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HIV-1 Prevention for HIV-1 Serodiscordant Couples

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Abstract

A substantial proportion of HIV-1-infected individuals in sub-Saharan Africa are in stable relationships with HIV-1-uninfected partners, and HIV-1 serodiscordant couples thus represent an important target population for HIV-1 prevention. Couple-based HIV-1 testing and counseling facilitates identification of HIV-1 serodiscordant couples, counseling about risk reduction, and referrals to HIV-1 treatment, reproductive health services, and support services. Maximizing HIV-1 prevention for HIV-1 serodiscordant couples requires a combination of strategies, including counseling about condoms, sexual risk, fertility, contraception, and the clinical and prevention benefits of antiretroviral therapy (ART) for the HIV-1-infected partner; provision of clinical care and ART for the HIV-1-infected partner; antenatal care and services to prevent mother to child transmission for HIV-1-infected pregnant women; male circumcision for HIV-1-uninfected men; and, pending guidelines and demonstration projects, oral pre-exposure prophylaxis (PrEP) for HIV-1-uninfected partners.

Keywords

HIV-1 serodiscordant couples; HIV-1 prevention; Africa; antiretroviral; ART; PrEP

Introduction

Sub-Saharan Africa has the highest prevalence of HIV-1 globally and has high incidence with approximately 1.8 million new HIV-1 infections in 2009 [1]. All HIV-1 transmissions occur from an infected to an uninfected partner, but sub-Saharan Africa is unique in that a high proportion of HIV-1 transmissions may occur in stable, long-term partnerships, in which one member is HIV-1-infected (i.e., an HIV-1 serodiscordant couple). We focus this review on HIV-1 prevention in HIV-1 serodiscordant couples, with an emphasis on sub-Saharan Africa. We address testing, couples counseling, and prevention interventions, including recent evidence of the strong prevention benefits of antiretroviral therapy (ART) for the HIV-1-uninfected partner [2••] and pre-exposure prophylaxis (PrEP) for the HIV-1-uninfected partner [3••]. We also review prevention strategies based on modifiable biological risk factors (e.g., lack of male circumcision) and behavioral risk factors (e.g., lack of condom use, multiple partners) associated with HIV-1 transmission in couples (Table 1).

Epidemiology of HIV-1 serodiscordance among heterosexual African couples

HIV-1 serodiscordance is common in sub-Saharan Africa. National population surveys and epidemiologic studies indicate that the majority of African HIV-1-infected individuals are married or in a stable, long-term relationship [4-6], and approximately half of couples in which at least one partner is HIV-1-infected are HIV-1 serodiscordant [5, 7, 8], resulting in 2-8% of all stable couples being HIV-1 serodiscordant in some settings [5, 6, 9]. Mathematical models suggest that a substantial proportion of new HIV-1 infections occur among HIV-1 serodiscordant couples in Africa, demonstrating that HIV-1 serodiscordant couples are an important population for HIV-1 prevention [10•-12]. Women are equally likely as men to be the HIV-1-infected member in a serodiscordant couple [13].

Many HIV-1 serodiscordant couples are unaware of their serodiscordant status, primarily because one or both partners have not been tested or have tested separately and not disclosed their HIV-1 status to their partner. More than three-quarters of stable couples with at least one HIV-1-infected partner sampled in nationally representative HIV-1 serosurveys in Kenya [6], Malawi [4], and Uganda [7] were unaware of their partner's HIV-1 status. Moreover, couples often report low levels of condom use; across five African countries, fewer than 11% of cohabiting couples reported condom use at last sex [4, 5]. Finally, the term 'stable HIV-1 serodiscordant partnerships' does not capture the reality of dynamic partnerships, as indicated by viral linkage of transmission pairs from recent studies of HIV-1 serodiscordant couples, which documented that 25-29% of HIV-1 transmissions occur from an outside partner [2••, 14]. Some of these HIV-1 transmissions occurred after dissolution of the HIV-1 serodiscordant partnership and formation of a new partnership, often with someone of unknown HIV-1 serostatus, with whom they were less likely to use condoms [15].

Couples HIV Testing and Counseling (CHTC)

HIV-1 testing is the essential first step in the identification of HIV-1 serodiscordant couples, and disclosure is facilitated if couples test for HIV-1 together with a counselor trained in pre- and post-test counseling techniques for couples, called Couples HIV Testing and

Counseling (CHTC) [16, 17]. The Centers for Disease Control and Prevention (CDC) curriculum for CHTC training has been used in many parts of sub-Saharan Africa, and has recently been adapted for brief counseling in clinical settings [18]. Couples counseling involves risk assessment with sensitivity in order to foster facilitated disclosure, avoid blame, and provide counseling messages about HIV-1 serodiscordance and referral for HIV-1 care and prevention (Figure 1) [19-22]. Importantly, knowledge of serostatus within serodiscordant couples is likely a highly effective HIV-1 prevention strategy. African and U.S. HIV-1 serodiscordant couples who have received CHTC report increased condom use, contraceptive use, and uptake of prevention of mother-to-child transmission (PMTCT) services [20-26]. HIV-1 transmission rates were as high as 20-25% per year among HIV-1 serodiscordant couples unaware of their HIV-1 status and before ART scale-up in Africa [20, 27]. In contrast, annual HIV-1 incidence rates of 6% were observed in couples who had participated in CHTC in an observational study [20] and 2% in a randomized trial of a biomedical HIV-1 intervention among HIV-1 serodiscordant couples [14]. Facilitated disclosure of serostatus within a stable partnership also fosters family support, which has been associated with improved engagement in HIV-1 care for HIV-1-infected partners and high adherence to ART [28, 29].

The counselors who communicated with thousands of African HIV-1 serodiscordant couples in the multi-site Partners in Prevention HSV/HIV Transmission Study and Partners PrEP Study indicate that denial, disbelief, and misconceptions about discordance are frequently encountered and require additional counseling. Common reactions expressed by couples upon learning their HIV-1 serodiscordant status include disbelief in the accuracy of the test results, desire for re-testing in hope of a different outcome, anger, blaming their partner for infidelity, sadness, fear, and concerns about their children's HIV-1 status. Studies in Kenya and Uganda found that misconceptions about HIV-1 serodiscordance were common among health care providers (e.g., that HIV-1 serodiscordance reflect that the HIV-1-uninfected partner is in the 'window period' of seroconversion and is always already infected) as well as among the newly-identified HIV-1 serodiscordant couples (e.g., believing that the HIV-1-uninfected partner is immune or has undetectable and latent virus) [30, 31].

HIV-1 serodiscordant couples have a range of needs that emerge after the initial couples counseling and testing session and are critical to ongoing HIV-1 prevention and treatment. Couples learning of their HIV-1 serodiscordance cannot be expected to retain all messages from the first counseling session, and may need additional support to understand that HIV-1 serodiscordance is common and does not reflect inaccurate test results or immunity for the uninfected partner. Common challenges reported by HIV-1 serodiscordant couples include feeling isolated, fear of disclosing their serodiscordance, personal desires and family pressures to have more children, relationship discord over perceived infidelity and blame, union dissolution, and in some cases physical violence and threats over refusal to have sex [31-34]. Some studies have found higher rates of divorce, separation, and intimate partner violence among HIV-1 serodiscordant couples than among HIV-1 seroconcordant couples, although most reports have found intimate partner violence to be relatively rare [31, 35-37]. Counselors can identify couples at risk of violence based on a history of abuse, help ensure safety and care for those who experience violence, and make appropriate referrals, including peer support groups for HIV-1 serodiscordant couples [38].

HIV-1 re-testing is suggested for HIV-1 serodiscordant couples, as with other populations at high risk of exposure to HIV-1, in order to promote early detection of HIV-1 infection and timely referral to care and treatment [39]. The World Health Organization (WHO) recommends that individuals with a known HIV-1-infected partner re-test in four weeks to assess for recent HIV-1 transmission and annually thereafter if they continue to be sexually active [39]. The frequency of HIV-1 testing for the HIV-1-uninfected partner couple should

typically be annual, and informed by the couples' risk of transmission, fertility intentions, and symptoms suggestive of acute HIV-1. Messages about referrals for care, support in disclosure, initial relationship concerns, and methods to reduce risk of HIV-1 transmission should be reinforced at follow-up counseling and testing visits. Clinical follow-up for the HIV-1-infected partner should be emphasized and include a) CD4 cell count testing and evaluation of their eligibility for ART according to national policies to ensure timely initiation and ongoing adherence, b) correct and consistent condom use, c) discussion of family planning, safe conception, and pregnancy, and d) PMTCT for HIV-1-infected pregnant women (Figure 1) [40•]. In addition, prevention strategies should be recommended for the HIV-1 uninfected partner, including condoms, male circumcision, and PrEP, as it becomes available (Figure 1).

Antiretroviral-based strategies to reduce HIV-1 transmission in serodiscordant couples

Antiretroviral therapy for HIV-1-infected partners

ART dramatically improves the health and survival of HIV-1-infected individuals [41, 42] and also significantly reduces their infectiousness and likelihood of transmitting HIV-1 to partners (Table 2) [2•, 14, 43-45]. A recent multi-national randomized clinical trial (HPTN 052) with HIV-1 serodiscordant couples demonstrated that early initiation of ART between CD4 counts of 350-550 cells/mm³ reduced the risk of HIV-1 transmission by 96%, compared to delayed ART initiation at CD4 of 250 cells/mm³ [2•]. Importantly, HPTN 052 used intensive measures throughout the study to maximize the prevention benefits of ART: quarterly viral load monitoring and enhanced adherence counseling for those who had detectable HIV-1 RNA on ART. Thus, HPTN 052 demonstrates that ART markedly reduces HIV-1 transmission, if adherence is sufficient to achieve and sustain virologic suppression. Encouraging data from observational studies of HIV-1 serodiscordant couples, in which ART was provided following national guidelines and with less intensive adherence counseling and typically without virologic monitoring, found 80-92% reduction in HIV-1 transmission from HIV-1-infected patients who initiated ART [43-46].

The WHO will be releasing guidelines on CHTC which will include recommending earlier ART for serodiscordant couples to reduce transmission to HIV-1-uninfected partners. Expanded use of ART for HIV-1 prevention will require careful analysis of resources and implementation strategies, including ethical, programmatic, and cost factors of earlier ART for HIV-1-infected partners who are in a serodiscordant partnership. A mathematical model predicted that treating HIV-1 serodiscordant couples in countries like Malawi and Lesotho, with high HIV-1 prevalence (7.1% and 19.5%) and where a large percentage of couples are serodiscordant (9.7% and 13.6%), could result in a substantial reduction in population-level HIV-1 incidence [47•]. Primary prevention strategies will also be needed for HIV-1 serodiscordant couples, as ART will not protect those who become infected from outside or new partners, which accounted for 25-29% of HIV-1 transmissions in HPTN 052 and the Partners in Prevention HSV/HIV Transmission Study [14, 48], but will be preventive for new partners of the HIV-1 infected partner on ART for prevention.

The success of ART for HIV-1 prevention depends on key implementation factors, including earlier identification of HIV-1-infected persons so that they can promptly initiate ART when they meet national guidelines and retention in care both pre- and post-ART, sustained adherence to ART, minimizing drug resistance, and reducing rates of treatment failure. These challenges will require expanded HIV-1 testing initiatives, strong linkages to care, and effective follow-up of HIV-1 infected persons who do not yet meet national ART guidelines. An additional consideration will be the acceptability and willingness of HIV-1-

infected partners to initiate ART when they are asymptomatic. Importantly, some studies have found a substantial minority of HIV-1-infected persons who are aware of being in an HIV-1 serodiscordant partnership, are reluctant to initiate ART, as demonstrated by 37% of HIV-1-infected partners eligible for ART in a cohort of Kenyan HIV-1 serodiscordant couples who did not initiate ART within 1 year of referral for free treatment [49•]. Higher CD4 count (>100 cells/mm³) and lower socioeconomic status, measured in home ownership and rent cost, were strong predictors of non-initiation of ART [49•]. In addition to economic obstacles and structural challenges such as drug stock-outs, fear of ART side effects, stigma and disclosure, concerns over sustainability of care, food insecurity, and preference for alternative medicines pose barriers to ART initiation and ongoing adherence [50]. However, if these barriers can be overcome through counseling, other support, and strengthening of health care systems, HIV-1 infected partners who initiate ART could benefit from adherence support and involvement of their partner [28, 29].

Pre-exposure prophylaxis

Topical and oral tenofovir (TDF)-based PrEP have shown substantial efficacy in some but not all trials (Table 2). Relevant to the focus of this review, in the Partners PrEP Study, daily oral TDF and FTC/TDF were shown to have 62% and 73% efficacy, respectively, among HIV-1-uninfected partners in East African HIV-1 serodiscordant couples [3••]. Very high adherence to study drug was observed in the Partners PrEP Study [51], with qualitative interviews indicating that adherence to pill-taking was fostered by support from their partner [52]. Peri-coital use of vaginal 1% tenofovir gel showed a 39% reduction in HIV-1 acquisition and 51% reduction in HSV-2 acquisition among South African women in the CAPRISA 004 study [53]. Daily oral emtricitabine/tenofovir (FTC/TDF) was shown to have an efficacy of 44% among men who have sex with men in the multinational iPrEx study [54] and 62% in young heterosexuals in Botswana [55]. In contrast, FEM-PrEP, a trial of daily oral FTC/TDF in high-risk women was recently stopped early due to lack of efficacy [56] and the daily oral tenofovir and daily vaginal 1% tenofovir arms of the VOICE trial were stopped due to inability to demonstrate efficacy in HIV-1 prevention [57]. Further data, available in 2012, will be important to understand whether lack of efficacy in the FEM-PrEP and VOICE trials was due to insufficient adherence or other biological and behavioral factors.

A rapid review ('rapid advice') of the PrEP efficacy data, including guidelines about PrEP for HIV-1 serodiscordant couples, will be issued by the CDC and WHO in 2012. It is important to consider both the prevention promise and the implementation challenges of PrEP among HIV-1 serodiscordant couples, for whom the efficacy data are substantial, and interest and adherence could be high. Demonstration projects for PrEP in serodiscordant couples will need to implement CHTC with messages about ART-based prevention and evaluate targeting of PrEP to highest-risk couples, cost-effective delivery strategies, adherence support tools, and provision of a comprehensive risk reduction package [58-62]. The use of PrEP in HIV-1 serodiscordant couples should be considered as part of a combination HIV-1 prevention strategy; PrEP could be most appropriate as an effective biomedical prevention strategy under the control of the HIV-1 uninfected partner if their HIV-1 infected partner is not on ART, not adherent with ART, or if they have multiple partners or partners of unknown HIV-1 status. Mathematical modeling suggests that a cost-effective 'staged' use of antiretrovirals for HIV-1 prevention could involve PrEP by the HIV-1 uninfected partner in a serodiscordant relationship before the HIV-1 infected partner initiates ART, with PrEP discontinuation a few months after ART is started (to allow time to achieve viral suppression) [63•]. Based on the high levels of efficacy of PrEP observed in the Partners PrEP Study and assuming PrEP costs less than 40% that of ART, PrEP could be as cost-effective, and potentially cost-saving, if very high-risk couples are targeted, as a

prevention strategy for couples compared to ART initiated before CD4 of 350 cells/ μ L for the HIV-1 infected partner [63•].

Family planning safe pregnancy, and prevention of mother to child transmission (PMTCT)

Many HIV-1 serodiscordant couples have high fertility; both HIV-1 infected and uninfected partners often report desires for having children with their partner [64-67•]. Over half of serodiscordant couples recruited from HIV-1 care centers in Uganda wished to have children in the future [68]. Regardless of fertility intentions, rates of highly effective contraception are often low and there are high rates of pregnancy among women of reproductive age in sub-Saharan Africa [69, 70]. Annual pregnancy rates among HIV-1 serodiscordant couples were 16.0% in the Partners in Prevention HSV/HIV Transmission Study and 9.7% in an observational cohort in Kenya [70, 71]. Pregnancy is a time of increased risk of sexual HIV-1 transmission and acquisition; pregnant women had a two-fold increased risk of male-to-female and female-to-male HIV-1 transmission in the Partners in Prevention HSV/HIV Transmission Study [67•].

Counselors and clinicians need to assess fertility intentions of HIV-1 serodiscordant couples and discuss contraceptive choices for couples not desiring children and safe conception strategies for couples who plan to have children. Less than two-thirds of women in HIV-1 serodiscordant couples surveyed in Rwanda and Zambia had ever used any contraceptive method, despite high awareness of contraception, with many citing concerns with side effects [72]. HIV-1 serodiscordant couples' childbearing desires are not always expressed to their health care providers [65]. Health care workers' knowledge may be incomplete and perpetuate misconceptions, and women may feel pressured by providers to terminate pregnancy or not report pregnancy intentions if they are HIV-1-infected [69, 73, 74]. An intervention that provided family planning counseling and free contraception to HIV-1 serodiscordant couples in Thika, Kenya led to significant declines in pregnancy and sustained high reports of condom use [75]. Thus, it is important to ascertain fertility desires of HIV-1 serodiscordant couples, counsel about available data on HIV-1 transmission risks during pregnancy, and encourage dual condom and contraceptive use for those not wanting to conceive [67•, 76•]. HIV-1 serodiscordant couples who do not want to conceive should be provided a choice of contraceptive options, including long-acting methods such as IUDs and implants.

HIV-1 serodiscordant couples who wish to conceive must consider options to reduce the risk of HIV-1 transmission to the HIV-1 uninfected partner. When intrauterine or intravaginal insemination is unavailable or too expensive, low technology options to reduce the risk of transmission during conception should be discussed, including delaying unprotected sex until viral load is suppressed using ART for the infected partner, screening and pre-treatment for sexually transmitted infections that might facilitate HIV-1 transmission, limited and timed unprotected sexual encounters, and male circumcision if the man is HIV-1 uninfected [77]. Safe conception may be feasible when the HIV-1 infected partner is virally suppressed on ART [78, 79]; a Swiss study of 46 HIV-1 serodiscordant couples noted no seroconversions when the HIV-1-infected male partners were on fully suppressive ART, practiced timed intercourse, and used PrEP pericoitally [80].

Further evaluation of antiretroviral-based prevention is warranted, including ART for the HIV-1 infected partner or periconception PrEP in the HIV-1 uninfected partner if their partner is not on ART or virally-suppressed [80, 81], in combination with timed unprotected intercourse during the most fertile days of the menstrual cycle [80, 81]. Advantages of periconception PrEP include autonomy of administration, which is important for HIV-1 uninfected partners, and shorter period of use which would have lower costs and may be associated with higher adherence than continuous PrEP [81].

Behavior change

Behavior change strategies available to HIV-1 serodiscordant couples to prevent HIV-1 transmission include sexual abstinence, correct and consistent condom use, and reduction of outside sexual partnerships. Couples-focused HIV-1 prevention behavioral interventions have reduced reported unprotected sex and dramatically increased reported condom use [20, 22-24]. In some studies, couples where the man was HIV-1 uninfected had higher sustainability of condom use than couples with an HIV-1 uninfected woman [20, 22]. In the Partners in Prevention HSV/HIV Transmission Study, in which HIV-1 serodiscordant couples received monthly risk reduction counseling and free condoms, self-reported unprotected sex decreased from 29% at baseline to 7% over up to 24 months of follow-up ($p < 0.001$) [14]. Correct and consistent use of condoms is a highly effective tool for HIV-1 prevention; analyses from the Partners in Prevention HSV/HIV Transmission Study found that male condoms were associated with 79% lower risk of HIV-1 transmission on a per-contact basis [82]. However, introducing condoms into a long-term sexual relationship can be challenging. Couples often stop using condoms when they commit to a partner and if they are trying to conceive [83]. Additional challenges include perceptions that condoms interfere with sexual pleasure, spontaneity, and are a cause of sexual dysfunction [32, 83, 84]. Finally, alcohol use has been linked to unprotected sex in serodiscordant couples [85-87]. Couples should be counseled about the high efficacy of condoms for HIV-1, STIs and pregnancy [88], how condoms can enhance sexual pleasure by reducing anxiety about risk of HIV-1 transmission and pregnancy, and can become a symbol of love and commitment to the partner's well-being [88].

Sexual abstinence is an effective strategy to eliminate risk of HIV-1 transmission, but it may not be a desirable or feasible, life-long strategy for many couples [31, 83]. Cultural and social norms of sex and childbearing within marriage and long-term relationships, as well as personal desires to conceive, present a major impediment to sexual abstinence for couples.

Sexual partners outside of the marriage or primary relationship present additional risks for HIV-1 infection. HIV-1 uninfected partners may perceive new outside partners to be a safer option for unprotected sex than their infected partners. The Partners in Prevention HSV/HIV Transmission Study and HPTN 052 study found through viral linkage that 25-29% of HIV-1 infections were from outside partnerships [2•, 14]. In the Partners in Prevention HSV/HIV Transmission Study, a significant increase in reported new partnerships was observed, however, most of these were not concurrent or overlapping partnerships and most were reported after partners reported no longer having sex with their known HIV-1 infected partner [15]. Condom use was reported to be much lower with their new partners than with their known HIV-1 infected partners. Some prior studies have noted lower reported condom use during extramarital sex [22, 89]. Risk reduction counseling for HIV-1 uninfected partners in serodiscordant relationships should emphasize the risk of infection from any unprotected sex and encourage HIV-1 testing, disclosure, and protection with all sex partners.

Male circumcision

Three randomized controlled trials provide strong evidence that male circumcision reduces the risk of female-to-male HIV-1 transmission by 50-60% [90-92]. Circumcision is not generally recommended for HIV-1-infected men, given conflicting evidence between observational data and a clinical trial in terms of reduced male-to-female HIV-1 transmission [19•, 93, 94]. However, male circumcision should be strongly promoted for HIV-1 serodiscordant couples in which the male partner is HIV-1 uninfected and uncircumcised. HIV-1 discordant couples may also represent early adopters of infant male

circumcision: over 90% of HIV-1 serodiscordant couples in Uganda were interested in circumcision for their male children for HIV-1 risk reduction [95].

Screening and treatment of sexually transmitted infections

The treatment of sexually transmitted infections in HIV-1 infected persons lowers genital viral load in most studies. Studies of stable HIV-1 serodiscordant couples suggest that the prevalence of curable STIs is low [96] and thus not a major driver of HIV-1 transmission within couples. However, treatment of STIs, when detected through laboratory screening or by symptomatic assessment, particularly in HIV-1 infected partners, should be done. Herpes simplex virus type 2 (HSV-2) infection is highly prevalent in HIV-1 serodiscordant couples, but acyclovir (400 mg bid) did not reduce HIV-1 transmission in three efficacy trials of HSV-2 suppression for HIV-1 prevention [14, 97, 98]. A recent cross-over study indicates that higher doses of HSV-2 suppression achieved $>1 \log_{10}$ reduction in plasma HIV-1 levels [99]; further consideration of higher doses of herpes suppression as a pre-ART intervention to reduce HIV-1 disease progression and infectiousness may be warranted.

Conclusion

HIV-1 prevention within HIV-1 serodiscordant couples encompasses a combination of strategies tailored to their needs and fertility intentions, including CHTC, disclosure of HIV-1 test results, condom promotion, ART for the HIV-1 infected partner, contraceptive use or safe conception strategies depending on their fertility intentions, male circumcision for HIV-1 uninfected male partners, treatment of sexually transmitted infections, and potentially, pending guidelines and demonstration projects, the use of PrEP by the HIV-1 uninfected partner. Couples HIV-1 testing and counseling is a fundamental core of HIV-1 prevention that needs to be scaled up, particularly in high prevalence settings in sub-Saharan Africa. Scale-up of counselor and clinician training in CHTC is needed to build skills in risk assessment, facilitated disclosure, discussion of HIV-1 serodiscordance and risk reduction strategies, and addressing the common challenges faced by HIV-1 serodiscordant couples. HIV-1 testing programs must ensure that knowledge of HIV-1 serostatus is coupled with strong linkages with ART and PMTCT programs and referrals for HIV-1 uninfected persons to effective prevention interventions. Partner testing should be consistently promoted and strongly encouraged in HIV-1 care settings. Forthcoming WHO guidelines will provide recommendations based on the recent HPTN 052 and Partners PrEP Study findings of significant efficacy of antiretrovirals to reduce HIV-1 risk within HIV-1 serodiscordant couples [17]. Implementation of ART for HIV-1-infected partners and PrEP for HIV-1 uninfected partners in HIV-1 serodiscordant couples must be informed by public health impact modeling, cost-effectiveness analyses, and demonstration projects. Antiretroviral-based strategies will be an important part of combination HIV-1 prevention among HIV-1 serodiscordant couples, delivered in the context of scale-up of couples HIV-1 testing and counseling to maximize the prevention impact of these effective biomedical tools.

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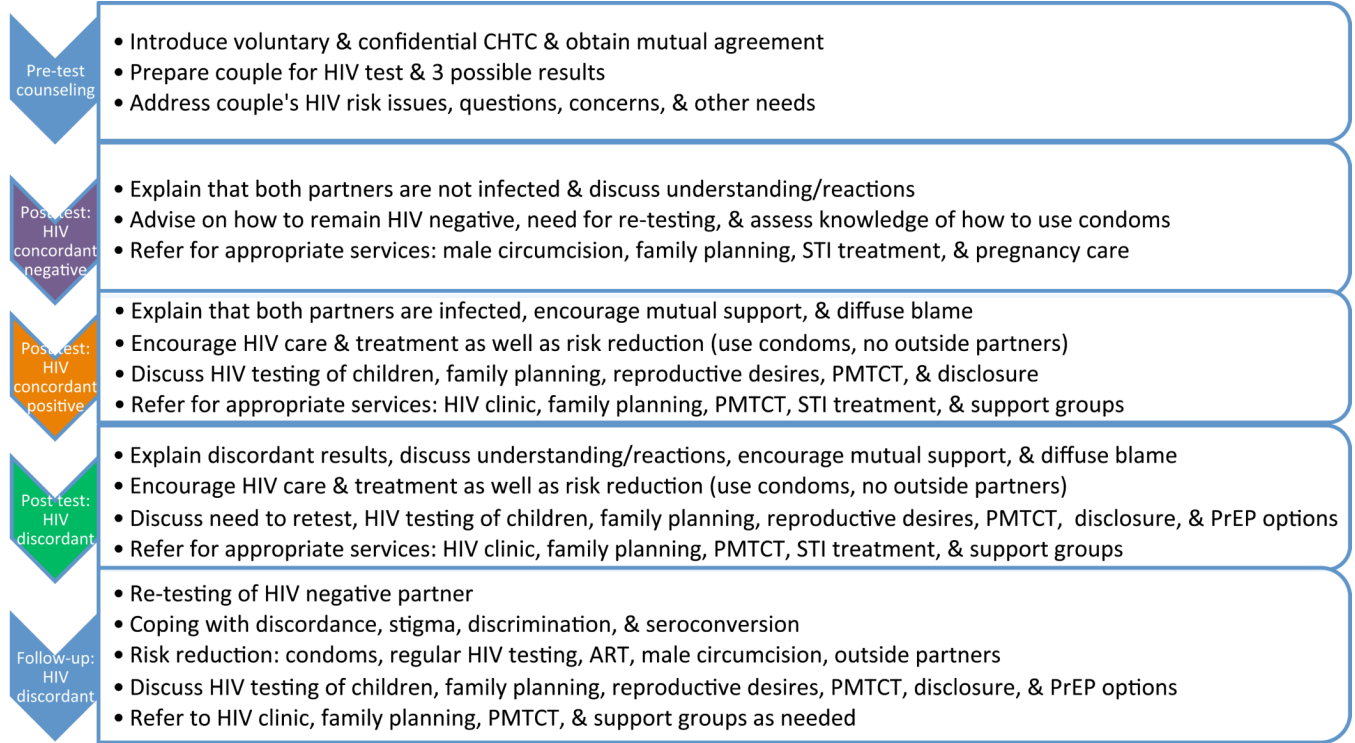
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Abbreviations: CHTC: couples HIV testing and counseling, STI: sexually transmitted infections, PMTCT: prevention of mother-to-child transmission, PrEP: pre-exposure prophylaxis, ART: antiretroviral therapy

Figure 1.
Couples HIV testing and counseling topics [18]

Table 1

Epidemiology of HIV-1 discordance among heterosexual African couples

HIV-1 serodiscordance is common	
<ul style="list-style-type: none"> ■ Half to two-thirds of HIV-1-infected adults in a cohabitating relationship in Africa have an HIV-1-uninfected partner [6-9] ■ Population-based studies indicate that the HIV-1-uninfected partner in heterosexual serodiscordant couples is equally as likely to be male as female [13] 	
HIV-1 transmission rates are high	
<p>HIV-1 incidence in studies with HIV-1 serodiscordant couples ranges from 2.0 to 11.8/100 person-years (p-y):</p> <ul style="list-style-type: none"> ■ 2/100 p-y with regular counseling and provision of free condoms [2••, 14] ■ 4/100 p-y for men and 9/100py women in couples VCT cohort study [20] ■ 8.7/100 p-y for men and 9.2/100py for women in a population-based cohort with low condom use [100] ■ 11.8/100 p-y in a retrospective cohort prior to ART scale-up [101, 102] 	
There are modifiable risk factors for HIV-1 transmission	
Plasma viral load	<ul style="list-style-type: none"> ■ High viral load is significantly associated with increased risk of transmission, with 2.3-2.5 increased risk per each log₁₀ increase in plasma viral [27, 101, 103]
ART use by HIV-1 infected partner	<ul style="list-style-type: none"> ■ Early initiation of ART at CD4 350-550 cells/mL reduces risk of transmission to HIV-1-uninfected partners by 96% in context of viral load monitoring, adherence support and risk reduction counseling [14] ■ Observational studies indicate 80-92% reduced HIV-1 transmission in context of ART use by HIV-1-infected partners without virologic monitoring [43-46] ■ In one observational study, equal transmission rate from HIV-1-infected partners on & off ART in context of limited monitoring and adherence counseling [104]
Contraception	<ul style="list-style-type: none"> ■ Effective methods can prevent unintended pregnancies ■ Hormonal contraception associated with two-fold increased risk of HIV-1 acquisition and transmission among HIV-1 serodiscordant couples [76•]; thus, dual condom use and contraceptive options need to be promoted
Pregnancy	<ul style="list-style-type: none"> ■ Pregnancy in the HIV-1-infected or uninfected female associated with two-fold increased risk of male to female and female to male HIV-1 transmission [67•]
Condom use	<ul style="list-style-type: none"> ■ Low condom use among couples, especially among those unaware of their serostatus [4, 7, 20, 23, 100] ■ Condom use is highly protective with 79% lower rate of transmission among HIV-1 serodiscordant couples on a per-act basis [82] ■ Lower infection rates among couples reporting consistent condom use [20, 22, 104] ■ Alcohol use associated with lower condom use [85]
Outside partners	<ul style="list-style-type: none"> ■ Risk from outside partners of unknown HIV-1 serostatus with whom condom use is lower [15] ■ Partners in Prevention HSV/HIV Transmission study: viral linkage indicates 29% of HIV-1 infections in serodiscordant couples were acquired from outside partners [14]. Most outside partnerships reported when the HIV-1-uninfected partner did not report sex with their known HIV-1-infected partner (i.e. were not concurrent) and condom use was lower with outside partners [15] ■ HPTN 052: viral linkage indicates 25% of HIV-1 transmissions from outside partners [2••]
Male circumcision	<ul style="list-style-type: none"> ■ Lack of male circumcision is associated with increased risk of HIV-1 acquisition in men and women [101, 102] ■ Circumcision of HIV-1-uninfected men significantly reduced risk of HIV-1 acquisition [90-92] ■ Observational data indicate circumcised HIV-1-infected men at lower risk of HIV-1 transmission to their female partners, most of whom were likely to have been circumcised prior to becoming HIV-1-infected [93], but circumcision of HIV-1-infected men did not reduce risk of transmission to female partners in randomized clinical trial [94]

Table 2

Antiretroviral-based HIV-1 prevention strategies for HIV serodiscordant couples

Trial	Population & Setting	Intervention	Status/Outcome
Partners PrEP Study [3••]	4758 HIV-1 serodiscordant heterosexual couples in Kenya & Uganda	Daily oral TDF; daily oral FTC/TDF	62% (95% CI: 34-78%) reduction in HIV-1 in TDF arm 73% (95% CI: 49-85%) reduction in HIV-1 in FTC/TDF arm
HPTN 052 [2••]	1763 HIV-1 serodiscordant couples with HIV-1-infected partners' CD4 count 350-550 in Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, & U.S.	Immediate ART for HIV-1-infected partners with CD4 350-550 cells/mm ³ vs. ART at CD4 of 250 cells/mm ³ (delayed arm)	96% (95% CI: 73-99%) reduction in HIV-1 among early ART arm

Abbreviations: ART: antiretroviral therapy, PrEP: pre-exposure prophylaxis, TDF: tenofovir; FTC: emtricitabine