Published in final edited form as:

J Acquir Immune Defic Syndr. 2013 July ; 63(0 2): S213–S220. doi:10.1097/QAI.0b013e3182986f3a.

Integrated Strategies for Combination HIV Prevention: Principles and examples for men who have sex with men in the Americas and heterosexual African populations

Connie Celum, MD, MPH^{1,2}, Jared M. Baeten, MD, PhD^{1,2}, James P. Hughes, PhD³, Ruanne Barnabas, MD¹, Albert Liu, MD, MPH⁴, Heidi Van Rooyen, PhD⁵, and Susan Buchbinder, MD⁴ On behalf of the HPTN Combination Integrated Strategies Working Group

¹Departments of Global Health and Medicine, University of Washington

²Department of Epidemiology, University of Washington

³Departments of Biostatistics, University of Washington

⁴San Francisco Department of Public Health, Department of Medicine, University of California, San Francisco

⁵Human Sciences Research Council, South Africa

Abstract

Combination HIV prevention is a high priority for increasing the impact of partially efficacious HIV prevention interventions for specific populations and settings. Developing the package requires critical review of local epidemiology of HIV infection regarding populations most impacted and most at risk, drivers of HIV infection, and available interventions to address these risk factors. Interventions should be considered in terms of the evidence basis for efficacy, potential synergies, feasibility of delivery at scale, which is important in order to achieve high coverage and impact, coupled with high acceptability to populations, which will impact uptake, adherence, and retention. Evaluation requires process measures of uptake, adherence, retention, and outcome measures of reduction in HIV infectiousness and acquisition. Three examples of combination prevention concepts are summarized for men who have sex with men (MSM) in the Americas, young women in sub-Saharan Africa, and HIV-1 serodiscordant couples.

Keywords

Combination HIV prevention; integrated prevention; men who have sex with men; young women in Africa; HIV-1 serodiscordant couples

Introduction

Control of HIV will require integrating a combination of evidence-based HIV prevention interventions, developed based on understanding of local epidemic patterns: local HIV prevalence, incidence, and epidemic factors and important risk factors among key populations. A growing number of interventions have shown partial efficacy against HIV, including knowledge of HIV serostatus, which leads to behavioral risk reduction particularly among those learning HIV-infected persons, condom use, medical male circumcision (MC)

Corresponding author: Connie Celum, International Clinical Research Center, Department of Global Health, University of Washington, Box 359927, 325 Ninth Avenue, Seattle, WA 98104, ccelum@uw.edu, Tel: 1-206-520-3825; fax: 1-206-520-3831.

Conflicts of Interest: None

for HIV-uninfected men, and antiretrovirals when used as therapy (ART) by HIV-infected persons and pre-exposure prophylaxis (PrEP) by HIV-uninfected persons. However, no single HIV prevention strategy will have complete uptake or perfect adherence, thus will have less than 100% effectiveness, making the rational packaging of interventions into integrated programs one of the most critical research and implementation questions for HIV prevention for the near future.

Thinking about combination HIV prevention

Making combination prevention work requires careful selection of component interventions and objectivity in reviewing data about key risk factors, most affected populations, and efficacy of individual interventions. Parsimony in selecting possible interventions is important, as scale, coverage, affordability, and impact could be compromised with more complex combination packages. Pilot work is important to determine the acceptability and feasibility of scaling these interventions to achieve high coverage by prioritizing the subset of the population most at risk of HIV transmission or acquisition, and acceptability of interventions to those populations.

A key first principle for choosing the components of a combination intervention package is synergy – ideally that the effect of a combination of interventions is at least the sum of the parts, if not greater. Just like combination ART is most effective when the components are active against different parts of the viral life cycle, a combination of prevention interventions directed at different risk factors and avenues for HIV transmission may have the greatest combined impact. An example of targeting different paths for transmission among heterosexuals in a generalized heterosexual epidemic would be a combination strategy that includes: 1) MC for HIV- men, 2) ART rollout in HIV-infected persons (including partners of those men), and 3) behavior change interventions that reduce risk and increase uptake and adherence to these interventions. Interventions that seek to reduce infectivity in HIV-infected individuals are likely to be most synergistic with interventions that reduce susceptibility among HIV-uninfected individuals¹. Mathematical models can be used to identify situations where interventions may have a ‘super-additive’ effect by reducing the basic reproductive number (R_0) of an infection below a critical threshold².

A second principle of combination HIV prevention is coverage, which is a function of access to the interventions and willingness of persons prioritized based on risk to utilize the interventions. A fundamental initial step towards achieving high coverage of HIV prevention interventions is HIV testing and knowledge of HIV serostatus, which is needed for targeting interventions to reduce HIV susceptibility or infectiousness. For HIV infected persons, prevention coverage entails breaking down the multiple steps in the cascade from HIV testing to linkage to care: clinic referral, ART eligibility assessment, pre-ART retention, ART initiation for those who are eligible, and sufficient adherence to achieve sustained viral suppression³, particularly among those most likely to transmit. Similarly, there is a cascade for ‘HIV prevention’ for persons who are HIV uninfected: learning one’s HIV status, uptake, and adherence to evidence-based prevention services, such as MC, as well as more user-dependent interventions such as pre-exposure prophylaxis (PrEP), coupled with prevention counseling. Achieving high coverage requires addressing the multiple steps in these ‘cascades’ beginning with knowledge of serostatus, demand stimulation (to increase awareness of HIV risk, benefits of and access to interventions), linkage, adherence and retention.

Economic analyses are important for estimating the cost-benefit of intervention packages in terms of HIV infections averted and lives saved. As an example, economic analyses of the impact of scaling up ART showed that at high ART coverage, over time, the intervention

costs incurred are balanced by reduced costs of HIV-associated morbidity, mortality and incident HIV cases averted^{4,5}. Economic analyses can estimate the initial cost outlay and time to 'break even' in costs based on infections prevented with a universal 'test and treat' scenario⁴, or scaling up ART coverage at different CD4 levels⁵. In assessing the health economic impact of combination prevention, the principles of synergy and coverage also apply. Interventions that reduce susceptibility, such as PrEP and MC, are cost-effective additions to ART for prevention through the synergistic effect of reducing HIV incidence at costs that, relative to life-long ART, are less^{6,7}. Nonetheless, costs for prevention can plateau over time. If strategies to reduce infectiousness and susceptibility are not adequately scaled up, then the number of new infections may remain constant rather than decreasing, thus increasing the overall costs in the long term⁴. One challenge for health economic analyses is to incorporate heterogeneity in costs, in addition to heterogeneity in disease modeling, because as programs are scaled up, smaller programs may have increased costs⁸. For HIV prevention interventions to be cost-effective over time, economic analyses support combining highly effective strategies, widespread coverage for ART, synergistic interventions that reduce susceptibility and identification of efficiencies in delivery of services throughout the cascade from testing, linkages to and retention in care⁶.

We describe three populations and relevant considerations in developing and testing possible strategies for combination HIV prevention in these populations to illustrate the differences in the populations to be reached, risk factors for new HIV infections, and interventions to be considered for combination HIV prevention packages.

HIV among men who have sex with men (MSM) and transgender women

MSM account for the majority of new HIV infections throughout North and South America. In the US, MSM comprised nearly two-thirds of new HIV infections in 2010; they are the only group in whom new infections are rising. Black MSM aged 13–24 years had more than three-fold the number of new HIV infections as white and Latino MSM, and increased the most from 2007–2010. Transgender women (people assigned 'male' at birth but identify as female and/or transgender) have extremely elevated infection rates in both North and South America^{9–12}. Although HIV infection rates are high in Asia and Africa as well, less is known about drivers of infection in these populations; research is ongoing to determine the feasibility of reaching MSM in Asia and Africa¹³, which will guide future HIV prevention efforts.

Recent modeling on the epidemiology of new infections in MSM in the Americas suggests that more than one-third of new infections occur within main partnerships, and approximately two-thirds of those infections occur within partnerships that are not known to be serodiscordant¹⁴. To address the major risk factors for HIV infection in MSM populations in the Americas, several approaches are being currently piloted individually; those with high uptake and adherence will be combined to test their ability to achieve synergistic reductions in infections (Table 1).

1. **Personalized risk calculators** can reduce risk behaviors and improve outcomes including HIV risk behaviors¹⁵, control of dyslipidemia¹⁶, bone mineral density^{17,18}, dietary behavior¹⁸ and alcohol abuse^{19,20}. Online tools, including education and videos can reduce risk, lower delivery costs, increase intervention fidelity and maximize dissemination²¹. An online tool is being piloted to determine if it is useful for MSM to assess their risk and set goals for improving sexual health, similar to diet and exercise websites. This website will then direct men to interventions, described below.

2. **PrEP** significantly reduces the risk of HIV in MSM²²; efficacy appears to be related to adherence²³. Interventions shown to be effective in increasing adherence to ART in HIV-positive persons or preventive medications in healthy individuals (e.g. malaria prophylaxis, HIV post-exposure prophylaxis, osteoporosis prevention) include SMS strategies^{24, 25}, client-centered counseling²⁶, cognitive behavioral therapy²⁷, and providing clinical feedback²⁸; these approaches have been utilized to support PrEP adherence and are currently being piloted in PrEP studies and demonstration projects^{29, 30}.
3. **HIV testing in sexual partnerships with emphasis on linkages to HIV care for HIV-infected men.** A substantial proportion of transmissions are occurring from MSM who are unaware of their HIV infection, including those in relationships that are believed to be sero-concordant negative. Rates of HIV testing and the proportion of HIV positives identified³¹ are significantly higher when “recruitment” occurs through social and sexual networks, particularly in young and African American MSM³²; these approaches are being piloted in combination with home self-testing. SMS reminders also increase testing rates³³.
4. **Brief couples HIV testing³⁴ and online strategies** are being piloted, given data that indicate a substantial minority of infections occurs in stable partnerships.
5. **Strategies to increase linkage to care for HIV positive MSM** are being evaluated in a number of programs to reduce the drop-off in the HIV care cascade and to achieve viral suppression in the majority³⁵.

Synergies for prevention in this population could be achieved by 1) addressing multiple components of the “transmission chain” (e.g., reducing per-act risk transmission through PrEP and reducing partner change rate through behavioral interventions); and 2) targeting populations with minimal overlap (e.g., PrEP for HIV negative men, HIV testing and linkage to ART to suppress viral load in HIV positive partners). The individual components of the proposed package are being piloted (Table 1) to determine which are desirable, scalable, culturally appropriate, potentially cost-effective, and have plausibility for having an impact on HIV seroincidence in both North and South America. Once the package is finalized, the integrated strategy will be tested in a two-stage process: a “vanguard” pilot study of the entire package, and if the combination impacts intermediate measures (e.g., uptake of and adherence to components and synergistic combinations), an efficacy trial.

Young women in sub-Saharan Africa

One of the highest priorities for delivery and evaluation of integrated strategies for HIV prevention is young women in sub-Saharan Africa³⁶. The magnitude of the HIV epidemic in heavily impacted areas such as KwaZulu-Natal province in South Africa is staggering, where a study of women attending family planning and STD clinics from 2004–7 found an HIV prevalence of 35.7% among young women whose median age was 22 years and an HIV incidence of 6.5/100 person-years³⁷. Data from the Africa Center in KwaZulu-Natal showed highest HIV incidence (6.6/100 person-years) among women at age 24 and a peak HIV incidence of 4.1% among men five years later (i.e., age 29)³⁸.

Drivers of HIV risk among young African women include unprotected sex, sexually transmitted infections in some populations, and age differences. Older partners have higher HIV prevalence and gender power disparities are greater, making it harder for women to negotiate safer sex^{39–41}. Gender-based violence may be an important driver in settings, as indicated by the alarming rape statistics from parts of Africa. However, evidence-based interventions are not available for some of the social and behavioral drivers of infection among young women in Africa. Young African women also are at risk for unwanted

pregnancy^{42, 43} among HIV-positive and HIV negative women, and require addressing cultural underpinnings and system access^{44, 45}. Social norms often dictate that young women should not engage in sex and thus influence provider attitudes about contraception and impact young women's access to prevention services, condoms, contraceptive services, sexual and reproductive health services, STI treatment, and HIV testing⁴⁶, increasing their risk when they are sexually active. There is a tremendous unmet need for contraception worldwide⁴⁷; the incidence of unplanned pregnancies among young women in Africa ranges from 4–16% in microbicide and HIV prevention trials^{48–50} and the risk of HIV acquisition and transmission has been found to be twofold higher during pregnancy^{51–53}. A complicating factor is that some observational data indicate a 1.4–2.0 fold increased risk of HIV acquisition among women who use injectable hormonal contraceptives, particularly among depot medroxyprogesterone acetate (DMPA) users^{54, 55}. However, the observational data are inconsistent and must be balanced by the safety, reversibility, contraceptive effectiveness and widespread availability and acceptance of DMPA among providers and women^{56, 57}.

Given the overlapping risks for HIV acquisition, pregnancy and the need for both HIV prevention and reproductive health services, combination prevention for young African women could be delivered through integrated reproductive health and HIV prevention services which include behavioral, biomedical and structural interventions (Table 2). It will be important to pilot different program models for providing youth-friendly integrated reproductive health and HIV prevention interventions to achieve high uptake of HIV testing, PrEP and long-acting, reversible contraception options, as described below.

1. **HIV Testing** and counseling strategies shown to be effective in reaching adolescents and young adults need to be implemented. Effective approaches include community mobilization and mobile vans, including peer-based outreach, and school-based HIV testing^{58, 59}.
2. **Linkages to HIV care.** Young women and men found to be HIV infected will be referred for HIV care in order to provide clinical benefits and reduce secondary transmissions, utilizing evidence for strategies that effectively link HIV-infected persons into care⁶⁰.
3. **Reproductive Health services and contraceptive planning:** The same population of young women at high risk of HIV is at high risk of unwanted pregnancies, and need user-friendly services with expanded contraception and counseling about the observational data on hormonal contraceptives and HIV risk⁶¹.
4. **PrEP with adherence support** is an evidence-based intervention to reduce HIV susceptibility among young HIV-uninfected women in some populations. Daily oral emtricitabine (FTC)/tenofovir (TDF) PrEP significantly reduces the risk of sexual HIV acquisition; efficacy rates among heterosexuals range from no efficacy in studies with low adherence to 62% and 75% among young heterosexuals in Botswana in the TDF-2 trial and HIV serodiscordant couples in the Partners PrEP Study^{62–64}. Gender and age specific subgroup results from Partners PrEP (>70% efficacy in women <30 years)⁶⁵, and the TDF2 trial in Botswana, found that PrEP provides high protection from HIV infection for women⁶². FTC/TDF as PrEP works when taken; adherence is strongly related to efficacy, as demonstrated by retrospective testing of plasma tenofovir levels in the trials with efficacy^{66, 67} and lack of efficacy^{63, 68}. PrEP would be offered to young women with a partner who is HIV-infected or of unknown serostatus, and could offset increased risk from DMPA, until additional data are available about HIV risk due to long-acting progestins and other contraception modalities. Thus, in a combination prevention package that includes PrEP for young women will require assessment of risk

assessment and motivations, as well as adherence monitoring and support, particularly in the first few months after PrEP initiation, through SMS support, and where feasible, real-time drug levels.

5. **HIV testing of male partners.** Young African women often do not know the status of their partners. In order to reduce HIV exposure, women will be encouraged to have their male partners tested for HIV, which will be facilitated by community mobilization and mobile HIV testing. Male partner involvement may increase contraception and PrEP uptake and adherence. Higher coverage of HIV testing among young men facilitates promotion of medical MC for HIV-uninfected men and increases uptake of ART for HIV-infected male partners, which each have indirect and direct benefits to young women.

Heterosexual HIV serodiscordant couples in sub-Saharan Africa

Population data from Africa suggest that a substantial fraction of new infections may occur within stable serodiscordant marital or cohabiting heterosexual relationships, with the majority of transmissions from the HIV-infected partner in the serodiscordant partnership and a substantial minority from an outside partner^{69–73}. Understanding HIV prevention choices and targeting prevention strategies to this group are public health priorities. A number of countries have identified HIV serodiscordant couples as a priority population for implementation of novel HIV prevention strategies, given their high risk, smaller number for targeting relative to the general population, ability to be targeted for prevention efforts through promotion of couples HIV counseling and testing, and clear advantage to the partnership to avert HIV transmission. Importantly, during the past two years, two pivotal novel prevention interventions – ART (through HPTN 052) and PrEP (through the Partners PrEP Study) – demonstrated high efficacy for HIV protection in clinical trials conducted among HIV serodiscordant couples and are the core of a potential integrated strategy for combination prevention in couples. WHO has released guidelines for counseling and HIV-1 prevention for HIV serodiscordant couples, which emphasize the centrality of ART and PrEP, along with attention to other HIV prevention interventions including male circumcision^{74, 75}. Determining **how** these efficacious interventions can effectively be delivered in real-world settings is the priority for combination prevention for this population.

HPTN 052 and Partners PrEP delivered their intervention strategies in the context of a combination package of HIV preventions, including frequent HIV counseling and testing, risk-reduction counseling (including as a couple) and access to condoms, male circumcision, ART according to national guidelines, and other prevention strategies (e.g., screening and treatment for sexually transmitted infections). The impact of these integrated services is reflected in substantially diminished HIV risk even in the delayed treatment or placebo arms of those trials. Thus, these clinical trials offer a model of combination HIV prevention for couples in the unique context of randomized clinical trials with intensive interventions and follow-up.

Recent WHO recommendations for earlier initiation of ART for HIV infected members of HIV serodiscordant couples require translation into programmatic contexts⁷⁵. WHO guidelines are evolving in some settings to include lifelong ART for HIV-infected mothers regardless of CD4 count for the prevention of mother to child transmission⁷⁶. Similarly, optimal strategies for PrEP delivery are yet to be defined and require demonstration projects and use of implementation science methods including demonstration of effectiveness among couples in which an HIV infected partner is not yet on ART, due to refusal or other reasons (i.e., PrEP as a bridge until ART is started and viral suppression achieved)^{77, 78}. Indeed, neither ART nor PrEP use were associated with 100% protective efficacy, indicating a need for examining the effect of strategic integration of these two efficacious interventions,

against a background of an effective prevention package. Thus, implementation science is needed to define:

1. **How to integrate testing and ongoing prevention and care for couples into routine service delivery**^{74–76}
2. **Choices couples make for HIV prevention** and the messages needed regarding different prevention strategies,
3. **Uptake and sustained adherence to HIV prevention interventions whether ART or PrEP**⁷⁹,
4. **Uptake and retention for new ways of delivering ART** (e.g., Option B+ for PMTCT with lifelong ART after pregnancy for HIV positive women, early ART at high CD4 counts)⁷⁶, and
5. Uptake of MC among HIV-uninfected uncircumcised men in couples.

A potential package of combination services to evaluate using implementation science is presented in Table 3.

Conclusions

Combination HIV prevention requires rigorous review of the epidemiology of HIV infection to identify populations most impacted and most at risk, drivers of HIV infection, and efficacy of available interventions to address these risk factors. Interventions should be considered in terms of potential synergies, feasibility of delivery at scale, and acceptability to populations. Evaluation of combination prevention packages requires a staged approach to evaluate acceptability, feasibility of delivery, and integration with other services, which should be followed by an evaluation of impact with outcome measurements, ideally based on HIV viral suppression in HIV infected persons and HIV incidence in uninfected persons. Economic evaluation is important for costing delivery components and to estimate the cost per HIV infection averted and lives saved.

Acknowledgments

Funding: National Institutes of Health R01 AI083034, R01 AI083034-02S2, R01AI083060-04, Directors Award RC4 AI092552, and HPTN UM1 AI068619.

References

1. Alsallaq RA, Baeten JM, Celum CL, et al. Understanding the potential impact of a combination HIV prevention intervention in a hyper-endemic community. *PLoS ONE*. 2013; 8:e54575. [PubMed: 23372738]
2. Anderson, R.; May, R. *Infectious diseases of humans*. Oxford: Oxford University Press; 1991.
3. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *PLoS Med*. Jul.2011 8:e1001056. [PubMed: 21811403]
4. Granich R, Kahn JG, Bennett R, et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050. *PLoS ONE*. 2012; 7:e30216. [PubMed: 22348000]
5. Hontelez JA, de Vlas SJ, Tanser F, et al. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. *PLoS ONE*. 2011; 6:e21919. [PubMed: 21799755]
6. Barnighausen T, Bloom DE, Humair S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. *Proc Natl Acad Sci U S A*. Dec 26.2012 109:21271–21276. [PubMed: 23223563]

7. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. *AIDS*. Jan 28.2013 27:447–458. [PubMed: 23296196]
8. Meyer-Rath G, Over M. HIV treatment as prevention: modelling the cost of antiretroviral treatment--state of the art and future directions. *PLoS Med*. 2012; 9:e1001247. [PubMed: 22802731]
9. Nemoto T, Operario D, Keatley J, Han L, Soma T. HIV risk behaviors among male-to-female transgender persons of color in San Francisco. *Am J Pub Health*. Jul.2004 94:1193–1199. [PubMed: 15226142]
10. Clements-Nolle K, Marx R, Guzman R, Katz M. HIV prevalence, risk behaviors, health care use, and mental health status of transgender persons: implications for public health intervention. *Am J Pub Health*. Jun.2001 91:915–921. [PubMed: 11392934]
11. Edwards JW, Fisher DG, Reynolds GL. Male-to-female transgender and transsexual clients of HIV service programs in Los Angeles County, California. *Am J Pub Health*. Jun.2007 97:1030–1033. [PubMed: 17463365]
12. Silva-Santisteban A, Raymond HF, Salazar X, et al. Understanding the HIV/AIDS Epidemic in Transgender Women of Lima, Peru: Results from a Sero-Epidemiologic Study Using Respondent Driven Sampling. *AIDS Behav*. May.2012 16:872–881. [PubMed: 21983694]
13. Beyrer C, Baral SD, van Griensven F, et al. Global epidemiology of HIV infection in men who have sex with men. *Lancet*. Jul 28.2012 380:367–377. [PubMed: 22819660]
14. Goodreau SM, Carnegie NB, Vittinghoff E, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PLoS ONE*. 2012; 7:e50522. [PubMed: 23209768]
15. Redding CA, Brown-Peterside P, Noar SM, Rossi JS, Koblin BA. One session of TTM-tailored condom use feedback: a pilot study among at-risk women in the Bronx. *AIDS Care*. Jan.2011 23:10–15. [PubMed: 21218272]
16. Grover SA, Lowensteyn I, Joseph L, et al. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. *Arch Intern Med*. Nov 26.2007 167:2296–2303. [PubMed: 18039987]
17. Winzenberg T, Oldenburg B, Frendin S, De Wit L, Riley M, Jones G. The effect on behavior and bone mineral density of individualized bone mineral density feedback and educational interventions in premenopausal women: a randomized controlled trial [NCT00273260]. *BMC Public Health*. 2006; 6:12. [PubMed: 16430773]
18. Wright JL, Sherriff JL, Dhaliwal SS, Mamo JC. Tailored, iterative, printed dietary feedback is as effective as group education in improving dietary behaviours: results from a randomised control trial in middle-aged adults with cardiovascular risk factors. *Int J Behav Nutr Phys Act*. 2011; 8:43. [PubMed: 21595978]
19. White A, Kavanagh D, Stallman H, et al. Online alcohol interventions: a systematic review. *J Med Internet Res*. 2010; 12:e62. [PubMed: 21169175]
20. Cunningham JA, Neighbors C, Wild C, Humphreys K. Ultra-brief intervention for problem drinkers: results from a randomized controlled trial. *PLoS ONE*. 2012; 7:e48003. [PubMed: 23110157]
21. Hirshfield S, Chiasson MA, Joseph H, et al. An online randomized controlled trial evaluating HIV prevention digital media interventions for men who have sex with men. *PLoS ONE*. 2012; 7:e46252. [PubMed: 23071551]
22. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. Dec 30.2010 363:2587–2599. [PubMed: 21091279]
23. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. Sep 12.2012 4:151ra125.
24. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. Nov 27.2010 376:1838–1845. [PubMed: 21071074]
25. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. Mar 27.2011 25:825–834. [PubMed: 21252632]

26. Roland ME, Neilands TB, Krone MR, et al. A randomized noninferiority trial of standard versus enhanced risk reduction and adherence counseling for individuals receiving post-exposure prophylaxis following sexual exposures to HIV. *Clin Infect Dis*. Jul 1.2011 53:76–83. [PubMed: 21653307]
27. Safren SA, O’Cleirigh C, Tan JY, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychol*. Jan. 2009 28:1–10. [PubMed: 19210012]
28. Delmas PD, Vrijens B, Eastell R, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *J Clin Endocrin Metab*. Apr.2007 92:1296–1304.
29. Psaros, C. Evaluation and Process Outcomes from an Adherence Intervention to Support HIV Pre-Exposure Prophylaxis (PrEP) Adherence in HIV-Serodiscordant Couples in Uganda. Paper presented at: 7th International Conference on HIV Treatment and Prevention Adherence; June 5, 2012; Miami, FL.
30. Amico K, McMahan V, Goicochea P, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. *AIDS Behav*. Jul.2012 16:1243–1259. [PubMed: 22460228]
31. Halkitis PN, Kupprat SA, McCree DH, et al. Evaluation of the relative effectiveness of three HIV testing strategies targeting African American men who have sex with men (MSM) in New York City. *Ann Behav Med*. Dec.2011 42:361–369. [PubMed: 21818527]
32. Fuqua V, Chen YH, Packer T, et al. Using social networks to reach Black MSM for HIV testing and linkage to care. *AIDS Behav*. Feb.2012 16:256–265. [PubMed: 21390535]
33. Bourne C, Knight V, Guy R, Wand H, Lu H, McNulty A. Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have sex with men. *Sex Transm Infect*. Apr.2011 87:229–231. [PubMed: 21296796]
34. Stephenson R, Rentsch C, Sullivan P. High levels of acceptability of couples-based HIV testing among MSM in South Africa. *AIDS Care*. 2012; 24:529–535. [PubMed: 22007940]
35. Mayer KH. Introduction: Linkage, engagement, and retention in HIV care: essential for optimal individual- and community-level outcomes in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Jan 15; 2011 52 (Suppl 2):S205–207. [PubMed: 21342908]
36. UNAIDS. World AIDS Day report. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2011.
37. Karim QA, Kharsany AB, Frohlich JA, et al. Stabilizing HIV prevalence masks high HIV incidence rates amongst rural and urban women in KwaZulu-Natal, South Africa. *Int J Epidemiol*. Aug.2011 40:922–930. [PubMed: 21047913]
38. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. Feb 22.2013 339:966–971. [PubMed: 23430656]
39. Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet*. Jun 1.2002 359:1896–1903. [PubMed: 12057552]
40. Pettifor AE, Rees HV, Kleinschmidt I, et al. Young people’s sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS*. 2005; 19:1525–1534. [PubMed: 16135907]
41. Luke, N. Cross-generational and transactional sexual relations in sub-Saharan Africa: a review of the evidence on prevalence and implications for negotiation of safe sexual practices for adolescent girls. Philadelphia: International Center for Research on Women; 2011.
42. MacPhail C, Pettifor AE, Pascoe S, Rees HV. Contraception use and pregnancy among 15–24 year old South African women: a nationally representative cross-sectional survey. *BMC Med*. 2007; 5:31. [PubMed: 17963521]
43. Schwartz SR, Rees H, Mehta S, Venter WD, Taha TE, Black V. High incidence of unplanned pregnancy after antiretroviral therapy initiation: findings from a prospective cohort study in South Africa. *PLoS ONE*. 2012; 7:e36039. [PubMed: 22558319]

44. Seutwadi, L.; Peltzer, K. Contraception. The use of dual or two methods for pregnancy and HIV prevention amongst 18–24-year-olds in a cross-sectional study conducted in South Africa. Published online 31 October 2012
45. Mkhwanazi N. Understanding teenage pregnancy in a post-apartheid South African township. *Cult Health Sex.* May.2010 12:347–358. [PubMed: 20162476]
46. Dickson-Tetteh K, Pettifor A, Moleko W. Working with public sector clinics to provide adolescent-friendly services in South Africa. *Reprod Health Matters.* May.2001 9:160–169. [PubMed: 11468833]
47. Ahmed S, Li Q, Liu L, Tsui AO. Maternal deaths averted by contraceptive use: an analysis of 172 countries. *Lancet.* Jul 14.2012 380:111–125. [PubMed: 22784531]
48. Sibeko S, Baxter C, Yende N, Karim QA, Karim SS. Contraceptive choices, pregnancy rates, and outcomes in a microbicide trial. *Obstet Gynecol.* Oct.2011 118:895–904. [PubMed: 21934454]
49. McCormack S, Ramjee G, Kamali A, et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. *Lancet.* Oct 16.2010 376:1329–1337. [PubMed: 20851460]
50. Reid SE, Dai JY, Wang J, et al. Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: relevance for HIV prevention trials among African women. *J Acquir Immune Defic Syndr.* Apr. 2010 53:606–613. [PubMed: 19838129]
51. Mugo NR, Heffron R, Donnell D, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. *AIDS.* Sep 24.2011 25:1887–1895. [PubMed: 21785321]
52. Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet.* 2005; 366:1182–1188. [PubMed: 16198767]
53. Moodley D, Esterhuizen T, Reddy L, et al. Incident HIV infection in pregnant and lactating women and its effect on mother-to-child transmission in South Africa. *J Infect Dis.* May 1.2011 203:1231–1234. [PubMed: 21398393]
54. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis.* Jan.2012 12:19–26. [PubMed: 21975269]
55. Morrison CS, Skoler-Karpoft S, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. *AIDS.* Feb 20.2012 26:497–504. [PubMed: 22156973]
56. Morroni C, Myer L, Hoffman M. Preferences between injectable contraceptive methods among South African women. *Contraception.* 2006; 73:598–601. [PubMed: 16730491]
57. Population Division. World Contraceptive Use: United Nations Department of Economic Social Affairs. 2006.
58. van Rooyen H, McGrath N, Chirowodza A, et al. Mobile VCT: Reaching Men and Young People in Urban and Rural South African Pilot Studies (NIMH Project Accept, HPTN 043). *AIDS Behavior.* Nov 11.2012 (published online 13 Nov).
59. Sweat, M.; Morin, S.; Celentano, D., et al. Increases in HIV testing and case detection: results from NIMH Project Accept (HPTN 043): a randomized community-based intervention in Tanzania, Thailand, and Zimbabwe. In press
60. Tumwebaze H, Tumwesigye E, Baeten JM, et al. Household-based HIV counseling and testing as a platform for referral to HIV care and medical male circumcision in Uganda: a pilot evaluation. *PLoS ONE.* 2012; 7:e51620. [PubMed: 23272125]
61. World Health Organization. Hormonal contraception and HIV: Technical statement. Geneva, Switzerland: World Health Organization; 2012.
62. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* Aug 2.2012 367:423–434. [PubMed: 22784038]
63. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* Aug 2.2012 367:411–422. [PubMed: 22784040]
64. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* Aug 2.2012 367:399–410. [PubMed: 22784037]

65. Murnane, P.; Celum, C.; Kahle, E., et al. Daily oral PrEP is highly effective among subsets of highest-risk participants in the Partners PrEP Study. Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections (CROI); Mar 3–6, 2013; Atlanta, GA.
66. Baeten, J.; Donnell, D.; Ndase, P., et al. ARV PrEP for HIV-1 prevention among heterosexual men and women. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI); March 5–8, 2012; Seattle, WA.
67. Donnell, D.; Baeten, J.; Hendrix, C., et al. Tenofovir disoproxil fumarate drug levels indicate PrEP use is strongly correlated with HIV-1 protective effects: Kenya and Uganda. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI); March 5–8, 2012; Seattle, WA. p. Abstract 30
68. Marrazzo, J.; Ramjee, G.; Nair, G., et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). Conference on Retroviruses and Opportunistic Infections (CROI); Atlanta, GA. 2013. p. Abstract 26LB
69. Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet*. Jun 28.2008 371:2183–2191. [PubMed: 18586173]
70. Chemaitelly H, Shelton JD, Hallett TB, Abu-Raddad LJ. Only a fraction of new HIV infections occur within identifiable stable discordant couples in sub-saharan Africa. *AIDS*. Oct 17.2012
71. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. Feb 4.2010 362:427–439. [PubMed: 20089951]
72. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11.2011 365:493–505. [PubMed: 21767103]
73. Bellan SE, Fiorella KJ, Melesse DY, Getz WM, Williams BG, Dushoff J. Extra-couple HIV transmission in sub-Saharan Africa: a mathematical modelling study of survey data. *Lancet*. Published online 04 Feb 2013.
74. Curran K, Baeten JM, Coates TJ, Kurth A, Mugo NR, Celum C. HIV-1 prevention for HIV-1 serodiscordant couples. *Curr HIV/AIDS Rep*. Jun.2012 9:160–170. [PubMed: 22415473]
75. World Health Organization. Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. Geneva, Switzerland: WHO Press; Apr. 2012
76. WHO. Programmatic Update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Geneva, Switzerland: WHO; 2012.
77. WHO. Organization WH. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva, Switzerland: WHO; 2012. [Accessed 19 February 2013]
78. Lingappa JR, Hughes JP, Wang RS, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. *PLoS ONE*. 2010; 5:e12598. [PubMed: 20856886]
79. Ware N, Wyatt M, Haberer J, et al. What's love got to do with it? A theory of adherence to once-daily oral pre-exposure prophylaxis (PrEP) for HIV prevention derived from qualitative data among HIV serodiscordant couples. *J Acquir Immune Defic Syndr*. 2012; 59:463–468. [PubMed: 22267018]
80. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of Per-Coital-Act HIV-1 Infectivity Among African HIV-1-Serodiscordant Couples. *J Infect Dis*. Feb.2012 205:358–365. [PubMed: 22241800]
81. Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1 serodiscordant couples for targeted HIV-1 prevention. *J Acquir Immune Defic Syndr*. Nov 26.2013 62:399–347.
82. Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr*. Apr 15.2012 59:463–468. [PubMed: 22267018]

83. Mills E, Cooper C, Anema A, Guyatt G. Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11,050 men. *HIV Med.* Jul. 2008 9:332–335. [PubMed: 18705758]
84. Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet.* Jul 18.2009 374:229–237. [PubMed: 19616720]
85. Baeten JM, Donnell D, Kapiga SH, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1-serodiscordant couples. *AIDS.* Mar 13.2010 24:737–744. [PubMed: 20042848]
86. Hallett TB, Alsallaq RA, Baeten JM, et al. Will circumcision provide even more protection from HIV to women and men? New estimates of the population impact of circumcision interventions. *Sex Transm Infect.* Mar.2011 87:88–93. [PubMed: 20966458]

Table 1

MSM in the Americas: Risk factors, considerations for interventions to include in a combination prevention package, and prioritization and delivery questions

Risk Factors
• Receptive anal sex accounts for 4/5 of new infections in North America and 2/3 in South America ¹⁴
• A substantial minority of infections are occurring in main partnerships, including between men who believe they are both HIV negative
• Substantial proportion of infections coming from those undiagnosed, diagnosed but untreated or not fully suppressed
• Young African-America and Latino men account for a disproportionate number of new HIV infections in North America
Prevention interventions considered for combination prevention package for MSM
• Novel strategies for HIV testing are needed to reach young minority MSM
• An online, confidential tool might help MSM assess their risk and develop sexual health goals
• Focus on testing and linkage to care for HIV-infected male partners
• PrEP can help reduce risk for MSM; given dependence of efficacy on adherence to daily oral PrEP, risk assessment, motivations to take PrEP & adherence support are needed
• Couples-based counseling may be useful in helping reducing risk among MSM couples
• Male circumcision would not substantially alter new infection rates because the preponderance MSM engage in both insertive and receptive anal sex
Prioritization and combination prevention delivery questions
• Will MSM use an online risk assessment tool and will it help them use prevention interventions that meet their needs?
• How to most effectively incorporate linkage to care and prevention into novel testing strategies?

Table 2

Young women in sub-Saharan Africa: Risk factors, considerations for interventions to include in a combination prevention package, and prioritization and delivery questions

Risk Factors
<ul style="list-style-type: none"> • Most women have partners of unknown HIV serostatus; their risk of HIV is high even with a single partner, given high HIV prevalence in some settings
<ul style="list-style-type: none"> • Condom use is protective, but difficult for women to condom use
<ul style="list-style-type: none"> • Substantial proportion of infections coming from those undiagnosed, diagnosed but untreated or not fully suppressed
<ul style="list-style-type: none"> • Sexually-transmitted infections increase the risk of HIV acquisition, with strongest evidence across studies for HSV-2 and BV
<ul style="list-style-type: none"> • Gender-based violence is a risk factor for HIV in some settings
<ul style="list-style-type: none"> • Young women are also at risk of unwanted pregnancies
<ul style="list-style-type: none"> • Long-acting progestins (e.g., DMPA) may increase the risk of HIV acquisition, based on inconsistent observational data
Prevention interventions considered for combination prevention package for young African women
<ul style="list-style-type: none"> • Novel strategies for HIV testing are needed to reach young women and increase testing of their male partners (e.g., coupons)
<ul style="list-style-type: none"> • Integrated delivery of youth-friendly reproductive health services, including contraception, and HIV prevention counseling and services may increase uptake of contraception & HIV prevention services
<ul style="list-style-type: none"> • Focus on testing and linkage to care for HIV-infected male partners
<ul style="list-style-type: none"> • PrEP can reduce risk for heterosexuals in Africa, but requires high adherence to daily oral PrEP for efficacy; risk assessment, motivations to take PrEP & adherence support are needed
Prioritization and combination prevention delivery questions
<ul style="list-style-type: none"> • What service delivery model for integrated reproductive health and HIV prevention is most acceptable and scalable?
<ul style="list-style-type: none"> • Would an interactive risk assessment tool help women select a contraceptive method in the context of expanded method mix and motivate women with greater risk to use and adhere to PrEP?
<ul style="list-style-type: none"> • What are effective strategies to reach their male partners for HIV testing, and achieve linkages to care for their HIV-infected male partners?

Table 3

Heterosexual HIV serodiscordant couples in sub-Saharan Africa: Risk factors, considerations for interventions to include in a combination prevention package, and prioritization and delivery questions

Risk Factors
<ul style="list-style-type: none"> • Viral load in the HIV infected partner, age, married and/or cohabiting partnerships, number of children, unprotected sex, and lack of circumcision in HIV-uninfected male partners are risk factors for HIV transmission in African HIV serodiscordant couples ^{78, 80, 81}
<ul style="list-style-type: none"> • Condom use is protective, but can be difficult for couples to use, particularly if they desire children
<ul style="list-style-type: none"> • Pregnancy increases risk of male to female and male to female transmission by two-fold ⁵¹
<ul style="list-style-type: none"> • Long-acting progestins (e.g., DMPA) have been associated with increased risk of HIV acquisition and transmission⁵⁴
Prevention interventions considered for combination prevention package for young African women
<ul style="list-style-type: none"> • ART significantly reduces risk of HIV transmission, in the context of intensive adherence counseling and viral suppression ⁷²
<ul style="list-style-type: none"> • PrEP significantly reduces risk of HIV acquisition in known HIV serodiscordant couples ⁶⁴; couples are motivated to take PrEP and provide adherence support⁸²
<ul style="list-style-type: none"> • Male circumcision reduces risk of HIV acquisition among adult HIV-uninfected men ⁸³; data are less consistent about relative risks and benefits of adult male circumcision of HIV- infected men ⁸⁴⁻⁸⁶
<ul style="list-style-type: none"> • PrEP can reduce risk for heterosexuals in Africa, but requires high adherence to daily oral PrEP for efficacy; risk assessment, motivations to take PrEP & adherence support are needed
Prioritization and combination prevention delivery questions
<ul style="list-style-type: none"> • Most effective strategies to scale up couples HIV counseling and testing? ⁷⁴
<ul style="list-style-type: none"> • What is the most effective strategy for couples assessment to develop a tailored prevention plan based on partnership characteristics, fertility desires, eligibility and readiness for ART or PrEP, MC, potentially structured around standardized risk assessment as a couple? ⁸¹
<ul style="list-style-type: none"> • Will HIV-infected partners in a known HIV serodiscordant couple be willing to initiate ART at an earlier stage for prevention as well as clinical benefits?
<ul style="list-style-type: none"> • For couples where the HIV-infected partner is not eligible for ART by national guidelines or eligible but not willing to initiate ART, will the HIV-uninfected partner be willing to initiate PrEP?
<ul style="list-style-type: none"> • Will HIV-infected pregnant women in a known HIV serodiscordant couple be willing to initiate ART at any CD4 count (option B-Plus) and continue ART post-partum to reduce risk of transmitting to her male partner as well as her infant?
<ul style="list-style-type: none"> • Will HIV-uninfected uncircumcised men be willing to be circumcised to reduce their risk of HIV acquisition?