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Serious Concerns Regarding a Meta-Analysis of PrEP Use and STI Acquisition

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SUMMARY:

We present serious concerns with a recent *AIDS* research letter comparing STI incidence between MSM using and not using PrEP. Findings do not account for historical increases in STI incidence, are impacted by inclusion of a large study not fulfilling stated inclusion criteria, and are based on numbers inconsistent with two published reports. Those holding anti-PrEP beliefs take liberties in their interpretations of PrEP-related findings, placing the onus on researchers to get it right.

KEYWORDS:

HIV pre-exposure prophylaxis; men who have sex with men; sexually transmitted infections; Tenofovir disoproxil fumarate
In a September 2016 article by Kojima, Davey, and Klausner (henceforth KDK2016) posit that the high-unadjusted rates observed for PrEP users in five studies, compared to the low unadjusted rates observed for PrEP non-users in 14 studies, relate to PrEP use[1]. They suggest increased behavioral risks following PrEP uptake as an explanation and recommend reconsidering how this important HIV prevention strategy is implemented.

Distortions of these findings were disseminated by activists opposing 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]. Not only are such portrayals incomplete and misleading, they may undermine efforts to stem both HIV and STIs in vulnerable communities.

The meta-analysis was presented with several caveats and limitations: (1) the mechanism(s) by which high STI incidence occurred was not identified; (2) the higher detection rates of STIs among those who may have been monitored more closely when on PrEP; (3) the inclusion of heterogeneous study populations with substantial variations in entry criteria; and (4) the selection effects contributing to who receives PrEP or is eligible for PrEP trials, with eligibility focused on higher-risk populations.

First, the research letter presented only unadjusted analyses comparing PrEP users and non-users from different studies. Therefore, the findings only indicate a higher STI rate in the PrEP-using populations compared to the non-PrEP using populations studied, not an increased rate of STIs over time due to PrEP use (as the quote above implies). PrEP and non-PrEP using populations also differ in their distributions of other factors associated with
STI acquisition, including race/ethnicity, gender, HIV status, and age[3]. For example, some non-PrEP studies included people living with HIV, whereas, all PrEP studies excluded those with detectable HIV infection.

STI incidence for MSM has seen dramatic increases that may help explain the findings. As just one example, CDC data show early syphilis cases among US MSM growing from less than 6,000 in 2007 to more than 12,000 in 2014, with the inflection point occurring before PrEP was widely available[4]. Additionally, condomless anal sex (CAS) among MSM increased from 2005-2014[4]. All but one of the included PrEP studies were published in 2015-2016 while the non-PrEP studies were published in 2004-2016, with one exception of 1998. While KDK2016 includes a sensitivity analysis excluding studies prior to 1999, this removed a single study. It did not address increases in STI incidence and CAS since 1999 that pre-dated widespread PrEP availability. It is notable that while PrEP availability has been expanding recently, uptake remains low among some groups with elevated rates of STIs, including MSM of color[5].

Second, KDK16 included the EXPLORE Study for which they indicated 36,628 person years of observation and an “any STI” rate of 5.8 per 100 person years http://links.lww.com/QAD/A944). Inclusion of this massive study produced an overall non-PrEP STI rate of 6.4 per 100 years, despite much higher incidence rates among the other, much smaller studies of non-PrEP users.

More problematic is that EXPLORE did not fit the KDK2016’s inclusion criteria of studies with “incidence rates reported with nucleic amplification testing.” Per EXPLORE investigator, Beryl Koblin, PhD (personal communication, 10/11/2016), EXPLORE ceased testing for bacterial STIs within its first year. Subsequently, EXPLORE only collected self-
reports of new STIs, and its published reports are limited to self-reported chlamydia and gonorrhea cases at baseline[6]. Since we do not have the EXPLORE dataset, we do not know whether its self-reported numbers of STI cases are consistent with KDK2016’s tables, but the number of person-years of follow-up are grossly inconsistent. EXPLORE followed participants for a total of 12,240 person-years[7], not the 36,628 person-years provided (http://links.lww.com/QAD/A944).

Third, adding to the inflated ratio estimates caused by incorrect EXPLORE data, the data in the letter’s supplemental tables are inconsistent for at least two other studies. For the PROUD Study, KDK2016 reports 276 and 124 incident STI cases for PrEP users and non-users, respectively. The published article on PROUD lists just 210 cases for PrEP users and 165 for non-users[8]. KDK2016 data referencing Burchell et al.’s study of HIV-positive, non-PrEP users also has incorrect estimates of MSM gonorrhea and chlamydia cases and person-years of observation among the minority of MSM who actually received testing[9].

When we re-calculated 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 users was 22.8/100 person-years versus 63.4/100 person-years. KDK2016’s data yields estimates of 5.8/100 person-years versus 67.7/100 person-years in non-PrEP users versus users. While the recalculated non-PrEP rate is still lower, the less extreme difference in STI rates is less prone to being sensationalized than is KDK2016’s inflated estimate. All of the KDK2016 data warrant vetting and comprehensive re-analyses.

Finally, persons on PrEP were monitored more closely and tested more frequently for STIs than non-PrEP users; however, KDK2016 do not adjust for this important covariate. The PROUD Study, which controlled for more frequent monitoring of PrEP
users in a concurrently observed population of MSM offered PrEP immediately and a
delayed control group, did not find statistically significant differences in STI rates between
groups. Furthermore, the immediate intervention group had significantly fewer new HIV
infections despite greater frequency of receptive CAS[8]. This point of effective HIV
prevention was not mentioned by KDK2016 and downplayed by subsequent media.

Exaggerated and incorrect data on potentially negative PrEP outcomes may
dissuade PrEP’s consideration as an HIV prevention strategy. We need more evidence-
based interventions to reduce STDs, not an 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 rates of STI acquisition among comparable groups of PrEP users and non-users is
relevant to both goals but must be carried out in a rigorous manner accounting for alternate
explanations.
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