Long-acting Cabotegravir for prevention – hope and reality

Sheena McCormack[1], Marta Boffito[2]

[1]MRC CTU at UCL

[2]SSAT/Imperial College, Chelsea and Westminster Hospital, London, UK

In the Lancet HIV, Markowitz et al. report the ECLAIR study assessing the safety and pharmacokinetics of the cabotegravir long-acting (CAB-LA) injections.[1] CAB-LA has been shown to prevent simian HIV infection following repeated rectal challenges,[2] and to provide high efficacy following repeated vaginal challenges.[3] These challenge studies suggest that integrase inhibitors alone can act as pre-exposure prophylaxis (PrEP) even though integration is a later step in the HIV life-cycle. In combination with long-acting rilpivirine, CAB-LA is also a promising HIV treatment approach to maintain viral suppression after induction with oral agents.[4] Considerable hope centres on the long-acting injections, as adherence to oral daily tenofovir/emtricitabine (TDF/FTC) PrEP has been low in some populations.[5] Long-acting injections for contraception have proved popular with users and public health programmes worldwide, and offering different modalities has increased uptake. Importantly, Markowitz et al. show that drug exposure in HIV-negative men who received 800mg of CAB-LA in two 2mL injections administered into the gluteal muscles every 12 weeks differed from predictions derived from mathematical models. Maximum concentrations were higher and trough concentrations lower than expected. As a consequence, the efficacy study is assessing single 3mL injections of 600mg of CAB-LA every eight weeks after two injections four weeks apart.[6] The injection phase is 52 weeks long, preceded by five weeks of oral cabotegravir or TDF/FTC, and followed by

48 weeks of TDF/FTC to minimise the risk of acquiring HIV during the long period in which cabotegravir is eliminated. Radzio et al. presented data at the 2017 Conference on Retroviruses and Opportunistic Infections on CAB-LA initiation in macaques with acute HIV infection, showing that mutations associated with resistance to integrase inhibitors (including G118R, E92Q, E92G) were selected. Some of these mutations were detected as early as eight weeks, persisted during the pharmacologic tail, and were detected in rectal and vaginal fluids, highlighting the potential for secondary transmission of these resistant viruses.[7] Injection site reactions were common in the CAB-LA group in the ECLAIR study, and may increase in severity with the larger injection volume. If this leads to discontinuation of product in the efficacy trial, the proportion completing the injection schedule may be even lower than the 82% reported by Markowitz. Nonetheless, if efficacy and acceptability are confirmed to be high, then there may be a substantial market demand in countries where injectables are common.

There is much to celebrate about the science of PrEP and the size of the pipeline, but we remain dismayed by the slow roll-out. In spite of two randomised controlled trials showing that TDF/FTC was highly effective at reducing HIV in men who have sex with men (MSM) in the UK and France[8, 9] and market authorisation, only two European countries have implemented a PrEP programme. Public health authorities cite the costs of the drug and PrEP delivery as the two most substantial barriers.[10] Uncertainty remains regarding the date when generic combinations of TDF/FTC will become available in Europe. Generic manufacturers have challenged the intellectual novelty of

Gilead's formulation, and the case is in the queue for the European Court of Justice. If the court finds in favour of the generic companies the cost of PrEP could be accommodated within current budgets through the savings made in treatment costs. Over 800 MSM have purchased PrEP via the internet and use our routine service to screen for HIV and sexually transmitted infections (STIs).[11] We saw a substantial decrease in the number of new HIV infections in 2016 in this population.[12] The fact that we still have no national programme to assist those who cannot afford to purchase their own PrEP is testimony to the complexity of evidence required to shift policy. We have to hope that this is resolved by the time we have efficacy data for CAB-LA.

Declaration of interests

SMc reports grants, non-financial support and other from Gilead Sciences plc to the institution.

MB has received speaking/advisory fees, travel grants and research grants (to the institution) from Gilead, ViiV, Teva, Cipla, Mylan, Janssen, Merck and BMS.

References

1. ECLAIR reference to add

2. Andrews CD, Spreen WR, Mohri H, et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 2014; 343:1151–1154.

3. Radzio J, Spreen W, Yueh YL, et al. The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge. Sci Trans Med 2015; 7:270ra275.

4. Margolis DA, Brinson CC, Smith GH, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis 2015;15:1145-55

5. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR et al Effectiveness and safety of oral HIV preexposure prophyllaxis for all populations AIDS 2016; 30(12):1973-83

6. https://clinicaltrials.gov/ct2/show/NCT02720094?term=cabotegravir&rank=7

7. Radzio J, Council O, Cong M, et al. Resistance emergence in macaques administered Cabotegravir long-acting (CAB LA) during acute infection. Conference on Retroviruses and Opportunistic Infections (CROI) February 13-16, 2017, Seattle WA.

8. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016;387:53-60.

9. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015;373:2237-46.

10. http://ecdc.europa.eu/en/publications/Publications/pre-exposure-prophylaxis-hiv-prevention-europe.pdf

11. Wang X, Nwokolo N, Korologou-Linden R, et al. InterPrEP: internet-based pre-exposure prophylaxis (PrEP) with generic tenofovir DF/emtricitabine (TDF/FTC) in London – analysis of pharmacokinetics, safety and outcomes. HIV Drug Therapy 2016. Glasgow, October 23-26, 2016.Abstract O315.

12. The Lancet HIV. The costs of inaction on PrEP. Lancet HIV 2017;4:e51.