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SUPPLEMENT ARTICLE

Is it ethical to isolate study participants to prevent HIV transmission during trials with an analytical treatment interruption?

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This commentary considers an extreme idea for protecting against human immunodeficiency virus (HIV) transmission to sex partners of individuals participating in HIV remission studies with an analytical treatment interruption (ATI). Other human challenge studies, such as studies of influenza, commonly isolate participants during the trial, to protect their contacts and the community against infection. Why should HIV studies with a treatment interruption be any different, one might wonder? This article concludes that isolation should not be used in HIV remission studies with an ATI but also shows that the matter is complex.

Keywords. HIV; research ethics; analytic treatment interruption; HIV cure–related studies; human challenge studies; isolation.

This journal supplement discusses ways to protect nonparticipants from human immunodeficiency virus (HIV) infection during HIV remission studies that include an analytical treatment interruption (ATI). The protections discussed so far have their limitations. For example, offering preexposure prophylaxis and education to study participants' sex partners in stable relationships would not be 100% effective for protecting them, and it would do nothing to protect sex partners in unstable relationships [1]. How, then, can overall protection be enhanced further?

A somewhat-parallel difficulty arises in the growing number of human challenge studies, in which people are being deliberately exposed to or infected with diseases [2]. Challenge studies must shelter participants' contacts and communities against infection.

In recent influenza challenge studies at the NIH Clinical Center, participants remained in hospital isolation for at least 9 days, presumably in order to protect their contacts from getting infected. For examples, see the following studies: Influenza A H3N2 Human Challenge Study in Healthy Adult Volunteers (NCT02594189), Influenza A 2009 H1N1 Challenge Study in Healthy Adults (NCT01646138), and Evaluation of Anti-Hemagglutinin (Anti-HA) Antibodies as Protection From the Flu in Healthy People (NCT01971255). Isolation was also used in other challenge studies that pose a risk to nonparticipants [2]. Commenting on a British typhoid and paratyphoid vaccine challenge study in which participants slept at home, an investigator estimated that such a study, which has a small risk of infecting nonparticipants if participants shed organisms and flush them down the toilet, could not take place in the US [2].

Some ethicists might support mandatory isolation for participants in HIV remission studies during any ATIs. After all, some urged considering isolation in any infectious disease study: "Careful study design may reduce the likelihood of creating indirect participants through strategies such as isolating the direct subject until the likelihood of contagion has passed. Otherwise, people may be subject to risks of the study… even though they are not themselves subjects of the research" [3] (p. 180).

This perspective asks whether, in HIV remission studies with an ATI, it would be justified to isolate study participants as a protection against HIV transmission. It argues that isolation is unwarranted but also that the ethics is complex. There is nothing wrong about the use of isolation in itself (consider the extreme case of patients with Ebola, including infected study participants), but certain factors can make it inappropriate in specific cases. While the extreme option of using isolation is not on the table for HIV remission studies with an ATI, understanding the case against it could help develop a consistent comprehensive approach to infectious disease studies and may become relevant to policy should this extreme option ever be proposed for these studies.

Let us start by explaining what is not wrong with isolation to protect nonparticipants whose sex partners are enrolled in HIV remission studies with an ATI.

TWO INCONCLUSIVE REASONS AGAINST ISOLATION

Isolation is a gross intrusion into a person's liberty. By itself, however, this reason against using isolation remains inconclusive,

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if, for example, notwithstanding the intrusion, isolation is on balance justified in some of the challenge studies mentioned above. Where a third party might be seriously infected, many arguments for maximal personal liberty do not apply. In particular, John Stuart Mill's no-harm principle generally forbids the transgression of a person's liberty for that person's own sake. But it permits liberty transgressions that prevent significant bodily harm to others [4]. While known HIV infection is manageable, it still seems like a clear case of bodily harm, and infection of sex partners in unstable relationships might remain unknown and far less manageable, potentially posing very serious harm.

Isolation of subjects in studies that include ATIs may also dissuade some from participating. This might be thought to stifle research too much. But current early-phase HIV remission trials typically require only a few participants. In fact, in some HIV remission or sterilizing-cure studies that include ATIs, building in some disincentive to participate may make decisions on whether to participate more balanced, because participants sometimes underappreciate the medical risks that participating in a trial would create for them [5, 6]. Objectively, isolation in a hospital or in a hotel environment for a limited period is arguably a smaller personal risk than interrupting antiretroviral therapy, at least in set point designs [7]. Yet the former risks may be plainer to lay patients and more effectively dissuade potential participants from inattentive volunteering. When a cure-related study involves serious risks to participants, a fully attentive decision on whether to participate matters greatly [8–10].

THE REAL CASE AGAINST ISOLATION

Nevertheless, mandatory isolation remains a bad idea for HIV remission studies with an ATI. First, HIV is less transmissible than some of the pathogens studied with isolation (including, in recent investigations, influenza virus, *Shigella*, norovirus, *Mycobacterium tuberculosis*, rhinovirus, *Salmonella typhi*, and *Giardia*) [2]. This means that even the worst-case scenario, in which a study participant's sex partner is infected and then transmits HIV to her own partners, does not risk a large outbreak and certainly not a pandemic. The limited potential channels of transmission also make it somewhat safer to count on the decision-making ability of participants, as well as on frequent counseling sessions addressing transmission precautions, as protections than it is in the case of airborne infections such as tuberculosis. It also means that there are relatively easy and effective precautions that sex partners should be using anyhow, partially undermining any sex partner's ethical standing to curb study participants' liberties for their partners' sake.

Additionally, the challenge studies mentioned above typically require isolation for less than a fortnight. This is far easier to accept than the presumably months-long isolation that some HIV remission studies with an ATI would require.

The bottom line is that there is a big quantitative difference between these challenge studies and HIV remission studies with an ATI. While the sheer fact that liberty is transgressed is not enough to defeat categorically any form of isolation, the large gap in the length of necessary isolation, as well as in transmissibility and, in some cases, virulence, matters. On balance, those weigh more than the risk of infection from avoiding isolation, in our judgment.

There is also a practical complication. Consider what to do if, during the ATI, a participant wishes to withdraw from the trial—one of the core rights of study participants [11]. They should then have the same rights as untreated HIV-infected individuals—namely, in the United States, every right to sleep wherever they are invited. One practical resolution might have been to mandate isolation only so long as the infectious person counts as a study participant. But complications arise. If the participant understands and internalizes this fully, it may create a disincentive to stay in the study and to protect nonparticipants. On the other hand, if her comprehension is lacking, this would undermine the quality of both her consent and the protective information that she may give nonparticipants. All that counts further against using isolation as a protective measure.

Finally, in the context of HIV, during Ronald Reagan's presidency it took so much activism to get the quarantine option off the table for all HIV-infected patients that there may be a historical case for not risking any sliding back. While actual quarantine policies are no longer realistic, stigma against people living with HIV remains a big hindrance, as does formal discrimination against them [12]. In the United States, people living with HIV/AIDS who are aware of their status and knowingly expose others commit a felony in many states that treat knowing exposure to deadlier diseases as a mere misdemeanor [13, 14]. And the shadow of quarantine has come to be associated in public memory with such stigma and with discrimination in general. To introduce isolation for HIV in any context risks confirming in some people's minds that that stigma and other injustices remain warranted [15]. Admittedly somewhat speculative, this risk to many people living with HIV arguably weighs more than the (less-than-definitive) risk to participants' sexual partners.

CONCLUSION

Isolation of study participants is a bad way to prevent onward transmission of HIV in remission studies that include an ATI, but only on balance. The case against that protection is more complex and less decisive than it may initially appear. There is a strong initial ethical impetus in favor of using this protection alongside many others in these studies. And there is no categorical flaw with this particular protection. Isolation is a poor solution, primarily for reasons that apply to this case but not to some other infectious disease studies. The reasons are simply that, in the case of HIV, transmissibility is relatively manageable and that, in remission studies with an ATI, in particular, isolation would have to be unacceptably long. Practical complications would also arise when a participant asks to withdraw from a study. And any isolation

policy would risk exacerbating stigma, given the public memory of the early days of the HIV/AIDS epidemic.

Notes

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