Making the most of oral PREP whilst waiting for CAB-LA

Two large randomised pre-exposure prophylaxis (PrEP) trials demonstrated that long-acting cabotegravir (CAB-LA) administered intramuscularly every eight weeks was superior to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in preventing HIV infection in diverse populations.[1,2] This was not a complete surprise as earlier placebo-controlled trials had observed a low proportion of participants with drug concentrations compatible with daily TDF/FTC, particularly in cisgender women in Sub-Saharan Africa[3,4], cisgender men who have sex with men (MSM) and transgender women (TGW) in Latin America.[5,6] In *The Lancet HIV* Mark Marzinke and colleagues report a secondary analysis from one of the CAB-LA trials focused on the 570 participants enrolled in the HIV Preventions Trials Network (HPTN) 083 under the umbrella of TGW.[7] Although the sample size was too small to achieve statistical significance, the magnitude and direction of effect were in line with the overall results. 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 MSM reporting gender affirming hormonal therapy (GAHT) at enrolment and during follow-up. There were no differences in CAB-LA concentrations between TGW reporting GAHT and those who did not which is reassuring, but additional pharmacological studies capturing the details of dosing are needed to fully assess drug-drug interactions.

Adherence in the CAB-LA treatment group was high with 91.8% of TGW and 91.6% of MSM receiving an injection within two weeks of the prescribed schedule. Adherence to TDF/FTC was assessed in a random subset and found to be significantly lower in TGW compared to MSM. Nonetheless, 58% had drug concentrations compatible with four or more doses of TDF/FTC a week which is more than twice that observed in preceding studies[5] in similar populations. Even though CAB-LA was much more effective, this improvement in adherence to TDF/FTC is encouraging. We think this is multi-factorial including greater awareness and confidence in PrEP effectiveness in the communities. The authors note the need to place PrEP in a socio-behavioural context that resonates with TGW if PrEP uptake is to improve in this community.

The World Health Organisation (WHO) released a new recommendation that CAB-LA ***may*** 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 two monthly injectable method that may require more sophisticated HIV diagnostics than are currently available in low-income countries. Although middle-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 in comparison to the generic equivalents of TDF/FTC, limiting access in national programmes in a different way.

Whilst the implementation evidence is being gathered for CAB-LA we must make the best of TDF/FTC and generics. As such, WHO's 2022 technical brief on Differentiated and Simplified PrEP for HIV prevention[9], released in 2022 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, trans 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 hours before sex and stop after two days of single tablets (the on-demand regimen). Everyone else is in the second category and a seven-day start and seven-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 characterizing PrEP concentrations within tissue sites that facilitate modelling population effectiveness and map well to clinical trial effectiveness.[10] There is consistent support that a TDF/FTC double-dose (two tablets) will achieve population effective drug concentrations within 24 hours in the peripheral blood, female genital tract and colorectal tissues. It is important for PrEP providers to ensure that PrEP users who fall into the second category described above are educated about a double-dose start since it is not always possible to initiate daily PrEP seven days prior to exposure.

References:

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