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Towards equity for people who inject drugs in HIV prevention drug trials

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People who inject drugs (PWID) make up approximately 10% of new HIV infections globally and 30% outside of Sub-Saharan Africa (WHO, 2020). Substance use has driven HIV outbreaks among PWID in multiple countries, threatening efforts to end the global HIV pandemic. Despite the urgent need for novel HIV prevention strategies for this population, PWID have been largely excluded from clinical trials of pharmacologic HIV pre-exposure prophylaxis (PrEP).

It has been over a decade since the Bangkok Tenofovir Study—the single randomized PrEP trial with PWID—completed enrolment. It ultimately demonstrated feasibility and efficacy of daily, oral tenofovir disoproxil fumarate for preventing HIV among PWID. Unfortunately, PWID have been systematically excluded from subsequent drug trials evaluating new PrEP agents. For example, the DISCOVER trial of daily oral tenofovir alafenamide/emtricitabine, which expands PrEP eligibility to those with chronic kidney disease, excluded individuals with active hepatitis C infection (highly prevalent in PWID) and drug use that study investigators judged to potentially interfere with “study compliance" (Gilead Sciences, 2018).

More recently, the HIV Prevention Trials Network (HPTN) released data from two studies of long-acting injectable PrEP that aimed to address challenges with daily pill adherence. HPTN 083, a double-blind safety and efficacy study of long-acting injectable cabotegravir administered every eight weeks to cisgender men and transgender women who have sex with men was stopped early for successfully meeting specified objectives. Interim analyses showed a 66% reduction in HIV incidence in the long-acting injectable PrEP group compared with daily oral PrEP with tenofovir/emtricitabine. This trial excluded individuals

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with hepatitis C antibodies, past 90-day injection drug use, past 6-month stimulant use, and "substance use that, in the opinion of the study investigator, would jeopardize the safety of the participant in the study" (HPTN 083, 2016).

Similarly, HPTN 084 among cisgender women was stopped early for demonstrating even greater (89%) superior efficacy of long-acting injectable cabotegravir compared to daily oral tenofovir/emtricitabine. It also excluded individuals with hepatitis C antibodies or "substance use that, in the opinion of the study investigator, would interfere with conduct of the study" (HPTN 084, 2017). These recent trials, by design, systematically excluded PWID, an at-risk population standing to benefit from long-acting injectable PrEP.

These troubling exclusion criteria may reflect unfounded concerns that PWID are incapable of adhering to study protocols (which have included daily oral medications). While PrEP implementation studies with PWID remain limited, an extensive literature shows that PWID *can* achieve effective adherence to daily medications for HIV and hepatitis C with appropriate supports (Grebely & Tyndall, 2011). Further, the Bangkok Tenofovir Study provided evidence for the feasibility of achieving adequate levels of PWID adherence in a phase III HIV prevention drug trial, when coupled with directly observed therapy, study incentives, and transportation support (Choopanya et al., 2013). Promising real-world data are also emerging demonstrating that patient navigation can support even highly marginalised PWID experiencing homelessness in achieving PrEP adherence similar to other priority populations (Biello et al., 2021).

With the advent of monthly, long-acting injectable buprenorphine to treat opioid use disorder (OUD), the exclusion of PWID from trials of long-acting injectable PrEP represents a particularly significant missed opportunity, limiting the integration of these novel strategies to maximize HIV prevention for the growing number of individuals at risk for HIV due to OUD. The exclusion of PWID from HPTN 083 and 084, and the absence of a separate trial of long-acting injectable PrEP for PWID, leaves significant data gaps regarding both the safety and efficacy of long-acting injectable PrEP in preventing HIV transmission among PWID, a population that experiences both sexual and injection-related HIV exposures.

The systematic exclusion of PWID from the contemporary HIV prevention agenda is symptomatic of broader problems with equity in biomedical research. For decades, clinical trials across disease stats have failed to adequately include woman and racial/ethnic minority groups, significantly limiting the generalisability of trial results or some of the most affected populations. Widespread advocacy for represntation of previously excluded populations in clinical trials where these groups stand to benefit offers a useful equity framework for advancing PWID inclusion in the HIV prevention research agenda. (NIH, 2017) United States (U.S.) regulatory approval of daily oral PrEP with tenofovir alafenamide/emtricitabine for HIV prevention despite the exclusion of cisgender women from the DISCOVER trial led to robust critique of the U.S. drug approval process, with expert commentary concluding that "equity and inclusion in clinical trial design are essential to scientific advancement, ensuring that the benefits of innovation and drug discovery safely reach everyone in need" (Goldstein & Walensky, 2019). Unfortunately, PWID often remain left out of such calls for representation despite their clear need for novel HIV prevention strategies.

Ensuring equitable access to the full range of current and future HIV prevention technologies will require adequate inclusion of PWID in clinical research. (UNAIDS/WHO, 2021) Whether through proactive inclusion of PWID in existing clinical trials with more general populations, or contemporaneous, parallel trials designed specifically for PWID, data on the efficacy and safety of novel PrEP agents in PWID is urgently needed. Without it, clinicians will remain reticent to offer new HIV prevention drugs to PWID for whom injection behaviours are significant sources of HIV risk. Furthermore, public and private payors may not cover these drugs when injection drug use is the primary HIV risk factor, further precluding access.

Equitably including PWID in drug trials will require coordinated commitments by the scientific research community (including principal investigators, institutional review boards, and peer reviewers), regulatory agencies, and public and private funders of drug trials. Given the high degree of addiction-related stigma and criminalisation faced by PWID globally, clinical trialists must do more than revise discriminatory exclusion criteria. They will have to actively recruit PWID and ensure appropriate incentives and structural supports for this population. Given the drug using community's legitimate fear and mistrust of medical research, their collaboration on trial design will be key to their ethical inclusion. Engaging PWID in these research efforts will be critical; at a minimum, they should be included meaningfully on advisory boards and study teams. (UNAIDS/WHO, 2021) Partnerships with drug treatment programs, harm reduction agencies, and community health centres with trusted expertise serving diverse PWID will also be essential. Mere inconvenience or financial rationales for failing to adopt such strategies and foregoing inclusion of key populations should be rejected, as they have been by the U.S. National Institutes of Health in guidelines for equity in clinical research (NIH, 2017).

It is widely recognized that the global HIV pandemic will not end with the advent of effective biomedical treatment and prevention technologies alone. Combining novel prevention strategies with robust programs to address the upstream determinants of HIV transmission and treatment outcomes—homelessness, poverty, racism, gender inequity, trans- and homo-phobia and the criminalisation and stigmatisation of HIV, substance use, and transactional sex—will be crucial. Even with the availability of effective daily oral PrEP for PWID since 2013, uptake has remained limited due to these social and structural barriers. Despite the complex challenges ahead, ensuring equitable access to the full range of biomedical HIV prevention options for PWID must become a core component of our global strategy to end the HIV pandemic. The first step towards realizing such equity must begin with adequate inclusion of PWID in HIV prevention drug trials.

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