Five Critical Statements on the Safety and Efficacy of Nevirapine for Mother-to-Child Transmission Prevention
24 March 2002

Here are five statements that affirm the safety and efficacy of Nevirapine for the prevention of mother-to-child transmission:

1. World Health Organisation (WHO) / UNAIDS Joint Press Statement

2. National Institute of Allergy and Infectious Diseases (NIAID) Statement (NIAID is a division of the NIH)

3. Centre for Disease Control Questions and Answers about NIAID Statement

4. Elizabeth Glaser Foundation Memo, Statement and Questions and Answers about Mother-to-Child Transmission Prevention and Nevirapine

5. Boehringer Ingelheim Statement about HIVNET 012 Trial

1. Joint WHO/UNAIDS Press Statement:

"WHO and UNAIDS continue to support use of Nevirapine for prevention of MTCT"

Geneva, 22 March 2002 - The statement released today by the United States National Institute of Health (NIH) concerning some reporting and documentation irregularities in clinical trial HIVNET012 does not warrant any change in the recommendations issued following a WHO technical consultaton on mother-to-child HIV transmission in October 2000.

This expert group, convened by WHO on behalf of UNICEF, UNFPA and the UNAIDS Secretariat, concluded that the safety and effectiveness of antiretroviral regimens, including Nevirapine, in preventing mother-to-child HIV transmission, has been clearly documented and that the use of these regimens is therefore warranted for preventing mother-to-child HIV transmission.

The simplest regimen requires a single dose of Nevirapine to the mother at delivery and a single dose to the newborn within 72 hours of birth. The NIH statement emphasised that, according to available information, there has been no evidence the scientific data from the HIVNET012 study demonstrating the safety and effectiveness of Nevirapine is invalid. Each year, more than 600 000 infants become infected with HIV, mainly through mother-to-child transmission. The WHO and the UNAIDS Secretariat recommend that the prevention of

mother-to-child transmission of HIV, including antiretroviral regimens such as Nevirapine, should be included in the minimum standard package of care for HIV-positive women and their children. We are aware of no information that would cause the WHO and UNAIDS to change its recommendations.

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2. Statement by National Institute of Allergy and Infectious Diseases: National Institutes of Health (NIH)

March 22, 2002

Review of HIVNET 012 (A Clinical 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)

Since 1997, funding from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), has supported a trial known as HIVNET 012, conducted by co-investigators at Makerere University in Kampala, Uganda, and the Johns Hopkins University in Baltimore, Maryland. The trial was designed to examine the effectiveness of Nevirapine (NVP) in blocking transmission of HIV from a mother to her newborn baby by treating the mother and baby at the time of birth.

NVP is approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV infection in adults and children. Enrolment in HIVNET012 was completed in 1999. The results, published in The Lancet in 1999, concluded that NVP significantly reduced the risk of HIV transmission from mother to child during the first week of life. Other studies conducted in the United States and internationally were consistent with the results from HIVNET 012. Based on the data from these studies, a U.S. Public Health Service Task Force currently recommends NVP as an option for prevention of mother-to-child transmission (MTCT) for women and their newborns in the United States who have not received antiretroviral therapy during pregnancy.

An examination of the data to support an extension of the indication for the use of NVP to include prevention of MTCT was recently begun. Although no evidence has been found that the conclusions of HIVNET 012 are invalid or that any trial participants were placed at an increased risk of harm, certain aspects of the collection of the primary data may not conform to FDA regulatory requirements. A comprehensive effort to access the primary data has begun to determine the applicability of the data collection processes to these regulatory requirements.

The reduction in perinatal transmission by the use of NVP, an accessible, inexpensive regimen, represents a major public health advance in resource-poor settings and NIAID believes there is no reason for programmes implementing this life-saving regimen to change their practices.

NIAID is committed to ensuring the highest standards of patient safety, investigator conduct and accountability, and regulatory co-operation in all clinical trials carried out in the United States and abroad. NIAID is a component of the NIH. NIAID supports basic and applied research to prevent, diagnose and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, HIV, mainly through illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

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3. Centre for Disease Control Media Questions and Answers – Response to HIAID Statement on HIVNET 012 March 21, 2002

What is your reaction to the NIAID statement regarding the problems with HIVNET012?

Based on the press statement, the NIAID preliminary review revealed no evidence that the scientific data produced during the study is invalid or that trial participants were placed at increased risk of harm. The reduction of perinatal transmission by an accessible, inexpensive regimen represents a major public health advance in resource poor settings, and CDC believes that there is no reason for other programmes implementing this life-saving regimen to change their practice. In addition to the HIVNET 012 trial, several other trials have evaluated the safety and/or efficacy of single dose NVP for peri-natal HIV prevention, and it has been demonstrated to be both safe and effective.

Does this change recommendations for the U.S. of NVP for peri-natal prevention in the U.S?

No, at this point, based on the information we have, the NIAID review has identified no problems that would warrant a change in the PHS Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the U.S. (www.hivatis.org)." Because HIV-infected women present at varying times during pregnancy, with varying levels of prenatal care and previous antiretroviral treatment, these guidelines present multiple clinical scenarios. For HIV-infected women who do not present for care until they are in labour and who have had no prior antiretroviral therapy, one of the recommended treatment regimens is the single dose NVP regimen for themselves and their babies. It will of course be important for NIAID to complete their review. If any problems are identified regarding the single-dose NVP regimen for prevention of mother-to-child HIV transmission, the USPHS peri-natal task force will review the data and current recommendations. Additionally, both domestic and international mother-to-child prevention programmes would be reviewed for appropriate guidance. At present, the benefit of NVP in preventing mother-to-infant HIV transmission has been clearly documented and available data indicate that this is a safe, inexpensive and effective regimen. Therefore, CDC continues to support NVP as one of four options for reducing peri-natal HIV transmission among women who learn of their HIV-infection late in the course of pregnancy or during labour.

Does this change the recommendations for use of NVP for peri-natal HIV prevention in the developing world?

WHO and UNAIDS are the agencies responsible for making recommendations for the use of preventive regimens in the developing world. CDC and NIH provide technical consultation as they develop their guidelines, but questions regarding any changes in recommendations should be directed to them. At present, UNAIDS and WHO, based on a review of safety and efficacy data from several large clinical trials, have concluded that single-dose NVP for the mother and the infant is safe and effective for the prevention of peri-natal HIV transmission and do recommend its use in the developing world.

Will CDC continue to support its use in developing nations?

The reduction of peri-natal HIV transmission by an accessible, inexpensive regimen represents a major public health advance in resource poor settings and there is no reason for programmes implementing this life-saving regimen to change their practice. Both WHO/UNAIDS recommendations and a USPHS peri-natal task force review of available safety and efficacy data conclude that NVP has been demonstrated to significantly reduce the risk of peri-natal HIV transmission (by 40 to 50%), and available data demonstrate an excellent short-term safety profile for this single dose regimen when given to mothers at labour onset and to their newborns. Therefore, CDC continues to support the use of NVP as part of peri-natal HIV prevention programs in the developing world. If any problems are identified regarding the single-dose NVP regimen for prevention of mother-to-child HIV transmission, CDC would, of course, review the data and both domestic and international mother-to-child prevention programmes for appropriate guidance.

Upon what data were the U.S. and international recommendations based?

In addition to the safety and efficacy data reported in the HIVNET 012 trial, a South African clinical trial (SAINT) of 660 mother/infant pairs who received NVP has reported similar efficacy and short-term safety data. In the US, two studies have provided data supporting the safety of single-dose NVP: a Phase I safety study of NVP in 17 mother/infant pairs (PACTG 250) and a large phase III clinical trial (PACTG 316) in which more than 600 women and their infants received a single dose of NVP in addition to other antiretroviral drugs during pregnancy.

Is CDC conducting other studies using NVP?

Yes, CDC is currently conducting studies in the U.S. and Thailand that use single-dose NVP for peri-natal HIV prevention. The U.S. study, MIRIAD, is evaluating the use of rapid HIV testing in women who

present for delivery without knowledge of their HIV status. Women who are found to be infected will be treated according to the PHS Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Peri-natal HIV-1 Transmission in the U.S. (www.hivatis.org). One of the four recommended treatment regimens for women who are HIV-infected, in labour and not on anti-retroviral therapy is a single dose of NVP to the mother and her infant. The Thailand study looks at the safety and feasibility of providing single dose NVP to Thai women and their infants along with short-course ZDV.

Will CDC studies be stopped?

No. CDC has no studies of NVP at the Uganda trial site under NIH review. Because the NIAID review of this site revealed no evidence that the scientific data on the safety or efficacy of NVP is invalid, there is no reason to suspend other studies of NVP at this time. It is of course important for NIAID to complete their review. If any problems are identified regarding the single-dose NVP regimen for prevention of mother-to-child HIV transmission, CDC would review the data and take appropriate action.

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4. Elizabeth Glaser Foundation Memo, Statement and Q&A

M E M O R A N D U M

TO: Members of the Board of Directors
FROM: Kate Carr and Catherine Wilfert, MD
DATE: March 20, 2002
RE: Nevirapine and FDA

We are writing to provide you with information regarding the supplementary application of Boehringer Ingelheim (BI) to the FDA for US approval of Nevirapine (Viramune) for the prevention of mother-to-child transmission. Today it was announced that this application has been withdrawn because of the need for additional information which will be required to prepare a complete application to the FDA. The NIH contracted with auditors to examine data from the study to support the manufacturer's application to expand Food and Drug Administration (FDA) approval for use of the drug to prevent mother-to-child transmission of HIV. The initial review recognised some reporting and documentation irregularities at the site of the HIVNET 012 trial in Kampala, Uganda. A comprehensive follow-up review will be initiated.

A statement by NIH indicates "no evidence that the scientific data

produced during the study is invalid or that trial participants were placed at increased risk of harm. The reduction of peri-natal transmission by an accessible inexpensive regimen represents a major public health advance in resource poor settings and NIAID believes that there is no reason for other programs implementing this life-saving regimen to change their practice."

The Elizabeth Glaser Pediatric AIDS Foundation continues to support the use of Nevirapine to prevent mother-to-child transmission of HIV in resource poor settings. Short-term safety and tolerance of single dose Nevirapine has been demonstrated in multiple clinical trials. Efficacy of the intervention has been established and documented in the SAINT trial in addition to HIVNET 012. A technical review conducted by WHO which was released in November, 2001 also clearly indicates that based on proven safety and efficacy Nevirapine may be used in programmes to prevent MTCT.

We have attached the statement from NIH as well as an overview document which we have prepared. Please contact us with any questions or concerns.

Press Statement:

The Elizabeth Glaser Pediatric AIDS Foundation supports the use of Nevirapine to prevent mother-to-child transmission of HIV in resource poor countries based on recommendations of the WHO and the NIH, peer-reviewed results published in established medical publications, and experience gained through our Call to Action Project. The Foundation has provided grants to over 100 health care sites in 13 countries to implement programmes to prevent mother-to-child transmission of HIV using several established interventions, including Nevirapine programmes in resource poor settings, where they have the potential to significantly lower the risk of transmitting HIV from a mother to her child.

Q & A:

Why are programmes to prevent mother to child transmission of HIV so critical?

Effective means to reduce mother to child transmission (MTCT) can have a substantial impact on the HIV/AIDS epidemic as UNAIDS estimates that 800,000 new infections occurred in children under 15 years of age in 2001. Over 90% of these newly infected children live in Sub-Saharan Africa and 95% of these children were infected through MTCT.

What interventions are available to prevent MTCT?

Provision of anti-retroviral drugs to a pregnant woman and her newborn can substantively reduce the transmission of virus from a mother to her child. In developed nations with access to combination anti-retroviral therapy and to replacement feeding, transmission has been reduced to 1-2%. The feasible and simpler drug regimens, including AZT administered for 4 weeks prior to delivery, AZT/3TC and Nevirapine (NVP) administered at the onset of labour and to the newborn for one week, and a two-dose regimen of NVP given once to a pregnant woman during labour and once to her infant at 48-72 hours of age, have been shown to substantively reduce peri-natal transmission.

How do we know NVP works?

In 1999, results of a joint Uganda/U.S. clinical trial known as HIVNET 012 indicated that an easy to administer, single-dose regimen of Nevirapine, given once to the pregnant woman during labour and once to her infant in the first three days of life, could reduce the risk of transmission of HIV from mother to child by 47 percent. These results were subject to peer-review and published in The Lancet. (Guay LA, Musoke P, Fleming T, et al. HIVNET 012 randomised trial. Intrapartum and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda, Lancet 1999.) Subsequently, the SAINT study in South Africa confirmed the efficacy of Nevirapine equivalent to that of AZT/3TC. We are not aware of any evidence that refutes or diminishes the data in these studies or the conclusions drawn from it.

What are the benefits of using Nevirapine?

A two-dose regimen of NVP, given once to a pregnant woman during labour and once to her infant at 48-72 hours of age, could reduce the risk of transmission by almost 50%. NVP is simple as the drug can be given by mouth and under direct observation. Mothers can take the drug confidentially. The drug does not require refrigeration. It is inexpensive and even obtainable free of charge through a donation programme. NVP is the only regimen administered as simply as two doses of medicine. The documented ability of CTA sites to deliver this intervention is twice as efficient as sites choosing to use a more complex regimen such as four weeks of AZT.

Is Nevirapine safe for use in preventing MTCT?

The single-dose NVP regimen has been studied in 3 large, randomised, comparative, phase III clinical trials comprising over 1,600 HIV-infected women and their infants and no significant clinical or laboratory toxicity has been observed. In these controlled clinical trials, it was concluded and reported in the WHO technical

consultation) that the benefits of these drugs in reducing mother to child HIV transmission greatly outweigh any potential adverse effects of drug exposure.

In addition to HIVNET 012, what studies have been done on Nevirapine?

There have been two phase I studies and two phase III clinical trials focusing on the prevention of MTCT of HIV using NVP. NVP was first administered as a single dose to 38 pregnant women and their infants in two phase I studies, one performed in the U.S., involving 17 mother-infant pairs (Pediatric AIDS Clinical Trials Group [PACTG] protocol 250) and the other in Uganda, involving 21 mother-infant pairs (HIVNET 006).

The single-dose NVP regimen has also been studied in 3 large, randomised, comparative, phase III clinical trials comprising over 1,600 HIV-infected women and their infants. In HIVNET 012, single-dose NVP was compared with an ultra-short intrapartum/1 week infant AZT regimen in Uganda. PACTG 316 was a phase III, randomised, double-blind clinical trial conducted in the U.S., Europe, Brazil and the Bahamas where 642 randomised women and their infants received the single-dose NVP regimen and 628 randomised women and their infants received a placebo. The SAINT trial was a phase III randomised comparative trial conducted in South Africa where a randomised group of 654 mothers were given a single dose of NVP at onset of labour and a second dose at 48 hours postpartum; their infants received a single 48-hour NVP dose. (Daya Moodley on behalf of SAINT Investigators team, abstract LbOr2 presented at the 13th International AIDS Conference, Durban, South Africa, July 2000)

What is known about the long-term effects of Nevirapine on infants?

Nevirapine has been approved by the FDA for regular use in adults since 1996 and children two months and older since 1998. While more research on this issue is encouraged, there are no indications that a single dose regimen of NVP will have long-term effects on infants. We are following the recommendations of WHO and the NIH to continue implementation of single-dose NVP programmes in resource-poor settings, where it has the potential to significantly impact the peri-natal HIV epidemic.

Has Nevirapine been approved for any applications by the FDA?

In 1996, the FDA approved the use of NVP combination with nucleoside analogues to treat adults with HIV infection who have experienced clinical and/or immunological deterioration. It was the ninth drug approved by the FDA for the treatment of people with HIV

infection. In 1998, NVP was approved for use in children over the age of two months.

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5. Boehringer Ingelheim Comments on HIVNET 012 Trial:

Ridgefield, CT, March 22, 2002

Boehringer Ingelheim is aware that questions have been raised regarding reporting and documentation in a study conducted in Uganda for prevention of the transmission of HIV from mother-to-child during birth called HIVNET 012. The study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Maryland, and conducted by Johns Hopkins University and Makerere University, evaluated the use of the Boehringer Ingelheim drug VIRAMUNE® (Nevirapine).
Study data from the HIVNET 012 trial were part of a pending supplemental NDA submitted by Boehringer Ingelheim in support of this indication in the U.S.

The study results, published in the British medical journal, The Lancet, concluded that Nevirapine significantly lowered the risk of HIV transmission from mother to child during the first weeks of life. Extensive data from other trials support the safety of Nevirapine in mothers and infants in this setting.

NIAID is vigorously undertaking a comprehensive review of all the data collected in the course of the study. Boehringer Ingelheim has offered to support NIAID in this effort and is confident that the results of this review will confirm the positive conclusions published in The Lancet. However, since this NIAID and Boehringer Ingelheim review could not be completed within the remaining timeline for FDA action for the supplement, Boehringer Ingelheim has notified the FDA of its decision to withdraw the U.S. NDA for prevention of mother-to-child transmission at this time.

Boehringer Ingelheim continues to support the use of nevirapine and will continue to offer the drug to developing countries for the prevention of mother-to-child transmission of HIV as part of the VIRAMUNE Donation Programme.

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