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Vaginal Tenofovir Gel Trial Results Suggest Substantial Nonsexual HIV Transmission

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Abstract

Abdool Karim and colleagues demonstrated that vaginal tenofovir gel provides partial protection against HIV in South African women. However, the study design of their double-blind, randomized, placebo-controlled CAPRISA 004 trial did not allow for determining the mode of HIV acquisition for participants with incident infection. The available evidence suggests substantial nonsexual transmission. Trial participants' reported exposure to HIV through penile-vaginal sex, at the aggregate level, was unrelated to HIV incidence over time. Moreover, the CAPRISA 004 trial data imply a questionably high nominal per act transmission probability for coital acts without a condom (1.8% in the tenofovir gel arm and 3.0% in the placebo arm). Based on the results of dosing studies, the vaginal tenofovir gel appears to be a somewhat inefficient vehicle for delivering tenofovir systemically, thereby serving to prevent HIV acquisition from either blood or sexual exposures. Further analysis of the trial data and making the full trial protocol and data public would allow competing interpretations of the CAPRISA 004 results to be investigated. New trials that include critical design features for determining modes of HIV transmission would provide the most definitive evidence.

Article

Abdool Karim and colleagues recently reported the results of the CAPRISA 004 double-blind, randomized, placebo-controlled trial of vaginal tenofovir gel for preventing HIV infection in South African women [1]. The CAPRISA 004 researchers demonstrated that vaginal tenofovir gel provides partial protection against HIV, with a 39% reduction in annual HIV incidence (5.6% in the gel arm vs. 9.1% in the placebo arm). They interpreted the trial results as indicating that the gel inhibited sexual transmission. Actually, their study design does not allow for such an inference. As with all prior HIV prevention trials in sub-Saharan Africa [2], the CAPRISA 004 trial involved no effort to ascertain modes of transmission or sources of infection.

Several design features are necessary to determine modes of HIV transmission, including: comprehensive assessment of both blood and sexual exposures in persons with incident HIV and in uninfected persons, tracing of their contacts, and DNA sequencing of infected persons' HIV isolates [3-5].

Even without such rigorous evidence, the available information from the CAPRISA 004 trial suggests significant nonsexual HIV transmission in trial participants. Five women reported no sex during the whole 30-month observation period, and one of these women seroconverted. The frequency of coital acts declined dramatically during follow-up, as did coital acts without condom use (by approximately 70% in the authors' Figure 3), while HIV incidence decreased only slightly in the tenofovir (by 7%) and placebo (by 18%) arms. That is, reported exposure to HIV through penile-vaginal sex, at the aggregate level, was unrelated to incident HIV.

Moreover, the CAPRISA 004 trial data imply a questionably high nominal per act transmission probability for coital acts without a condom. Based on participants' number of person-years, reported frequency of coitus and condom use during the trial, number of seroconversions, and HIV prevalence in men in KwaZulu Natal (trial site), the overall estimated nominal transmission probability per penile-vaginal act is 2.4% (see Appendix). Corresponding estimates of the nominal transmission probability per act are 1.8% in the tenofovir gel arm and 3.0% in the placebo arm. These conservative estimates are an order of magnitude higher than the estimate derived from a meta-analysis of studies involving self-reported vaginal exposures in poor countries [6], which itself may be inflated due to confounding by unmeasured blood exposures [7].

The high CAPRISA 004 trial transmission probability estimates suggest that the absolute level of protection provided by the tenofovir gel is quite low. Moreover, in a double-blind, randomized, placebo-controlled trial of oral tenofovir for preventing HIV infection in African women [8], nominal transmission probabilities per penile-vaginal act were much lower, even if higher than expected (0.2% for women in the oral tenofovir arm and 0.6% for women in the placebo arm) (see

Appendix).

Both the very high nominal transmission probability per penile-vaginal act associated with tenofovir gel and the protective effect of tenofovir gel compared to placebo may point to HIV acquisition through nonsexual routes. Vaginal application of tenofovir gel results in some systemic absorption, with apparently greater absorption during first use than after two weeks of daily use [9]. Intermittent use of the gel in the CAPRISA 004 trial (intended for application 12 hours before and 12 hours after penile-vaginal sex and an observed mean of 5 applications per month) might produce systemic absorption similar to first use. The amount of tenofovir absorbed systemically from the vaginal gel is lower than that from a standard 300 mg oral dose of tenofovir (received by participants in the oral tenofovir trial [8] and by patients with established HIV infection). However, one-quarter (75 mg) of this standard oral dose of tenofovir is sufficient to reduce HIV viral load by approximately one-third in patients with established HIV infection [10]. Thus, the amount of tenofovir absorbed from the gel might be sufficient to inhibit establishment of infection some of the time, given the far fewer virions and affected cells after initial HIV entry. This interpretation is consistent with the weaker protective effect in the CAPRISA 004 trial (incidence rate ratio = 0.61) than in the oral tenofovir trial (incidence rate ratio = 0.35) [8], even though this difference is not statistically reliable because of low incidence in the oral tenofovir trial. The protection provided by oral tenofovir was considerable despite participants' moderate adherence (< 70%) to the daily medication regimen. In short, the vaginal tenofovir gel may simply be an inefficient vehicle for delivering tenofovir systemically, which then serves to prevent HIV acquisition from either blood or sexual exposures.

Both our and CAPRISA 004 researchers' interpretations of the trial results are speculative. The only way to evaluate the merit of the competing hypotheses is to conduct trials incorporating the critical design features we highlighted. Until then, the precise mechanism of effect is a black box.

Analyses can be performed with existing CAPRISA 004 data to probe modes of transmission. For instance, the authors could compute the HIV incidence for intervals in which women reported consistent condom use or no sexual contact (including women who did report sexual contact during other intervals). Furthermore, multivariate analyses are needed of the association between time-varying factors and incident HIV. Such analyses should be conducted separately by trial arm and include month-by-month data on factors such as the number of coital acts without a condom, number of coital acts with a condom, number of anal sex acts, gel use adherence, and pregnancy termination (representing potential blood exposures involved with induced or spontaneous abortion; for those with < 3 months of discontinued gel use), as well as baseline characteristics, including a specific indicator of injectable contraception use. Such time-dependent analyses are closer to the spirit of investigating an infectious disease (as HIV is acquired at particular points in time in relation to specific exposures and protective factors, such as tenofovir use, at immediately prior points in time). The authors' analyses (their Table 2), such as those that control for baseline characteristics only, do not reflect the dynamics of infectious disease transmission. The urgency for thorough analysis and more rigorously designed trials is underlined by accumulating evidence of bloodborne HIV transmission through unhygienic healthcare and rituals in sub-Saharan Africa [11-18].

Regardless of any additional analyses CAPRISA 004 trial researchers perform, it is incumbent on them to make de-identified trial data and the complete trial protocol publicly available in accordance with Science's (http://is.gd/ijh32) and the National Institutes of Health's (http://is.gd/ijhbi) policies that apply to the CAPRISA 004 trial. Data sharing is essential for credible science [19], and in this case may be especially useful for understanding the paradoxical CAPRISA 004 trial results.

Appendix

The formula we used to estimate the nominal per penile-vaginal act HIV transmission probability is:

number of seroconversions /

(mean number of coital acts per month X % of coital acts without a condom X 12 months X person-years X HIV prevalence in local adult men).

Table A1 shows the empirical estimates of these parameters and the resulting transmission probabilities. Ordinarily, these probabilities would be computed with individual level data, but such data were not available to us. Therefore, we used parameter estimates based on aggregate data. This would cause error in our estimates only if reported number of coital acts was associated with reported rate of condom use during coitus.

To estimate HIV prevalence in women's probable sex partners, we relied on probability sample serosurvey data from the same communities where the trials were conducted. For the CAPRISA 004 trial, we used the estimated HIV prevalence among adults age 15 to 49

in KwaZulu-Natal in 2008 [20]. This is likely an overestimate of the prevalence in CAPRISA 004 participants' partners, because women, especially in the age of range of participants, were several times more likely to be HIV infected. To the extent this is the case, the resulting transmission probability is underestimated.

In the oral tenofovir trial [8], participants were recruited from Douala, Cameroon (43%), Tema (in greater Accra), Ghana (42%), and Ibadan, Nigeria (15%). Participating women generally had frequent sex and many partners, and most were assumed to work as prostitutes. We used a three-step process to estimate the HIV prevalence in their male sex partners. First, we noted the HIV prevalences among men age 15 to 49 in Douala (3.6%) and greater Accra (1.6%) from the corresponding Demographic and Health Surveys (conducted in 2004 in Cameroon and in 2003 in Ghana) [21-22]. Then we computed the HIV prevalence ratio in each country between urban men who reported having ever paid for sex and those who had reported not having done so (Cameroon = 3.4, Ghana = 1.2) (frequencies were too small for the particular communities for such calculations). Finally, we multiplied the HIV prevalences for men in Douala and greater Accra, respectively, by the corresponding prevalence ratios for urban men in their countries, and averaged the results (7.1%). To our knowledge, there are no probability sample data on HIV prevalence in men in Ibadan.

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Illustrations

Illustration 1

Table A1

. Estimated nominal per penile-vaginal act HIV transmission probabilities

Trial	Person-years	Mean number of coital acts /month	Mean % of coital acts without a condom	Seroconversions	Estimated prevalence (%) in local adult men	Estimated nominal per act transmission probability (%)
CAPRISA 004[a]						
Overall	1341.3	5	19.7	98	25.8[e]	2.4
Tenofovir gel arm	680.6	5[c]	19.7[c]	38	25.8[e]	1.8
Placebo gel arm	660.7	5[c]	19.7[c]	60	25.8[e]	3.0
Oral tenofovir trial[b]						
Overall	473.9	60	8	8	7.1[f]	0.4
Tenofovir arm	232.6	60[c,d]	8[c]	2	7.1[f]	0.2
Placebo arm	241.3	60[c,d]	8[c]	6	7.1[f]	0.6

[a][1]

[b][8]

[c]Data reported only for trial participants overall in source article [1].

[d]Reported weekly average multiplied by 4.

[e][20]

[f][21-22]

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