Case 12

Short-course AZT to prevent mother-to-child transmission of HIV

The risk of vertical transmission of HIV during pregnancy and delivery has been estimated at 15-30%, depending on several factors, including the stage of the mother's illness and whether it has been treated. In the mid-1990s, the best-known method for prevention of maternal HIV transmission was the "076 regimen", or long-course AZT treatment, in which a pregnant HIV-positive woman received zidovudine (AZT) five times a day orally from weeks 14 to 34 of the pregnancy and intravenously at the time of delivery. The infant would also be given AZT orally four times a day for 6 weeks after delivery. This regimen reduces vertical transmission of HIV by about 68%, provided that breastfeeding does not occur.[1]

However most public health experts in sub-Saharan Africa at the time that the study was designed considered that the "076" long-course regimen was impractical, because:

- prenatal visits do not begin until just before delivery;
- most deliveries do not occur in hospital, and of those that do, intravenous infusion during labour is not viable for most; and
- the cost of AZT for the long-course treatment is not affordable for most patients in most countries in sub-Saharan Africa.

To address these barriers, researchers proposed a series of multi-site, placebo-controlled trials in sub-Saharan Africa and the Asia-Pacific region to evaluate the efficacy of a short course of AZT for the prevention of vertical transmission of HIV. Participating mothers would begin treatment with AZT or a placebo 2 days before delivery; infants would also receive the drug (or placebo) for 2 days postpartum. The researchers were uncertain whether the short course would be as effective as the long course; however, a short course of treatment would be much less expensive than a long course and could increase access to care because it would be more in accord with delivery patterns in these two regions. Even if the short-course regimen proved less effective than the long-course regimen, the researchers hoped the short course would be adopted as standard preventive therapy in the absence of other feasible alternative regimens.

The researchers proposed to use a placebo control, since:

- the clinically relevant comparison was with the treatment that pregnant women were receiving at the time, which was no treatment at all;
- due to the practical and financial barriers, the long-course regimen would not be widely implemented, and thus local public health officials in the study countries found it unethical to provide it to the control groups in the clinical trials; and
- because the short-course regimen requires less time to complete, the study countries could adopt the short course much sooner if it proved effective.

Critics, mainly in the West, argued that the control groups should be given the "076" regimen rather than a placebo, because:

- the decision to use a placebo, rather than long-course treatment in the control groups, violated the explicit provisions of the *Declaration of Helsinki*;[2]

[1] WHO recommends that HIV-infected women should use exclusive breastfeeding for the first 6 months of a child's life unless replacement feeding is acceptable, feasible, affordable, sustainable, and safe for them and their infants before that time. If those criteria are met, avoidance of all breastfeeding by HIV-infected women is recommended. WHO HIV and Infant Feeding Technical consultation. Consensus Statement. Geneva, Switzerland: Inter-agency Task Team (IATT) on Prevention of HIV Infections in Pregnant Women, Mothers and their Infants, 2006.

[2] In June 1964, the World Medical Association (WMA) adopted the "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Although the original version did not address the issue of placebos, the issue emerged in subsequent revisions. Paragraph 32 in the 2008 version (based upon paragraph 29 in the earlier 2004 version) states that "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best proven current method, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no proven current method exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of a method and the patients who receive placebo or no treatment will not be subject to any additional risk of serious or irreversible harm."

For more information, visit http://www.wma.net/e/policy/b3.htm (accessed 5 June 2009).

- the researchers were using a double standard since they would not be permitted to run a placebo-controlled trial in their own countries, on the ground that an effective therapy existed; and
- even though results would take longer – and be more expensive – to achieve with active rather than placebo controls, trials could be designed that excluded placebo controls.

Questions

1 If the health authorities in the African and Asia-Pacific countries declared the proven effectiveness of long-course treatment irrelevant and impractical to their needs, should research ethics committees in the donor institutions still insist on long-course treatment for the controls?

2 If the researchers believed that short-course AZT would be effective but less so than long-course treatment, should the short course have been tested at all (even if the control group received the long course)?

3 If the test could not be conducted in a high-income country, would this, by definition, lead to a double standard for therapeutic intervention?

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