Use of antiretroviral drugs to prevent the transmission and acquisition of HIV

In 2016, London became the third city in the world to achieve the United Nations 90:90:90 HIV target (90% of people living with HIV diagnosed, 90% of those diagnosed are on treatment and 90% of those on treatment have an undetectable viral load) attaining 90:97:97 (88:96:97 for England as a whole) (Public Health England, 2017). New HIV diagnoses among gay, bisexual and other men who have sex with men have also fallen for the first time since the epidemic began 30 years ago (Public Health England, 2017).

This remarkable progress is a result of a combination of interventions. This editorial outlines two of these which use antiretrovirals for the prevention of transmission and acquisition of HIV.

Preventing transmission: treatment as prevention and 'U=U'

Following the introduction of antiretroviral therapy in the 1990s, it was observed that a reduction in the HIV viral load among people living with HIV was associated with a reduction in the risk of HIV seroconversion among their HIV-negative partners (Quinn et al, 2000; Petra Study Team, 2002). In 2008, driven by a need to protect people living with HIV from criminalisation for consensual sex, Swiss experts released the following (initially) controversial statement:

Dr Nina Vora, Academic Clinical Fellow, UCL Centre for Clinical Research in Infection and Sexual Health, University College London, Mortimer Market Centre,Central and North West London NHS Foundation Trust, London WC1E 6JB

Dr John Saunders, Consultant in Genitourinary and HIV Medicine, UCL Centre for Clinical Research in Infection and Sexual Health, University College London, Mortimer Market Centre, Central and North West London NHS Foundation Trust, London

Correspondence to: Dr N Vora (nina.vora@ucl.ac.uk)

> **'HIV-positive individuals not suffering from any other sexually transmitted disease and adhering to an effective antiretroviral treatment (a blood viral load that has been consistently undetectable for more than 6 months) do not transmit HIV sexually' (Vernazza et al, 2008).**

This paved the way for discussion around treatment as prevention and several trials to provide evidence to support this statement.

The largest of these, HPTN 052, recruited 1763 serodifferent (homosexual and heterosexual) couples and randomized the HIV-positive partner to receive early or delayed antiretroviral therapy (Cohen et al, 2012). An interim analysis showed a 96% reduction of HIV transmission within couples in the early antiretroviral therapy group and no transmissions when the viral load was undetectable. In the observational PARTNER study (Rodger et al, 2016) more than 58 000 episodes of sex without condoms were reported by the 485 heterosexual and 282 men who have sex with men serodifferent couples recruited. There were no HIV transmissions observed when the HIV-positive partner had an undetectable viral load. A third study among 358 serodifferent homosexual men also found no transmissions during 17 000 sex acts when the partner with HIV had an undetectable viral load (Bavinton et al, 2014).

As a result of these studies, the undetectable = untransmittable (U=U) message, endorsed by more than 400 organizations from 60 different countries, was launched. The message is simple: a person living with HIV, on treatment, who has had an undetectable viral load for over 6 months cannot transmit HIV to his/her sexual partners. The effect of the campaign on the mental health of those living with HIV cannot be underestimated, both by assuring their partners that they do not need to fear infection and to help reduce stigma (Kall, 2018).

Preventing acquisition: pre-exposure prophylaxis

The U=U message helps those living with HIV have greater control over their sexual health and risk of transmission, but there is a need for those who are HIV negative but at risk of acquiring HIV to have control too. Pre-exposure prophylaxis (PrEP) is the use of antiretrovirals by someone without HIV in order to reduce their risk of acquiring the infection if exposed. Currently, oral PrEP using emtricitabine and tenofovir is the most commonly used form.

PrEP can be highly effective when taken correctly, with an 86% reduction in HIV acquisition seen in the PROUD (McCormack et al, 2016) and IPERGAY (Molina et al, 2015) studies. Oral PrEP has been shown to be effective among a range of key populations including men who have sex with men and transgender women (Grant et al, 2010; Molina et al, 2015; McCormack et al, 2016), people who inject drugs (Choopanya et al, 2013) and heterosexual men and women (Baeten et al, 2012; Thigpen et al, 2012). Efficacy varies depending on adherence (Marrazzo et al, 2015; Koss et al, 2017) but may also be influenced by other factors such as the presence of bacterial vaginosis in the case of vaginal preparations of tenofovir (Klatt et al, 2017).

Oral PrEP is generally well tolerated. Approximately 10% of people have described a 'start up syndrome' consisting of gastrointestinal symptoms (nausea, abdominal pain, flatulence and vomiting) and non-gastrointestinal symptoms (dizziness and fatigue) which tend to occur within the first month and resolve by 3 months (Glidden et al, 2016) without the need to stop PrEP.

Longer term concerns include a mild, non-progressive and reversible reduction in creatinine clearance (which is more pronounced in those aged over 40 years and those with predisposing renal dysfunction), and a reversal reduction in bone density by 1–2% (with no long-term data on bone

health or evidence of increased fracture risk). Thus, UK PrEP guidelines recommend an annual estimated glomerular filtration rate is measured in those under 40 years of age with an estimated glomerular filtration rate greater than 90 ml/min/1.73m^2 at baseline, biannually if estimated glomerular filtration rate is 60–90 ml/min/1.73m^2, aged >40 years or concomitant risk factors for renal function and specialist input should be sought on a case by case basis for those with an estimated glomerular filtration rate<60 ml/min/1.73m^2. Patients should be informed of the risk of reduced bone mineral density following 48 weeks of treatment but no routine monitoring is required in those with no additional risk factors (British HIV Association and British Association for Sexual Health and HIV, 2018).

Currently, access to PrEP in Scotland is free via the NHS. In Wales it is accessed via the PrEPared project. In England, PrEP access is via the PrEP Impact trial or self-sourcing (and self-funding) the drug (it is legal to buy generic PrEP online, sourced from outside the EU, so long as this is for personal use). PrEP is not currently available in Northern Ireland. With an unknown number of individuals self-sourcing PrEP it is important that all physicians remain vigilant, particularly with regards to monitoring renal function and to the possibility of any drug–drug interactions, which can be checked at www.hiv-druginteractions.org.

Conclusions

In England, we are at a turning point in the HIV epidemic and the combination of frequent testing, PrEP and treatment as prevention are undoubtedly instrumental in this. However, key inequalities exist with regards to HIV outcomes, awareness and knowledge of HIV and prevention, and access to services and further work will need to be done to strengthen prevention efforts. Clinicians working across hospital specialties are crucial to this in identifying those who may benefit from PrEP and the U=U message, especially in an era of reduced access to sexual health clinics. **BJHM**

Baeten JM, Donnell D, Ndase P et al; Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012 Aug 02;367(5):399–410. https://doi.org/10.1056/NEJMoa1108524

Bavinton BR, Jin F, Prestage G et al; Opposites Attract Study Group. The Opposites Attract Study of viral load, HIV treatment and HIV transmission in serodiscordant homosexual male couples: design and methods. BMC Public Health. 2014 Dec;14(1):917. https://doi.org/10.1186/1471-2458-14-917

British HIV Association, British Association for Sexual Health and HIV. 2018. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018. (accessed 23 August 2018) https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf

Choopanya K, Martin M, Suntharasamai P et al; Bangkok Tenofovir Study Group. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013 Jun;381(9883):2083–2090. https://doi.org/10.1016/S0140-6736(13)61127-7

Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS. 2012 Mar;7(2):99–105. https://doi.org/10.1097/COH.0b013e32834f5cf2

Glidden DV, Amico KR, Liu AY et al. Symptoms, side effects and adherence in the iPrEx open-label extension. Clin Infect Dis. 2016 May 01;62(9):1172–1177. https://doi.org/10.1093/cid/ciw022

Grant RM, Lama JR, Anderson PL et al; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010 Dec 30;363(27):2587–2599. https://doi.org/10.1056/NEJMoa1011205

Kall M. 2018. 8th May. (accessed 29 May 2018) https://twitter.com/kallmemeg/status/993872663041970176.

Klatt NR, Cheu R, Birse K et al. Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women. Science. 2017 Jun 02;356(6341):938–945. https://doi.org/10.1126/science.aai9383

Koss CA, Bacchetti P, Hillier SL et al; on behalf of the MTN-003 Protocol T. Differences in cumulative exposure and adherence to tenofovir in the VOICE, iPrEx OLE, and PrEP demo studies as determined via hair concentrations. AIDS Res Hum Retroviruses. 2017 Aug;33(8):778–783. https://doi.org/10.1089/aid.2016.0202

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 Jan;387(10013):53–60. https://doi.org/10.1016/S0140-6736(15)00056-2

Marrazzo JM, Ramjee G, Richardson BA et al; VOICE Study Team. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015 Feb 05;372(6):509–518. https://doi.org/10.1056/NEJMoa1402269

Molina JM, Capitant C, Spire B et al; ANRS IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015 Dec 3;373(23):2237–2246. https://doi.org/10.1056/NEJMoa1506273

Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. Lancet. 2002 Apr;359(9313):1178–1186. https://doi.org/10.1016/S0140-6736(02)08214-4

Public Health England. 2017. Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK. (accessed 12 April 2018) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/675809/Towards_elimination_of_HIV_transmission_AIDS_and_HIV_related_deaths_in_the_UK.pdf

Quinn TC, Wawer MJ, Sewankambo N et al; Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med. 2000 Mar 30;342(13):921–929. https://doi.org/10.1056/NEJM200003303421303

Rodger AJ, Cambiano V, Bruun T et al; PARTNER Study Group. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-Positive partner is using suppressive antiretroviral therapy. JAMA. 2016 Jul 12;316(2):171–181. https://doi.org/10.1001/jama.2016.5148

Thigpen MC, Kebaabetswe PM, Paxton LA et al; TDF2 Study Group. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012 Aug 02;367(5):423–434. https://doi.org/10.1056/NEJMoa1110711

Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. Bulletin des médecins suisses| Schweizerische Ärztezeitung| Bollettino dei medici svizzeri. 2008;89(5):165–169.

KEY POINTS

- Undetectable = untransmittable: a person living with HIV, on treatment, who has had an undetectable viral load for over 6 months cannot transmit HIV to their sexual partners.
- Pre-exposure prophylaxis (PrEP) can be highly effective when taken correctly, with an 86% reduction in HIV acquisition and is effective among a range of key populations including men who have sex with men, transgender women, people who inject drugs, and heterosexual men and women.
- Access to PrEP varies throughout the UK; in Scotland it is freely available on the NHS, in Wales via the PrEPared project and in England via the Impact trial. It is not available in Northern Ireland. For those who are unable to access PrEP through these means, it is often self-sourced.
- PrEP is well tolerated with the majority of mild symptoms resolving by 3 months. Renal monitoring may be necessary in some patients.