8. Special clinical considerations

Aboriginal and Torres Strait Islander people

The rate of human immunodeficiency virus (HIV) infection is rising in Aboriginal and Torres Strait Islanders (hereafter referred to as Indigenous) Australians. Between 2013-2017, the age standardised rate of HIV notifications increased by 41% in Indigenous populations, compared to a 12% decline in Australian-born non-Indigenous people (1). Furthermore, a greater proportion of HIV notifications during 2015-2017 in Indigenous populations was ascribed to heterosexual sex (21%) and injecting drug use (18%), compared to Australian-born non-Indigenous populations (18% and 3%, respectively) (1).

There are few data currently available regarding pre-exposure prophylaxis (PrEP) knowledge, acceptability and use in Indigenous populations. Notably, 2.1% of participants in the Expanded PrEP Implementation in Communities New South Wales (EPIC-NSW) study identified as Indigenous (2) as did 2.94% in the QPrEPd study in Queensland (3). A recent qualitative analysis examined the obstacles to PrEP use faced by Indigenous men who have sex with men (MSM) (4). These obstacles included individual barriers, such as unwillingness for Indigenous MSM to identify with mainstream gay communities, stigma towards HIV and MSM within Indigenous communities and attitudinal differences towards the use of Western medicine (4). Provider barriers that were identified include overburdened and under-resourced Aboriginal medical services, a perceived lack of confidentiality in these services and a lack of government leadership and funding. Regarding the way forward, many respondents felt community involvement was essential for effective PrEP promotion and that sexual health and PrEP promotion should be better funded and driven by the community. Respondents felt that both mainstream sexual health clinics and Aboriginal Community Controlled Health Organisations can provide appropriate services, although general practitioners, nurses and indigenous health workers need to improve HIV and sexual literacy (4). Healthcare practitioners must provide an environment that does not stigmatise Indigenous patients. Health-care practitioners must take a careful and culturally appropriate history to ascertain risk factors for HIV infection and PrEP suitability and must provide appropriate treatment and referral to support people who inject drugs.

In 2017, the notification rate of newly diagnosed hepatitis B infection in Indigenous populations was more than double that of non-Indigenous population (45.1 per 100,000 versus 19.2 per 100,000) (5). Given the higher rates of hepatitis B infection in Indigenous versus non-Indigenous people, clinicians caring for Indigenous patients must carefully follow these ASHM PrEP guidelines and screen for hepatitis B infection and, as required, provide hepatitis B vaccinations. Note that people with chronic hepatitis B should only be offered daily PrEP to maintain sustained virological suppression of hepatitis B.

People ineligible for Medicare including newly-arrived Asian-born men who have sex with men

Reports during 2013-2017 from a large, sentinel sexual health service in Victoria showed that the proportion of newly-arrived Asian-born MSM with incident HIV infection did not decline whereas the proportion of all other MSM attending the clinic with incident HIV infection declined by 45% (6). At the same clinic during 2017, newly-arrived Asian-born versus all other MSM were less likely to report use of PrEP.

In Australia, access to Medicare is required to receive subsidised PrEP and HIV antiretroviral therapy. People who come to Australia to study who are ineligible for Medicare are required to have Overseas Student Health Cover, however anecdotal reports suggest that some students are reticent to use their private health cover for sexual health testing, prevention and treatment because of concerns about data privacy. People who come to Australia on a Working Holiday Visa (417) may be eligible for Medicare if they come from countries with reciprocal health cover arrangements, although none of these countries is within Asia (7).

Clinicians should refer people who are ineligible for Medicare or who are unable or unwilling to use private health-care cover to public sexual health clinics that offer free HIV and sexually transmissible infection (STI) testing and provide PrEP prescriptions. These PrEP prescriptions can be filled by paying the full, unsubsidised amount for a private script, or by personal importation of PrEP through online pharmacies.

Transgender women

Transgender women have a high prevalence of HIV infection (8) and experience high HIV incidence rates compared to non-transgender men and women (9). Furthermore, transgender women have represented less than 1% of study participants in PrEP trials (10) and this paucity of data may help explain the overall low uptake of PrEP by transgender women (11).

The Iniciativa Profilaxis Pre-Exposición (iPrEX) clinical trial enrolled the highest number of transgender women to date and found that compared to MSM, transgender women were more likely to report transactional sex, condomless anal intercourse and more recent sexual partners (12). In iPrEX, no HIV infections were observed in transgender women whose blood levels were compatible with taking four or more doses of PrEP weekly. However, using stratified analyses, PrEP did not provide a benefit for transgender women in the iPrEX study [hazard ratio 1.1, 95% confidence interval (CI): (0.5 to 2.7) compared to the overall 44% reduced HIV incidence in the active study arm (12).

A recent retrospective analysis of the iPrEX study sought to determine whether the differential efficacy of PrEP in MSM versus transgender women was a result of different baseline clinical and behavioural factors that could make PrEP less efficacious in transgender women (10). The authors found that baseline characteristics between MSM and transgender women explained almost 100% of the difference in PrEP's efficacy during the iPrEX study (11). However, the authors were not able to comment on whether the use of gender-affirming hormone therapy (GAHT) (13) may have contributed to PrEP being less effective in the transgender women study participants (11).

Oestrogen, which is used as part of GAHT, increases the activity of 5'-nucleotidase enzymes and can decrease the active metabolites of tenofovir and emtricitabine, or increase the nucleotides that compete against the active metabolites of tenofovir and emtricitabine within cells. Therefore, oestrogen could plausibly reduce cellular levels of tenofovir and emtricitabine in transgender women, making PrEP less efficacious. There have been some small studies in transgender women taking GAHT and PrEP. One study of 20 Thai transgender women commencing GAHT and PrEP showed a 12% reduction in plasma tenofovir levels in the presence of GAHT (14), although PrEP did not reduce oestrogen levels. In another study, 31% lower levels of plasma tenofovir were observed in eight transgender women taking GAHT compared to eight cis-gender men; plasma emtricitabine was also significantly lower in the transgender study participants (13). A further study compared the rectal tissue levels of the active metabolites of

tenofovir and emtricitabine in four HIV-positive transgender women taking GAHT versus four HIV-positive post-menopausal cis-gender women. This study reported that there was a significantly lower ratio of the active metabolite of tenofovir diphosphate to its competing nucleotide dATP in the rectal tissue of the trans-gender versus cis-gender participants (15). However, this study did not find a decrease in the ratio of the active metabolite emtricitabine triphosphate to its competing nucleotide, dCTP. Further larger pharmacological studies are needed urgently to determine whether GAHT reduces the levels of tenofovir disoproxil* and emtricitabine (TD*/FTC), or vice versa in transgender women.

The ASHM PrEP Guidelines Panel will continue to monitor the data on potential drug-drug interactions between GAHT and TD*/FTC.

As noted, in a post-hoc analysis of transgender women in the iPrEX study, no HIV infections were observed in transgender women whose blood levels were compatible with taking four or more doses of PrEP weekly (12). Therefore, supporting transgender women to optimise their PrEP adherence is important until larger studies have determined whether GAHT reduces levels of TD*/FTC in transgender women taking GAHT. To help support transgender women to optimise their PrEP use and adherence, it is recommended that health practitioners provide gender-affirming care (16). Such clinical care includes appropriate use of preferred pronouns and names, safe access to bathrooms of choice and appropriate treatment and referral for hormone therapy and surgery (16).

Transgender men

There are very few data regarding PrEP knowledge, acceptability and use in transgender men. Nor are there data regarding whether GAHT influences PrEP drug levels or vice versa in transgender men. A 2016 review of HIV and STI research undertaken in transgender men was unable to find any data on the use of PrEP in transgender men (17). In a 2017 study of 181 transgender youth from the USA, of 42 people identifying as transgender men (23.2%), only 16 had ever used HIV prevention services and none had ever used PrEP (18). Transgender men were significantly less likely to have ever used PrEP than transgender women (18). To optimise HIV prevention and PrEP use, clinicians caring for transgender men need to actively raise PrEP as an HIV prevention option for them and take a sensitive and detailed sexual behaviour history bearing in mind that transgender men may be sexually active with male and female partners. Gender-affirming care should be provided to transgender men by health practitioners. For more information see: a language guide: Trans and gender diverse inclusion

Women taking PrEP during conception, pregnancy and breastfeeding

Conception in serodiscordant couples

Women without HIV infection who have sexual partners with documented HIV infection are at risk of HIV acquisition during natural attempts to conceive (i.e. without a condom) if their HIV-positive partner has a detectable or variably detectable plasma viral load. Providers should discuss with their patients the available information about the potential risks and benefits of PrEP in these circumstances (19). For women wanting to conceive where their HIV-positive male partner is stably virologically suppressed on combination antiretroviral therapy (cART), PrEP should still be offered to the woman if she expresses concerns about the risk of acquiring HIV in this setting.

Pregnancy

Among women without HIV infection, the risk of acquiring HIV increases by approximately two-fold during pregnancy (20). In addition, if a woman acquires HIV infection during pregnancy there is a higher risk of HIV transmission to the infant than if the woman were to become pregnant during chronic HIV infection because the HIV viral load is much higher during acute HIV infection.

The current evidence suggests that PrEP can be used safely during pregnancy and breastfeeding (21).

The use of TD*-containing regimens by HIV positive women throughout pregnancy has not been associated with adverse pregnancy outcomes, but lowered BMD has been observed in newborns exposed to TD* in utero (22) as has a lower length and head circumference at 1 year of age (23).

In the Partners PrEP study, which compared the efficacy of tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) versus TDF versus placebo to reduce HIV transmission in African heterosexual HIV-serodifferent couples, 431 pregnancies occurred; the average duration of in utero PrEP exposure was 5 weeks (24). There was no difference in the incidence of pregnancy, birth outcomes or infant growth in women who received TDF or TDF/FTC versus placebo PrEP (24). However, the authors noted that the confidence intervals for these findings were wide and therefore definitive statements about the safety of TDF/FTC as PrEP during pregnancy could not be made based on this study's findings. A subsequent study from this group examined the pregnancy outcomes of 30 women who continued to use PrEP during pregnancy compared to 96 pregnancies without PrEP exposure. The authors found that there was no increase in adverse pregnancy outcomes, or restrictions in infant growth between the two groups (25).

The World Health Organization has included PrEP as an HIV prevention strategy during pregnancy (26) and a number of other jurisdictions recommend PrEP for safe conception and for use during pregnancy and breastfeeding (27).

Some women with HIV-positive partners may prefer to continue PrEP while pregnant, due to the increased risk of acquisition of HIV if their partners are not reliably virologically supressed during pregnancy, or due to high levels of anxiety (27).

Providers should discuss with their patients available information on potential adverse pregnancy outcomes when beginning or continuing PrEP during pregnancy so that they can make an informed decision. It should be noted that TD* is classified as category B3 by the Australian Therapeutic Goods Administration (TGA) (29), meaning that, to date, tenofovir has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. However, studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Therefore, the ASHM PrEP Guidelines Panel's recommendation is that PrEP may be continued during pregnancy in women at risk for HIV acquisition, or who are unduly affected by anxiety about HIV acquisition.

Breastfeeding

Although experience with PrEP during breastfeeding is lacking, there is substantial experience with the use of TD*/FTC during the breastfeeding period by HIV-positive women taking TD*/FTC based antiretroviral therapy. TD* and FTC are secreted in breast milk, although at much lower concentrations (0.3 and 2%, respectively), of the levels achieved with the doses recommended for the treatment of infants with HIV infection (30). In the PrEP setting, a study evaluating antiretroviral excretion in breast milk and infant absorption suggests PrEP can be safely used during breastfeeding with minimal infant drug exposure (28).

If a woman acquires HIV infection during breastfeeding, the risk of transmission to her infant is higher than in an established infection, because of high viral load soon after seroconversion. Therefore, PrEP can be continued during breastfeeding in women at risk of HIV acquisition.

The ASHM PrEP Guidelines Panel will continue to monitor the safety of TD*/FTC PrEP regimens when used during pregnancy and breastfeeding.

Patients with chronic active HBV infection

Both TD* and FTC are active against HIV and hepatitis B virus (HBV) infections. They may prevent the development of significant liver disease by suppressing HBV replication. Only TD*, however, is currently approved for this use in Australia. Therefore, ongoing treatment with TD*/FTC may be especially indicated in people with active HBV infection who are also at risk of HIV acquisition.

Of note there are two case reports of patients who were receiving TD* for treatment of hepatitis B and who acquired HIV infection (31). Plasma levels of tenofovir and prescription refills suggested that the patients' medication adherence was good. These guidelines recommend that people with established hepatitis B infection who require treatment for hepatitis B infection receive combined TD*/FTC and have ongoing monitoring for HIV PrEP and hepatitis B infection.

All people who test positive for hepatitis B surface antigen (HBsAg) should be evaluated by a clinician experienced in the treatment of HBV infection. For clinicians without this experience, co-management with an infectious disease or liver specialist should be considered.

People living with chronic HBV infection should be tested for HBV DNA by the use of a quantitative assay to determine the level of HBV replication before PrEP is prescribed, and at regular intervals (e.g. every 3–6 months) while taking PrEP (32). TD* presents a very high barrier to the development of HBV resistance. However, it is important to reinforce the need for consistent adherence to the daily doses of TD*/FTC to prevent reactivation of HBV infection with the attendant risk of hepatic injury, and to minimise the possible risk of developing TD*-resistant HBV infection (33). For these reasons, on-demand PrEP is contraindicated in patients with chronic hepatitis B infection.

If PrEP is no longer needed to prevent HIV infection in a patient with chronic hepatitis B, a separate determination should be made about whether the patient requires ongoing treatment for HBV infection. Acute flares resulting from the reactivation of HBV infection have been seen in those with and without HIV infection after stopping TD* and other medications used to treat HBV infection. When people living with chronic hepatitis B elect to discontinue PrEP, they should first be evaluated by a clinician experienced in the management of HBV infection to ascertain their need for ongoing HBV treatment, and to monitor for any hepatic flares that occur if PrEP is ceased.

Patients with chronic renal failure

Patients without HIV infection and with established chronic renal failure, e.g. with estimated glomerular filtration rate (eGFR) that is stably less than 60 mL/min/1.73 m^2 should not be prescribed PrEP. The only PrEP regimen proven effective to date and approved by the TGA is TD*/FTC, which is not indicated for those with chronic renal failure (34). However, if a patient with chronic renal failure is at substantial risk of HIV, their condition should be discussed with specialists in the management of HIV and renal disease.

Adolescent minors

As a part of primary health care, HIV screening should be discussed with all adolescents who are sexually active, or have a history of injecting drug use. Parental or guardian involvement in an adolescent's health care is often desirable, but is sometimes contraindicated for the safety of the adolescent, and can compromise full disclosure.

Clinicians should carefully consider the data discussed below on the safety and efficacy of daily PrEP taken by persons under 18 years of age, including the possibility of loss of bone mineral density, and other toxicities among youth who are still growing. Data are also available about the safety of TD*/FTC when used in treatment regimens for young people with HIV infection (35). The clinician and the patient may conclude that the short-term, proximal risk of acquiring HIV infection greatly outweighs any short-term, or as yet undetermined, long-term risk of PrEP toxicity. Clinicians are encouraged to seek expert advice in complex situations.

Adherence to PrEP in adolescents may be suboptimal: a PrEP demonstration program involving daily PrEP use for 18–22-year-old HIV-negative MSM reported that tenofovir diphosphate intracellular levels, a marker of cumulative TD* adherence, were consistent with good adherence peaking at 56% at month, but declining thereafter (36). In another open-label 48-week study of 78 adolescent MSM commencing PrEP, Project PrEPare, highly protective levels of PrEP were observed in 54% of adolescents at week 4 but declined thereafter (37).

Following this finding that PrEP levels declined markedly in these adolescent participants after the first week 4 visit, the authors recommended that adolescents should be offered more frequent clinical monitoring to enhance their PrEP adherence. **The ASHM PrEP Guidelines Panel endorses this approach and encourages clinicians to work with adolescents taking PrEP to design an augmented clinical review schedule.**

In the Project PrEPare study, there was no observed elevation in serum creatinine levels and significant increases were observed in bone mineral density for the spine, hip and total body between baseline and week 48 (37). However, there was a slight but statistically significant decline in the total body Z-score during this time (37), suggesting that bone growth may have been suboptimal in the study participants. Although not observed in this study, higher levels of PrEP adherence as measured by red blood cells levels of tenofovir diphosphate have been associated with lower hip bone mineral density in adolescents (38). Further research is needed to determine whether there is a long-term increased risk of bone fractures in young MSM who have had PrEP.

Globally until recently, regulatory approval of Truvada (tenofovir disoproxil fumarate (TDF (FTC)) PrEP was limited to adults over 18 years of age. However, on 15 May 2018, the US Food and Drug Administration (FDA), based on data from the Project PrEPare study discussed above, expanded its approval of Truvada as PrEP against HIV to include adolescents at risk weighing at least 35 kg.

PrEP use for prevention of HIV in adolescents has not been approved by the TGA in Australia. However, clinicians are able to prescribe PrEP off-label for adolescents. In this setting, a decision to prescribe PrEP for a person under 18 years of age should be made at the discretion of the prescriber who is responsible for obtaining informed consent from their patient. Informed consent should take into account the risks and benefits of that treatment versus other available treatments or no treatment at all based on the individual circumstances. Of note, the TGA does not regulate health professionals or clinical practice. Medical practitioners are required to prescribe in accordance with Good Medical Practice, the code of conduct published by the Medical Board of Australia – this code highlights the importance of informed consent.

Adolescents may obtain PrEP via the Personal Importation Scheme of the TGA once they have received an off-label prescription from their clinician.

References

1. Kirby Institute. HIV in Australia: annual surveillance short report 2018. Sydney: Kirby Institute, UNSW Sydney; 2018.
2. NSW Ministry of Health. NSW HIV Strategy 2016–2020 Quarter 1 2019. Data Report. Available at: https://www.health.nsw.gov.au/endinghiv/Publications/q1-2019-nsw-hiv-data-report.pdf (last accessed 2 September 2019).
3. Queensland Pre-exposure Prophylaxis Demonstration Project Expansion (QPrEPd) Monitoring and Evaluation Annual Report Number 1 2017. Available at: https://www.comeprepd.info/wp-content/uploads/2018/04/qprepd-first-report.pdf accessed September 10th 2019 (last accessed 11 September 2019).
4. Hope A, Haire B. No-one's driving this bus – qualitative analysis of PrEP health promotion for Aboriginal and Torres Strait Islander gay and bisexual men. Aust N Z J Public Health 2019 Feb;43:18-23.
5. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: Kirby Institute, UNSW Sydney; 2018. Available at: https://kirby.unsw.edu.au/report/hiv-viral-hepatitis-and-sexually-transmissible-infections-australia-annual-surveillance (last accessed 2 September 2019).
6. Medland NA, Chow EPF, Read THR, et al. Incident HIV infection has fallen rapidly in men who have sex with men in Melbourne, Australia (2013–2017) but not in the newly arrived Asian-born. BMC Infect Dis 2018;18:410.
7. Australian Government. Department of Human Services. Enrolling in Medicare. Available at: https://www.humanservices.gov.au/individuals/subjects/how-enrol-and-get-started-medicare/enrolling-medicare#whocan (last accessed 2 September 2019).
8. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N; HIV/AIDS Prevention Research Synthesis Team. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav 2008;12:1-17.
9. Centers for Disease Control and Prevention. HIV Surveillance Reports. 2011; volume 23. Published February 2013. Available at: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2011-vol-23.pdf (last accessed 2 September 2019).
10. Escudero DJ, Kerr T, Operario D, Socías ME, Sued O, Marshall BD. Inclusion of trans women in pre-exposure prophylaxis trials: a review. AIDS Care 2015;27:637-41.
11. Mehrotra ML, Westreich D, McMahan VM, et al. Baseline characteristics explain differences in effectiveness of randomization to daily oral TDF/FTC PrEP between transgender women and cisgender men who have sex with men in the iPrEx Trial. J Acquir Immune Defic Syndr 2019; 81:e94-8.
12. Deutsch MB, Glidden DV, Sevelius J, et al; iPrEx investigators. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. Lancet HIV 2015;2:e512–9.
13. Shieh E, Marzinke M, Fuchs E, et al (presenter Hendrix C). Transgender women on estrogen have significantly lower tenofovir/emtricitabine concentrations during directly observed dosing when compared to cis men. Abstract OA23.03. HIV Research for Prevention conference (HIVR4P); 21-25 October 2018; Madrid, Spain. Available at: http://www.professionalabstracts.com/hivr4p2018/iPlanner/#/presentation/205 (last accessed 2 September 2019).

14. Hiransuthikul A, Janamnuaysook R, Himmad K, et al; iFACT Study Team. Drug-drug interactions between feminizing hormone therapy and pre-exposure prophylaxis among transgender women: the iFACT study. J Int AIDS Soc 2019;22:e25338
15. Cottrell ML, Prince HMA, Schauer AP, et al. Decreased tenofovir diphosphate concentrations in a transgender female cohort: Implications for HIV pre-exposure prophylaxis (PrEP). Clin Infect Dis 2019 Apr 9. pii: ciz290 [Epub ahead of print].
16. Grant RM, Sevelius JM, Guanira JV, Aguilar JV, Chariyalertsak S, Deutsch MB. Transgender women in clinical trials of pre-exposure prophylaxis. J Acquir Immune Defic Syndr 2016;72 Suppl 3:S226-9.
17. Reisner SL, Murchison GR. A global research synthesis of HIV and STI biobehavioural risks in female-to-male transgender adults, Glob Public Health 2016;11:866-87.
18. Reisner SL, Jadwin-Cakmak L, White Hughto JM, Martinez M, Salomon L, Harper GW. Characterizing the HIV prevention and care continua in a sample of transgender youth in the U.S. AIDS Behav 2017;21:3312–27.
19. World Health Organization (WHO). WHO Technical brief: preventing HIV during pregnancy and breastfeeding in the context of pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/bitstream/handle/10665/255866/WHO-HIV-2017.09eng.pdf;jsessionid=2033F808E98CC3BE9143A7D9AB4D6EEA?sequence=1 (last accessed 2 September 2019).
20. Mugo NR, Heffron R, Donnell D, et al; Partners in Prevention HSV/HIV Transmission Study Team. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1 serodiscordant couples. AIDS 2011;25:1887–95.
21. Horgan L, Blyth CC, Bowen AC, Nolan DA, McLean-Tooke AP. Pre-exposure prophylaxis for HIV prevention during pregnancy and lactation: forget not the women and children. Med J Aust 2019;210:281-4.
22. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. Clin Infect Dis 2015;61:996-1003.
23. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT study: assessment of the safety of in utero exposure to antiretroviral drugs. Front Immunol 2016;7:199.
24. Mugo NR, Hong T, Celum C, et al; Partners PrEP Study Team. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomised clinical trial. JAMA 2014;312:362–71.
25. Heffron R, Mugo N, Hong T, et al; Partners Demonstration Project and the Partners PrEP Study Teams. Pregnancy outcomes and infant growth among babies with in utero exposure to tenofovir-based preexposure prophylaxis for HIV prevention. AIDS 2018;32:1707-13.
26. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=D9DE8E4B08AE7817BDF0A3439A6F90B6?sequence=1 (last accessed 2 September 2019).
27. Davies N, Heffron R. Global and national guidance for the use of pre-exposure prophylaxis during peri-conception, pregnancy and breastfeeding. Sex Health 2018;15:501–12.

28. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-term study of antiretroviral excretion in breast milk and infant absorption. PLoS Med 2016;13:e1002132.
29. The Royal Women's Hospital Victoria Australia. Pregnancy and Breastfeeding Medicines Guide [internet]. Tenofovir. Available at: https://thewomenspbmg.org.au/medicines/tenofovir (last accessed 2 September 2019).
30. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob Agents Chemother 2011;55:1315- 7.
31. Fox J, Brady M, Alexander H, et al. Tenofovir disoproxil fumarate fails to prevent HIV acquisition or the establishment of a viral reservoir: two case reports. Infect Dis Ther 2016;5:65- 71.
32. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). B Positive. Hepatitis B for primary care. Clinical assessment of patients with hepatitis B virus infection [internet]. 2018 update. Available at: http://www.hepatitisb.org.au/clinical-assessment-of-patients-with-hepatitis-b-virus-infection/ (last accessed 2 September 2019).
33. Hongthanakorn C, Chotiyaputta W, Oberhelman K, et al. Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. Hepatology 2011;53:1854-63.
34. Gilead Sciences. Full prescribing information. Issued June 2013. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/021752s035lbl.pdf (last accessed 2 September 2019).
35. Purswani M, Patel K, Kopp JB, et al. Tenofovir treatment duration predicts proteinuria in a multiethnic United States Cohort of children and adolescents with perinatal HIV-1 infection. Pediatr Infect Dis J 2013;32:495-500.
36. Hosek SG, Rudy B, Landovitz R, et al; Adolescent Trials Network (ATN) for HIVAIDS Interventions. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. J Acquir Immune Defic Syndr 2017;74:21-9.
37. Hosek SG, Landovitz RJ, Kapogiannis B, et al. Safety and feasibility of antiretroviral preexposure prophylaxis for adolescent men who have sex with men aged 15 to 17 years in the United States. JAMA Pediatr 2017;171:1063-71.
38. Havens PL, Stephensen CB, Van Loan MD, et al; Adolescent Medicine Trials Network for HIV/AIDS Interventions 117 study team. Decline in bone mass with tenofovir disoproxil fumarate/emtricitabine is associated with hormonal changes in the absence of renal impairment when used by HIV-uninfected adolescent boys and young men for HIV preexposure prophylaxis. Clin Infect Dis 2017;64:317-25.