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# Correspondence

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## Serious concerns regarding a meta-analysis of preexposure prophylaxis use and STI acquisition

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An article in *AIDS* by Kojima and colleagues posits that high unadjusted rates for sexually transmitted infections (STIs) among preexposure prophylaxis (PrEP) users in five studies, compared with low unadjusted rates for PrEP nonusers in 14 studies [1], reflect increased sexual risk behaviors following PrEP uptake. They conclude with a call to reconsider how this important HIV prevention strategy is implemented.

Distortions of these findings were disseminated by activists opposing widespread PrEP implementation. One large provider of HIV treatment and testing services, summarized the research letter as ‘a damning new report. . . showing a dangerous link between the usage of PrEP by MSM and an astronomical increase in STIs [2].’ In an effort to understand more about the claims of Kojima *et al.* [1], we reviewed the data and the analyses and found several serious problems.

First, Kojima *et al.* [1] presented only unadjusted analyses comparing PrEP users and nonusers from different studies. The findings only indicate higher STI rates in the PrEP-using compared with the non-PrEP-using samples, not an increased rate of STIs. These PrEP-using and non-PrEP-using samples also differ in their distributions of other factors associated with STI acquisition, including year, race/ethnicity, sex, HIV status, and age [3,4].

STI incidence for men who have sex with men (MSM) has seen dramatic increases in the past decade that may help explain the findings [4]. Condomless anal sex (CAS) among MSM also increased from 2005 to 2014 [5]. Four of five PrEP studies were published in 2015–2016, whereas all but two non-PrEP studies were published before 2015. Kojima *et al.* [1] did not address the increases in STI incidence and CAS that predated widespread PrEP availability. We further note that although PrEP availability has expanded recently, uptake remains low among some groups with elevated rates of STIs, including MSM of color [6,7]. In other words, factors other than PrEP may explain both increases in STI rates and differences among MSM groups.

Second, Kojima *et al.* [1] included the EXPLORE study for which they indicated 36 628 person-years of observation and an ‘any STI’ rate of 5.8/100 person-years (<http://links.lww.com/QAD/A944>). Inclusion of this massive study disproportionately influenced the overall non-PrEP STI rate estimate of 6.4 per 100 years despite the higher incidence rates in the other much smaller studies of non-PrEP users.

More problematic is that EXPLORE did not fit the inclusion criterion of Kojima *et al.* [1] for studies with ‘incidence rates reported with nucleic amplification testing.’ Per EXPLORE investigator, Beryl Koblin, PhD (personal communication, 11 October 2016), EXPLORE ceased testing for bacterial STIs within its first year. EXPLORE only collected self-reports of new STIs, and its published reports are limited to self-reported chlamydia and gonorrhea cases at baseline. Furthermore, EXPLORE followed participants for a total of 12 240 person-years [8], not the 36 628 person-years provided (<http://links.lww.com/QAD/A944>).

Third, adding to the inflated risk ratio estimates caused by incorrect EXPLORE data, the letter includes inconsistent data for at least two other studies. For the PROUD study, Kojima *et al.* [1] report 276 and 124 incident STI cases for PrEP users and nonusers, respectively. The published article lists 210 cases for PrEP users and 165 for nonusers, not to mention different numbers of person-years [9]. The data of Kojima *et al.* [1] referencing the study by Burchell *et al.* [10] of HIV-positive, non-PrEP users also have incorrect estimates of MSM gonorrhea and chlamydia cases and person-years of observation for the minority who actually received STI testing.

When we recalculated the overall STI rates excluding EXPLORE and using the published numbers of incident STIs and person-years for PROUD, the STI rate in non-PrEP users versus PrEP users was 22.8/100 person-years versus 63.4/100 person-years. The data of Kojima *et al.* [1] yield estimates of 5.8/100 person-years versus 67.7/100 person-years in non-PrEP users versus users. Although the recalculated non-PrEP rate is still lower, the less extreme difference in STI rates is less prone to being sensationalized than the inflated estimate of Kojima *et al.* [1]. All of the data reported by Kojima *et al.* [1] warrant vetting and reanalyses.

Finally, persons on PrEP are monitored more closely and tested more frequently for STIs than non-PrEP users; however, Kojima *et al.* [1] do not adjust for this difference. The PROUD study, which did control for more frequent monitoring of PrEP users, did not find statistically significant differences in STI rates compared with a concurrently observed delayed control group. Furthermore, the immediate PrEP intervention group acquired significantly fewer new HIV infections despite greater frequency of receptive CAS [9]. This point of effective HIV prevention was not mentioned by Kojima *et al.* [1] and was downplayed by subsequent media.

Exaggerated and incorrect data on negative potential outcomes of PrEP use may discourage PrEP's consideration as an HIV prevention strategy. We need more evidence-based interventions to reduce STIs, not abandonment of a highly effective HIV prevention method. Indeed, it is critically important for HIV researchers to pursue how best to harness PrEP for the welfare of those at highest risk of HIV, while minimizing potential risks. We also need more STI prevention interventions, improved diagnostic and surveillance capacity, and increased STI funding. Scientific inquiry to estimate accurately relative STI rates among comparable groups of PrEP users and nonusers is relevant to both goals but must be carried out in a rigorous manner accounting for alternate explanations.

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## Conflicts of interest

There are no conflicts of interest.

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## Addressing concerns regarding preexposure prophylaxis meta-analysis

We appreciate the commentary [1] about our analysis and agree that preexposure prophylaxis (PrEP) for HIV is a critical strategy for the prevention of acquisition of HIV infection. The authors of the commentary [1]

acknowledge the importance of our findings; however, they raise concerns that our findings might partially be explained by the overall general increase in incidence of sexually transmitted infections (STIs) among MSM