An Introduction to Global Health and Global Health Ethics: HIV/AIDS and Research in Developing Countries

By M. A. Palilonis

Learning Objectives:

1. Describe the components of a clinical research trial
2. Evaluate the special considerations for research in a developing country
3. Analyze the extra responsibilities research may or may not have when conducting trials in a resource-poor setting

HIV/AIDS: Origins and History

Human Immunodeficiency Virus (HIV) is a retrovirus, meaning once it enters the body the virus attacks infection fighting cells of the immune system and incorporates itself, allowing it to exist and replicate silently for years before causing symptoms. The history of the HIV tells a similar story. Scientists trace the first HIV strains back to the beginning of the 20th century in West-Central Africa. It its thought that the Simian Immunodeficiency Virus (SIV), a virus that affected non-human primates, mutated and crossed species through a process called zoonosis. HIV is thought to have existed in humans since the early 20th century and was contained for decades within small, high-risk groups in West-Central Africa until the 1960s when increased international travel brought HIV to countries around the world.[i]

It was not until the 1980s, that the symptoms of HIV came to international attention. In the body, HIV continues to replicate and slowly depletes the supply of helper T-cells, a type of immune cell that works to coordinate the body's defense against bacteria, fungus and other viruses. In 1981, physicians noted a rare form of pneumonia, formerly found in only in immunosuppressed cancer patients, among a group of young, gay men in Los Angeles. The first case described in Africa, in 1982, was of a patient with what was known as "slim disease."[ii] By 1983, scientists had determined HIV to be the causative agent of Acquired Immunodeficiency Syndrome (AIDS), the collection of opportunistic infections and syndromes that result from the virus's destruction of helper T-cells.[iii] By the early 1990s, HIV had spread causing epidemics in countries throughout the world. Mortality rates were rising, and initially, there were no proven treatments for the disease.

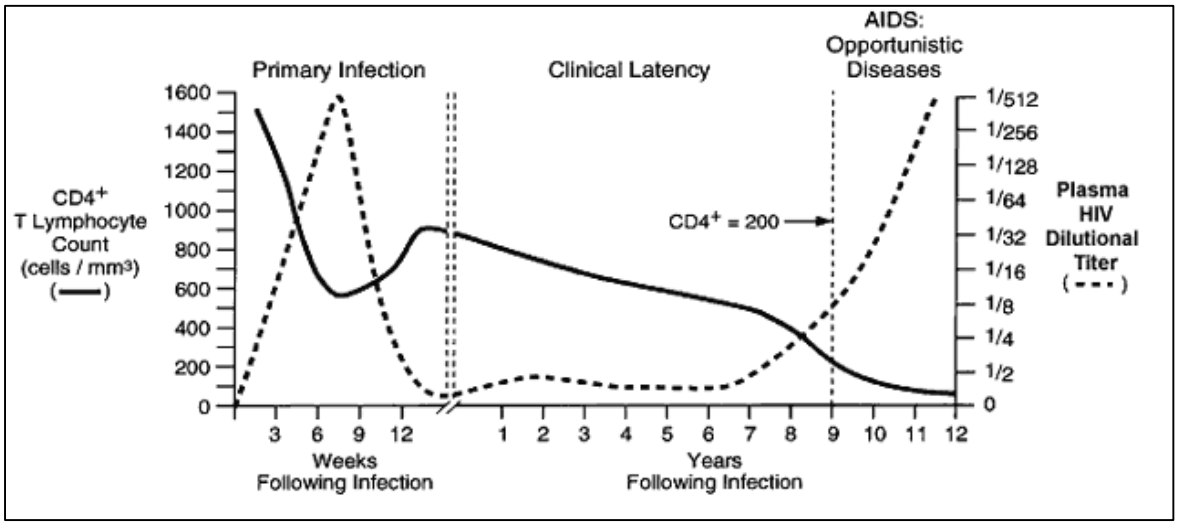
HIV/AIDS[iv]

Etiology: There are two strains of the virus - HIV-1, found throughout the world, and HIV-2, found mainly in West Africa. HIV is a retrovirus which infects helper T-cells (CD4 cells). T-cells are part of the body's immune system whose main job is to regulate and signal other immune cells to respond to infections such as bacteria, viruses, parasites and funguses.

Natural History: HIV has three phases. If untreated, individuals usual progress to severe disease and death in 10-15 years.

> *Acute Phase*: Usually begins 2-4 weeks after infection. Individuals will experience fever, sore throat and mono-like symptoms that will resolve in 1-2 weeks. Antibodies to the virus begin to appear during this time.
> *Latent Phase*: Virus continues to replicate and spread among CD4 cells causing a slow decline. Individuals are asymptomatic during this time.

Acquired Immunodeficiency Syndrome (AIDS): This is the final stage of the virus as CD4 cells fall below 200 cells/mm^3 (normal >500cells/mm^3). The individual is susceptible to opportunistic infections such as pneumocystis pneumonia (PCP), disseminated fungal infections and Kaposi's sarcoma which cause disability and eventual death.



Transmission: In most cases, HIV has a low rate of transmission; rates vary from 0.5 to 67 per 10,000 exposures depending on the route. HIV is infectious at all stages and risk of transmission increases with higher levels of the virus in the system

Sex: HIV is transmitted when virus-containing fluid (semen, vaginal secretions, anal secretions, saliva) comes in contact with the mucosal surface of the vagina, penis, anus or throat. Vaginal intercourse is the source of 70% of HIV infections worldwide.

Blood: Injection of HIV containing blood is another route of transmission. Before reliable testing, blood transfusions caused many cases of HIV. Today, needle sharing among intravenous drug users (IDU) is a significant cause of new infections and accounted for 80% of HIV infections in Eastern Europe and Central Asia (UNAIDS 2006). Accidental needle-sticks have low rates of transmission (32 per 10,000 exposures).

Birth: Babies born to untreated HIV-infected mothers have a 1 in 3 chance of infection. Transmission can occur during pregnancy, during labor and delivery and through breastfeeding. Perinatal transmission accounts for 5-10% of HIV infections worldwide.

Diagnosis: Initial diagnosis can be done through testing for HIV antibodies or clinically, based on the presence of disease-defining opportunistic infections. In high-income countries (HIC) individuals are monitored with blood tests for CD4 counts and viral load (number of copies of HIV). In developing countries progression is followed through WHO Stages based on symptoms, functional status and presence of opportunistic infections.

Prevention and Treatment: Individuals are treated with antiretroviral therapy (ART), a combination of 3 or more drugs which that suppresses the virus and prevents loss of CD4 cells.

Counseling and education about protected sex as well as needle-sharing are examples of some public health measures to prevent spread of HIV.

HAART and the Developing World

By the end of 1998, 33.4 million people were infected with HIV. Although HIV/AIDS affected people all over the world, the pandemic in Sub-Saharan Africa had reached plague proportions. Of the 5.8 million new cases of HIV in 1998, 4 million were in the 34 countries of Sub-Saharan Africa, a region that accounted for 91% of AIDS deaths in the late 1990s. Countries like Zimbabwe saw their national life expectancy go from 61years in 1993 to 49 years by 2000.[v] Initially, public health workers focused on counseling, prevention and treatment of opportunistic diseases, as there were no treatments available to address the virus.

Researchers were working furiously to find treatments for HIV and in 1987 the US Food and Drug Administration (FDA) approved ziouvudine (AZT) as the first drug approved from the treatment of HIV. In 1995, Saquinavir and then nevirapine (1996) were approved and became part of Highly Active Antiretroviral Therapy (HAART), a treatment that could suppress HIV and reduce mortality from AIDS.[vi] Other research trials looked at methods of preventing maternal-infant transmission (MIT), and in 1994 the AIDS Clinical Trial Group study 076 found a regimen for pregnant women that reduced MIT from 25% to 8%. The research trial included oral AZT during the 2nd and 3rd trimesters to prevent in utero transmission, IV AZT during labor and had infants bottle-fed and given oral AZT drops for the first 6 weeks of life. The dramatic decrease in MIT, led developed countries to adopt the 076 protocol almost immediately as the new standard of care.[vii]

However, the cost of these new treatments for HIV made it difficult for low- and middle-income countries (LMICs) to adopt treatment in the same way countries like the US had. Initial pricing of HAART drugs meant cost per person, per year was between US$10,000 and $15,000. The 076 protocol cost between $800 and $1000 per birth.[viii] These amounts were many times more than the total amount most developing countries had for total health expenditures per person.

So, in 1994 the World Health Organization (WHO) convened over 50 experts to consider the implications of the 076 Protocol for the developing world. The consensus was that shorter, simpler and less costly regimens were needed to reduce mother-infant transmission of HIV in limited resource settings. The WHO organized 16 clinical trials in 11 developing countries of Africa and Southeast Asia to look for alternative methods to reduce MIT. Half of the trials looked into shorter courses of AZT while others examined the use of Vitamin A or cleansers during delivery as alternative methods to reduce MIT. Nine of the 16 trials were sponsored by the National Institutes of Health (NIH) and Centers for Disease Control (CDC).[ix] Placebos were used in all of the trials except one, in Thailand, that used a 076-type regimen in the control group.[x]

In 1997, an article was published in the *New England Journal of Medicine* arguing that the placebo-controlled trials were unethical. Critics argued that women in the placebo groups should be receiving the standard treatment to prevent MIT that was developed in the 076 trials, as they would have if the research trials had taken place in the US.[xi] The debate that resulted covered many of the issues of conducting research among poor populations in resource-limited settings.

Components of a Clinical Trial[xii]

Research Question: Clinical trials are designed to address a specific question or hypothesis. Clinical trials can address questions in medicine, surgery, public health, psychology and other fields within healthcare.

Researchers: These are the people that develop, organize and implement a research project. The principal investigator in clinical trials is usually a PhD or medical doctor. Assistants may be medical professionals (physicians, nurses), technicians or lay-person volunteers.

Subjects/Participants: These are the people who participate in research by being part of either the control group(s) or intervention arm(s). Subjects are chosen based on criteria that can include, age, gender, socioeconomic status and medical conditions along with various other factors researchers might include in their study design. Subjects are then assigned to one of the groups included in the study.

Intervention Group(s): Subjects receive the intervention(s) being studied in the research question. There can be more than one type of intervention per study and can include new medicines, new regimens of existing medicines, different surgical techniques, behavior changes, etc.

Control Group(s): Subjects receive a therapy comparable to the intervention being studied.

> **Placebo-control**: Placebos are physiologically inactive versions of interventions. For example, testing a new migraine medication, subjects in the control group will receive an identical "sugar-pill" instead of the medication. Placebos allow researchers to compare the physiological effect of an intervention by keeping other aspects equal.
> **Active-control**: In active control trials, subjects receive an active therapy comparable to the intervention to treat the medical condition under investigation.
> **Historical-control:** Some studies include only intervention arms and use data collected from prior research or existing medical records in order to compare outcomes.

Global Health Research

90/10 Gap

This phrase, "the 90/10 gap", is commonly referred to when discussing research in global health. It refers to a major disparity in health research, that 90% of research dollars are spent on

10% of diseases,[xiii] or put another way, developing countries account for approximately 90% of the global burden of disease, but only 10% clinical trials study disease in developing countries.[xiv] One reason for this discrepancy is that most low- and middle-income countries (LMICs) do not have the resources to fund research. As a result, almost all of the funding for global health research comes from national agencies of high-income countries (50%), pharmaceutical companies (42%) and private trusts or other philanthropic agencies (8%).[xv] Though progress is being made to increase funding to global health research through partnerships between public and private organizations, the gap persists.

Social Value of Research

Another consideration for global health research is the type of research question being investigated in the clinical trials that do take place in developing countries. As part of an overall trend, research trials tend to focus on new technologies and biomedical advancement, where new patents or expanded use of medicines can return profits to the companies undertaking the research. However, this focus can spill over into trials in developing countries where technologies and medicines are tested that may be impracticable in the resource poor setting.[xvi] An example would be to test a new formulation of a medicine in a low-income country, even though the drug won't become available to the population it was tested on.[xvii] Concerns about exploitation in research have led many to argue that research in developing nations should be limited to questions that concern the population participating in the study.[xviii]

Research on the Ground

Finally, research taking place in developing nations be very different from clinical trials taking place in developed nations. Researchers face the question of how to adapt research methods to a different environment. There are several considerations that make conducting clinical trials in developing nations:

Study Design: The lack of medical care in developing countries can change the design of a clinical trial. Research in LMICs may be designed not to improve upon existing best effective treatment, but rather attempting to come up with a treatment that is better than what is available.[xix] As a result deciding whether to use a placebo control or deciding what should be the active control has a lot to do with what type of medical care the research population has access to. However, it is important to recognize that while this type of research may find better treatments, it is not designed to address the underlying inequities that prevent the best effective treatments from being available.

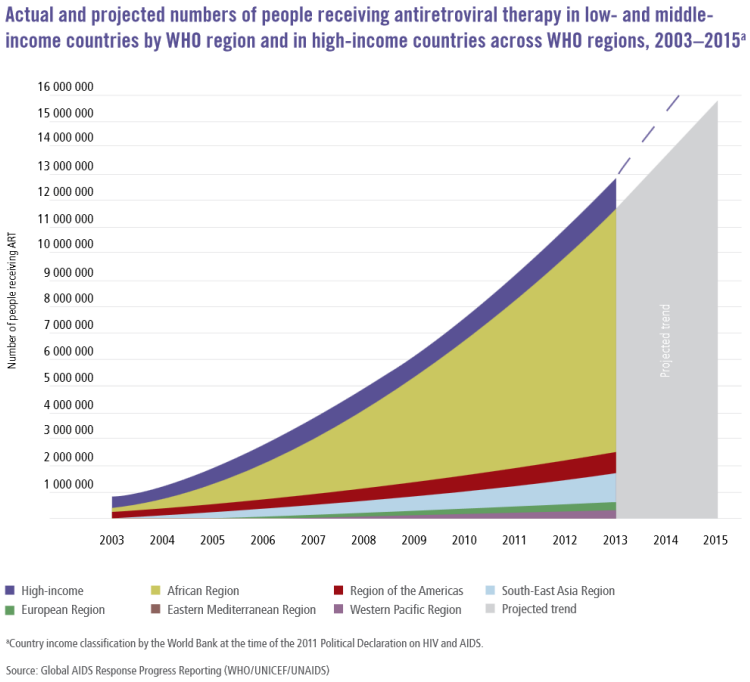
Ethical Review: In many countries, researchers using human subjects must submit their research for review to organizations such as Institutional Review Board (IRB) in the US, or Research Ethics Boards (REBs) in other countries. This is a step which allows outside parties to evaluate the study for scientific and ethical concerns. However, many times developing countries lack similar structures to review studies to be conducted in their communities.[xx] The review could be

a place where local communities and governments can set standards for research, examine the research questions and evaluate study design.

Communication: Obtaining the informed consent of subjects before they participate in research is a mainstay of clinical trials. Persons must be able to understand the research question, design and possible risks and benefits of being in either the intervention or control groups before they can freely consent to participate. Differences in language and culture as well as illiteracy can prevent good communication between researchers and participants.[xxi] Good communication with research populations and obtaining proper consent is crucial to maintaining trust between researchers and the communities the work in.[xxii]

HIV/AIDS Today

The HIV/AIDS pandemic was a force that galvanized efforts within global health. In response to the suffering of people in developing nations, countries like the US expanded their international aid to levels never before seen. International partnerships like the Global Fund to Fight AIDS, Tuberculosis and Malaria (2002) and UNAIDS, raised billions of dollars for the prevention, treatment and research of HIV/AIDS.[xxiii] Public-private partnerships were successful in lowering the price of ART, from US$1,200 to US$100 per person per year.[xxiv] As a result, more and more people gained access to treatment and mortality rates declined.



As of 2013, 35 million people were living with HIV/AIDS,[xxv] with sub-Saharan Africa accounting for 68% of HIV infections.[xxvi] However, expansions in treatment and prevention have transformed HIV for many, from a death sentence to a chronic illness. The availability of antiretroviral therapy greatly increased and an estimated 8 million people received access to

ART in 2011, a 20 fold increase since 2003.[xxvii] As a result the number of people living with HIV has increased, while mortality rates have decreased.[xxviii]

In addition, with expanded access to ART, the WHO 2010 recommendations include oral AZT for pregnant women from 14 weeks gestation through the end of breastfeeding along with oral nevirapine for breastfeeding infants.[xxix] Though many women and their babies are not able to access these therapies, their inclusion in the WHO recommendations reflects a changing view of what is possible for HIV-infected people in developing nations.

After Research Ends

Below is a link to the TED talk of Boghuma Kabisen Titanji, a clinical researcher for HIV/AIDS. She discusses the ethical considerations of doing clinical research in resource-poor settings.

Boghuma Kabisen Titanji: Ethical riddles in HIV research [xxx]

In the video, Ms. Taitanji, tells the story of Celine, woman with HIV living in the West-Central African country of Cameroon. Celine was diagnosed with HIV 6 years ago and at that time participated in a research trial where she received antiretroviral therapy as well as bus fare to travel to the research clinic. But, like all research trials, it came to an end. When Ms. Taitanji met Celine she had been without ART for 18 months because once the study ended she had no money for bus fare to the clinic and was too ill to walk the 35km.

In her talk, Ms. Taitanji covers many of the considerations of doing research in developing countries and also talks about what should happen when research trials end. Researchers must have plans to ensure any treatments found to be beneficial during the trial are made available to participants once the trial is over and to maintain effective treatments in the wider community.

Post-trial benefits: Why is it the responsibility of researchers to provide ongoing treatment to participants? What is it about the setting of research that confers this responsibility?

What other benefits should researchers consider for post-trial benefits? Ongoing free medications? Continued assistance for Celine to get to the clinic?

---

[i] L B Chavan, "History of HIV & AIDS," *National Journal of Community Medicine* 2, no. 3 (2011): 502–3, doi:10.1098/rstb.2001.0863.PMC.

[ii] Ezekiel J Emanuel, "Global Justice and the 'Standard of Care' Debate," in *Global Justice and Bioethics*, ed. Joseph Millum and Ezekiel J Emanuel (Oxford: Oxford University Press, 2012).

[iii] Lisa V Adams and Godfrey B Woelk, "Tuberculosis and HIV/AIDS," in *Understanding Global Health*, ed. W H Markle, M A Fisher, and R A Smego Jr, 2nd ed. (New York, NY: McGraw-Hill, 2014).

[iv] John G Bartlett, "The Natural History and Clinical Features of HIV in Adults and Adolescents," *UpToDate*, 2015, https://www-uptodate-com.go.libproxy.wakehealth.edu/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-adolescents?source=search_result&search=HIV&selectedTitle=2~150.; Adams and Woelk, "Tuberculosis and HIV/AIDS."

[v] Esther Scott, "The Debate Over AZT Clinical Trials," *Ethics in International Research*, 1999, http://www.hks.harvard.edu/case/azt/ethics/home.html.

[vi] Luke Messac and Krishna Prabhu, "Redefining the Possible: The Global AIDS Response," in *Reimagining Global Health: An Introduction*, ed. Paul Farmer, Arthur Kleinman, and Jim Yong Kim (Berkeley, CA: University of California Press, 2013).
[vii] Nancy E Kass, "Just Research in an Unjust World: Can Harm Reduction Be an Acceptable Tool for Public Health Prevention Research?," in *Global Bioethics: Issues of Conscience for Twentieth Century*, ed. Ronald M Green, Aine Donovan, and Steven A Jauss (Oxford: Oxford University Press, 2008).
[viii] Scott, "The Debate Over AZT Clinical Trials."
[ix] Emanuel, "Global Justice and the 'Standard of Care' Debate."
[x] Scott, "The Debate Over AZT Clinical Trials."
[xi] Kass, "Just Research in an Unjust World: Can Harm Reduction Be an Acceptable Tool for Public Health Prevention Research?"
[xii] R S Greenberg et al., *Medical Epidemiology*, 4th ed. (New York: McGraw-Hill, 2005).; Martin, "Epidemiology, Biostatistics, and Surveillance."
[xiii] Alan Wertheimer, "The Obligations of Researchers Amidst Injustice or Deprivation," in *Global Justice and Bioethics*, ed. Joseph Millum and Ezekiel J Emanuel (Oxford: Oxford University Press, 2012).
[xiv] Ghaiath Hussein and Ross E G Upshur, "Ethical Challenges in Global Health Research," in *An Introduction to Global Health Ethics*, ed. Andrew D. Pinto and Ross E G Upshur (Hoboken, NJ: Taylor & Francis, 2013).
[xv] Sandra J MacLean and David R MacLean, "The Political Economy of Global Health Research," in *Heath for Some: The Political Economy of Global Health Governance*, ed. Sandra J MacLean, Sherri A Brown, and Pieter Fourie (Basingstoke: Palgrave Macmillan, 2009).
[xvi] Alex John AJ London and Jonathan Kimmelman, "Justice in Translation: From Bench to Bedside in the Developing World," *The Lancet* 372 (2008): 82–85, doi:10.1016/S0140-6736(08)60996-4; MacLean and MacLean, "The Political Economy of Global Health Research."
[xvii] Wertheimer, "The Obligations of Researchers Amidst Injustice or Deprivation."
[xviii] London and Kimmelman, "Justice in Translation: From Bench to Bedside in the Developing World."; Emanuel, "Global Justice and the 'Standard of Care' Debate"; Hussein and Upshur, "Ethical Challenges in Global Health Research."
[xix] Kass, "Just Research in an Unjust World: Can Harm Reduction Be an Acceptable Tool for Public Health Prevention Research?"
[xx] Hussein and Upshur, "Ethical Challenges in Global Health Research."
[xxi] Ibid.
[xxii] Dean Harris, *Ethics in Health Services and Policy A Global Approach* (Hoboken, NJ: Jossey-Bass, 2011).
[xxiii] Messac and Prabhu, "Redefining the Possible: The Global AIDS Response."
[xxiv] Adams and Woelk, "Tuberculosis and HIV/AIDS."
[xxv] "WHO | HIV/AIDS," *WHO.int*, accessed April 5, 2015, http://www.who.int/gho/hiv/en/.
[xxvi] Leslie Doyal, *Living with Hiv and Dying with Aids : Diversity in the Global Pandemic* (Farnham, Surrey: Ashgate Publishing Ltd, 2015).
[xxvii] Adams and Woelk, "Tuberculosis and HIV/AIDS."
[xxviii] Doyal, *Living with Hiv and Dying with Aids : Diversity in the Global Pandemic*.
[xxix] Adams and Woelk, "Tuberculosis and HIV/AIDS."
[xxx] Boghuma Kabisen Titanji, "Ethical Riddles in HIV Research" (TED Talks, 2012), https://www.ted.com/talks/boghuma_kabisen_titanji_ethical_riddles_in_hiv_research#t-535751.