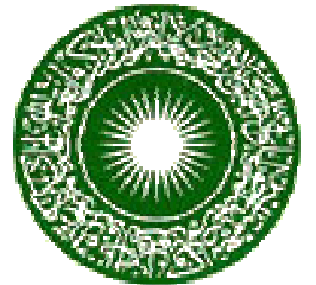




# Standard of care

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# Declaration of Helsinki

- Paragraph 29
- (1) "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods". And
- (2) "this does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic methods exists"

# Outline of presentation

- Low dose AZT trail
- Increased vulnerability because of poverty which is caused and or perpetuated by global health disparity.
- Comparing the issue clinical standard and other standard practises

# Outline of presentation (contd.)

- Dual standards by researcher for various domains within the same research trail.
- Higher moral obligation of the researcher
  - researcher/subject relationship
  - physician/patient relationship.
- Should science be placed ahead of ethics

# A tale of a trial

Low dose AZT trial

# Clinical Trials Group (ACTG) 076: Vertical Perinatal HIV Transmission

- Antiretroviral drug zidovudine administered orally in the prenatal period, intravenously during labor, and administered orally to the newborn reduced HIV infection in the newborn by two-thirds
- Study terminated at first interim analysis
- Within two months the Public Health Service announced that HIV positive women should receive this treatment.

# Post-ACTG 076: USA

- zidovudine was estimated to have reduced neonatal HIV death by 50% in the US and Europe.



# Post ACTG-076: Africa

- In Africa, accounting for 70% of the global HIV burden, therapy played no role because of cost
- Therapeutic regimens as effective but less expensive than zidovudine needed for developing countries



# Research design to search for a less expensive regimen?

June, 1994, WHO convened expert panel to advise research agenda for perinatal HIV transmission

“Placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent [perinatal] transmission of HIV.” (WHO 1994)

# 18 trials to explore alternative interventions

- \* In trials conducted in the US, subjects in all study groups had full access to zidovudine or other antiretroviral drugs.
- In 15 of the 16 trials in developing countries, some or all of the patients were not provided with antiretroviral drugs.
- 9/15 studies conducted in other countries were funded by the US government through the CDC or NIH.

# Reduction of Maternal-Infant Transmission of HIV Virus Type 1 with Zidovudine Treatment

NEJM Vol 331 (18) Nov 3, 1994 Edward M. Connor et al

- **Background and Methods** Maternal-infant transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV). We conducted a randomized, double-blind, placebo-controlled trial of the efficacy and safety of zidovudine in reducing the risk of maternal-infant HIV transmission.

# Reduction of Maternal-Infant Transmission of HIV Virus Type 1 with Zidovudine Treatment

NEJM Vol 331 (18) Nov 3, 1994 Edward M. Connor et al

- **Conclusions** In pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during the pregnancy, a regimen consisting of zidovudine given ante partum and intra partum to the mother and to the newborn for six weeks reduced the risk of maternal-infant HIV transmission by approximately two thirds.

# The CIOMS guideline 10

## Vulnerable subjects

- “Groups or classes may be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people...”

- "Fate has allowed humanity such a pitifully meager coverlet that in pulling it over one part of the world, another has to be left bare"

Rabindranath Tagore, Nobel Laureate 1913

As quoted by Dr Zulfiqar A. Bhutta

BMJ 2000;321:809-812 ( 30 September )

# Limited Global Resources

- World population living on 4% world GNP 45%
- Number of billionaires owning 4% world GNP 385
- World population living on <US\$300/year 50%

# Limited Global Resources

- Debt and aid savoir or curse for the developing world
- Developing countries paid back **US\$13 for very US\$1** that they received in grants in 1998.
- % of GNP spent on healthcare
  - Sub-Saharan Africa (1980) 5.8%
  - Sub-Saharan Africa (1997) 1.6
- IMF extracted US\$ 1billion from Africa (alone) in 1997-98.

# Military expenditure

- Developed countries
  - % of GNP spent on military 5.3
  - % of GNP spent on aid to developing countries 0.24
  - % of GNP spent by USA on aid to developing countries 0.1
  - World wide expenditure on military good & services ('95) 0.75trillionUS\$

# INDIA

- GDP \$735.6 billion (2005 est.)
- Military expenditures 2.93% (2005/06)  
% of GDP
- Health expenditures 6.1% (2002)  
% of GDP (both public  
& private)

# Research disparity

- 90% of all medical research is being undertaken on those diseases that causes 10% of the global burden of disease
- US government R&D expenditure spent on military research 66%

- Resource poor or developing nations live with the reality of armed conflicts, huge debts, even bigger debt repayment schedule and massive corruption.
- Therefore the standard of clinical practise is compromised.
- Thus the more expensive the treatment protocol the less likely it will be a standard practise.

# Adopting dual standards within the same trail

- “women were followed up every 4 weeks until 32 weeks gestation then weekly until delivery” and “[T]he infants were evaluated at birth and at 1, 2 or 3, 6, 12, 24, 36, 48, 60, 72, and 78 weeks of age,”
- This (I am sure) is not the local standard practise of monitoring and follow-up visits in sub-Saharan Africa.

# Adopting dual standards within the same trail (contd.)

- Diagnostic tests as “[P]eripheral-blood mononuclear cells obtained from infants were cultured for HIV...” and “HIV cultures of peripheral-blood mononuclear cells and lymphocytes phenotyping were performed in certified laboratories according to published standard methods. The French site used an equivalent program to ensure quality”
- Local laboratory was used

# Other 'standard' practices in the developing world

- International Labour Organization, resolution 182 tabled in 1999 and ratified by 138 countries
  - Child labour is condemned internationally
  - Products made in countries (where child labour is standard practise) have to be certified that they were not made by children.
  - International sanctions, legislation and boycott of the products of child labour are some ways of discouraging this practice.



- Although health is a basic human right, as envisaged in Article 25 (1 & 2) of the Universal Declaration of Human Rights (1948)
  - Provision of health has not received the same attention as the issue of child labour.
  - Healthcare that falls short of standard should be condemned
  - Research trails exploiting this unacceptable local standards should not be published

# Higher moral obligation of the researcher

- in the doctor/patient relationship the patient seeks the doctor and the main focus is the patient
- in researcher/patient relationship the researcher seeks the patient and the main focus is research and not healthcare

- 'One may be exempted from moral responsibility if the needy can only be reached with difficulty, but it would be maleficent to deny help to someone close by (who one has contacted oneself and) who could be easily assisted.'

Kottow M H, Who is my brother's keeper,

J Med Ethics 28(1): 24-27, Feb 2002

# Low dose AZT Ugandan Trial

## In the US & Europe

- Routine use of high dose AZT begun midway in pregnancy & given IV during childbirth(076 regimen)

## In trials in developing countries

- Lower dose of AZT, given only orally, & started later in pregnancy
- Compared to placebo

# “Standard of Care”

- The term “Standard of care” refers to the nature of the prevention and/or care that will be provided to participants in research
- It has been used variously to refer to:
  - the general care and treatment that investigators agree to provide all participants in clinical research
- And more specifically to:
  - the quality of care that should be provided to people in the control arm of a RCT – i.e. those that are not receiving the experimental intervention

# Standards of care

- International debate about standard of care that should be provided to control group in research:
  - Universal (the best treatment available anywhere in the world)
  - Non-universal (the treatment available in a defined region)

# The Standard of Care Debate

- The appropriate “Standard of Care” in international trials has been subject to intense debate
- Heated up around controversial HIV trials to prevent mother to child transmission in the developing world
- Commentators questioned the ethics of trials that used a “placebo” when an existing regimen 076 had been shown to reduce perinatal transmission of HIV in the United States

- Defenders argued that the 076 protocol was not “relevant” to the health care needs or priorities of the developing world, because it could not viably be implemented

# THE ISSUES

- 076 regimen: not feasible in developing countries
- Alternative: not permissible ethically in US & Europe in view of availability of 076
- As a matter of principle, if unethical in US, should be unethical anywhere
- Practically speaking, if 076 is unaffordable, and not feasible in developing countries, should not cheaper / more feasible alternatives be examined?
- Ugandan government gave permission
- Participants were duly informed
- Dose it make it ethical?

# POINTS OF VIEW

- Standard of Care: 'No care' is the usual,
- Hence placebo is OK
- 076: Never likely to be affordable
- Alternative, if effective , will be usable and ?affordable

THEREFORE, NOTHING UNETHICAL

# INITIAL PREMISE

## SPONSOR

- Risk benefit ratios are radically different in developing countries
- Subjects are not placed at greater risk than if they were not in the study at all
- Potential benefit
- Procedural requirements followed

## PUBLIC CITIZEN GROUP

- Because the study could not be done in US, lower standards were used in the developing countries
- Double standards not acceptable

# Standard of Care Debate: Can Research in Developing Countries be Ethical and Responsive to Countries' Health Needs?

Wendler D et al. Am J Public Health 2004;94:923-8

- Scientific necessity:
  - What is chance trial will answer important question and need for the host community?
  - What is chance same question can be answered by trial using only 'best method'?
- Relevance for the host community:
  - Is intervention implementable if successful?

# Standard of care debate (contd)

- Subject and host community nonmaleficence:
  - Research should not harm existing health system and doesn't leave pts less well off.
  - Equipoise between proposed new treatment and standard of care in host community.

# Equipoise

- The state in which we have no reason to believe that one experimental condition or intervention is superior to another
- “The necessity for investigators to be in this state of equipoise applies to placebo-controlled trials, as well. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo”.  
Angell NEJM 1997 847-849

# Placebo Control versus no control (“Science versus ethics”)

- Equipoise: the gateway to and the foundation for a placebo-controlled trial.
- The randomized, placebo-controlled trial is upheld as the paradigm of the excellence in science
- Is the overarching need for a placebo-controlled trial “placing science ahead of ethics”?

# Issues raised

- Is it ever ethical to provide different health packages in different settings?
- Should we be more concerned about North/South inequities or exacerbating local inequities?
- Is it possible to conduct ethical research in a fundamentally unjust world?
- Whose voices should be part of the decision making process?

