Published in final edited form as:
Curr HIV/AIDS Rep. 2014 December ; 11(4): 434–446. doi:10.1007/s11904-014-0225-9.

Advances in HIV Prevention for Serodiscordant Couples

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Abstract

Serodiscordant couples play an important role in maintaining the global HIV epidemic. This review summarizes biobehavioral and biomedical HIV prevention options for serodiscordant couples focusing on advances in 2013 and 2014, including World Health Organization guidelines and best-evidence for couples counseling, couples-based interventions, and the use of antiviral agents for prevention. In the past few years marked advances have been made in HIV prevention for serodiscordant couples and numerous ongoing studies are continuously expanding HIV prevention tools, especially in the area of pre-exposure prophylaxis. Uptake and adherence to antiviral therapy remains a key challenge. Additional research is needed to develop evidence-based interventions for couples, and especially for male-male couples. Randomized trials have demonstrated the prevention benefits of antiretroviral-based approaches among serodiscordant couples; however, residual transmission observed in recognized serodiscordant couples represents an important and resolvable challenge in HIV prevention.

Keywords

treatment as prevention; TasP; pre-exposure prophylaxis; PrEP; PEP; serodiscordant; HIV; AIDS; couples; prevention

Compliance with Ethics Guidelines

Conflict of Interest Kathryn E. Muessig declares that she has no conflict of interest.
Myron S. Cohen is an advisory board member for Roche Molecular Systems, BMGF HIV EAP, and Janssen Global Services.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION HIV SERODISCORDANT COUPLES: BACKGROUND, DEFINITIONS AND GUIDELINES

I. What is a serodiscordant couple?

The term “serodiscordant couple” refers to an intimate partnership in which one person is HIV-positive and the other is HIV-negative. In research studies, the “couple” relationship is typically defined by marital, cohabitating or co-parenting status or by length of relationship (e.g. minimum of 3-6 months), intention to stay together, or reporting a certain minimum number of sexual acts with this partner within a given timeframe [1]. A number of considerations exist for research and prevention among serodiscordant couples. In general, the couple does not stay discordant forever. By definition, the HIV-negative partner is considered as “exposed and uninfected”. Indeed, trying to understand the basis for apparent protection from HIV has been the source of much investigation [2]. In addition, “stable couples” are more fluid than the definition belies: they may temporarily or permanently dissolve, reunite, or involve outside others (i.e. concurrent sexual relationships by one or both of the partners). Furthermore, couples themselves interpret serodiscordance differently in different cultural or relationship contexts [3]. For example, couples interviewed in Uganda understood serodiscordance to mean undetected infection or HIV immunity among the HIV-negative partner [4].

Serodiscordant couples play a role in maintaining the global HIV epidemic. In surveillance studies, it is common to detect large numbers of serodiscordant couples: in concentrated epidemics, 0 to 6% of all couples may be serodiscordant, while in generalized epidemics this figure ranges from 9 to 17% [5]. HIV transmission within serodiscordant couples can contribute substantially to the overall burden of disease. In high prevalence areas like sub-Saharan Africa, approximately half of HIV-positive persons have negative partners, and in low prevalence settings, this proportion may be as high as 75% [5]. A 2013 modeling study among 20 countries in sub-Saharan Africa estimated that 29% (range 10-52%) of new infections occurred within stable serodiscordant couples [6]. An earlier estimate for Zambia alone attributed 60.3 to 94.2% of all new heterosexual HIV infections to serodiscordant married or cohabitating couples [7]. Among MSM, an estimated 33 to 67% of new HIV infections occur within a primary partnership [8, 9].

In this review we summarize biobehavioral and biomedical HIV prevention options for serodiscordant couples focusing on advances in 2013 and 2014 (up to July 1). We begin with the recent World Health Organization (WHO) guidelines for serodiscordant couples, review the evidence for couples counseling, couples-based interventions, and use of antiviral agents as a prevention strategy and briefly address well-accepted forms of prevention including screening and treatment for other sexually transmitted infections (STI) and male circumcision.

II. International guidelines for serodiscordant couples

Serodiscordant couples have attracted a substantial amount of attention for HIV prevention activities - so much so that they have been defined as a “special population” whose care is outlined in multiple sets of normative guidelines beginning with the August 2011 PEPFAR

guidelines [10] and the April 2012 WHO guidelines for serodiscordant couples (Figure 1) [11, 12]. These guidelines include a strong recommendation for Couples HIV Testing and Counseling (CHTC) with support for mutual status disclosure, initiation of antiretroviral therapy (ART) irrespective of CD4 cell count or clinical disease stage for people in serodiscordant partnerships, and consideration under some circumstances for the use of pre-exposure prophylaxis (PrEP) for HIV-uninfected persons in serodiscordant partnerships [12]. By year-end 2012, 19 out of 70 countries (27%) had national ART treatment guidelines that matched the WHO's treatment guidelines for serodiscordant couples [13]. An updated 2014 review of 124 low and middle income countries found that only 26% countries had comparable guidelines in place [14].

PREVENTING HIV TRANSMISSION WITHIN SERODISCORDANT COUPLES

I. Biobehavioral approaches

Couples HIV Testing and Counseling: It works—Worldwide, 30 to 70% of HIV-positive persons remain unaware of their status [15]. Over 20 years of history shows evidence that Couples HIV Testing and Counseling (CHTC) increases testing, increases condom use and decreases seroconversion [16, 17]. In the Partners in Prevention HSV/HIV Transmission randomized controlled trial (RCT) (South Africa, 2004 – 2008) knowledge of one's HIV status and of serodiscordance within the relationship both led to sustained reductions in condomless sex [18]. Furthermore, within the two largest trials of ART treatment as prevention - the Partners Preexposure Prophylaxis (PrEP) Study and the HPTN 052 study - anticipated transmission among couples was greatly reduced with regular testing and intense couples counseling. These studies brought linked HIV transmission events in the study *control arms* to under 2 events per 100 person years, representing a new standard for prevention in the absence of biomedical intervention [19, 20].

In a recent review, Medley and colleagues catalogue the benefits of CHTC to serodiscordant couples including: decreased transmission within all sexual partners, safer conception, increased psychosocial support, decreased unplanned pregnancy, and increased uptake of and adherence to family planning services, ART, and prevention of mother to child transmission services (PMTCT) [21]. In addition to HIV testing, services that can be provided or referred via CHTC include earlier initiation of ART, reproductive health services, risk reduction counseling and condom distribution, STI screening and treatment, repeat HIV-testing for HIV-negative partners, and voluntary medical male circumcision for HIV-negative male partners [21]. Reproductive health services for serodiscordant couples who wish to conceive may include pre-conception counseling, PMTCT and services such as sperm washing with intrauterine insemination or In Vitro Fertilization [22].

Despite proven benefits, demand for CHTC remains low. One study from Rakai, Uganda, found that uptake of CHTC did not exceed 29% any year from 2003 to 2009 [23]. Additionally, CHTC has traditionally not been available for MSM couples [24] though recent studies demonstrate that it is acceptable and feasible among diverse MSM populations in the U.S., Africa and China [25-27]. The U.S. CDC is currently developing MSM-specific CHTC training guidelines [24].

Additional advances that are changing the landscape of couples-based testing include the July 2012 U.S. Food and Drug Administration's (FDA) approval of a rapid HIV self-test, OraQuick®, which may facilitate in-home, self-guided couples testing. eSTAMP is a current CDC funded study to explore MSM's use of OraQuick® and Sure Check ® (a comparable HIV self-test) (http://clinicaltrials.gov/show/NCT02067039). Risk estimators and assessment tools are also under development to help couples make informed sexual health decisions [28] and help care providers identify high-risk serodiscordant couples to guide decisions around use of ART and PrEP [29].

Couples-based interventions—Beyond CHTC, interventions designed specifically for couples may be more effective than individual-focused interventions alone at reducing transmission risk among serodiscordant couples [30]. These interventions promote established risk reduction behaviors (e.g. condom use, decreasing number of partners) as well as couple-relevant strategies including communication and negotiation skills. Although commonly delivered at the dyadic level, group-level couples-focused interventions are also effective. For example, the Zambia NOW2 project compared a couples-focused intervention delivered in pairs or in gender-matched groups (e.g. all females with female counselor). Both study conditions found increased willingness, acceptability, and use of male and female condoms, decreased intimate partner violence and increased positive communication [31]. Couples-based initiatives focused on peer support are also being explored, such as the serodiscordant Couples' Clubs that are being promoted in Uganda [32].

Couples-based biobehavioral interventions remain an underdeveloped resource. As of April 2014, within the U.S. CDC's HIV/AIDS Prevention Research Synthesis Project for Evidence Based Interventions (EBIs), out of 84 risk reduction EBIs, none focused on MSM couples and only two addressed heterosexual couples [33]: *Connect 2* provided couples counseling for low-income drug users in New York City and significantly reduced unprotected vaginal sex acts over a 12 month period with both the study partner and outside partners [34]. Adaptations of *Connect* have shown preliminary efficacy in groups as diverse as young, heterosexual couples in South Africa [35] and methamphetamine-involved Black MSM couples in the U.S. [36]. The second EBI, *Eban*, delivered an intervention tailored for African American heterosexual serodiscordant couples in four U.S. cities and found increased consistent condom use and decreased number of unprotected sex acts [37]. *Eban* is currently being scaled-up through a community-based implementation trial [38].

A recent systematic review identified 27 biobehavioral interventions for serodiscordant couples [1]. Thirteen studies focused on psycho-educational skills building but the majority had insufficient power to demonstrate change in a biological outcome. The primary elements of skills-building interventions included HIV/STI knowledge, condom use, couple-focused communication, negotiation, problem-solving, goal setting, addressing relationship power imbalances and decision making, strategies for maintaining healthy relationships, and specific focus on negotiating unsafe injection practices among people who inject drugs. An additional 13 studies focused on CHTC for heterosexual couples and one study focused on medication adherence for heterosexual and MSM couples [1].

The limited number of interventions for MSM couples [1, 24] and high prevalence of undiagnosed serodiscordant MSM couples [39] argues for increasing MSM couples-based interventions. A pilot test adapting *Connect* for use with methamphetamine-involved Black MSM couples shows promise but needs large-scale testing [36]. New interventions should be generated in close collaboration with the specific target communities to work within social and sexual norms. For example, one study found that serodiscordant MSM couples who adopt a "we" (versus "me") orientation have less unprotected insertive and receptive anal intercourse [40]. Other qualities of MSM couples such as relationship commitment, relationship intimacy and sexual satisfaction are associated with risk taking behavior [41] and may be relevant constructs for MSM-tailored couples interventions. A range of seroadaptive strategies for HIV prevention have also evolved within the MSM and transgender community including serosorting, seropositioning, and negotiated safety [24]. A WHO evidence based review of serosorting for MSM and transgender persons recommends the practice only "under specific circumstances as a harm reduction strategy" but emphasizes the limits of current evidence and specifies that condom use is recommended over serosorting [42].

II. Biomedical approaches

Medical male circumcision—Male circumcision is one of the most effective biomedical interventions for preventing HIV acquisition in heterosexual men as established through three RCTs and a number of observational studies [43]. The reduction in HIV acquisition among heterosexual circumcised men is approximately 60% [44]. Within heterosexual serodiscordant couples where the male is HIV-negative, medical male circumcision is recommended [42]. However, circumcision is not currently recommended for HIV-positive men within serodiscordant relationships or MSM [42]. Two earlier meta-analyses found moderate protective benefit of circumcision among MSM who primarily practice insertive anal intercourse [45, 46] but recent individual studies [47, 48] and an updated WHO evidence review have not confirmed that the benefits of circumcision outweigh potential risks for MSM [42].

Testing and treatment for sexually transmitted infections—Sexually transmitted infections (STI) are common among people living with HIV [49] and amplify transmission [50]. Both partners within serodiscordant couples should be regularly tested as STI may increase both transmission and acquisition vulnerability for HIV [51, 52]. Regular screening and follow-up treatment should be provided to both the HIV-negative and HIV-positive partner to maximize prevention benefit.

Antiretroviral Treatment as Prevention (TasP) **(Table 1)—**A key element in the serodiscordant couples' prevention strategy is the use of antiviral agents as either pre-exposure prophylaxis (PrEP) or in the form of treatment as prevention (TasP) [53]. Blood, viral load [54] and genital tract viral load [55] of the HIV-positive index case predict transmission probability. In 11 out of 13 observational studies [53, 56, 57] and one large RCT [19], antiretroviral treatment reduced HIV transmission within serodiscordant couples, presumably by suppressing viral replication (Table 1). The HPTN 052 study provided an absolute number to the prevention benefits of early ART among serodiscordant heterosexual

couples – a reduction in transmission of 96% [19]. A meta-analysis of heterosexual serodiscordant couple studies where the HIV-positive partner is on ART and virally suppressed found 0 transmissions per 100 person years [58], while another similar review of partners on combination ART for at least 6 months found a per act transmission risk estimated at between 1 and 13 per 100,000 sex acts whether or not full viral suppression was achieved [59].

A meta-analysis of 50 publications related to discordant couples studies found a 91% (79 – 96%) reduction in per-partner HIV-1 incidence among couples using ART [60]. In perhaps the largest sample to date, a retrospective cohort analysis of 38,862 serodiscordant heterosexual couples in the People's Republic of China found a 26% relative reduction in transmission among those on ART [61]. Numerous confounders and the observational nature of this study suggest that it may be a conservative estimate of the actual transmission prevention benefit of ART [62].

There are concerns that controlled trial environments overestimate the "real-world" effectiveness of TasP. We have previously reviewed this topic in detail [63]. Tanser et al. reported that for every 1% increase in ART availability, a 2% decrease in HIV incidence was observed in community settings in KwaZulu-Natal, South Africa [64]. In British Columbia, widespread availability of ART for people who inject drugs appears to have reduced HIV incidence as well [65]. It should be noted that four community-based clinical trials of TasP are underway [66].

There are further challenges to consider. First, unlinked transmissions from outside of the partnership (non-monogamy) are possible. Up to 27% of transmission events in the HPTN052 and Partners Study were attributable to external events [19, 67]. In a recent modeling study of extra-couple HIV transmission in sub-Saharan Africa, researchers estimated that 27 to 61% of all HIV infections among men and 21 to 51% of infections among women were attributable to extra-couple events [68]. Second, couples may not want to start ART early. For example, in a study of 1958 HIV-infected partners in Kenya and Uganda, 50.1% of those eligible for ART had not started therapy within six months of determined eligibility. Even at 24 months, 12.4% of those eligible still had not started therapy [69]. Third, successful TasP approaches require consistent high medication adherence – a constant challenge in practice. Fourth, there are concerns about behavioral risk compensation negating the prevention benefits of earlier ART initiation. A recent study among 957 participants in Cote d'Ivoire does not support this concern as no significant difference was found in sexual behavior risk among early versus standard initiators [70]. In addition, in the face of suppression of viral replication, risk behaviors are unlikely to result in HIV transmission [57].

TasP for MSM couples—The body of evidence and at least one new observational study suggest that TasP confers a similar prevention benefit to MSM serodiscordant couples [57, 71]. The Partner Study is assessing the occurrence of linked transmission among serodiscordant heterosexual and MSM couples who have condomless sex, are not taking PrEP, and have a most recent viral load under 200 c/mL. Thus far, among 308 couple years of follow-up among MSM couples, no linked transmissions were observed [57]. The

Opposites Attract Study (running 2012 to 2015), is an observational cohort study enrolling MSM dyads in Australia, Brazil and Thailand (www.OppositesAttract.net.au). This study was designed to allow estimates for HIV transmission among partners on and not on ART, virally suppressed versus not virally suppressed, and practicing various levels of condomless anal intercourse.

Antiretroviral Pre-Exposure Prophylaxis (PrEP) (Table 2)

Pre-Exposure Prophylaxis (PrEP) refers to the provision of antiretrovirals to an uninfected person prior to exposure to HIV to prevent seroconversion following possible exposure. Thus far PrEP has been tested or is under development in the form of oral pills, vaginal/rectal microbicides, and long-acting vaginal rings and intramuscular injectables [72, 73]. PrEP has been demonstrated to be effective at reducing HIV acquisition among both men and women in four RCTs [20, 74-76] (Table 2).

Oral PrEP—Using daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), the Pre-Exposure Prophylaxis Initiative (iPrEx) RCT among 2499 MSM found a 44% reduction in HIV incidence [75] while the TDF2 study among 1200 heterosexual men and women found a 63% reduction [76] and the Partners PrEP study among 4747 heterosexual serodiscordant couples found a 75% reduction [20]. In contrast, prevention benefit of oral TDF/FTC was not found in the Fem-PrEP [77] or the Vaginal and Oral Interventions to Control the Epidemic (VOICE) RCTs [78]. The most probable explanations for these divergent trial results have focused on suboptimal adherence. The U.S. FDA approved TDF/FTC (Truvada®) for use as PrEP in July 2012 and the U.S. CDC released new clinical practice guidelines for PrEP in May 2014 [79]. In brief, these guidelines focus on the recommended use of PrEP for sexually active MSM, heterosexual men and women, and injection drug users who are at “substantial risk of HIV acquisition” and the consideration of PrEP as “one of several options for serodiscordant heterosexual couples during conception and pregnancy”. NEXT-PrEP (HPTN-069) is assessing the safety of maraviroc for HIV-negative people compared to TDF/FTC among MSM, heterosexual men and women and transgender men in 13 U.S. cities (http://www.nextprepstudy.org/).

Vaginal gel—The CAPRISA 004 study tested tenofovir 1% vaginal gel (TFV) used peri-coitally among 889 heterosexual women at high risk of HIV infection and found a 39% reduction in infections overall and a 54% reduction among women who used at least 80% of prescribed doses [74]. Conversely, the VOICE trial (MTN-003) which tested daily TFV use among 5029 heterosexual women in HIV high prevalence areas was discontinued for futility [78]. The Follow-on African Consortium for Tenofovir Studies (FACTS) 001 trial is enrolling women age 18 to 30 across nine sites in South Africa for another trial of TVF. FACTS 001 (2015 anticipated trial completion) will assess the protective benefit of TFV applied pre and post-intercourse for HIV and HSV-2 prevention and FACTS 002 is in the planning phase for a similar trial among adolescent women age 16 – 17 (http://www.facts-consortium.co.za/).

In development and testing—Numerous ongoing developments in PrEP science include testing new dosing regimens and new drugs for PrEP including dapivirine, rilpivirine,

maraviroc, and new integrase inhibitors (Table 2). Additionally, new drug formulations and delivery methods are under development, including gels, films, long-acting vaginal rings and injectables [72, 80]. Trials in Malawi are underway of the Dapivirine intravaginal ring (RING and ASPIRE – MTN020) [81]. Phase 1 trials are being conducted of long-acting injectables [82]. Five Phase I rectal microbicide trials have been completed in the U.S. and a Phase II trial (MTN017) will be conducted in the U.S., Peru, Thailand and South Africa to compare oral PrEP to TFV gel [83]. There are multipurpose prevention technologies under development that could provide combination protection against pregnancy, HIV, and HSV-2 [84]. Finally, intermittent versus regular use of PrEP is also being studied [85]. Both dosing strategies have been shown to be safe, acceptable and able to achieve adherence in heterosexual couples [86] and MSM [87]. Prevention efficacy of intermittent PrEP is under investigation in at least two ongoing trials in the U.K. (PROUD) (http://www.proud.mrc.ac.uk/) and France (IPERGAY) (http://www.ipergay.fr/).

PrEP for conception (PrEP-C)—Vernazza et al. described a strategy combining TasP and PrEP for safe conception among serodiscordant couples [88] (PrEP-C). A more recent study tested the use of PrEP with serodiscordant couples wishing to conceive naturally: Among 23 couples, TDF/FTC taken before and after timed ovulatory intercourse was safe and effective for preventing transmission during conception for serodiscordant couples where the male was HIV-positive and female was HIV-negative [89]. No transmission events were observed but further large-scale research is needed to validate the results.

Considerable barriers remain for the application of PrEP through primary care clinics. Knowledge and use of PrEP among providers is limited and education interventions are needed. Among doctors in American Academy of HIV Medicine surveyed in Sept 2011, although most were familiar with the results of PrEP studies (90%) and CDC guidelines (78%), only 19% had prescribed PrEP [90]. In a survey of 1175 infectious disease physicians in the U.S. and Canada, while the majority supported the use of PrEP, only 9% had prescribed it [91]. Physicians were most concerned about the real-world effectiveness of PrEP, adherence, risk compensation, toxicity, cost/reimbursement, moral issues, and drug resistance [91]. Much of data needed to address these concerns is (or will soon be) available. For example a sub-analysis of Partners PrEP data found no significant increase in STI, pregnancy or sexual risk taking behavior assessed before and after July 2011 when there was unmasking and knowledge of efficacy of PrEP for HIV prevention [92].

In general, people move in and out of lifestyles that put them at risk for HIV. Thus the 2014 CDC PrEP guidelines for those “at substantial risk of HIV acquisition” are only a starting point for decisions in every-day clinical practice (not to mention the daily decisions that individual patients will make regarding their own self-assessment and interpretation of “substantial risk”). There are logical temporal situations that warrant short-term PrEP use, such as PrEP-C or for a new partnership until concordant HIV-negative status is confirmed, or until an HIV-positive partner is virally suppressed on ART.

Use of monoclonal antibodies

Broadly neutralizing antibodies that form late in HIV infection also have potential to be used for HIV prevention. Several monoclonal broadly neutralizing antibodies have been described [93]. Moncolonal antibodies including VRC01 and PGT121 are entering safety trials with the idea that these antibodies might be used for PrEP or PEP (see below). In addition, Baltimore et al. have generated an adeno-associated virus (AAV) vector that can constitutively generate the PG9 monoclonal antibody [94]. This reagent can protect humanized mice from HIV infection. A similar construct has entered safety trials in Europe [95].

Non-occupational Post-Exposure Prophylaxis (nPEP)

Post-exposure Prophylaxis (PEP) refers to ARVs used soon after a high-risk exposure to HIV to avert infection. The U.S. Public Health Service issued guidelines for PEP in 1996 which were updated in 2005 [96]. Although typically used for occupational exposures, PEP may be recommended following high-risk non-occupational exposures (nPEP) such as unprotected sex with a known or likely HIV positive partner, sexual assault, or injection drug use with a shared or used needle. nPEP is not recommended for those with recurrent HIV exposures, and thus is generally not used for preventing transmission among serodiscordant couples except in emergency cases (e.g. condom failure, rape). However, advances in PrEP technology may also offer new options for nPEP. For example, macaque studies found that a 1% Raltegravir gel applied vaginally three hours after exposure to SHIV prevented transmission in five out of six macaques and showed no evidence of developed drug resistance with repeated use [97].

Conclusion

Marked advances have been made in the past few years in HIV prevention for serodiscordant couples. However, a number of barriers and challenges remain. First, there is great need to scale-up CHTC and advance serodiscordant couples-based interventions, especially for MSM. Second, research is needed to understand how individuals and couples are adopting and adapting to the growing range of biomedical prevention tools (e.g. PrEP, TasP) and how best to promote and maintain use of these tools. Third, many remain unaware of the prevention benefits of ART and ART use faces continued barriers of concern about stigma and side-effects [98].

Adherence is a cross-cutting theme for the success of biomedical prevention efforts among serodiscordant couples and represents one of many examples of how biomedical and behavioral interventions must work in combination. Despite decades of knowledge about adherence barriers, facilitators and interventions [99, 100], optimal, sustained adherence remains elusive. There are only 10 CDC EBIs for HIV medication adherence, none of which are rated as “best-evidence” grading [33].

Combination approaches to HIV prevention show added benefit over individual strategies [101, 102] and are recommended by the WHO [103]. Combination prevention for serodiscordant couples can be implemented at the population level - for example through

policies and guidelines to support earlier initiation of ART - as well as at the individual level, such as combining TasP with medical male circumcision and CHTC. In fact, HPTN 052 and the Partners PrEP studies were essentially combination prevention strategies: intensive couples counseling was provided along with a host of other benefits and incentives [104, 105].

Ultimately, all behaviorally acquired HIV transmission depends on risk behaviors within a serodiscordant couple. Focus on the prevention of HIV within these couples remains a critical consideration. Well-demonstrated reductions in risk of transmission reflect the results of intense investigation and critical RCTs. Complete reduction of transmission among serodiscordant couples is theoretically possible. Accordingly, residual transmission observed in recognized serodiscordant couples represents an important and resolvable challenge in HIV prevention.

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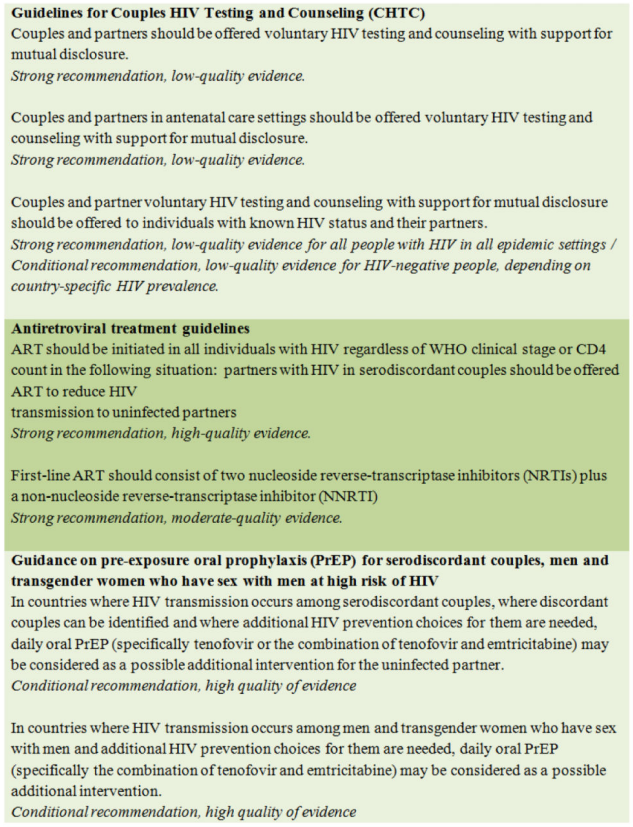

Figure 1.
WHO Guidelines for couples

Table 1

Serodiscordant HIV Treatment as Prevention (TasP) studies (Table adapted and expanded from Cohen AIDS 2013)

Author, Year (Reference)	Study location	No. of couples	Study population	Conclusions
Randomized Controlled Trials				
Cohen et al., 2011 [19]	9 countries; 13 sites	1763	ART naïve serodiscordant couples assigned to early or delayed therapy	Early ART was associated with a 96% reduction in transmission.
Prospective cohorts				
Birungi et al., 2012 [106]	Uganda	586	Serodiscordant heterosexual couples. Group A: CD4 ≥ 250 starting ART, Group B: CD4 > 250, not yet on ART	Transmission rate ratio comparing those on ART vs. not on ART: 0.91 (95% CI, 0.38-2.20)
Bunnell et al., 2006 [107]	Uganda	926	ART-naïve HIV+ adults enrolled in home-based ART program reporting on their partners	ART, prevention counseling, and partner VCT associated w/ reduced estimated risk of HIV transmission during first 6 months of therapy
Del Romero et al., 2010 [108]	Spain	424	Couples recruited through HIV+ patients at an HIV/STI clinic	Heterosexual infectivity of HIV in individuals taking effective ART is low.
Donnell et al., 2010 [109]	Botswana, Kenya, Rwanda, S. Africa, Tanzania, Uganda, Zambia	3381	HIV+ and HSV+ individuals and their HIV- partners	Provision of ART to HIV infected patients could be an effective strategy to achieve population-level reductions in HIV transmission.
Hernando et al., 2009 [110]	Spain	339	HIV+ patients and their partners attending a HIV/STD clinic	Couples based safe sex counseling and ART can reduce but not eliminate sexual HIV transmission.
Melo et al., 2008 [111]	Brazil	93	HIV clinic patients and their seronegative partners	Transmitters showed significantly higher median viral loads, suggesting that heterosexual transmission of HIV is more a function of viral load than gender of index case.
Reynolds et al., 2011 [112]	Uganda	250	Serodiscordant couples offered free ART if eligible	HIV transmission may be reduced among HIV discordant couples after initiation of ART due to reductions in viral load and increased condom use.
Roger et al., 2014 [57]	14 European countries	1110	Heterosexual and MSM serodiscordant couples	Transmission rate of zero (95% CI: 0-0.40 per 100 years follow-up) Upper limit 95% CI for transmission for condomless anal sex: 0.96/100 (any); 1.97/100 (receptive anal sex MSM). Study is ongoing.
Sullivan et al., 2010 [113]	Rwanda, Zambia	2993	Serodiscordant couples initiated on ART if eligible	94% reduction in HIV transmission ART associated with ART
Wang et al., 2010 [114]	China	1927	Former plasma donors and their seronegative	Seroconversion rate of 1.71 per 100 person-years. No difference in rate
Lu et al., 2010 [115]			spouses	of seroconversion between couples who had a spouse on ART (4.8%) vs. not on ART (3.2%) (p = 0.12).

Author, Year (Reference)	Study location	No. of couples	Study population	Conclusions
Retrospective cohorts				
Castilla et al., 2005 [116]	Spain	393	HIV clinic patients and their seronegative partners	Combined ART applied according to current guidelines has a great potential for preventing HIV transmission to sexual partners.
Jia et al., 2012 [61]	China, national sample	38,862	Serodiscordant heterosexual couples	26% relative reduction in HIV transmission associated with ART (adjusted hazard ratio 0.74, 95% CI 0.65-0.84)
Musicco et al., 1994 [117]	Italy	436	HIV+ clinic and surveillance center clients and seronegative partners	ART in HIV infected men reduces, but does not eliminate, heterosexual transmission of infection.

ART=antiretroviral therapy. STI = sexually transmitted infections. VCT = voluntary counseling and testing. HSV = herpes simplex virus.

Table 2

PrEP studies (Table adapted and expanded from Cohen AIDS 2013)

Trial	Location	Formulation	Study population	Outcome	Comments
iPrEX [75]	North and South America, Thailand, South Africa	Daily oral TDF/FTC	2499 MSM at high risk of infection; approximately 70% of mixed ethnicity; mean age in TDF/FTC group 27.5 years	44% protection; 92% protection calculated for subjects with detectable drug concentrations	High TFV-DP concentrations in rectal tissue might be critical for efficacy
TDF2 [76]	Botswana	Daily oral TDF/FTC	1200 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% age 21-29 years	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately
Partners PrEP [20]	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	4747 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years	62% protection with TDF alone; 73% protection with TDF/FTC	Discordant couples may be a distinct, unique population
FEM-PrEP [77]	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	1951 heterosexual women at high risk of infection aged 18-35 years	Trial discontinued for futility in April, 2011	Adherence assessment with monthly clinical samples to measure drug concentration is pending
CAPRISA 004 [74]	South Africa	TFV 1% gel	889 heterosexual women at high risk of infection, aged 18-40 years	39% protection; 54% protection calculated in participants using >80% of doses	High TFV-DP concentration in vaginal and cervical tissue critical for efficacy
VOICE (MTN-003) [78]	Uganda, South Africa, Zimbabwe	Daily oral TDF, daily oral TDF/FTC, daily TFV 1% gel	5029 heterosexual women aged 18-45 years in high-prevalence areas	Oral TDF group discontinued for futility in September, 2011; TFV 1% gel and placebo gel groups discontinued for futility in November, 2011; oral	For TDF, the tissue concentration may be critical; for TFV 1% gel, adherence analysis is pending

Trial	Location	Formulation	Study population	Outcome	Comments
				TDF/FTC group continues	
West African Trial [118]	Ghana, Cameroon, Nigeria	Daily oral TDF	936 heterosexual women	Seroconversions: 2 in drug arm (0.86 per 100 person-years); 6 in placebo (2.48 per 100 person-years). Rate ratio: 0.35 (95% CI, 0.03-1.93)	Cameroon and Nigeria sites closed early due to operational problems
NEXT PrEP (HPTN 069)	US	Maraviroc, TDF, FTC	MSM, heterosexual men and women, transgender male. Target enrollment: 400 - 600	Anticipated study completion: July 2015	http://www.nextprepstudy.org/ http://clinicaltrials.gov/ct2/show/NCT01505114?term=HPTN+069&rank=1
PROUD	U.K.	TDF/FTC: Intermittent dosing	545 Gay/bisexual men who have condomless anal sex recruited as of Nov. 2012. Target enrollment: 5000	Participants assigned to immediate or delayed PrEP. Trial is ongoing	http://www.proud.mrc.ac.uk/
IPERGAY	France, Quebec	TDF/FTC: Intermittent dosing	Gay/bisexual/transgender men who have condomless anal sex. Target enrollment: 1900	Pilot phase completed. Trial is ongoing	http://www.ipergay.fr/
(FACTS) 001	South Africa	TFV gel	Planned enrollment: 2200 – 2900 heterosexual HIV-negative women age 18-30	Anticipated trial completion: 2015	http://www.facts-consortium.co.za/ FACTS 002 is in planning phase for adolescent women age 16-17.
RING (IPM-027) [81]	South Africa	Dapivirine intravaginal ring	1650 HIV-negative women	Anticipated results: 2015	http://www.ipmglobal.org/the-ring-study
ASPIRE (MTN-020) [81]	Malawi, Uganda, South Africa, Zimbabwe	Dapivirine intravaginal ring	3476 HIV-negative women	Anticipated results: 2015	http://www.mtnstopshiv.org/news/studies/mtn020/factsheet

Trial	Location	Formulation	Study population	Outcome	Comments
MTN-017 [83]	US, Peru, Thailand, South Africa	Rectal microbicide: Oral vs. topical RG-TFV 1% gel	186 HIV-negative MSM, age 18 and older	Trial is ongoing, anticipated study completion: January 2015	http://clinicaltrials.gov/ct2/show/NCT01687218?term=MTN-017&rank=1
MWRI-01 [72]	US	Intramuscular injection: 600 vs. 1200 mg of rilpivirine	Estimated enrollment: 90 HIV-negative men and women age 18-45.	Trial is ongoing, anticipated study completion: December 2015	http://clinicaltrials.gov/ct2/show/NCT01656018 Monthly tissue collection (colorectal, cervicovaginal) for four months

TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; TFV = tenofovir gel 1%; IPM = International Partnership for Microbicides; MTN = microbicide trails network; MWRI = ; RG = Raltegravir