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Guidelines for Expanding Combination Prevention and Treatment Options: Oral Pre-Exposure Prophylaxis (PrEP) and Test and Treat (T&T)

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Abbreviations and Acronyms

AGYW	Adolescent girls and young women
ART	Antiretroviral therapy
ARV	Antiretroviral
CHW	Community health worker
FTC	Emtricitabine
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HTS	HIV testing services
M&E	Monitoring and evaluation
MCC	Medicines Control Council
MDR-TB	Multidrug resistant - tuberculosis
MSM	Men who have sex with men
NDoH	National Department of Health
PEP	Post exposure prophylaxis
PHC	Primary healthcare
PMTCT	Prevention of mother to child transmission
PrEP	Pre-exposure prophylaxis
SAHIVCS	South Africa HIV Clinicians Society
SAHMS-FSW	South Africa Health Monitoring Survey of Female Sex Workers
SRH	Sexual and reproductive health
STI	Sexually transmitted infection
SW	Sex worker
T&T	Test and treat
TAPS	Treatment and Prevention demonstration project
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine (Truvada)
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VMMC	Voluntary medical male circumcision
WHO	World Health Organization

Definition of Key Terms

Term	Working definitions in these guidelines
Adolescent	Young person aged 15 to 19 years, inclusive
AGYW	Adolescent girls and young women aged 15 to 24 years
Adult	Person older than 19 years
ANC	Antenatal care
ART	Antiretroviral therapy refers to the use of a combination of three ARV drugs to achieve viral suppression and is given for life
ARV	Antiretroviral drugs refer to the medicines active against HIV
Combination HIV prevention	A combination of behavioural, biomedical, and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition
Continuum of care	A comprehensive package of HIV prevention, diagnostics, treatment, care, and support services provided for people at risk of or living with HIV, and their families
Gender	"Gender" refers to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women. Gender requires us to ensure that health policy, programmes, services, and delivery models are responsive to the needs of women, men, girls, and boys in all their diversity
Gender-based violence	Any act of physical, sexual, or psychological harm or suffering, including threats of such acts, coercion, or arbitrary deprivations of liberty in public or in private life
Healthcare provider	Anyone who renders healthcare; includes doctors, nurses, pharmacists, trained counsellors, and community health workers
Priority populations	Groups who are at increased risk and vulnerability to HIV due to specific high risk behaviours. Includes sex workers, MSM, incarcerated populations, people who use drugs or alcohol, transgender populations, and AGYW
PEP	The preventive ARV medical treatment started immediately after exposure to HIV in order to prevent infection
PrEP	The use of antiretroviral drugs by HIV-negative people before potential exposure to prevent the acquisition of HIV. Currently, PrEP refers to oral daily PrEP (tenofovir/emtricitabine or tenofovir alone) but may incorporate other formulations over time
Serodiscordant couples	Couples in an ongoing sexual relationship in which one partner is HIV-positive and the other is HIV-negative
Sex worker	Women, men, and transgendered people of all ages, who work with the primary intention of exchanging money for sex.
Substantial risk	Substantial risk of HIV infection is defined as a population group with an HIV incidence greater than 3 per 100 person-years in the absence of PrEP
Transgender population	Refers to people whose gender identity and expression are different to the social expectations of gender. They may see themselves as male, female, gender non-conformist, or one of many other gender-

	variant categories
Use of ARV drugs for HIV prevention	Refers to the HIV prevention benefits of using ARV drugs. This can include preventing mother-to-child transmission of HIV by treating the mother during pregnancy and breastfeeding, using ARV drugs to reduce the transmission of HIV among serodiscordant couples, using ARV drugs to prevent people from acquiring HIV when they are exposed to HIV (post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP)), and ART for HIV-positive individuals to reduce viral load.
Young women	Women aged 20 to 24 years, inclusive

1. Background and Rationale

1.1. WHO Recommendations

The World Health Organization (WHO) guidelines on the use of antiretroviral therapy (ART) have evolved since first published in 2002. Over the years, additional evidence has emerged showing that earlier initiation of ART results in better, long-term clinical outcomes for people living with HIV, resulting in a population impact on HIV transmission. Clinical trial results have also confirmed the efficacy of the drug tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), for use as PrEP to prevent people from acquiring HIV in a wide variety of settings and populations.[1] The use of PrEP to prevent people from acquiring HIV is an important new additional prevention option for populations who are at a substantial risk of acquiring HIV.

In September 2015, the WHO released an early release to their new guidelines on when to start ART for early treatment of HIV infection and on the use of ART for HIV prevention.[2] These guidelines were then updated in June 2016.[3] These new guidelines recommend the following:

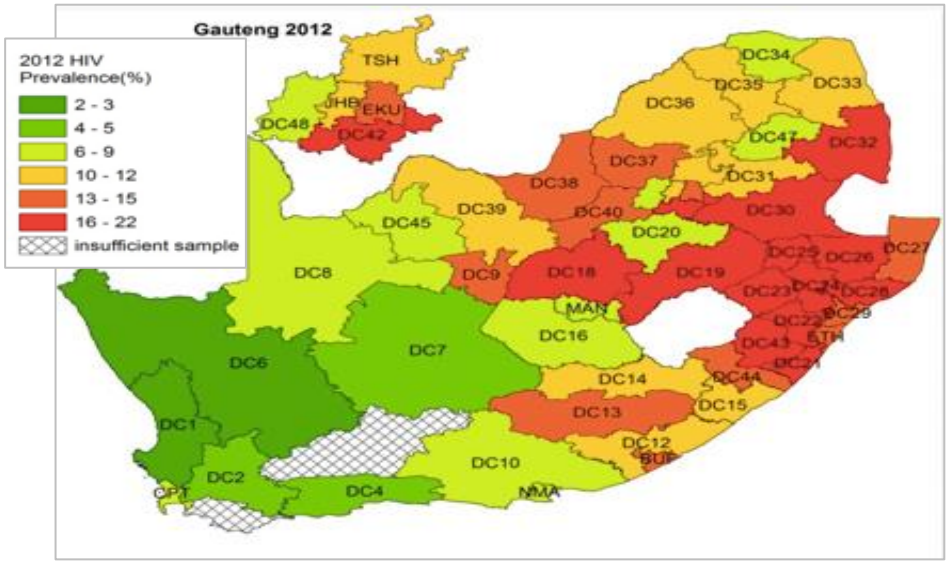
- ART should be initiated in everyone living with HIV regardless of their CD4 cell count.
- People with a substantial risk of HIV infection should be provided with daily PrEP as part of a combined HIV prevention strategy.

1.2. South Africa Context

South Africa has the largest HIV epidemic in the world, with 6.8 million people aged 15 to 49 living with HIV, representing 19 percent of the global HIV burden.[4] The South Africa HIV programme was launched in 2009. As of 2015, there are just over 3.3 million people on antiretroviral treatment (ART), creating the largest ART programme in the world.[5] Despite this accelerated progress in initiating and treating HIV-positive people, there are still more than 3 million additional people that need treatment in line with the 2015 WHO ART guidelines.[6]

The epidemic has varied significantly across and within different provinces in South Africa. Even though the epidemic is generalised, it is also over-represented in some populations, specifically sex workers (SW) and men who have sex with men (MSM). It is also concentrated in the populations with very high vulnerability to HIV, such as adolescent girls and young women (AGYW). This contextual understanding of the HIV epidemic is critical to develop and implement effective HIV interventions. Differential vulnerability levels, social risk factors, high-risk sexual practices, and limited access to appropriate HIV interventions influence HIV incidence among these populations.[7,8,9]

FIGURE 1.HIV PREVALENCE BY DISTRICT, SOUTH AFRICA 2012[10]



In June 2016 the South African National Department of Health (NDoH) rolled out oral PrEP to select sex workers sites. At that time, the guidelines were specific for the sex worker rollout. These guidelines have now been updated to include additional target populations, including men who have sex with men, serodiscordant couples, and adolescent girls and young women. The inclusion of these additional target populations in the PrEP rollout will be at the direction of the NDoH, over time, targeting prioritized populations in phased approaches.

These guidelines focus on the provision of PrEP and universal test and treat (T&T) as part of a comprehensive combination prevention and expanded treatment policy, and should be read in conjunction with the National PrEP and T&T Policy, the South African National Sex Worker HIV Plan (2016 – 2019), the National Strategic Plan for HIV, TB and STIs (2012 – 2016), the National HIV Testing Services: Policy (2016), and the National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults (2015).

1.2.1. Sex workers

In these guidelines, sex workers include: women, men, and transgendered populations, who sell sex regularly and occasionally, and those who may or may not self-identify as sex workers. Sex workers range in age and socio-economic status and are of diverse sexual orientation and gender identities.

The 2013 rapid population size estimate reported that there were around 153,000 sex workers in South Africa.[11] Sex workers have disproportionately higher risk for HIV acquisition because behavioural, legal, and social barriers increase their vulnerability.[12] An estimated 20 percent of the 350,000 people annually infected with HIV in South Africa are connected with sex work.[13]

Female sex workers carry an enormous burden of HIV: at least one-third have been infected with HIV by the age of 24; among those 25 and older, as many as 4 in 5 are HIV-positive[14]. HIV prevalence amongst female sex workers in South Africa is estimated to be 59.8 percent.[15] The SA Health Monitoring Survey of Female Sex Workers[16] estimates the prevalence of HIV among female sex workers at 71.8 percent in Johannesburg, 39.7 percent in Cape Town, and 53.5 percent in eThekwini. Fortunately, the vast majority have tested for HIV, and more than three-quarters of HIV-positive female sex workers are aware of their status.

The same report observed marked increases in HIV prevalence among female sex workers as they get older, comparing those 16 to 24 to those 25 and older (Johannesburg, 59.0 percent vs 78.8 percent; Durban 29.4 percent vs 71.2 percent). Young sex workers may be more vulnerable to HIV than their older counterparts because of less power to negotiate condom use, greater susceptibility to violence, and greater number of sexual partners due to exploitation and male age preferences.[17] These high rates confirm the urgency of focusing interventions on HIV-positive sex workers, as well as preventing acquisition in HIV-negative sex workers. By making PrEP and T&T available to sex workers, their HIV risk can be reduced.

The evidence for inclusion of PrEP for sex workers is strong and there are existing platforms for healthcare delivery specifically targeted to these high-risk, hard to reach populations. For these reasons, rollout of PrEP and T&T should be considered in this group first.[18] In this respect, sex workers in South Africa have been prioritized as a population at substantial risk due to lack of power to insist on condoms, high rates of gender based violence and rape, and lack of legal protection.

1.2.2. Men who have sex with men

Up to 1 percent of South Africa's adult population may be engaging in same sex practices. This implies there were approximately 1.4 million MSM between the ages of 15 and 49 years old in South Africa in 2014.[19] Young MSMs are even more vulnerable to HIV as they may engage in overlapping risk behaviours, such as injecting drugs and selling sex.[20] There are structural, social, and individual-level risk factors for HIV among MSM, which make the HIV epidemic among MSM fundamentally different from other groups at risk.[21] MSM HIV prevalence is between 1.89 to 4.65 times higher than non-MSM males of similar ages, where representative surveys have been conducted.[22] There is a need to scale up and improve sustained, comprehensive, and effective HIV prevention efforts targeting MSM. Offering PrEP to MSM, especially those that do not use condoms, showed the largest impact in the prevention of HIV infection.[23]

1.2.3. Serodiscordant couples

HIV-1 transmission occurs among HIV serodiscordant couples, where one of the partners is HIV-positive and the other is HIV-negative, with or without the knowledge of each other's status.[24] This results in repeated risk of HIV transmission over time. Knowledge of HIV status is still low among South Africans, with only 37.5 percent of males and 52.6 percent of females knowing their HIV status in 2012.[25] HIV discordant couples represent an important

target population for HIV prevention. Couple-based HIV testing facilitates identification of HIV serodiscordant couples. Serodiscordant couples also often demonstrate minimal condom use and are therefore at considerable risk if the HIV-positive partner is not consistently virally suppressed. Provision of ART for the infected partner reduces sexual transmission by 96 percent and PrEP for the uninfected partner may reduce sexual transmission by as much as 75 percent.[26].

A study conducted in China showed that approximately 85 percent of serodiscordant couples were willing to use PrEP, whether to protect HIV-negative partners or for safer conception.[27] To effectively reduce HIV incidence among serodiscordant couples, it is recommended that the HIV-positive partner should be initiated on ART regardless of CD4 count while the HIV-negative partner uses PrEP.*

1.2.4. Adolescent girls and young women

UNAIDS and the WHO estimate there are about 380,000 new HIV infections among adolescent girls and young women (AGYW) aged 15 to 24 every year.[28,29] In 2013, almost 60 percent of all new HIV infections in this age group occurred among females.[30] In sub-Saharan Africa, women acquire HIV infection at least 5 to 7 years earlier than men.[31] Between 2005 and 2012, the global number of HIV-related deaths fell by 30 percent, but the corresponding number among adolescents increased by 50 percent.[32].

It is important to focus HIV prevention efforts on adolescents as they are at high risk of acquiring HIV and transmitting HIV to others.[33] Young girls with a mean age of 18 years are infected by men that are about 8 years older than themselves.[34] In their mid-20's, the same young women infect similar-age partners, who may then continue the cycle by engaging in sex with young uninfected girls.

Factors that make young women more vulnerable than men to acquiring HIV during sex include: biology; having sex with older men who are more likely to be infected;[35] multiple concurrent relationships;[36] low marriage rates;[37] transactional sex; low consistent condom use rates;[38] and limited skills in negotiating safer sex practice and sexual and gender-based violence (GBV). Despite this greater vulnerability, women have few options to reduce the acquisition of HIV.

1.3. COMBINATION PREVENTION

Combination HIV prevention is an approach that seeks to achieve maximum impact on preventing new HIV infections by combining biomedical, socio-behavioural, and structural interventions that are human-rights-based and evidence-informed. The combination prevention package includes: condoms, lubricants, STI management, screening and

* PrEP use in the HIV-negative partner does not need to stop when the HIV-positive partner is virally suppressed. Personal choice and other potential risk factors should be considered by the clinician and client.

management of intimate partner violence, sexual and reproductive health services, and HIV services, including counselling and testing, HIV management, ART, PEP, and PrEP.[39]

BOX 1. WHAT IS A COMBINATION PREVENTION PROGRAMME?

Combination prevention programmes are: ...rights-based, evidence-informed, and community-owned programmes that use a mix of biomedical, behavioural, and structural interventions, prioritized to meet the current HIV prevention needs of particular individuals and communities, so as to have the greatest sustained impact on reducing new infections. Well-designed combination prevention programmes are carefully tailored to national and local needs and conditions; focus resources on the mix of programmatic and policy actions required to address both immediate risks and underlying vulnerability; and they are thoughtfully planned and managed to operate synergistically and consistently on multiple levels (e.g. individual, relationship, community, society) and over an adequate period of time. They mobilize community, private sector, government and global resources in a collective undertaking; require and benefit from enhanced partnership and coordination; and they incorporate mechanisms for learning, capacity building, and flexibility to permit continual improvement and adaptation to the changing environment.

- UNAIDS Prevention Reference Group

1.4. TEST AND TREAT ALL

Globally, around one-third of the 15 million individuals who are eligible for treatment are currently receiving ART.[40] For each person started on ART, at least two more individuals become newly infected with HIV. This causes a continuous increase in the number of HIV-positive people who will require ART in future. The WHO recommends that ART should be initiated among all adults and children with HIV regardless of WHO clinical stage and at any CD4 cell count, prioritising those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤500 cells/mm^3. Earlier initiation of ART results in better long-term clinical outcomes for HIV-positive people and reduces an individual's viral load and, therefore, their infectiousness.

The HIV Prevention Trials Network (HPTN) 052 study showed that starting ART early reduced the overall risk of HIV sexual transmission to uninfected partners by 93 percent.[41] With approximately 6.8 million people infected with HIV in South Africa, and just over 3 million on ART, the unmet need is approximately 50 percent. T&T is proposed as a new, highly effective HIV prevention strategy. T&T interventions are built around two main components. First, HIV testing services are offered to all members of a defined high-risk population to identify those already infected with HIV but not yet linked to care, followed by regular and repeat HIV testing of those who test HIV-negative to identify new positives as early as possible after seroconversion. Second, the initiation of life-long ART immediately after HIV diagnosis, regardless of CD4 count.[42, 43, 44]

To test and treat all has the potential to cause a very steep reduction in HIV incidence, will reduce HIV-related morbidity and mortality, and could potentially eliminate HIV as a public health problem over a period of 15 to 20 years.[45] WHO recommends that all HIV infected individuals are started on ART regardless of their CD4 count.

As of September 2016, South Africa is implementing T&T for all. All HIV positive people will be offered immediate initiation on ART, regardless of CD4 count or clinical staging, in line with the National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents, and Adults (2015) and the National HIV Testing Services: Policy (2016).

1.5. Oral Pre-Exposure Prophylaxis

PrEP is defined by the WHO as the use of antiretroviral drugs by HIV-negative people before potential exposure to HIV to prevent HIV acquisition. Oral PrEP is an evidence-based HIV risk-reduction intervention to be offered to all people at *substantial risk* of acquiring HIV.[46] The WHO defines substantial risk as a population group with an HIV incidence greater than 3 per 100 person-years in the absence of PrEP.[47] Defining who should be offered PrEP requires a country to balance the risk of HIV exposure, the risk of adverse events, and available resources.

The WHO recommends that PrEP (containing tenofovir disoproxil fumarate (TDF)) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of a combination of prevention approaches that include: HTS, counselling, male and female condoms, lubricants, ART for HIV-positive partners in serodiscordant couples, and VMMC. Populations who would benefit most from PrEP are often underserved and likely to have low levels of HIV testing and high levels of undiagnosed HIV, and may need to be linked to other services.

PrEP has been shown to be safe with minimal side effects.[48,49] One of the main guiding principles for PrEP as an intervention is that it will enable and empower people to have an informed and additional choice of an HIV prevention method. The evidence and benefits of PrEP are summarized in Appendix 1.

1.6. Implementation of PrEP and T&T

To inform the implementation of PrEP and T&T, the evidence from several demonstration projects will be used. The demonstration projects will enable the country to scale up PrEP and T&T. The current platform of delivery for PrEP is through existing sex worker programmes and linkage to primary healthcare facilities, where appropriate, with the aim of integrating them into existing public health services. Additional delivery mechanisms and target populations will be incorporated in a phased approach with NDoH direction.

1.7. Oral PrEP Drugs: TDF and TDF/FTC

Tenofovir (TDF) and tenofovir/emtricitabine (TDF/FTC) in a single tablet fixed dose combination (FDC) are the oral antiretroviral agents used in oral PrEP studies to date. A systematic review and meta-analysis of PrEP trials containing TDF demonstrated that the level of protection from TDF versus TDF/FTC did not differ by age, gender, regimen, or mode of acquiring HIV (rectal, penile, or vaginal). In a May 2015 meta-analysis of all PrEP trials, daily oral TDF has comparable efficacy to TDF/FTC. However, the use of TDF monotherapy for HIV prevention has not been investigated in some key populations and on this basis, the

Southern African HIV Clinicians Society (SAHIVCS) recommends the use of TDF/FTC in combination for oral PrEP.

Gilead's TDF/FTC combination pill, Truvada®, was approved for use as PrEP by the Medicine Control Council (MCC) in December 2015, in combination with safer sexual practices. Four additional TDF/FTC products have received approval for use as PrEP in South Africa as of July 2016: Aspen (Truvada and Tencitab), Cipla (Didivir), and Mylan (Tenemine).

TDF alone has not yet been approved for use as PrEP by the MCC and no applications have been made to the MCC for registration of TDF for PrEP use to date.

1.7.1. Daily PrEP vs non-daily PrEP

The WHO does not currently recommend intermittent use of PrEP. The ADAPT study (HPTN 067) conducted among women in Cape Town evaluated the feasibility of non-daily oral PrEP using Truvada.[50] The study showed better adherence and coverage of potential sexual exposure when PrEP is taken daily. Daily adherence is more forgiving in the case of missed doses and results in more sustained use during periods of HIV acquisition risk, as opposed to intermittent use.[51]

1.8. ADHERENCE

Adherence is important in both PrEP use and HIV treatment and will form an integral part of the combination prevention and T&T programme. Adherence is a significant modifier of PrEP effectiveness. PrEP can be started and stopped as a person moves through "seasons of risk," whereas ART is lifelong.

BOX 2. EFFECTIVE USE

Effective use of PrEP requires daily usage. It should be taken for a specified period, initially for attainment of full protection, followed by daily use for the duration of possible exposure to HIV infection, followed by a continuous use for one month after the cessation of exposure. Good quality counselling fosters adherence and supports a comprehensive plan for sexual and reproductive health.

It is important to offer a combination prevention package of services for PrEP users to further decrease risk of HIV infection. These include: VMMC, consistent and correct use of condoms, use of lubricants, and risk assessment and reduction.

1.9. HIV DRUG RESISTANCE

The risk of HIV drug resistance to either TDF or FTC is low, occurring in approximately 1 in 1,000 PrEP users in clinical trials, and was mainly seen in those with acute undetected HIV infection at the time of initiating PrEP. Various trials have shown that the overall implementation of PrEP is expected to decrease the public health burden of HIV drug resistance.[52,53,54] Had the averted infections occurred in the absence of PrEP, more resistance would be expected to occur during the treatment of these infections than occurred due to PrEP use.

1.10. PREGNANCY AND BREASTFEEDING

Oral PrEP is contraindicated for use in pregnancy and breastfeeding by the South Africa MCC. Therefore, the stance of the NDOH is that PrEP shall not be offered to pregnant or breastfeeding women without further guidance from the MCC.

The WHO is doing additional research on the benefits and risks of PrEP in pregnancy and has recently released the following statement:

> *'Although additional surveillance is important, at the present time, given the available safety data, there does not appear to be a safety-related rationale for discontinuing PrEP during pregnancy and breastfeeding for HIV-uninfected women receiving PrEP who become pregnant and remain at continuing risk of HIV acquisition'.*[55]

Pregnancy itself is associated with an increased risk of becoming infected with HIV.[56] The use of PrEP around the time of conception and during pregnancy offers a means of protection to the uninfected partner. HIV-negative women in serodiscordant relationships are at risk of acquiring HIV infection whilst trying to conceive through unprotected sex.

PrEP trials involving heterosexual women excluded pregnant women from enrolment; those who fell pregnant during the conduct of the study were discontinued from PrEP. One study of 46 uninfected women in serodiscordant relationships demonstrated no adverse effects on the pregnancy or cases of HIV transmission when TDF was used around the time of conception. There are several ongoing demonstration projects that will allow women to continue PrEP if they fall pregnant, which will provide additional data to inform future recommendations. In addition, the Antiretroviral Pregnancy Registry shows no evidence of adverse outcomes amongst infants exposed to these medications when used as ART in utero.

2. Guiding Principles

PrEP and T&T will contribute to the country's targets for HIV reduction by 2030, as reflected in the National Development Plan. South Africa supports the UNAIDS Fast Track approach, the 90-90-90 targets, and the prevention target of reducing the number of new HIV infections by 75 percent by 2020. To achieve these goals, there is a need for an expanded and accelerated scale up of HIV treatment and combination prevention, including PrEP.

These new guidelines will assist in providing the necessary guidance towards improved management of HIV prevention across different populations.

BOX 3. OBJECTIVES OF THE PREP AND TEST & TREAT GUIDELINES

- **Expanded prevention options:** Offer and promote PrEP in the context of combination prevention
- **Integration:** Integrate PrEP and T&T into other HIV prevention programmes, policies, and services, as well as sexual and reproductive health, contraception, and fertility planning services, and ANC services
- **Quality of care:** Provide PrEP within the broader framework of quality health service provision
- **Communication and community-based strategies:** Implement appropriate, evidence-informed, communication and advocacy strategies to increase healthcare provider and public awareness of PrEP and T&T within the context of HIV prevention without stigmatising the intervention and potential users, nor increasing risky sexual behaviour
- **Monitoring and evaluation:** M&E systems are in place to monitor and evaluate provision, quality of care, outcomes, and impact

From the National PrEP and T&T Policy

2.1. ENABLING AND EMPOWERING INDIVIDUALS TO HAVE AN INFORMED CHOICE OF HIV PREVENTION

These guidelines are underpinned by a rights-based approach, whereby individuals are provided with information that will enable them to make decisions on options for HIV prevention. A rights-based approach also includes confidentiality and equal access to non-discriminatory healthcare, privacy, prevention choice, informed decision-making, and shared responsibility.

2.2. INCREASED EFFECTIVENESS AND EFFICIENCY FOR THE HIV PROGRAMME

Two important objectives of the HIV programme are to avert new HIV infections and improve access to ART. Both PrEP and T&T will contribute to increased effectiveness of the HIV programme. Averted HIV infections translates to a reduced burden on the national health system and each newly identified HIV-positive person treated reduces the burden on the clients and their families and communities.

2.3. INTEGRATION OF PREP AND TEST & TREAT ACROSS VARIOUS ENTRY POINTS

PrEP and T&T will be integrated into all the entry points of the public health system (primary healthcare (PHC) clinics, HTS, ANC, SRH services, contraception and fertility services, VMMC

services, STI and TB screening, termination of pregnancy services, post-rape care services, etc.). This will mitigate stigmatisation when trying to obtain HTS and PrEP services.

3. PrEP Clinical Guidelines

The implementation of PrEP will increase the use of HTS, which will assist in getting people to know their HIV status. Those that test HIV-positive during screening should immediately be referred for HIV treatment and care. It is therefore important to establish a seamless transition between PrEP and HIV treatment programmes.

PrEP should not displace or undermine the use of other effective and well-established HIV combination prevention interventions. PrEP should be promoted as an additional prevention choice among sex workers in conjunction with other appropriate prevention methods.

For those that test HIV positive during HTS, please refer to the National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents, and Adults (2015) and the National HIV Testing Services: Policy (2016) for the appropriate treatment options.

3.1. Enrolment for PrEP

Following HIV testing, if client is HIV-positive, immediately refer for ART initiation. If client is HIV-negative, PrEP should be offered after screening as part of a combination prevention package (refer to algorithm on page 16).

Some individuals requesting PrEP are likely to be at ongoing or substantial risk for HIV and might always fall into a window period when trying to confirm HIV status (e.g. a sex worker with recurrent daily exposures). These individuals should not be excluded from accessing PrEP, as they potentially have the most to gain from the intervention.

Risk assessment questions can be used as part of combination prevention to explore risk and risk reduction and prevention strategies.

Box 4. Risk Reduction Counselling

Explore the following topics, as appropriate:

- Avoiding unprotected sex
- Consistent and correct use of condoms
- Knowing your HIV status and your partner's HIV status
- Are you or your partner on ART?
- Use of recreational or injection drugs for you or your client or partner
- Sex under the influence of alcohol and/or drugs
- Experience of intimate partner violence/sexual violence
- Use of ARVs to prevent HIV following unprotected sex (PEP)

3.2. Contraindications for PrEP

The following are contraindications for PrEP use:

- Pre-existing HIV infection
- Creatinine clearance of less than 60mL/min
- Adolescents <35kg or <15 years of age who are not Tanner stage 3 (sexual maturity rating) or greater
- Unwilling/unable to adhere to daily PrEP
- Pregnancy (as per Truvada package insert) *refer to section 1.10

Other important considerations include:

- TDF/FTC is active against Hepatitis B infection. Discontinuation of TDF/FTC requires close monitoring in those infected with Hepatitis B due to the concern for rebound viraemia.
- Persons with osteopenia/osteomalacia/osteoporosis may be at risk of bone loss associated with TDF.
- Women who want to conceive and are eligible for PrEP must be monitored.
- TDF should not be co-administered with other nephrotoxic drugs, e.g. aminoglycosides.
- Standard TB medication does not interact with PrEP drugs and there is no need for dose adjustments.
- Clients on MDR-TB medications may have increased risk of renal side effects. PrEP should therefore be avoided. Other prevention methods should be recommended and PrEP screening should be delayed until the end of MDR-TB treatment.
- Standard hormonal contraception does not affect PrEP effectiveness, nor does PrEP affect contraceptive effectiveness.[57]
- There are currently no published studies on the use of PrEP for individuals under 18.
- Offer immediate treatment if the PrEP user seroconverts.

3.3. Eligibility for PrEP Use

Providers should educate and counsel potential PrEP users about PrEP, which should always be provided as part of a combination prevention package.

Box 5. Eligibility Criteria for PrEP Use

- No contraindications to TDF or FTC
- HIV-negative
- No suspicion of acute HIV infection (refer to Table 1, below)
- Willing and able to adhere to PrEP

Table 1. Acute Viral Symptoms of HIV Seroconversion[58, 59]

Symptom	Sign
Malaise, anorexia, myalgia, headache, sore throat, sore glands, rash	Fever, sweating, viral meningitis, generalised lymphadenopathy, hepatosplenomegaly, pharyngitis, truncal rash, orogenital herpetiform ulceration, oral/oesophageal candidiasis, cervical adenopathy

If the client has symptoms or signs of acute HIV infection, PrEP should be postponed until symptoms subside and a repeat rapid HIV test after 4 weeks remains negative.

3.4. Baseline Investigations

Table 2. Clinical Screening Investigations

Investigation	Purpose
HIV test (using algorithm in the HTS guidelines)	Assessment of HIV status
Creatinine clearance	To identify pre-existing renal disease
Hepatitis B surface antigen (HBsAg)*	To identify undiagnosed hepatitis B infection To identify those eligible for vaccination against hepatitis B
ALT if HBsAg positive	To determine if vaccination against HBV infection or treatment of HBV is required
Urine pregnancy test	To identify if client is pregnant
Syphilis rapid plasma reagin (RPR)	To diagnose syphilis infection for treatment
Syndromic STI screening	To diagnose and treat STI
• Clients with acute or chronic hepatitis B infection can be safely initiated onto PrEP but require liver function monitoring.[60] • Bone density measurements are not needed	

Clients with abnormal renal function (estimated creatinine clearance <60 mL/min) should be informed to stop taking PrEP and the test must be repeated after two weeks. If renal function returns to normal and other PrEP criteria are met, PrEP may be re-started.

3.5. Prescription of PrEP drugs

The recommended regimen, which can be used in all populations is:

- TDF/FTC 1 tablet by mouth (PO) daily – Brand: Truvada (Gilead), Tenemine (Mylan), Didivir (Cypla), Emtevir (Adcock), Tencitab (Aspen)

Prescription intervals:

- At initiation – provide 1-month supply
- At 1 month – repeat HIV test and provide 3-month prescription (for collection every month)
- Every 3 months – repeat HIV test and provide 3-month prescription (for collection every month)

Other HIV prevention methods should be discussed and provided at all visits. Users should be advised that a negative HIV test is required before PrEP drugs can be prescribed at initiation and with every prescription refill, as well as when restarting after a discontinuation. It should be made clear that PrEP is not treatment for HIV, despite using the same medicines, and therefore it should not be shared with people who have not tested HIV negative.

BOX 6. REACHING FULL PROTECTION

Clients initiating PrEP need 20 days of daily dosing to reach adequate tissue levels of PrEP drugs. During this period, other protective precautions should be used, such as abstinence or condoms.

3.6. SIDE EFFECTS

The major toxicities associated with TDF/FTC are rare in PrEP exposure to date. Minor side effects are relatively common but are mild and self-limiting if they do occur (approximately 1 in 10 individuals in the first 1 to 2 months), and do not require discontinuation of PrEP.

BOX 7. POTENTIAL SIDE EFFECTS

Major side effects: renal toxicity and metabolic complications (decreased bone mineral density, which is reversible in adults upon stopping PrEP), extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
Minor side effects: gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), which are self-limiting and typically end within first month of use; unintentional weight loss
Less predictable side effects: hypersensitivity reactions and flares of hepatitis B in those who are chronic carriers if they stop TDF/FTC

3.7. PREP CLIENTS WHO TEST HIV-POSITIVE

3.7.1. HIV-positive prior to initiation of PrEP

Clients who test HIV-positive must be offered ART as soon as possible, regardless of CD4 count. They must be linked to HIV care, treatment, and support. Where possible, their partners should be encouraged to test for HIV.

3.7.2. HIV-positive after initiation of PrEP

HIV seroconversion after initiating PrEP can occur, and may be due to non-adherence or being in the window period at the time of testing. As soon as an HIV-positive test has been confirmed, ART should be immediately initiated using first-line regimens, and the client must be linked to HIV care and treatment. Resistance testing, or use of second-line regimens, is not recommended, as only about 3 percent of seroconverters who have received PrEP may have resistance to FTC or TDF.

3.8. PREP FOLLOW-UP AND MONITORING

TABLE 3. PREP FOLLOW-UP AND MONITORING

Activity	Following PrEP Initiation
Confirmation of HIV-negative status	At 1 month, then every 3 months
Address side effects	Every visit
Adherence counselling	Every visit

Creatinine clearance test	At 1 month, then every 3 months for the first year, then annually[†]
STI screening and treatment	Every visit
PrEP medication issuance	1 month supply, then 3 monthly prescription for monthly supply
Behavioural sexual risk reduction counselling	Every visit

3.9. Risk Reduction Counselling

Risk-reduction counselling is a behavioural intervention that attempts to decrease an individual's chances of acquiring HIV and other STIs, and should be implemented together with HIV prevention counselling and sexual reproductive health and contraceptive counselling at all follow-up visits for PrEP users.[61]

The main objective of risk-reduction counselling is for clients to assess individual risk and set realistic goals for behaviour change that could reduce their risk of contracting HIV and other STIs, as well as reduce unwanted pregnancies. This is most effective when it is non-prejudicial and user-centred. Risk reduction counselling can be provided by any trained healthcare provider and should address the following points:

- Explore the context of the client's specific sexual practices and psychosocial status, and assist client to recognise which of their behaviours are associated with higher risks for HIV infection. Healthcare providers should also be aware that clients might not always perceive their own risk, or be in denial about it.
- Identify the sexual health protection needs of the potential PrEP user and reflect on what their main concerns appear to be.
- Strategize with the client on how they can manage these concerns or needs.
- Agree on which strategies the client is willing to explore and guide them to decide on how to implement the strategy.

3.10. Discontinuation of PrEP

PrEP should be stopped if the client:

- Tests HIV-positive
- Develops renal disease
- Is non-adherent to PrEP
- Does not need or want PrEP
- No longer meets eligibility criteria
- If there are safety concerns where the risks of PrEP use outweigh potential benefits

The duration of PrEP use may vary and individuals are likely to start and stop PrEP depending on their risk assessment at different periods in their lives. Because PrEP is user-

[†] The TAPS program will implement creatinine testing every 6 months. This additional data may provide evidence, which will allow for guideline updates in the future.

driven, users should be given information on the correct way to stop PrEP to ensure effectiveness. Users who want to stop PrEP should do so after consultation with the healthcare provider. PrEP medication should be continued for 28 days after the last potential HIV exposure to ensure coverage and protection.

3.11. Reducing The Risk Of Antiretroviral Resistance

To minimise the risks of developing ARV resistance, HIV testing must be done every three months with a symptom screen and a targeted examination to exclude acute HIV infection. HIV testing should also be repeated whenever symptoms of a viral illness are present.

Box 8. Resistance Risk Reduction

- Feasibly exclude acute HIV infection before initiating PrEP by:
  - HIV testing before commencing or re-prescribing PrEP
  - Conducting a clinical screen to detect signs and symptoms of acute HIV infection
  - Delaying PrEP and investigating ff there are suspicions of acute HIV infection
- Assess adherence with every visit - enquire about pill taking patterns and missed doses
- Support the client to maximise adherence
- Provide adequate supply of drugs and give consideration to the individual needs
- Revisit eligibility criteria every time the client re-starts PrEP;this must be done by the healthcare provider, not by the client
- Discontinue when client's risk profile has changed and client is no longer at substantial risk

3.12. Hepatitis B Management

TDF and FTC both have hepatitis B antiviral activity. The potential risk exists that exposure to these antivirals may treat unidentified chronic hepatitis B infection with a consequent viral flare (rebound) upon drug withdrawal that can result in a liver injury.[62] To avoid this risk, screening for hepatitis B surface antigen and antibodies occurs prior to PrEP commencement.

If hepatitis B surface antigen (HBsAg) is positive, the user should be investigated prior to commencement of short-term PrEP. PrEP is not contraindicated in those with HBV but liver function monitoring should be performed. PrEP users with persistently elevated or abnormal liver function tests should be referred for assessment. Liver function tests should be checked after stopping PrEP in those with chronic hepatitis B infection. People with chronic hepatitis B infection may choose to continue using tenofovir to control their hepatitis, even if they do not require these drugs any longer for the indication of PrEP.

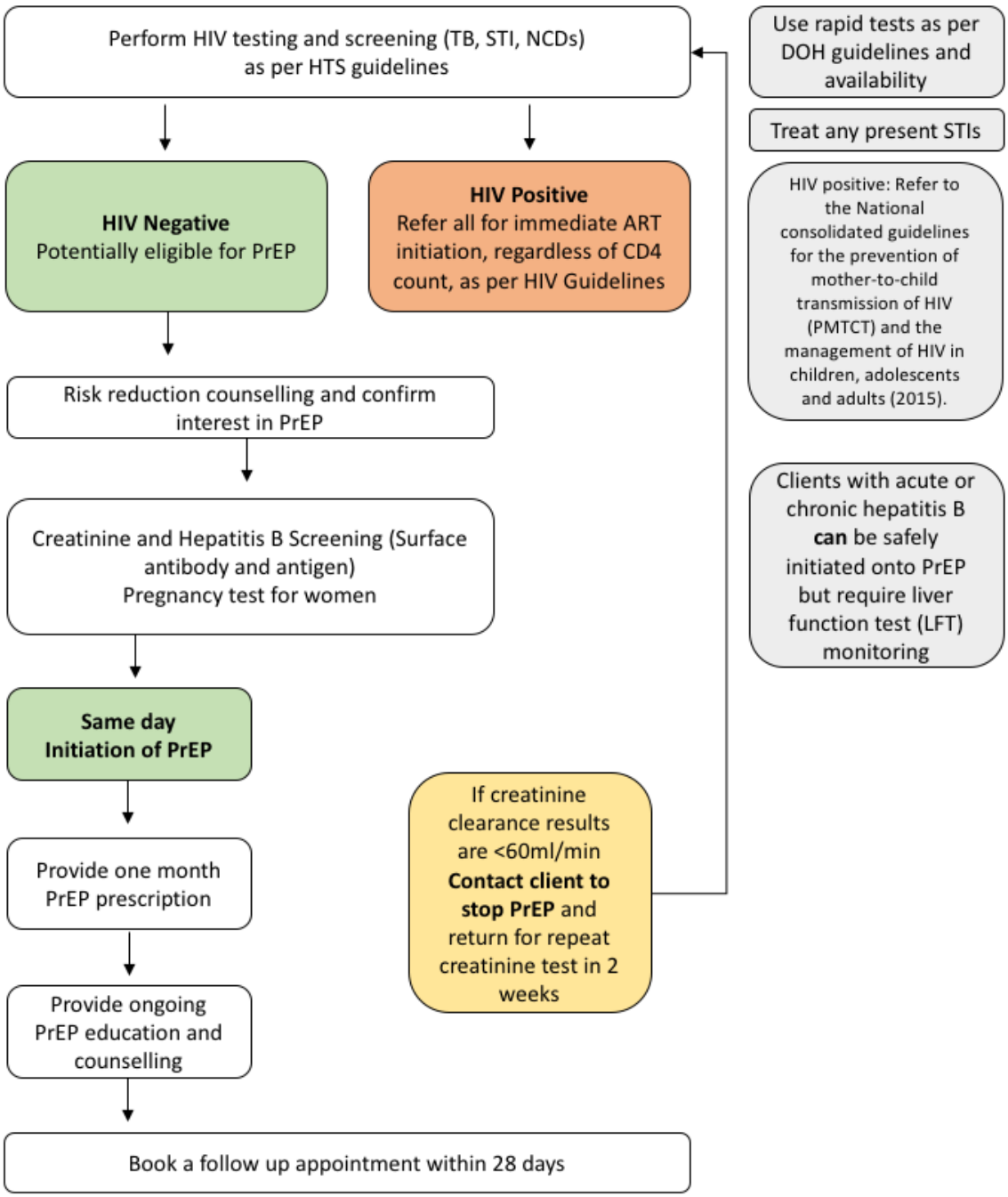
Users with a history of injecting drug use should be screened for hepatitis C and, if positive, referred for further care.

Table 4. Hepatitis B Immune Status and PrEP Eligibility

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP, vaccinate concurrently if available

Negative (-)	Positive (+)	Start PrEP, no vaccine needed
Positive (+)	N/A	Refer for evaluation

FIGURE 2. PREP AND T&T SCREENING AND INITIATION ALGORITHM



4. Service Delivery Guidance

4.1. Capacity Building of Healthcare Providers

The National Department of Health Operational Guidelines for HIV, STI, and TB Programmes for Key Populations in South Africa acknowledges the need for healthcare provider sensitisation training in order to better support public healthcare services and adolescent friendly services for priority populations.[63]

In the context of PrEP and T&T sex worker programmes, healthcare provider sensitisation training may promote stronger uptake and retention in care by creating a non-stigmatising and supportive space for delivery of PrEP and T&T in the sex worker population. All healthcare providers involved in the provision of PrEP and ART services should be involved in such training, including doctors, clinical nurse practitioners, staff nurses, counsellors, pharmacists, pharmacy assistants, outreach workers, other healthcare providers, and peer supporters.

In addition to sensitivity and competency training for sex workers, all healthcare providers affiliated with PrEP and ART service delivery should complete a PrEP and T&T implementation training programme, including clinical management, adherence, combination prevention, and risk reduction counselling.

4.2. Follow-Up and Retention in PrEP

After clients have initiated PrEP, the core focus of the service provider should be to support retention and maintain adherence among those using PrEP. For populations at substantial risk, there are important considerations that can affect their ability to be retained. Strategies for supporting follow-up and retention are discussed in Box 6 below.

4.2.1. Provide ongoing counselling and education

At each follow-up visit, providers should assess if the use of PrEP has changed for their client and the effect this may have on the effectiveness of PrEP. Providers should support the client to identify strategies for improving adherence, which take into consideration the client's individual barriers and facilitators. Adherence counselling should be client-centred. Barriers and facilitators to adherence should be identified by the client and not prescribed by the provider. Ongoing education and counselling should then be provided to the client at each PrEP-related visit.

BOX 9. STRATEGIES FOR SUPPORTING PREP ADHERENCE

- Use alternative methods of communication: SMS, social networking, mobile applications, etc.
- Integrate mobile services and outreach into existing services
- Enhance peer support strategies, such as the use of clubs
- Provide alternative clinic hours, if possible
- Collect additional contact information for each client
- Provide clients with referral partners in the event that they migrate, or provide with additional stock/prescription

4.2.2. Promote client retention and follow-up

Individuals may face challenges in attending regular follow-up visits required for PrEP services. Strategies should be used to address the specific challenges faced by individuals to support retention in PrEP services and adherence. For example, sex worker populations may be highly mobile, may not consistently visit the same clinic or service provider over an extended period of time, and may find it difficult to attend clinic services during regular office hours.

BOX 10. STRATEGIES FOR SUPPORTING RETENTION AND COMMUNICATION

- Schedule medication taking time to correspond with the user's daily routine activities
- Use reminders, e.g. cell phone, alarms, beepers, calendars
- Use pillboxes
- Review disclosure issues to identify those who can support the user's intentions to adhere or barriers to adherence due to lack of disclosure/privacy at home
- Join an on-line support group, e.g. Facebook: PrEP Rethinking HIV Prevention or #wethebrave

4.3. MONITORING AND EVALUATION OF CLINICAL PREP PROVISION

Initial PrEP programmes should be accompanied by significant monitoring and evaluation (M&E) plans to measure programme rollout and the success of various implementation approaches, and also to capture lessons learned on the many unanswered questions regarding the best methods for screening and initiating clients and client monitoring (refer to the PrEP and T&T Implementation Plan).

5. About the Development of the PrEP and Test & Treat Guidelines

On 23 October 2015, a meeting was held at the National Department of Health to discuss the programmatic implications for adopting and implementing the new WHO guidelines for Test and Treat (T&T) and HIV Pre-Exposure Prophylaxis (PrEP). During that meeting it was decided that a core group of experts would convene to review evidence, programmatic implications, and develop national guidelines for PrEP.

The core group met on 23-24 November 2015 to prepare the draft PrEP guidelines. The Southern Africa HIV Clinicians Society's PrEP guidelines were used as the basis of the clinical section. The draft guidelines were shared with the expert community on 15 December 2015. Comments were incorporated and a revised version was shared with Dr. Yogan Pillay. Upon receipt of comments from Dr. Pillay, and recognising a number of outstanding issues still needed to be addressed, a third meeting with a larger group of experts and representatives from the South Africa HIV programme community was held on 13 January 2016 at the National Department of Health.

Based on the outcome of the January meeting, a revised version of guidelines, as well as a draft policy, was shared with the larger group for comment in early February. Feedback was incorporated and the revised guidelines and policy were discussed with the larger technical working group members in a meeting on 25 February 2016.

In coordination with the launching of the South African National Sex Worker HIV Plan on 11 March 2016, a revised version of the PrEP and Test & Treat guidelines were developed, which focused on the provision of PrEP and T&T services, in the context of combination prevention and expanded treatment, for the sex worker population. The new, focused guidelines were shared with the expert group and discussed at an NDoH meeting, chaired by Dr. Pillay, on 10 March 2016.

In preparation for the inclusion of other target populations in the national PrEP rollout, the guidelines were updated in December 2016, with additional minor updates to this current version in February 2017.

6. Appendixes

Appendix 1. Evidence and Benefits of PrEP

Appendix 2. Costing and Implementation

Appendix 3. Organizations and Stakeholders Involved in the Drafting of the PrEP Guidelines

Appendix 4. Ongoing and Planned PrEP Trials and Demonstration Projects

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