Perspective

HIV Prevention: Integrating Biomedical and Behavioral Interventions

Recommendations for HIV prevention in clinical care settings by an IAS–USA panel were recently published. They include recommendations on HIV testing, antiretroviral therapy initiation, risk-reduction counseling, and antiretroviral therapy adherence counseling for HIV-infected individuals. For individuals at risk for HIV infection, recommendations for preexposure prophylaxis, other risk-reduction strategies, adherence counseling, and postexposure prophylaxis are included. Many HIV-infected individuals in the United States are not fully engaged in HIV care and are not virologically suppressed, thus a crucial component of efforts to reduce HIV transmission is moving patients through the HIV care continuum. This article summarizes an IAS–USA continuing education webinar presented by Carlos del Rio, MD, in September 2014.

Keywords: HIV, prevention, antiretroviral therapy, preexposure prophylaxis, PrEP, postexposure prophylaxis, PEP, HIV testing, adherence, HIV care continuum

In 2012, there were approximately 2.3 million new HIV infections worldwide, including approximately 50,000 new infections in the United States.[1] Clinicians play a crucial role in implementing HIV prevention interventions, from HIV testing to ensuring that persons on antiretroviral therapy are virologically suppressed. The IAS–USA HIV Prevention Recommendations Panel recently published recommendations for the biomedical and behavioral prevention of HIV infection in clinical care settings.[1] These recommendations seek to consolidate best practices for clinicians for a range of HIV prevention issues.

Data from the Centers for Disease Control and Prevention (CDC) for 2010 indicate approximately 38,000 (range 33,400-42,600) new HIV infections in adult and adolescent men (80% of total) and approximately 9500 (range 8100-10,900) new infections in adult and adolescent women.[2] The number of new HIV infections in the United States has remained stable for the past decade, but there have been major changes in specific transmission categories. Between 2002 and 2011, the number of infections decreased in most transmission categories, including among all those who were not men who have sex with men (MSM; 47% reduction), heterosexual women (36% reduction), heterosexual men (35% reduction), injection drug users (69% reduction among women and 65% reduction among men), and MSM who were also injection drug users (58% reduction). The number of infections remained stable among MSM overall, but increased by 132% among MSM aged 13 years to 24 years (Figure 1).[3] CDC data for the period of 2008 to 2010 indicate that the greatest numbers of new infections were among blacks, followed by whites and Hispanics, and among MSM (25,000-30,000 cases per year; 12% increase during this period).[2]

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Recommendations for HIV Testing

Knowledge of HIV serostatus is the pivotal step in directing interventions to prevent HIV infection. Approximately 50% of people infected with HIV worldwide are unaware of their serostatus.[4] In the United States, HIV-infected individuals who are unaware of their serostatus are accountable for 45% of new infections.[5] IAS–USA HIV Prevention Recommendations for HIV testing with regard to HIV prevention efforts are listed in Table 1.[1]

Prevention Measures for HIV-Infected Individuals

Suppression of infectious HIV RNA in blood and genital secretions through effective antiretroviral therapy reduces the risk of ongoing HIV transmission. The President's Emergency Plan for AIDS Relief and the World Health Organization (WHO) now recommend antiretroviral treatment for HIV-serodiscordant partners regardless of CD4+ cell count.[6,7] For other HIV-infected individuals, WHO now recommends initiating therapy at CD4+ cell counts of 500/μL or less, regardless of symptoms, and at CD4+ cell counts

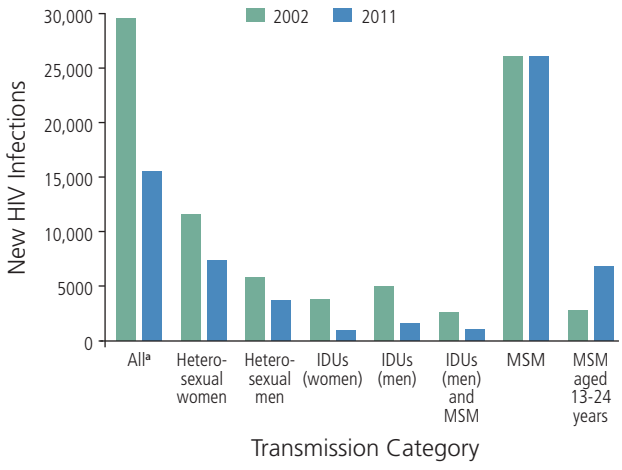

Figure 1. Centers for Disease Control and Prevention estimates of new HIV infections, by transmission category, for the years 2002 and 2011. IDU indicates injection drug user; MSM, men who have sex with men. Adapted from Johnson et al.[3]

[a]Excluding MSM.

Table 1. IAS–USA HIV Prevention Recommendations for HIV Testing, Antiretroviral Therapy, and Risk Reduction

HIV Testing	Antiretroviral Therapy	Risk Reduction
• Adults and adolescents between 15-65 years should be offered HIV testing at least once • High-risk individuals should be tested more frequently, as appropriate • Individuals should be informed prior to HIV testing; however, pretest counseling should be sufficient only to meet the individual's needs and to comply with local regulations. • Persons at risk with a negative HIV test result should be informed about the possibility of having a false-negative test result during the HIV infection "window period" and should be encouraged to undergo repeat HIV testing • Risk-reduction counseling is warranted for people with negative HIV test results who are in high-risk populations (eg, individuals in HIV-serodiscordant sexual relationships) • HIV tests with the best sensitivity and specificity should be used • Rapid HIV testing should be prioritized for individuals who are less likely to return at a later date for their results • HIV self-testing and home testing should be considered for those with recurrent risk or who have difficulties with testing in clinical settings	• Clinicians should provide education about the personal and public health benefits of antiretroviral therapy and assess patients' readiness to initiate and adhere to long-term antiretroviral therapy • Antiretroviral therapy should be offered to patients on diagnosis of HIV infection • Adherence strategies should be developed according to individual patient needs • Patients should be monitored for nonspecific presentation of acute HIV infection, and diagnostic testing (ie, for plasma HIV RNA level) should be pursued if acute infection is suspected	• HIV-infected individuals should have regular assessment of sexual and injection drug use practices • Sexually transmitted infection screening, condoms, and harm-reduction services should be provided to injection drug users (IDUs) in conjunction with adherence strategies • Assistance should be provided for patient- or clinician-based notification of sex and IDU partners to facilitate HIV testing and linkage to care, and patients should be encouraged to disclose HIV infection to relevant partners and persons • IDUs should be provided access to antiretroviral therapy, needle and syringe exchange programs, supervised injection sites, medicalized heroin, and medically assisted therapy (eg, opioid-substitution therapy) • Individuals who use substances in ways other than injection should be offered antiretroviral therapy, adherence support, and behavioral counseling

Adapted from Marrazzo et al.[1]

greater than 500/μL in some specific clinical settings. In the United States, IAS–USA and Department of Health and Human Services antiretroviral treatment guidelines recommend that antiretroviral treatment be offered to all HIV-infected individuals, regardless of CD4+ cell count, who are ready and willing to initiate and adhere to long-term antiretroviral therapy.[8,9]

Data on HIV-serodiscordant couples, including that presented in a classic study by Quinn and colleagues of couples in Uganda (Figure 2),[10] show a greater risk of HIV transmission (man to woman or woman to man) when the HIV-1 viral load in the HIV-infected individual is high and a reduced risk of HIV transmission at lower HIV-1 viral loads. Analysis of several cohort studies showed that taking effective antiretroviral therapy reduced the risk of HIV transmission by 66% (rate ratio, 0.34; 95% confidence interval, 0.13-0.92).[11] The strongest and most direct evidence of the effect of antiretroviral therapy in reducing HIV transmission came from the HIV Prevention Trials Network (HPTN) 052 trial, a double-blind, placebo-controlled trial in which 1763 HIV-serodiscordant couples (the HIV-infected partners had CD4+ cell counts of 350/μL-550/μL) were randomized to receive immediate or delayed antiretroviral therapy.[12] Of 29 linked transmission events, 28 occurred in the delayed-treatment group, yielding a relative risk reduction of transmission of 96% with immediate antiretroviral therapy initiation.

A recent analysis outside the clinical trial setting showed an estimated HIV transmission rate of 0% with condomless sex among heterosexual or same-sex couples in which the HIV-infected partner was taking effective antiretroviral therapy and had a plasma HIV RNA level of less than 200 copies/mL.[13] This analysis included vaginal sex with ejaculation among couples in which the man was HIV-infected (192 couple-years of follow-up [CYFU]), vaginal sex among couples in which the woman was HIV-infected (272 CYFU), receptive anal sex with ejaculation (33 CYFU) and without ejaculation (157 CYFU) among MSM, and insertive anal sex among MSM (262 CYFU). However, there is still uncertainty regarding the upper bounds of the 95% confidence intervals for the

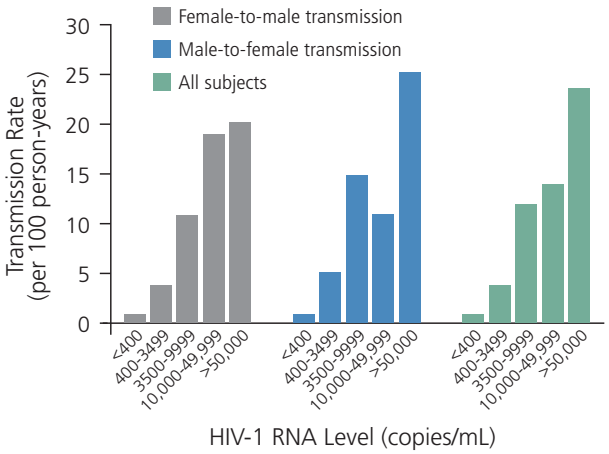

Figure 2. Plasma HIV RNA levels and HIV infection rates among HIV-serodiscordant couples in Uganda. Adapted from Quinn et al.[10]

Table 2. IAS–USA HIV Prevention Recommendations for PrEP and PEP

Preexposure Prophylaxis (PrEP)	Postexposure Prophylaxis (PEP)
• Daily tenofovir and emtricitabine as PrEP should be offered to: - Individuals at high risk for HIV infection based on background incidence (>2%) or recent diagnosis of sexually transmitted infection (especially syphilis, gonorrhea, or chlamydia) - Individuals who have taken PEP more than twice in the past year - Injection drug users who share injection equipment, inject 1 or more times per day, or inject cocaine or methamphetamines • PrEP should be part of an integrated risk-reduction strategy and may become unnecessary with behavioral changes. Patient risk should be regularly assessed and PrEP discontinuation considered if behavioral modifications (ie, reduction in high-risk sexual or injection drug use practices) have been made • PrEP considerations for HIV-serodiscordant couples should include whether the HIV-infected partner is taking antiretroviral therapy, the HIV-uninfected partner's access to care, and associated costs	• PEP should be offered as soon as possible, within 72 hours, to all individuals who have sustained a mucosal or parenteral exposure to HIV • The US Public Health Service preferred PEP regimen, currently tenofovir and emtricitabine with raltegravir, should be used • Women who are prescribed PEP should also be offered emergency contraception to prevent pregnancy • Individuals who are prescribed PEP should be rescreened for HIV infection with a fourth-generation HIV antigen and antibody test 3 months after completion of the treatment course

Adapted from Marrazzo et al.[1]

risk estimates, particularly for receptive anal sex with ejaculation. Additional follow-up is needed to provide more precise risk estimates. Of note, duration of prior antiretroviral therapy without HIV transmission of patients included in this analysis may have selected for lowest-risk HIV-serodiscordant couples.

The IAS–USA HIV Prevention Recommendations for HIV antiretroviral therapy and risk-reduction interventions are listed in Table 1.[1]

Prevention Measures for Individuals at Risk for HIV Infection

Preexposure Prophylaxis

Several randomized, double-blind, placebo-controlled studies have investigated the efficacy of antiretroviral preexposure prophylaxis (PrEP) in preventing HIV transmission. In the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial of 2499 HIV-seronegative MSM and transgender women in South America, Africa, and southeast Asia, there were 64 HIV infections among 1248 placebo recipients and 36 HIV infections among 1251 patients receiving a fixed-dose combination of tenofovir and emtricitabine (44% preventive efficacy).[14] In the Partners PrEP trial of 4758 heterosexual HIV-serodiscordant couples in Africa, in which the HIV-infected partners were not taking antiretroviral therapy and had CD4+ cell counts greater than 495/μL, 52 HIV infections occurred among 1584 couples in the placebo group, 17 HIV infections among 1584 couples in which the HIV-uninfected partner received tenofovir, and 13 HIV infections among 1579 couples in which the HIV-uninfected partner received tenofovir and emtricitabine (67% efficacy with tenofovir; 75% efficacy with tenofovir and emtricitabine).[15] In the TDF2 trial of 1219 heterosexual men and women in Botswana, 24 HIV infections occurred among 608 placebo recipients and 9 HIV infections occurred among 611 tenofovir and emtricitabine recipients (62% efficacy).[16] In the Bangkok Tenofovir Study of 2413 injection drug users, there were 33 HIV infections among 1209 placebo recipients and 17 HIV infections among 1204 tenofovir recipients (49% efficacy).[17]

In contrast, in the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) trial of 2120 heterosexual women in Kenya and South Africa, 35 HIV infections occurred among 1058 placebo recipients and 33 HIV infections among 1062 patients receiving tenofovir and emtricitabine; the trial was stopped for futility.[18] In the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, 5029 heterosexual women in Uganda, Zimbabwe, and South Africa received tenofovir and emtricitabine, tenofovir tablets, or placebo and were randomized to receive tenofovir gel or placebo. The comparison of tenofovir tablets and gel was stopped for futility, and tenofovir and emtricitabine exhibited no preventive efficacy.[19]

The difference in PrEP efficacy in these trials can be explained by differences in patient adherence to the assigned medication. The 44% preventive efficacy rate in the iPrEx trial was observed in the context of a 51% adherence rate to the prophylactic regimen. The 75% efficacy rate in the Partners PrEP trial occurred in the context of an 82% adherence rate. The 6% efficacy rate in the FEM-PrEP trial occurred in the context of a less than 40% adherence rate. However, there are important discrepancies between measures of adherence and drug detection. In the iPrEx trial, among those reporting perfect adherence, 51% had detectable drug levels, but this varied by site, with higher correlations between adherence measures in the United States and lower correlations between adherence measures in the Andean region of South America.[20] In the open-label extension of the iPrEx trial, the HIV incidence rate was 4.7 per 100 person-years among those with no detectable drug levels in dried blood spots, 2.3 per 100 person-years if the drug concentrations suggested use of fewer than 2 tablets per week, 0.6 per 100 person-years for those who used 2 to 3 tablets per week, and 0.0 per 100 person-years for those who used 4 or more tablets per week.[21,22]

IAS–USA HIV Prevention Recommendations for PrEP are listed in Table 2.[1] CDC guidance on PrEP recommends prescribing a once-daily tablet of tenofovir and emtricitabine after a negative HIV antibody test result is obtained.[23,24] Further, acute HIV infection should

be ruled out with HIV-1 RNA testing if there are suggestive or nonspecific symptoms, patients should receive counseling regarding safer sexual practices, pregnancy should be ruled out for women, patients should be screened for hepatitis B virus infection, and creatinine clearance should be greater than 60 mL/min. A 90-day supply of tenofovir and emtricitabine should be given and a follow-up HIV test and assessment of adherence performed before refill. Monitoring for sexually transmitted infections (STIs) should be performed every 6 months and blood urea nitrogen and serum creatinine levels should be assessed every 12 months.

There are several concerns with PrEP that must be addressed with longer follow-up periods and continued study. Risk compensation has thus far not been observed in clinical trials.[25] Renal insufficiency has been rare and reversible, although individuals were required to have normal renal function to participate in clinical trials. Statistically but not clinically significant bone demineralization has been observed after 18 months of PrEP; additional follow-up is needed to determine whether bone demineralization becomes of clinical importance. Transmission of resistance has thus far been observed only in patients taking PrEP who had acute HIV infection and were therefore receiving inadequate antiretroviral therapy. All but 1 case of HIV transmission involved the M184V resistance mutation.[26]

Postexposure Prophylaxis

Occupational postexposure prophylaxis (PEP) is recommended for health care workers who have been exposed to HIV-infected material via needlesticks or cuts. Nonoccupational PEP, for sexual or other exposures, is administered to those who have had mucosal contact with an HIV-infected individual's blood or genital secretions. IAS–USA HIV Prevention Recommendations for PEP are listed in Table 2.[1]

HIV Prevention Efforts in Clinical Care

Improvement in moving patients through the continuum of HIV care and increasing efforts in risk assessment, risk reduction, and screening for and treatment of STIs are crucial to HIV prevention. IAS–USA HIV Prevention Recommendations for STI screening and treatment, as well as reproductive health and hormonal contraception, are listed in Table 3.[1]

The CDC estimates that in 2011 there were approximately 1.2 million persons with HIV disease in the United States, 86% were diagnosed, 40% were engaged in care, 37% were prescribed antiretroviral therapy, and 30% achieved virologic suppression.[27] Given that effective antiretroviral therapy substantially reduces transmission risk, there is enormous room for improving all stages of the HIV continuum of care and ultimately increasing the percentage of people living with HIV who achieve sustained virologic suppression. IAS–USA HIV Prevention Recommendations for improving linkage to HIV care are listed in Table 3.[1]

Summary

After 30 years, an AIDS-free generation seems possible. However, the involvement of clinicians is paramount to achieve this goal. All adults and adolescents should be offered HIV testing. For all persons with or at risk for HIV infection, injection drug use and sexual risk practices should be regularly assessed. Antiretroviral therapy and adherence support should be offered to all individuals with confirmed HIV infection, and PrEP and adherence support should be offered to those at risk for HIV infection. A high index of suspicion should be maintained for nonspecific

Table 3. IAS–USA HIV Prevention Recommendations for Sexually Transmitted Infection Screening, Linkage to HIV Care, and Reproductive Health and Hormonal Contraception

Sexually Transmitted Infection Screening	Linkage to HIV Care	Reproductive Health and Hormonal Contraception
• Regular screening for common sexually transmitted infections should be performed based on sexual history • HIV-infected individuals should be tested for hepatitis C virus at entry to care and reassessed at regular intervals • Quadrivalent human papillomavirus vaccination should be offered to all HIV-infected individuals who meet Advisory Committee for Immunization Practices criteria • HIV-infected individuals who have not already been infected with hepatitis B virus (HBV) should be offered HBV vaccination • Routine herpes simplex virus 2 (HSV-2) infection screening should be considered for HIV-infected individuals who do not know their HSV-2 serostatus considering suppressive antiviral therapy to prevent HSV-2 transmission	• Linkage to HIV care should be actively facilitated as soon as possible following a new diagnosis of HIV infection • Case management interventions utilizing individual patients' personal strengths should be incorporated to promote linkage to and retention in HIV care • Patient support services should be employed, including assistance with patient health navigation, community and peer outreach, culturally appropriate print media, verbal encouragement from clinic staff promoting health care utilization and retention, and youth-focused case management and support where appropriate	• Currently, data are not sufficiently conclusive to restrict use of any hormonal contraception method • Women using injectable progestin-only contraception should also be advised to always use condoms and to use other HIV preventive measures as feasible • Counseling with regard to the range of options for family planning, including hormonal contraception, should be offered to HIV-infected women

Adapted from Marrazzo et al.[1]

presentation of symptomatic acute HIV infection. Linkage to HIV care should be emphasized and supported. Finally, individualized risk-reduction counseling should be facilitated and regular STI screening should be performed.

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