Update in HIV Medicine for the Generalist

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INTRODUCTION

This update examines and summarizes the most recent data on prevention, testing, and treatment of HIV infection for the general internist. Our aims were: (1) to describe the most recent data on HIV prevention; (2) to discuss the recommendations and emerging evidence for routine HIV screening, particularly in community-based settings; (3) to interpret the most recent data on initiation and selection of antiretroviral therapy; and (4) to facilitate the application of these findings to the clinical practice of the generalist.

We performed a PUBMED search of from March 2008 through April 2010, using the Medial Subject Heading (MeSH) term “HIV,” limited to English language articles focusing on human subjects. Additionally, the authors each reviewed studies published between March 2008 and April 2010 in the major internal medicine and HIV journals. We also performed targeted searches using the search terms “HIV prevention” and “HIV testing.” Articles were included after review by consensus among a group of experts, all practicing HIV clinicians and researchers, if they met the following criteria: (1) offered novel findings in HIV prevention, HIV testing, or initiation of antiretroviral therapy; and (2) had the potential for direct clinical relevance to the practicing generalist. We narrowed down our selection by group consensus with the goal of presenting the eight to ten most relevant papers published since March 2008.

PREVENTION

Celum et al. Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2. *NEJM*. 2010. 362:427–439

In HIV-1 infected populations, the seroprevalence of HSV ranges from 60–90%¹, and studies suggest that HSV may

increase HIV transmission. In coinfecting cells, HSV proteins bind HIV and promote transcription^{2–5}. HSV reactivation is associated with increased HIV levels in blood and the genital tract,^{6–9} and rates of sexual HIV transmission are markedly higher from persons with genital ulcers.¹⁰ Additionally, several randomized clinical trials (RCTs) demonstrate that anti-HSV therapy decreases plasma HIV levels.^{6,11–14}

This study is an RCT designed to evaluate the effect of daily acyclovir therapy on HIV transmission.¹⁵ The investigators enrolled HIV serodiscordant heterosexual couples from seven sites in southern Africa and seven sites in eastern Africa. For each couple, the HIV-infected partner was seropositive for HSV, had CD4 cell count ≥ 250 cells/mm³, no AIDS-related conditions, no current antiretroviral therapy, and no persistent genital ulcers. The HIV-negative partner was eligible whether HSV-negative or positive. The intervention group received acyclovir 400 mg twice daily, and the control group received an identical-appearing placebo. The primary outcome was HIV incidence. HIV sequencing was used to classify the transmission as ‘linked’ or ‘unlinked.’

There were 3,360 discordant couples included in the final analysis. In 68% of couples, the woman was HIV-infected. The median CD4 count was 462 cells/mm³. Sixty-eight percent of HIV-negative partners had HSV-2. There were 132 new HIV infections, corresponding to an incidence of 2.7 per 100 person-years (95% CI: 2.3 to 3.2). Eighty-four linked transmissions were included in the analysis, 41 in the acyclovir group and 43 in the placebo group (HR 0.92; 95% CI: 0.60–1.41).

The Bottom Line: Suppressive doses of acyclovir given for up to 2 years did not reduce HIV transmission, despite significantly decreased HIV viremia and symptomatic genital ulcers.

Wawer et al. Circumcision in HIV-Infected Men and Its Effect on HIV Transmission to Female Partners in Rakai, Uganda: A Randomised Controlled Trial. *Lancet* 2009.374:229–37

The World Health Organization (WHO) recommends male circumcision as a male HIV prevention strategy¹⁶ on the basis of several recent RCTs that reduced HIV transmission from females to their male partners^{17–19}.

This study enrolled 922 HIV-infected uncircumcised men aged 15–49 years of age who were randomized to receive

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either immediate circumcision or circumcision delayed for 24 months²⁰. One hundred sixty HIV-negative female partners were also enrolled. The primary outcome was the rate of acquisition of HIV among female partners, including all couples with at least one follow-up visit for the female partner. Seventeen of 92 (18%) women in the intervention group and 8 of 67 (12%) in the control group had incident HIV infection during the study period. Over 24 months, the cumulative probability of HIV infection was 21.7% (95% CI: 12.7–33.4) for women in the intervention group and 13.4% (95% CI: 6.7–25.8) for those in the control group. In a Cox proportional hazards regression analysis, the adjusted hazard ratio (HR) was 1.49 (95% CI: 0.62–3.57; $p=0.368$). There were no significant differences in HIV incidence by participant characteristics or by women's self-reported risk behaviors.

The Bottom Line: The trial was stopped early because of ineffectiveness: male circumcision of HIV-infected men did not reduce transmission of HIV to female partners of HIV-infected men in this study over a 24-month period.

Van Damme et al. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission. NEJM. 2008. 359:463-472

More than half of all adults living with HIV/AIDS in sub-Saharan Africa are women.²¹ Most strides that have been made in HIV prevention (condoms, circumcision) depend largely on male cooperation. Topical microbicides offer the possibility of initiation by women. Cellulose sulfate is an entry inhibitor with in-vitro activity against HIV and demonstrated safety and tolerability. This was a randomized, double-blind, placebo-controlled trial²² of cellulose sulfate gel for prevention of HIV.

Women who were 18 or older, had a negative HIV-antibody test and reported three or more acts of vaginal intercourse/week and three or more different partners in the previous 3 months were recruited from five sites in Africa and India. The intervention group received 6% cellulose sulfate gel and controls an identical placebo (the pH of the compounds were different). The primary outcome was incident HIV infection.

Among 1,398 women, at the prespecified interim analysis point, there were 24 new HIV infections in the cellulose sulfate group and 11 among those receiving placebo (HR: 2.23, 95% CI: 1.05–5.03, $p=0.02$), prompting early termination of the trial. While this suggested increased risk of HIV transmission among women using cellulose sulfate, the interim analysis did not include an additional six incident cases that had not been entered in the database. Analysis including these cases yielded HR: 1.61 (95% CI: 0.86–3.01, $p=0.13$). An additional pre-planned analysis censoring data from participants who interrupted cellulose or placebo use (most often due to pregnancy) yielded a HR 2.02 (95% CI 0.97–4.18, $p=0.05$).

In summary, there was a higher incidence of HIV in the cellulose sulfate group; however, this did not reach significance in the primary effectiveness analysis. It was noted by the investigators that there were non-differential pregnancy rates in the two groups. Given the contraceptive profile of cellulose sulfate, non-adherence might have been a factor in the observed results.

The Bottom Line: Cellulose sulfate is not effective in the prevention of vaginal HIV transmission.

Rerks-Ngarm et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. N Engl J Med. 2009. 361:2209-2220

This was a multicenter community-based, randomized double-blind, placebo-controlled trial in Thailand to evaluate the efficacy of vaccines to prevent HIV.²³ The vaccine protocol consisted of a primer of a recombinant canarypox vector vaccine (ALVAC-HIV) (four injections) and two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E). A total of 16,402 HIV-uninfected persons aged 18–30 years were enrolled. HIV testing was performed at baseline, 24 weeks, 26 weeks, and every 6 months for 3 years of follow-up. The primary outcomes were HIV infection and early HIV viremia.

There were 132 new HIV infections, 56 in the vaccine group and 76 in the placebo group over a total of 52,985 person-years of follow-up in the intention-to-treat analysis. This result translated to an observed efficacy of 26.4% (95% CI: -4.0–47.9, $p=0.08$). A modified intention-to-treat analysis excluded seven persons found to be HIV-infected at baseline. In this group, there were 125 new HIV infections, 51 in the vaccine group and 74 in the placebo group over 52,985 person-years of follow-up, corresponding to an observed vaccine efficacy of 31.2% (95% CI: 1.1–52.1, $p=0.04$). A per-protocol additional analysis included only those who received all scheduled vaccinations in the series, maintained eligibility in the study, and had not acquired HIV by the fourth vaccination. Among this group, there were 86 new HIV infections, 36 in the vaccine group and 50 in the placebo group in 36,720 person-years of follow-up corresponding to an observed vaccine efficacy of 26.2% (95% CI: -13.3–51.9, $p=0.16$).

The Bottom Line: While the intention to treat analysis demonstrated only a trend towards efficacy, after excluding those with HIV at baseline, there was a significant reduction in HIV incidence in the vaccination group. Future studies must address the immune mechanisms involved as well as whether vaccine efficacy varies over time and in certain populations.

EXPANDING HIV TESTING

Bokhour et al. Barriers and Facilitators to Routine HIV Testing in VA Primary Care. J Gen Intern Med. 2009 24:1109–14

Implementing expanded HIV testing in primary care requires an understanding of the context into which broad testing will be introduced. Bokhour and colleagues conducted focus groups with patients ($N=28$) and health-care providers ($N=13$) from primary care clinics at two US Veterans Administration facilities to better understand issues in the expansion of HIV testing.²⁴ Patients in the four focus groups were HIV-negative men aged 35–88 years, predominantly low income, with a range of educational backgrounds. The two provider focus groups consisted of men ($N=6$) and women ($N=7$), and included physicians, nurse practitioners, and a registered nurse.

Semi-structured group interviews led to several recurrent themes. Both patients and health-care providers felt that HIV testing should be routine. Many felt that routine testing could reduce stigma. Concerns were expressed about special written consent forms and the anxieties that they may cause. Though “normalizing” the HIV testing was a consistent theme, results showed that patients wanted to be aware that HIV testing was being done and that it should be explicitly offered, with the option to decline. They also pointed out the need for clear and prompt communication of results.

The Bottom Line: Veteran patients are likely to accept routine testing, but attention to issues of stigma and clear communication about results are important for both patients and providers. To help with patient-centered discussions, the authors developed “Six R’s” for routine testing: (1) Raise the topic; (2) Reassure the patient that the offer is routine; (3) provide Rationale for the test; (4) Respond to questions; (5) Request the test; and (6) tell the patient when and how they will get Results.

Arbelaez et al. Emergency Provider Attitudes and Barriers to Universal HIV Testing in the Emergency Department. J Emerg Med. 2009 Oct 13. (Epub ahead of print)

The Centers for Disease Control and Prevention (CDC) HIV testing guidelines include emergency departments (EDs) as target locations for expanded routine HIV testing.²⁵ This research study surveyed ED providers before and 6 months after institution of an ED-based HIV testing program to understand attitudes toward testing and how they might change with experience.²⁶

One hundred eight providers (43% nurses, 29% resident physicians, 17% attending physicians, 7% nursing assistants, and 4% physician assistants) completed both pre- and post-surveys. Before starting the HIV testing intervention in the ED, many providers identified barriers to HIV testing such as inadequate resources (70%), inadequate time (51%), and concerns about assuring follow-up (50%). After experience with the intervention, two of these barriers were more frequently reported than at baseline: inadequate time (62%) and follow-up care (59%). In multivariate modeling, female providers, providers who felt they had sufficient time to test, and providers reporting sufficient legal understanding of testing issues were more likely to favor HIV testing in the ED. While most providers favored HIV testing in general (86%), fewer supported doing it in the ED (56%), and still fewer expressed willingness to offer it themselves (37%).

The Bottom Line: For HIV testing in the ED to be substantially adopted, provider perceptions about barriers must be addressed, including concerns about inadequate time and legal ramifications of testing.

Myers et al. Routine Rapid HIV Screening in Six Community Health Centers Serving Populations at Risk. J Gen Intern Med. 2009. 24:1269–74

Federally qualified community health centers (CHC) are a crucial part of the health-care delivery system for predominantly underserved populations. In late 2006 the National Association of Community Health Centers supported the

expansion of point-of-care HIV testing programs across North Carolina, South Carolina, and Mississippi. Myers and colleagues conducted a before-and-after analysis of data from six CHCs who adopted routine rapid HIV screening.²⁷ Efforts included redesign of patient flow, written protocol development, clinic in-service trainings, on-site technical assistance, follow-up support, and dissemination of patient educational materials.

During the year prior to program rollout, approximately 3% (N=3,078) of patients seen for care were tested for HIV. During the 13 months after rollout, 16,148 were offered testing, and 10,769 (66%) accepted. Thirty-nine persons tested positive on rapid test results, of whom 20 were confirmed HIV-positive and 17 were new HIV diagnoses. Rates of infection were lower than expected by the investigators, but still higher than thresholds disseminated by the CDC for identifying health-care settings eligible for routine testing. Twelve of the 17 newly diagnosed patients were successfully linked to HIV care. Patients who were white were significantly less likely than African-Americans or Latinos to be HIV tested, as were the oldest patients (those aged 55–64 years). While false positives occurred at rates to be expected for the rapid tests, staff were not fully prepared for false positives, and had to develop procedures for understanding and communicating the inherent uncertainty of the initial, preliminary rapid test results.

The Bottom Line: Routine point of care testing markedly increased screening rates in community health centers.

WHAT TO START IN ANTIRETROVIRAL NAÏVE PATIENTS

Table 1 summarizes the current (2009) US Department of Health and Human Services (DHHS) recommendations on which combinations of antiretroviral medications to initiate in the naïve patient.²⁸

WHEN TO START ANTIRETROVIRAL THERAPY

Mari Kitahata et al. Effect of Early Versus Deferred Antiretroviral Therapy for HIV on Survival. N Engl J Med. 2009. 360:1815–1826

When to Start Consortium Timing of Initiation of Antiretroviral Therapy in AIDS-Free HIV-1-Infected Patients: A Collaborative Analysis of 18 HIV Cohort Studies. Lancet. 2009. 373:1352–63

When to start antiretroviral therapy (ART) has been an ongoing controversy.^{29,30} The decision regarding when to start therapy has to balance anticipated benefits with potential side effects, impact on quality of life, and risk of therapeutic burnout and virologic resistance. Potential benefits of starting early include: modulation of the inflammatory response, lowering of the viral set point, higher rates of immune reconstitution, and use of treatment as prevention.^{31,32}

Kitahata, writing for the NA-ACCORD investigators, investigated the effects of starting therapy at different levels of CD4 counts³³. The NA-ACCORD group consists of 22 clinical cohorts in North America. They identified antiretroviral naïve

Table 1. Antiretroviral Regimens Recommended for Treatment-Naïve Patients. Adapted from Table 5a, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>, Page 39

Preferred Regimens: (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use)

Non-nucleoside reverse transcriptase inhibitor -based regimen

efavirenz/tenofovir/emtricitabine[†]

Protease inhibitor-based regimens

atazanavir/ritonavir + tenofovir/emtricitabine[†]

darunavir/ritonavir (once daily) + tenofovir/emtricitabine[†]

Integrase strand transfer inhibitor -based regimen

raltegravir + tenofovir/emtricitabine[†]

Preferred regimen for pregnant women

lopinavir/ritonavir (twice daily) + zidovudine/lamivudine[†]

Alternative Regimens:

(Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)

Non-nucleoside reverse transcriptase inhibitor -based regimens

efavirenz + (abacavir or zidovudine)/lamivudine[†]

nevirapine + zidovudine/lamivudine[†]

Protease inhibitor-based regimens

atazanavir/ritonavir + (abacavir or zidovudine)/lamivudine[†]

fosamprenavir/ritonavir (once or twice daily) + either [(abacavir or zidovudine)/lamivudine[†]] or tenofovir/emtricitabine[†]

lopinavir/ritonavir (once or twice daily) + either [(abacavir or zidovudine)/lamivudine[†]] or tenofovir/emtricitabine[†]

saquinavir/ritonavir + tenofovir/emtricitabine[†]

Acceptable Regimens:

(Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.)

Non-nucleoside reverse transcriptase inhibitor -based regimen

efavirenz + didanosine + (lamivudine or emtricitabine)

Protease inhibitor-based regimen

Atazanavir + (abacavir or zidovudine)/lamivudine[†]

Comments:

Efavirenz should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.

Atazanavir/ritonavir should not be used in patients who require >20 mg omeprazole equivalent per day.

Nevirapine:

- Should not be used in patients with moderate to severe hepatic impairment
- Should not be used in women with pre-ARV CD4 >250 cells/mm³ or men with pre-ARV CD4 >400 cells/mm³

Abacavir:

- Should not be used in patients who test positive for HLA-B*5701
- Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV-RNA >100,000 copies/mL

Once-daily lopinavir/ritonavir is not recommended in pregnant women.

Efavirenz + didanosine + emtricitabine or lamivudine has only been studied in small clinical trials.

Atazanavir/ritonavir is generally preferred over unboosted atazanavir. Unboosted atazanavir may be used when ritonavir boosting is not possible.

[†]lamivudine may substitute for emtricitabine or vice versa. Abbreviations: ARV=antiretroviral

patients who began therapy at CD4 counts greater than 500 cells/mm³, at CD4 counts between 350 and 500 cells/mm³, and patients who chose to defer therapy between 1996 and 2006. The main outcome was survival comparing earlier therapy (at either greater than 500 cells/mm³ or between 350 and 500 cells/mm³) with deferred therapy. At both levels,

deferred treatment was associated with increased death rates [500 cells/mm³: RR 1.94; 95% CI, 1.37 to 2.79, 350–500 cells/mm³: RR: 1.69; 95% confidence interval (CI), 1.26 to 2.26].

Evidence supporting starting ART above 350 cells/mm³ was also recently released by the ART-Cohort Collaboration.³⁴ They found an increased hazard of death (HR 1.28, 95% CI 1.04–1.57) for starting ART in the 250–350 cells/mm³ CD4 count range versus 350–450 cells/mm³. It should be noted that patients with a history of injection drug use were excluded from this study, which may account for the lower hazard ratio. The ART-CC study did not observe a benefit of starting above 450 cells/mm³, and it is unclear why there is a discrepancy at this higher range. Even larger differences were seen for comparisons with lower CD4 counts at time of treatment initiation.

Because both of these studies are based on observational cohort data, the potential for unmeasured confounders exists. ART initiation is no doubt strongly associated with health status, physician expectations, and patient health seeking behaviors. Both studies adjusted for or excluded patients with a history of injection drug use as a major potential confounder. The NA-ACCORD investigators performed a sensitivity analysis that found a large confounder effect would be needed to reduce or negate their findings. However, an effect of this magnitude was uncovered by the Women's Health Initiative trial of hormone replacement therapy in primary prevention of coronary heart disease compared to prior observational cohort studies.³⁵ An RCT of ART, the Strategic Timing of AntiRetroviral Treatment (START) trial, is underway and may help to establish the validity of the guidelines.

The Bottom Line: Antiretroviral therapy should be initiated once the CD4 declines below 500 cells/mm³ and may be beneficial at CD4 counts above 500 cell/mm³.

Summary and Implications for Practice

Prevention.

- Much work remains to be done, particularly regarding methods initiated and controlled by women, as well as prevention of transmission between serodiscordant couples. Further work is needed to evaluate sexual transmission prevention strategies among men who have sex with men.
- These studies highlight the importance of continuing to recommend condom use as a proven HIV prevention strategy.
- Further research on optimal vaccination regimens, immune responses to vaccination, and the safety and efficacy of vaccinations in specific target populations is still needed.

Testing.

- Routine point of care testing can markedly increase screening rates.
- Attention to issues of stigma and clear communication about results are important for both patients and providers.
- Provider perceptions must be addressed, including concerns about inadequate time and legal ramifications.

Initiation of Treatment. The studies presented both favor earlier treatment in the 350–500 cells/mm³ range and possibly above. The combined data have led to a change in DHHS Guidelines²⁸:

- As before, ART should be initiated if the CD4 count is less than 350 cells/mm³ or in cases of pregnancy, HIV-

associated nephropathy, and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated.

- Now, the expert panel recommends starting therapy between 350–500 cells/mm³ and is divided on therapy at CD4 counts above 500 cells/mm³ with 50% in favor and 50% viewing it as optional.
- It is important to note that most patients are diagnosed with a CD4 under 350 cells/mm³. Increased adoption of routine testing may identify those with HIV at earlier CD4 counts.

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