TECHNICAL BRIEF

PREVENTING HIV DURING PREGNANCY AND BREASTFEEDING IN THE CONTEXT OF PREP

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Content

Introduction

In many countries with high-prevalence generalized HIV epidemics, women continue to acquire HIV during pregnancy and breastfeeding. Women who become infected during this time also risk transmitting HIV to their infants. Incident HIV infection during pregnancy and breastfeeding contributes to a significant proportion of infants with HIV in very high incidence settings, and is of public health relevance for antenatal services that seek to test and treat all women with HIV as part of programmes for prevention of mother-to-child transmission (PMTCT).

Several strategies for preventing HIV infection in pregnant and breastfeeding women are well established, including provision of male and female condoms, partner testing, provision of antiretroviral therapy (ART) to partners with HIV, providing harm reduction services to women who inject drugs and management of sexually transmitted infections (STI). Despite their effectiveness, these strategies are not offered routinely in antenatal and postnatal services, and their use in high prevalence settings should be promoted. Oral pre-exposure prophylaxis (PrEP) using antiretroviral (ARV) drugs, is an approach that could complement established HIV prevention strategies as part of an expanded comprehensive package to reduce HIV infection among women and transmission from mothers to infants.

> PrEP could complement established HIV prevention strategies for pregnant and breastfeeding women as part of a comprehensive package to reduce HIV infections among women and transmission from mothers to infants in settings with high HIV incidence.

PrEP services are being developed for adolescent girls and women in many high incidence settings. For those who desire pregnancy or become pregnant while taking PrEP, continuing PrEP during pregnancy and breastfeeding should be considered if they continue to be at substantial risk[1] of HIV infection.

This technical brief seeks to:

- Summarise existing data on safety and efficacy for the use of oral PrEP in pregnant and breastfeeding women, as well as women who conceive while taking PrEP.
- Describe the rationale for offering PrEP as part of a comprehensive HIV prevention package that is integrated with PMTCT, antenatal and postnatal care programmes in settings of high HIV incidence.
- Discuss considerations for offering PrEP for safer conception.
- Outline a framework to strengthen HIV prevention during the antenatal and postnatal period for mothers, their partners and infants.

What is PrEP?

PrEP is the use of daily oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) to prevent HIV acquisition. PrEP has been shown to be effective in a wide range of HIV-negative populations.

WHO recommendation on PrEP

In 2015, the World Health Organization (WHO) recommended that oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk[1] of HIV infection, as part of combination HIV prevention approaches *(1)*. This recommendation was based on a systematic review and meta-analysis *(2)* of high-quality evidence on PrEP's effectiveness from clinical trial research. WHO included this recommendation in its 2016 update of the consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection *(3)*.

The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection consider the use of PrEP during pregnancy and breastfeeding and state that, in PrEP trials, exposure to TDF-containing PrEP during the first trimester of pregnancy was not associated with adverse pregnancy or infant outcomes *(3)*. The WHO guidelines development group concluded that in such situations the risk of HIV acquisition and accompanying increased risk of mother-to-child HIV transmission (MTCT) outweigh any potential risks of PrEP, including any risks of fetal and infant exposure to TDF in PrEP regimens. The 2016 WHO guidelines

> The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection.

1 Substantial risk is provisionally defined as HIV incidence greater than three per 100 person-years in the absence of PrEP.

note the need for active surveillance of pregnant and breastfeeding women receiving PrEP as countries roll out PrEP to this population *(3)*. The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection. TDF, along with 3TC (or FTC), is part of the WHO preferred first-line ART regimen recommended for adults, including pregnant women. It is widely used with good tolerance and no increased reports of safety and adverse events.

2015 WHO RECOMMENDATION ON PREP

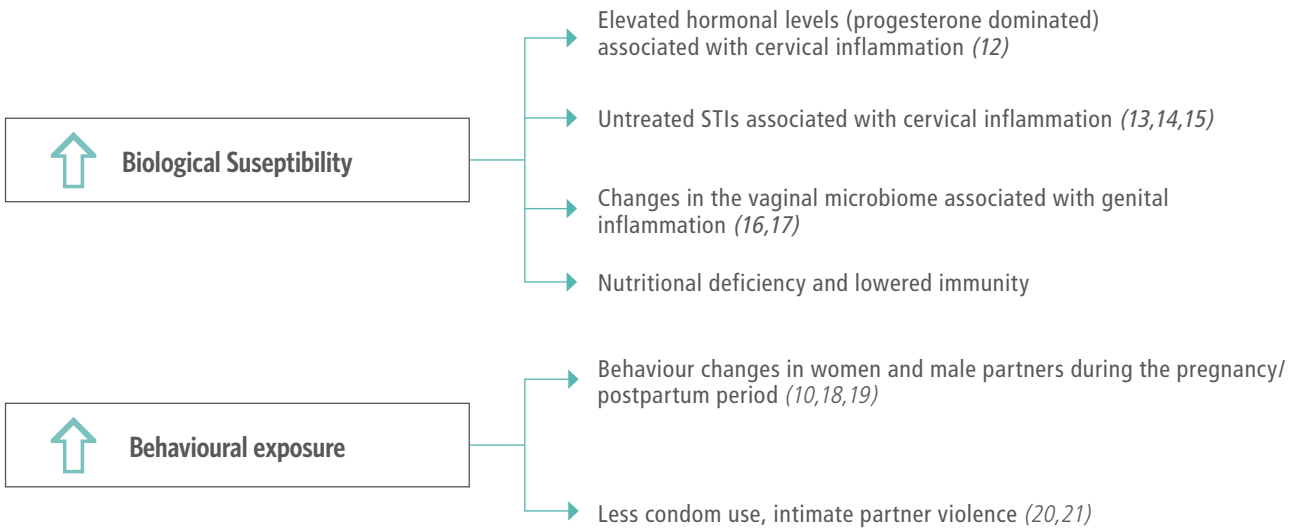
Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

High quality evidence, strong recommendation

Why offer PrEP to pregnant and breastfeeding women?

Pregnant and breastfeeding women living in settings where HIV incidence is greater than three per 100 person–years, particularly in sub-Saharan Africa, often remain at substantial and increased risk of HIV acquisition during pregnancy and breastfeeding. Biological factors increase susceptibility, and social and behavioural factors may increase exposure to HIV infection (Figure 1). Pregnant and breastfeeding women who acquire HIV at this time have a greater risk of transmitting HIV to their infant than women who became infected with HIV before pregnancy.

Figure 1. Women may be at increased risk of acquiring HIV during pregnancy, breastfeeding and the postpartum period



Source: Moodley D. 2017 *(4)*

Strong evidence supports the efficacy of a number of interventions for preventing HIV infection, including during pregnancy and breastfeeding. National HIV programmes should consider implementing these interventions based on HIV prevalence and incidence and epidemiological context. WHO recommends in all settings HIV testing of all pregnant women during antenatal care (ANC) in order to identify those who are HIV-positive and need ART, as well as women who are HIV-negative and may require HIV prevention interventions, including PrEP. Partner testing should be offered for all sexual and injecting drug partners, and assisted partner notification services[1] should be provided for all who are diagnosed with HIV infection *(5).*

PrEP safety during pregnancy and breastfeeding

The 2016 WHO guidelines state that there is no safety-related rationale for disallowing or discontinuing PrEP use during pregnancy and breastfeeding for HIV-negative women who are receiving PrEP and remain at risk of HIV acquisition *(1).* The guidelines conclude that in such situations the benefits of preventing HIV acquisition in the mother, and the accompanying reduced risk of mother-to-child HIV transmission outweigh any potential risks of PrEP, including any risks of fetal and infant exposure to TDF and FTC in PrEP regimens. The results from a WHO systematic review conducted in late 2016, summarized below, provide further support to this conclusion.

Safety of TDF during pregnancy and breastfeeding: systematic review of the evidence

In 2016, WHO conducted a systematic review to assess available data on the safety of TDF in pregnancy and breastfeeding in HIV-positive and HIV-negative women and their infants *(6)*. Thirty-three papers published between 2011 and 2016 reported comparative data for the primary analysis. Of these, 26 papers addressed TDF-containing ART in HIV-positive pregnant women; 20 compared TDF-ART with non-TDF-ART, two compared TDF-ART with zidovudine/single-dose nevirapine (AZT/sdNVP), and four compared different TDF-ART durations of use during pregnancy. Five papers reported on TDF use for the treatment of hepatitis B (HBV) among HIV-negative pregnant women, and two papers reported data from PrEP trials on HIV-negative pregnant women.

Data from this review, which are consistent with those reported in previous reviews, showed few adverse events in pregnancy and infant outcomes and are detailed below.

Summary of PrEP safety evidence

- **Evidence from HIV-negative pregnant women taking PrEP**
  The data on adverse events reported from two PrEP studies of TDF and TDF/FTC among HIV-negative women are reassuring. The VOICE study was confounded by poor adherence to PrEP. This was not true for the Partners PrEP study, where adherence was excellent, particularly among women on PrEP around the periconception period. Women randomized to receive PrEP and who became pregnant during the study had to discontinue taking PrEP, per protocol. In both studies, no significant differences in maternal and infant outcomes were reported between women who received PrEP and those who received placebo.

- **Evidence from HIV-positive pregnant women taking ARVs**
  The majority of studies in women with HIV on ART show no adverse effects of exposure to TDF ART on maternal or infant outcomes. Most data on TDF or TDF/FTC during pregnancy and breastfeeding come from HIV-positive women receiving combination ART, primarily initiated in the second or third trimester of pregnancy, although an increasing proportion of women are on ART at the time of conception. Data comparing pregnancy and infant outcomes of women receiving TDF-containing combination ART versus combinations without TDF showed no differences. Details can be found in the 2016 ARV Guidelines, section 4.6.6. Special considerations for toxicity monitoring during pregnancy and breastfeeding *(1).*
  Women with HIV generally have poorer pregnancy outcomes than HIV-negative women. This makes it difficult to strike a comparison between HIV-positive women on treatment and HIV-negative women on PrEP. Still, pregnancy outcomes are unlikely to be worse in HIV-negative women taking PrEP than in HIV-positive women taking ART.

1 Partner notification services: also known as disclosure or contact tracing; is defined as a voluntary process whereby a trained provider asks people diagnosed with HIV about their sexual partners and/or drug injecting partners, and then, if the HIV-positive client agrees, offers these partner(s) HIV testing services. Partner notification is provided using passive or assisted approaches.

Studies in HIV-positive pregnant women comparing ART (TDF ART or non-TDF ART) with single-drug *in utero* exposure with AZT or intrapartum single-dose nevirapine (sdNVP) generally show lower rates of adverse outcomes with AZT or sdNVP than with ART regimens. In addition, in the postpartum component of the PROMISE trial, there were no significant differences between women receiving TDF ART and those receiving no ART during breastfeeding in composite adverse events, severe adverse events or maternal mortality.

- **Evidence from HIV-negative pregnant women taking TDF to treat HBV infection**
  Studies of HBV mono-infected women taking TDF-containing treatment have demonstrated adverse event rates much lower than seen in HIV-positive women. In these studies, no significant differences in any adverse outcomes (maternal, pregnancy, or birth) were observed among women who received TDF, lamivudine (3TC) and placebo or no drug exposure.

- **TDF/FTC levels in breast milk**
  TDF and FTC are secreted in breast milk at very low concentrations (0.3–2% of the levels required for infant treatment). Data from a prospective short-term, open-label study of daily oral TDF/FTC PrEP among 50 HIV-negative breastfeeding African mother–infant pairs between one and 24 weeks postpartum indicate negligible levels of tenofovir in breast milk *(7).*

In summary, based on an increasing number of studies of women with HIV, maternal, pregnancy and growth outcomes appear to be generally similar among TDF-containing ART, other ART regimens and no ART. These data, combined with the PrEP clinical trial data in HIV-negative women, appear reassuring for women who conceive while receiving PrEP and for those who continue PrEP during pregnancy and breastfeeding. In settings with high risk of HIV acquisition and accompanying increased risk of mother-to-child HIV transmission (MTCT), the advantages of using PrEP outweigh any potential risks, including any risks of fetal and infant exposure to TDF in PrEP regimens.

Maternal, pregnancy and growth outcomes appear to be generally similar among TDF-containing ART, other ART regimens and no ART.

While the data for PrEP use in HIV-negative pregnant women are reassuring, and the benefits of preventing HIV infection outweigh the risks of TDF use during pregnancy and breastfeeding, more data are needed on TDF and TDF/FTC safety during this period. Further research is needed to assess the extent and consequences of adverse pregnancy outcomes with preconception ART use, whether there are differences by type of ART regimen, and the ultimate effects on neonatal and infant mortality, and to better understand the pathogenesis and determine whether there are potential interventions to reduce these outcomes. More data are needed on the effects of *in utero* TDF exposure on infant bone development and growth, and on maternal toxicity. More data are also needed to determine whether the use of TDF during breastfeeding increases the normal loss of bone mineral density observed during breastfeeding in the mother and, importantly, if accelerated loss of bone mineral density does occur, whether it reverses when breastfeeding stops or it persists. If TDF use accelerates loss of bone mineral density in the mother, it could result in excess bone fragility among women during breastfeeding or after.

Based on the available safety data, WHO considers that PrEP should not be discontinued during pregnancy and breastfeeding for women who continue to be at substantial risk of HIV infection. PrEP can also be considered as an additional prevention choice for HIV-negative pregnant women who are at substantial of HIV infection, as part of a comprehensive PMTCT package.

The choice to start, continue or discontinue PrEP when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. PrEP also should be considered as part of a safer conception package for women wanting to become pregnant and who are at high risk of acquiring HIV.

Providing PrEP to women who would most benefit

Although there is limited experience with the use of PrEP in antenatal and postnatal care services, it is an important new HIV prevention method to consider, particularly for high-burden settings where women remain at significant HIV risk. There are three scenarios for which PrEP may be considered among HIV-negative pregnant and breastfeeding women:

1. a woman taking PrEP who subsequently becomes pregnant and remains at substantial risk of HIV infection;
2. a pregnant or breastfeeding HIV-negative woman living in a setting with high HIV incidence who is at substantial risk of HIV acquisition; or
3. a woman whose partner is HIV-positive but is not virally suppressed[1].

In such cases, PrEP combined with screening for acute infection, adherence counselling, safety monitoring and HIV retesting every three months, in addition to other existing HIV prevention options, including condoms, should be offered.

PrEP as part of PMTCT in settings of high HIV incidence

For high burden settings and for populations with high HIV incidence in low burden settings, all HIV-negative women should be offered prevention interventions at antenatal and postnatal visits (Box 1). In addition, PrEP could be offered as part of an enhanced comprehensive HIV prevention approach in selected sites where women experience ongoing high HIV incidence. Note that the other elements described in Box 1 should be considered for women in other antenatal and postnatal settings where PMTCT programmes are established but incidence does not warrant prioritization of PrEP.

Box 1. Eight elements of comprehensive HIV prevention in antenatal and postnatal care settings where HIV incidence is high

1. **HIV testing services (HTS):** to identify women who are HIV-negative and may benefit from HIV prevention services, or who are HIV-positive and require treatment. Testing can be repeated every three months during pregnancy and postnatally.
2. **HTS should be offered for all sexual and drug injecting partners:** offer through passive or assisted partner notification approaches. Service providers offering partner notification services should discuss potential