Pre-exposure prophylaxis for HIV prevention during pregnancy and lactation: forget not the women and children

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Summary

- Pregnancy is known to be a time of increased susceptibility to acquiring to human immunodeficiency virus (HIV) infection and this increased maternal risk places the unborn child at risk of vertical transmission.
- Pre-exposure prophylaxis (PrEP) involves the provision of antiretroviral therapy to an HIV-negative individual with ongoing risk of HIV exposure to limit the likelihood of HIV transmission.
- The inclusion of PrEP as part of a comprehensive strategy is recognised as an effective and safe means of reducing HIV infection in serodiscordant couples, thereby reducing the risk of vertical transmission of HIV.
- Current data suggest that PrEP is safe to continue during pregnancy and breastfeeding in HIV-negative women who remain vulnerable to acquiring HIV.
- The recent Pharmaceutical Benefits Scheme subsidisation of PrEP has reduced the financial and practical obstacles of PrEP provision, and a subsequent increase in patient awareness and acceptance of PrEP is expected.
- The framework for appropriately identifying and managing at-risk pregnant and lactating women requiring PrEP is poorly defined and warrants further clarification to better support clinicians and this patient group.
- This review discusses the current recommendations highlighting the gaps in the guidelines and makes some recommendations for future guideline development.

Epidemiological studies confirm that pregnancy is a time of heightened human immunodeficiency virus (HIV) susceptibility[1,2] and that this increased maternal risk places unborn infants at risk of vertical HIV transmission. Studies have demonstrated a higher pooled incidence rate in pregnancy (4.7/100 person-years) equivalent to other high risk populations such as female sex workers and HIV-serodiscordant couples.[3] It has recently been shown that the risk of HIV transmission per sexual exposure steadily increases throughout the pregnancy, with the greatest risk in late pregnancy and postpartum.[2] It is likely that this observation is multifactorial in origin, with biological, social and behavioural factors increasing exposure to HIV.[4–7] The national HIV surveillance report for Australia confirms a decreasing vertical transmission rate reflective of the advent of effective antiretroviral treatment in addition to wider antenatal screening and evidence-based interventions.[8] Nonetheless, vertical HIV transmission is still a reality, typically in circumstances where the maternal HIV infection is unknown. In addition, acute HIV infection during pregnancy or lactation is linked with higher vertical transmission rates relative to mothers with chronic HIV infection.[9,10] Breastfeeding is recognised as a risk factor for vertical transmission of HIV[11] and current guidelines recommend that Australian HIV-positive women avoid breastfeeding even when established on antiretroviral therapy (ART).[12]

Several approaches for the prevention of HIV infection in pregnant and lactating women are well established, including male and female barrier protection, partner screening, provision of ART to partners with HIV, and treatment of sexually transmitted infections. For couples known to be HIV-1 serodiscordant, infected partner compliance with ART provides substantial, although incomplete, protection against HIV-1 transmission, noting that estimates that 25–30% of cases of HIV-1 infection involving serodiscordant couples are derived from infected partners outside the couple.[13] Antenatal screening is established as one method demonstrated to reduce the rates of vertical HIV transmission by allowing commencement of ART early in pregnancy, planning of appropriate management of delivery, and counselling regarding breastfeeding.[14] Screening is currently recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists in all women at the first antenatal visit.[15] Strategies for safe conception in serodiscordant couples are well recognised but many women do not access prenatal conception counselling, with 40% of pregnancies being unintended.[16] In addition, the uninfected partner in a serodiscordant couple may not receive the targeted prenatal counselling due to confidentiality concerns or lack of disclosure.

Pre-exposure prophylaxis (PrEP) involves the provision of ART to HIV-negative pregnant and breastfeeding women who are at risk of ongoing HIV exposure. Despite only limited experience in the use of PrEP during antenatal and postnatal care, the inclusion of PrEP has become accepted in combination with a multifaceted strategy to further reduce HIV infection and vertical transmission. In 2018, PrEP medications were approved for subsidisation by the Australian Government through the Pharmaceutical Benefits Scheme. A surge in the use of PrEP can be anticipated and it is important that further education, increased awareness and clear guidelines are available to empower medical professionals in the management of at-risk pregnant and lactating women.

Here we review the review current evidence and guidelines for the use of PrEP during pregnancy and lactation. Citations were derived from PubMed using the terms "pregnancy and HIV" or "pregnancy and HIV and pre-exposure prophylaxis" or "lactation and HIV and pre-exposure prophylaxis", as well as by searching the bibliographies of recent relevant review articles and guidelines. Searches were limited to the English language with no limitation on years, and relevance was assessed by title and abstract.

The efficacy of PrEP

The efficacy of PrEP was first established in studies of serodiscordant couples including the seminal Partners PrEP study, which reported a risk reduction of 75% in HIV-1 infection in over 4500 heterosexual serodiscordant couples taking two co-formulated

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antiretroviral drugs, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), in conjunction with other HIV-1 prevention strategies.[17] Subsequently, in a Partners PrEP sub-study where TDF levels were measured in patients randomised to commence TDF–FTC, a measurable drug level correlated with a 90% reduction in the risk of HIV infection.[18] Of importance, no TDF or FTC resistance mutations emerged in those infected after enrolment in the study.[17]

Patient compliance, however, is paramount to the efficacy of PrEP, further emphasising the need for the implementation of shared decision making before PrEP initiation. Studies such as the FEM-PREP trial and VOICE study have demonstrated minimal additional benefit of PrEP relative to placebo in patient groups where compliance is < 50%.[19,20]

PrEP is therefore recognised as effective in combination with a comprehensive HIV prevention management plan including adherence counselling, screening for acute infection both on initial presentation and every 3 months, sexually transmitted infection screening and treatment, condom promotion, partner counselling and referral for ART if HIV-positive.[21]

PrEP safety during pregnancy and lactation

Existing safety data from PrEP studies of TDF and co-formulated TDF–FTC are reassuring, but with some notable limitations. Unfortunately, the majority of PrEP studies ceased therapy at diagnosis of pregnancy, thus limiting PrEP safety data throughout the entirety of pregnancy and the lactating period. A Partners PrEP sub-study identified 431 women who incidentally conceived while taking PrEP and had an exposure to PrEP to maximum 7 weeks' gestation.[22] No significant differences were seen in pregnancy loss, preterm birth, congenital anomalies or failure to thrive.

World Health Organization (WHO) guidelines advise that there is no safety-related indication to recommend discontinuing PrEP use during pregnancy and breastfeeding for HIV-negative women who are receiving PrEP and remain at risk of HIV acquisition.[23] In addition, the guidelines state that the benefits of preventing HIV infection in the mother and related risk of vertical transmission outweigh any potential risks of PrEP to the unborn fetus or infant.[23]

TDF–FTC is used extensively in the treatment of HIV-1-positive pregnant and breastfeeding women and its use is supported by robust safety data in this patient population. In terms of TDF safety data, a WHO-funded systematic review of TDF use in pregnancy included 26 studies involving HIV-infected women on TDF antiretroviral therapy, five on TDF for hepatitis B mono-infection and two on HIV-uninfected women from PrEP trials.[24] Fetal exposure to TDF varied from initiation of treatment at pre-conception through to the third trimester. All studies reported no significant difference in low birth weight between women exposed to TDF versus non-TDF antiretroviral regimens. Seven studies reported on birth defects and demonstrated no significant differences in birth defects regardless of the trimester during which the infant was exposed to TDF. Additionally, no significant increase in pregnancy loss, preterm birth, infant mortality or maternal mortality was found. The systematic review concluded that there was no clear evidence of any safety concern to warrant restriction of PrEP use during pregnancy and lactation or need to discontinue PrEP in HIV-uninfected women receiving PrEP who become pregnant with ongoing risk of HIV acquisition.

Additionally, the very low concentrations at which TDF and FTC are secreted in breast milk (0.3–2% of the therapeutic level required for infants) support the continuation of TDF–FTC during the lactation period if there is ongoing maternal risk of HIV acquisition.[25] Pharmacokinetic studies provide further reassurance in this regard, identifying that infant TDF–FTC exposure through breast milk is even lower than exposure in utero.[26]

Despite the overall encouraging safety profile of TDF in pregnancy and lactation, uncertainty exists regarding the impact of TDF on infant bone development and growth. Unreplicated inconclusive studies have demonstrated a decrease in bone mineral density among infants exposed to TDF in utero, although the duration and clinical significance of this remained unknown.[27] Even so, this decreased bone mineral content is suggested not to be specific to TDF but rather a side effect which may be inflicted on the fetus by any triple antiretroviral therapy regimen.[28]

While ongoing surveillance will remain important, overall, the existing safety data for co-formulated TDF–FTC has not suggested a firm justification to deny pregnant and lactating women the benefits that PrEP offers in reducing maternal HIV infection and ultimately vertical transmission. This view is supported in existing guidelines, which recommend the continuation or commencement of PrEP in this patient cohort if there is anticipated ongoing risk of HIV infection.[21,29–31]

Behavioural risk assessment and eligibility for PrEP

Various clinical practice guidelines pertaining to PrEP exist.[21,29,32] However, while the majority of PrEP guidelines do briefly refer to the management of pregnant and lactating women, they fail to suggest clearly defined frameworks for the appropriate identification of at-risk patients, treatment protocols and follow-up of such patients. Existing guidelines recommend the provision of PrEP for individuals at high risk of HIV acquisition, including women of reproductive age. The continuation of PrEP is recommended at pregnancy diagnosis for those already on PrEP.[29,30] Overall, existing local and international guidelines suggest a low threshold for the initiation of PrEP in at-risk HIV-negative women supported by robust safety data and proven efficacy.

In 2017, the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine released updated clinical practice guidelines[32] outlining behavioural eligibility criteria for PrEP provision (Box). Particular patient groups addressed include heterosexual, transgender and gender diverse people, and men who have sex with men. These guidelines do not provide detailed risk or behavioural eligibility criteria which incorporate consideration of risk specific to pregnant or lactating women. Nonetheless, within the heterosexual patient group behavioural eligibility criteria, PrEP is advised for a female patient who is in a serodiscordant relationship and is planning natural conception while there is ongoing sustained risk of transmission.

A 2017 WHO technical brief addressing PrEP usage in pregnancy[21] suggested three settings in which PrEP may be used among HIV-negative pregnant and lactating women: a woman taking PrEP who subsequently becomes pregnant and remains at substantial risk of HIV infection; a pregnant or lactating HIV-negative woman living in a setting with high HIV incidence who is at substantial risk of HIV acquisition; or a pregnant or lactating woman whose partner is HIV-positive but is not virally suppressed.

These guidelines recognise that PrEP may be indicated in cases where the HIV-infected partner is not compliant with ART, has been on ART for less than 6 months, or uncertainty exists regarding the HIV-infected partner's viral suppression.[21] They also suggest that risk assessment tools could be helpful in identifying

Behavioural eligibility criteria for pre-exposure prophylaxis (PrEP) for heterosexual men and women

High risk — recommend prescribing daily PrEP if the patient acknowledges

Having had any of the following in the past 3 months: • being a regular sexual partner of an HIV-positive person (not on treatment and/or with detectable viral load) with whom condoms have not been consistently used • at least one episode of receptive anal or vaginal condomless intercourse with any casual HIV-positive partner of a male homosexual or bisexual partner of unknown status • a female patient in a serodiscordant heterosexual relationship, who is planning natural conception in the next 3 months	*and*	Being likely to have in the next 3 months (indicating sustained risk): • multiple episodes of condomless intercourse with or without sharing intravenous drug equipment

Medium risk — consider prescribing daily PrEP, based on a case-by-case approach if discussion reveals

The patient acknowledges having had any of the following in the last 3 months: • at least one episode of condomless intercourse with a heterosexual partner, not known to be HIV-negative, from a country with high HIV prevalence	*and*	Being likely to have in the next 3 months (indicating sustained risk): • multiple episodes of condomless intercourse with a heterosexual partner, not known to be HIV-positive but at high risk of being HIV-positive with or without sharing equipment

Case-by-case approach

Based on a complete sexual and alcohol and other drug history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then a PrEP prescription may be considered despite the absence of the reported high or medium risk factors above. Specific consideration should be given to recommending PrEP to a patient who is travelling to one or more countries with high HIV prevalence and is likely to be sexually active while travelling.

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patients who would benefit from PrEP, but note that such tools will need to be developed and validated as currently available validated existing tools[33,34] do not incorporate any consideration of risk specific to pregnant and lactating women. Such risk assessment tools could subsequently be incorporated into antenatal screening procedures. The WHO guidelines also acknowledge that women who request PrEP should be considered for treatment based on an individualised assessment of their HIV exposure risk.

Current Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines suggest repeat HIV screening at 28 weeks' gestation for women deemed to be at high risk of infection with HIV.[15] Nonetheless, a risk assessment tool or behavioural criteria for adequate identification of these women to support midwives and clinicians in this decision is not referenced.

Clear guidelines exist outlining the laboratory and clinical follow-up of heterosexual, transgender and gender diverse people, and men who have sex with men who are established on PrEP.[32] There is a paucity of published protocols for laboratory monitoring of pregnant or breastfeeding women susceptible to HIV who have commenced PrEP. There is also a lack of guidance on surveillance of HIV-positive male partners during HIV-negative women's antenatal and postnatal periods. Regular testing of pregnant and lactating women vulnerable to HIV is vital to detect acute seroconversion. Ideally, an HIV-infected male with an HIV-negative pregnant or lactating partner would have regular viral load and sexually transmitted infection monitoring, with results being communicated to the woman's specialist. This ideal is limited by the absence of relevant guidelines and confidentiality constraints. Recently updated PrEP guidelines released by the Centers for Disease Control and Prevention[31] recognise that clinicians managing HIV-negative patients may be constrained by not having access to an HIV-positive partner's medical records to assess their viral load. Within these guidelines, the use of PrEP during the peri-conception period and pregnancy is recommended in circumstances where the partner is known to have HIV infection but an uncertain or detectable viral load.[31]

Conclusion

Despite pregnancy being identified as a time of increased HIV susceptibility, with risks to both the mother and unborn infant of HIV acquisition, there is a paucity of guidelines, eligibility criteria and risk assessment tools pertaining specifically to the usage of PrEP in pregnancy and lactation. Existing local and international guidelines suggest a low threshold for the initiation of PrEP in serodiscordant HIV-negative women. It is imperative that the needs of such patients be met through the implementation of strategies to enable appropriate and timely prescription of PrEP.

Moreover, with the commencement of availability of Pharmaceutical Benefits Scheme-subsidised PrEP, the financial and practical obstacles to PrEP provision will be reduced and a subsequent increase in patient awareness and acceptance of PrEP is anticipated. However, the logistics and responsibility of providing PrEP and subsequent necessary follow-up for pregnant and lactating women at risk of HIV infection has not been sufficiently considered or formalised (ie, general practice versus antenatal clinic).

We therefore recommend development of multidisciplinary guidelines on the prevention of mother-to-child transmission of HIV among Australian pregnant and lactating women. These guidelines should include information about PrEP. Development of the guidelines must also engage with clinicians treating male patients to ensure that uninfected female partners of child-bearing potential are not forgotten. The guidelines will require multidisciplinary input including expertise in the areas of HIV, obstetrics, midwifery, general practice and paediatrics, and commitment to:

- outlining the appropriate circumstances for the provision of PrEP during peri-conception, pregnancy and lactation;
- creation of behavioural eligibility criteria and risk assessment tools which recognise the risks specific to pregnant and lactating women;
- outlining the appropriate follow-up of patients commenced on PrEP during pregnancy and lactation;

- defining the setting in which PrEP will be prescribed and post-prescription surveillance will be undertaken for the pregnant and lactating patient cohort;
- targeted education of health professionals tasked with the provision of PrEP to the pregnant and breastfeeding patient group; and
- creation of patient information resources to maximise serodiscordant couple awareness of the requirement for pre-conception counselling and treatment options available.

We believe such a framework is vital to guide and empower medical professionals in the appropriate usage of PrEP in this patient cohort and ultimately provide the best patient care.

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