



THE REBECCA PROJECT FOR HUMAN RIGHTS

Health Safety and Dignity for Vulnerable Families

**UNETHICAL MEDICAL RESEARCH
IN AFRICA**
**Funded or Assisted by the
US Government or other US-Based Institutions**

THE OUTSOURCING OF TUSKEGEE
Part II

Preface

The purpose of this note is to call attention to recent and even continuing unethical medical research in sub-Saharan Africa directed and supported from the United States (US) and to motivate responses to stop unethical research – through public awareness and criticism (transparency) as well as through Congress and the courts (enforcing adequate laws and regulations).

This note lists studies sponsored or assisted by the US government and/or private organizations headquartered in the US that, based on available information cited in this note, appear to violate ethical standards and/or US regulations. Studies are listed and discussed according to offenses: (1) not getting informed consent; (2) not warning people about specific identified risks; (3) exposing babies to unnecessary risks; and (4) not reporting or investigating unanticipated problems.

For each project cited for alleged ethical and/or regulatory offences, this note:

(a) describes the alleged offence(s) with references to published evidence;

(b) cites relevant ethical guideline(s) in the World Medical Association's Declaration of Helsinki (DoH; available at: <http://www.wma.net/en/30publications/10policies/b3/17c.pdf>) and/or the relevant text in the US Code of Federal Regulations, Title 45 Part 46, Protection of Human Subjects (45 CFR 46; available at: <http://ohsr.od.nih.gov/guidelines/45cfr46.html>); and

(c) references previous attention to the alleged offences.

This is not intended to be an exhaustive list of all medical research in Africa managed and/or funded by US-based institutions with serious ethical or regulatory offenses.

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Table of contents

	page
Preface	2
1. Ethical issue: Not getting informed consent	4
1.1 Ghana, 1993-99: Trial of four methods to deliver family planning services in Kassena-Nankana District	4
1.2 Nigeria, 1996: Trial of Trovan to treat meningitis in children	4
1.3 Uganda, 1997-2001: Trial of nevirapine to prevent HIV mother-to-child transmission	5
1.4 Uganda and Zimbabwe, 2004-06: Trial of antiretroviral treatment (ART) structured treatment interruption	7
1.5 Cameroon, Ghana, and Nigeria, 2004-06: Trial of pre-exposure prophylaxis (PrEP) to prevent HIV infection among high risk women	8
2. Ethical issue: Following people at risk without warning them of their risk	10
2.1 Uganda, 1989-ongoing: Study of HIV transmission and HIV-related mortality in a large rural cohort	10
2.2 Zimbabwe, 1997-2001: Trial of vitamin A to prevent mother-to-child HIV transmission	12
2.3 Uganda, 2003-07, continuing to 2013: Trials of male circumcision to protect men or women from HIV	11
3. Ethical issue: Exposing babies to unnecessary risks	13
3.1 Gambia and Kenya, 2010-2012: Trial of an HIV vaccine in children	14
4. Ethical issue: Not reporting and investigating adverse events	16
4.1 2002-06, Kenya: Trial of male circumcision to protect men from HIV	16
4.2 2003-05, Malawi: Case control study of women's risks for HIV incidence	17

1. Ethical issue: Not getting informed consent

1.1 Ghana, 1993-99: Trial of four methods to deliver family planning services in Kassena-Nankana District

Study identification		
Study name:	Navrongo Health Research Center Community Health and Family Planning Project	
US research organization:	Population Council	
US funders:	Population Council, Rockefeller Foundation, USAID, Gates Foundation, Andrew Mellon Foundation	
Study ID number:	No number	
Study synopsis:		
<p>The “Navrongo experiment” (Phillips 2006) tested four modalities to deliver family planning information and services in four parts of Kassena-Nankana District: clinic-based without community meetings; clinic-based with community meetings; village service delivery without community meetings; village service delivery with community meetings. To evaluate these different ways to deliver information and services, the study team elected a “sample of approximately 1,900 compounds” which they visited annually during 1993-1999. During these visits, the project surveyed all married women of reproductive age about “reproductive behavior and preferences, contraceptive use, and fertility determinants.” The project surveyed the women’s spouses about similar issues during 1995-99 (p. 146, Debpuur 2002). The project reported that various interventions reduced desired family size and fertility. Health care workers in the “Navrongo experiment” promoted Depo-Provera, an approved but controversial drug. Among women in the project area who used modern birth control methods, more than 90% used Depo-Provera vs. only 24% of such women in Ghana in 1998 (Debpuur 2002; UN 2011).</p>		
Ethical issues		
Alleged offenses	Relevant DoH, CFR clause	
Not asking an institutional review board to review and approve its plans for repeat surveys of adults followed for as long as 6 years, including sensitive questions about reproductive attitudes and sexual behavior.	DoH 15; CFR 46.109(a)	
Not getting informed consent from participants repeatedly surveyed on sensitive issues: Within approximately 1,900 compounds, the project surveyed 8,998 women an average of 2.4 times as well as an unreported number of spouses an unreported number of times.	DoH 24; CFR 46.116	
Not telling patients what part of their medical care is related to research: The project linked women interviewed in 1993 to their medical records, making their medical care part of the research record (p. 147, Debpuur 2002). Women were not told their care was related to medical research.	DoH 34	
Public criticism, investigation, litigation		
Rebecca Project (2011) raised these issues in Nonconsensual Research in Africa.		
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Debpuur C, Phillips J, Jackson EE, et al. The impact of the Navrongo Project on contraceptive knowledge and use, reproductive preferences, and fertility. <i>Studies in Family Planning</i> 2002; 33: 141-164.		
Phillips JF, Bawah AA, Binka FN. Accelerating reproductive and child health programme impact with community-based		

services: the Navrongo experiment in Ghana. Bull WHO 2006; 84: 949-955.
Rebecca Project for Human Rights. Nonconsensual Research in Africa: the Outsource of Tuskegee. Washington DC: Rebecca Project, 2011. Available at: http://www.rebeccaproject.org/images/stories/files/NonConsensualResearch20111120.pdf (accessed 7 February 2012).
UN, Department of Economic and Social Affairs, Population Division. World Contraceptive Use 2010; and World Contraceptive Use 2011. UN, 2011. Available at: http://www.un.org/esa/population/publications/wcu2010/Main.html (accessed 1 March 2012).

1.2 Nigeria, 1996: Trial of Trovan to treat meningitis in children

Study identification		
Study name:	Unknown	
US research organization:	Pfizer	
US funders:	Pfizer	
Study ID number:	No number	
Study synopsis:		
Pfizer arranged for doctors in Kano, Nigeria, to test trovafloxacin (Trovan), an experimental drug to treat bacterial meningitis, on children during a meningitis outbreak. One hundred and ninety children were included in the trial. Children in the control arm allegedly received a non-standard low dose of the recommended drug, ceftriaxone (Lin 2005; McNeil 2011). Eleven children died during the trial, and others suffered permanent health damage.		
Ethical issues		
Alleged offenses	Relevant DoH and/or CFR clause	
Not getting an institutional review board to review proposed research.	DoH 15	
Not getting informed consent.	DoH 24	
Not explaining that medical care was linked to research.	DoH 34	
Public criticism, investigations, litigation		
The Center for Research on Multinational Corporations (SOMO 2008) and the Rebecca Project (2011) have called attention to ethical misconduct in this study. Cases against Pfizer have been filed in Nigeria and in the US. The suit in the US was brought under the Alien Tort Statute. In 2009, Pfizer reached a \$75 million out-of-court settlement with Nigeria's Kano state government, including payments to victims' families, sponsorship of Kano state health programs, and legal costs (McNeil 2011; Smith 2011).		
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Lin A. Class Action Against Pfizer Is Dismissed. New York Law Journal, 24 Aug 2005, Available at: http://www.law.com/jsp/law/international/LawArticleFriendlyIntl.jsp?id=900005545000 (accessed 22 February 2012).		
McNeil Jr DG. Nigerians receive first payments for children who died in 1996 meningitis drug trial. New York Times, 11 August 2011. Available at: http://www.nytimes.com/2011/08/12/world/africa/12nigeria.html (accessed 22 February 2012).		
Nigeria sues drugs giant Pfizer. BBC News, 5 June 2007. Available at: http://news.bbc.co.uk/2/hi/africa/6719141.stm (accessed 22 February 2012).		
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Smith D. Pfizer pays out to Nigerian families of meningitis drug trial victims. 11 August 2011. Available at:		

http://www.guardian.co.uk/world/2011/aug/11/pfizer-nigeria-meningitis-drug-compensation (accessed 1 March 2012).
Stephens J. Panel Faults Pfizer in '96 Clinical Trial In Nigeria. Washington Post, 7 May 2006. Available at: http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html (accessed 22 February 2012).
Uwugiaren I. Nigeria: Pfizer Directors Declared Wanted. AllAfrica, 10 January 2008. Available at: http://allafrica.com/stories/200801100283.html (accessed 22 February 2012).

1.3 Uganda, 1997-2001: Trial of Nevirapine to prevent HIV mother-to-child transmission

Study identification		
Study name:	HIVNET 012: Phase IIB trial to evaluate the efficacy of oral Nevirapine and the efficacy of oral AZT in infants born to HIV-infected mothers in Uganda for prevention of vertical HIV transmission.	
US research organization:	Johns Hopkins University	
US funders:	National Institutes of Health (NIH), Boehringer Ingelheim	
Study ID number:	NCT00006396	
Study synopsis:		
<p>The study recruited 626 pregnant HIV-positive women, then randomized them to two groups to test two treatments to prevent mother-to-child HIV transmission. One group of mothers and babies received nevirapine; the other group received a short-course of zidovudine (AZT). The study reported that a lower percentage of babies in the nevirapine group vs. the zidovudine group got HIV (8.2% vs. 10.4% at birth; and 13.1% vs. 25.1% by age 14-16 weeks). From these results, short-course zidovudine had little or no impact on HIV transmission, while nevirapine roughly halved mother-to-child transmission through 4 months.</p>		
Ethical issues		
Alleged offenses		Relevant DoH, CFR clause
The study team did not get informed consent from participants about changes in the trial protocol.		DoH 24; CFR 46.116
The study team did not report serious adverse events.		DoH 15; CFR 46.111(a)
Public criticism, investigations, litigation		
<p>In 2002, an internal NIH report from an audit of HIVNET 012 identified problems with the study, including incomplete reporting of adverse events. After a senior official in NIH revised the report, the expert responsible for the audit restated his concerns in a public statement (Fishbein 2004), charging the trial with: “1. failure to record thousands of adverse events, 2. failure to obtain proper informed consent, 3. failure to maintain satisfactory clinical and pharmacy records, and 4. failure of the investigators to assess adverse events through direct observation.”</p> <p>In 2002, the Office for Human Research Protections (OHRP), in a determination letter to Uganda’s National Council of Science and Technology (the organization responsible for supervising medical research in Uganda), noted deficiencies in monitoring and reporting adverse events (OHRP 2002). Although OHRP’s letter did not chastise US institutions that funded and managed the trial, these institutions were equally deficient in monitoring adverse events.</p> <p>The Center for Research on Multinational Corporations (SOMO 2008) summarized problems in the trial: “In the HIVNET 012 trial, investigators failed to get patients’ consent about changes in the experiment and administered wrong doses. There were serious problems in</p>		

<p>record keeping and delays and underreporting of fatal and life threatening problems. Fourteen deaths were not reported. Researchers acknowledged thousands of side effects and adverse reactions were not disclosed. Procedures for divulging Serious Adverse Events (SAEs) were not followed. Boehringer Ingelheim, the company that markets the drug and audited the trial, asked the US National Institutes of Health to destroy an early copy of the research report in case the study would be audited by the US Food and Drug Authority...”</p> <p>The Rebecca Project (2011) has also criticized the study.</p>
<p>References</p>
<p>Center for Research on Multinational Corporations (SOMO). SOMO briefing paper on ethics in clinical: #1: Examples of unethical trials, updated February 2008. Amsterdam: SOMO, 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 7 February 2012).</p>
<p>ClinicalTrials.gov. Effectiveness of AZT and Nevirapine in preventing HIV transmission from Ugandan mothers to their newborns, last updated 24 September 2008. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00006396 (accessed 8 February 2012).</p>
<p>Fishbein JM. Fishbein Clarifies Allegations: NIH Officials Betray Public Trust, Perpetuate Widespread Cover-up of Clinical Trial Data. Message, 22 December 2004. Available at: http://www.mombu.com/medicine/medicine/t-aids-scientific-whistleblower-comes-clean-5033805.html (accessed 23 February 2012).</p>
<p>Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. <i>Lancet</i> 1999; 354: 795-802.</p>
<p>HIVNET 012: Phase IIB trial to evaluate the efficacy of oral nevirapine and the efficacy of oral AZT in infants born to HIV-infected mothers in Uganda for prevention of vertical HIV transmission. Protocol version 2.0, 14 May 2003. Available at: http://www.hptn.org/Web%20Documents/HIVNET_Protocols/HIVNET012v2.pdf (accessed 23 February 2012).</p>
<p>Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: an 18-month follow-up of the HIVNET 012 randomised trial. <i>Lancet</i> 2003; 363: 859-868.</p>
<p>Office for Human Research Protections (OHRP). Determination letter to Uganda National Council of Science and Technology: RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 00001293, Single Project Assurances (SPA) S-6233 and S-6234, and Cooperative Project Assurances (CPA) T-5124 and T-5125. Research Project: A Phase III Efficacy Trial of Oral AZT vs. Oral Nevirapine in HIV-1 Infected Pregnant Ugandan Women (HIVNET 012). OHRP, 16 July 2002. Available at: http://www.hhs.gov/ohrp/detrm_lettrs/YR02/jul02d.pdf (accessed 23 February 2012).</p>
<p>Rebecca Project for Human Rights. Nonconsensual Research in Africa: the Outsource of Tuskegee. Washington DC: Rebecca Project, 2011. Available at: http://www.rebeccaproject.org/images/stories/files/NonConsensualResearch20111120.pdf Page 7-9 (accessed 7 February 2012).</p>
<p>Solomon J. AP Exclusive: Top U.S. officials warned of concerns before AIDS drug sent to Africa. <i>Lubbock Avalanche-Journal</i>, 13 December 2004. Available at: http://www.lubbockonline.com/stories/121304/upd_075-4013.shtml (accessed 23 February 2012).</p>
<p>Whistleblower says government bungles AIDS study. <i>USA Today</i>. Available at: http://www.usatoday.com/news/washington/2005-01-04-nih-aids_x.htm (accessed 23 February 2012).</p>

1.4 Uganda and Zimbabwe, 2004-06: Trial of antiretroviral treatment (ART) structured treatment interruption

Study identification	
Study name:	Development of Anti-Retroviral Therapy in Africa – a randomized trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa
US research organization:	[managed from the Medical Research Council, United Kingdom]
US funders:	Rockefeller Foundation; Gilead
Study ID number:	Trial ID number: ISRCTN13968779
Study synopsis:	
The trial randomized 813 HIV-positive adults to two groups. One group received continuous antiretroviral treatment (ART), while the other received ART with structured treatment	

<p>interruption: 12 weeks on and 12 weeks off. In some cases, the study reduced time off ART, based on participants' health and CD4 count. The trial began in July 2004. After reviewing data to May 2005, the Data Safety and Monitoring Committee allowed the trial to continue. After a second review in March 2006 found that participants getting interrupted treatment had a greater than 2-fold risk of disease progression (new/recurrent WHO stage 4 or death), the study shifted everyone to continuous treatment. This trial paralleled other trials of structured treatment interruption which reached similar conclusions, including: the SMART trial in the UK, US, and Copenhagen, 2002-06 (clinicaltrials.gov identifier NCT00027352); and the TRIVACAN trial in Cote-d'Ivoire, 2002-07 (clinicaltrials.gov identifier NCT00158405).</p>		
<p>Ethical issues</p>		
	Alleged offenses	Relevant DoH, CFR clause
	Information provided to participants prior to their consenting to join the trial did not adequately detail health risks. Specifically, the patient information sheet (pp. 68-70, DART Protocol 1.2, 2004) did not clarify that participants on structured treatment interruption had an increased risk to develop resistance.	DoH 24
	Participants randomized to structured treatment interruptions were pressured to remain in the trial to access ART.	DoH 9, 22, 24
	The project did not ensure post-trial access to second- and third-line ART for participants who developed resistance to ART drugs during structured treatment interruption.	DoH 6, 11
	The trial continued after structured treatment interruption could be seen to be bad for health. Months before the trial was stopped in March 2006, a Cochrane review (Pant Pai 2005) reported: "Timed-cycle STI [structured treatment interruption] fell out of favor due to reports of development of resistance in many studies."	DoH 6, 11
<p>Public criticism, investigations, litigation</p>		
	<p>Trial participants and concerned others, including the media in Uganda (Kavuma 2006) and ACT-UP Paris (2006), raised several ethical concerns. During the trial, participants in the structured treatment interruption arm complained their health was suffering (Kavuma 2006). The Centre for Research on Multinational Corporations (SOMO 2008) criticized the study for reasons listed above.</p>	
<p>References</p>		
	<p>ACT-UP Paris. DART: a fact sheet. Paris: ACT-UP, 11 December 2006. Available at: http://www.actupparis.org/IMG/pdf/Fact_sheet_on_problems_with_DART.pdf (accessed 24 February 2012).</p>	
	<p>Centre for Research on Multinational Corporations (SOMO). SOMO briefing papers on ethics in clinical trials: #1: examples of unethical trials, updated February 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 14 December 2011).</p>	
	<p>Danel C, Moh R, Chaix M-L, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. <i>J Infect Dis</i> 2009; 199: 66-76.</p>	
	<p>Danel C, Moh R, Minga A, CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomized trial. <i>Lancet</i> 2006; 367: 1981-1989.</p>	
	<p>DART trial team. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/μl. <i>AIDS</i> 2008; 22: 237-247.</p>	
	<p>Development of Anti-Retroviral Therapy in Africa – a randomized trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa. Available at: http://www.controlled-trials.com/ISRCTN13968779/13968779 (accessed 14 December 2011).</p>	
	<p>Development of Antiretroviral Therapy in Africa. Protocol number 1.2. 24 August 2004. Available at: http://www.actupparis.org/IMG/pdf/DART-PROTOCOL.pdf (accessed 14 December 2011).</p>	

Kavuma RM. AIDS research kill 50 – angry activists claim. Weekly Observer (Uganda), 8 Jun 2006.
Pant Pai N, Tulsy JP, Lawrence J, et al. Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD005482. DOI: 10.1002/14651858.CD005482.
The Strategies for Management of Antiretroviral therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. NEJM 2006; 355: 2283-2296.

1.5 Cameroon, Ghana, and Nigeria, 2004-2006: Trial of pre-exposure prophylaxis (PrEP) to prevent HIV infection among high risk women

Study identification	
Study name:	Study of tenofovir disoproxil fumarate (TDF) for prevention of HIV
US research organization:	Family Health International (FHI)
US funders:	Gilead, NIH, Bill and Melinda Gates Foundation
Study ID number:	ClinicalTrials.gov identifier: NCT00122486
Study synopsis:	
<p>This was a phase 2 trial (safety and efficacy) of daily oral tenofovir for HIV prevention among women with multiple sex partners. The study enrolled and randomized 936 women: 400 in Ghana, 400 in Cameroon, and 136 in Nigeria. Recruitment and follow-up went as planned in Ghana. After activists in Cameroon and Paris raised ethical concerns, government of Cameroon cut short follow-up, and Family Health International stopped recruitment and follow-up in Nigeria. The study team reported that the intervention (daily oral tenofovir) reduced HIV incidence by 65% (with a 24% chance the reduction was a statistical error).</p>	
Ethical issues	
Alleged offenses	Relevant DoH, CFR clause
Participant information sheets and informed consent forms were not available in a relevant language when recruitment began (French).	DoH 24; CFR 46.116
The project did not provide women with female condoms.	DoH 6, 11
The project did not assure post-trial access to the intervention drug.	DoH 14, 33
The project did not arrange antiretroviral treatment for women who contract HIV infections during the trial.	DoH 6, 11
Vulnerable participants (women in sex work) may not have received adequate special protections.	DoH 9
Public criticism, investigations, litigation	
<p>Non-government organizations (NGOs) in Cameroon (Reseau Ethic Droit et SIDA) and France (ACT-UP) brought four ethical concerns (first four listed above) to Family Health International, government of Cameroon, and the media (Yomgne 2009). Several practices criticized in the Cameroon portion of this trial (no assured post-trial access to the intervention drug; no assured antiretroviral treatment for women who contract HIV during the trial) have been common in HIV prevention trials in Africa. What was unique with respect to this trial was that local and European organizations criticized these practices. The Centre for Research on Multinational Corporations (SOMO 2008) noted, inter alia, that vulnerable sex workers “may not have received the required special protections.”</p>	
References	
Centre for Research on Multinational Corporations (SOMO). SOMO briefing papers on ethics in clinical trials: #1: examples of unethical trials, updated February 2008. Available at: http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (accessed 14 December 2011).	
FHI 360. Study of Tenofovir disoproxil fumarate (TDF) for prevention of HIV. Clinicaltrials.gov, 2006. Available at	

	http://clinicaltrials.gov/ct/show/NCT00122486 (accessed 13 December 2011).
	FHI ends clinical trial of ARV drug Tenofovir. Plus NEWS, 10 Aug 2005.
	Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, Grant R, et al. Tenofovir disporxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2007; 2: e27. Available at: http://clinicaltrials.plospubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pctr.0020027#s5 (accessed 13 December 2010).
	The trials of Tenofovir trials. Lancet 2005; 365: 1111. Available at: http://www.thelancet.com/journals/lancet/article/PIIS014067360571850X/fulltext (accessed 13 December 2011).
	Yomgne CT. The Cameroon experience, pp 19-28 in: Ukpong M, Peterson K. Oral Tenofovir controversy II: voices from the field. Lagos: New HIV Vaccines and Microbicides Society, 2009. Available at: http://www.nhvmas-ng.org/publication/TDF2.pdf (accessed 13 December 2011).

2. Ethical Issue: Following people at risk without warning them of their risk

Background

In 1988, the US Office for Protection from Research Risks established the policy that “Individuals may not be given the option ‘not to know’ the result” of their HIV test (Department of Health and Human Services [DHHS], Policy on informing those tested about HIV serostatus; available at: <http://www.hhs.gov/ohrp/policy/hsdc88jun.html>). Despite this policy, the US government subsequently funded studies of risks for HIV in Africa that enrolled and followed participants who did not receive their HIV test results at baseline or during follow-up. One defense researchers give for following HIV-positive participants who do not know they are infected is that the participants do not want to know. But there is another way to approach the issue: If someone does not want to receive their HIV test results, the researcher can refuse to enroll them in the study.

Moreover, several US policies direct health care providers who are aware that a patient is HIV-positive to take steps to warn his or her sexual partners. DHHS tells health care providers working for the Department: “To the extent possible, known partners...shall be notified that they may have been exposed to HIV” (DHHS, PHS policy on partner notification, 1990; available at: <http://www.hhs.gov/ohrp/policy/hsdc90may.html>). Moreover, US law requires states receiving federal funds for specific health programs to ensure that “a good faith effort be made to notify a spouse of a known HIV-infected patient that such spouse might have been exposed to the human immunodeficiency virus” (DHHS, A compilation of the Ryan White CARE Act of 1960, available at: http://www.caear.org/downloads/RW_1996_amendments.pdf).

2.1 Uganda, 1989-ongoing: Study of HIV transmission and HIV-related mortality in a large rural cohort

Study identification	
Study name:	Rakai Community Cohort Study
US research organization:	Columbia University, Johns Hopkins University
US funders:	NIH, Rockefeller Foundation, USAID, John Snow Inc.
Study ID number:	Current NIH grant number: 5U01AI075115-05
Study synopsis:	
In 1989, the study began to follow an open cohort of more than 1,000 rural adults in Rakai, Uganda. The study expanded to circa 12,000 adults in 50 villages from 1994/95. The study has tested adults for HIV every 10 months to a year, and has at times tested children. The cohort	

<p>has been used as the basis for many studies. For adults who wanted to know their HIV status, the project offered HIV tests and counseling. As of 1994, only 10% of participants knew their HIV status; this increased to 80% by 2002 (p. 41, Kumwenda 2008). In recent years, the study has encouraged people to learn their HIV-status and to share it with their partners (Kairana 2011).</p>		
<p>Ethical issues</p>		
	<p>Alleged offenses</p>	<p>Relevant DoH, CFR clause</p>
	<p>Not protecting participants (HIV-negative partners of HIV-positive men or women): The study followed HIV discordant couples (one spouse infected, the other not infected) who were not aware of their situation to observe spouse-to-spouse HIV transmission. For example, during 1994-98, the project followed 415 discordant couples, recording 90 new infections in formerly HIV-negative spouses (Quinn 2000). In a large subsample of these couples “56% of HIV-1-positive partners...had requested and received HIV counseling, and 25% stated that they had informed their spouses” (p. 1152, Gray, Wawer, et al., 2001).</p>	<p>DoH 3, 11; CFR 46.111(a)(1)</p>
	<p>Not protecting participants (uninfected babies of HIV-positive mothers): The study followed pregnant and breastfeeding HIV-positive women not aware they were infected and their babies to study mother-to-child HIV transmission. During 1994-98, the study identified 725 HIV-positive pregnant women. Only 49% of all pregnant women received their test results (Gray, Wabwire, et al., 2001). The project followed babies to age 2 years, determining that 16% were infected before or during birth and 16% during a median 20 months of breastfeeding (Brahmbhatt 2006). Prevention of mother-to-child transmission was possible: In 1994, the US Public Health Service recommended zidovudine to reduce mother-to-child transmission by two-thirds (Lurie 1997). Even if this intervention is deemed too difficult for Uganda, the project could have protected infants by warning HIV-positive mothers to avoid breastfeeding after 6 months.</p>	<p>DoH 3, 11; CFR 46.111(a)(1); CFR subpart D: additional protections for children</p>
	<p>Not protecting participants (HIV-positive adults): The study followed HIV-positive participants who did not know they were infected, without offering them prophylaxis for opportunistic infections or antiretroviral therapy (ART), to record participants’ HIV-related sickness and death. During annual home visits, the study team asked about and looked for symptoms characteristic of opportunistic infections and recorded deaths. During 1994-98, the death rate for HIV-positive adults was 19.8 time greater than for HIV-negative adults. Survival with AIDS was often less than 1 year (Sewankambo 2000). Not until the President’s Emergency Plan for AIDS Relief (PEPFAR) arrived in 2004 did the study arrange ART for HIV-positive participants.</p>	<p>DoH 3; CFR 46.111(a)(1)</p>
<p>Public criticism, investigations, litigation</p>		
	<p>In 2000, the editor of the New England Journal of Medicine criticized the study for not warning spouses at risk, noting that “such a study could not have been performed in the United States” (p. 967, Angell 2000). Gisselquist criticized the study for following and not warning in a 2008 book and 2009 article (see references, below).</p>	

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2.2 Zimbabwe, 1997-2001: Trial of vitamin A to prevent mother-to-child HIV transmission

Study identification		
Study name:	Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO)	
US research organization:	Johns Hopkins University	
US funders:	USAID; Bill and Melinda Gates Foundation; Rockefeller Foundation	
Study ID number:	ClinicalTrials.gov identifier: NCT00198718	
Study synopsis:		
<p>This randomized controlled trial enrolled 4,495 HIV-positive mothers within 4 days of delivery, and then followed mothers and babies for up to 2 years, observing HIV infections and deaths in the children (Humphrey 2005). In the intervention arms, the trial gave mothers and/or babies vitamin A to see if it would reduce mother-to-child HIV transmission; it had no effect. As the study was designed (p. 951, Piwocz 2005) "Mothers could learn their [HIV test] results at any time during the study..., but they were not required to do so. This feature makes ZVITAMBO unique. All other studies of infant feeding and HIV have been conducted among mothers who knew their HIV status."</p>		
Ethical issues		
Alleged offenses		Relevant DoH, CFR clause
Not protecting participants (HIV-negative babies of HIV-positive mothers): The study did not warn HIV-positive mothers they were infected and could infect their children through breastfeeding. Only about 15% of HIV-positive women learned their HIV status during the 2 years of the project (Piwocz		DoH 3; CFR 46.111(a)(1); CFR subpart

2005). One hundred and forty-one HIV-positive mothers infected their babies, presumably through breastfeeding, between month 6 and month 24 after delivery (Humphrey 2010).	D: additional protections for children
Public criticism, investigations, litigation	
Gisselquist criticized the study for following and not warning in a 2008 book and 2009 article (see references in section 2.1, above).	
References	
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2.3 Uganda, 2003-07, continuing to 2013: Trials of male circumcision to protect men or women from HIV infection

Study identification		
Study name:	Two studies are linked: Male Circumcision for HIV Prevention in Rakai, Uganda (NCT00425984); Trial of Male Circumcision: HIV, Sexually Transmitted Disease (STD) and Behavioral Effects in Men, Women and the Community (NCT00124878).	
US research organization:	Johns Hopkins University	
US funders:	The National Institutes of Health (NIH) funds NCT00425984; the Bill and Malinda Gates Foundation funds NCT00124878	
Study ID number:	ClinicalTrials.gov identifiers: NCT00425984, NCT00124878	
Study synopsis:		
<p>The study funded by NIH recruited 4,996 HIV-negative men, randomly assigning them to the intervention group (to be circumcised) or to the control group (to remain intact). Over two years the study reported men in the circumcised group acquired HIV only 49% as fast as men in the control group. The NIH study refused to recruit men who did not want to hear the results of their HIV test; “willing to hear HIV results” was an inclusion criteria (ClinicalTrials.gov, NCT00425984).</p> <p>The study funded by Gates enrolled men and women, including those who did not want to hear their HIV test results, as follows: (a) 922 HIV-positive men, (b) HIV-negative men who did not want to hear the results of their HIV test; and (c) 3,700 women partners of HIV-positive men in both the NIH- and Gates-funded studies. The study randomized HIV-positive men to be circumcised or to remain intact, then followed wives to see who got HIV. Wives of circumcised men acquired HIV 49% faster than wives of men who remained intact.</p>		
Ethical issues		
Alleged offenses		Relevant DoH, CFR clause
Not protecting participants (HIV-negative men and women with HIV-positive spouses): The study followed HIV discordant couples (only one spouse infected) not aware of their situation to observe spouse-to-spouse HIV transmission. In the trial of circumcising HIV-positive men to see if it		DoH 3; CFR 46.111(a)(1)

<p>affected HIV transmission to their wives, the study followed 159 HIV-negative wives, of which 25 acquired HIV. The trial did not insist that HIV-positive men learn their test results and tell their wives.</p> <p>In the trial of circumcising HIV-negative men to see if it protected them from HIV infection, the study tested the HIV status of several thousand wives, but did not insist that they learn their test results or that they share their results with their husbands. The study reported 49 HIV infections among men reporting no non-marital relationship, but has not reported the HIV-status of any wives (Gray 2007).</p>	
Public criticism, investigations, litigation	
Gisselquist (2011) has noted and criticized this aspect of the project.	
References	
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3. Ethical Issue: Exposing babies to unnecessary risks

3.1 Gambia and Kenya, 2010-2012: Trial of an HIV vaccine in children

Study identification	
Study name:	<p>The trial can be found under several names:</p> <p>In documents of the European and Developing Countries Clinical Trials Partnership (EDCTP), the trial has a short name, PedVacc, and a long name, Development of an infant vaccine against mother-to-child transmission of HIV-1 through breast milk.</p> <p>In the Pan African Clinical Trials Registry the name for the portion of the trial in Gambia is: Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-uninfected mothers.</p> <p>In the Pan African Clinical Trials Registry the name for the portion of the trial in Kenya is: Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-infected mothers.</p>
US research organization:	University of Washington
US funders:	The Bill and Melinda Gates Foundation

Study ID number:	Kenyan trial: Pan African Clinical Trials Registry, and WHO's Integrated Clinical Trials Registry Platform identifier: PACTR2009010001152787 Gambian trial: Pan African Clinical Trials Registry identifier PACTR2009010001152787	
Study synopsis:		
<p>These are Phase 1/2 trials to study vaccine safety and immune response, but are not designed to study its effectiveness in stopping HIV. The stated overall goal of these and proposed HIV vaccine trials in infants is to develop a vaccine to prevent mother-to-child transmission of HIV through breast milk. The MVA.HIVA vaccine used in these trials is “a component of a more complex future vaccine” that “has been previously tested in 13 studies in the UK and Africa, involving a total of 375 adult volunteers and is safe and well tolerated” (EDCTP 2011) but has not demonstrated effectiveness in preventing HIV.</p> <p>The Gambian trial administered HIV vaccine to 24 5-month old healthy infants with HIV-negative mothers (not infected with either HIV-1 or HIV-2) and a placebo to 24 similar children in a control group. The trial followed children for 36 weeks, with the last follow-up visit in October 2010 (Afolabi 2011).</p> <p>The Kenyan trial planned to administer HIV vaccine to 36 5-month old healthy HIV-negative infants with HIV-1-infected mothers and a placebo to 36 similar children in a control group (Pan African Clinical Trials Registry, PACTR2009010001152787). In the Kenyan trial, intervention and control groups were both divided into sub-groups of breastfed and formula-fed children. As of April 2011, 20 children had received the HIV vaccine (Okwemba 2011). The trial follows children for a year and is expected to end in 2012.</p> <p>A parallel trial, funded by the Medical Research Council of the UK and European and Developing Countries Clinical Trial Partnership tested the vaccine among children in South Africa.</p>		
Ethical issues		
Alleged offenses	Relevant DoH, CFR clause	
Not protecting children: Because current WHO recommendations to give mothers and babies antiretroviral drugs can reduce mother-to-child HIV transmission during breastfeeding to approximately 0.2% per month only (WHO 2010), and because no vaccine tested among adults shows more than a marginal impact on HIV transmission, there is little reason to expect for the foreseeable future that a vaccine would have much impact on children's risk for HIV. There is no good reason to submit babies to unknown risks with an unproven and likely ineffective vaccine.	DoH 3; CFR 46.111(a)(1); CFR subpart D: additional protections for children	
Public criticism, investigations, litigation		
Rebecca Project (2011) criticized an earlier vaccine trial in Ugandan children.		
References		
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	Pan African Clinical Trials Registry. PACTR2009010001152787. Available at: http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?.nfpb=true&_pageLabel=portals_app_atmregistry_portal_page_10_page_11 (accessed 26 February 2012). [This appears to describe the Kenyan trial.]
	Plus News, Nairobi. Steady progress in infant AIDS vaccine trials. 27 April 2011. Available at: http://www.plusnews.org/PrintReport.aspx?ReportID=92591 (accessed 9 February 2012).
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	WHO, international clinical trials registration platform. Safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1/2-infected mothers [in Kenya], last updated 7 February 2012. Available at: http://apps.who.int/trialsearch/Trial.aspx?TrialID=PACTR2009010001152787 (accessed 9 February 2012).

4. Ethical Issue: Not reporting and investigating adverse events

Background

To protect research participants anywhere in the world, researchers who are funded by agencies of the US government that accept the Common Rule (45 CFR 46) as well as their US institutional review boards and US-based managing institutions are legally obligated to report and investigate “unanticipated problems.” An unanticipated problem is a serious adverse event that appears to be linked to someone’s participation in research (Office for Human Research Protections, Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events, 15 January 2007, available at: <http://www.hhs.gov/ohrp/policy/advevntguid.html>).

4.1 Kenya, 2002-06: Trial of male circumcision to protect men from HIV infection

Study identification	
Study name:	Male circumcision and HIV rates in Kenya
US research organization:	University of Illinois, Research Triangle Institute, University of Washington
US funders:	NIH
Study ID number:	ClinicalTrials.gov identifier: NCT00059371 International Standard Randomized Controlled Trial Number: ISRCTN47258104
Study synopsis:	
The trial recruited 2,784 men willing to be circumcised, then on a random basis assigned half	

<p>to an intervention group to be circumcised first and half to a control group to remain intact (uncircumcised) until the end of the study. The study team followed and retested all men – circumcised and intact – at scheduled visits over as long as 2 years. The study reported that men in the intervention (circumcised) group got HIV only 47% as fast as men in the control group. Overall, 69 men got HIV during the trial.</p>		
Ethical issues		
	Alleged offenses	Relevant DoH, CFR clause
	<p>Not reporting and investigating unanticipated problems: The trial reported incident HIV infections in 4 men one month after circumcision (tests found no HIV in blood from the baseline survey). Three of the 4 men reported no sexual activity during the month (Bailey 2007). Among circumcised men, HIV incidence at the rate of 3.8% per year during the first month after circumcision (calculated from 4 infections in 1,268 circumcised men) exceeded average annual incidence of less than 1% during the remainder of the trial. Possible paths for HIV transmission during circumcision include contaminated skin-piercing instruments and contaminated multidose vials of local anesthetic. The study’s published account of adverse events does not recognize or include these (reportedly) non-sexual HIV infections shortly after circumcision as adverse events. There is no indication the study team, institutional review board, institutions managing research funds, or the Office for Human Research Protections considered these infections to be unanticipated problems to be reported and investigated.</p>	DoH 15; CFR 46.109(e)
	<p>Not protecting participants: Failure to investigate unanticipated problems may have left participants receiving circumcisions and other procedures from the study with unknown and avoidable risks.</p>	DoH 3, 11; CFR 46.111(a)(1)
Public criticism, investigations, litigation		
	<p>Gisselquist identified HIV infections statistically linked to circumcisions provided by the project as unanticipated problems in an article (Gisselquist 2009) and in a letter to the Office for Human Research Protections (OHRP). The OHRP responded in a letter denying the infections were unanticipated problems.</p>	
References		
	<p>Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. <i>Lancet</i> 2007; 369: 643-656.</p>	
	<p>ClinicalTrials.gov. Male circumcision and HIV rates in Kenya, last updated 28 May 2008. Available at: http://clinicaltrials.gov/ct2/show/NCT00059371?term=NCT00059371&rank=1 (accessed 8 February 2012).</p>	
	<p>Gisselquist D. HIV infections as unanticipated problems during medical research in Africa. <i>Account Research</i> 2009; 16: 199-217.</p>	

4.2 Malawi, 2003-05: Case control study of women’s risks for HIV incidence

Study identification		
	Study name:	Intravaginal treatment of disturbances of vaginal flora among infected and uninfected women in Malawi
	US research organization:	Johns Hopkins University
	US funders:	Bill and Melinda Gates Institute for Population and Reproductive Health; Johns Hopkins Bloomberg School of Public Health; 3M Pharmaceuticals

Study ID number:	ClinicalTrials.gov identifier: NCT00140764	
Study synopsis		
<p>This case control study of risks for HIV incidence was embedded in a randomized controlled trial of the impact of routine use of metrodinazole gel on the incidence of bacterial vaginosis in a total of 1,686 HIV-negative and HIV-positive women. The gel had modest impact on the prevalence of bacterial vaginosis, but no impact on HIV incidence. The study tested women for HIV and collected information on behavioral risks every 3 months. In a review of data from 27 cases (women who acquired HIV infection) and 54 controls (women who remained HIV-negative), the study team noted that use of hormone injections for birth control at the previous quarterly visit was associated with a 10.4 times greater risk to test HIV-positive at the current visit.</p>		
Ethical issues		
Alleged offenses		Relevant DoH, CFR clause
Not reporting and investigating unanticipated problems: Based on the reported 10.4 times greater risk for incident HIV in women receiving hormone injections, an estimated 24 (77%) of the total 31 incident infections observed during the trial were statistically linked to hormone injections (according to standard epidemiological analyses and terms, the population attributable fraction of HIV incidence associated with hormone injections is 77%). This statistical link could be pointing to contaminated injections, to the impact of hormones on women's susceptibility to HIV from sexual contact, and/or to some other factor. It could also be a statistical accident. The study protocol suggests the project clinic administered some if not all hormone injections. An investigation could determine if unsafe hormone injections in the study clinic infected women with HIV.		DoH 15; CFR 46.109(e)
Not protecting participants: Failure to investigate unanticipated problems may have left participants receiving hormone injections and other procedures from the study with unknown and avoidable risks.		DoH 3; CFR 46.111(a)(1)
Public criticism, investigations, litigation		
<p>Gisselquist called attention to HIV infections statistically linked to hormone injections as unanticipated problems in a journal article (Gisselquist 2009) and in letters to the Office for Human Research Protections (OHRP) and to Johns Hopkins. The OHRP responded in a letter that the project was not under their jurisdiction; Johns Hopkins has not responded.</p>		
References		
<p>ClinicalTrials.gov. Intravaginal treatment of disturbances of vaginal flora among infected and uninfected women in Malawi, last updated 9 August 2011. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00140764 (accessed 8 February 2012).</p>		
<p>Gisselquist D. HIV infections as unanticipated problems during medical research in Africa. <i>Account Research</i> 2009; 16: 199-217.</p>		
<p>Kumwenda NI, Kumwenda J, Kafulafula G, Makanani B, Taulo F, Nkhoma C, Li Q, Taha TE. HIV-1 incidence among women of reproductive age in Malawi. <i>Int J STD AIDS</i> 2008; 339-341.</p>		
<p>Kumwenda JJ, Makanani B, Taulo F, et al. Natural history and risk factors associated with early and established HIV type 1 infection among reproductive-age women in Malawi. <i>Clin Infect Dis</i> 2008; 46: 1913-1920.</p>		
<p>Taha TE, Kumwenda NI, Kafulafula G, et al. Intermittent intravaginal antibiotic treatment of bacterial vaginosis in HIV-uninfected and -infected women: a randomized clinical trial. <i>PLoS Clin Trials</i> 2007; 2: e10. Available at: http://clinicaltrials.plospubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pctr.0020010 (accessed 14 December 2010).</p>		