline

Date	Event
February 1996	Investigational new drug application #49,991 opened by DAIDS and later reviewed and accepted by FDA
July 1997	Protocol approved by Johns Hopkins Joint Committee on Clinical Investigation (JCCI) and Ugandan AIDS Research Committee (ARC)
	Data and Safety Monitoring Board (DSMB) meeting (July 1, 1997)
August 1997	Protocol version 1.0 sent to FDA
November 1997	HIVNET 012 enrollment begins
February 1998	Enrollment stopped; placebo arms are dropped (Amendment I to Protocol Version 1.0)
March 1998	Investigators ask JCCI and ARC to approve redesigned study
April 1998	Enrollment begins into revised protocol
May 1998	Enrollment stopped because of drug unavailability and drug packaging issue
July 1998	Enrollment resumes into 2-arm trial DSMB meeting (July 16, 1998)
April 1999	HIVNET 012 enrollment completed
June 1999	DSMB meeting (June 24, 1999)
July 1999	DSMB telephone conference (July 12, 1999)
September 1999	Early results of HIVNET 012 published in *The Lancet*
April 2000	Protocol amended to follow women and infants for 5 years (Amendment II to Protocol Version 1.0)
June 2001	Boehringer Ingelheim (BI) submits supplemental new drug application (sNDA) for NVP to FDA
January 2002	BI study site visit
February 2002	Westat study site visit
March 2002	BI withdraws NVP sNDA
July to December 2002	DAIDS audit (remonitoring) of HIVNET 012
March 2003	DAIDS remonitoring report released
September 2003	Second *Lancet* paper published
September 2004	IOM committee convened

REFERENCES

CDC (Centers for Disease Control and Prevention), UNAIDS (Joint United Nations Programme on HIV/AIDS), NIH (National Institutes of Health), and ANRS (Agence Nationale de Recherche sur le SIDA). 1998. Joint Statement by the Centers for Disease Control and Prevention (CDC), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the National Institutes of Health (NIH) and the Agence Nationale de Recherche sur le SIDA (ANRS), Following the Announcement by the Ministry of Public Health of Thailand and the CDC of Results from their Mother-to-Child Transmission Trial, February 18, 1998.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181): 795-802.

HIVNET 012 Investigators. 2000. Protocol HIVNET 012. Amendment II. Extended Mother and Child Follow-Up.

Jackson B, Mmiro F, Guay L, Musoke P, Fowler MG. 1997. Protocol HIVNET 012: A Phase III Placebo-Controlled Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

Shaffer N, Chuachoowong R, Mock P, Bhadrakom C, Siriwasin W, Young N, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro T, Simonds R. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353(9155):773-780.

UNICEF (United Nations Children's Fund). 2000. *State of the World's Children 2000*. [Online] Available at http://www.unicef.org/sowc00/. Accessed February 27, 2005.

3

Study Design, Treatment Assignment, and Adherence to Study Regimens

The committee interpreted its charge as encompassing scientific elements of the design of HIVNET 012, including the research setting, eligibility criteria for participants in the study, drug regimens, the randomization scheme, sample size, and statistical methods. This chapter addresses these issues. This chapter also addresses the implementation of the randomization procedure, drug management procedures, and participants' adherence to study regimens. Chapter 4 focuses on issues related to efficacy and safety data, and Chapter 5 focuses on ethical issues related to the design and conduct of the study.

BACKGROUND

Mother-to-child transmission of HIV-1 can occur *in utero* (antepartum), at the time of labor and delivery (intrapartum), or during breastfeeding (postpartum) (Working Group on Mother-To-Infant Transmission of HIV, 1995). Enrollment in HIVNET 012 began in November 1997. At that time, the standard of care for preventing mother-to-child transmission in both the United States and Europe was based on the results of AIDS Clinical Trials Group (ACTG) protocol 076. That trial showed that a three-part maternal-infant zidovudine (ZDV) regimen reduced the rate of transmission by about two-thirds, from 25.5% to 8.3%, compared to a placebo (Connor et al., 1994). The drug regimen studied in ACTG 076 consisted of 100 milligrams of ZDV given orally five times daily to HIV-1-infected pregnant women beginning at 14–34 weeks gestation, followed by

an intravenous infusion of ZDV during labor (2 milligrams per kilogram of body weight in the first hour, and 1 milligram per kilogram of body weight each hour until delivery). Infants received oral ZDV (2 milligrams per kilogram of body weight every 6 hours) for the first 6 weeks of life.

Women enrolled in ACTG 076 had CD4+ lymphocyte counts greater than 200/μL and generally formula-fed their infants. These findings spurred the Centers for Disease Control and Prevention and other groups to recommend that all pregnant women in the United States should be offered testing for HIV-1 infection, and that ZDV should be administered to those found to be infected, as well as to their infants. Rapid implementation of these recommendations led to a prompt and dramatic decrease in rates of mother-to-child transmission (Fiscus et al., 1996). A strong public health infrastructure and federal and state commitment of additional resources made that implementation successful.

Despite that success, the ACTG 076 regimen was too expensive for many resource-constrained settings, required identification of HIV-1 infection before or during pregnancy, and necessitated patients to adhere to daily multidose ZDV regimen for weeks or months. The regimen also required inpatient delivery, facilities and expertise in administering intravenous ZDV and in administering and monitoring ZDV therapy for 6 weeks in the newborn infant. The approach was clearly not practical or affordable in sub-Saharan Africa and resource-limited settings globally, where most mother-to-child transmission occurred in 1997 and still occurs today. Recognition of this fact led to a number of trials—HIVNET 012 among them—designed to evaluate simpler, less-expensive approaches for use in resource-limited settings.

CHOICE OF UGANDA AS STUDY SITE

Uganda has been hard hit by the HIV/AIDS epidemic. In 1997 the prevalence of HIV-1 among pregnant women in Kampala was estimated at 15% (USAID, 2005). In 2001, some 280,000 women ages 15 to 49 were living with HIV-1 infection (UNDP, 2002).

Of the 170,000 infants born each year to HIV-1-infected Ugandan women, some 43,000 would be expected to acquire HIV-1 infection. Vertical transmission accounts for 15–20% of all new HIV-1 infections in Uganda (Uganda AIDS Commission Secretariat, 2002). Antiretroviral therapy was largely unavailable in Uganda while HIVNET 012 was being conducted, and there were no programs for preventing mother-to-child transmission. Poor public health, clinical, and laboratory infrastructure and capacity, as well as high rates of out-of-hospital delivery, made the ACTG 076 regimen impractical for use in Uganda.

With some 1,500 beds, Mulago Hospital is the largest government referral hospital in Uganda and the main teaching hospital for Makerere University School of Medicine in Kampala. The hospital provides both tertiary care to Ugandan residents and primary care to the country's poorest residents who cannot afford care elsewhere. The Department of Obstetrics and Gynaecology provides inpatient and outpatient services including normal deliveries, emergency care for women with complicated pregnancies, care for gynecological emergencies, and postnatal care. The Department of Paediatrics and Child Health also has an acute-care unit, a neonatal intensive-care unit, specialized outpatient clinics, a nutritional unit, and the Child and Health Development Center. When HIVNET 012 was initiated, approximately 85% of hospital admissions were HIV-related (Guay et al., 2002). Thus Mulago Hospital and its staff had the capacity and experience to conduct a clinical trial of a less intensive regimen for preventing mother-to-child transmission.

CHOICE OF DRUG REGIMENS

Given the impracticality of the intense ACTG 076 regimen for resource-limited settings, investigators in Africa and elsewhere soon began evaluating simpler, less expensive regimens for preventing mother-to-child transmission. Nevirapine (NVP) was considered promising because of its potent and rapid antiretroviral effect (Bardsley-Elliot and Perry, 2000; Mirochnick et al., 1998). Data from a preliminary study of 10 mothers given either 100 or 200 milligrams of NVP orally at the onset of labor also produced positive results (Mirochnick et al., 1998). In that study, the median maternal serum level was 714 ng/ml. Infants whose mothers had received doses at least 2 hours before delivery maintained serum levels of NVP greater than 100 ng/ml for 3 days. This level was thought to be potentially protective against HIV-1. Appreciable levels of NVP were also found in breast milk. Hence NVP was readily absorbed and passed directly to the fetus at levels that might prevent transmission of HIV-1, and no toxicity was noted in either mother or child. On that basis, the HIVNET 012 investigators chose to study an NVP regimen consisting of 200 milligrams taken orally by pregnant women at the onset of labor, followed by 2 milligrams per kilogram of body weight for infants within 72 hours of birth.

The impetus for the short-course ZDV regimen used in HIVNET 012 was the belief that a simpler, less expensive version of the ACTG 076 three-part ZDV regimen might retain most or all of its benefits, thereby enabling widespread prevention of mother-to-child transmission in resource-poor settings. The HIVNET 012 investigators chose a ZDV regimen consisting of 600 milligrams orally to the mother at the onset of labor, followed by

300 milligrams every 3 hours until delivery and 4 milligrams per kilogram of body weight orally twice daily to infants for 7 days after birth.

The investigators did not expect either the single-dose NVP regimen or the short-course ZDV regimen selected for use in HIVNET 012 to have much of an effect on in utero HIV-1 transmission, as the first dose of both regimens was to be administered at the onset of labor. As essentially all the women were expected to breastfeed their infants, neither regimen was expected to have an effect on transmission through breast milk after the first several days of life. Finally, HIVNET 012 was solely focused on preventing mother-to-child transmission and not on treating HIV/AIDS.

Enrollment to HIVNET 012 began in November 1997. However, within 3 months, in February 1998, a trial in Thailand found that a short-course regimen of ZDV during pregnancy reduced transmission from 18.9% to 9.4%, as compared with placebo. This treatment consisted of 300 milligrams given orally to pregnant women twice daily beginning at 36 weeks of gestation and every 3 hours from onset of labor until delivery was found to reduce MTCT in Thailand (CDC, UNAIDS, NIH, and ANRS, 1998; Shaffer et al., 1999).

After learning of these results, the HIVNET 012 investigators immediately stopped randomizing women to the study's placebo arms.[1] They considered whether to replace the HIVNET 012 ZDV regimen with the ZDV regimen found to be effective in the Thai trial but concluded that that regimen was fairly expensive and thus would not be available to the majority of women in Uganda. The investigators also noted that the Thai regimen might be less effective in a breastfeeding population, and that the regimen did not include a postnatal dose.

The investigators therefore decided to seek approval for continued open-label enrollment in the original NVP and ZDV arms.[2] This request

[1]At that time, 72 women had been enrolled and assigned to one of the placebo arms, and 48 had already delivered. The remaining 24 were unblinded. Seventeen of those women had been assigned to either ZDV or NVP active arms. The 7 who had been assigned to a placebo arm were contacted and offered the active regimen corresponding to the placebo arm they had been part of; if they agreed, those previously assigned to ZDV placebo were reassigned to the ZDV arm, and those previously assigned to NVP placebo were reassigned to the NVP arm (SCHARP, 2004a).

[2]The original trial was double-blind with respect to both ZDV and NVP. "The investigators' Proposed Interim Plan (HIVNET 012 Investigators, 1998) indicates that NIH and other bodies recommended that placebo arms of their sponsored trials be discontinued. The investigators also indicated that it would take several months to redesign the trial and asked to continue the trial as an open-label trial until 'we can design and implement a revised protocol with an appropriate control arm.' This strategy was justified in part by the argument that, if the trial were stopped while the design was being revised, HIV infected women already enrolled or screened would receive nothing" (page 2) (HIVNET 012 Investigators, 1998).

was reviewed and approved by the relevant Institutional Review Boards at Johns Hopkins University and in Uganda as well as the Data and Safety Monitoring Board (DSMB).[3] Enrollment in the revised protocol began in April 1998.

Finding: The committee finds that Uganda was a reasonable setting for evaluation of short-course regimens for preventing mother-to-child transmission of HIV-1. Moreover, the regimens chosen for study were reasonable in the context of knowledge about prevention of mother-to-child transmission at that time. The decision to stop the placebo arms of the trial and continue with the originally designed active arms was reviewed and approved appropriately.

ELIGIBILITY CRITERIA

The investigators sought to develop eligibility criteria that were broadly inclusive, subject to the constraints of the appropriate age and stage of gestation of the mother, her ability to participate in the study, and contraindications to the study regimens. Thus, women were eligible to participate in HIVNET 012 if they were at least 18 years old, at more than 32 weeks gestation, HIV-1-infected, and lived within 15 kilometers of the hospital. Potential participants were excluded if they were receiving antiretroviral therapy or other disallowed drugs, had active serious non-HIV-1-related infection or illness, had known hypersensitivity to benzodiazepine, were using drugs or alcohol, had uncontrolled hypertension, were participating in other therapeutic or vaccine perinatal trials, or had abnormal hemoglobin, ALT (SGPT) or creatinine levels.

Finding: The committee finds that the inclusion and exclusion criteria employed in HIVNET 012 were reasonable.

DESIGN AND IMPLEMENTATION OF THE RANDOMIZATION PROCEDURES

The creation of comparable treatment groups through randomization is fundamental to the validity of randomized clinical trials. This section reviews the design and implementation of the randomization procedures used in HIVNET 012, as well as the comparability of the resulting treatment groups. We begin by noting concerns addressed in the 2002 Westat

[3]A DSMB is an independent committee composed of statisticians, clinicians, community representatives and ethicists who examine a study and resultant data before it begins and on an ongoing basis.

review, and address these by evaluating the design and implementation of the study randomization.

The Westat concerns were based on what they considered to be nonrandom patterns in the study data based on an apparent imbalance in the treatment assignments in a subset of enrolled women listed as born between 1973 and 1974 (Chamberlin et al., 2002). The Statistical Center for HIV/AIDS Research and Prevention (SCHARP) argued that the imbalance was less substantial than suggested by the Westat review and that the probability that an imbalance of this magnitude or greater would occur by chance (without adjusting for multiple testing) was 4%. Rather than attempting to resolve whether an imbalance did exist in a subsample of enrolled women, the committee chose to review the entire randomization design and implementation for all mothers (see below).

Westat also raised concerns about unexplained gaps in identification numbers for study participants which they believed should have been sequential (Chamberlin et al., 2002). In a response to the Westat report, the investigators explained that these gaps were due to the dropping of the placebo arms in February 1998 (HIVNET 012 Investigators, 2002). The committee investigated this by examining the entire process of assigning study identification numbers (see below).

The original design of HIVNET 012 randomized mother/infant pairs to four treatment arms: NVP, NVP placebo, ZDV, and ZDV placebo, in proportions of 2:1:2:1. This resulted in equal allocations to NVP, ZDV, and placebo, with the intent of comparing each active drug to placebo. The trial included two placebo preparations to provide partial blinding of both active drug regimens.

The randomization procedure was based on permuted blocks of 12. This algorithm randomly assigned four infants each to NVP, ZDV, and placebo after each consecutive set of 12 assignments. The randomization list was generated by SCHARP and matched to consecutive patient identification numbers (IDs) beginning with 512-0001, 512-0002, and so on. The resulting patient IDs were then sent to Johns Hopkins University to guide packaging of study drugs.[4] The resulting kits were labeled with the ID but did not include any information that would reveal the assigned treatment. The last step in the process was to assign IDs, and hence drug kits, to women enrolled into the study in the chronological order of their enrollment.

[4]In April 1998, a new drug-handling and -packaging procedure was implemented in which the medications packaged in the manufacturer's bottles were shipped to Uganda. A pharmacist on-site in Uganda prepared the drug kits.

This randomization plan was sound. The use of a relatively large block size of 12 in the permuted blocks scheme was appropriate given the partially blinded design. Members of our committee verified that the actual randomization list did correctly construct block sizes of 12 according to the indicated proportions. (The first block intentionally had only 9 assignments to introduce an additional component of randomness [Donnell, 2004].) The procedures for preparing and labeling drug kits were also sound.

In February 1998, after 72 women had been randomized into HIVNET 012, randomization was temporarily suspended because of the emerging results from the perinatal HIV prevention trial in Thailand (CDC, UNAIDS, NIH, and ANRS, 1998). With consultation from the HIVNET 012study's Data and Safety Monitoring Board, the HIVNET 012 investigators concluded that it would be unethical to continue randomizing women to placebo, and therefore terminated the placebo arms of the study. The Institutional Review Boards at Johns Hopkins University and in Uganda reviewed and approved the revised study design and in April 1998 the study resumed enrolling patients into the remaining ZDV and NVP arms.

At the time when the placebo arms were discontinued, 24 women had been enrolled and assigned to a study regimen but had not yet delivered. Seventeen of these women had been assigned either to ZDV or NVP and remained on their assigned treatment. The remaining 7 had been assigned to placebo (4 to ZDV placebo and 3 to NVP placebo). These 7 women were switched to the active drug corresponding to the placebo arm to which they had been assigned. Hence 4 mothers switched from ZDV placebo to ZDV, and 3 switched from NVP placebo to NVP (SCHARP, 2004a).

The revised randomization plan assigned women to ZDV or NVP in equal proportions, using permuted blocks of 26, so that each successive group of 26 randomized women would include 13 randomized to ZDV and 13 randomized to NVP. Kits and IDs were modified to reflect this new randomization plan. Other features of the randomization procedure remained unchanged (SCHARP, 2004a). The use of a permuted block size of 26 is also appropriate because the revised design was not blinded, and because this was a single-site study. The larger block size minimized the possibility of predicting future treatment assignments, one potential source of bias in unblinded trials.

Finding: The committee finds that the designs of the original and modified randomization procedures were scientifically sound and appropriate for the research setting.

Randomization occurred at the time of enrollment into the study when an individual participant was assigned a study ID number. The study coordinator assigned the expectant mother the next sequential study ID number

and its corresponding kit. During the placebo-controlled phase of the trial, both the study staff and participants were blind to the assignment of drug or placebo. Later, in the open-label phase of the trial, the assignment was known once the kit was opened (Guay et al., 2002). Blinding of study treatment guards against two potential sources of bias: differential ancillary treatment of participants and differential assessment of study endpoints. In HIVNET 012, lack of knowledge about the efficacy of these unproven short-course regimens and the complexity of the care setting made it unlikely that ancillary care would have differed between the two treatment arms. By focusing on the "hard" efficacy endpoints of HIV-1 infection and survival status, the investigators minimized the possibility of differential assessment of efficacy endpoints.

The committee independently verified the randomization procedure and its implementation by reviewing the treatment assignment lists and checking them relative to treatment assignments of individual mothers. A consultant to the committee reviewed the chronological order in which women were enrolled in HIVNET 012 to determine whether kits were assigned in consecutive order.

This review established that only four women did not receive kits in the order corresponding to the chronological order of their enrollment. In two of the four instances, the woman received the treatment assignment that she would have received if she had been randomized correctly. In the other two cases, the assigned drug was different from the assignment corresponding to the intended order of randomization. In one instance, NVP was assigned instead of ZDV; in the other, ZDV was assigned instead of NVP.

Comments at the time by those involved in HIVNET 012 suggest that these few errors were accidental and arose from special situations during enrollment of expectant women. The committee found no evidence of a deliberate violation of the randomization plan. Moreover, the number of assignment errors is negligible relative to the total enrollment in the study. Thus, the committee finds that analysis of the results based on the treatment actually assigned is appropriate. Moreover, because only two mothers received a different treatment assignment than if all kits had been assigned in chronological order of enrollment, reanalysis of the results using the "intended" assignment would yield virtually identical results.

As shown in Table 1 of the 1999 *Lancet* paper, the characteristics at enrollment of women who gave birth were similar in the two treatment groups. Aside from a significant difference in mean birthweight of 100 grams, the characteristics of study infants did not differ between the two treatment groups (Fleming, 2004; HIVNET 012 Investigators, 2002).

Finding: The committee finds that the HIVNET 012 randomization procedures were implemented with a high level of accuracy, achieving the scientific goal of creating two comparable treatment groups.

SAMPLE SIZE

As originally designed, HIVNET 012 had four treatment arms: ZDV, ZDV placebo, NVP, and NVP placebo. These were to be analyzed as a three-arm study comparing the safety and efficacy of two short-course regimens of NVP and ZDV with the combined placebo arms. The two placebo arms were created to provide partial blinding of treatment assignments for both active regimens.

The primary endpoint for determining sample size was the rate of HIV-1 positivity in infants up to 18 months of age (Jackson et al., 1997). The resulting sample size was also used to assess power for the endpoint of HIV-1 infection-free survival through 18 months, and safety and tolerance of the drug.

The original trial was designed to yield 90% power to detect an absolute 33% reduction in the primary endpoint, at the one-sided 0.025 significance level favoring the active drugs. To achieve these design characteristics, a target sample size of approximately 500 mother/infant pairs was to be enrolled in each of the three treatment regimens, for a total sample size of 1,500 randomized mothers (Fleming, 2004).

As noted, the placebo arms were discontinued and the study interrupted in February 1998. In April 1998, when enrollment into the ZDV and NVP arms resumed, the investigators considered whether and how the study design should be modified. The intermediate goals of the study became the comparison of the ZDV and NVP arms, in a two-arm open-label Phase IIB screening trial, aimed at selecting one arm to advance to a future phase III trial with an anchor comparison arm. The anchor was expected at that time to be a regimen selected from another African trial (Petra Study Team, 2002). The two-arm trial was designed as a non-inferiority comparison of the NVP regimen to the ZDV regimen, owing to the ease of administration and lower cost of NVP.

The HIVNET 012 Proposed Interim Plan (HIVNET 012 Investigators, 1998) outlines the design characteristics for a total sample size of either 250 or 500 randomized mothers. This approach would result in one of three possible outcomes: (1) NVP alone to be selected if the estimated transmission rate was no more than 3% higher in the NVP group than in the ZDV group; (2) both ZDV and NVP to be selected if the estimated transmission rate difference between the two groups was 3–5%; and (3) ZDV alone to be selected if the estimated transmission rate difference exceeded 5%, favoring ZDV.

Assuming that 500 mother/infant pairs were to be enrolled, this new design had more than an 80% probability of selecting NVP alone, and less than a 10% probability of selecting ZDV alone, if the true transmission rates for the NVP and ZDV regimens were identical. The efficacy of a two-stage approach, continuing with a phase IIB screening trial, followed by a

Phase III randomized controlled trial after the PETRA[5] results were known, motivated the decision to reinitiate enrollment with a new target sample size of approximately 400–600 eligible HIV-1 infected pregnant women. In fact, the trial achieved a total sample size of 626 randomized mothers, equally balanced with 313 receiving NVP and 313 receiving ZDV. Thus, for an absolute difference in transmission of 12%, this design realized more than the planned 80% probability of correctly choosing NVP alone as the preferred regimen for further study in a Phase III randomized controlled trial.

Finding: The committee finds that the original and revised sample size targets for the HIVNET 012 trial were sufficient to achieve the study goals.

STATISTICAL METHODS

Guay and colleagues (1999) used standard failure time methods for assessing HIV infection and HIV-free survival. Specifically, they used the method of Kaplan and Meier (1958) to estimate the distribution of time to HIV positivity and HIV-free survival time. From these time-to-event distributions, they estimated the probabilities at weeks 6–8 and 14–16 for each treatment arm, using standard methods for survival data to compare the estimated probabilities in the two treatment groups. While HIV infection was evaluated only periodically, the approach used by the authors is both valid and efficient because infants in the ZDV and NVP arms had the same evaluation schedule, there were very low rates of incomplete information, and the treatment groups were evaluated at the times of scheduled PCR[6] evaluations. The use of 2-sided p values is also appropriate, and the reporting of nominal p values, without adjustment for interim analyses, is appropriate because of the conservative spending function used during the interim analysis of the study results.

Finding: The committee finds that the statistical methods employed in HIVNET 012 and described in the publications were appropriate. The results obtained from the analyses of HIV infection and HIV-free survival were properly interpreted by the study authors. Additional analyses of efficacy in the Results and Discussion sections of Guay et al.

[5]The PETRA study was begun in 1998 in South Africa, Tanzania, and Uganda under the auspices of UNAIDS, and investigated the combination of ZDV and lamivudine (3TC) (in a 4-arm, randomized, placebo-controlled trial) for the prevention of perinatal HIV transmission (Peiperl, 2002).

[6]PCR stands for HIV-1 RNA polymerase chain reaction, a test used to determine HIV infection status.

(1999) and Jackson et al. (2003) were presented in a balanced manner and with appropriate qualifications.

DRUG MANAGEMENT

The original HIVNET 012 protocol stipulated that on-site investigators would maintain complete records of all study drugs received from Boehringer Ingelheim and Glaxo Wellcome, including how drugs were dispensed. Unused drugs were to be returned to the manufacturer or destroyed once the study was complete (Jackson et al., 1997).We review the major components of the drug management system briefly below.[7]

Drug Packaging and Handling Before Enrollment

The study relied on two sets of procedures for packaging and handling of study drugs prior to enrollment. Initially, manufacturers sent the drugs directly to the Johns Hopkins University pharmacy, where active and placebo preparations were packaged into either small white bottles for syrups or single-dose cellophane/foil strips for tablets that were identical in appearance. Outer package labeling was identical for all arms and contained no information that could be used to identify the study arm (Jackson and Guay, 2004). The bottles were labeled with the study identification number (given at randomization) and secured with tamper-proof seals, to verify that they had not been opened before the mother enrolled and was given a bottle. This drug-packaging system was used for the first two batches of study products sent to Uganda on October 7, 1997, and April 17, 1998 (see Table 3.1 for details).[8]

After the site received the first two batches of drugs, and after enrollment was suspended in February 1998 to allow the redesign of the study without placebo arms,[9] enrollment was stopped for a second time on May

[7]For a more detailed discussion of drug packaging, handling, and dosing, please see the *2002 Description of Study Procedures* (Guay et al., 2002). Facts were confirmed in email communication from L. Guay, March 29, 2005 (Guay, 2005d).

[8]The first batch of drug kits (study ID number 512-0001 to 512-0150) along with replacement study product was brought by Dr. Jackson in checked baggage to the study site on October 7, 1997. A second shipment of prepackaged study product was sent from Johns Hopkins University by courier and received on the site on April 21, 1998 (see Table 3-1). (Guay et al., 2002).

[9]On February 18, 1998, the placebo arms were discontinued. SCHARP unblinded the 24 enrolled, randomized mothers who had not yet delivered. Seven of the 24 women had been assigned either NVP or AZT placebo. The placebo kits were removed and replaced with the matching active agent. The remaining placebo kits on site that had not been assigned to a woman were removed from the supply and destroyed at the end of the study (Guay et al., 2002).

25, 1998, and resumed on July 7, 1998, after the packaging procedure had been changed. Under the new procedure, the Division of AIDS Clinical Research Products Management Center (CRPMC) sent the drugs (packaged in their original manufacturer's bottles) and pre-labeled empty drug kits directly to Uganda for on-site kit preparation by a pharmacist at the time of enrollment.[10] These changes were introduced in response to concerns raised by Division of AIDS (DAIDS) about lack of information on the stability of the drug in small bottles (Guay et al., 2002; Jackson and Guay, 2004). SCHARP generated a new randomization schedule for use in packaging and labeling with a new series of ID numbers beginning with 512-0401 through 512-0888. CRPMC made three drug shipments on July 6, 1998, November 2, 1998, and March 15, 1999 (see Table 3.1).

Each weekday morning, the pharmacist prepared drug kits according to the number of women expected for enrollment that day, based on a note in the pharmacy log from the study coordinator, beginning with the next sequentially numbered empty kit. The pharmacist signed the note once he completed making the kits, but these notes are no longer available. The information was recorded in the pharmacy log though (Guay et al., 2002; Guay, 2005a). All study staff members except the on-site pharmacist were blinded to the drug assignment schedule until after enrollment was complete. Dr. Guay, one of the HIVNET 012 co-investigators, periodically reconciled the quantities of drugs received and dispensed and recorded this information in the pharmacy log (Guay et al., 2002).

Drug Handling After Enrollment and Dosing

Women enrolled in the study at antenatal clinics. Each woman received an identification number after study staff had verified her eligibility and obtained informed consent. When notified that a woman scheduled for enrollment had arrived at the clinic, the study coordinator collected the next sequentially numbered set of source files from the Mulago University-Johns Hopkins University data center and corresponding study drug kits from the storage room. A staff member delivered the appropriate files and kits to the antenatal clinic and gave them to the study midwife in charge. After the placebo arm was dropped, the staff could determine whether the regimen was NVP or ZDV once the kit was opened and documented this on the enrollment form (Guay et al., 1999).

[10]Family Health International contracted with McKesson Bioservices to prepare and label the empty individual drug kits. Individual drug containers inside the kit were labeled with the specific study regimen. Labeling on the outside of the kit was identical for the two study arms (Guay et al., 2002)

Women were instructed to take their initial dose at the onset of labor. When a participant arrived at the labor ward, she gave her estimated time of labor onset and time of initial dose to the nurse. For mothers assigned to ZDV treatment, study staff administered doses of ZDV every 3 hours. A drug dosing chart in the source file recorded the drugs, doses, their dates and times, and the person who administered them. The hospital chart did not include records of drug dosing (Guay et al., 2002).

Study staff gave the infant dose of NVP at the time of discharge. The majority of infants were dosed within 24 hours. For women who delivered at home or arrived at the labor ward later, the protocol allowed infant dosing up to day 7. Women who delivered at home were encouraged to bring their infants to the research site at Mulago Hospital as soon as possible, and infants were administered medication when they arrived (Guay et al., 2002).

The infants in the ZDV arm were given the study drug twice a day. The staff initially administered the ZDV exactly 12 hours after delivery, but later changed the procedure and gave dosings at 8:00 a.m. and 8:00 p.m. to make it easier for mothers when they returned home. The doses given by hospital staff were documented on the chart. Mothers were instructed to come back for the 7-day visit, told when to stop the drug, and asked to return their vial.

The pharmacy return log recorded the number of unused tablets and syrup returned from the labor ward and participant along with a final accounting of the amount received, used, and returned. It appears that all unused and returned study products were destroyed in January 2002 except for eight kits which were transported back to the United States in July 1998 for quality control checks and which were later destroyed (Guay et al., 2002).

Reviews of Pharmacy Procedures

The Westat Site Visit Report (Chamberlin et al., 2002) expressed several concerns including that the study site did not use a subject treatment assignment list, several types of dosing errors occurred, and the temperature was not monitored in the rooms where the study products were stored. (Subsequent temperature monitoring under similar conditions by the investigators was in the acceptable range for the study products [Jackson et al., 2003a]). In a Summary of the Westat Debriefing, DAIDS noted that the Westat report "was unable to establish the full extent of such [dosing] errors or their significance for the validity of the study conclusions" and that those areas identified would require "more detailed review" (DAIDS, NIAID, 2002).

DAIDS also noted that the HIVNET 012 statisticians provided analyses

TABLE 3.1 Shipments of Study Drug

Batch / Shipment	Date Received On Site	Shipment Method	Number of Drug Kits Shipped	ID of Drug Kits Shipped	Additional Study Drug Shipped	Dates Kits Were Used[a]
For shipments 1 and 2, drug kits were prepared and filled by Johns Hopkins University (JHU) and sent to Uganda.						
1	10/7/97	B. Jackson; checked baggage on commercial airline	142 (8 kits removed for quality control check at JHU)	512-0001–512-0150[b]	6 bottles of study tablets; 6 bottles of study syrup (sent as replacement stock)	11/3/97–4/21/98
2	4/21/98	Shipped from JHU via TNT Express	72[c]	512-0151–512-0257	None	4/22/98–5/25/98
For shipments 3, 4, and 5, drugs and prelabeled empty kits were sent to Uganda for packaging by an on-site pharmacist.						
3	7/6/98	Shipped from CRPMC via World Courier	400 (200 ZDV and 200 NVP)	512-0401–512-0801[d]	30 bottles of study tablets; 40 bottles of study suspension	7/7/98–2/23/99[e]
4	11/2/98	Shipped from CRPMC via World Courier	0	N/A	10 bottles study tablets; 20 bottles of study syrup	N/A
5	3/15/99	Shipped from CRPMC via World Courier	199 (100 NVP and 99 ZDV)	512-0799, 512-0802–512-0999[f]	25 bottles tablets; 9 bottles of study syrup	3/16/99–4/30/99

[a]Of the 813 drug kits, 652 were used for study participants. 161 were not used and were later destroyed (Guay, 2005c).
[b]The following 8 kits were randomly selected by the statistical center and removed from the batch prior to shipment for quality control: 512-0011; 512-0037; 512-0081; 512-0109; 512-0120; 512-0129; 512-0144; 512-0150.
[c]Of 107 kits in Batch #2, 35 kits were assigned to placebo and were never made or shipped to the site because the placebo arm was dropped. Patients were not assigned these ID numbers (Guay, 2005b).
[d]SCHARP generated a new randomization schedule for use in packaging and labeling with a new series of ID numbers beginning with 512-0401. Kit #512-0799 was inadvertently skipped and not included in Batch #3 (Guay, 2005d; Guay et al., 2002). This was not formally documented at the time of receipt, but a note was sent to the study monitor (FHI) regarding the missing drug kit. This kit was later shipped as part of Batch #5. The last kit used was #512-0888 (Guay et al., 2002).
[e]Kits received from CRPMC (shipments 3 and 5) were used from July 7, 1998, to April 30, 1999 (the end of enrollment) (Guay et al., 2002).
[f]An additional drug kit (512-0889) was prepared in anticipation of another enrollment, but no participant was assigned to this kit, and it was returned to the pharmacy and disposed of with other unused products (Guay et al., 2002).
SOURCE: Guay (2005d); Guay et al. (2002).

showing that errors reported by Westat would "have little or no impact on the validity of the study's core conclusions" (DAIDS, NIAID, 2002). The study statisticians and the HIVNET 012 investigators themselves described non-adherence as reflective of real-world conditions, and attributed most of the dosing errors cited in the Westat report to participant non-adherence (HIVNET 012 Investigators, 2002). The investigators also corrected several inaccuracies in the Westat report's description of procedures related to drug storage and handling (HIVNET 012 Investigators, 2002).

The DAIDS Pharmaceutical Affairs Branch also visited Uganda in July 2002 to review the drug-management procedures at the site. They examined study drug treatment assignment, drug kit preparation by the pharmacist, drug distribution, documentation of dispensing procedures, drug return, chain of custody, and destruction of unused drugs. The DAIDS remonitoring team expressed concerns about some inadequate documentation and dosing errors as well. They noted various ways in which more detailed information in the pharmacy records and source documents could have more fully documented the pathway from packaging of study drugs to dosing of the mothers and infants, thereby providing more robust evidence regarding the management of study drugs and level of adherence to study regimens (DAIDS, NIAID, 2003).

HIVNET 012 investigators acknowledged some deficiencies and missing documentation relating to drug management, but noted that the study achieved a very high level of adherence to treatment regimens (Jackson and Guay, 2004), as described in *The Lancet* articles (Guay et al., 1999; Jackson et al., 2003a).

After reviewing all relevant information, the committee concluded that a number of sources document the distribution and administration of assigned study drugs to study mothers and their infants in accordance with their treatment assignments. In both the first and second method of drug packaging, the proper packaging of study drug in accordance with the randomization schedule is well documented. Information available in the source documents indicates that drug kits were consistently provided to the appropriate mothers and caregivers. Thus, the information available to the committee indicates that the potential deficiencies in documenting drug management noted by Westat and DAIDS were, in fact, deficiencies of documentation, not drug delivery, and that study drugs were consistently and appropriately provided to study participants.

ADHERENCE

The committee also reviewed the available information on participants' adherence to study treatments. HIVNET 012 measured such adherence both directly and indirectly. All patients were asked about their adherence

to the medications and answers were recorded on the case report form. In addition, the nursing and labor and delivery staff were queried regarding adherence. In the ZDV arm, 17 of 308 women delivered outside of Mulago Hospital. In the NVP arm, 20 out of 311 women delivered at a site other than Mulago Hospital (SCHARP, 2004b). In the ZDV arm, 50 women were redosed (for reasons such as false labor or vomiting), 3 of whom had delivered outside of Mulago Hospitals. Of the 244 women in the ZDV arm who delivered at the hospital and who were not redosed, 142 women took a dose prior to arrival, 101 received a dose after arrival at the maternity ward, and for 1 woman, the study database did not state where the dose was taken. In the NVP arm, 12 women were redosed, 2 of whom had delivered outside of Mulago Hospitals. Of the 281 women in the NVP arm who delivered at the hospital and who were not redosed, 166 women took their dose prior to arrival, 111 received their dose after arrival at maternity ward, 3 were not dosed, and for 1 woman no information was available (SCHARP, 2004c).

Cord blood was obtained from the infants in both arms and specimens were frozen for later analysis.[11] In the ZDV arm, specimens were obtained for 278 of 308 infants (90%), and NVP was detected in only 1 specimen (<1%). In the NVP arm, specimens were available for 275 of the 311 infants (88%). Of these, 3 were never dosed and had no detectable NVP. Of the remaining 272 specimens, 256 (94%) had detectable blood concentrations of NVP. In the 16 specimens obtained from the 18 patients[12] randomized to placebo (89%), no NVP was detected. Only NVP concentration was measured as NVP has a long half-life (Jackson et al., 2003b). The investigators did not attempt to measure ZDV in the cord blood due to its short half-life which would make findings difficult to interpret. For example, if one tested for ZDV but none was found, one would not be able to determine whether the drug was not taken or if it was taken several hours prior to the blood draw. Without careful timing of the intake of ZDV dose in relation to sampling time, interpretation of ZDV blood levels would be meaningless.

Studies have shown that the majority of women who received a single dose of NVP had detectable NVP levels 2 weeks after a single dose (Cressey et al., 2005; Jackson et al., 2005; Muro et al., 2004). Since ZDV has a short half-life of 1.1 hours in non-pregnant women and clearance is increased by

[11]Cord blood was not available for all subjects for several reasons: some women delivered at home or elsewhere outside of the hospital, some cord blood samples were not obtained (especially in instances of emergency C-section), and cord blood was clotted before it was drawn. The investigators did tests on all available cord blood specimens (Jackson, 2005).

[12]Of the 19 patients who were enrolled to the placebo arm, one was lost to follow-up. As a result, there are only 18 deliveries recorded (Jackson, 2005; Jackson et al., 2003a).

47 to 65% in pregnant women (Mirochnick et al., 1998), inability to detect ZDV in the cord blood could indicate either that the mother had not taken the drug or that she took her ZDV dose more than 3 hours prior to the blood draw. As a result, the investigators did not attempt to measure ZDV in the cord blood.

Two other measures of adherence were available to the committee. In the group of mothers assigned to NVP, HIV RNA concentration decreased by approximately one log one week after dosing, returning to baseline by the 6-week blood sample. There was no change in HIV RNA concentration in the mothers who took ZDV, which is to be expected given the short half-life of ZDV. Finally, HIV resistant mutations to NVP were only seen in the mothers who took NVP (Jackson and Guay, 2004). This finding is consistent with the DAIDS remonitoring evaluation which concluded that the assigned drugs were given to the appropriate participants (DAIDS, NIAID, 2003).

Finding: The committee finds that the HIVNET 012 investigators used appropriate practices for packaging and distributing study drugs, so that the assigned drug was consistently provided to the appropriate mothers and their infants. Evidence from cord blood specimens indicates that participants achieved a high level of adherence to the NVP regimen. Though no direct evidence is available on blood levels of ZDV, the maternal reports of high levels of adherence to the treatment regimen, the fact that hospital personnel administered a substantial fraction of the ZDV regimen, and the absence of detectable levels of NVP in the blood of participants in the ZDV arm suggest that high levels of adherence were also achieved in the ZDV arm. The high level of adherence to study regimens indicates that the treatment arms formed an appropriate basis for assessing the efficacy and safety of the study regimens.

REFERENCES

Bardsley-Elliot A, Perry CM. 2000. Nevirapine: A review of its use in the prevention and treatment of paediatric HIV infection. *Paediatric Drugs* 2(5):373-407.

CDC (Centers for Disease Control and Prevention), UNAIDS (Joint United Nations Programme on HIV/AIDS), NIH (National Institutes of Health), and ANRS (Agence Nationale de Recherche sur le SIDA). 1998. Joint Statement by the Centers for Disease Control and Prevention (CDC), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the National Institutes of Health (NIH) and the Agence Nationale de Recherche sur le SIDA (ANRS), Following the Announcement by the Ministry of Public Health of Thailand and the CDC of Results from their Mother-to-Child Transmission Trial, February 18, 1998.

Chamberlin J, Gustavson SA, Hensley M, Lander. 2002. Site Visit Report, Kampala, Uganda, February 18-28, 2002. Westat Corporation, MD.

Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, JimenezE,O'Neill E, Bazin B, Delfraissy J, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J, for The Pediatric AIDS Clinical Trials Gropu Protocol 076 Study Group. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 331(18): 1173-1180.

Cressey TR, Jourdain G, Lallemant MJ, Kunkeaw S, Jackson JB, Musoke P, Capparelli E, Mirochnick M. 2005. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *Journal of Acquired Immune Deficiency Syndromes* 38(3):283-288.

DAIDS, NIAID (Division of AIDS, National Institute of Allergy and Infectious Diseases). 2002. *DAIDS Summary of March 19 Westat Debriefing*.

DAIDS, NIAID. 2003. *HIVNET 012 Monitoring Report*.

Donnell D. 2004, November 24. Mem to Alicia Gable: Listings of randomization scheme.

Fiscus SA, Adimora AA, Schoenbach VJ, Lim W, McKinney R, Rupar D, Kenny J, Woods C, Wilfert C. 1996. Perinatal HIV infection and the effect of zidovudine therapy on transmission in rural and urban counties. *Journal of the American Medical Association* 275(19):1483-1488.

Fleming T. 2004. Powerpoint Presentation to Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study on September 30, 2004: HIVNET 012 Institute of Medicine Review.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181): 795-802.

Guay L, Mmiro F, Musoke P, Fanning M. 2002. HIVNET 012: Phase IIB Trial to Evaluate the Efficacy of Oral Nevirapine and the Efficacy of Oral AZT in Infants Born to HIV-Infected Mothers in Uganda for Prevention of Vertical HIV Transmission. Description of Study Procedures.

Guay L. March 27, 2005a. Re: Pharmacy logs. E-mail to Guay L, Gable A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Guay L. March 28, 2005b. Re: Minor question. E-mail to Jackson JB, Gable A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Guay L. March 29, 2005c. Re: Additional question. E-mail to Guay L, Gable A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Guay L. March 29, 2005d. Re: Verification on drug management procedures. E-mail to Guay L, Gable A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

HIVNET 012 Investigators. 1998. *HIVNET 012 Proposed Interim Plan*.

HIVNET 012 Investigators. 2002. Summary Sheet of Major Inaccuracies in the Westat Report.

Jackson B. March 28, 2005. Re: 012 cord blood nevirapine levels. E-mail to Alicia Gable.

Jackson B, Guay L. 2004. Powerpoint Presentation to Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study on September 30, 2004: HIVNET 012: Safety and Efficacy at 18 months.

Jackson B, Parsons T, Musoke P, Nakabiito C, Donnell D, Fleming T, Mirochnick M, Mofenson L, Fowler M, Mmiro F, Guay L, and HIVNET 012. 2005. *Association of Cord Blood Nevirapine with Self-Reported Timing of Dose and HIV-1 Transmission in the HIVNET 012 Study, Abstract #71*. [Online] Available at http://www. retroconference .org/org/2005/cd/Abstracts/25816.htm. Accessed March 7, 2005.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003a. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

Jackson B, Parsons T, Musoke P, Nakabiito C, Donnell D, Fleming T, Mirochnick M, Mofenson L, Fowler MG, Mmiro F, Guay L. 2003b. Strong correlation of cord blood nevirapine level with self reported timing of dose and HIV-1 transmission in the HIVNET 012 study.

Jackson B, Mmiro F, Guay L, Musoke P, Fowler MG. 1997. Protocol HIVNET 012: A Phase III Placebo-Controlled Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates.

Kaplan EL, Meier P. 1958. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 53(282):457-481.

Mirochnick M, Fenton T, Gagnier P, Pav J, Gwynne M, Siminski S, Sperling RS, Beckerman K, Jimenez E, Yogev R, Spector SA, Sullivan JL. 1998. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *Journal of Infectious Diseases* 178(2):368-374.

Muro E, Droste J, ter Hofstede H, Bosch M, Dolmans W, Burger D. 2004. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose NVP: Implications for intervention studies. *Conference on Retroviruses & Opportunistic Infections*, Abstract No. 891.

Peiperl L. 2002. Antiretroviral Treatments to Reduce Mother-to-Child Transmission of HIV. HIV InSite, University of California San Francisco. [Online] Available at http://hivinsite.ucsf.edu/InSite.jsp?page-home-00-00&doc=3098/0098#19/ Accessed March 21, 2005.

Petra Study Team. 2002. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): A randomised, double-blind, placebo-controlled trial. *Lancet* 359(9313):1178-1186.

SCHARP (Statistical Center for HIV/AIDS Research and Prevention). October 25, 2004a. Memo: Implementation of randomization in HIVNET 012.

SCHARP. 2004b. File: t_m_delivery.pdf.

SCHARP. 2004c. File: t_m_dosing.pdf.

Shaffer N, Chuachoowong R, Mock P, Bhadrakom C, Siriwasin W, Young N, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro T, Simonds R. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353(9155):773-780.

Uganda AIDS Commission Secretariat. 2002. *HIV/AIDS in Uganda: The Epidemic and the Response*. [Online] http://www.aidsuganda.org/pdf/hiv_aids_impact.pdf. Accessed March 7, 2005.

UNDP (United Nations Development Programme). 2002. *Human Development Report 2002*. Chapter 7: Leading global health crises and challenges.

USAID (United States Agency for International Development). 2005. *Uganda*. [Online] Available at http://www.usaid.gov/our_work/global_health/aids/Countries/africa/uganda.html. Accessed May 1, 2005.

Working Group on Mother-To-Infant Transmission of HIV. 1995. Rates of mother-to-infant transmission of HIV-1 in Africa, America, and Europe: Results from 13 perinatal studies. *Journal of AIDS Retrovirology* 8:506-510.

4

Efficacy and Safety

This chapter evaluates the HIVNET 012 trial efficacy endpoints (HIV-1 positivity and HIV-1-free survival[1] of infants) and safety endpoints—their design, their implementation, and the committee's analysis.

DESIGN OF EFFICACY AND SAFETY ENDPOINTS

Primary Endpoints

Efficacy

The primary efficacy endpoints for HIVNET 012 were infant HIV-1 positivity and HIV-1-free survival at 6–8 weeks, 14–16 weeks, and 18 months of age. At the time the initial results were reported in *The Lancet* (Guay et al., 1999a), referred to in this report as *Lancet* I, there was insufficient duration of follow-up to enable reporting of 18-month efficacy; thus, the focus was on efficacy at the 6–8 week and 14–16 week evaluation times. A second paper published in *The Lancet* (Jackson et al., 2003), referred to in this report as *Lancet* II, reports results through month 18 of follow-up.

Samples for determination of infant HIV-1 infection status were obtained within 24 hours of birth, and at 6–8 weeks, 14–16 weeks, and 18

[1]HIV-1-free survival refers to absence of HIV-1 infection or death from any cause.

months of age. These timepoints for sampling were chosen to optimize the determination of antepartum, intrapartum, postpartum (breast feeding), and cumulative HIV-1 positivity. In addition, because infant mortality was of paramount interest in any potential intervention for mother-to-child transmission, a composite endpoint of HIV-1-free survival was included (Guay et al., 1999; Jackson et al., 2003).

HIVNET 012 used qualitative plasma HIV-1 RNA polymerase chain reaction (PCR) assay for determination of HIV-1 infection status of infants at 24 hours, 6 weeks, and 14 weeks of age. Positive test results were confirmed by quantitative plasma HIV-1 RNA PCR assay or HIV-1 culture. An HIV-1 EIA (enzyme immunoassay) test was performed at 18 months of age; a positive result was confirmed by HIV-1 Western blot (Guay et al., 1999; Jackson et al., 2003).

Qualitative plasma HIV-1 RNA PCR, quantitative plasma HIV-1 RNA PCR, and qualitative HIV-1 DNA PCR assays have been shown in multiple studies to be highly sensitive and specific for diagnosis of HIV-1 infection in young infants, especially after the first week of life. Simonds and colleagues (1998) reported a direct comparison of qualitative plasma HIV-1 RNA and DNA PCR assays performed on paired specimens from HIV-1-infected and uninfected infants less than 3 months of age. The sensitivity of the qualitative RNA assay was 38% at <7 days of age (95% confidence interval [CI], 22–56%), 97% at 7–41 days of age (95% CI, 88–100%), and 95% at 42–93 days of age (95% CI, 83–99%). Test specificity was 99% (95% CI, 97–100%). The authors concluded that the qualitative RNA assay was highly specific and more sensitive than qualitative HIV-1 DNA PCR for diagnosis of HIV-1 infection in young infants. These findings were confirmed in another comparative study reported by Cunningham et al. (1999).

Finding: The committee finds that the testing schedule and assays used in HIVNET 012 to diagnose HIV-1 infection in infants were appropriate. Use of HIV-1 positivity and HIV-1-free survival at 6–8 weeks, 14–16 weeks, and 18 months of age as the primary efficacy endpoints also was appropriate.

Safety

HIVNET 012 included as one of three primary study endpoints the "safety/tolerance of oral nevirapine (NVP) and oral zidovudine (AZT, now ZDV) given to pregnant Ugandan women during labor and their neonates in the first week of life." Both adverse events (AEs) and serious adverse events (SAEs) were recorded on case report forms (CRFs) and transmitted to the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). SAEs also were reported directly to the Division of AIDS (DAIDS) through the adverse experience reporting mechanism in place at the time.

The HIVNET 012 study protocol specified that mothers be followed for AEs and SAEs for 6 weeks after delivery (HIVNET Group, 1997). Infants were followed for AEs until 6 weeks of age, and for SAEs until 18 months of age. For mothers, clinical and laboratory evaluations for safety were performed at delivery, and at 24–48 hours, 7 days, and 6–8 weeks postpartum. Infants were evaluated at the ages of 24 hours, 7 days, 6 weeks, 10 weeks, 14 weeks, 6 months, 9 months, 12 months, and 18 months of age. Laboratory testing, which included hematology and serum chemistries, was not required at every visit. The HIVNET 012, *Study Specific Procedures* (version 1.0, November 1997) state that toxicities were graded based on the DAIDS Toxicity Tables[2] for neonates, children, and adults, with a range from Grade 1 (mild) to Grade 4 (life-threatening) (SCHARP, 1997). A special grading system, outlined in the *Study Specific Procedures* manual was used for cutaneous/skin rash/dermatitis adverse experiences and maternal hemoglobin values (SCHARP, 1997). Dose modification for management of adverse events was not used in the study.

The HIVNET 012 protocol, version 1.0, defined an SAE as follows:

> A serious adverse event is defined as any experience that is fatal or life-threatening, permanently disabling, requires in-patient hospitalization, is a congenital anomaly, cancer or overdose or is otherwise judged to be serious by the onsite clinician (HIVNET Group, 1997).

This definition was consistent with the definition of an SAE as it appeared at the time in the Code of Federal Regulations (21 CFR 312). After HIVNET 012 was initiated in its original form (November 1997), and about the time that enrollment was re-initiated after the placebo arms had been dropped (April 1998), the SAE definition in the Code of Federal Regulations (21 CFR 312) was revised. However, based on information from DAIDS and the U.S. Food and Drug Administration (FDA), HIVNET 012, which was already ongoing, was not required to adopt the revised regulations.

Finding: The committee finds that the definitions of adverse events and serious adverse events specified in the protocol were reasonable. The committee finds that the follow-up periods and schedule of evaluations established for mothers and infants participating in HIVNET 012 were reasonable and were sufficient to capture relevant information about adverse events.

[2]DAIDS pediatric and adult toxicity tables are available online at http://rcc.tech-res-intl.com/tox_tables.htm.

STUDY IMPLEMENTATION WITH REGARD TO THE ENDPOINTS

Infants were evaluated clinically during study visits, and were administered laboratory tests to determine HIV-1 infection status at established time points during their first 18 months of life. For infants who missed a scheduled study visit, survival status was confirmed by health visitors who conducted outreach and follow-up. For participants who were confirmed dead, this information was documented in the source documents and onto CRFs for transmittal to SCHARP. (As noted earlier, the HIVNET 012 study staff maintained records of adverse event experiences in all participants through 6 weeks, and of SAEs in infants through 18 months of age, later extended to 5 years of age as per protocol.) Adverse event information was generally recorded on source documents that were transcribed to CRFs and regularly transmitted to SCHARP for entry into the study database and analysis (Guay, 2004; SCHARP, 2004).

Laboratory Data

The audit and remonitoring of HIVNET 012 conducted by DAIDS in 2002 reported no major deficiencies related to the laboratory, from the collection and storage of samples, to the laboratory source documentation. Westat's limited laboratory audit reported that although the laboratory was not yet certified, it had participated in several proficiency programs, there was documentation of ongoing quality assurance programs, and laboratory standard operating procedures were documented and implemented (Chamberlin et al., 2002). The DAIDS remonitoring reported that the laboratory was operating according to Good Laboratory Procedures and that laboratory values in the clinic source file matched the actual laboratory source documents (DAIDS, NIAID, 2003a).

Laboratory data completeness and accuracy was monitored by SCHARP, which would e-mail the site for resolution of any inconsistencies. Inconsistencies that would generate such an e-mail included, for example, a positive HIV-1 PCR test followed by a negative test, missing laboratory results from a scheduled visit, a positive HIV-1 test result without confirmation and inconsistent results between an HIV-1 antibody test and PCR (SCHARP, 2004).

Finding: The committee finds no issues of concern regarding the reliability and validity of laboratory test results obtained in HIVNET 012, or the completeness and accuracy of study laboratory records.

Identifying Serious Adverse Events

In the implementation of HIVNET 012, the investigators had to contend with the practical implications of identifying and reporting to the

study database a great many adverse events (AEs and SAEs), the majority of which represented co-morbid conditions common among HIV-1-infected and HIV-1-uninfected women and infants in Uganda, for example, malaria, anemia, or tuberculosis. With a principal objective of capturing all clinically relevant events while at the same time reducing the background noise introduced by the high prevalence of co-morbid conditions, the investigators consistently interpreted the SAE definition contained in the 1996 and 1997 Code of Federal Regulations and the protocol so as to use hospitalization as the primary determinant of seriousness for capture of SAEs. If a study participant experienced a condition that required hospitalization, that condition was considered an SAE. To the extent possible, investigators attempted to capture unifying conditions or diseases by name (e.g., gastroenteritis), rather than as a collection of individual symptoms or signs (e.g., vomiting and diarrhea). The investigators interpreted the last phrase of the SAE definition (". . . or is otherwise judged to be serious by the onsite clinician") in a specific manner; rather than using this criterion to capture a wide range of conditions that were neither life-threatening nor triggering hospitalization, the investigators used it narrowly, to capture infrequent occurrences that had not resulted in hospitalization. (See Tables 4-1 and 4-2 for a breakdown of reported SAEs by mother and infant.) As a result of this interpretation, in practice some conditions that may have been considered serious in a different clinical context but that did not result in hospitalization in the local clinical setting were not identified as SAEs.[3]

The investigators' interpretation of the definition of SAEs in the Code of Federal Regulations and protocol led to concerns on the part of some auditors and monitors that the use of hospitalization as the principal determinant of seriousness of clinical events may have resulted in undercounting of SAEs. In their 2002 site visit, Westat auditors reported that HIVNET 012 study staff informed them about the SAE definition being used in the study. Westat site visit staff expressed their concern that the protocol definition seemed in practice to make hospitalization the primary threshold for SAEs, which if true, would mean that other serious conditions that were not considered "hospitalizable" might potentially be missing. (As noted earlier in this chapter, the committee finds that the interpretation of SAE used by the HIVNET 012 investigators was reasonable under the circumstances.)

The remonitoring effort overseen by DAIDS in 2002 also expressed

[3]For example, in the United States a baby or mother with malaria would automatically be hospitalized but in Uganda, where malaria is ubiquitous, it would be rare to hospitalize anyone with malaria unless it was life-threatening. In one country, such a condition would be automatically classified as an SAE but not in the other by the definition used by the investigators but in neither country would they be due to drug toxicity.

TABLE 4.1 Serious Adverse Events in HIVNET 012 Infants

Type of SAE	Number
Total reported	636
Fatal or life-threatening SAEs	165
Required in-patient hospitalization	526
Congenital anomaly (none were cancer or study drug overdose)	18
Permanently disabling	Not available[a]
Otherwise judged to be serious by the on-site clinician (and had none of the above attributes)	41
SAEs fitting multiple categories	
Either congenital anomaly, or fatal/life-threatening, or required hospitalization or a combination of these attributes	595
Fatal/life threatening and also required hospitalization	107
Congenital anomaly and also required hospitalization	6
Congenital anomaly and also fatal/life-threatening	1
Fatal/life-threatening only	57
Required hospitalization only	413
Congenital anomaly only	11

[a]Study staff did not collect information whether an SAE was permanently disabling. Nonetheless a review of the frequency distribution of the SAEs did not indicate any permanent disabilities.
SOURCE: Mwatha (2005c).

TABLE 4.2 Serious Adverse Events in HIVNET 012 Mothers

Type of SAE	Number
Total reported	121
Fatal or life-threatening (including 4 stillbirth deliveries)	72
In-patient hospitalization	65
Cancer (none were congenital anomaly or study drug overdose)	1
Permanently disabling	Not available[a]
SAEs fitting multiple categories	
Otherwise judged to be serious by the on-site clinician (and had none of the above attributes)	10
Cancer, or fatal/life-threatening, or required hospitalization or a combination of these attributes	107
Fatal/life-threatening and also required hospitalization	25
Cancer, required hospitalization and was fatal/life-threatening	1
Fatal/life-threatening only	42
Hospitalization only	39

[a]HIVNET 012 study staff did not collect information whether an SAE was permanently disabling. Nonetheless a review of the frequency distribution of the SAEs did not indicate any permanent disabilities.
SOURCE: Mwatha (2005c).

concern about an apparent difference between the protocol (both the original versions and the long-term follow-up amendment) and the "algorithm used by investigators" (DAIDS, NIAID, 2003a). (See committee's conclusion below, that the definition of SAE had not been altered but that the interpretation of its criteria functioned to make hospitalization the primary threshold for reporting an SAE.) The remonitoring team reported that investigators defined SAEs as "those clinical events leading to hospitalization or death," noted that this interpretation of the definition was not formally approved by DAIDS or submitted to the Investigatinal New Drug (IND) file, and identified several events unrelated to the study drug that they believed should have been considered SAEs (LaMontagne, 2004; Jackson et al., 2003). While the protocol definition of SAEs used by HIVNET 012 was properly reviewed and approved by the relevant IRBs, protocols do not usually spell out the planned interpretation of each definition.

Finding: The committee finds that the HIVNET 012 investigators interpreted definitions contained in the 1996 and 1997 Code of Federal Regulations and the protocol so as to use hospitalization as the primary, but not sole, determinant of seriousness for capture of serious adverse events. Although this well may have been a practical and appropriate interpretation of the definition of serious adverse events, it means that the safety results, while meaningful in a Ugandan context and other similar settings, may not be entirely generalizable to settings in which the definition of seriousness is interpreted differently and where thresholds for hospitalization vary.

Recording Serious Adverse Events

HIVNET 012 study staff documented clinical and laboratory findings in the source documents and transcribed these to CRFs for each participant. Westat and remonitoring teams reported that some AEs and SAEs were not consistently noted on the proper forms, including CRFs. Also, they reported the absence of documentation about the resolution of some SAEs (Chamberlin et al., 2002; DAIDS, NIAID, 2003a).

According to the 2002 *Description of Study Procedures* (Guay et al., 2002), data on study participants were collected on a variety of source documents appropriate to the nature of the visit, and key data were transcribed on CRFs that were later transmitted to SCHARP via the DataFax system for input into the study database. A source file (binder) was created for each mother/infant pair of HIVNET 012 study participants. The source file contained primary documentation of clinic visits, including clinical and laboratory information, and scheduled and unscheduled visit forms, secondary documentation such as a "hospital admissions form" tracking a

study participant's hospitalization at Mulago Hospital (later, actual copies of original hospital admission records), and notes based on patient's statements about other clinical encounters outside of the study clinic. CRFs were filed in a parallel set of binders for each mother/infant pair. There was no requirement to report unscheduled visits in the CRFs, unless the infant had an AE or SAE or a laboratory test was performed.

The HIVNET 012 investigators created a series of CRFs to capture adverse events. Questions about deaths were asked on the following four CRFs: the Delivery Form (DF-1 for stillbirth), the Illness/AE Form for mothers and infants (AE-N), the Missed Visit Form for mother and infant (MV-01), and Status Change Notice for mothers and infants (SCN-01). Specific questions about adverse events were asked on the following six forms: Delivery Form (DF-2), Follow-up Form (MFU-1), the Concomitant Medications Log for the mother and infant (CM-1), the Birth Form (IB-1), the Infant's Follow-up Form (IF-1) and the Illness/AE Form (AE-N). Physical exam findings were asked about on the Mother's Enrollment Form (ME-2), the Delivery Form (DF-1 for meconium in amniotic fluid, chorioamnionitis, and blood loss and DF-2 for physical exam findings), Follow-up Form (MFU-1), Birth Form (IB-1), and Infant's Follow-up Form (IF-1). Abnormal laboratory tests and severity grading were noted on the Laboratory Results Form for both mothers and infants (LR-1). The AE-N form also assigned grades, relatedness to study drug, and outcome. Thus, deaths, adverse events, abnormal physical exam findings, and abnormal laboratory data could be captured on several different forms. These were used by SCHARP to assess internal consistency (SCHARP, 2004).

Health visitors' (outreach workers) logs and notes, developed after visits to participants who missed scheduled visits, or required follow-up, were an additional source of information, especially in identifying participant deaths (DAIDS, NIAID, 2003a).

Record Keeping at the HIVNET 012 Site

The Westat site visit team conducted a limited assessment of the quality of record keeping and the conditions of record storage (Chamberlin et al., 2002). The Westat team reported that source primary records and CRFs were generally well organized, and with a few exceptions, were stored in adequately secure locations, but they expressed concern about "hospital admission forms," which were re-creations by study staff of hospital records. In addition, each time a patient was admitted to Mulago Hospital, the patient was assigned a new unique hospital chart number rather than a consistent unique identifier, thus making it difficult to readily identify all of a given patient's hospital admissions without a manual search of hospital files. These issues later were clarified as the study staff indicated a goal of

maintaining a comprehensive profile on every study participant, and the investigators received permission from the hospital to gather all records of participants and organize them alphabetically, thus giving HIVNET 012 staff access to the primary hospital files.

Other concerns raised by the Westat audit team included the completeness and accuracy of data recording, and quality assurance mechanisms, such as regular investigator review of CRFs (Chamberlin et al., 2002). In a subsequent visit to the site, the DAIDS remonitoring team reported finding that source files were not consistently dated and signed, and also that changes, inconsistencies, and explanations for protocol violations were not recorded. The Westat team also concluded that corrections on CRFs or other documents were sometimes not properly made (i.e., a single line drawn through) and were not consistently initialed and dated (DAIDS, NIAID, 2003a).

In response to some of the auditors' concerns, HIVNET 012 investigators took additional steps to ensure adherence to good data-collection and record-keeping practices, including hiring additional staff to conduct quality control and assurance activities, developing standard operating procedures (e.g., for the submission of regulatory documents), and ensuring regular implementation of proper dating and initialing procedures on study forms (Guay and Jackson, 2003).

Co-Enrollment into a Vitamin A Study

The Westat site visit team expressed concern about the fact that HIV-positive children who had completed the HIVNET 012 study regimen were enrolled beginning at ages 6 to 7 months in a vitamin A study seeking to determine the supplement's effects on HIV-related deaths and illnesses. DAIDS agreed that such co-enrollment could "potentially complicate the analysis of long-term safety data," but found that the co-enrollment was permitted by the protocol which allowed any opportunity for treatment to HIV-infected children participating in HIVNET 012 (DAIDS, NIAID, 2003a).

A small number of infants from both the active arms and the early placebo arms of HIVNET 012 were enrolled in the vitamin A study, including 33 HIV-positive infants from the ZDV arm and 23 infants from the NVP arm. Of the 56 children from the active arms of HIVNET 012 (infants who received placebo were not included in most analyses), only 24 (16 ZDV and 8 NVP) received vitamin A and the remainder received placebo (SCHARP, 2005).

The committee notes that participation in the vitamin A (or any other) trial following infant HIV infection does not have any impact on the

HIVNET 012 primary efficacy endpoints of HIV-1 positivity and HIV-1-free survival, as these endpoints would have occurred prior to enrollment into the vitamin A trial. Additionally, participation in the vitamin A study would have no impact on (nonserious) AEs captured in HIVNET 012 because those were only collected until 6 weeks of age, whereas participation in the vitamin A study did not begin until at least 6 months of age. However, it is possible, in theory, that participation in the vitamin A study could have affected the incidence of SAEs captured in HIVNET 012, since SAEs were collected until 18 months of age. A total of 33 ZDV and 23 NVP infants from HIVNET 012 participated in the vitamin A study. Of these, 16 (ZDV) and 14 (NVP) had at least one SAE after enrolling in the vitamin A study. Therefore, the SAEs occurring after 6 months in these 30 infants, representing 5% of the HIVNET 012 infants, could have been related to vitamin A (Mwatha, 2005a; Mwatha, 2005b).

The incidence of SAEs in the vitamin A study was somewhat lower in infants receiving vitamin A than in those receiving placebo, suggesting either no effect or a possible protective effect of vitamin A on SAE risk. Since more ZDV infants than NVP infants participated in the vitamin A study, a protective vitamin A effect would have the consequence of biasing the HIVNET 012 SAE data in favor of ZDV, since more ZDV infants participated than did NVP infants. If vitamin A had no effect on SAE rates, then participation would neither affect nor bias the HIVNET 012 SAE results.

Thus, while the possibility exists that participation in the vitamin A study may have affected the number of SAEs that were captured in HIVNET 012, the opportunity for this is limited because of the small number of infants that participated, and we see no evidence or reason that such participation could have led to an understated relative safety of NVP in the HIVNET 012 study.

Finding: The committee finds that participation of HIVNET 012 infants in the vitamin A study had no impact on the HIVNET 012 efficacy endpoints or AEs, and finds no evidence that such participation might have biased the comparative SAE rates in HIVNET 012 in favor of NVP.

Impact of Flooding and Other Natural Phenomena on Study Records

In its report, the Westat site visit team stated that it found that one of the health visitors' log books, containing notes about follow-up visits to participants' homes, appeared to be a recent transcription. Upon asking study staff about that, Westat team members were informed that the origi-

nal had been damaged by flooding caused by a plumbing problem. Those log books were secondary materials not used as source documents for the study, and it appears that much of the information contained in the damaged notebook(s) was legible and copied into a new notebook or notebooks (Guay, 2004).

A second concern about the state of study documentation arose when study staff obtained hospitalization records from Mulago Hospital on study participants and began to reorganize those records. Study staff found that a small number of the records had been slightly damaged by rodents or insects, but not to an extent that rendered them unusable (Guay, 2004). None of the participants' source documents was affected by this event. Based on its review of secondary sources (Westat and DAIDS remonitoring reports) and information heard during the investigators' presentation before the committee, this committee has concluded that the extent and significance of missing documents was quite limited and has no bearing on the integrity of the study.

Finding: The committee finds that the record-keeping system implemented in HIVNET 012 was reasonable and appropriate. While there were some documentation and procedural deficiencies reported by auditors, none appeared to have affected the results of the study. There is no evidence that flooding or any other natural phenomenon significantly impacted the completeness of study records.

COMMITTEE'S REVIEW OF THE COMPLETENESS AND ACCURACY OF EFFICACY AND SAFETY ENDPOINTS

Because of the various and somewhat inconsistent reports about the quality and completeness of the HIVNET 012 study data, the committee undertook its own evaluation of HIVNET 012 for the purpose of assessing the quality and completeness of source documents, the consistency between information in source documents and the CRFs, the information captured in the SCHARP data sets, and the timeliness and accuracy with which information was transferred from the source documents/CRFs to the SCHARP database. We focused on infant survival status, HIV-1 PCR/EIA results, adverse events, SAEs, and hospitalizations. Because of the importance of survival status information, the committee examined a subsample of the random sample of 80 mother/infant pairs identified by the EMMES Corporation for the DAIDS remonitoring effort, as this was intentionally selected to oversample infants that died.

Based on its detailed examination of study data, the committee found no evidence of misrepresentation or inappropriate manipulation of the reporting of the original study results.

Methods of Committee's Review

The committee asked the HIVNET 012 study investigators to provide copies of all source documents on file at the study site in Uganda for 80 mother/infant pairs that were previously identified through a weighted random sample by the EMMES Corporation (EMMES Corporation, 2002). In its review, the committee used a sequential sampling procedure to evaluate a subset of these 80 mother/infant pairs. Only infant records were included in the committee's review. Because of the greater frequency of adverse events and scheduled PCR/EIA evaluations than SAEs, deaths, and hospitalizations, it was decided that the committee would conclude its review of source documents when information was collected for at least 100 adverse events occurring within the first 6 weeks of life in no fewer than 20 infants. The rationale for evaluating at least 100 adverse events in source documents was that this would allow an estimation of the probability that these would be captured in the analysis database with adequate precision (estimated standard error of 0.03).

Based on this strategy, source documents representing 47 mothers and 49 infants (two sets of twins), were reviewed. Twenty-three deaths and 26 hospitalizations were recorded among the infants included in this cohort. Twenty-seven infants received ZDV, 17 received NVP, and 5 received no study drug. The imbalance in the number of ZDV and NVP infants is a result of the sampling design, which oversampled infant deaths, and the fact that there were more infant deaths in the ZDV arm of HIVNET 012 than in the NVP arm.

Copies of the source documents were transferred from the study site in Uganda to Baylor College of Medicine in Houston, Texas, for processing and review. Approval for copying and review of study documents was obtained from Human Subjects committees at Mulago Hospital/Makerere University and Johns Hopkins University.

Copies of CRFs and data files corresponding to the requested source documents were obtained from SCHARP. All study patient identification numbers were redacted from copies of source documents, CRFs, and data files before review by any committee member or consultant assisting the committee with the review. New, unique committee review identification numbers were assigned to each record to allow linkage between source and SCHARP records to maintain confidentiality. Three sources of information were reviewed for each record:

1. Source documents for each mother/infant pair
2. CRFs for each mother/infant pair
3. SCHARP data file for each mother/infant pair

Two consultants to the committee performed primary review and abstraction of information from these documents. Nancy R. Calles, B.S.N., R.N., A.C.R.N., is a pediatric HIV/AIDS nurse-specialist with more than 14 years of experience as a study coordinator for a wide variety of pediatric and perinatal HIV/AIDS clinical trials. Meg Ferris, M.P.H., has worked for 12 years in pediatric and perinatal HIV/AIDS clinical trials and health-professional education and training. She served for 5 years as a clinical trials specialist for the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Pediatric AIDS Clinical Trials Group. Ms. Calles conducted primary reviews of CRFs. Ms. Ferris was primary reviewer for the source documents and SCHARP data files.

For each set of records reviewed, the following information was abstracted from source documents and CRFs, and compared to information contained in the corresponding SCHARP data files:

- Date of birth of the infant
- Dates of all scheduled or unscheduled study visits by the infant
- Infant adverse events and dates of occurrence
- Infant clinical serious adverse events and dates of occurrence
- Study drug assignment (ZDV or NVP)
- Date and result of each PCR or EIA assay
- Date of death
- Date study site became aware of death
- Source of verification of death

For the purposes of this review, study definitions of clinical adverse events and serious adverse events were employed. Infant adverse events were recorded through 6 weeks of life; serious adverse events were recorded through 18 months of life.

Survival Status

The committee evaluated the records of the sample of 49 infants to assess the completeness of ascertainment and verification of survival status in the source documents, the timeliness by the site in ascertaining infant deaths, the degree to which survival status information in source documents was accurately transferred to the SCHARP database, and the timeliness in reporting survival status to the SCHARP database. Because of the dynamic nature of information gathering during the conduct of a trial, our comparisons of the source and analysis databases were based on the status of both in June 1999, when the study database was "frozen," or locked, in preparation of the first publication (Guay et al., 1999a) of the study results,

and in April 2001, when the analysis database was frozen for the second major publication (Jackson et al., 2003).

Site Ascertainment and Verification

To assess the completeness and accuracy with which infant deaths (in the sample of 49 infants) were captured by the HIVNET 012 staff, the committee examined the sources of information that led to the ascertainment/verification of infant deaths as well as the completeness of scheduled visits.

Of the 23 deaths noted in the source documents, 16 (70%) occurred in a clinic or hospital, and thus the death and date of death were directly observed and verified. The remaining 7 infants died at home, with the site learning about the deaths a median of 34 days later. In 4 of the 7 cases, the death was verified by the infant's mother (3 infants) or other relative (1 infant). In 1 case, the source of verification was from neighbors, resulting from a home visit. In 2 cases, the source documents did not indicate the basis for verifying the infant death, but indicated that the site learned of the deaths 34 and 48 days later.

The possibility of unreported infant deaths (false negatives) was assessed by determining each infant's last study visit prior to the June 1999 and April 2001 data freeze dates for the main study publications. Missed visits immediately prior to the freeze dates could, in theory, reflect unrecognized infant deaths. There were three infants that became lost to follow-up prior to their 18-month visit, and missed at least one study visit prior to either the *Lancet* I or *Lancet* II freeze dates. One infant's last visit was the 12-month visit, which coincided with the last scheduled visit before the June 1999 (in preparation for *Lancet* I) freeze date. Her/his (missed) 18-month visit would have occurred after the *Lancet* I but before the *Lancet* II freeze dates. Another infant's last visit was the 6-week visit. Her/his missed 9-month (18-month) visit would have occurred prior to the *Lancet* I (II) freeze date. The third infant was lost to follow-up immediately after birth. Her/his missed 9-month (18-month) visit occurred prior to the *Lancet* I (II) freeze date. Thus, the opportunity for an unrecognized death at the time of the *Lancet* I freeze date is limited to two infants, and the opportunity for an unrecognized death at the time of the *Lancet* II freeze date is limited to three infants.

Finding: In its review of HIVNET 012 records, the committee finds no evidence of and only a very limited opportunity for either unreported deaths or erroneous reports of deaths.

Timeliness and Accuracy in Reporting Survival Status to the SCHARP Database

All deaths, death dates, and last dates known alive for infants were accurately reported to the SCHARP database. The median time between the site awareness of the 23 infant deaths and the recording of the death in the (SCHARP) database was 19 days. For each of the 26 infants that did not die, the last date known to be alive by the site was transferred to SCHARP prior to the earlier *Lancet* data freeze following the study visit.

Finding: Source document information regarding survival status was accurately transferred to the SCHARP database in a timely manner.

HIV-1 Status

For the assessment of infant HIV-1 infection in the 49 sampled infants, we examined the degree to which scheduled PCR/EIA assessments were completed by the site, and whether the information about PCR/EIA positivity/negativity in the source documents/site CRFs was verified by inclusion of laboratory slips. We also compared this information to that in the SCHARP database to determine whether infant HIV-1 positivity was correctly captured in the analysis dataset. The primary analyses of HIV-1 positivity in HIVNET 012 were at 6–8 weeks, 14–16 weeks, and 18 months of age. The initial study publication (Guay et al., 1999a) considered only the first two of these time points, as well as the Day 1 sample, because not enough time had elapsed from the initiation of the trial to allow a thorough assessment at 18 months of age. The second study publication (Jackson et al., 2003) examined all four time points. Thus, we focused on the completeness of the HIV-1 PCR/EIA data at these four time points, and the fidelity and timeliness with which the data were transferred to SCHARP relative to the *Lancet* I and *Lancet* II data freeze dates.

It is important to note here that the rates of retention and follow-up of study participants were high, so there were few missing blood specimens. As noted in the HIVNET 012 remonitoring report, "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 AZT [ZDV] and 98% for those in the NVP group. The 18 month follow-up completion rates of the study were also high, with 93.8% for the AZT [ZDV] group and 96.1% for the NVP group" (DAIDS, NIAID, 2003a).

Completeness and Timeliness of Reporting HIV-1 Positivity to the SCHARP Database

Of the 49 infants whose charts were reviewed, 43 (88%) had all of their scheduled HIV-1 tests (PCR or EIA). Of the 131 possible PCR/EIA tests that could have been done (excluding visit dates occurring after an infant died or became HIV-1 positive), a total of 11 (8%) were not completed.

In 47 (96%) of the 49 infants, all available PCR/EIA information was transferred to the SCHARP database, and done so before the following (*Lancet* I or *Lancet* II) data freeze. In two infants, a week 14–16 PCR result was found in the source records that was not transferred to SCHARP. However, both had previously been found to be HIV-1 infected by PCR and this information had been transferred to SCHARP. Thus, in terms of information used in the analysis of HIV-1 positivity, all available relevant information for the 49 infants was transferred to SCHARP.

Finding: The committee finds that in the subset of 49 infants whose charts it reviewed, PCR and EIA information in the source documents used to assess HIV-1 infection status was accurately transferred to the SCHARP database, and done so in a timely manner so that all results available at the time of the data freeze for study publications were included in the analyses.

Capture of Adverse Events, Serious Adverse Events, and Hospitalizations

The committee's review of AEs, SAEs, and hospitalizations for the subset of 49 infants began with a review of source documents, followed by review of corresponding CRFs and database information. Information was collected from the source documents for 106 individual AEs. More than one AE often occurred concomitantly. Eleven of the 106 AEs noted in the source documents were not found in the corresponding CRFs. These AEs are shown in Table 4.3 as they appear in the source documents.

One other AE (infant number 22, "septic cord") was reported in the CRFs but was not found in the source documents. All of the AEs that were found in the CRFs were found in the SCHARP data files. Two infants (1 NVP, 1 ZDV) were reported to not have had any AEs when in fact the source documents report an AE. The proportions of infants with an unreported AE, among those with at least one AE, was not significantly different (p=0.23) between the NVP (5/13) and ZDV (4/25) arms.

Excluding deaths, 87 individual clinical SAEs were found in the source documents of the 49 infants that were included in this review. Seventeen of those 87 SAEs were not entered into the corresponding CRFs. On every occasion on which one or more SAEs occurred, at least one of those concurrent SAEs was reported in the case report form. For subjects who had a

TABLE 4.3 Infant Adverse Events Found Only in the Source Documents

Committee Review Identification Numbers	Treatment Arm	AEs Not in CRF According to Committee Review	Concurrent AEs and SAEs Reported in CRF
3	ZDV	Left axillary lymph-adenopathy at birth	None
15	NVP	Unknown—two types for fever at week 6	None
22	NVP	Hepatomegaly (2 cms) at week 6	None
34	NVP	Cord wrapped around neck at birth Fever, cough, nasal congestion at week 6	None
38	NVP	Regurgitates feeds and gynecomastia at week 6	None
42	ZDV	Common cold at week 6	None
50	ZDV	Urinary tract infection at week 4	None
68	ZDV	Mild flu at week 6	None
80	NVP	Generalized wasting at birth	Foul smelling cord

single SAE occurring in isolation, that event was always recorded in the case report form. In no case did the review reveal a failure to record in the CRF an SAE that occurred in isolation or all SAEs occurring concomitantly. All hospitalizations found in the review of the source documents were recorded in the CRFs. The 17 SAEs that were found in the source documents but not in the corresponding CRFs are shown in Table 4.4.

Only 2 of the 23 infant deaths identified in the source documents were recorded in the CRFs as serious adverse events. However, all deaths were recorded in the corresponding CRFs as a change of status. All of the SAEs found in the CRFs (including all deaths) were found in the SCHARP data files. All SAEs that were reported on the CRFs were also reflected in the source documents.

In assessing the implications of unreported AEs and SAEs in HIVNET 012, several points should be noted and considered. First, unreported events

TABLE 4.4 Infant Clinical Serious Adverse Events Found Only in the Source Documents

Committee Review Identification Numbers	Treatment Arm	Missed SAEs According to Committee Review	Concurrent SAEs Reported in CRFs
1	NVP	Fever, oral thrush, dehydration, electrolyte imbalance, hypotonic at month 6	Diarrhea and marasmus at month 6
4	ZDV	Malaria, respiratory distress at week 15	Dehydration and diarrhea at week 15
6a	NVP (drug not given; infant died at birth)	Prematurity at birth	Respiratory distress at birth
6b	NVP (drug not given; infant died at birth)	Prematurity at birth	Respiratory distress at birth
13	NVP	Malaria week 15 Pneumonia month 9	Pneumonia at week 15 Gastroenteritis, dehydrated, malaria at month 9
34	NVP	Cardiohypertrophy, septicemia, urinary tract infection at week 6	Febrile convulsions, bronchopneumonia week 6
36	NVP	Pneumonia at month 15	Diarrhea, failure to thrive, dehydration, poor nutrition, death at month 15
53	ZDV	Paralytic ileus at week 11	Malaria, septicemia, diarrhea, electrolyte imbalance
78	ZDV	Oral thrush at month 7	Diarrhea, anemia, death at month 7

had no implications for the care of the infants that participated in the study, but rather, could possibly affect the published study results. Second, because the sample of charts reviewed by the committee was weighted to over-represent infants that died, the numbers and rates of AEs and SAEs identified in the sample do not reflect those in the entire study.

It is also important to note that assessments of whether an AE or SAE may be due to a study drug are often difficult. Subjects have morbidities due to underlying disease or general environmental factors. As a result, it is common (and appropriate) to report all AEs and SAEs that occur in a trial, regardless of whether or not they are believed to be related to study drug. In a randomized comparative study, such as HIVNET 012, this provides a valid assessment of the relative safety of the treatments being compared. Nondifferential missed AE/SAE rates between the ZDV and NVP arms will not cause biased safety comparisons. However, because the overall rates of AEs and SAEs reflect both side effects of treatment and background comorbidities, one cannot in general extrapolate these overall rates to settings with different rates of background AEs and SAEs.

In assessing the effects of underreporting of some AEs on safety comparisons between the treatment arms, an important consideration is whether the rate of underreporting differs by treatment arms. If not, then underreporting will not affect the Type I error[4] when comparing AE rates between treatment arms; that is, it will not increase the probability of declaring a treatment difference in safety rates when one does not exist, and thus such comparisons remain unbiased. Underreporting can, however, decrease the power of a study to detect real differences in AE rates between the treatment groups. In our review of the reporting practices in HIVNET 012, we saw no reason that could cause differential underreporting of AEs and SAEs, and in the sample we reviewed, there were no significant differences between the non-reporting AE rates of the NVP and ZDV groups. On this basis, the committee concludes that any underreporting of non-serious AEs and concomitant SAEs did not affect validity (that is, Type 1 error) of the comparisons of AEs between the NVP and ZDV arms in HIVNET 012, though it could have decreased the power to detect a real difference.

Finding: The committee finds that infant deaths, hospitalizations, and visits where an infant experienced an SAE were accurately reported to the SCHARP database, although, in some instances, not all concomitant SAEs were reported. The committee also finds that some (non-serious) adverse events noted in the source documents were not reported on the case report forms. The underreporting of some (non-

[4]"The error of rejecting a true null hypothesis, i.e., declaring that a difference exists when it does not" (Last, 1995).

serious) AEs and some concomitant SAEs that accompanied a reported SAE may limit the generalizability of absolute adverse event rates and counts to other settings. However, the committee finds no reason to believe that the rates of unreported adverse events varied by treatment group, suggesting that the comparative safety analyses reported by the HIVNET 012 investigators are valid.

HYPERBILIRUBINEMIA

Concerns were raised in a DAIDS IND safety report issued on April 8, 2003, to FDA about a possible high frequency of neonatal hyperbilirubinemia[5] (jaundice) in HIVNET 012 that was "probably related to the study drugs" (DAIDS, NIAID, 2003c). The IOM committee determined that it was important to evaluate the appropriateness of toxicity values used in the IND safety report to assess hyperbilirubinemia and to determine whether there was an increased incidence of hyperbilirubinemia among all infants enrolled in HIVNET 012. Consultants to the committee, Thomas Newman, M.D., M.P.H., a pediatrician and professor of epidemiology and biostatistics, with expertise in hyperbilirubinemia and other pediatric conditions, and Valerie Flaherman, M.D., M.P.H., a pediatrician and epidemiologist, conducted this assessment.

Appropriateness of Toxicity Tables

The HIVNET 012 investigators used the *Harriet Lane Handbook* (Barone, 1996) as a source for the reference value for an upper limit of normal (ULN) bilirubin in U.S. infants, specifically 7 mg/dL (Guay [on behalf of HIVNET 012 protocol team], 2003). Study infant bilirubin levels were then assigned a grade of severity based on DAIDS tables grading serious adverse events as multiples of the ULN. Using these criteria, the authors reported one SAE of hyperbilirubinemia among all participants (Jackson et al., 2003). When the data hyperbilirubinemia data were re-evaluated in the April 8, 2003, IND safety report, DAIDS initially applied an incorrect upper limit of normal of 1.2 mg/dL for all infants ≥ 7 days of age as the criterion for hyperbilirubinemia. Based on that incorrect crite-

[5]Jaundice is a condition that causes a pronounced yellow tint to the skin and the white part of the eyes as a result of a higher-than-normal amount of bilirubin in the blood (hyperbilirubinemia). Bilirubin is a substance produced by the breakdown of red blood cells and hemoglobin, the protein in red blood cells that carries oxygen from the lungs to the rest of the body. In healthy breast-fed infants, jaundice usually appears to some degree about 2 to 4 days after birth. Jaundice usually disappears or lessens on its own within a week or two without causing problems. In breast-fed infants, mild jaundice sometimes continues or returns about 10 to 14 days after birth and may last for a month or slightly longer.

rion, the IND safety report stated that there were 63 Grade 4 bilirubin abnormalities in the ZDV group and 24 Grade 4 abnormalities in the NVP group. This report was subsequently retracted by DAIDS (DAIDS, NIAID, 2003b) when the error in defining the criterion for hyperbilirubinemia was recognized. When the bilirubin levels were evaluated relative to age-appropriate bilirubin normal values, DAIDS found no increased incidence of Grades 3 and 4 hyperbilirubinemia.

Finding: The committee concurs with the HIVNET 012 investigators' determination that 1.2 mg/dL, as suggested in the April 8, 2003, IND Safety Report, was not an appropriate upper limit of normal value for bilirubin in newborns, whose bilirubin levels change rapidly over the first few days after birth and are normally substantially higher than those in adults. The committee also concurs with DAIDS' decision to withdraw its initial IND safety report finding of excess hyperbilirubinemia because it was derived from the application of an incorrect criterion to study data.

Incidence of Hyperbilirubinemia in HIVNET 012

In the absence of data on bilirubin levels that would be of concern among Ugandan newborns, clinically significant hyperbilirubinemia was defined as a total serum bilirubin (TSB) level at which the American Academy of Pediatrics recommends phototherapy for infants in the U.S. However, the committee modified these thresholds to reflect a possible higher risk of bilirubin toxicity in the Ugandan infants. Thus, bilirubin levels of term, normal birth weight study infants were analyzed as if they were U.S. infants with one risk factor for bilirubin toxicity, such as prematurity or hemolysis. In addition, preterm or low birthweight study infants were analyzed as if they were U.S. infants with two or more risk factors.

The committee obtained all bilirubin levels for study infants in the first 2 weeks of life. Using the definition of significant hyperbilirubinemia described above, there was no significant difference in the incidence of significant hyperbilirubinemia between study infants who received NVP (4/319) and study infants who received ZDV (8/310) (P=0.26 by Fisher's exact test, risk difference –0.013, 95% CI for risk difference (–0.035, 0.008)). Furthermore, mean maximum bilirubin levels measured at days 1 and 7 were significantly lower in the NVP arm (5.32 ± 3.13 mg/dL) when compared to both the placebo arms (6.87 ± 4.14 mg/dL; P<0.05) and the ZDV arm (6.58 ± 3.52 mg/dL; P<0.001).[6]

[6]Although placebo data was not included in other analyses of HIVNET 012 data, such as the results published in the 1999 and 2003 *Lancet* articles, data gathered from the placebo arms discontinued in February 1998 was used as a comparator in the assessment of hyperbilirubinemia in HIVNET 012 infants.

Finding: The committee finds no evidence in HIVNET 012 of an increased risk of clinically significant hyperbilirubinemia in the infants who received NVP compared to the infants who received ZDV.

COMPARISONS TO OTHER PERINATAL HIV PREVENTION STUDIES USING NVP AND AZT

The committee and consultants compared the efficacy and safety results of HIVNET 012, which was the first study to look at this regimen of nevirapine, with findings from other trials with similar NVP and ZDV arms. The results from this review are described below (see Appendix B for a discussion of methods).

The review identified five randomized controlled trials that included single-dose NVP-only arms for prevention of mother-to-child transmission of HIV (Kiarie et al., 2003; McIntyre et al., 2004; Moodley et al., 2003; Taha et al., 2003; Taha et al., 2004). The proportions of infants infected in the antepartum period were similar between HIVNET 012 and these five studies. The review of the five randomized studies also showed that rates of Grades 3 and 4 adverse events in HIVNET 012 infants were similar to those of other studies.

Rates of transmission in the intrapartum and immediate postpartum periods were lower in HIVNET 012 (3.9%) compared to the other five studies that reported this variable (8.0%). However, after excluding the NVAZ study (Taha et al., 2003), in which mothers were not treated with NVP, this proportion was lower (6.0%) and thus more similar to the HIVNET 012 results. The NVAZ study was a Malawi study that randomized infants of women who presented in late stages of labor with unknown HIV status and did not receive NVP. The newborns were randomized to receive one dose of NVP or one dose of NVP plus a week of ZDV. The investigators subsequently analyzed the subset of infants born to mothers who were found to be infected with HIV. Since the mothers did not receive NVP, the infants were likely less protected against intrapartum transmission than those whose mothers did receive NVP. Hence, the intrapartum plus early postpartum transmission rates from this study are not directly comparable to those of HIVNET 012 or the other four studies.

The ZDV-only arm of the HIVNET 012 trial was less directly comparable to other randomized controlled trials for prevention of MTCT that included ZDV. Of the five trials reviewed, all included antepartum treatment of the pregnant women prior to labor for varying periods during pregnancy with ZDV, while HIVNET 012 ZDV-only arm included treatment of women during labor. Previous studies have suggested that the duration of antenatal treatment with ZDV is a strong predictor of efficacy of prevention of antepartum transmission (Shaffer et al., 1999). However,

when excluding transmission during the antepartum period (as measured by infant infection at 1 to 3 days of age), the rate of intrapartum and early postpartum transmission found in the two studies conducted in breast-feeding populations (10.5%) was similar to that found in HIVNET 012 (10.3%). These findings suggest that the findings in both arms of the HIVNET 012 trial are consistent with other studies that have used similar interventions, although over much shorter time periods.

Observational studies have also suggested similar rates of transmission and adverse events when the HIVNET 012 NVP regimen has been employed. For example, Stringer and colleagues (2003) have followed two observational cohorts of HIV-exposed infants who received single-dose nevirapine and whose mothers received intrapartum NVP in Zambia. They found transmission rates of 11.7% at 4 to 6 weeks (Stringer et al., 2004) and 11.2% at 6 to 8 weeks of age (Stringer et al., 2003). Other published observational studies which examined the effectiveness of NVP in practice in Kenya (Quaghebeur, 2004) and South Africa (Sherman et al., 2004) found higher rates of transmission (13% at 6 weeks, 18.1% at 14 weeks, respectively), but a study in Cameroon (Ayouba et al., 2003) found a lower rate of transmission (10.6% at 6 to 8 weeks). No maternal or infant complications or adverse effects were reported from Cameroon (Ayouba et al., 2003).

In conclusion, the findings from both the NVP and ZDV arms from HIVNET 012 appear to be consistent with findings on HIV transmission from other randomized controlled trials that tested similar treatment regimens. Additionally, the observed rates of serious adverse events were similar to those observed in randomized controlled trials that tested similar NVP regimens, randomized controlled trials that used NVP plus other antiretrovirals, a randomized postnatal prophylaxis trial, HIVNET-023 (Shetty et al., 2003), and observational studies.

REFERENCES

Ayouba A, Tene G, Cunin P, Foupouapouognigni Y, Menu E, Kfutwah A, Thonnon J, Scarlatti G, Monny-Lobe M, Eteki N, Kouanfack C, Tardy M, Leke R, Nkam M, Nlend AE, Barre-Sinoussi F, Martin PM, Nerrienet E. 2003. Low rate of mother-to-child transmission of HIV-1 after nevirapine intervention in a pilot public health program in Yaounde, Cameroon. *Journal of Acquired Immune Deficiency Syndromes* 34(3): 274-280.

Barone, M. 1996. *The Harriet Lane Handbook*, 14th ed. Table 6.1. St. Louis, MO: Mosby-Year Book, Inc.

Chamberlin J, Gustavson SA, Hensley M, Lander S. 2002. Site Visit Report, Kampala Uganda, February 18-28, 2002. Westat Corporation, MD.

Cunningham C, Charbonneau T, Song K, Patterson D, Sullivan T, Cummins T, Poiesz B. 1999. Comparison of human immunodeficiency virus 1 DNA polymerase chain reaction and qualitative and quantitative RNA polymerase chain reaction in human immunodeficiency virus 1-exposed infants. *Pediatric Infectious Diseases Journal* 18(1):30-35.

DAIDS, NIAID (Division of AIDS, National Institute of Allergy and Infectious Diseases). 2003a. *HIVNET 012 Monitoring Report.*

DAIDS, NIAID. May 19, 2003b. Letter to All Relevant Parties.

DAIDS, NIAID. 2003c. Investigational New Drug (IND) Safety Report Issued on April 8, 2003 Re: Hyperbilirubinemia.

EMMES Corporation. 2002. Clinical Site Data Audit Report Stage I, NIH/NIAID/DAIDS/ HIVNET 012 Re-Monitoring Study. The EMMES Corporation.

Guay L. 2004. Presentation to IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study. Transcript of September 30, 2004, Data-Gathering Meeting.

Guay L (on behalf of the HIVNET 012 protocol team). May 12, 2003. Letter to Fanning M.

Guay L, Mmiro F , Musoke P , Fanning M. 2002. *HIVNET 012: Phase IIB Trial to Evaluate the Efficacy of Oral Nevirapine and the Efficacy of Oral AZT in Infants Born to HIV-Infected Mothers in Uganda for Prevention of Vertical HIV Transmission. Description of Study Procedures.*

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999a. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181): 795-802.

HIVNET 012 Investigators. 2003. Makerere University–Johns Hopkins University Quality Management Plan.

HIVNET Group. Protocol Version 1.0, 2 June 1997. A Phase III Placebo-Controlled Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. 2003. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. *AIDS* 17(1):65-71.

LaMontagne J. September 7, 2004. Re: FW: HIVNET 012 follow-up. E-mail to Kington R.

Last JM. 1995. *A Dictionary of Epidemiology, 3rd edition.* New York: Oxford University Press.

McIntyre J, Martinson N, Investigators for the Trial 1413, Boltz V, Palmer S, Coffin J, Mellors J, Hopley M, Kimura T, Robinson P, Mayers D. 2004. Addition of short course combivir (CBV) to single dose viramune (sdNVP) for prevention of mother to child transmission (MTCT) of HIV-1 can significantly decrease the subsequent development of maternal NNRTI-resistance virus. eJournal of the International AIDS Society.

Moodley D, Moodley J, Coovadia H, Gray G, McIntyre J, Hofmyer J, Nikodem C, Hall D, Gigliotti M, Robinson P, Boshoff L, Sullivan JL. March 1, 2003. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *Journal of Infectious Diseases* 187(5):725-735.

Mwatha A. March 27, 2005a. *Re:* Please disregard previous messages [regarding vitamin A study coenrollment]. E-mail to Baciu A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Mwatha A. March 28, 2005b. Re: Co-enrollment in vit A study. E-mail to Baciu A on behalf of the IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Mwatha A. March 9, 2005c. Re: FW: An inquiry to SCHARP [regarding breakdown of serious adverse events for infants and mothers in HIVNET 012]. E-mail to Gable A on behalf of IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study.

Quaghebeur A, Mutunga L, Mwanyumba F, Mandaliya K, Verhofstede C, Temmerman M. 2004. Low efficacy of nevirapine (HIVNET 012) in preventing perinatal HIV-1 transmission in a real-life situation. *AIDS* 18:1854-1856.

SCHARP. 2005. Number of Reported SAEs by Vitamin A Study Arm and HIVNET 012 Study Arm (Table).

SCHARP. 2004. Data Collection, Management, and Quality Control of HIVNET 012.

SCHARP. 1997. HIVNET 012 Study-Specific Procedures: Phase III Efficacy Trial of Oral AZT vs Oral Nevirapine in Pregnant Ugandan Women and Their Neonates for the Prevention of Vertical Transmission of HIV-1 Infection.

Shaffer N, Chuachoowong R, Mock P, Bhadrakom C, Siriwasin W, Young N, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro T, Simonds R. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353(9155):773-780.

Sherman GG, Jones SA, Coovadia AH, Urban MF, Bolton KD. 2004. PMTCT from research to reality—results from a routine service. *South African Medical Journal* 94(4):289-292.

Shetty A, Coovadia H, Mirochnick M, Maldonado Y, Mofenson L, Eshleman S, Fleming T, Emel L, George K, Katzenstein D, Wells J, Maponga C, Mwatha A, Jones S, Abdool KS, Bassett M, HIVNET 023 Study Team. 2003. Safety and trough concentrations of NVP prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *Journal of Acquired Immune Deficiency Syndromes* 34(5):482-490.

Simonds RJ, Brown TM, Thea DM, Orloff SL, Steketee RW, Lee FK, Palumbo PE, Kalish ML. 1998. Sensitivity and specificity of a qualitative RNA detection assay to diagnose HIV infection in young infants. Perinatal AIDS Collaborative Transmission Study. *AIDS* 12(12):1545-1549.

Stringer JS, Sinkala M, Goldenberg RL, Kumwenda R, Acosta EP, Aldrovandi GM, Stout JP, Vermund SH. 2004. Universal nevirapine upon presentation in labor to prevent mother-to-child HIV transmission in high prevalence settings. *AIDS* 18(6):939-943.

Stringer JS, Sinkala M, Chapman V, Acosta EP, Aldrovandi GM, Mudenda V, Stout JP, Goldenberg RL, Kumwenda R, Vermund SH. 2003. Timing of the maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single-dose nevirapine. *AIDS* 17(11):1659-1665.

Taha TE, Kumwenda NI, Hoover DR, Fiscus SA, Kafulafula G, Nkhoma C, Nour S, Chen S, Liomba G, Miotti PG, Broadhead RL. 2004. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: A randomized controlled trial. *Journal of the American Medical Association* 292(2):202-209.

Taha TE, Kumwenda NI, Gibbons A, Broadhead RL, Fiscus S, Lema V, Liomba G, Nkhoma C, Miotti PG, Hoover DR. 2003. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 362(9391):1171-1177.

5

Review of Ethical Issues

Clinical research using human subjects—whether in the United States or in resource-limited settings—is replete with ethical complexity. Protecting the rights and welfare of those who volunteer to participate in research is a fundamental tenet of ethical research,[1] and the research community has made a great deal of progress in recent decades in incorporating this ethical responsibility more fully into study design and implementation.[2] Within

[1]The Nuremberg Code was the first international standard for conducting research with human subjects. The Nuremberg Tribunal, the court, through the Nuremberg Code, insisted that human rights in research be protected. The code gives to subjects the authority to protect themselves. The code contains a strict requirement that research subjects provide informed, voluntary, competent, and understanding consent (principle 1) and they retain the right to withdraw from research at any time (principle 9). Because the Nuremberg Code was linked to Nazi atrocities, murder, and torture, many physicians and medical organizations felt that the code was too absolute to be applied to modern research. In 1953, the World Medical Association (WMA), representing 80 countries including the United States, led a dialogue that resulted in the promulgation of the Declaration of Helsinki. Published in 1964, the declaration offered guidance for researchers in the conduct of research involving human subjects. Chief among its principles is the recognition of the validity of surrogate consent for subjects who lack the capacity or legal competence to render consent themselves, such as children (Murphy, 2004).

[2]The principles underlying the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* have served as a leading source of guidance on the ethical standards that should govern research with human participants in the United States for over 20 years. The Belmont report emphasized that research must respect the autonomy of

the federal government, these efforts have included the formation in 1974 of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and the activities in the early 1980s of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

The research community itself has largely supported two essential protections for human participants: independent review of research to assess its risks and potential benefits, and an opportunity for people to voluntarily and knowledgeably decide whether to participate in a particular study.

Independent review is essential because it improves the likelihood that decisions are free from inappropriate influences that could distort the central task of evaluating risks and potential benefits. No one should participate in research unless independent review concludes that the risks are reasonable in relation to the potential benefits for both participants and society. This is a precondition to offering people the opportunity to volunteer, as informed consent alone cannot justify enrollment. In the United States, the institutional review board, or IRB, has been the principal structure responsible for conducting such reviews.

In U.S.-supported international research—that is, research by U.S. investigators working in another country—U.S. investigators subject to regulation either by the National Institutes of Health (NIH) or the U.S. Food and Drug Administration (FDA) may adopt the ethical standards and procedures of the host country, provided that such protections are substantially equivalent to those in the United States.[3] In its own study of this

participants, must be fair in both conception and implementation, and must maximize potential benefits while minimizing possible harms. The report's recommendations provided a coherent rationale for the federal policies and rules that underlie the current U.S. system of decentralized, independent research review, coupled with some degree of federal oversight (Office of Human Subjects Research and National Institutes of Health, 1979).

[3]The procedures and standards for reviewing the study can be changed where the United States has recognized the host country as having a system of equivalent protections. 45 CFR Part 46.101(h) states: "When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Association Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the Department or Agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in Department or Agency procedures" (DHHS, 2004).

topic, the National Bioethics Advisory Commission recommended that independent bodies in both the United States and the host country ensure that studies are consistent with ethical requirements in both countries. Where necessary, the commission recommended, resources should be given to the host country to perform this review. The Department of Health and Human Services (DHHS) is now soliciting comments on ways to improve international research by better identifying equivalent principles and practices for protecting human subjects in research conducted abroad (DHHS, 2005).

Before HIVNET 012 began, two IRBs provided oversight of the study's design and protocol. The U.S.-based IRB, at Johns Hopkins University, was the Joint Committee on Clinical Investigation (JCCI). The Ugandan-based IRB, of the Uganda National Council for Science and Technology, was the AIDS Research Committee (ARC). Both IRBs approved the protocols and consent forms for the study, and continued their oversight during its implementation.

The decision to participate in research must be voluntary as well as informed. Even when risks are reasonable and investigators obtain informed consent, soliciting certain people as participants may nonetheless be unacceptable. Studies should not enroll people who are not fully capable of resisting the request to become participants—such as prisoners and other institutionalized or otherwise vulnerable persons—merely because they are accessible.

The historical emphasis on protecting people from exploitation, however, has failed to anticipate a time when, at least for some areas of medical research, people would demand the right to join certain studies because they might provide access to an innovative therapy, or provide the only chance for medical care for life-threatening diseases. In international research, some commentators have suggested that the general absence of adequate health care in resource-limited-settings can make the offer of enrollment in a research trial nearly impossible to resist. Studies in resource-limited countries, therefore, demand a high level of justification. Studies that exploit a population's vulnerability—such as those that recruit people in poorer countries solely to benefit people in wealthier countries—should not be done. If, on the other hand, studies in resource-limited countries are designed to address important health problems in those same countries and could not be performed elsewhere, then the research is justified, and the consent process is used to help ensure that subjects are genuinely informed before volunteering (National Bioethics Advisory Commission, 2001a,b).

This chapter focuses on four ethical issues related to HIVNET 012:

- Compliance with requirements for independent IRB oversight.
- The use of placebo control arms.
- The circumstances that made the placebo control no longer appropriate.
- The informed-consent process.

This chapter begins with a discussion of the decision to proceed with the HIVNET 012 study under an investigational new drug application (IND).

THE INVESTIGATIONAL NEW DRUG APPLICATION

When the FDA approves drugs for sale in the United States, that approval is based on studies that examine the drug with respect to a particular use. Once approved, the drug is labeled for that indication, and the manufacturer may advertise it for that indication only. But it is perfectly legal and commonplace for physicians to prescribe—and investigators to study—approved drugs for indications that go beyond their labels. Indeed, in the United States, estimates show that almost 80% of the medications prescribed for some conditions are off-label, and that off-label use is particularly frequent in pediatric patients (GAO, 1996; Radley et al., 2004; 't Jong et al., 2000). Physicians are expected to exercise good judgment when prescribing approved drugs for off-label use, basing their decisions on both anecdotal reports and the results of studies that specifically examine such off-label uses. In general, only when a manufacturer wishes to file a Supplemental New Drug Application (sNDA) to obtain the right to advertise an already approved drug for another indication will it have any incentive or need to approach FDA for permission to proceed with a study, or to abide by FDA requirements regarding conduct of the study.

Although not required by FDA, HIVNET 012 was conducted under an IND held by the Division of AIDS (DAIDS). There is no requirement for non-U.S. studies or non-U.S. sites of multinational studies to operate under an IND; this is determined by the sponsor. However, where the sponsor decides to conduct a study under an IND, FDA's IND regulations must be followed for the study and at all such sites.[4]

[4]The need for sponsors of non-U.S. studies/sites to operate under an IND has changed over the years, most notably since the passage of the FDA Modernization Act (FDAMA) in 1997. Prior to FDAMA, one of the mechanisms for the export of a U.S. manufactured investigational product (for use in a clinical trial outside of the U.S.) was to agree to conduct the study under an IND at its non-U.S. sites. FDAMA created options for exporting a U.S.-manufactured investigational product outside of the IND process (e-mail communication, D. Lepay, March 31, 2005).

INDs permit sponsors to begin testing investigational drugs in preparation for a New Drug Application (NDA) or to formalize the testing of new indications for an already approved drug in preparation for submission of an sNDA. FDA did not require an IND for HIVNET 012 because both zidovudine (ZDV) and nevirapine (NVP) were already approved for marketing in the United States and the manufacturer was not intending to submit an sNDA based on the trial's data to change the labeling or advertising for either ZDV or NVP. Furthermore, HIVNET 012 would take place in a foreign country, outside FDA's jurisdiction.[5] DAIDS nevertheless decided to conduct the study under an IND because, in 1997, the agency pursued the vast majority of trials under such an application. DAIDS' reasons to submit the study to an existing IND (application made to FDA in 1996) included:

- In 1997, the vast majority of DAIDS trials occurred under IND. The safety mechanism for reporting "off-label use" adverse events in a non-IND trial would have been MEDWATCH, a voluntary as opposed to a mandatory system.
- The initial trial included a placebo arm and was using two different drug regimens, both of which were off-label under both FDA and Ugandan regulations. When DAIDS is the sponsor of a study that used a product off-label in a protocol, that is, it has not been specifically reviewed and approved by any regulatory entity for this particular indication, DAIDS generally submits it under an IND.
- The trial was conducted in two "vulnerable" populations: pregnant women and newborns.
- The IND extends reporting requirements and oversight beyond the sponsor, IRB, and the Data Safey Monitoring Board (DSMB). It adds

[5]While the National Bioethics Advisory Commission recommended that FDA not accept data from foreign-based studies that fail to meet FDA standards, the agency has not enacted such regulations. Thus trials conducted abroad need not follow FDA regulations, even if the data from those trials might later be used in a submission to FDA for approval of a new drug or indication. Instead, FDA sets requirements for minimal ethical standards for such trials. FDA regulations permit the acceptance of foreign clinical studies in support of an application for marketing approval of a human drug, biological product, or device if certain conditions are met. Foreign studies performed under an IND or investigational device exemption (IDE) must meet the same requirements of 21 CFR Part 312 or 21 CFR Part 812, respectively, that apply to U.S. studies conducted under an IND or IDE (FDA and DHHS, 1996; Lin and Meschino, 1993).

Under 21 CFR 312.120(c)(1), FDA will accept a foreign clinical study not conducted under an IND only if the study conforms to the ethical principles contained in the Declaration of Helsinki (Declaration), as set out in 21 CFR 312.120(c)(4), incorporating the 1989 version of the Declaration, or with the laws and regulations of the country in which the research was conducted, whichever provides greater protection of the human subjects.

additional measures of oversight, including IND safety reporting, annual IND reports, and oversight by the FDA (e-mail communication, C. Hudgings, February 7, 2005).

Conducting research under an IND places specific obligations on both the sponsor and the investigators. Many of these obligations merely echo good research practices pursued in non-IND trials, but others require more stringent record keeping, drug management, and quality-control checks than would be employed in a typical study.

According to the IND regulations in effect in 1997, the sponsor had to select qualified investigators, provide them with the information they needed to conduct their work, and ensure proper monitoring. The sponsor also had to ensure that the investigation followed the general plan and protocols in the IND, and that FDA and all participating investigators were promptly informed of significant new adverse effects or risks (FDA and DHHS, 1997).

The IND subjected the investigators to the following requirements:

- Conduct the investigation according to the signed investigator statement, the investigational plan, and applicable regulations.
- Protect the rights, safety, and welfare of research subjects.
- Control the drugs under investigation.
- Keep and retain specific records.
- Provide progress, safety, and final reports to the sponsor. (Investigators had to promptly report adverse effects reasonably regarded as caused by, or probably caused by the drug, and to immediately report an alarming adverse effect.)
- Assure that an IRB would be responsible for initial and continuing reviews and approvals; report to the IRB all changes in research activities and unanticipated problems, and make no changes in research without IRB approval (FDA and DHHS, 1997).

FDA Form 1572, which all investigators must sign, lists these requirements.

Although HIVNET 012 was conducted under an IND, documentation of its compliance with FDA regulations did not proceed entirely like that of a typical IND trial, as its purpose was neither to obtain a first approval of an investigational drug nor to obtain approval for a labeling change concerning a new indication of an approved drug. When Boehringer Ingelheim (BI) later decided to use the trial data to support a supplemental new drug application in order to obtain that labeling change and its associated advertising rights, that decision triggered a higher level of scrutiny of specific aspects of the trial, particularly record keeping. As noted elsewhere in this report, BI conducted a preliminary site visit, followed by a pre-FDA audit site visit by Westat Corporation, a DAIDS contractor.

Applying this higher level of scrutiny concerning documentation of applicable procedures, the Westat site visit resulted in a report that includes assertions of several procedural lapses. The Westat team attributed some of the lapses to a general lack of awareness of and training in so-called good clinical practice (GCP) guidelines.[6] DAIDS' remonitoring report also raised concerns about procedural lapses, such as undated and unsigned observations on case report files, missing documentation, multiple dosing errors, lack of source documentation to confirm serious adverse events, and improper correction of errors. [DHHS' Office for Human Research Protections (OHRP) investigated claims of misdosing and faulty error reporting but failed to confirm these problems;[7] see below for a discussion of the procedural lapses it did identify with respect to the Ugandan IRB.]

The phrase "good clinical practice" can be used in two different ways. First, it may refer to the substantive and procedural practices with a long history and that are generally understood as the essential attributes of good research and appropriate medical care in the context of clinical trials. The phrase can also be used more narrowly to refer to the Good Clinical Practice (GCP) Guideline, a published set of guidelines that constitute one standard for conducting scientifically sound and ethical research (ICH, 1996). GCP Guideline have been developed over the last 20 years by the International Conference on Harmonisation (ICH) in order to facilitate the mutual acceptance of clinical data by the regulatory authorities in Europe, the United States, and Japan, and thus speed the process for approval of new pharmaceuticals and increase patient access to new treatments (DHHS and FDA, 1997).

The ICH GCP Guideline describes the responsibilities of investigators, monitors, sponsors, and IRBs, and also covers aspects of monitoring, reporting, and archiving of clinical trials and their data. When FDA moved to adopt much of the harmonized guideline, it stated that:

> This guideline represents the agency's current thinking on good clinical practices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both (DHHS and FDA, 1997).

---

[6]It is worth noting that—despite the name—investigators can engage in excellent clinical practice without following the precise contours of the Good Clinical Practice Guidelines (ICH, 1996).

[7]See March 15, 2002, and July 16, 2002, letters from Patrick McNeilly, Compliance Oversight Coordinator, Division of Compliance Oversight, OHRP to Zerababel M. Nyiira, Secretary, Ugandan National Council of Science and Technology (McNeilly, 2002a; McNeilly, 2002b).

For a study (whether in or outside the United States) that is designated as being conducted under an IND, FDA IND regulations (including those in 21 CFR [Code of Federal Regulations] Parts 312, 50, 54, and 56) must be met. The ICH GCP Guideline has no bearing on IND requirements (which must be met for any IND study), and that has been the case since before 1997, the year enrollment in HIVNET 012 began (e-mail communication, D. Lepay, March 31, 2005).

Thus, the FDA does not require adherence to the ICH GCP Guideline, although FDA has incorporated some elements of the Guideline into its own regulations governing research trials.[8] FDA regulations are more detailed in certain requirements, particularly those for Ethics Committees and their operation, although the ICH GCP Guideline provides more detail about sponsor monitoring and auditing of studies, which FDA views as good guidance if not already an FDA regulatory requirement. Since FDA regulations do not currently impose ICH GCP Guidelines as a regulatory requirement, there is no obligation for investigators (either in or outside the United States) to be educated or trained in the ICH GCP Guideline and procedures. The FDA regulations simply require that investigators (and site staff) be qualified by education, training, and experience to perform their designated or assigned tasks.

Overall, then, in research subject to an IND or related to a new drug application, the Guidelines inform but do not define the FDA's own requirements pertaining to informed consent; IRB review; and the responsibilities of sponsors, contract research organizations, and investigators. FDA also requires adherence to other requirements, including IRB-imposed requirements not already covered in FDA regulations. In other words, investigators are responsible for fulfilling every requirement imposed by an IRB.

FDA regulations do allow for waivers of specific IND requirements if these are requested by the sponsor and agreed to by FDA. This has allowed some sponsors to conduct non-U.S. studies under an IND when they know that specific IND requirements can not be met (e.g., some of the specific requirements of Ethics Committees, for example). Sponsors have, for example, requested a waiver of one or more IND requirements by indicating that they will follow the corresponding provisions in ICH GCP Guideline (which tend to be less detailed for the operation of Ethics Committees), and FDA has generally granted such waivers. But again, the waiver must be formally requested by the sponsor under the IND—and formally granted by FDA. In HIVNET 012, no such waiver was requested, and thus the trial proceeded under the more stringent FDA regulations rather than under the more relaxed ICH GCP Guideline.

[8]See FDA regulations relating to good clinical practice and clinical trials at http://www.fda.gov/oc/gcp/regulations.html (FDA, March 9, 2005).

Thus, the HIVNET 012 investigators were not obligated to be trained in or to follow the ICH GCP Guideline, but rather were obligated to comply with the more stringent requirements laid out by FDA for IND studies and by the respective IRBs as a condition for approving the protocol. Their obligations with respect to administrative and procedural tasks—such as dating and signing specific forms or providing certain kinds of documentation—were defined by FDA regulation or by their IRBs, and not by the GCP Guideline.

Thus, it would be an error to conclude that the HIVNET 012 study was either flawed or unethical simply because the investigators did not precisely follow the GCP Guideline that was different from the requirements imposed upon them by the FDA and their IRBs. A more accurate interpretation of auditors' criticisms is that they considered the staff's performance uneven in some aspects (such as the precise format for recording changes on a document).[9]

Many of the procedural areas subject to assertions of uneven staff performance involved technical requirements that did not affect the rights or welfare of the research subjects. Instead, many of these supposed requirements reflected the precise documentation usually associated with formal submissions to the FDA for approval of a new drug or indication. Thus, it would not be fair to conclude that the trial was characterized by a lack of good clinical practice, or that the staff did not implement good medical care across all aspects of the program.

Findings:

The committee finds that HIVNET 012 was conducted under an IND as a matter of DAIDS policy, and that the study was not originally intended to provide data for later submission to FDA to support a

[9]With regard to non-IND studies, there may soon be a more significant role for ICH GCP Guidelines. FDA regulations provide a mechanism to submit non-U.S., non-IND studies to the agency in support of marketing applications. These regulations are currently undergoing revision. Until the revision finalizes, these regulations require that certain broad requirements be met for non-U.S., non-IND studies: including certification of conformance with the Declaration of Helsinki (Declaration) or with local laws (when these provide greater protection for subjects than Declaration), conduct of studies by qualified investigators, applicability of the study to the U.S. population, and the ability for FDA to inspect the study. The revision to FDA regulations (currently published as a proposed rule for public comment) will link FDA's acceptance of non-U.S., non-IND studies to internationally accepted GCP standards (e.g., ICH) and will require submission of certain documentation to establish that GCP standards were followed. But in 1997 and still today, unless and until the FDA revised rule finalizes, FDA regulations do not specifically cite or suggest ICH GCP as a requirement for acceptability of non-U.S., non-IND studies. Rather, ICH GCP is guidance; if followed, this should ensure that the current regulatory expectations for non-U.S., non-IND studies will be met.

labeling change for NVP, an already approved drug. The decision by Boehringer Ingelheim to use the findings to support such a submission led to evaluating the documentation of regulatory compliance by the trial in light of a standard that did not apply when the trial began.

The committee finds that the HIVNET 012 investigators met their ethical obligation to design and conduct the study in accordance with international standards for the ethical conduct of research and ethical management of patient care. The HIVNET 012 investigators also complied with their legal obligation to design and conduct the study in accordance with FDA regulations and under the oversight of IRBs in both Uganda and the United States. The HIVNET 012 trial was not required to comply with specific procedural rules outlined in the voluntary Good Clinical Practice Guidelines published by the International Conference on Harmonisation, and an ethical evaluation of HIVNET 012 should not rest directly or indirectly on the degree to which it conformed to GCP Guidelines, but rather on the degree to which it conformed to the FDA, IRB, and general medical ethics standards to which it was subject. The validity of the study's findings is sustained by the fact that the trial was conducted in accordance with FDA requirements and met international standards for the ethical management of clinical trials.

COMPLIANCE WITH REQUIREMENTS FOR INSTITUTIONAL REVIEW BOARDS

As noted, HIVNET 012 was overseen by JCCI, the IRB at Johns Hopkins University; and by ARC, the IRB of the Uganda National Council for Science and Technology (UNCST). UNCST operates under a federal-wide assurance (FWA)[10] and has agreed to follow guidelines from the Council for International Organizations of Medical Sciences (CIOMS) for review of protocols by its IRB. It is worth noting that U.S. rules and regulations are not the only ones that investigators may choose to follow in order to satisfy ethical requirements. The CIOMS rules represent an alternative to the U.S. regulations found in 45 CFR (for DHHS except FDA) and 21 CFR (for FDA). A failure to follow DHHS rules does not necessarily mean that researchers failed to conduct a study ethically, but only that they did not follow the particular method chosen by DHHS.

[10]The DHHS Office of Human Research Protections requires federal-wide assurances for institutions conducting human subjects research with funding from DHHS agencies, such as NIH (FDA and DHHS, 2001).

Before October 5, 2001, and at the time of HIVNET 012, the DHHS-supported research conducted by UNCST fell under single project assurances and cooperative project assurances, which required Makerere University to follow DHHS regulations for protecting human subjects. Pursuant to these regulations, the Ugandan IRB (ARC) approved HIVNET 012 protocol version 1.0 in July 1997, reviewed it again in March 1998 when the placebo arms were dropped (Amendment I), then again when the efficacy data was reported in July 1999 (Guay et al., 1999), and finally when Amendment II was submitted in April 2000 (PPD, 2003).

In 2002, in response to allegations of noncompliance with DHHS regulations, the DHHS Office of Human Research Protections (OHRP) undertook a review of ARC. In correspondence with UNCST, OHRP identified what it perceived as a change in the protocol [a change in the interpretation of serious adverse events (SAEs)] that ARC and JCCI had approved. (As discussed in Chapter 4, the committee believes that the investigators' interpretation of the serious adverse events definition was appropriate.) DHHS regulations require that IRBs review and approve such changes, except when they are necessary to eliminate immediate hazards to participants (National Bioethics Advisory Commission, 2001a).[11] Specifically, OHRP found what it identified as discrepancies between the definition of adverse events in the protocol and the definition that UNCST said was actually used at the site. The discrepancies, according to OHRP, consisted of using modified severity scales for rash and hemoglobin in order to address high background rates of rash and anemia, and use of hospitalization as the primary criterion for identifying a condition as a serious adverse event. (See Chapter 4 for a full discussion of the definition and interpretation of serious adverse events used by HIVNET 012 investigators as well as the findings of the committee with respect to the allegations described above.) OHRP reported that it did not find documentation that the definitions and interpretations used in the field were ever approved by the IRBs and that the change in reporting adverse events might have represented a failure to minimize risk to participants. Nonetheless, OHRP never found that those risks were, in fact, higher than necessary.

[11]Concerns that the study did not implement the standard definition of adverse events, and did not follow the updated 1998 U.S. Code of Federal Regulations definition for SAE, also surfaced during the Westat site visit and the DAIDS remonitoring process. It should be noted, however, that the updated 1998 definitions (which differed slightly from the earlier regulations that governed HIVNET 012) did not apply to HIVNET 012, which was already underway subject to the regulations in place at the time HIVNET 012 was approved. When new versions of regulations are enacted, they apply prospectively to new trials, and only in exceptional circumstances do they apply retroactively to ongoing trials (FDA and DHHS, 1998).

As noted in Chapter 4, the committee reviewed both version 1.0 of the protocol and *Study Specific Procedures*, and found that all of the definitions and tables were consistent with the applicable federal regulations and were written prior to beginning enrollment (HIVNET Group, 1997; SCHARP, 1997). The language used to define serious adverse events was not changed after the protocol had been approved by the IRBs. However, the HIVNET 012 investigators interpreted the definition, particularly its criterion concerning clinical judgment that a condition was serious, so as to use hospitalization as the primary determinant of seriousness for capture of serious adverse events. Although this well may have been a practical and appropriate interpretation of the definition of serious adverse events, it was the cause for OHRP's perception of a difference between the protocol definition of SAE and the field interpretation of SAE.

In addition, based on information it received from ARC and UNCST, OHRP identified deficiencies in the documentation maintained and review processes employed by ARC in its oversight of HIVNET 012 and other studies. For example, OHRP concluded that ARC had failed to maintain a system for notifying investigators of the need to submit progress reports, as is usually required on at least an annual basis. OHRP also cited ARC's statement that it had not received those annual reports for HIVNET 012. Based on these statements, in a July 2002 letter to UNCST, OHRP found that ARC had failed to conduct "continuing review" of the HIVNET 012 study, as required by DHHS regulations, and that ARC lacked the capacity to track studies in a fashion that would ensure such continuing review in the future. That failure was not attributed to the HIVNET 012 investigators, and OHRP requested clarifications and changes from UNCST to ensure that appropriate host-country oversight would be in effect in the future. Because of these and other deficiencies regarding ARC's general capacity for keeping records of its meetings, recording minutes, sending notices to investigators, and managing other procedural tasks, OHRP asked ARC to do an internal audit of all studies under its authority, and to submit a plan by August 2002 for corrective action on record keeping and continuing review.[12]

On October 28, 2002, OHRP sent a letter to UNCST acknowledging its satisfaction with ARC's actions, as outlined in its August reports (McNeilly, 2002c). On March 24, 2003, following up on ARC's improve-

[12]As noted above, OHRP's initial contact with UNCST stated that OHRP had received allegations of misdosing and errors in data reporting but OHRP's subsequent communication, in which OHRP listed the deficiencies it had confirmed, did not mention these potentially serious problems, and listed only the definitional and procedural issues discussed in the text (McNeilly, 2002c; McNeilly, 2003a).

ments in staffing, record keeping, and annual review of ongoing protocols, OHRP restated its satisfaction and noted that no further action with respect to HIVNET 012 or any other prior study would be needed (McNeilly, 2003a).

Although OHRP did find a number of problems with the management and oversight of HIVNET 012, at no point did OHRP find that the study did in fact expose subjects to unacceptable risk or violate their rights. In response to the deficiencies, OHRP did not withdraw ARC's FWA, or discipline JCCI, but rather, insisted on improvements in both process and documentation as a condition for ARC's continued eligibility for a federal-wide assurance.

The committee learned that OHRP found cause to fault UNCST and ARC, the Ugandan oversight bodies, for their implementation of the plan for monitoring the study. However, the committee noted that OHRP was satisfied with the remedial measures taken by UNCST, and that there is no evidence of harm to study subjects stemming from failures in local oversight.

Findings:

The committee finds no evidence that the definitions used for adverse events and serious adverse events in HIVNET 012 placed human subjects at increased risk.

The committee finds no evidence that the failures identified by OHRP with respect to ARC's continuing review procedures resulted in a loss of information that would, had it been obtained at the time, have altered the risk-benefit balance in a way that would have triggered either a change in the protocol or a change in the information given to human subjects.

THE USE OF A PLACEBO ARM

The use of placebo arms in controlled trials presents a special challenge (Djulbegovic et al., 2000; Edwards et al., 1998; Ellenberg and Temple, 2000; Lilford and Djulbegovic, 2001; Temple and Ellenberg, 2000). For example, subjects often find it difficult to grasp the concept of a randomized trial with a placebo arm. But placebo arms, when appropriate, are generally recognized as providing the gold standard for controlled studies.

Some argue that the principal advantage of the placebo-controlled trial is that a positive result has only one interpretation: that the intervention is superior to no treatment. These analysts argue that, without a placebo control, it is unclear whether the trial has "assay sensitivity." If a non-inferiority design is used—that is, a new treatment is compared to an active

control, and the two treatments achieve similar results—then there may be ambiguity as to whether both are effective or neither is effective.

Sometimes a trial with an active control relies on a non-inferiority design. Non-inferiority trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin. For example, in a study of regimens intended to prevent maternal-to-child transmission of HIV, a non-inferiority trial would seek to show that the difference in transmission rates between the new treatment and the standard treatment is no greater than a pre-specified "non-inferiority margin." The non-inferiority design introduces some challenging issues, including the choice of the non-inferiority margin. Such a design requires a larger sample size if the non-inferiority margin is smaller than the benefit of the active control, as it should be.

When research subjects have serious conditions and a standard treatment exists, placebo-controlled trials are usually done in the context of substantial other treatment, so that the typical trial is standard treatment plus placebo versus standard treatment plus experimental agent.[13] At the time of the HIVNET012 trial, while there were effective treatments to prevent maternal-to-child transmission of HIV available in wealthier countries, there was no such treatment in Uganda.

Pure placebo arms are ethically unjustified if a treatment is available that can prevent serious harm, such as death or irreversible injury. In the latter situation, studies compare standard therapies with new ones. In the United States, for example, the American Medical Association states that "protocols that involve conditions causing death or irreversible damage cannot ethically employ a placebo control if alternative treatment would prevent or slow the illness progression. In general, the more severe the consequences and symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists" (American Medical Association, 1999). The National Bioethics Advisory Commission agreed that it is ethically unacceptable to perform placebo-controlled clinical trials when effective, established treatments exist.

Even under these circumstances, however, exceptions may be made if an established effective treatment does not work in certain populations, or has such serious side effects that some patients refuse treatment. Thus when no established intervention exists to treat or prevent a condition, comparing an experimental intervention to a placebo control is generally considered ethically acceptable.

[13]The participants in HIVNET 012 represented a somewhat different case, because the fetus of an HIV-positive mother does not have a serious condition unless after birth the infant becomes HIV-positive.

A number of researchers also consider placebo controls to be ethically acceptable when a standard effective therapy exists but is not locally available, whether due to cost, logistical difficulties, or cultural barriers to use. That may occur, for example, in a resource-limited country where health care resources are scanty and study participants do not have access to established, effective treatments. Access may be limited solely by financial constraints or by logistical problems as well, such as a lack of climate-controlled drug storage facilities or equipment for screening patients. Another kind of logistical barrier is created when one health imperative—breastfeeding in a country without a safe water supply for infant formula—renders an otherwise effective intervention futile, such as avoidance of breastfeeding in conjunction with other therapies. In such situations, researchers can regard the population as not having, for all practical purposes, an effective standard treatment, thereby making a placebo control acceptable. In these cases, some would argue, measuring the absolute efficacy of a new and potentially more affordable and available intervention is more relevant than comparing it to an established treatment that is unlikely to be available in the host country (Levine, 1999).

Other researchers, when considering placebo controls in settings where effective therapy exists but is not locally available, will acknowledge the greater usefulness of the resulting data if a study includes a placebo control. However, they will nonetheless argue that when poverty makes people eligible to enroll in a trial that would be unacceptable in wealthier settings, it is a form of exploitation. This debate remains unresolved among ethicists, policy makers, and the research community (Cohen, 1997).

Overall, then, placebo or other controls using less than an effective, established treatment are disfavored in the case of serious illness, but may nonetheless be justified under special circumstances, such as where effective, established treatments are difficult to provide or maintain. The burden of justification lies with the investigators, however, and such study designs should be the exception, not the rule (National Bioethics Advisory Commission, 2001a).

HIVNET 012 initially adopted placebo controls as part of a four-arm study. The protocol chair described the need for the placebo arms in a June 6, 1997, request to JCCI, the Johns Hopkins University IRB. In response to a JCCI request for more information on the need for the placebo arms, the protocol chair indicated that the standard of care in Uganda was to provide no antiretroviral therapy to prevent mother-to-child transmission or to treat mother or infant. This was due in part to the expense of delivering such antiretroviral interventions, estimated at $100 for interventions initiated at 38 weeks of pregnancy, $200 for interventions initiated at 36 weeks of pregnancy, and $1,000 for the oral and intravenous three-part ZDV regime used in the AIDS Clinical Trials Group (ACTG) 076 study. By

contrast, the protocol chair stated, per capita annual health care expenditures in Uganda are about $3.50 (Jackson, 1997).

Investigators presented the placebo arms as necessary because they would allow the study to compare the effectiveness of both ZDV and NVP not only to each other, but also to the prevailing situation in Uganda, where no antiretroviral therapy was available. Thus the placebo arms would efficiently allow the trial to determine whether either ZDV or NVP reduced transmission rates in this setting, while also assessing which of these two antiretroviral drugs was more effective.

As an alternative to placebo, investigators could have compared their findings to historical rates of mother-to-child transmission in Uganda. But the HIVNET 012 protocol chair wrote that such an approach would have been unreliable, owing to the great variability of those rates. Such variability reflected differences in the factors influencing mother-to-child transmission, such as the stage of mothers' HIV-1 disease and CD4+ lymphocyte counts, as well as variations in follow-up. The protocol chair also noted that the NIH DSMB would review the study on an ongoing basis and evaluate the results, taking rules for halting the study developed by the protocol team into account.[14] The chair indicated that the DSMB would include a Ugandan representative.

In light of these justifications, JCCI approved the study with placebo. In its own review of the study protocol, ARC asked investigators to revise the consent form to share this justification with study participants. The revised consent form included the following statement: "Uganda, like many other developing countries, does not currently have the resources or capabilities to offer this complicated treatment [referring to long-term therapies used in the United States] to pregnant women. There is a need to find simpler treatments that work which could be used in Uganda. Therefore the purpose of this trial is to compare a placebo with NVP or AZT [ZDV]." JCCI approved this revision on September 29, 1997 (Hendrix, 1997).

As noted, in February 1998, shortly after enrollment into the original four-arm trial began, the results of the Thai trial on prevention of mother-to-child transmission were announced. In light of the demonstrated effectiveness of an intervention that could be feasible in a setting such as Uganda, HIVNET 012 investigators concluded that placebo controls were no longer justifiable. They discontinued the placebo arms, modified the protocol, and assigned new participants to the two active arms only (Jackson et al., 2003). The process of submitting justification for a placebo arm to indepen-

[14]Data Safety Monitoring Boards (DSMBs) evaluate research data on an ongoing basis to ensure participant safety and/or study integrity.

dent review, and then reevaluating the acceptability of a placebo arm after new relevant information appeared, is consistent with accepted practices for both investigators and IRBs, as they seek to maximize scientific benefit without violating their duties to study participants.

Finding:

The committee finds that the initial design of the HIVNET 012 trial, which incorporated two placebo arms, was properly reviewed and approved by the Johns Hopkins University and Ugandan IRBs, and that justifications for the use of placebo arms were adequately presented.

The committee also finds that the HIVNET 012 trial was promptly and properly reevaluated and the placebo arms discontinued when new data emerged from other studies.

COMPLIANCE WITH INFORMED CONSENT

Even when risks are reasonable and a study design is acceptable, no one should participate in research without giving voluntary informed consent.[15] Investigators must make appropriate disclosures and ensure that participants understand the information and their choices—not only at the time of enrollment but throughout the research. By engaging in this process, researchers demonstrate their concern and respect for those they aim to enroll in a study. The process also allows those who do not wish to participate to protect themselves.

Investigators must tailor both the information and the way they convey it to the needs of participants in the particular research context while meeting full disclosure requirements. Researchers must also adapt requirements for documenting such disclosure to the research setting. This requires a consent process that is culturally appropriate, forms of documentation that are sensitive to local concerns (e.g., in some settings, a fear of signing documents), and information delivery geared to the educational levels and cultural understandings of the local population (Benatar, 2002; Gostin, 1995; Lindegger and Richter, 2000; Marshall, 2001; Molyneux et al., 2004). In HIVNET 012, not only were consent forms translated into local languages, but the Ugandan IRB reviewed the entire consent process and the information given to participants, including language pertaining to placebos and randomization.

[15]Some exceptions can be made for research that poses minimal risk. Investigators can obtain consent from incompetent subjects, such as children or those with neurological impairment, from an appropriate surrogate.

Studies funded by DHHS involving children or pregnant women are subject to additional consent requirements. These include consent from appropriate guardians (in the case of children) and fathers (in some research involving pregnant women), and—if the research is of no possible direct medical benefit to the fetus or child—limits on the risks a study can impose upon the fetus or child. As HIVNET 012 did offer the prospect of direct medical benefit to the children, once born, it was not subject to special limits on the risks it could impose. Nonetheless, special consent requirements apply even to this research.

When research with a pregnant woman holds out the prospect of benefit to herself as well as the fetus, DHHS regulations (45 CFR Part 46.203) state that investigators must minimize risks to the extent possible, and that they must obtain the consent of the woman but not that of the father. In other words, women do not need the consent of a second party to enroll in research that might be of some benefit to themselves. By contrast, where the research is solely of possible benefit (and risk) to the fetus, consent of the father is also required, unless "he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest."

Per DAIDS policy, the HIVNET 012 consent forms included a line that the father of the fetus or infant could sign if he was available (HIVNET 012 Investigators, 1998). In-country researchers regularly counseled participants to involve the fathers in the consent process. Where study participants refused or were unable to involve the fathers, citing an array of concerns, the research team deemed those fathers "unavailable."

Because the DHHS Office of Human Research Protections offers little guidance for interpreting "unavailability," it is impossible to evaluate the investigators' interpretation of the term. There is evidence that study staff encouraged pregnant women to involve the fathers, but since staff did not have independent access to the fathers, they could not involve them without cooperation from the pregnant women. The research team was also severely constrained by concerns about violating confidentiality by revealing the women's HIV status to the fathers, especially given the stigmatization of HIV-positive individuals. The team felt that such disclosure would have been a breach of medical ethics and would have put the women at risk—social, economic, and physical—if confidentiality were breached. Thus, after counseling women to involve the fathers, if the women failed to help investigators locate the fathers, then these men were deemed to be unavailable.

Where fathers were available, their consent was required prior to enrollment, as per the approved protocol. In an example given by the investigators, one woman's partner came with her when she was considering participating in the study. The father did not consent, and the woman was

not permitted to participate in the study, despite her own interest in doing so.

Federal regulations requiring paternal consent apply only when research is of "no possible medical benefit" to the pregnant women themselves. Here, because some medical benefits arguably did accrue to the pregnant women, the requirement of paternal consent would seem to be premised primarily on DAIDS policy rather than federal research regulations. Because requiring the fathers' consent appears to be supererogatory—that is, it exceeds DHHS requirements and is an additional requirement imposed by DAIDS and the IRBs—any failure to comply would not violate U.S. regulations, but rather would fail to meet the terms under which the IRBs approved the study. The remedy for such a deviation from protocol, therefore, would not lie with DHHS but rather with DAIDS and the IRBs.

HIVNET 012 does not appear to have failed to comply with the DAIDS requirement for paternal consent, where available. Given that the investigators' interpretation of paternal unavailability is consistent with the federal regulations and the IRB requirement, the deviation from protocol would be the failure to document attempts to obtain paternal consent, rather than a failure to obtain it.

The rules governing research on children—relevant here because they received ZDV or NVP and remained in the study for follow-up weeks and months after birth—stipulate that investigators should ideally obtain consent from both parents. Again, however, exception is made when one of the parents is unavailable.

Because consent is an ongoing process and participants have the right to withdraw from a study at any time, investigators must provide for situations where the consenting parent dies or becomes unavailable. In such cases, a new decision maker—whether father or guardian—must be sought and assurances received that the child is still authorized to participate. In HIVNET 012, infant follow-up proceeded even in cases of maternal demise. If a participating mother died during the first 18 months of the study, no additional consent for follow-up of the child was obtained since the mother had already given consent for 18 months of follow-up. No study products were being administered, only follow-up was being performed (e-mail communication, L. Guay, March 22 and 23, 2005).

Despite having obtained consent for the 18-month follow-up prior to the mother's demise, a guardian should have been identified to take over for the absent mother. As all seminal research ethics documents note, research subjects are entitled to withdraw from research at any time, and in the case of children, a guardian is needed at all times so that withdrawal remains an option.

Although they were not receiving treatment, children were exposed to some limited risks during the follow-up period. Physical risks were limited to the blood draws needed to confirm HIV status, and blood draws, at least in U.S.-based studies, are considered to entail minimal risk. But social risks remained as well; if a child's HIV-positive status became widely known, it might trigger social stigma or other harmful reactions by members of the community. Even if these risks were minimal, opportunity ought to have been provided at all times during the follow-up for a responsible adult to terminate a child's participation. An exception could have been made if the relevant IRBs had concluded that the criteria for waiving consent had been met, but no such request appears to have been made to the IRBs.

Investigators explained that they were constrained by respect for confidentiality of the information that the deceased woman had shared with the research team, including her HIV status (Guay, 2004). Reaching out to other family members for consent for continued follow-up of the infant would have required disclosing the mother's and the infant's status. Nonetheless, absent a waiver from the relevant IRBs, research practices dictate making some arrangement for an appropriate, competent adult to oversee a child's participation in a study at all times.

With respect to obtaining consent for extended follow-up to age 5, the investigators did recognize the need to identify a responsible adult in cases where the mother had died. The investigators report that, in most cases, a child was then under the care of a relative who was not the father of the child. As a result, the investigators sought guidance from the DAIDS regulatory affairs branch and ARC about who was allowed to consent on behalf of the child. ARC indicated that a parent or legal guardian could consent. Investigators then grappled with local rules governing who constitutes a "legal guardian" after the death of the mother for the purpose of consenting on behalf of the child. The Uganda IRB referred the investigators to the Uganda courts, and after a lengthy process of review, the Ugandan courts determined that, under the Ugandan Child Welfare Act, the individual (parent, relative, guardian) who assumes primary care and support of the child in terms of providing for the welfare of the child (i.e., assumes "parental responsibility") has the right to sign consent on behalf of the child. Investigators used this guidance to determine who could consent to a child's participation in the extended follow-up.

Findings:

The committee finds that the initial study design incorporated all relevant protections relating to the need for voluntary informed consent, the acceptability of placebo control, the discontinuation of placebo control, and overall compliance with IRB reviews.

The committee finds that the investigators correctly identified appropriate guardians to consent to extended 5-year follow-up in situations where the original consenting parent had died, but that the investigators failed to do this in situations where the consenting parent died while the child was still enrolled in the original, 18-month follow-up.

The committee finds that requesting additional consent from the fathers before enrolling the pregnant women or their infants in the study was not necessarily required by U.S. federal regulations but was required per DAIDS policy and was therefore incorporated into the IRB-approved protocol.

Finally, the committee finds that the failure to obtain such additional paternal consent was based on the practical unavailability of the fathers and the ethical constraints that prevented the research staff from contacting fathers in the absence of the mother's support and consent.

In the case of HIVNET 012, the Westat site visit team and the DAIDS remonitoring team pointed to a number of deficiencies regarding the process and documentation of informed consent. These deficiencies include, for example, a lack of a date-stamp or version number on informed-consent forms to verify the timing of IRB approvals (DAIDS, NIAID, 2003). The investigators acknowledged procedural deficiencies and implemented procedures to correct them (HIVNET 012 Investigators, 2003). However, the Westat and the DAIDS remonitoring reports did not find that subjects failed to give informed consent.

A key element in determining whether a study violated subjects' rights is the evaluation of the risks and benefits of participating. If the study had shown that the rate of adverse events—serious or not, by any definition—was significantly different than that described at the time of enrollment, researchers would have had to alert both new and existing subjects, and apply updated information to new enrollments.

As noted by OHRP and Westat, the Ugandan IRB did not provide effective continuing review. On the other hand, the change from a four-arm placebo-controlled study to a two-arm study with active arms represented exactly the kind of change in risk-benefit analysis that triggers a reevaluation of both the study design and the consent process. This information was promptly shared with the relevant IRBs, and the change in the study design was approved. Once the two-arm portion of the study began, however, enrollment proceeded rapidly, and no apparent finding from the interim data collected in the months between commencing and concluding the study enrollment would have changed the risk-benefit balance.

While OHRP did criticize the Ugandan IRB for its inadequate continu-

ing review, the primary purpose of such review is to determine whether an alteration in the study protocol or the informed-consent process is in order, as mandated by both DHHS regulations and DAIDS special guidance for HIV research (Lin and Meschino, 1993). Per the protocol design, the NIH Data Safety and Monitoring Board or an independent body or group of experts provides the analysis of adverse events and interim data on which the IRB bases its decision. In this case, even assuming the absence of effective local review, the study did not produce evidence of differential risk of adverse effects that should have led to modifications in study design. Nor does it appear that the emerging evidence of efficacy could have led to an early decision to terminate randomization, given the need to document the HIV-1 status of infants and the fast pace of enrollment.

Finding: The committee finds that while auditors reported procedural lapses by the Ugandan IRB, there was evidence of rapid and appropriate response by the IRB in approving modification of the design of HIVNET 012 and discontinuation of placebo arms. There was also no evidence that participants signed the wrong version of the consent form.

In sum, most of the criticisms concerning the ethics of HIVNET 012 are either based on a misunderstanding of procedural standards (as with compliance with GCP Guidelines), disputes over the interpretation of serious adverse events (where the committee finds that the interpretation used was appropriate), concerns regarding continuing review by the host country (although with no evidence of injury to subjects as a result), and concerns regarding full and precise documentation of compliance with all aspects of review and informed consent (again, without evidence of injury to subjects). The one exception concerns the absence, in some circumstances, of a responsible adult to take over for a deceased parent who had originally gave consent to enroll a child in the 18-month follow-up period. While there is no evidence that this lapse harmed any children, neither is the absence of such a substitute guardian consistent with proper research practices.

Ethical management of a research trial does not consist solely of following procedures. It entails ensuring that subjects are protected, by requiring a reasonable balance of risks and benefits before commencing the study, and by insisting that subjects give free and informed consent before enrolling. Specific procedures exist to reduce the likelihood that ethical lapses will occur. As such, it may be appropriate for agencies such as the FDA to refuse to accept data from trials that do not meet all these procedural requirements. Such an approach may promote adherence to these procedures by those planning and implementing various studies. But for the scientific and

medical community at large, the failure to follow some or even all of the procedures does not render a particular trial unethical, absent evidence that subjects were exploited or harmed. Using valid data from such trials to pursue further research and improve patients' lives is entirely appropriate.

Findings:

Despite some lapses in documentation, the committee finds no evidence that study subjects failed to give voluntary informed consent.

The committee finds that HIVNET 012 met the substantive standards for ethical conduct of research and was implemented in substantial compliance with regulations governing protection of human subjects, especially independent review of risks and benefits to them.

The committee finds that there is no reason based in ethical concerns about the design or implementation of the study that would justify excluding its findings from use in scientific and policy deliberations.

REFERENCES

American Medical Association. 1999. Current Opinions of the Council on Ethical and Judicial Affairs. E-2.075 The Use of Placebo Controls in Clinical Trials. *American Medical Association Code of Ethics*.

Benatar S. 2002. Some reflections and recommendations on research ethics in developing countries. *Social Science & Medicine* 54(7):1131-1141.

Cohen J. 1997. Ethics of AZT studies in poorer countries attacked. *Science* 276:1022.

DAIDS, NIAID (Division of AIDS, National Institute for Allergy and Infectious Diseases). 2003. HIVNET 012 Monitoring Report.

DHHS (Department of Health and Human Services). 2005. Protection of Human Subjects, Proposed Criteria for Determinations of Equivalent Protection. *Federal Register* 70(57): 15322-15327.

DHHS. 2004. Code of Federal Regulations: Public Welfare. 45 CFR § 46.101.

DHHS and FDA (U.S. Food and Drug Administration). 1997. International Conference on Harmonization (ICH); Guideline on Stability Testing for New Dosage Forms; Availability. *Federal Register* 62(90):25691-25709.

Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH. 2000. The uncertainty principle and industry-sponsored research. *Lancet* 356(9230):635-638.

Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. 1998. Ethical issues in the design and conduct of randomised controlled trials. *Health Technology Assessment* 2(15):i-vi, 1-132.

Ellenberg SS, Temple R. 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. *Annals of Internal Medicine* 133(6):464-470.

FDA and DHHS. 2001. Code of Federal Regulations: FDA Investigational New Drug Application. 45 CFR § 46.

FDA and DHHS. 1998. Code of Federal Regulations: FDA Investigational New Drug Application. 21 CFR § 312.

FDA and DHHS. 1997. Code of Federal Regulations: FDA Investigational New Drug Application. 21 CFR § 312. Subpart D: Sections 312.50 and 312.60.

FDA and DHHS. 1996. Code of Federal Regulations: FDA Investigational New Drug Application. 21 CFR § 312.

FDA. *FDA Regulations Relating to Good Clinical Practice and Clinical Trials*. [Online] Available at: http://www.fda.gov/oc/gcp/regulations.html. Accessed March 9, 2005.

GAO (General Accounting Office, now Government Accountability Office). 1996. Prescription Drugs: Implications of Drug Labeling and Off-label Use. *Testimony of Sarah Jagger, Director of Health Services Quality and Public Health Issues of the Health, Education, and Human Services Division of the U.S. General Accounting Office, Before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, U.S. House of Representatives*, GAO/T-HEHS-96-212.

Gostin L. 1995. Informed consent, cultural sensitivity, and respect for persons. *Journal of the American Medical Association* 274(10):844-845.

Guay L. 2004. Presentation to IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study. Transcript of September 30, 2004, Data-Gathering Meeting.

Guay L, Jackson B. 2003. Makerere University–Johns Hopkins University Quality Management Plan.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181): 795-802.

Hendrix TR. September 22, 1997. Letter to Jackson B.

HIVNET Group. Protocol Version 1.0, 2 June 1997. A Phase III Placebo-Controlled Trial Too Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates.

HIVNET 012 Investigators. 2003. MUJHU Quality Management Plan.

HIVNET 012 Investigators. 1998. Sample Informed Consent Form.

ICH (International Conference on Harmonisation). 1996. Guideline for Good Clinical Practice. Available at http://www.ich.org.

Jackson B. July 9, 1997. Letter to Hendrix TR.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

Levine RJ. 1999. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 341(7):531-534.

Lilford RJ, Djulbegovic B. 2001. Declaration of Helsinki should be strengthened. Equipoise is essential principle of human experimentation. *BMJ* 322(7281):299-300.

Lin MH, Meschino JA. September 13, 1993. Letter to colleague.

Lindegger G, Richter L. 2000. HIV vaccine trials: Critical issues in informed consent. *South African Journal of Science* 96(313-317).

Marshall P. 2001. The Relevance of Culture for Informed Consent in U.S.-funded International Health Research: Findings and Recommendations from the Case Study on Informed Consent for Genetic Epidemiological Studies of Hypertension, Breast Cancer, and Diabetes Mellitus in Nigeria. *Commissioned Paper for National Bioethics Advisory Commission: Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* II:C1-C38.

McNeilly P (OHRP). March 24, 2003a. Letter to Nyiira ZM and Sewankambo NK. [Online] Available at http://www.hhsgov/ohrp/detrm_letrs/YR03/mar03e.pdf. Accessed February 15, 2005.

McNeilly P (Office of Human Research Protections, OHRP). March 15, 2002a. Letter to Nyiira ZM and Sewankambo NK.

McNeilly P (OHRP). July 16, 2002b. Letter to Nyiira ZM and Sewankambo NK.

McNeilly P (OHRP). October 28, 2002c. Letter to Nyiira ZM and Sewankambo NK. [Online] Available at http://www.hhsgov/ohrp/detrm_letrs/YR02/oct02e.pdf. Accessed February 15, 2005.

Molyneux C, Peshu N, Marsha K. 2004. Understanding of informed consent in a low-income setting: Three case studies from the Kenyan coast. *Social Science & Medicine* 59:2547-2559.

Murphy T. 2004. *Case Studies in Biomedical Research Ethics*. Cambridge, MA: MIT Press.

National Bioethics Advisory Commission. 2001a. *Ethical and Policy Issues in Research Involving Human Participants*. Available at http://www.bioethics.gov/reports/past_commissions/nbac_human_part.pdf.

National Bioethics Advisory Commission. 2001b. *Ethical and Policy Issuses in International Research: Clinical Trials in Developing Countries. Volume 1: Report and Recommendations of the National Bioethics Advisory Commision*. Available at http://www.bioethics.gov/reports/past_commissions/nbac_international.pdf.

Office of Human Subjects Research, National Institutes of Health. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.

PPD. 2003. Clinic Site Monitoring Group HPTN Interim Site Visit Report. 1Q03 Regulatory File Review, February 3-7, 2003.

Radley D, Stafford R, Finkelstein S, Cockburn L. 2004. Powerpoint Presentation: Off-label Prescription among Outpatient Physicians. [Online] Available at http://www.academyhealth.org/2004/ppt/radley.ppt. Accessed March 14, 2005.

SCHARP (Statistical Center for HIV/AIDS Research and Prevention). 1997. HIVNET 012 Study-Specific Procedure: Phase III Efficacy Trial of Oral AZT vs Oral Nevirapine in Pregnant Ugandan Women and Their Neonates for the Prevention of Vertical Transmission of HIV-1 Infection.

't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. 2000. Unapproved and off-label use of drugs in a children's hospital. *New England Journal of Medicine* 343(15):1125.

Temple R, Ellenberg SS. 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Annals of Internal Medicine* 133(6):455-463.

6

Response to the Charge to the Committee

This IOM committee was given a specific charge related to various aspects of the design and implementation of HIVNET 012. The preceding chapters of this report describe the planning and initiation of HIVNET 012, discuss the published findings, and assess issues and concerns regarding the study. In this chapter, the committee draws on the findings presented in Chapters 3 through 5 of this report to answer the nine questions posed to the committee.

The statement of task transmitted from NIH to IOM is as follows:

> At the request of the National Institutes of Health (NIH), the Institutes of Medicine will conduct an independent review of the HIVNET 012 clinical trial conducted in Uganda. . . . The IOM committee will address methodological and data interpretation questions related to protocol design, data collection, recordkeeping, quality control, and analysis. The committee will assess the impact of these issues on the validity of the overall findings and conclusions of the trial.

The charge to the committee included nine questions. They are listed here in the order the chapters discuss them:

Study Design

1. Was the protocol design appropriate?

Implementation of the Study

2. Does the fact that, in many cases, there were no informed consent forms from the fathers cause enough significant concern to invalidate the conclusions?

3. Are there results available (published or unpublished) of assays of drug levels and should consideration be given to what, if any, impact they might have on the conclusions?

4. Was the protocol followed sufficiently to conclude that the data are sustainable?

Quality Control Procedures and Quality of the Data

5. Was the quality control sufficient to uphold the conclusions?

6. A certain number of documents were destroyed by a natural disaster. Is this a significant deterrent to drawing conclusions?

7. Can the integrity of the data be sustained in view of the deficiencies of the data collection, and the consistency of its recording?

Conclusions

8. Are the conclusions supportable by the data?

9. Is there any reason to suggest the need to retract the publications or to revise the conclusions?

FINDINGS REGARDING THE STUDY DESIGN

1. Was the protocol design appropriate?

Chapters 3 and 4 provide a detailed discussion of both the initial and modified design of HIVNET 012. In view of the enormous burden of mother-to-child transmission of HIV-1 in sub-Saharan Africa—which remains a critical public health problem—and the need to identify regimens that can be delivered widely to HIV-infected pregnant women with limited access to health care, the effort of HIVNET 012 investigators to study new regimens suitable for widespread use in a resource-poor setting was appropriate. The partnership between investigators at Johns Hopkins University and Makerere University, along with the resources of Mulago Hospital, brought together the medical knowledge, research expertise, and antenatal and postpartum care services needed to conduct the study.

The treatment regimens chosen for evaluation in preventing mother-to-child transmission were appropriate. As no short-course oral regimen of

ZDV or NVP had been shown to be effective at the time the study began,[1] the inclusion of a placebo group in the initial design was ethically justified. Once results from a study in Thailand indicated that a short course of ZDV was effective in reducing the rate of mother-to-child transmission of HIV (Shaffer et al., 1999), the investigators promptly discontinued the placebo arms and continued the study as a Phase IIB study comparing two short-course regimens, ZDV versus NVP. The modified design was also appropriate and highly relevant to settings with substantial rates of mother-to-child transmission and limited resources.

As described in Chapter 3, the committee found that the eligibility criteria for participation in the study were appropriate. In addition, the randomization procedures were properly designed and implemented, resulting in two treatment groups that were comparable at enrollment with respect to measured characteristics. Moreover, the initial and revised sample sizes in the original Phase III placebo-controlled design and the subsequent Phase IIB trial were sufficient to meet the scientific objectives of the initial and modified studies. The statistical methods employed in the HIVNET 012 publications were appropriate.

As discussed in Chapter 4, the efficacy endpoints and timing of assessments were appropriate, and the plans for interim monitoring of safety and efficacy by the Data Safety Monitoring Board, as described in the study protocol, were scientifically appropriate and met ethical and regulatory requirements.

As discussed in Chapter 5, the committee found that the initial study design, which included a separate placebo arm for each of ZDV and NVP, was properly reviewed by the relevant institutional review boards (IRBs) in the United States and Uganda. Moreover, the initial study design incorporated all relevant human subject protections and an appropriate follow-up period to identify both the risks and benefits of the treatment regimens. The study design also incorporated all relevant human subject protections relating to the need for voluntary informed consent. Moreover, although paternal informed consent may not have been necessary based on the nature of the study, the decision to seek paternal informed consent, if feasible, was consistent with federal regulations. Finally, the plan for oversight by the relevant IRBs and the DAIDS Data and Safety Monitoring Board (DSMB) met the requirement for monitoring of ongoing research. Thus the design of

[1]At the time of the HIVNET 012 study, the only regimen available for preventing mother-to-child transmission was from the Pediatric AIDS Clinical Trials Group (PACTG) 076 trial. That trial demonstrated that an intensive three-part regimen of ZDV—given to the mother during pregnancy, labor, and delivery, and to newborns in the first 6weeks of life—could reduce mother-to-child transmission by two-thirds (Connor et al., 1994). The complexity and expense of this regimen made it prohibitive for use in most developing countries.

HIVNET 012—both before and after the discontinuation of the placebo arms—met all relevant ethical requirements.

In summary, the committee found that the protocol designs for HIVNET 012—both before and after the discontinuation of the placebo arms—were appropriate.

FINDINGS REGARDING THE IMPLEMENTATION OF THE STUDY

2. Does the fact that, in many cases, there were no informed-consent forms from the fathers cause enough significant concern to invalidate the conclusions?

The Department of Health and Human Services (DHHS) has adopted additional regulations that specifically address research with pregnant women. These regulations distinguish between research of possible benefit to the woman, to which she can consent without consulting the father, and research of no possible benefit to her but of possible benefit (or risk) only to the fetus, in which case paternal consent is required. Even here, however, paternal consent may be foregone if one of several exceptions are met, including the unavailability of the father.

Because the protocol approved by the IRBs asked for paternal consent if the fathers were reasonably available, study staff regularly counseled potential participants regarding the need to involve the fathers in the consent process. For various reasons, however, including physical distance of the fathers or the fear of intense stigmatization, social and economic repercussions, and even violence against the women if their HIV status became known (Fitzgerald et al., 2004), the women were rarely able or willing to produce the fathers so that their consent could be sought.

Federal regulations provide little or no guidance on how to interpret the phrase "reasonably available," and the investigators understood it to mean that if, after counseling a woman, the father was unavailable to the investigators, then one of the criteria for an exception had been met. The practices followed by the investigators with respect to paternal consent therefore would not violate U.S. regulations but rather would, if deficient, violate the terms under which the IRBs approved the study. Given the seeming permissibility of the interpretation of "unavailable," the investigators did not fail to comply with the protocol, but rather did not provide written documentation of their efforts to comply (PPD, 2003)—that is, to document each discussion and whether it yielded an agreement to produce the father. The remedy for such deviations from protocol (but not from federal regulations) would lie not with DHHS but with the IRBs. However, the committee considered the absence of paternal consent as reflecting an appropriate effort to balance ethical concerns—one that weighed the obli-

gation to involve both parents in decisions about research that might affect their fetus and the desire for confidentiality on the part of the mother. Therefore, the absence of paternal informed consent is not a basis for disregarding the conclusions of the study.

3. Are there results available (published or unpublished) of assays of drug levels and should consideration be given to what, if any, impact, they might have on the conclusions?

As described in Chapter 3, tests on stored cord blood specimens indicate that there was a high level of adherence to the study regimens (Jackson et al., 2003; Jackson et al., 2005). Cord blood was obtained from the infants in both treatment arms and frozen for later analysis. In the ZDV arm, specimens were available for 278 of 308 infants. Among these infants, NVP was detected in cord blood in only one sample. In the NVP arm, specimens were available for 275 of the 311 infants. Of these, 3 infants did not receive NVP and no NVP was detected in cord blood. Among the remaining 272, 256 (94%) had a detectable concentration of NVP in cord blood.

These observations indicate a high degree of adherence in the NVP arm. Because ZDV has a short half-life of 1.1 hours in non-pregnant women and possibly a shorter half-life in pregnant women, obtaining direct evidence of blood levels of ZDV in those assigned to ZDV therapy was not feasible.

In addition to information based on NVP cord blood levels, other data support adherence to study regimens. Only 37 women enrolled in HIVNET 012 did not deliver at Mulago Hospital. In the two treatment groups combined, 308 women reported taking their study-assigned treatment before arriving at the hospital, 212 women received their assigned treatment after arriving at the hospital, and no data on dosing were available for 2 women. Aside from 9 babies who died or were lost to follow-up, 13 infants did not start study treatment (6 in the zidovudine group and 7 in the nevirapine group). The median number of zidovudine doses received by neonates was 14, the number specified in the protocol (SCHARP, 2004).

Two other measures of adherence were available to the committee. In the group of mothers assigned to NVP, HIV RNA concentration fell by approximately one log 1 week after they received the dose and returned to baseline by the 6-week sample. This is consistent with the expected prompt and substantial effect of NVP on HIV replication. No similar change in HIV RNA concentration was noted in mothers assigned to ZDV treatment, as expected given the short half-life of this drug. Finally, HIV resistance to NVP was found only in mothers assigned to NVP treatment, consistent with prior exposure to this medication.

Based on a review of this evidence, including the fact that the drugs were identifiable during the unblinded phase and study staff performed a substantial fraction of drug administrations, the committee concluded that participants achieved a high level of adherence to the study regimens, as reported by the HIVNET 012 investigators in their *Lancet* publications (Guay et al., 1999; Jackson et al., 2003).

4. Was the protocol followed sufficiently to conclude that the data are sustainable?

In almost every respect, the HIVNET 012 investigators followed the study protocol closely. The committee did find that the investigators interpreted the protocol definition of serious adverse effects (SAEs) to be predominantly, but not solely, hospitalizations, severe laboratory toxicities, life-threatening illness, and death, which was a reasonable interpretation based on the background rates of illness in Uganda. As a result, conditions that might have been judged to be serious by other investigators in resource-rich countries but did not result in hospitalization in Uganda may not have been recorded as serious adverse events by the HIVNET 012 investigators. The committee did, however, review the source documents, case report forms, and entries in the study data base for a sample of 49 infants, and found that all deaths and hospitalizations experienced by these infants were consistently and accurately recorded in the case report forms and study data base. Thus, the data on survival and hospitalization are accurate and provide a reliable basis for assessment of the safety of the study regimens.

FINDINGS REGARDING DATA COLLECTION AND QUALITY CONTROL

5. Can the integrity of the data be sustained in view of the deficiencies of the data collection, and the consistency of its recording?

As discussed in Chapter 4, the methods used to collect and record HIVNET 012 data were, in most respects, sound. Study staff maintained source files that consisted of a binder of medical information for each mother/infant pair. Because of difficulties in obtaining records of hospitalizations at Mulago Hospital beyond those from regular antenatal, delivery/birth, and follow-up study visits, the investigators supplemented study source documents with "hospital admission forms" designed to record abstractions of relevant information about study participants' hospitalizations (Guay, 2004). In addition, the investigators used appropriately designed case report forms, stored in participant-ID-labeled binders for each

mother/infant pair, to transmit data accurately and in a timely fashion to the data-coordinating center for the study. Rates of retention and adherence to the schedule for study visits were high and a high percentage of blood samples required by the study protocol were obtained, leading to accurate assessment of rates of transmission of HIV-1 and HIV-1-free survival in both treatment groups. According to the remonitoring study and the investigators, detailed information on the chain of custody of study drugs was sometimes not available. However, notations in the source files, participant reports, the substantial fraction of dosing that occurred in the hospital, and the findings regarding blood levels of NVP and viral load all support the published report by the HIVNET 012 investigators that a high level of adherence to study regimens was accomplished among study participants. Evidence of oral informed consent before the initial blood draw was not consistently documented. However, the committee finds that these reported lapses in documentation are of minor significance and do not threaten the findings from this study.

The committee also focused on the collection of data about adverse events. As discussed in Chapter 4, the investigators classified clinical events as serious adverse events primarily but not exclusively if they were associated with hospitalization. That was done taking into account the prevalence of co-morbid conditions in Uganda such as tuberculosis and malaria and clinician judgment in terms of assessment of severity of events. The grading system for hemoglobin and rash were modified prior to study start to reflect local conditions and these modifications were written in the *Study Specific Procedures*. The acceptable, but narrow, interpretation of "serious" may have led to reporting of fewer serious adverse events than would have been reported with a broader interpretation. To gain a greater understanding of study practices, the committee reviewed a sample of source documents and case report forms for 49 infants. In this review, the committee found some evidence of underreporting of concomitant serious adverse events present when an SAE was reported. However, if a participant's source documents showed one or more serious adverse events had occurred simultaneously, at least one of those events on that occasion was noted in the case report form and documented in the study database. In addition, the committee found that all deaths and all hospitalizations occurring in the subset of infants whose records were reviewed by the committee had been recorded in the study database. Thus, the committee concluded that information on the number of hospitalizations and deaths among participants is complete and accurate.

Although the methods employed by the investigators apparently led to some underreporting of adverse events, the committee found no evidence to suggest that this possible underreporting occurred differentially in the two treatment arms. In summary, with the few qualifications noted above and

based on the body of information it reviewed, the committee concludes that the integrity of the study data can be supported.

6. Was the quality control sufficient to uphold the conclusions?

Quality control was reported in previous audits (Chamberlin et al., 2002; DAIDS, NIAID, 2003) as deficient in some procedural areas, including a lack of written standard operating procedures, inconsistent signing or initialing and dating of forms, corrections not made according to generally accepted standards, and a lack of systematic review of case report forms by investigators before transmittal to the statistical center. The investigators disagreed with audit findings in some areas, and they took steps to improve procedures in the remaining areas. However, quality control procedures in the laboratory were satisfactory, and the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) employed internal quality-control mechanisms to regularly review and "clean" data in a timely fashion—identifying inaccuracies, inconsistencies, and missing information across various forms in the database, correcting some problems, and checking with the study site to address the remainder.

The committee established that data on study participants were gathered, recorded in source documents, recorded on case report forms, and transmitted to the statistical center in a timely manner. The committee has also documented a high degree of concordance between the data recorded on the source documents and in the study database. Because the source documents—along with hospital admission forms and later actual hospital records obtained by study staff—were intended to serve as a readily available and substantially complete medical record, this consistency leads the committee to conclude that the data were accurately ascertained and recorded. Moreover, this approach to collection of the information ordinarily maintained in the patient medical record was an effective and realistic way to maintain the analogue of a primary medical record in a setting where health organizations did not maintain longitudinal medical records for patients. Thus, the approach to record keeping employed in this study was reasonable and sufficient to meet the research objectives of the study. In the judgment of this committee, the occasional gaps in these source documents arising from circumstances such as provision of care by individuals not associated with the study does not cast doubt on the accuracy of the research database.

7. A certain number of documents were destroyed by a natural disaster. Is this a significant deterrent to drawing conclusions?

Based on a review of secondary sources (Westat Site Visit Report and

DAIDS remonitoring report and materials) and the investigators' presentation before the committee, the committee concludes that no primary study data appear to have been destroyed. First, when study staff obtained records from Mulago Hospital on participants and began to reorganize those records, they found that a small number had been slightly damaged by rodents or insects, but not to an extent that rendered them unusable (Guay, 2004). Second, a broken pipe caused some flooding or water damage that affected one or more of the health visitors' log books, containing notes about their visits to participants' homes (Chamberlin et al., 2002). These were secondary materials not used as source documents for the study, and much of the information contained in the damaged notebook(s) was legible and copied into a new notebook or notebooks (Guay, 2004). None of the participants' clinical charts or other primary source documents was affected by this event. Thus, the extent and significance of missing documents was quite limited and has no bearing on the integrity of the study.

FINDINGS REGARDING THE STUDY CONCLUSIONS

8. Are the conclusions supportable by the data?

Based on the information summarized in this report, the committee concludes that the findings from HIVNET 012 regarding efficacy of NVP—including the reduction in rate of mother-to-child transmission of HIV-1 and HIV-1 infection-free survival at 4–6 weeks, 14–16 weeks, and 18 months in the NVP arm—are sound and fully supportable by the data. The reported high levels of adherence to treatment regimens can also be supported.

Taken together, these two sets of results published in the two *Lancet* articles show a substantial reduction in the rate of transmission of HIV-1 infection in the NVP arm compared to the ZDV arm at 6–8 weeks, 14–16 weeks, and 18 months (Guay et al., 1999; Jackson et al., 2003). Similarly the probability of HIV-1-free survival at these three time points was significantly increased in the NVP treatment group. The committee concludes that these findings on the efficacy of the NVP treatment regimen relative to the ZDV regimen studied in HIVNET 012 are well supported by the study's design and conduct and the quality of the data and are therefore appropriate for use in policy making.

The modified HIVNET 012 study was an actively controlled trial with no placebo group, so the trial was not able to demonstrate the safety of the two active regimens relative to untreated controls. However, there was no evidence that the rates of unreported adverse events varied by treatment group, suggesting that the comparative safety analyses reported by the HIVNET 012 investigators are not biased. From our review of the full data-

base, laboratory data and data on deaths were largely complete. In addition, in a review of 49 infants, we found that all hospitalizations and deaths were in the database as well as at least one SAE on each occasion on which one or more SAEs occurred. Thus, the committee concludes that the investigators' findings regarding similarity of the rates of infant serious adverse events in the two treatment groups are supportable.

9. Is there any reason to suggest the need to retract the publications or to revise the conclusions?

Based on its review, the committee finds no reason to retract the publications or alter the conclusions of the HIVNET 012 study. The committee concludes that data and findings presented in Guay et al. (1999) and Jackson et al. (2003) are sound and presented in a balanced manner and can be relied upon for scientific and policy-making purposes. The reasons for the committee's confidence in data and findings reported in these publications are several-fold. First, the randomization procedures were properly designed and implemented, meeting the goal of creating two comparable treatment groups, which serves as the basis for valid conclusions about safety and efficacy. Second, based on information from drug assay tests and other data, participants received the appropriate drug, and there was a high level of adherence to the study regimens. Furthermore, the investigators achieved high rates of retention and follow-up among participants. The committee's analyses indicate that the efficacy data are well-supported. Despite the narrow interpretation of the definition of SAE employed in the field and the failure to capture some AEs recorded in the source documents in the study database, all infant hospitalizations, severe laboratory abnormalities, laboratory toxicities, and mortality data reviewed by the committee were captured in the database. The committee also found that some (non-serious) adverse events noted in the source documents were not reported on the case report forms. The underreporting of some (non-serious) AEs and some concomitant SAEs that accompanied a reported SAE may limit the generalizability of absolute adverse event rates and counts to other settings. However, the committee has found no reason to believe that the rates of unreported adverse events varied by treatment group, suggesting that the comparative safety analyses reported by the HIVNET 012 investigators are valid.

REFERENCES

Chamberlin J, Gustavson SA, Hensley M, Lander S. 2002. Site Visit Report, Kampala Uganda, February 18-28, 2002. Westat Corporation, MD.

Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, Jimenez E, O'Neill E, Bazin B, Delfraissy J, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J, for The Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 331(18): 1173-1180.

DAIDS, NIAID (Division of AIDS, National Institutes of Allergy and Infectious Diseases). 2003. *HIVNET 012 Monitoring Report*.

Fitzgerald DW, Maxi A, Marcelin A, Johnson WD, Pape JW. 2004. Notification of positive HIV test results in Haiti: Can we better intervene at this critical crossroads in the life of HIV-infected patients in a resource-poor country? *AIDS Patient Care and STDs* 18(11):658-664.

Guay L. 2004. Presentation to IOM's Committee on Reviewing the HIVNET 012 Perinatal HIV Prevention Study. Transcript of September 30, 2004, Data-Gathering Meeting.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354(9181):795-802.

Jackson B, Parsons T, Musoke P, Nakabiito C, Donnell D, Fleming T, Mirochnick M, Mofenson L, Fowler M, Mmiro F, Guay L, and HIVNET 012. 2005. *Association of Cord Blood Nevirapine with Self-Reported Timing of Dose and HIV-1 Transmission in the HIVNET 012 Study, Abstract #71*. [Online] Available at http://www.retroconference.org/org/2005/cd/Abstracts/25816.htm. Accessed March 7, 2005.

Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Owor M, Ducar C, Deseyve M, Mwatha A, Emel L, Duefield C, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Gigliotti M, Bray D, Mmiro F. 2003. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362(9387):859-868.

PPD. 2003. Kampala Issues List–HIVNET 012 Re-Monitoring and Ongoing Monitoring Visits.

SCHARP (Statistical Center for HIV/AIDS Research and Prevention). 2004. File: t_m_delivery.pdf. Document sent as part of an e-mail from Deborah Donnell to A. Gable, October 25. Re: Data information requests for IOM study.

Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro TD, Simonds RJ. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353(9155):773-780.

Appendix A

Agendas of Information-Gathering Meetings

Meeting One
September 30, 2004
The National Academy of Sciences Building
2100 C St., N.W., Board Room
Washington, D.C.

8:45-9:15 a.m.	Registration
9:15-9:30 a.m.	Welcome, Introductions, and Opening Statement *Stephen Lagakos, Ph.D.* *IOM Committee Member*
9:30-9:45 a.m.	Charge to the Committee (via phone) *Ruth Kirschstein, M.D.* *Senior Advisor to the Director* *National Institutes of Health*
9:45-10:00 a.m.	Questions from the Committee

10:00-10:45 a.m.	Overview of HIVNET 012 Trial *J. Brooks Jackson, M.D., M.B.A.* *HIVNET 012 Principal Investigator* *Johns Hopkins University* *Laura Guay, M.D.* *HIVNET 012 Co-Investigator* *Johns Hopkins University* *Tom Fleming, Ph.D.* *HIVNET 012 Co-Investigator* *University of Washington*
10:45-11:15 a.m.	Questions from the Committee
11:15-11:45 a.m.	Review of Perinatal HIV Prevention Trials Involving Nevirapine: Safety and Efficacy Data *Lynne Mofenson, M.D.* *Pediatric, Adolescent and Maternal AIDS Branch* *Center for Research for Mothers and Children* *National Institute of Child Health and Human Development* *National Institutes of Health*
11:45 a.m.-12:00	Questions from the Committee
12:00-1:00 p.m.	Lunch
1:00-1:30 p.m.	NIH Remonitoring Study of HIVNET 012 *John LaMontagne, Ph.D.* *Deputy Director* *National Institute of Allergy and Infectious Diseases* *National Institutes of Health*
1:30-2:00 p.m.	Questions from the Committee

2:00-2:45 p.m.	Comments from HIVNET 012 Investigators on NIH Remonitoring Study *J. Brooks Jackson, M.D., M.B.A.* *HIVNET 012 Principal Investigator* *Johns Hopkins University* *Laura Guay, M.D.* *HIVNET 012 Co-Investigator* *Johns Hopkins University* *Tom Fleming, Ph.D.* *HIVNET 012 Co-Investigator* *University of Washington*
2:45-3:15 p.m.	Questions from the Committee
3:15-3:55 p.m.	Public Comment Period
3:55-4:00 p.m.	Closing Remarks *Stephen Lagakos, Ph.D.* *IOM Committee Member*
4:00 p.m.	Adjourn

Meeting Three
January 4, 2005
Keck Center of the National Academies
500 Fifth Street, N.W., Room 201
Washington, DC

10:00-10:05 a.m.	Opening Remarks *James Ware, Ph.D.* *IOM Committee Chair*
10:05-10:45 a.m.	Comments on the HIVNET 012 Perinatal HIV Prevention Trial *Jonathan Fishbein, M.D. (Former Director of Office for Policy in Clinical Research Operations, Division of AIDS, NIAID, NIH)*
10:45-11:15 a.m.	Questions from the committee

Appendix B

Comparisons to Other Perinatal HIV Prevention Studies Using NVP and ZDV

INTRODUCTION

This review compares primary and secondary outcomes from the HIVNET 012 trial with results from similar study arms in other trials. Specifically this review describes the range and weighted mean average of the effects of the simplified maternal-infant nevirapine (NVP)- and zidovudine (ZDV)-dosing regimens employed in the HIVNET 012 trial on the risk of mother-to-child transmission of HIV and on the occurrence of serious adverse events and secondarily compares these outcomes with those of the two treatment arms of the HIVNET 012 trial.

METHODS

Criteria for Considering Studies for This Review

Types of Studies

This review was limited to randomized controlled trials.

Types of Participants

Infants born to HIV-infected mothers.

Types of Interventions

Nevirapine or zidovudine administered both in the intrapartum period, i.e., labor, to HIV-infected mothers and/or in the immediate postpartum period to exposed infants. In HIVNET 012 the NVP regimen was 200 milligrams (mg) of NVP orally to the mother at onset of labor plus 2 mg per kilogram (kg) of body weight of NVP orally to the infant at 72 hours of age or at discharge from hospital, whichever occurred first. The maternal dose could be repeated if vomited within 30 minutes. It could also be redosed if labor failed to progress and there were more than 48 hours until next onset of labor. Infants born outside the study hospital could receive a dose up to 7 days postpartum. The ZDV regimen included two 300-mg tablets at the start of labor followed by one 300-mg tablet every 3 hours during labor plus 4 mg per kg of body weight orally twice daily for 7 days after birth. Interventions that included the treatment of mothers or infants with other antiretroviral drugs or with combinations of NVP and ZDV were excluded.

Types of Outcome Measures

The primary outcome measure was the proportion of HIV-exposed infants in each arm who were infected during the first 6–8 weeks of age. This includes infants infected in the antepartum, intrapartum, and early postpartum periods. The secondary outcome measure was the proportion of infants infected in the intrapartum and early postpartum periods, excluding the antepartum period. Intrapartum and early postpartum transmission, if not specifically described, was calculated for each study by subtracting the number of HIV-infected infants at 1–3 days of age from the total number of infants with HIV infection at 6–8 weeks of age. We used the same denominator as the number of infants uninfected at the end of 3 days of age unless otherwise specified (that is, we made no allowance for infants lost to follow-up from 3 days to 6–8 weeks of age unless specified in the report). Other secondary outcome measures were the proportion of infants infected in the antepartum period as measured by the presence of a positive HIV DNA test at 1–3 days of age and the proportion of infants who developed Grades 3 or 4 adverse events during the trial (serious adverse effects).

Identification of Studies

Search

We used the Cochrane Collaborative Review Group on HIV Infection and AIDS' search strategy for identifying randomized controlled trials and included additional search terms for NVP or ZDV and prevention of

mother-to-child transmission. Searched databases included MEDLINE, AIDSLINE, the Cochrane Controlled Trials Register and EMBASE. Abstracts from the XIV International AIDS Conference (Bangkok, 2004) were hand searched for trials. We supplemented this by searching bibliographies of identified studies, relevant editorials, and review articles. There were no language restrictions.

We examined studies initially identified by database or hand searches for eligibility. We included data from studies that had arms that administered NVP or ZDV but not other antiretrovirals to HIV-infected mothers and HIV-exposed infants.

Data Abstraction

We abstracted data from eligible studies including the country where the trial was conducted, study population, inclusion and exclusion criteria, intervention, timing of outcomes, HIV-related outcomes for infants (HIV infection and HIV-1-free survival), adverse events among mothers and infants, and proportion of infants breast fed. If authors reported data in more than one study, we abstracted data from the most recent article.

Statistical Methods

We recorded the ranges of the outcome variables and the weighted mean average effects of the included trials (without HIVNET 012 results). We compared these primary and secondary outcomes of the included studies with those of the HIVNET 012 trial[1] (1-5). We did not attempt to model interstudy variation, for instance using fixed effects or random effects models.

RESULTS

Nevirapine

Description of Included Studies

We identified five trials in addition to HIVNET 012 (6-12) that had NVP-treatment arms (Table B.1).

Kiarie and colleagues (6) randomized HIV-infected Kenyan women to either the HIVNET 012 intervention or the Thai-Centers for Disease Con-

[1]Results from the HIVNET 012 study were reported in five articles. For purposes of this review we abstracted data from Jackson (4).

TABLE B.1 Description and Outcomes of Included Studies (NVP arms only)

Author, Study, and Reference	Study Population Randomized	Study Arms	Infants Infected Antepartum (%)
Kiarie (2003) [6]	HIV-infected pregnant women in Kenya	NVP/NVP v. Thai-CDC	
Moodley (2003) SAINT [7, 8]	HIV-infected pregnant women in South Africa	NVP/NVP v. ZDV+3TC	45/643 (7%)
Taha (2003) NVAZ [9, 10]	Infants born to HIV-infected, untreated mothers in Malawi	NVP v. NVP+ZDV	56/551** (10.2%)
	98/468 (20.9%)		31/554 (5.6%)
Taha (2004) [11]	Infants of HIV-infected, NVP-treated mothers in Malawi	NVP v. NVP+ZDV	36/445 (8.1%)
McIntyre (2004) Trial 1413 [12]	Infants of HIV-infected, NVP-treated mothers in South Africa	NVP v. ZDV+3TC	4/68 (5.9%) (both arms)
Non-HIVNET 012 trials combined			141/1707 (8.3%)
Non-HIVNET 012 trials combined excluding NVAZ [9][a]			86/1156 (7.4%)
Jackson (2003) HIVNET 012 [1-5]	HIV-infected pregnant women in Uganda	NVP/NVP v. ZDV v. placebo	25/308 (8.1%)

NOTES: NVP (nevirapine), ZDV (zidovudine), 3TC (lamivudine); *includes antepartum; **as reported.

trol and Prevention (CDC) regimen (ZDV twice daily from 36 weeks gestation and 3-hourly during labor). The primary outcome of this trial was compliance with antiretroviral regimens. However, data were also reported on rates of transmission; 9% of mothers on the Thai-CDC regimen had transmitted HIV to their infants by the first 6 weeks of life (antepartum, intrapartum, and early postpartum transmission combined) compared to 22% of mothers on the HIVNET 012 regimen. The primary finding of this

Infants Infected Intrapartum and Early Postpartum (%)	Total Infant HIV Infections By 6–8 Weeks (%)	Infant Serious Adverse Events (%)
	12/55 (22%)	—
28/491 (5.7%)	68/496 (13.7%)	60/663 (9.1%)
51/421 (12.1%)**	—	—
23/353 (6.5%)	59/389 (15.2%)	22/448 (4.9%)
1/18 (5.6%)	—	—
103/1283 (8.0%)	242/1488 (16.7%)	113/1665 (6.8%)
52/862 (6.0%)	144/980 (14.7%)	82/1111 (7.4%)
11/283 (3.9%)	36/308 (11.7%)	29/320 (9.1%)

[a]NVAZ study excluded because of no NVP treatment in mothers.

study was that 41% of patients complied with the Thai-CDC ZDV regimen and 87% with the HIVNET 012 regimen ($p<0.001$).

Moodley and colleagues (7, 8) reported on the South African Intrapartum Nevirapine Trial (SAINT), an open-label trial that compared two doses of NVP to the mother at onset of labor and 24–48 hours postpartum plus one dose to the baby at 24–48 hours to a multiple dose intrapartum and 7 days postpartum regimen of zidovudine and lamivudine (3TC), similar to

the regimen that had been evaluated in the Promoting Evaluation, Teaching, and Research on AIDS Project (PETRA) study. The primary outcome of this study was intrapartum and early postpartum transmission. Excluding antepartum transmission, new infections were detected in 5.7% of infants in the NVP group and 3.6% of infants in the zidovudine-lamivudine group at 8 weeks of age.

Taha and colleagues (9, 10) conducted the NVAZ trial in Malawi and compared single-dose NVP alone to twice-daily zidovudine for 1 week plus single-dose NVP among HIV-exposed infants. In this trial mothers presented late in labor, were untreated at the time of delivery, and were diagnosed in the postpartum period, and thus there was no maternal dose of NVP. The primary outcome was HIV infection at 6–8 weeks of age. At 6–8 weeks of age among babies who were HIV-uninfected at birth, 7.7% who had received NVP plus zidovudine were infected compared to 12.1% of those who had received NVP alone (p=0.03).

Taha and colleagues (9, 11) also conducted a second trial in Malawi that randomized infants of HIV-infected, NVP-treated mothers to receive NVP or NVP plus zidovudine, the same regimens tested in the NVAZ trial. The primary outcome was postpartum HIV transmission. Among infants uninfected at birth, transmission was 6.5% in those who received NVP alone and 6.9% among those who had received NVP and zidovudine (p=0.88).

In a separate publication, spanning both the NVAZ trial and the second trial conducted in NVP-treated mothers, Taha and colleagues reviewed hepatic and hematologic toxicity data (10), comparing the four arms of the two trials plus an unexposed and untreated control group. At 6 weeks of age geometric mean serum alanine aminotransferase levels were significantly higher among the treated groups (16.2–19.1 U/L) than in controls (11.5 U/L). Similarly hematologic parameters (hemoglobin, hematocrit, granulocytes, and platelets) were significantly lower among the treated groups than controls at 6 weeks of age, consistent with Grade 1 (mild) toxicity.

McIntyre and colleagues (12) reported preliminary data from Trial 1413 in South Africa that compared standard maternal-infant NVP with NVP plus two regimens of a fixed-dose zidovudine-lamivudine combination given to infants for 4 or 7 days. The primary endpoint of this study is antiretroviral resistance, and this abstract reported 50% resistance to nonnucleoside reverse transcriptase inhibitors at 2 and 6 weeks in infants in the NVP-alone arm compared to 5% in the NVP plus 4-day zidovudine-lamivudine regimen and 13% in the 7-day regimen. Data on risk of transmission were also reported. Four of 68 infants had intrauterine transmission; one of 18 infants in the NVP-alone arm was infected in the intrapartum or early postpartum periods.

Outcomes

The proportion of infants in the NVP arm infected with HIV in HIVNET 012 was 8.1% at birth, 11.7% at 6–8 weeks, 13.3% at 14–16 weeks, 14.9% at 12 months, and 15.3% at 18 months of age (4).

Antepartum transmission. Four of the other trials (8, 10, 11, 12) reported the proportion of infants infected immediately following birth. Overall, 141 (8.3%, range 5.9–10.2%) of the 1,707 infants in these studies were infected in the antepartum period, and this was consistent with the 8.1% reported by HIVNET 012.

Antepartum, intrapartum, and early postpartum transmission. Four of the other trials (6, 7, 8, 9, 11) reported the total proportion of infants infected at approximately 6 weeks of age. Overall, 242 (16.7%, range 13.7–22%) of the 1,488 infants in these studies were infected by approximately 6 weeks of age, while in HIVNET 012 11.7% were infected.

Intrapartum and early postpartum transmission. In HIVNET 012 the proportion of infants uninfected at birth that became infected during the intrapartum plus early postpartum period as measured at 6–8 weeks of age was 3.9%. Four other studies (8, 9, 11, 12) contributed data on this outcome. Overall in these four studies, 103 (8.0%, range 5.6–12.1%) of 1,283 initially uninfected infants were infected by 6–8 weeks of age. This was higher than the rate of 3.9% observed in HIVNET 012. However, excluding the NVAZ trial in which HIV-infected mothers did not receive a dose of NVP, which presumably would have contributed to a decrease in intrapartum transmission, 52 (6.0%, range 5.6%–6.5%) of 862 infants were infected in the three remaining studies during this period. This proportion was not significantly different from the proportion observed in HIVNET 012 (Odds Ratio [OR], 0.61, 95% confidence interval, 0.32–1.18).

Serious adverse events. HIVNET 012 and three other studies (7, 9, 10, 11) reported detailed information on serious adverse events among infants receiving NVP. In HIVNET 012, 29 (9.1%) of 320 infants had experienced Grades 3 or 4 events by 6–8 weeks of age. In the other three studies, overall 113 (6.8%, range 4.9–9.1%) of 1,665 had experienced Grades 3 or 4 events by this age. There was no difference between the rates of these adverse events between HIVNET 012 and other studies combined (OR, 1.37, 95% confidence interval, 0.89–2.10). Removal of the NVAZ trial made no difference.

Description of Excluded Studies

Three randomized controlled trials were excluded because they either combined NVP with other antiretrovirals (13-18) or included multiple doses of NVP postnatally (19) (see Table B.2).

Zidovudine

Description of Included Studies

We identified five trials that had ZDV-treatment arms similar, but not identical, to HIVNET 012. In HIVNET 012 there was no antepartum treatment with ZDV; 600 mg was given at the onset of labor and 300 mg every 3 hours during labor. The neonatal dose was 4 mg/kg twice daily for 7 days. There were no other studies that we could identify that used this exact dosing regimen.

Dabis and colleagues (20) randomized 431 HIV-infected pregnant women in Côte d'Ivoire and Burkina Faso to a regimen of 300 mg orally twice daily beginning at enrollment, 600 mg ZDV orally at onset of labor, and 300 mg orally twice daily for 7 days after delivery. There was no treatment given to the newborn. The Kaplan-Meier probability of HIV infection in the infant at 6 months was 18.0% in the ZDV group and 27.5% in the placebo group (p=0.027).

Kiarie and colleagues (6) randomized HIV-infected Kenyan women to either the HIVNET 012 intervention or the Thai-CDC regimen (ZDV twice daily from 36 weeks gestation and every 3 hours during labor). The primary outcome of this trial was compliance with antiretroviral regimens. However, data were also reported on rates of transmission; 9% of mothers on the Thai-CDC regimen had transmitted HIV to their infants by the first 6 weeks of life (antepartum, intrapartum, and early postpartum transmission combined), compared to 22% of mothers on the HIVNET 012 regimen. The primary finding of this study was that 41% of patients complied with the Thai-CDC ZDV regimen and 87% with the HIVNET 012 regimen (p<0.001).

Lallemant and colleagues (21) studied 1,437 HIV-infected Thai women and randomized them into four ZDV-treatment arms. The first arm began 300 mg of ZDV orally twice daily at 28 weeks gestation with 6 weeks of ZDV, 2 mg/kg every 6 hours, in the infant (long-long); this was equivalent to the Pediatric AIDS Clinical Trials Group (PACTG) 076 trial regimen. The second arm started treatment at 35 weeks gestation with 3 days of treatment in the infant (short-short). The other two arms' regimens were the long course in the mother and the short course in the infant (long-short) and the short course in the mother and long course in the infant (short-

TABLE B.2 Excluded Studies (NVP arms)

Author, Study, and Reference	Study Population Randomized	Study Arms	Reason for Exclusion	Infant Serious Adverse Events (%)
Dorenbaum (2002) [13-16]	HIV-infected pregnant women receiving standard antiretroviral therapy in U.S., Europe, Brazil, Bahamas	Maternal NVP/infant NVP v. placebo/placebo	Combination antiretroviral regimens	237/714 (33%)
Lallemant (2004) PHPT [17, 18]	HIV-infected pregnant women receiving ZDV in Thailand; infants received 1 week of ZDV and were formula fed	Maternal NVP/infant NVP v. NVP/placebo v. placebo/placebo	Combination antiretroviral regimens	Not specifically reported (no significant difference among groups)
Shetty (2003) HIVNET-023 [19]	Breast-feeding infants of HIV-infected pregnant women in South Africa and Zimbabwe	NVP daily v. NVP twice weekly v. NVP weekly for 24 weeks	Multiple NVP doses to infant	Not specifically reported (no serious adverse events related to study drug)

NOTES: NVP (nevirapine), ZDV (zidovudine).

TABLE B.3 Description and Outcomes of Included Studies (ZDV arms only)

Author, Study and Reference	Study Population Randomized	Study Arms
Dabis (1999) [20]	HIV-infected pregnant women in Côte d'Ivoire and Burkina Faso	Ante-, intra-, and postpartum ZDV v. placebo
Kiarie (2003) [6]	HIV-infected pregnant women ≤35 weeks gestation in Nairobi	ZDV v. antepartum and intrapartum NVP
Lallemant (2000) [21]	HIV-infected pregnant women in Thailand	4 ante-, intra-, and postpartum ZDV regimens: long-long, short-short, long-short, short-long
Shaffer (1999) [22]	HIV-infected pregnant women in Thailand	Ante- and intrapartum ZDV vs. placebo
Wiktor (1999) [23]	HIV-infected pregnant women in Côte d'Ivoire	Ante- and intrapartum ZDV vs. placebo
Non-HIVNET 012 trials combined		
Non-HIVNET 012 trials combined excluding [22]		
Jackson (2003) HIVNET 012 [1-5]	HIV-infected pregnant women in Uganda	NVP/NVP v. ZDV v. placebo

NOTES: NVP (nevirapine), ZDV (zidovudine).

long). All mothers received of 300 mg zidovudine orally (or intravenously if not tolerated orally) at the start of labor and every 3 hours. All infants were formula fed. At the first interim analysis, the short-short arm was suspended, and the trial was redesigned as an equivalency trial to compare the long-long regimen with the two remaining arms. Transmission rates were 6.5% for the long-long regimen, 4.7% for the long-short regimen, and 8.6% for the short-long regimen. However, higher rates of antepartum transmission were observed with the short-long regimen. Transmission rates in the short-short arm, the regimen closest to the HIVNET 012 ZDV arm, were estimated to be 10.5% at 6 months by Kaplan-Meier analysis.

Infants Infected Antepartum (%)	Infants Infected Intrapartum and Early Postpartum (%)	Total at 6–8 Weeks
5/182 (2.6%)	23/177 (13%)	28/155 (18.1%)
—	—	5/55 (9%)
24/229 (10.5%) at 6 months in short-short arm	—	—
9/188 (4.8%)	9/173 (5.2%)	18/188 (9.6%)
6/123 (4.9%)	9/117 (7.7%)	15/122 (12.3%)
20/503 (4.0%)	41/482 (8.5%)	66/520 (12.7%)
—	32/294 (10.9%)	48/332 (14.5%)
31/302 (10.3%)	28/271 (10.3%)	59/302 (19.5%)

Shaffer and colleagues (22) randomized 397 Thai women to placebo or 300 mg of zidovudine twice daily from 36 weeks gestation and every 3 hours during labor. Infants were not treated and were not breastfed. Estimated transmission rates at 6 months were 9.4% in the zidovudine group and 18.9% in the placebo group (p=0.006).

Wiktor and colleagues (23) studied a regimen identical to the one used by Shaffer and colleagues but in a breast-feeding population in Côte d'Ivoire. Estimated transmission rates at 3 months were 15.7% in the zidovudine group and 24.9% in the placebo group (p=0.07).

Outcomes

The proportion of infants in the zidovudine arm infected with HIV in HIVNET 012 was 10.3% at birth, 19.5% at 6–8 weeks, 21.5% at 14–16 weeks, 23.2% at 12 months, and 24.8% at 18 months of age (4).

Antepartum transmission. All identified trials treated mothers in the antepartum period starting at approximately 36 weeks, and there is no basis for comparing the HIVNET 012 regimen, which started treatment at the onset of labor. As expected, the antepartum transmission rate in HIVNET 012 was 10.3%, substantially higher than the 4.0% observed in the three trials that reported HIV infection rates at days 1–3 (20, 22, 23).

Antepartum, intrapartum, and early postpartum transmission. Four trials reported total transmission rates at approximately 6 weeks. Overall, 66 (12.7%, range 9–18.1%) of 520 infants were infected at 6–8 weeks of age. This compares with 59/302 (19.5%) of infants in the HIVNET 012 ZDV. Because all these trials included antepartum treatment of the mother, which presumably results in lower risk of transmission in comparison to mothers treated only in the intrapartum period as in HIVNET 012, we also calculated the proportion of infants uninfected at birth who developed HIV infection as the result of exposure during the intrapartum and early postpartum periods.

Intrapartum and early postpartum transmission. Three trials (20, 22, 23) also reported rates of transmission during the intrapartum and early postpartum periods. One of these trials (22) was conducted in a non-breastfeeding population in Thailand and may not be directly comparable. Also, one African trial (23) reported data at 4 weeks, rather than the 6–8 weeks in HIVNET 012 and the other two trials. Nonetheless, the rates reported in these three trials averaged 8.5% and ranged from 5.2–13%. Excluding the study conducted in Thailand, the two remaining trials ranged from 7.7–13% and averaged 10.9%. The comparable proportion of uninfected infants who were infected by 6–8 weeks in the HIVNET 012 trials was 10.3%.

Description of Excluded Studies

We excluded three studies because the duration and intensity of their antepartum and postpartum zidovudine treatment regimens were substantially dissimilar to HIVNET 012 (18, 24, 25) and one study (11) because it did not contain a ZDV-only arm (Table B.4).

TABLE B.4 Excluded Studies (ZDV-only arms)

Author, Study and Reference	Study Population Randomized	Study Arms	Reason for Exclusion
Bordeguez (2003) [24]	PACTG 288—HIV-infected pregnant women in U.S. and France 14–34 weeks	Ante-, intra-, and postpartum ZDV vs. placebo	Follow-on study of Connor [25], infant outcomes not reported
Connor (1994) [25]	PACTG 076—HIV-infected pregnant women in U.S. and France at 14–34 weeks	Ante-, intra-, and postpartum ZDV vs. placebo	Ante- and postpartum ZDV regimens not similar to HIVNET 012
Lallemant [18,19]	Pregnant HIV-infected women treated with ZDV beginning at 28 weeks	Three arms: mother receives NVP and infant receives placebo, both get NVP, both get placebo. All infants treated with ZDV for 7 days.	Antepartum ZDV regimen not similar to HIVNET 012
Taha (2004) [11]	Malawi HIV-infected pregnant women receiving NVP	NVP plus ZDV vs. NVP plus placebo	No ZDV-only arm

NOTES: NVP (nevirapine), ZDV (zidovudine).

DISCUSSION

Five randomized controlled trials included single-dose NVP-only arms for prevention of mother-to-child transmission of HIV. The proportions of infants infected in the antepartum period were similar between HIVNET 012 and the other studies. The review also showed that Grades 3 and 4 adverse events among infants were similar between HIVNET 012 and the other studies.

Rates of transmission in the intrapartum and immediate postpartum periods were lower in HIVNET 012 (3.9%) compared to the other five studies that reported this variable (8.0%). However, after excluding the NVAZ study, in which mothers were not treated with NVP, this proportion

was lower (6.0%) and thus more similar to the HIVNET 012 results. The NVAZ study was a Malawi study that randomized infants of women who presented in late stages of labor with unknown HIV status and did not receive NVP. The newborns were randomized to receive one dose of NVP or one dose of NVP plus a week of ZDV. The investigators subsequently analyzed the subset of infants born to mothers who were found to be infected with HIV. Since the mothers did not receive NVP, the infants were likely less protected against intrapartum transmission than those whose mothers did receive NVP. Hence, the intrapartum plus early postpartum transmission rates from this study are not directly comparable to those of HIVNET 012 or the other four studies. The ZDV-only arm of the HIVNET 012 trial was less directly comparable to other randomized controlled trials for prevention of mother-to-child transmission (MTCT) that included ZDV.

Of the five trials we analyzed, all had employed antepartum treatment with ZDV, which was not part of the HIVNET 012 ZDV arm. Previous studies have suggested that the duration of antenatal treatment with ZDV is a strong predictor of prevention of antepartum transmission (22). However, when excluding transmission during the antepartum period (as measured by infant infection at 1–3 days of age), the rate of intrapartum and early postpartum transmission found in the two studies conducted in breast-feeding populations (10.5%) was similar to that found in HIVNET 012 (10.3%). These findings suggest that the findings in both arms of the HIVNET 012 trial are consistent with other studies that have used similar interventions, although over much shorter time periods.

Other experimental trials that combined maternal and neonatal NVP with either ongoing highly active antiretroviral therapy (PACTG 316) (13-16) and ZDV during the third trimester (Perinatal HIV Prevention Trial [PHPT]) (17-18) showed similar or higher rates of serious adverse events. In PACTG 316 there was one Grade 3 rash-toxicity, 235 Grades 3 and 4 non-rash-toxicity, and one hepatic-toxicity (elevated liver transaminases) events from among 714 infants who received NVP (33% overall); this was no different than among infants who received placebo (14). In PHPT there were no significant differences among treatment groups in terms of rashes, elevated alanine aminotransferase levels, presence of hyperbilirubinemia, and rates of serious adverse reactions (18). Additionally HIVNET 023 (19), a trial of three separate regimens of postpartum NVP (daily, twice weekly, and weekly for 24 weeks) in infants of HIV-infected breast-feeding mothers found no severe skin, hepatic, or renal toxicity related to NVP; neutropenia occurred in 8 of 36 infants monitored at the Zimbabwe site. Anemia and thrombocytopenia also occurred in 2 infants each (total hematologic abnormalities 12/36 [33%]). None of the enrolled infants had Grades 3 or 4 elevations in serum alanine transferase levels.

Observational studies have also suggested similar rates of transmission

and adverse events when the HIVNET 012 NVP regimen has been employed. For example, Stringer and colleagues have followed two observational cohort studies of HIV-exposed infants who received single-dose NVP and whose mothers received intrapartum NVP in Zambia (26-27). They found transmission rates of 11.7% at 4–6 weeks (26) and 11.2% at 6–8 weeks of age (27). Other observational studies have been published, which examined the effectiveness of NVP in practice in Kenya (28), South Africa (29), and Cameroon (30). The studies from Kenya and South Africa found higher rates of transmission (13% at 6 weeks, 18.1% at 14 weeks, respectively), while the study from Cameroon found a slightly lower transmission rate of 10.6% at 6–8 weeks. No maternal or infant complications or adverse effects were reported from Cameroon (30).

In conclusion, the findings from both the NVP and ZDV arms from HIVNET 012 appear to be consistent with findings on HIV transmission from other randomized controlled trials that tested similar treatment regimens. Additionally the observed rates of serious adverse events were similar to those observed in randomized controlled trials that tested similar NVP regimens, randomized controlled trials that used NVP plus other antiretrovirals, a randomized postnatal prophylaxis trial (HIVNET 023), and observational studies.

REFERENCES

1. Guay LA, Musoke P, Fleming T, et al. 1999. Intrapartum and neonatal single-dose NVP compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354:795-802.
2. Deseyve M, Duefield C, Musisi M, et al. 2000. The one year safety and efficacy data of the HIVNET 012 trial. XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000 [Abstract LbOr1].
3. Eshleman SH, Mracna M, Guay LA, et al. 2001. Selection and fading of resistance mutations in women and infants receiving NVP to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 15:1951-1957.
4. Jackson JB, Musoke P, Fleming et al. 2003. Intrapartum and neonatal single-dose NVP compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362:859-68.
5. Jackson JB, Musoke P, Fleming T, King S. 2004. Short course NVP was better than zidovudine for reducing the risk of mother to child transmission of HIV-1 infection. *Evidence-Based Medicine* 9:53.
6. Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. 2003. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. *AIDS* 17: 65-71.
7. Moodley D, on behalf of the SAINT Investigators Team. 2000. The SAINT trial: Nevirapine (NVP) versus zidovudine (ZDV) + lamivudine (3TC) in prevention of peripartum HIV transmission. XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000 [Abstract LbOr2].

8. Moodley D, Moodley J, Coovadia H, et al. 2003. A multicenter randomized controlled trial of NVP versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *Journal of Infectious Diseases* 187:724-735.
9. Taha TE, Kumwenda NI, Gibbons A, et al. 2003. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 362:1171-1177.
10. Taha TE, Kumwenda N, Gibbons A, et al. 2002. Effect of HIV-1 antiretroviral prophylaxis on hepatic and hematological parameters of African infants. *AIDS* 2002; 16:851-858.
11. Taha TE, Kumwenda NI, Hoover DR, et al. 2004. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: A randomized controlled trial. *Journal of the American Medical Association* 292:202-209.
12. McIntyre J, Martinson N, Investigators for the Trial 1413, et al. 2004. Addition of short course combivir (CBV) to single dose viramune (sdNVP) for prevention of mother to child transmission (MTCT) of HIV-1 can significantly decrease the subsequent development of maternal NNRTI-resistant virus. XV International AIDS Conference, Bangkok, Thailand, 12-18 July 2004 [Abstract LbOrB09].
13. Cunningham CK, Chaix ML, Rekacewicz C, et al. 2002. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum NVP to prevent perinatal human immunodeficiency virus type 1 transmission: A substudy of pediatric AIDS clinical trials group protocol 316. *Journal of Infectious Diseases* 186:181-186.
14. Dorenbaum A, Cunningham CK, Gelber RD, et al. 2002. Two-dose intrapartum/newborn NVP and standard antiretroviral therapy to reduce perinatal HIV transmission: A randomized trial. *Journal of the American Medical Association* 288:189-198.
15. Dransfield K, Dorenbum-Kracer A, Sullivan J, et al. 1998. Antiretroviral use in pregnancy in PACTG 316: A phase III randomized, blinded study of single-dose intrapartum/neonatal NVP to reduce mother to infant HIV transmission. XII International AIDS Conference, Geneva, Switzerland, 28 June-3 July 1998 [Abstract no. 23281]: 397.
16. Fiore S, Thorne C, Newell ML. 2003. European participation in an international perinatal trial. *Medycyna wieku rozwojowego* 7 (4 Pt 1):449-458.
17. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. 2004. Intrapartum exposure to NVP and subsequent maternal responses to NVP-based antiretroviral therapy. *New England Journal of Medicine* 351:229-240.
18. Lallemant M, Jourdain G, Le Coeur S, et al. 2004. Single-dose perinatal NVP plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *New England Journal of Medicine* 35:2172-228.
19. Shetty AK, Coovadia HM, Mirochnick MM, et al. 2003. Safety and trough concentrations of NVP prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *Journal of Acquired Immune Deficiency Syndromes* 34: 482-490.
20. Dabis F, Msellati P, Meda N, et al. 1999. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: A double-blind placebo-controlled mullticentre trial. *Lancet* 353:786-792.
21. Lallemant M, Jourdain G, Le Coeur S, et al. 2000. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *New England Journal of Medicine* 343:982-991.

22. Shaffer N, Chuachoowong R, Mock PA, et al. 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial. *Lancet* 353: 773-780.
23. Wiktor SZ, Ekpini E, Karon JM, et al. 1999. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: A randomised trial. *Lancet* 353:781-785.
24. Bardeguez A, Shapiro DE, Mofenson LM, et al. 2003. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *Journal of Acquired Immune Deficiency Syndromes* 32:179-181.
25. Connor EM, Sperling RS, Gelber R, et al. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 331:1173-1180.
26. Stringer JSA, Sinkala M, Goldenberg RL, et al. 2004. Universal NVP upon presentation in labor to prevent mother-to-child transmission in high prevalence settings. *AIDS* 18:939-943.
27. Stringer JSA, Sinkala M, Chapman V, et al. 2003. Timing of the maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single-dose NVP. *AIDS* 17:1659-1665.
28. Quaghebeur A, Mutunga L, Mwanyumba F, et al. 2004. Low efficacy of NVP (HIVNET 012) in preventing perinatal HIV-1 transmission in a real-life situation. *AIDS* 18: 1854-1856.
29. Sherman GG, Jones SA, Coovadia AH, Urban MF, Bolton KD. 2004. PMTCT from research to reality—results from a routine service. *South African Medical Journal* 94: 289-292.
30. Ayouba A, Tene G, Cunin P, et al. 2003. Low rate of mother-to-child transmission of HIV-1 after NVP in a pilot public health program in Yaoundé, Cameroon. *Journal of Acquired Immune Deficiency Syndromes* 34:274-280.

Appendix C

Committee Biographies

James H. Ware, Ph.D. (*Committee Chair*) is Dean for Academic Affairs and Frederick Mosteller Professor of Biostatistics at the Harvard School of Public Health. His research focuses on methods for the analysis of longitudinal and environmental data, and on the application of biostatistics to environmental epidemiology and clinical research. Dr. Ware recently served as the Director of the Data Coordinating Center for the Treatment of Lead Exposed Children Trial. This trial, sponsored by the National Institute of Environmental Health Sciences, investigated the effects of chelation to lower blood lead levels in children with high blood lead levels on subsequent cognitive development. Dr. Ware is a statistical consultant to the *New England Journal of Medicine*, teaches courses on clinical trials and analysis of longitudinal data, and writes occasional papers on statistical issues in clinical research. He previously served on the Institute of Medicine (IOM) Committee to Review the Health Consequences of Service During the Persian Gulf War and on the National Research Council (NRC) Panel on Statistics for an Aging Population.

R. Alta Charo, J.D., is the Associate Dean for Research and Faculty Development at the University of Wisconsin (UW) Law School, and is the Elizabeth S. Wilson-Bascom Professor of Law and Bioethics on the faculties of both the Law School and the Medical School's Department of Medical History and Bioethics. In addition, she has served on the UW Hospital clinical ethics committee, the UW Institutional Review Board for the pro-

tection of human subjects in medical research, and the UW Bioethics Advisory Committee. Professor Charo is the author of over 75 articles, book chapters, and government reports on topics including voting rights, environmental law, family planning and abortion law, medical genetics law, reproductive technology policy, and science policy and ethics. Professor Charo is a member of the board of the Alan Guttmacher Institute and the Foundation for Genetic Medicine, a member of the National Medical Advisory Committee of the Planned Parenthood Federation of America, and has been on the boards of the Society for the Advancement of Women's Health Research and the American Association of Bioethics. She serves on several expert advisory boards of organizations with an interest in stem cell research and is a consultant to the California Institute for Regenerative Medicine. She has served as a consultant to the Institute of Medicine and the National Institutes of Health (NIH) Office of Protection from Research Risks. In 1994 Professor Charo served on the NIH Human Embryo Research Panel, and from 1996-2001, she was a member of the presidential National Bioethics Advisory Commission, where she participated in drafting its reports on topics such as human cloning, stem cell research, and ethical and policy issues relating to clinical trials in developing countries. Since 2001 she has been a member of the National Academy of Sciences' Board on Life Sciences and serves as its liaison to its committee to develop national voluntary guidelines for stem cell research. She also served as a member of the Institute of Medicine's Committee on Smallpox Vaccination Program Implementation.

Ezra C. Davidson, Jr., M.D., is Associate Dean, Primary Care and Professor (past chairman 1971–1996) of the Department of Obstetrics and Gynecology at the Charles R. Drew University of Medicine and Science. He is Professor of Obstetrics and Gynecology at the David Geffen School of Medicine, University of California, Los Angeles. He was Chief-of-Service, Department of Obstetrics and Gynecology, at the King/Drew Medical Center in Los Angeles (1991–1996). He was a Robert Wood Johnson Health Policy Fellow at the Institute of Medicine (1979-1980) and has served on a number of Institute of Medicine committees including the Committee on Perinatal Transmission of HIV. He served as the President of the American College of Obstetricians and Gynecologists and its National Secretary for 6 years. His other major organizational responsibilities have included Chair of the Board of Trustees of the National Medical Association, President of the North American Society of Pediatric and Adolescent Gynecology, and President of the Association of Professors of Gynecology and Obstetrics. He has chaired the Secretary's Advisory Committee on Infant Mortality (U.S. Department of Health and Human Services) and the Advisory Committee for Reproductive Health Drugs of the U.S. Food and Drug Adminis-

tration (FDA). He served on the National Institutes of Health Advisory Committee to the Director and the Advisory Committee on Clinical Research. He was a member of the Council on Graduate Medical Education and Past Chair of the Board of Directors for the California Wellness Foundation. He is Chair of the Board of Trustees of the Blue Shield of California Foundation and Immediate Past President of the Association of Academic Minority Physicians. He has been elected to the National Black College Alumni Hall of Fame, Fellowship ad eundem, Royal College of Obstetricians and Gynecologists, and the Institute of Medicine.

Wafaa El-Sadr, M.D., M.P.H., M.P.A., is Professor of Clinical Medicine and Epidemiology, Mailman School of Public Health, Columbia University, and Chief of the Division of Infectious Diseases at Harlem Hospital Center. Dr. El-Sadr has led the Division of Infectious Diseases at Harlem Hospital since 1988 and was instrumental in the development of an acclaimed comprehensive HIV program at that institution. She developed HIV care programs that were specifically designed to meet the needs of patients from the Harlem community, including women and substance users with HIV/AIDS. She is the Director of the Center for Infectious Diseases Epidemiologic Research and the International Center for AIDS Care and Treatment Programs (ICAP) at the Mailman School of Public Health. She has been involved in the design and conduct of HIV and tuberculosis (TB) research studies domestically and internationally for many years. She established the Harlem AIDS Treatment Group in 1989, one of the Units of the Community Programs for Clinical Research on AIDS (CPCRA), and serves as its principal investigator. She has played various leadership roles in that network, most recently as the Co-Chair of its Steering Committee. She led efforts in the design and implementation of several CPCRA-supported clinical trials. She currently co-chairs the SMART study, one of the largest clinical trials in HIV therapeutics. Dr. El-Sadr is also the principal investigator of the New York Unit of the HIV Prevention Trials Network. In terms of tuberculosis research, Dr. El-Sadr has played a similar leadership role. She is principal investigator of the Harlem Unit of the Centers for Disease Control and Prevention (CDC)-funded Tuberculosis Clinical Trials Consortium (TBTC) and the Tuberculosis Epidemiologic Studies (TBES) Network. She is also a member of the Core Science Group for the TBTC. Dr. El-Sadr, as Director of the International Center for AIDS Care and Treatment Programs, has successfully led efforts to establish HIV care and treatment programs in 10 resource-limited countries (primarily in sub-Saharan Africa) around the world through support by foundations, CDC, and U.S. Agency for International Development (USAID). She serves as a member of the Department of Health and Human Services (DHHS)-supported Panel on Guidelines for Use of Antiretroviral Drugs in Adults and Adolescents.

She obtained her M.D. from Cairo University, an MPH (Epidemiology) from the Columbia University Mailman School of Public Health, and an MPA from the Kennedy School for Government at Harvard University.

Mark W. Kline, M.D., is Professor of Pediatrics, Chief of Retrovirology, Director of the AIDS International Training and Research Program, and Director of the Baylor-CDC Global AIDS Project, all at the Baylor College of Medicine and Texas Children's Hospital in Houston. Dr. Kline has extensive experience in pediatric HIV/AIDS care and treatment, health professional training, and clinical research in the United States, Africa, and Eastern Europe. He is the author of more than 200 scientific papers and textbook chapters. Dr. Kline is board-certified in pediatrics and infectious diseases. He has served on the Executive Committee for Infectious Diseases of the American Academy of Pediatrics, and is immediate past-Chair of that organization's Committee on Pediatric AIDS. He is a Fellow of the Infectious Diseases Society of America and a member of the Society for Pediatric Research and the American Pediatric Society.

Stephen W. Lagakos, Ph.D., is Henry Pickering Walcott Professor of Biostatistics and Chair of the Department of Biostatistics at Harvard School of Public Health. Dr. Lagakos is also currently Director of Harvard's Center for Biostatistics in AIDS Research. Dr. Lagakos' research interests involve a variety of statistical issues arising in clinical trials and other longitudinal studies, with particular emphasis on statistical methods and analyses relating to HIV and other infectious diseases. Dr. Lagakos is a member of the Institute of Medicine and has served on several committees including the Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy and the Roundtable for the Development of Drugs and Vaccines Against AIDS and is currently serving on the Committee on Postmarket Surveillance of Pediatric Medical Devices. He received his Ph.D. from The George Washington University.

J. Richard Landis, Ph.D., is Professor of Biostatistics in the School of Medicine, and holds a secondary appointment as Professor of Statistics in the Wharton School, within the University of Pennsylvania. He serves as Director of the Division of Biostatistics, and Vice-Chair of the Department of Biostatistics and Epidemiology, as well as Director of the Biostatistics Unit within the Center for Clinical Epidemiology and Biostatistics (CCEB), a multidisciplinary research center within the School of Medicine. Dr. Landis also serves as Co-Director of the Clinical Research Computing Unit (CRCU), a designated core research facility formed within the CCEB to support the conduct of multicenter clinical trials and patient-oriented clinical research projects. Dr. Landis is a Fellow of the American Statistical

Association, elected member of the International Statistical Institute, recipient of the Mortimer Spiegelman Gold Medal Award, and recipient of an Environmental Protection Agency Scientific and Technical Achievement Award. He previously served on the IOM Committee for Assessment of Centers of Excellence Programs at NIH. Dr. Landis received his Ph.D. in Biostatistics from the University of North Carolina at Chapel Hill in 1975, and served on the biostatistics faculty at the University of Michigan for 13 years, and at the Pennsylvania State University for 9 years, prior to moving to the University of Pennsylvania in 1997.

George W. Rutherford III, M.D., is Salvatore Pablo Lucia Professor of Preventive Medicine, Professor-in-Residence of Epidemiology, Preventive Medicine, Pediatrics and Family and Community Medicine, Head of the Division of Preventive Medicine and Public Health, and Director of the Institute for Global Health at the University of California, San Francisco School of Medicine. He is also Adjunct Professor of Epidemiology and Health Administration at the School of Public Health at the University of California, Berkeley. Dr. Rutherford is a leading expert on the epidemiology of AIDS and HIV infection and the public health aspects of the AIDS epidemic. He served as State Health Officer and State Epidemiologist for the California Department of Health Services from 1990–1995. He also formerly served as the Director of the AIDS Office in the San Francisco Department of Public Health in the 1980s and as Director of the Division of Immunizations for the New York City Department of Public Health. His principal research interests are the natural history of HIV infection and the epidemiology and prevention of AIDS and HIV infection in California and Latin America. He is the Coordinating Editor for the Cochrane Collaborative Review Group on AIDS and HIV Infection, an international effort to systematically review intervention trials in the treatment and prevention of AIDS and HIV infection. He is the former Chair of the Department of Veterans Affairs' National Research Advisory Council. He served on the Institute of Medicine Committee on the Ryan White CARE Act: Data for Resource Allocation, Planning, and Evaluation, and currently serves on the Committee on Gulf War and Health: Review of the Medical Literature Relative to Gulf War Veterans' Health. Dr. Rutherford received his M.D. from Duke University.

Charles M. van der Horst, M.D., is Professor of Medicine and Associate Chief, Division of Infectious Diseases, in the School of Medicine at the University of North Carolina-Chapel Hill (UNC). He is the Developmental Core Director for the UNC Center for AIDS Research. He is also a Visiting Professor at University of the Witwatersrand in Johannesburg, South Africa. Dr. van der Horst's interests include the treatment of HIV/AIDS in

resource-poor settings, prevention of mother-to-child transmission during breast feeding, as well as use of weaning foods and nutrition of pregnant mothers. Dr. van der Horst has been providing care for HIV/AIDS patients since 1981. He has conducted research and published extensively on the treatment of HIV and opportunistic infections since 1986. He has conducted HIV clinical trials both domestically and in Africa for 20 years. He received his M.D. from Harvard Medical School.