Optimising oral PrEP while awaiting long-acting cabotegravir

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Two large randomised trials of pre-exposure prophylaxis (PrEP) showed that long-acting cabotegravir administered intramuscularly every 8 weeks was superior to daily oral tenofovir disoproxil fumarate plus emtricitabine in preventing HIV infection in diverse populations.[1,2] This was not a complete surprise because earlier placebo-controlled trials had observed a low proportion of participants with drug concentrations compatible with daily tenofovir disoproxil fumarate plus emtricitabine, particularly in cisgender women in sub-Saharan Africa,[3,4] and cisgender men who have sex with men and transgender women in Latin America.[5,6] In *The Lancet HIV*, Mark Marzinke and colleagues[7] report a secondary analysis from the HIV Preventions Trials Network (HPTN) 083 trial of injectable cabotegravir, focused on the 570 participants enrolled under the umbrella of transgender women. Although the sample size was too small to achieve statistical significance, the magnitude and direction of effect were in line with the results from the overall trial population. Gender identity was only captured at enrolment and the authors recommend that this be assessed longitudinally in future trials as they observed fluidity in this demographic variable, with self-identified men who have sex with men reporting gender affirming hormonal therapy at enrolment and during follow-up. There were no differences in cabotegravir concentrations between transgender women reporting using gender affirming hormone therapy and those who did not, which is reassuring. However, additional pharmacological studies capturing the details of dosing are needed to fully assess drug–drug interactions.

Adherence in the injectable cabotegravir treatment group was high, with 92% of both transgender women and men who have sex with men receiving an injection within 2 weeks of the prescribed schedule. Adherence to tenofovir disoproxil fumarate plus emtricitabine was assessed in a random subset of participants and found to be significantly lower in transgender women than in men who have sex with men. Nonetheless, 58% had drug concentrations compatible with four or more doses of tenofovir disoproxil fumarate plus emtricitabine per week, which is more than twice that observed in preceding studies[5] in similar populations. Even though injectable cabotegravir was much more effective, this improvement in adherence to tenofovir disoproxil fumarate plus emtricitabine is encouraging. We think the reasons for this improvement are multifactorial, including greater awareness and confidence in PrEP effectiveness in the communities. Marzinke and colleagues note the need to place PrEP in a sociobehavioural context that resonates with transgender women if PrEP uptake is to improve in this community.

WHO released a new recommendation that injectable cabotegravir might be offered as part of combination HIV prevention approaches.[8] This guideline acknowledged the expansion of oral PrEP access and uptake, and the willingness of a few countries to include the dapivirine vaginal ring for cisgender women, albeit not yet provided. This somewhat cautious recommendation balances the overwhelming evidence for efficacy and a need for choice against the evidence gap for implementing a 2-monthly injectable method that might require more sophisticated HIV diagnostics than are currently available in low-income countries. Although middle-income and high-income countries are likely to have access to the diagnostics, this requirement adds to the cost of delivering a drug that is on patent and expensive compared with the generic equivalents of tenofovir disoproxil fumarate plus emtricitabine, limiting access in national programmes in a different way.

While the implementation evidence is being gathered for injectable cabotegravir, we must make the best of tenofovir disoproxil fumarate plus emtricitabine and generics. As such, WHO's 2022 technical brief on differentiated and simplified PrEP for HIV prevention[9] is most welcome. The brief embraces self-testing as an additional choice for PrEP users and provides clear guidance on starting and stopping oral PrEP for two categories of population. Cisgender men, transgender, and gender diverse populations assigned male at birth who have sexual exposure and are not taking exogenous estradiol-based hormones are in one category. They can start with a double dose (two tablets) 2–24 h before sex and stop after 2 days of single tablets (the on-demand regimen). Everyone else is in the second category, for whom a 7-day start and 7-day stop are recommended. The level of evidence supporting the double dose start is available from randomised placebo-controlled trials for the first category, but not for the second category, as

the trials have only evaluated daily oral PrEP. However, there have been well designed pharmacological studies characterising PrEP concentrations within tissue sites that facilitate modelling population effectiveness and map well to clinical trial effectiveness.[10] There is consistent support that a tenofovir disoproxil fumarate plus emtricitabine double-dose (two tablets) will achieve population effective drug concentrations within 24 h in the peripheral blood, female genital tract, and colorectal tissues. It is important for PrEP providers to ensure that PrEP users in the second category described above are educated about a double-dose start since it is not always possible to initiate daily PrEP 7 days before exposure.

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Eliminating HIV in the UK among men who have sex with men

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The number of new diagnoses of HIV among gay and bisexual men who have sex with men (GBMSM) in the UK have decreased by two thirds from more than 3000 in 2014 to around 1000 in 2021.[1] This is likely to be due to a combination of interventions. In the past decade, increased HIV testing has been implemented across various health-care settings in the UK and HIV self-testing has become available.[1] Additionally, for those diagnosed with HIV, antiretroviral therapy (ART) became available for all in 2015, regardless of CD4 cell counts—widely referred to as a treat-all strategy.[2] The development and availability of pre-exposure prophylaxis (PrEP) for people without HIV,[3] targeted at those deemed to be at highest risk, was also likely to have been influential in the decline in HIV incidence in the UK. Due to the limited availability of PrEP early on, many GBMSM self-sourced it over the internet; however, since mid-2020, PrEP has been offered free of charge to all those at risk.[3]

Despite this decrease in transmission, the estimate of around 1000 new infections among GBMSM in 2021 shows that HIV is an ongoing concern in the UK, with sex between men being the main mode of HIV acquisition. The UK government has set a target to eliminate HIV transmission, defined as fewer than 50 newly acquired infections per year among GBMSM by 2030 in England,[4] where 90% of the UK's transmission occurs.[1]

In *The Lancet HIV*, Valentina Cambiano and colleagues[5] aimed to understand the contribution of different interventions in reducing HIV incidence in the UK up to now. Additionally, they projected trends in future HIV incidence that would occur with continuation of current policies on PrEP, HIV testing, and condoms, and with scale-up of these interventions, to see if the target of fewer than 50 HIV infections per year could feasibly be reached. Last, they estimated how much money should be spent on these interventions to offer value for money. To do this, they used mathematical modelling comparing scenarios of what was observed with counterfactual scenarios including reduced HIV testing and no treat-all strategy for HIV, with or without the introduction of PrEP. They found that the introduction of PrEP and the increase in HIV testing with a treat-all strategy have each substantially reduced HIV incidence up to 2022. Indeed, without either of these interventions, HIV incidence would be double what it currently is.