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HIVNET 012 controversy puts ART programmes at risk

Associated Press story puts antiretroviral programmes at risk

By Theo Smart

Officials of the US National Institutes of Health (NIH) have been accused of covering up flawed research on the use of nevirapine in the developing world.

The allegations, made in an "exclusive" series of articles published last week by John Solomon of the Associated Press (AP), concern the pivotal HIVNET 012 trial conducted in Kampala, Uganda.

See:

<http://www.guardian.co.uk/uslatest/story/0,1282,-4673434,00.html>

<http://www.newsday.com/news/local/state/ny-bc-ct-aidsdrug1214dec14,0,1412100.story?coll=ny-region-apconnecticut>

<http://www.guardian.co.uk/worldlatest/story/0,1280,-4671613,00.html>

HIVNET 012 was the first clinical study to show that giving a single dose of nevirapine (sdN) to both mother and baby was a very safe and effective way to prevent the mother to child transmission (PMTCT) of HIV.

Since the first edition of HATIP in March 2003, many other studies have explored the optimal PMTCT regimen and HATIP has spent much of the past year discussing these studies and more recent nevirapine data. We should note that many of the clinicians and treatment advocates on our advisory panel have voiced concerns about the ongoing use of sdN used described by the HIVNET 012 study. But it is a complex issue, and one that is only tangentially addressed in the AP series on HIVNET 012 - which seems more intent on uncovering a US government scandal.

In fact, the AP report simply rehashes old news and appears, to this writer at least, to be deliberately misleading. A cynic could see the NIH story as kind of a me-too series, drafted to take advantage of current hullabaloo in the States over the perceived failure of the Food and Drug Agency to protect the public from the dangers of approved marketed pharmaceuticals such as Vioxx. Like the FDA issue, the NIH/HIVNET story even comes with its own "whistle-blower," the disgruntled consultant hired by the NIH to review the HIVNET 012 study and who has now set up his own website <http://www.honestdoctor.org/>.

Regardless of whether the AP NIH articles are really news or not, the alarm the story has spread is genuine enough. What's worrisome is that such fearmongering has a way of snowballing and taking on a life of its own.

Accepting the allegations as fact, some web-based blogs/newsgroups have concluded that the US used Africans as guinea pigs in the study, and writers have decried nevirapine PMTCT programmes as modern day Tuskegee experiments.

Meanwhile, in South Africa, the report plays into the hands of AIDS denialists in the government who would like to turn back the roll-out of antiretroviral drugs in the public health sector. TAC activist

Zachie Achmat says the drive to provide antiretroviral treatment in that country is danger of "going back to square one."

And back in the US, also apparently believing the AP story, Jesse Jackson has reacted with outrage, issuing a press release declaring that the NIH officials have conducted "a crime against humanity" and accusing the Bush administration of trying to foist a "deadly drug" upon Africa.

According to the NIH: "As a result of distortions of facts resulting from the recent press reports concerning nevirapine and the HIVNET 012 trial, there is a real possibility that physicians and health care providers in developing countries will not use the lifesaving single-dose nevirapine regimen to block mother-to-infant transmission of HIV in situations where there are no other options, such as multiple drug antiviral treatments."

Community-based advocacy organizations agree and are desperately trying to set the record straight. See:

http://www.pedaids.org/press_release_nevirapine_december_14_2004.htm

http://www.niaid.nih.gov/Newsroom/Releases/global_strategies.pdf

http://www.niaid.nih.gov/newsroom/Releases/project_inform.pdf

The AP NIH story misconstrues so many facts that it is difficult to tackle them all, but we will try to address some of the key points.

Data management issues in HIVNET 012

The AP report starts off by claiming that, in 2002, "top U.S. health officials were warned that research on the key drug was flawed and may have underreported thousands of severe reactions, including deaths."

The study in question, HIVNET 012, began in 1997 and results from the trial were published in the Lancet in 1999. At that point, the NIH and much of the HIV treatment community were already well aware that there were record keeping inconsistencies in HIVNET 012. The issue also kept cropping up whenever the South African government made a case against supplying the drug to pregnant women through the public health system.

The data management problems did not affect HIVNET 012's primary conclusions. They also should not be interpreted to mean that single dose nevirapine caused any serious side effects - though that is what the AP article implies.

According to the NIH press release: "This implication is absolutely false. Remonitoring reports of HIVNET 012 found no additional serious adverse reactions related to nevirapine. The original published study and the multiple subsequent reviews of the HIVNET 012 trial that have carefully scrutinised its data have found only a very small number of serious adverse reactions that potentially might be due to nevirapine."

In the 320 infants who received nevirapine, 35 infants experienced serious adverse events, only two of which were thought to be "possibly" due to nevirapine. Of the 306 mothers who received nevirapine, 16 experienced serious adverse events, and only one was thought "possibly" to be due to nevirapine.

The safety of single dose nevirapine has subsequently been confirmed by half a dozen other studies.

The 2002 "warnings" referred to in the AP article, came about when Boehringer-Ingelheim became interested in applying to the FDA for an expanded indication to allow nevirapine to be prescribed for PMTCT in the US because of the unexpected benefit seen in the study.

As part of the evaluation of the HIVNET 012 trial for this new indication, NIAID and NIH initiated several reviews and re-reviews of the study and investigated whether the data could be "cleaned up" to meet the rigorous standards the FDA requires in order to consider a drug for approval. It could not and it was too late to retrofit the study.

This resulting analysis of the "procedural flaws in the study" led NIAID to make changes in how it conducts collaborative research with international sites.

These changes are not always welcome - fulfilling American regulatory requirements is not usually the first priority of HIV clinicians and researchers treating HIV patients abroad.

The "cover up"

The AP story also claims that the procedural flaws in HIVNET 012 were deliberately concealed so as to not detract from President Bush's public relations/AIDS funding tour of Africa. Email quotes used to justify such claims in the piece don't provide enough context to be certain what the NIH officials actually were saying. Again, it is left up to the reader to infer that the officials' comments are in support of the authors' assertion. Full transcripts of the emails would have been more telling.

But what would have been the point in a cover up? Most of the news on HIVNET 012 procedural problems was already out there. Furthermore, support for sdN as PMCT no longer rested solely on the HIVNET data. Several other studies had already validated HIVNET 012 primary conclusions.

Besides, nevirapine-based PMTCT programmes were really only a small part of the President's projected \$15 billion Emergency Plan For AIDS Relief (PEPFAR).

In fact, if the aim of the AP NIH series was to criticise the Bush administration's AIDS efforts, they should investigate whether the President intends to stick to his five year funding promise given the costs of the war on Iraq and calls for reducing the US government's budget deficit.

And given that there have been no significant serious adverse event findings in any of the sdN studies or clinical use of the drug in thousands of women, the conclusion by NIH officials, that the safety concerns about single doses of nevirapine were overblown, seems a fair one, especially in light of the potential benefit that a simple, inexpensive and discreet option for PMTCT could offer women and infants in resource limited settings.

A death in Memphis

Without any evidence that sdN is associated with serious toxicity, the AP recounted the tragic story of a pregnant woman who died in a different study of nevirapine. Her death was probably due to a side effect that only occurs in some patients who take the drug over an extended period of time.

Continued administration of nevirapine can be associated with certain life-threatening side effects, namely Stevens Johnson Syndrome and serious liver inflammation - both of which may be the result of severe allergic reactions to the drug.

Reports of nevirapine's liver toxicity first began to surface in 1999 and 2000. By 2000, regulatory authorities in both Europe and the US issued warnings about the danger.

The greatest risk of liver toxicity occurred in the first six weeks of treatment and the regulatory agencies recommended that patients should receive liver enzyme monitoring at baseline and every two weeks during the first month of treatment and regularly thereafter.

If any moderate or severe abnormalities in liver enzymes occur, nevirapine should be interrupted immediately.

The woman in question entered a PMTCT study in Memphis, Tennessee in 2003 - at a time when enough was known about nevirapine's risks that her death should have been avoidable.

It is not clear whether she was adequately advised of the early signs of this side effect. The AP article points out that the toxicity is first mentioned on page 6 of a sixteen-page informed consent form - however it was the very first nevirapine-related potential adverse event that the consent form warned patients about.

What is clear is that the trial site failed to check the results of her liver function tests when they should have.

Her death was truly heartbreaking and senseless. But it has little to do with the HIVNET 012 story, other than to serve as a cautionary tale of what can happen if clinical research is not held to the highest of standards.

Four weeks of a drug, any drug, is usually very different from a single dose of the drug. One cannot deduce harmful effects of a short-term course of nevirapine based on studies that examine long-term, continued use of the drug. Furthermore subsequent data suggest that the toxicity is more likely to affect patients with higher CD4 cell counts (above 250) or percentages (above 25%). Inherited characteristics may also play a role.

For more on the risks of toxicity on extended nevirapine see <http://www.aidsmap.com/en/news/C24D11DE-1C19-48B0-A216-1A62B1DADA9F.asp>

<http://www.aidsmap.com/en/news/09A83419-9455-438E-9481-318A4F6D58F5.asp>

<http://www.aidsmap.com/en/news/C1316A81-32F9-4AA9-A94F-93E3EB4E0DOE.asp>

The fact that nevirapine is very safe when administered as a single dose appears to have been lost on many readers of the AP NIH story.

Nevirapine resistance

The only real danger in the ongoing use of sdN as PMTCT is that it could lead to the development of resistance to nevirapine and the related drug efavirenz in some patients. Resistance has been observed in the virus of some patients exposed to just a single dose of nevirapine. Earlier this year, data from a clinical study also showed that some women who took sdN had a less robust virologic response to subsequent antiretroviral therapy (see <http://www.aidsmap.com/en/news/1E48C7B9-97EC-4FC8-B6EB-6435E0707609.asp>).

Some experts quite reasonably fear that the use of sdN could significantly limit future treatment options for a woman - and if infected despite PMTCT, possibly her infant as well.

This danger is cited in the AP story but it isn't really discussed at any length. But this too, needs to be put in perspective.

Persistent resistance (lasting more than a few months) has only been observed in a minority of patients - and is only really relevant in those in need of immediate treatment. Furthermore, preliminary clinical data suggest that resistance can be avoided simply by adding Combivir to sdN for four to seven days after childbirth.

But more study is needed to see whether this is a feasible and effective option for most women in resource limited settings (see <http://www.aidsmap.com/en/news/24D285A4-1292-4306-A68A-45BE5ABBF2A9.asp>).

Combination therapy not always a woman's best option

It is a mistake to think that sdN is a lower standard of care foisted upon the developing world simply because it is cheap.

There are many other reasons besides expense that make the initiation of longer and/or more complex antiretroviral regimens for PMTCT difficult in many parts of the world.

First and foremost, not all pregnant women with HIV need to go on antiretroviral therapy for their own health. Many don't want to make their pregnancy more challenging with combination antiretroviral therapy - particularly if they have low viral loads anyway (and are thus less likely to transmit the virus to the infant).

Other women only discover their infection as they go into labour and there is no time to start combination therapy before delivery

Still others must first to deal with issues at home such as bias and HIV disclosure and cannot risk being caught taking antiretroviral medications by potentially violent husbands or others.

For all of these women, sdN may represent an attractive option for PMTCT. Their interests are not well served by irresponsible journalism that implies that the strategy is neither safe nor effective when a large body of evidence shows that it is. Until better options are found or can be administered, sdN should continue to be made available for women who want to prevent the transmission of HIV to their infants.

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of aidsmap.com