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

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

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

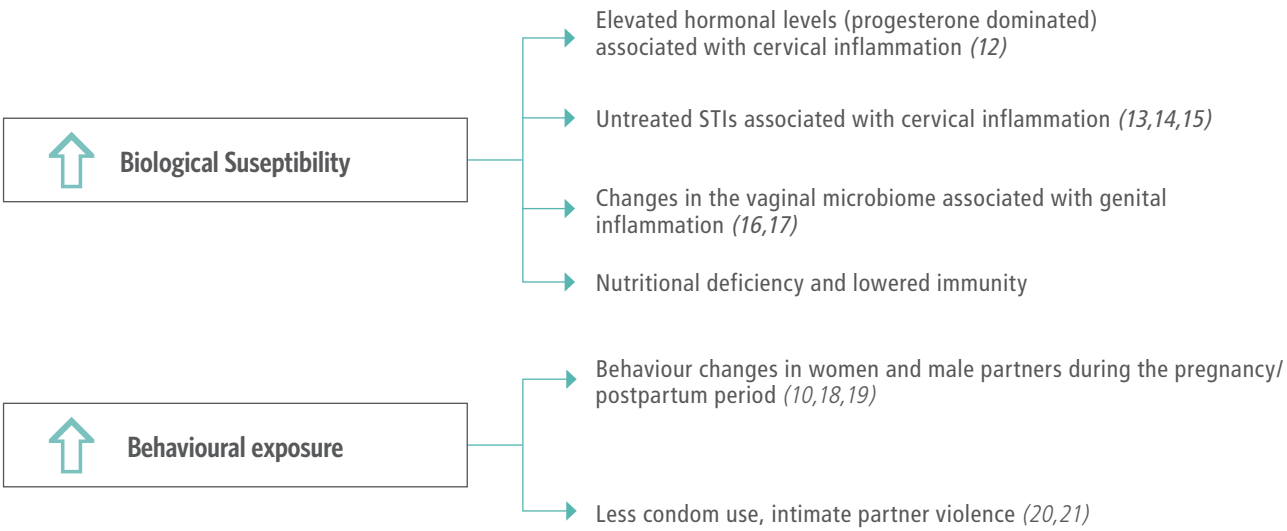
Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

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.

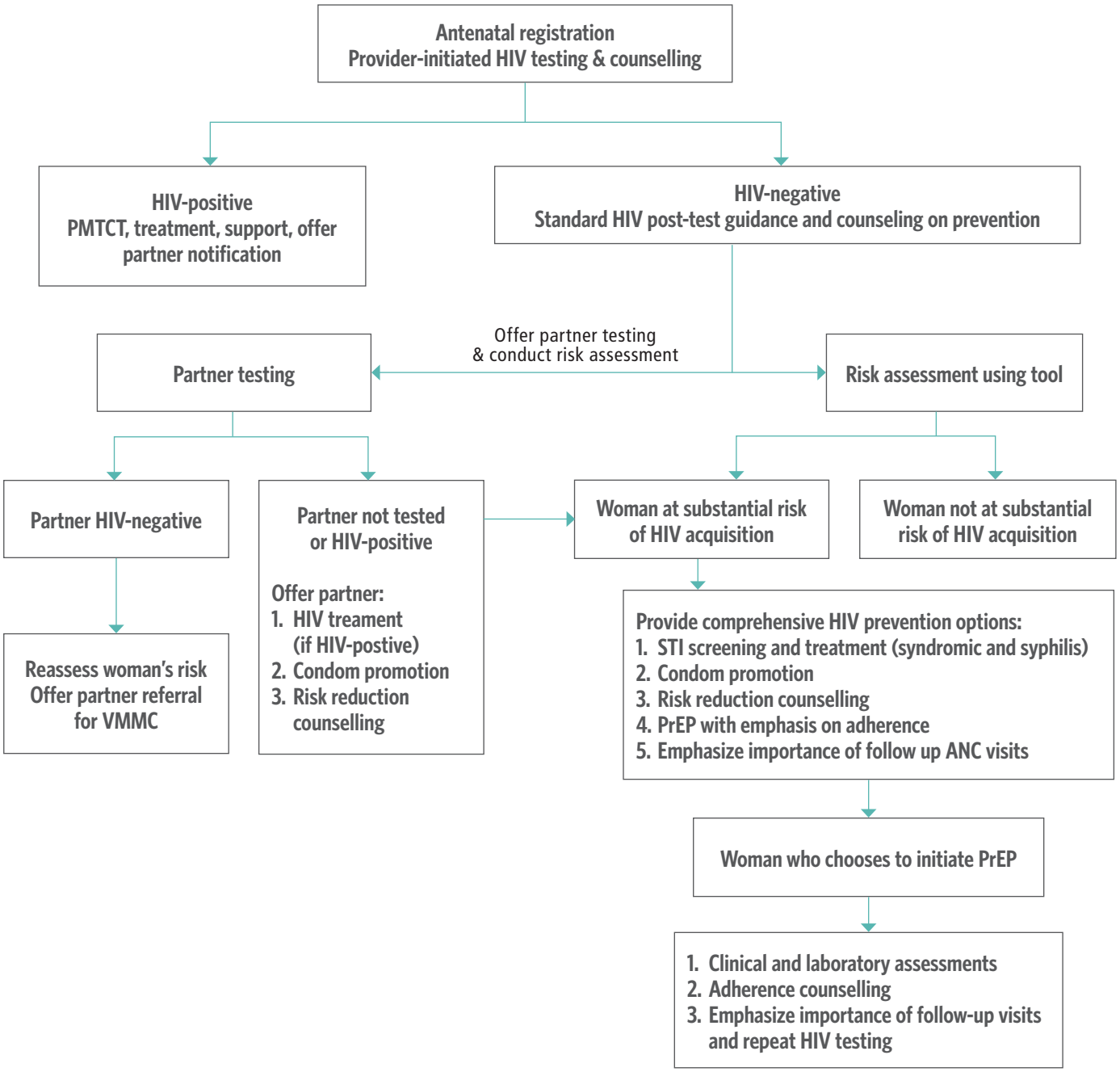
Box 1. Eight elements of comprehensive HIV prevention in antenatal and postnatal care settings where HIV incidence is high

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 risk for harm before providing these services.
3. **Partner referral for ART if HIV-positive:** establish referral mechanism for partner ART.
4. **Male partner referral for voluntary medical male circumcision (VMMC) (in VMMC priority countries) if HIV-negative:** establish referral mechanism for VMMC.
5. **STI screening and treatment:** manage STIs, in particular syphilis, at all antenatal and postnatal visits.
6. **Condom promotion:** offer male and female condoms with education on their correct and consistent use.
7. **Risk reduction counselling:** following a discussion of risk or a risk assessment, provide women with appropriate risk reduction counselling at HTS visits.
8. **Offer, start or continue PrEP:** based on individual risk with discussion of benefits and risks.

1 This could be a woman whose partner(s) is tested during the antenatal/postnatal periods but who is not taking ART or who has been on ART for less than six months. This also applies when a woman who does not know the details of her partner's viral suppression if on treatment, including when the partner is known to have poor ARV adherence.

Programmes should develop an algorithm for offering these interventions in a logical series of steps as part of a larger prevention algorithm (Figure 2).

Figure 2. A suggested prioritization framework for offering PrEP to pregnant and breastfeeding women *(4)*



PrEP could be offered to all HIV-negative women in high incidence antenatal and postnatal settings. Alternatively, depending on the epidemiologic context, programmes may consider using HIV risk assessment tools. Such tools could help to identify HIV-negative pregnant women who would benefit most from PrEP while minimizing unnecessary PrEP use among women at lower risk. Risk should be assessed periodically, as a person's risk and situation may change over time so that PrEP may no longer be necessary or the person may prefer other means of HIV prevention. Similarly the risk of those who are initially assessed as low-risk should also be reassessed periodically.

> Programmes may consider using HIV risk assessment tools for pregnant women.

An HIV risk assessment tool developed by a cohort study in Kenya (8) yields a simplified risk score based on factors that include whether the respondent knows her male partner's HIV status, lifetime number of sexual partners and laboratory-confirmed syphilis (Figure 3). In the Kenyan study, women with simplified scores greater than 6 accounted for 16% of the population but 56% of HIV acquisitions. The authors conclude that a combination of indicators routinely assessed in antenatal clinics predicted HIV risk and could be used to prioritize which pregnant women are offered PrEP.

Two other studies in Kenya and South Africa identified genital infections and partner demographic and behavioural characteristics associated with incident HIV infection in pregnant women *(9,10)*. Developing risk screening tools using factors such as these from locally-available data may be beneficial in identifying pregnant women at increased risk of acquiring HIV. Ideally, screening tools should be validated before they are used widely.

Screening tools, if developed and used, should not be used to exclude women who request PrEP from receiving PrEP and support for its use. Women who request PrEP may have already identified their own risks and also may be more motivated to take PrEP as recommended.

Figure 3. Kenyan risk assessment scoring tool

Risk factor	Value per factor	Complete score	Simplified score
No. of lifetime sexual partners			
1 point per sexual partner	Enter at least 1		
Male partner HIV status			
Known or no male partner	0		
Unknown	6		
Syphilis			
RPR nonreactive	0		
RPR reactive	5		
Bacterial vaginosis			
Negative or not screened	0		
Positive	2		
Candidiasis			
Negative or not screened	0		
Positive	3		
	Total risk score		

Source: Pintye et al, 2016 *(8)*

PrEP for safer conception

HIV-negative women in high prevalence settings remain at high HIV risk during the period of conception when their partners are of unknown status, or their partners are living with HIV and are either (a) not on ART or (b) are not virally suppressed (including partners recently starting ART, whose full viral suppression may take up to six months). Offering PrEP during this time could decrease the risk of viral transmission to the HIV-negative woman and reduce anxiety about HIV transmission at a time when couples are not always using condoms to prevent HIV transmission. The decision whether to take PrEP should always be made by the woman, following discussion of the risks and benefits with her health-care provider.

> PrEP can be offered to an HIV-negative woman who is trying to conceive if her partner is HIV-positive and not virally suppressed or she does not know his HIV status.

Monitoring PrEP use by pregnant and breastfeeding women

Although the currently available data are reassuring regarding the safety of PrEP during pregnancy and breastfeeding, active surveillance of mother and infant outcomes during PrEP use in pregnancy and breastfeeding should be part of a PrEP programme. WHO currently recommends[1] that the active surveillance of ARV drug toxicity during pregnancy and the breastfeeding period focus on three areas. These three areas should also be monitored during PrEP use.

1. **Maternal adverse outcomes:** monitoring treatment-limiting toxicities associated with ART in pregnant women, particularly mortality;

2. **Adverse birth outcomes:** monitoring toxicity in the fetus *in utero*, manifesting as stillbirths, preterm births, low birth weight, major congenital anomalies or early infant deaths. Adverse birth outcomes may be routinely monitored by integrating an additional indicator into the national monitoring and evaluation system;

3. **Adverse infant and child outcomes:** monitoring health outcomes in infants and young children exposed to ARV drugs *in utero* or via breast milk, particularly any impact on growth and development.

WHO encourages countries to consider active toxicity surveillance for ARV use during pregnancy and breastfeeding.

WHO encourages countries to implement active toxicity surveillance for ARV use during pregnancy and breastfeeding. Sites that provide PrEP to women should ensure that maternal, birth and infant outcomes are actively recorded for those who become pregnant while on PrEP. Where systems exist for routinely monitoring ARV drug toxicities, indicators for PrEP regimens and duration of PrEP use could be included. To optimize access to PrEP, the site at which PrEP was initiated could continue to provide PrEP during the pregnancy and breastfeeding period. However, linkages and referral to antenatal care should be established for pregnant women, with systematic recording of pregnancy, birth and infant outcomes for women at ANC sites. Also, before PrEP services are offered, referrals and linkage protocols should be established between ANC clinics and the facilities that will provide continuing PrEP to women who remain at substantial risk of HIV infection after the breastfeeding period. Adverse events should also be reported into national surveillance systems for ARV toxicity and/or birth defects. WHO provides advocacy tools, technical guidelines and technical assistance to countries and organizations implementing ARV toxicity surveillance during pregnancy and breastfeeding.

1 For more on ARV toxicity monitoring, see the WHO web page Monitoring toxicity of ARVs, http://www.who.int/hiv/topics/arv_toxicity/en/ and March 2014 supplement (Chapter 12): http://www.who.int/hiv/pub/guidelines/arv2013/arv2013supplement_to_chapter11.pdf?ua=1.

Summary of issues and considerations

Issues	Considerations
Pregnancy and breastfeeding	PrEP can be started or continued during pregnancy and breastfeeding in women at substantial risk of HIV acquisition. A range of interventions should be offered to HIV-negative women in pregnancy and breastfeeding to prevent and detect incident HIV. These include condom promotion, counselling to reduce risk, risk assessment, STI screening and treatment, partner testing and treatment, repeat HIV testing and PrEP for women at substantial risk of HIV infection.
Desire to conceive	Consider PrEP for HIV-negative women in serodiscordant relationships desiring pregnancy, particularly women whose partners are not on ART or not fully virally suppressed. In such cases, PrEP can be used as a bridge to viral suppression on ART. In addition, PrEP can benefit women who do not know their partners' HIV status or who, in very high prevalence settings, have partners who are unwilling to test.
Family planning	Women who choose to start or continue taking PrEP during the postpartum period should also be offered a range of family planning choices, as should all women postpartum.
Gender-based violence	The sociocultural barriers and facilitators to PrEP among women should be examined given the context of gender inequalities, including gender-based violence.
Sex workers	Countries are beginning to focus on offering PrEP to sex workers. Improving linkages to health services, particularly family planning and antenatal services, is critical.
Adolescent girls	This population requires more support for adherence and enhanced comprehensive sexual and reproductive health information. Consent requirements may be a barrier in initiating PrEP and other health services.

Key messages

- **PrEP is safe during pregnancy and breastfeeding.** The ARVs used for PrEP, TDF and TDF/FTC, are frequently used in combination with other ARVs for HIV treatment. The latest WHO systematic review suggests that there does not appear to be a safety-related rationale for disallowing or discontinuing PrEP during pregnancy and breastfeeding for HIV-negative women who are at continuing risk of HIV acquisition.
- **PrEP could be provided as part of a comprehensive package.** PrEP is part of a package of combination HIV prevention and other services that includes HIV testing services, assisted partner notification, provision of male and female condoms and lubricants, contraception choices and screening and treatment of STIs.
- **Adherence matters.** When women understand the benefits of PrEP and want to take it, they are more likely to adhere to it. Some women will find their own ways to maintain adherence to daily PrEP; others will benefit from advice and support. Adolescents may need special support for adherence.
- **Disclosure can have benefits.** Some women may find disclosure of their PrEP use to their partners helpful in supporting their own adherence.
- **Recognize "seasons of risk".** A woman's risk may vary over time as circumstances change. Women should be supported to start and to stop PrEP if their HIV risk changes. Risk for HIV acquisition is not constant.
- **Hormonal contraception.** PrEP can be used with hormonal contraception. Recommended PrEP regimens do not appear to alter the effectiveness of hormonal contraception.
- **PrEP can be cost-effective.** A recent analysis found that providing PrEP to HIV-negative pregnant and breastfeeding women at high HIV risk in sub-Saharan Africa was cost-effective *(11)*.
- **PrEP in not for everyone.** It is a choice, and women should be making an informed decision based on their risk for HIV.
- **Ongoing surveillance is necessary.** Active surveillance of pregnant and breastfeeding women receiving PrEP is needed as countries begin to implement PrEP in this population. National surveillance should identify and record adverse pregnancy and infant outcomes.

For more detailed information on what is required before initiating or maintaining a pregnant or breastfeeding woman on PrEP and on additional monitoring, please refer to the clinician module in the forthcoming WHO PrEP Implementation Guidance.

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