Designing research in vulnerable populations: lessons from HIV prevention trials that stopped early

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Activist groups have been successful in promoting research and better treatment for people with HIV infection, but they can also stop trials if their views are not considered

Methods to prevent HIV infection are one of the most urgent global public health needs.[1] One novel method in clinical trials is pre-exposure prophylaxis with the antiretroviral drug tenofovir. The trials have, however, been criticised by activist groups, citing human rights, ethical concerns, and a lack of community involvement.[2] This opposition and media coverage has stopped two trials in Cambodia and Cameroon and threatens the stability of planned and recruiting trials among intravenous drug users in Thailand and other developing nations. The issues raised by activists, academics, and the research community highlight the poor communication between these stakeholders and the need for mutual understanding of values. The differences threaten to undermine the progress of prevention trials and ultimately affect the most important stakeholders, those who are at risk.[3]

Trials stopped early

Cambodia

The first randomised trial planned to assess the safety and efficacy of prophylactic tenofovir was in Phnom Penh, Cambodia. The study, funded by the US National Institutes of Health and the Bill and Melinda Gates Foundation, planned to recruit 960 sex workers and was led by researchers from the United States and Australia.[3] In July 2004, activists mounted the first large demonstration against the trial at the Gilead booth at the International AIDS Society conference in Bangkok, a protest that captured the world's media attention.[4] This protest, as well as local remonstration to the Ministry of Health in Cambodia, resulted in the Cambodian prime minister closing the trial before recruitment.

The government has provided no official reasons for its decision. The primary scientific reasons identified by activists and sex worker advocacy groups are a lack of safety data supporting the long term use of tenofovir in healthy participants and starting phase II trials when phase I trials have not been conducted in HIV negative participants.[4] In addition, activists objected to the lack of long term insurance against adverse events, inadequate care for participants who seroconvert during the trial, and lack of community involvement in design of the trial (table).[5]

Cameroon

In February 2005, another trial in Cameroon was suspended by the national Ministry of Public Health.[2] Media attention again acted as a catalyst, raising concerns about the quality of treatment provided to participants and the quality of care that might be provided afterwards. Act up Paris, an international AIDS activist group that participated in the Bangkok protest, collaborated with Réseau Éthique Droit et Santé, a Cameroon based AIDS activist group, to protest against the trial.[4] A documentary examining the activists' allegations on French television made the trial international news.

STR/AFP/GETTY IMAGES

This protest at the 2004 International AIDS Society Conference helped stop the Cambodian tenofovir trial

In response to the allegations, the Cameroon government established an independent inquiry into the trial. The Ministry of Public Health ruled that the trial could not proceed without regular reporting and a formal accreditation of the satellite trial clinic as a study site.[6] The inquiry subsequently recommended that the trial resume after the trial administrators had dealt with the reporting issues and attained site accreditation. However, in July 2005, Family Health International, who organised the study, announced that the suspension was too long to allow the trial to continue collecting efficacy data and closed the trial.

Nigeria

In March 2005, Family Health International announced that the Nigerian arm of the tenofovir trial would stop early. It voluntarily closed the trial because of logistical difficulties that illustrate the challenge of conducting research in resource poor settings.[7] In conjunction with the external, independent data and safety monitoring committee, the organisation determined that the study team was unable to comply with the required operational and laboratory procedures.

P+ *Details of current trials are on bmj.com*

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BMJ 2005;331:1403–6

Trials of prophylactic tenofovir that have stopped early

Country	No of participants		Reasons for early termination
	Planned	Randomised	
Cambodia	960 sex workers	0	Participant groups criticised: lack of post-trial insurance for adverse events, inadequate care for those who seroconvert during the trial, and no community involvement in planning the trial
Cameroon	400 sex workers	400	Participant groups cited lack of adequate informed consent and education regarding prevention; an investigation by the Cameroon ministry of health did not agree with accusations
Nigeria	400	136	Trialists determined that the study team was unable to comply with the required operational and laboratory procedures

Activists report that they will continue to protest against trials of prophylactic tenofovir in other countries (see bmj.com).[8 9]

Contention

Activist groups argue that because the primary outcome in the trials is HIV infection, researchers may provide less than adequate counselling to prevent infection. They identify that the primary outcome of interest may also show inadequate counselling. Participants have been requested to reduce the number of sexual partners during the trial. Activists argue that this recommendation is unrealistic for impoverished sex workers and doesn't reflect adequate counselling. In Cameroon, participants were provided with male condoms as a proved prevention strategy. Activists argue that as the women may not make the decision about safe sex, female condoms should have been provided.[9]

Advocacy groups for sex workers have widely argued against enrolling sex workers into trials as they are a vulnerable population and may not receive the intervention if it proved beneficial. The trials of nonoxynol-9, which was found to increase genital ulceration, have been used as an example of trials increasing risk among participants from this community.[10] Sex workers are at a higher risk of infection because of the number of sexual partners and their vulnerability in negotiating safe sex. Activist groups argue that statistical power does not justify enrolling solely this vulnerable subgroup and excluding the general population from trials.

Consumer research

The closure of these trials shows the ability of activists and non-governmental organisations to engage the media and bring about change.[4] Such activism is not in response to research per se but to research that is perceived as unethical. Although such tactics may seem extreme, some groups are experienced at bringing about change and have strong lobbying potential. The research community must conduct trials according to the highest ethical standards and to meet new ethical concerns as they emerge. Just as involving the participant groups in planning trials is important, engaging in discussion with the activist groups and incorporating and addressing ethically sound concerns at an early stage may prevent dissent and prevent the trial from becoming a media spectacle.[3]

Of course, such discussion will not necessarily succeed in building a working relationship. However, the current situation in which researchers, study participants, communities, and advocacy groups work in isolation and opposition is clearly ineffective. Waiting for (inevitable) conflicts to occur serves no useful purpose, squanders time and resources, engenders enmity, and fosters misunderstanding. We have little to lose and much to gain from innovations in collaborative and cooperative research designs.

Such an approach should be initiated early in the research process and include consultation both with communities that are being invited to participate in the trial and wider civil society.[11] Local consultation could comprise focus group discussions with research participants and interested community based organisations and the establishment of standards for community advisory boards.[12] Wider consultation could occur through open invitation public forums or responsible media coverage.[4] Such a partnering approach could foster a communal sense of ownership in the research and help prevent a damaging break in relations should disputes arise.

In the Cambodian and Cameroon trials, the trialists conducted formative research at the outset of the trial but did not reach all activist communities. Indeed, it is probably impossible to reach all groups.[13] This shows the difficulties that trialists have in determining the legitimacy of stakeholder groups. Both countries have many advocacy groups for sex workers. Trialists did engage sex worker groups, but not all of them, which created hostility among those excluded.

Consumer research, founded on social marketing principles, may be an effective way to engage all the interested parties before the trial and deal with difficulties before they escalate.[14–16] Consumer research has already been used to raise awareness in the community and identify concerns at the onset of the AIDS prevention programmes.[14] This research has been used to shape the development and dissemination of the intervention messages.[15]

Impending difficulties

As well as identifying issues of concern, researchers must reach agreement with stakeholders on strategies to resolve these issues. The current protests against a trial of prophylactic tenofovir among intravenous drug users in Thailand is a good illustration.[8] The Thai Drug Users Network, a respected human rights organization, and other Thai AIDS advocacy groups, oppose the planned trial, citing ethical flaws in the design and lack of community involvement. They argue that their attempts to discuss issues with the trial investigators have been rejected.[8] The activists are concerned that recruiting participants at methadone clinics may represent coercion and withholding the provision of clean injection equipment is unethical.

Clean equipment is a standard prevention tool and would be offered to trial participants in other countries. However, the US government policy prohibits the provision of needles to intravenous drug users in US funded projects. Thailand has been criticised for

inadequate harm reduction policies for intravenous drug users and the government's war on drugs has been blamed for widespread crimes against humanity affecting intravenous drug users.[17] Instead participants will be offered follow-up in a methadone drug treatment programme and receive bleach and instructions on how to use it to clean needles.[18] This trial highlights the need for researchers to advocate for the rights of participants and the duty to care.[19] The concerns identified by the Thai advocacy groups and the pledge of allegiance from international activist groups raise concerns that this trial may also close early if the differences are not resolved.

Importance of activism

The importance of activism is not in question here. Most investigators and advocates for HIV and AIDS patients laud the work of activist groups in attracting the world's attention to the HIV epidemic.[20] Activism has an important role in ensuring that researchers and sponsors maintain ethical standards and adapt trials as new ethical concerns emerge. Indeed, many researchers consider themselves activists. Most activists and advocacy groups are aiming to promote and protect the rights of individuals who are unable to voice their own concerns. Their concern is warranted considering recent examples of research that have taken advantage of participants in resource and education poor settings.[21–24]

In the tenofovir trials standard of care has been an important issue for activists. Since the roll out of the World Health Organization's "3 by 5" programme to increase access to antiretroviral drugs, the question should no longer be if infected participants should have access to antiretroviral drugs but how. Many researchers seem not to have caught up with this shift. The planned care for participants who seroconvert during the tenofovir trial is counselling and referral for treatment.[25] In the Family Health International trials, participants receive symptomatic medical treatment until they reach the WHO criteria for AIDS, at which time they would get antiretroviral drugs. Advocates argue that best proved therapeutic interventions should be available internationally, as stated in the Helsinki Declaration article 30.[26] Others aim to be more pragmatic in developing nations and argue for a standard of care relative to that routinely available in the respective countries.[27] In Cambodia, Cameroon, and Thailand, standard care does not include antiretroviral therapy for patients with CD4 counts below 0.2×10^9/l.

The Council for International Organizations for Medical Sciences guidelines state that "Any product developed through such research [should] be made reasonably available to the inhabitants of the host community or country at completion of successful testing."[28] In the case of tenofovir, Gilead has stated that the drugs would be available to the host countries at cost. Researchers need to anticipate criticisms and be ready to answer local demands for equity and defend research in less developed countries.

Summary points

Activism has contributed to the closure of two trials of pre-exposure prophylaxis with tenofovir to prevent HIV infection in developing countries

Criticisms have centred around ethics of the trial design, inadequate care after the trial, and lack of consultation

Researchers need to engage with all stakeholders to ensure ethical concerns are identified and dealt with early on

Strategies to improve dialogue between activists, participants, and researchers

Develop sustained dialogue through standardised community advisory boards, fact finding missions, and education on key issues

Create national ethics committees that can set clear guidelines on national practice and over-rule foreign committees and train local ethics committees with community membership

Host nations should define standard care—national guidelines may prevent the values of foreign activists or researchers from guiding clinical trials in host countries

Before a trial the host nation should agree a definition of effectiveness and determine access to and the cost of the intervention in their country

Increase community participation—engage and educate a wide range of stakeholders as active and informed partners in decision making about the research

Ensure documented medical follow-up of participants after the study to monitor adverse events related to trial interventions

In communities and countries where the rights of the target community are threatened, researchers should determine if it is appropriate to engage in research, seek help from human rights monitors when appropriate, and advocate for their participants if they are able to do so

Strategies for change

The tenofovir trials have challenged the scientific community and the activist and advocacy communities. We have to learn from the difficulties of these trials and move forward in an educated and prepared manner so as to engage the activists, participants, and researchers to resolve differences. The box proposes strategies that may resolve several of the key concerns of activist and participant groups. These strategies will require widespread discussion with patient and participant groups as well as activists, ethicists, and clinical researchers. This proposal reinforces the need for consideration of human rights and ethical and social dimensions of research from the inception of a trial to its completion and dissemination.

The HIV activist community has shown that its powerful lobbying skills can be used to promote research as well as to stop it. By engaging activist and participant groups at an early stage, we can hope to prevent philosophical divides. We cannot combat AIDS effectively without research and development of new technologies, especially in resource constrained

settings. While we search for the magic bullet that would make research undeniably ethical, the complex challenge is to link research in resource poor settings to the services demanded by poor people.[29] Today's AIDS research environment is no longer local but global in the actual conduct of research and in its implications for health policy and access to safe and effective methods of diagnosis, prevention, and treatment. The era of researchers, study participants, and activists living in separate silos must come to an end if meaningful progress is to be made in halting the HIV pandemic.

Contributions: All authors contributed to the concept, writing, and critical revisions and approved the final manuscript.

Competing interests: None declared.

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(Accepted 2 September 2005)

A patient who changed my practice

Honesty is the best policy

A few years ago, I had just obtained my first job at specialist registrar level and was posted to a new hospital. Having only limited endoscopy skills, I was naturally apprehensive about the responsibilities of the new job and the expectations of being a specialist registrar. After the morning induction period, I was suddenly told that I was due on the endoscopy unit that afternoon and was expected to do my own list as the previous registrar had done over the past year. Supervision was provided by a consultant doing another list in an adjoining room.

After a brief introduction of myself to the nursing staff, I was hustled off to the endoscopy room. There I was confronted with a different set of equipment from what I had used before. The endoscopes were from a different manufacturer and had a different feel and image quality to them. Nevertheless, I was determined to carry on and prove myself to be capable.

The first two cases went well, but I could still feel the eyes of all the staff in the room on me as they assessed the new registrar. The third case proved to be much more difficult and, try as I might, I could not obtain adequate views of the distal oesophagus. I could feel the tension and impatience building as time ticked by, and the patient became more restless. I asked for the consultant to come over and have a look but was told that he was in the middle of a difficult procedure and could not leave his patient.

I would be lying if I claimed that it did not cross my mind to say that the procedure was now complete and provide a report saying everything looked normal. Fortunately, I did not and arranged for the patient to be rescoped on another list, when a small lesion was found in the distal oesophagus and biopsies confirmed adenocarcinoma.

This incident drummed into me several important lessons:

- Always be honest about what you see and find on your examinations: saying something is normal when you have not conducted an adequate examination is unacceptable
- Do not attempt unsupervised procedures for which you are not adequately trained—insist on having someone present if you are unsure about your capabilities
- When starting a job in a new environment get familiar with your equipment before attempting a procedure
- Do not succumb to the pressure around you: you may need to prove yourself capable, but patient safety and care come first.

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