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# Sex partners as bystanders in HIV prevention trials: Two test cases for research ethics

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**Abstract**

Research involving human subjects can impose risk on some 'bystanders'– people who are not themselves research subjects but whom the study may affect. We examine the consequences of research for a particular category of bystanders – research subjects' sex partners – in trials testing interventions to reduce (1) HIV transmission (HIV treatment-as-prevention trials) and (2) HIV acquisition (HIV pre-exposure prophylaxis trials). Both types of trials provide useful test cases for assessing whether bystanders to research deserve special consideration in ethics reviews, and potentially some of the benefits and protections that research subjects receive. In HIV treatment-as-prevention trials, there are two groups of people who are alike in many important respects but treated very differently by research ethics: research subjects who contribute data on the primary endpoint of the trial (because some of them have sex with the people receiving the treatment conditions of the trials) – and bystanders who are not enrolled in the trials but who could have contributed primary endpoint data in the same way as the first group. In pre-exposure trials, the sex partners of people participating in pre-exposure prophylaxis trials are bystanders, even though they are necessary for the success of the trial. Research subjects' autonomy is fiercely protected by trial enrolment processes. Bystanders, by contrast, often have no choice but to be affected by the study, because of their relationship to a research subject. In HIV prevention trials, standing by can come with important risks, including the same ones on which the success of the research hinges. It is thus important to consider the ethical obligations to protect bystanders, and the related procedural responsibilities.

**Keywords**

Trial ethics, research subjects, bystanders, HIV prevention, HIV treatment-as-prevention, HIV pre-exposure prophylaxis

## Prevention of HIV transmission: HIV treatment-as-prevention trials

Several large, population-based treatment-as-prevention trials have recently been carried out in sub-Saharan Africa[1–5] to test the hypothesis that high levels of HIV treatment coverage can reduce HIV incidence at the population level. In these trials, the people who receive the treatment conditions are not the same as the people in whom the endpoint is measured. The latter are people who are HIV-negative at the inception of the trial, live in the communities participating in the trials, and have given their individual consent to participating in the HIV incidence cohorts required for endpoint assessment.[1,2,4,5] As research subjects, these people are protected by the rules and processes of formal ethics review and oversight. The reason why the people enrolled in the HIV incidence cohort are needed for the research is that some of them will have sex with the people receiving the treatment conditions of the trials. The comparison of HIV incidence among those who have sex with the trial participants receiving the intervention versus the control condition is a measure of the effectiveness of treatment-as-prevention in preventing the transmission.

Other people, however, will also have sex with the people who are receiving the treatment conditions of the trials. These people face many of the same risks as those enrolled in the incidence cohorts of the trials – such as increased risk of HIV acquisition because of behavioural risk compensation, or increased risk of acquiring a resistant strain of HIV because of resistance

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development. These people are bystanders, because they face study-borne risks without being study subjects.

There are thus two groups of people who are alike in many important respects but treated very differently by research ethics regulations and by the resulting processes. The first group is research subjects who contribute data on the primary endpoint of the trial, because some of them have sex with the people receiving the treatment conditions of the trials. The second group is bystanders who are not enrolled in the trials but who could have contributed primary endpoint data in the same way as the first group, because some of them also have sex with the people receiving the treatment conditions. Indeed, in several of the treatment-as-prevention trials, the people offered participation in the HIV incidence cohorts for endpoint assessment are randomly selected from the larger population of people who are HIV-negative and live in the communities where the trials take place.[1,2] This random selection into trial participation ensures that the two groups will indeed be equal in all respects, with the exception of the prospective endpoint measurement.

The existence of the two groups raises questions for research ethics. Ought these two groups be treated equally within the trial operations? Should they have similar consent rights? Should they receive the same benefits and protections, such as, in one of the treatment-as-prevention trials, 'on-the-spot voluntary counselling and testing using rapid HIV test kits' and referral 'to a health centre for further management' if an HIV test is positive?[2] Currently, only one group – those who contribute endpoint data – receives those benefits and protections. The other group – bystanders – does not.

## Prevention of HIV acquisition: HIV pre-exposure prophylaxis trials

Administering antiretroviral drugs to people who do not have HIV, but who are at high risk of contracting the disease, is commonly referred to as HIV pre-exposure prophylaxis. The hope is that pre-exposure prophylaxis will prevent acquisition of HIV if someone is exposed.[6] Sex partners of people participating in pre-exposure prophylaxis trials are bystanders as well, but of a very different type. In these trials, sex partners are necessary in order to ensure that some primary research subjects are at risk of incident HIV infection, the endpoint of the trial. Indeed, in pre-exposure prophylaxis trials, having a sex partner is often an inclusion criterion.[7,8] The sexual partners who 'stand by' are thus not only intimately connected to the research subjects but also a necessary requirement for the success of the research. And these bystanders face potential risks from the research subjects' participation in the pre-exposure prophylaxis trial. Such risks include the risk of becoming infected with a resistant strain of HIV – for example, if the trial subject adheres only partially to the pre-exposure prophylaxis regimen,[9] or increased risk of acquiring another sexually transmitted disease – if the trial subject 'compensates' for the perceived reduced risk of HIV acquisition by increasing the frequency of unprotected sex.[10] Bystanders who are sexual partners of people participating in pre-exposure prophylaxis trials may also face a range of other risk, such as stigma, dignitary harms, HIV status disclosure and violence. Stigma and dignitary harms could come to the 'community' of trial participants' sexual partners, if it became known that many of them are HIV-positive and can thus transmit the virus. HIV infections observed in a pre-exposure prophylaxis trial imply that a participant's sex partner is HIV-positive, which might lead to status disclosure and violence. Some pre-exposure prophylaxis trials are conceived as 'couple studies', enrolling both partners in HIV-discordant couples. Many others, however, enrol only the person who receives pre-exposure prophylaxis, while her sex partner remains an unenrolled bystander – unknown to the trial management and without the benefits, consent rights, and protections that research subjects typically receive.[11]

## Benefits and protections for bystanders?

Both treatment-as-prevention and pre-exposure prophylaxis trials provide useful test cases for assessing whether certain bystanders to research deserve special consideration in ethics review, and potentially some of the benefits and protections that research subjects receive. For instance, research subjects' autonomy is fiercely protected by trial enrolment processes. By contrast, bystanders are rarely informed about the trial and its nature. Often their relationship to the trial subject leaves them no choice except to be affected by the study. In HIV prevention trials, standing by can come with important risks, including the same ones on which the success of the research hinges. It is thus important to consider the ethical obligations to protect bystanders, and the related procedural responsibilities.

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