

Global Strategies for HIV Prevention

Comments compiled on a recent media article on the HIVNET 012 Uganda study

Comments by Global Strategies for HIV Prevention

December 15, 2004

Most of you probably heard or saw a recent new report on issues related to the safety and effectiveness of nevirapine to prevent HIV transmission from mothers to children (PMTCT). It is important to understand whether the recent news report impacts on current recommendations for the use of nevirapine for PMTCT in developing countries.

Some facts:

1- This is not new news. Questions were asked by the scientific community following the publication in 1999 of the initial study known as HIVNET 012, a clinical study performed in pregnant women and their infants in Uganda. The scientific community knew that the study was not designed as a clinical study directed towards FDA approval of nevirapine. This would have required a greater stringency in quality control, monitoring and data collection. Thus most of us concluded that additional studies would be required to confirm the effectiveness and safety of nevirapine. Nevertheless, the result of the study, a 50% reduction in HIV transmission to infants, was considered to be of such great significance that recommendations could be made for the use of nevirapine for PMTCT while additional studies were being pursued. Historically, this was in keeping with making life saving drugs available while still under evaluation – some thing that all advocates and activists for AIDS argued strongly for beginning in 1985. Basically, it would have been unethical to withhold a treatment when the drug cost was less than \$1 and where effectiveness (infants would be spared a fatal HIV infection) outweighed any immediate risk.

2- Current recommendations for the use of nevirapine for PMTCT are not based on the HIVNET 012 study alone. In fact, there are now 17 clinical trials throughout the world, conducted by multiple investigators, from many different countries, using either single dose nevirapine or combination of other antiretroviral drugs along with single-dose nevirapine, to evaluate safety and effectiveness in PMTCT.

3- Seven on the 17 clinical trials now show that single dose nevirapine for mothers and infants or single-dose in combination with other antiretroviral drugs, reduces HIV transmission, in some instances by as over 90%.

4- None of the 17 clinical trials raise any major safety concern regarding the use of single dose nevirapine for PMTCT. No fatalities have been attributed to single dose nevirapine in any of these studies. Nevirapine can cause significant rash, liver disease and occasional fatalities when used as chronic therapy to treat HIV infection in either men or nonpregnant women. This is not how nevirapine is used for PMTCT. Health care workers have been aware of these complications for over 5 years.

5- Based on safety and effectiveness, single dose nevirapine or single-dose nevirapine in combination with other antiretroviral drugs, its use is recommended by all international health agencies and national governments conducting PMTCT programs. This includes the World Health Organization, UNAIDS, the US Public Health Service including the CDC, British and European national health organizations, the International AIDS Society, the Elizabeth Glaser

Pediatric AIDS Foundation and Global Strategies for HIV Prevention. In addition, all countries conducting PMTCT programs include the addition of single-dose nevirapine as an appropriate approach to PMTCT in resource poor countries.

The issue of resistance to nevirapine and its impact on subsequent use in HIV-infected women has also been debated. Several important facts need to be considered.

1- Nevirapine resistance occurs even with single-dose nevirapine given to mothers. This resistance is transient and there is no evidence that it prevents the effectiveness of nevirapine in subsequent pregnancies. Health care workers have known about nevirapine resistance for over five years and have taken this into consideration in making recommendations for PMTCT.

2- All drugs used to treat HIV infection result in resistance. HIV rapidly mutates and resistance is inevitable. The use of combination antiretroviral drugs, which controls viral replication, reduces but does not eliminate the possibility of resistance. It is not logical to withhold nevirapine to save the life of an infant based on theoretical concerns regarding subsequent responses to therapy. Resistance can develop whether nevirapine is used for PMTCT or for treatment of HIV infection.

3- WHO, UNAIDS and other international and national health organizations recommend combination drug therapy to treat HIV-infected adults who meet certain criteria for initiation of treatment. Several low-cost regimens include nevirapine as recommended therapy in resource poor countries. Resistance to nevirapine can occur with any of the recommended regimens for treatment of HIV-infected individuals.

4- The “threat of resistance” arguments are backwards. The greatest threat for the development of widespread nevirapine resistance is not from its use as single-dose nevirapine for PMTCT in several hundreds of thousands of pregnant women. Rather widespread nevirapine resistance is more likely to result from its use with combination drugs to treat millions of HIV-infected individuals worldwide and could jeopardize its use for PMTCT.

5- Withholding nevirapine, on the theoretical basis of blunting a subsequent response if used in combination therapy to treat HIV infection, would result in HIV infection and subsequent death of hundreds of thousands of infants for whom no other options are available. In contrast, over 17 antiretroviral drugs are available which can be used in various combinations to treat HIV infection if resistance occurs. In most resource poor countries the only option for preventing HIV-infected babies is single-dose nevirapine.

Conclusion

So what is behind the recent publication of information that has been known for over 4 years by the FDA, the international AIDS community, WHO, UNAIDS and the scientific community? Basically the media report deceptively presents itself as new information. Importantly however, the clinical research and scientific community have gone far beyond the 1999 HIVNET 012 report and have conducted multiple additional studies to confirm both the effectiveness and safety of nevirapine used either as a single dose for PMTCT or in combination with other antiretroviral drugs. Many of these studies are completed and confirm the safety and effectiveness of single-dose nevirapine and its much greater effectiveness when used with other antiretroviral agents to reduce HIV transmission by over 90%. The media report fails to acknowledge these advances.

It is absolutely essential that PMTCT programs move forward quickly to save the lives of infants from fatal HIV infection. Once an opportunity is missed to prevent HIV infection, one cannot go back and eradicate an already established and ultimately fatal infection. We all want to treat with the best combination antiretroviral drugs available to prevent as many infections of babies as possible. We also want to optimally treat the mother’s HIV infection. But as we move toward that goal, single dose nevirapine may be the only option for resource poor countries until more effective therapy becomes available.

Global Strategies for HIV Prevention will continue to support programs in resource poor countries using single-dose nevirapine alone or in combination with other antiretroviral therapy to reduce the number of newly HIV-infected infants, which number 1,800 each day.

Comments by National Institutes of Health

STATEMENT December 14, 2004

The HIVNET 012 Study and the Safety and Effectiveness of Nevirapine in Preventing Mother-to-Infant Transmission of HIV

In 1997, a clinical trial known as HIVNET 012 was begun in Uganda to address the developing world's urgent need for safe, effective and affordable regimens to prevent mother-to-infant transmission of HIV. The study was funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) and conducted by co-investigators from The Johns Hopkins University and Makerere University in Kampala, Uganda.

The purpose of HIVNET 012 was to examine whether a simple, inexpensive regimen of the drug nevirapine could effectively block mother-to-infant HIV transmission. In the study, both mother and baby were treated with a single dose of nevirapine, a drug licensed for the treatment of HIV-infected adults and children in the United States.

The researchers found that this intervention reduced the risk of mother-to-infant HIV transmission by approximately 50 percent. The results of this landmark study were published in *The Lancet* in 1999. The HIVNET 012 nevirapine regimen subsequently has been endorsed by the World Health Organization (WHO), the Joint United Nations Programme on AIDS (UNAIDS) and other international organizations. NIAID stands by the accuracy of the results of HIVNET 012.

The simple and cost-effective nevirapine regimen has been used in developing countries to prevent HIV infection in thousands of infants; it represents a major public health advance and is one of the true success stories in HIV prevention.

The results of HIVNET 012, including the safety and effectiveness of the nevirapine regimen, have been subjected to multiple reviews. In every instance, the initial conclusions of the HIVNET 012 investigators have been found to be correct. In addition, findings of other studies conducted in the United States and internationally have consistently supported the results of HIVNET 012.

Because of the striking results of HIVNET 012, in 2001 the manufacturer of nevirapine decided to apply to the U.S. Food and Drug Administration (FDA) for an expanded indication for nevirapine in the United States to include use of the drug to prevent mother-to-infant transmission of HIV. As part of the evaluation of the HIVNET 012 trial for this new indication, the conclusions of HIVNET 012 were re-affirmed as valid. Certain aspects of the collection of some of the primary data, however, did not strictly conform to FDA regulatory requirements. For this reason, the study could not serve as a single pivotal trial leading to an expanded indication.

As noted above, NIAID and NIH initiated several reviews and re-reviews of HIVNET 012. These reviews identified procedural flaws in the study that led NIAID to implement improvements in the conduct of clinical research it supports both in the United States and abroad. We understand that certain previously recognized criticisms of the conduct of HIVNET 012 have re-emerged, but stress strongly that throughout multiple reviews, the overall conclusions regarding the safety and efficacy of single-dose nevirapine in this setting have remained intact.

Moreover, NIH has contracted the Institute of Medicine (IOM), part of the National Academy of Sciences, to conduct an additional independent review of HIVNET 012. The results of the IOM review are anticipated in March 2005. NIAID is confident that the previous conclusions regarding the integrity of the HIVNET 012 data will be upheld.

The reduction of perinatal HIV transmission by the use of the readily accessible, inexpensive nevirapine regimen studied by the HIVNET 012 investigators represents a major public health advance for developing countries. No new data exist to suggest that current recommendations regarding use of this regimen should be changed, and we urge clinicians and policymakers to continue to heed the current WHO and UNAIDS guidance on single-dose nevirapine.

Media inquiries can be directed to the NIAID OCPL media group at 301-402-1663.

NIAID is a component of the National Institutes of Health, an agency of the U.S. Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies.

Press releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at <http://www.niaid.nih.gov>.

Prepared by:

Office of Communications and Public Liaison
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD 20892
U.S. Department of Health and Human Services

Comments by Project Inform – San Francisco

Articles from the Associated Press (AP) and other media sources appear to raise serious questions about the use of single-dose nevirapine to prevent mother-to-child transmission of HIV in resource poor countries. Although there is no new information about the safety and effectiveness of the use of this prevention strategy, the articles appear to raise questions about how the results of a study in Uganda were reported by the National Institute of Allergy and Infectious Diseases.

Project Inform, a national HIV/AIDS treatment information and advocacy organization that has served hundreds of thousands of people living with HIV since its inception in 1985, contends it would be an enormous disservice to people struggling to fight HIV worldwide to conclude from these stories that this use of nevirapine should be stopped or curtailed.

There are currently only two scientifically proven regimens for the treatment of mother-to-child transmission. The first, and oldest, requires that the mother be treated with AZT for six weeks prior to delivery and given intravenous AZT during delivery, followed by six weeks of AZT given to the infant. The second approach is a single dose of the drug nevirapine given once to the mother and once to the infant. Both regimens have demonstrated approximately equal effectiveness in reducing the risk of transmitting HIV to the infant. It is self evident that the second approach offers many practical advantages over the first, including a major cost advantage. In many resource

poor settings, the regimen based solely on AZT is not even feasible, given the common lack of health care infrastructure and limited funds for treatment. Also, as a general rule, a single dose of nevirapine creates fewer side effects for both mother and infant. These factors have made the use of single-dose nevirapine a highly popular approach for preventing mother-to-child transmission of HIV.

The study in Uganda mentioned in the AP article and related stories did not reach any conclusions that should discourage the use of single-dose nevirapine. This approach has been used in tens of thousands of pregnant women in studies and in common usage. The scientific data shows it to be both safe and effective and far more convenient than alternative regimens in resource poor settings. There are potentially significant toxicities associated with long-term use of nevirapine, as there are with many drugs used in the treatment of AIDS, but these long-term effects are rarely seen in single-dose, short-term use. The Ugandan study and other studies have demonstrated that a single dose of nevirapine can sometimes produce resistance to the drug. It is incorrect to say that this precludes effective treatment for HIV for the mother or infant in the future. Unfortunately, the AP story gives the reader this mistaken impression. There is no evidence from clinical trials showing long-term treatment failure in women treated with single-dose nevirapine at the time of childbirth. Additional research around this question is important and deserves support. However, even if future studies were to show a lasting resistance to nevirapine in some subset of women treated at childbirth, it would only affect a single class of anti-HIV drugs. There is no scientific basis for expecting that other classes of anti-HIV drugs would be affected. Additionally, new drugs of the same class as nevirapine but which may overcome resistance to nevirapine are already under study in advanced stage clinical trials.

There have been three major studies of single dose nevirapine in recent years: (1) the HIVNET 012 study in Uganda; (2) PACTG 316 in the US, Europe, Brazil and the Bahamas; and (3) the SAINT trial in South Africa. Collectively, these studies involved more than 1600 HIV-infected women and their infants. No significant laboratory or clinical toxicity was found in any of these studies, again contrary to the impression given in recent press articles. There is, therefore, no scientific reason to delay or halt the use of this regimen.

The Ugandan Study, HIVNET 012, was initiated in 1999 as a "proof of concept study." It was also meant to be a pilot exercise for Ugandan researchers. It was not a study designed to meet US FDA standards. However, when the study was stopped early because of its high success rate in preventing transmission to the infants, the manufacturer of nevirapine, Boehringer Ingelheim, unexpectedly sought to use the data to seek a new label indication for the drug in the US. This had the effect of retroactively imposing the FDA standards and requirements for a formal proof of efficacy study on HIVNET 012. It was a standard the study was never designed to meet and subsequent reviews of the data found many errors in data collection. The AP press report presented a highly exaggerated view of these errors, suggesting that the study may have had "thousands" of serious adverse events. In fact, the final review of the study showed no such thing. There were 37 adverse events experienced by women or infants using the AZT protocol, seven of which were believed to be caused by AZT. In the group using single-dose nevirapine, there were 34 adverse events, two of which were believed caused by nevirapine. Such findings do not warrant the level of concern raised in the media. It is irresponsible of the media to claim or report that the study encompassed "thousands of adverse events."

The world currently faces the greatest pandemic in its history. The UN reports that as many as 1900 children are infected with HIV daily. No vaccine appears likely any time soon. Treatment is difficult, expensive and often out of reach. Every available tool must be used to try to reduce the rate of new infections. The use of single-dose nevirapine, like currently available alternatives, may not be a perfect solution to blocking mother-to-child transmission of HIV, but it is a useful and effective tool in its current form. Additional research is underway testing other, newer methods, including combinations of nevirapine and AZT, combinations of other drugs, and single pill interventions using other drugs. We may speculate that one or another of these alternative approaches might be superior to single-dose nevirapine or pose fewer risks, but we cannot reach such a conclusion until the appropriate clinical trials are completed. For now, single-dose nevirapine remains a critically important and well-proven tool.

The questions raised about the Uganda trial do not ultimately raise real concerns about the safety or effectiveness of single-dose nevirapine. Exaggerated reports and emotional language in the media can only exacerbate the difficult challenges facing the world in its efforts to bring HIV infection under control in resource poor settings. To the extent that media stories about the Ugandan single-dose nevirapine study cause pregnant women or their governments to doubt the value of this approach to prevention, they are only adding to the problem. Whether it is possible, appropriate, or necessary for studies conducted in such settings to fully replicate the standards expected of research in the US or Europe is an important question which must be addressed as more studies are conducted in such international settings. But it is not a question that should be used to delay or thwart access to proven solutions.