

The importance of replicating results from randomised trials

Although I share the impatience of Kuhn and colleagues¹ to accelerate implementation of new HIV prevention methods, particularly for young women, I believe their criticism of the importance of replicating results from randomised controlled trials is misplaced. Their argument concerns studies of tenofovir gel, a vaginal product inserted around the time of sexual intercourse to prevent HIV infection. In 2010 this product was shown to reduce the risk of HIV by 39% (95% CI 6–60) when used by women in KwaZulu Natal according to the BAT24 regimen.² A further study among women in South Africa, Uganda, and Zimbabwe with the same product but used daily irrespective of anticipated or actual occurrence of intercourse was already underway when the first study results were announced and eventually showed no protective effect (risk reduction 15%, 95% CI –21 to 39).³ A third study, designed to replicate closely the South African study was launched in 2011 and also showed no reduction in HIV risk—incidence 4 per 100 person-years in both study arms.⁴ Poor adherence to product use was considered the most likely explanation for the divergent study results, despite intensive motivational counselling to use the product as intended.

Rather than considering these trials as “disastrous, because their results now cast inappropriate doubt on the preventive effects of tenofovir”, I believe we have learnt a great deal. Even if tenofovir gel does reduce the risk of HIV infection when used as intended (which is not yet established), either the effect is too small to overcome departures from the prescribed schedule, or the product is too difficult or impractical to use by the very women it is intended to protect. There are grave dangers in using a product of uncertain efficacy

to prevent HIV infection, not least the false sense of security, and diversion of resources from discovering and promoting a method that is both efficacious and easier to use. Replication is a powerful approach and I fully support the requirement of regulatory authorities to require stronger evidence than a single study with a significant p value before considering a product for licensure.

I declare no competing interests.

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Authors' reply

Tim Farley's letter precisely illustrates our argument, that unless a high level of adherence can be assured, a randomised controlled trial is the wrong design from which to assess efficacy of a treatment. His inference that these trials cast doubt on the efficacy of the product is flawed. True, as he notes, some useful information on adherence can be gleaned from the two so-called replication trials of the tenofovir gel, but no useful information can be gleaned about efficacy.

Although Farley may claim to share our impatience, we do not share his pessimism that the product is too difficult or impractical to use. We agree that adherence is a challenge and that additional formulations and approaches are needed. However, blinded randomised trials are not the most sensible study design to learn

about adherence. We do not doubt that the investigators worked hard to achieve adherence in their trials but the blinded design works against them. Designs that directly harness the motivation and intentions of women by informing them what product we wish them to use have a much greater likelihood of yielding results that are relevant to ultimate use.

In the meantime, the field has moved on. We now know a great deal about biological and social processes involved in using antiretroviral drugs for HIV prevention. Policy makers are now better informed about the potential uses and abuses of the placebo-controlled randomised trial design. We trust that regulatory agencies will now not misinterpret the results of these trials to derail the burgeoning global movement to make antiretroviral prophylaxis accessible to women.

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PrEP: why we are waiting

Scientific research has proven that pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV transmission in men who have sex with men. Therefore, the people are now asking decision makers why we are waiting.¹ So far, research on PrEP has primarily focused on apparently objective aspects of PrEP, such as biomedical effectiveness and costs. Normative aspects have received little attention, such as people's own responsibility to use a condom, the relevance of being free of fear for HIV infection when having sex, and the

relative importance of preventing HIV versus a possible rise in other sexually transmitted diseases because of reduced condom use. We argue that this lack of attention explains why we are waiting. Decision makers do not only base their decisions on the objective aspects, they are also responsive to normative arguments put forward by various stakeholders.

Such normative arguments are common in the popular media and raise questions on desirability.² PrEP has been labelled a “fun-pill”,³ only taken to avoid use of condoms by people with little regard for their own responsibility to stay healthy. We recently did an analysis of the perspectives of Dutch stakeholders on PrEP for men who have sex with men,

involving decision makers, citizens, advocacy groups, and potential PrEP users. Our survey confirmed that the introduction of PrEP currently hinges on normative issues.⁴

To facilitate decision making for the introduction of PrEP at the national level clarification of both objective and normative considerations is crucial. The research community can play an important part in doing ethical analyses, as a basis for a broader social debate on the desirability of PrEP. This is what we are waiting for.

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