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

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. 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. 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.

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. 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. 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. 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).

Cameroon

In February 2005, another trial in Cameroon was suspended by the national Ministry of Public Health. 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...
Activists report that they will continue to protest against trials of prophylactic tenofovir in other countries (see bmj.com). Activists 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.

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. 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.

### Contention

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### Consumer research

The closure of these trials shows the ability of activists and non-governmental organisations to engage the media and bring about change. 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.

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. Local consultation could comprise focus group discussions with research participants and interested community based organisations and the establishment of standards for community advisory boards. Wider consultation could occur through open invitations public forums or responsible media coverage. 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. 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. Consumer research has already been used to raise awareness in the community and identify concerns at the onset of the AIDS prevention programmes. This research has been used to shape the development and dissemination of the intervention message.

### 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. 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. 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. 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. This trial highlights the need for researchers to advocate for the rights of participants and the duty to care. 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. 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 inadequate settings. Poor settings.

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

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 countries.
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." 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 and 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.

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