Special Contribution
Update of the Past Year: A Review from IDSA 2011

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The Infectious Diseases Society of America (IDSA) Annual Meeting serves as a time of expert review of the year’s most important innovations. Important new information on HIV infection incidence was discussed. The remarkable efficacy of “treatment as prevention” in the HIV Prevention Trials Network (HPTN) 052 study and the proper place of oral preexposure prophylaxis were among the important prevention topics. Key engagement-in-care research indicates that only 19% of HIV-infected persons in the United States have a plasma HIV RNA level below the limits of assay detection. Among antiretroviral topics, the role of the newly approved non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine was discussed. Primary care topics for the HIV-infected population included treatment of triglyceride level elevations and bone health. The newly published data on the proper timing of antiretroviral therapy initiation after starting tuberculosis treatment were highlighted. Finally, exciting advances in the treatment of hepatitis C virus (HCV) infection necessitate that practitioners understand the complexities of treating HIV/HCV coinfections.

The Infectious Diseases Society of America (IDSA) Annual Meeting is a forum for the presentation of new data (in abstract and poster sessions) and serves as a review of important recent advances in the field over the past year. This year’s IDSA meeting, held from October 20 to 23, 2011, in Boston, presented participants with an opportunity to reflect on how recent innovations will impact their practice. This article highlights some of this year’s key messages from the meeting. This content will update HIV clinicians on advances presented at IDSA 2011, focusing on the US epidemic.

Update on Incidence: For Young African American MSM, the Bad News is Getting Worse

Currier’s update on HIV during the “What’s Hot in ID and HIV” Symposium began with a discussion of new US HIV infection incidence data released by the Centers for Disease Control and Prevention (CDC) in August pertaining to the years 2006 to 2009.1 The new figures are considered more accurate than those previously released, owing to new methodologies used in their calculation. The CDC report warns that as methodologies improve, total incidence is likely to undergo further revision, and that the most important data are those indicating the trends and risk groups affected.

Overall the incidence of HIV infection has not changed in recent years, with around 50,000 new infections in the United States annually. An estimated 95% of new infections occur in women, members of ethnic and racial minority groups, and injection drug users. Black/African Americans are contracting HIV at a rate 10 times that of whites. For Latinos, the rate is 3 times to 4 times the rate in whites.

Transmission in men who have sex with men (MSM) accounts for 61% of new infections. An alarming finding was the HIV infection incidence among young (aged 13-29 years) black MSM, which had increased 48% (or 12.2% annually). With the release of these data, contemporary at-risk groups to whom prevention can be targeted have been more clearly delineated.

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Update on Prevention

Treatment Takes Center Stage

Because of the remarkable efficacy shown in the HIV Prevention Trials Network (HPTN) 052 study, treatment as prevention was among Currier’s most important prevention topics. HPTN 052 was an international study of 1763 HIV-serodiscordant couples in which the HIV-seropositive partner did not meet current criteria for antiretroviral therapy. The HIV-seropositive partners were randomly assigned to immediate antiretroviral therapy versus standard treatment (standard treatment being antiretroviral therapy initiation based on clinical events or a CD4+ cell count < 250(μL). The primary outcomes were transmission to the seronegative partner and clinical disease progression in the seropositive partner. Viral sequencing was performed so that transmission events could be linked to the seropositive partner. Only 1 of the total 28 linked transmission events occurred in the early antiretroviral therapy group (a 96% reduction in transmission). Clinical events were also statistically significantly fewer in the early therapy group, largely because of a reduction in extrapulmonary tuberculosis.

Initial CDC Guidance Regarding Oral PrEP

Smith of the CDC discussed oral preexposure prophylaxis (PrEP) at the “State-of-the-Art in HIV” symposium. Oral PrEP refers to the active use of oral medications to protect against HIV infection. The results of the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study on oral PrEP have been known for almost a year. This international trial randomly assigned 2499 high-risk HIV-seronegative MSM to either daily tenofovir/emtricitabine or placebo, with all participants receiving...
equivalent preventive services and education. A substantial reduction (44%) in new HIV infections occurred in the intervention group during a median follow-up of 1.2 years (100 new infections: 64 in the placebo group and 36 in the intervention group). This decrease was even more pronounced when adherence (measured by detection of serum antiretroviral drug levels) was factored in.

Although any positive trial in the field of HIV prevention is a reason for celebration, many questions regarding feasibility, safety, cost, and effectiveness of oral PrEP have been raised. Smith noted that comprehensive PrEP guidelines are forthcoming, and presented the initial guidance. The target population for oral PrEP is HIV-seronegative MSM who are not monogamous with their HIV-seronegative partner and report inconsistent condom use; who have any sexually transmitted infection (STI); or who have ongoing sexual contact with HIV-seropositive partners. The CDC estimates that 275,000 persons meet these criteria. Primary care practitioners and health departments are thought to be the most likely providers of PrEP. Smith highlighted a practical challenge, which is that many primary care practitioners do not have a thorough understanding of their patients’ sexual practices.

Mayer and colleagues’ poster presentation focused on primary care practitioners and HIV specialist physicians’ knowledge and practice regarding PrEP (Abstract 493). The authors’ survey of Massachusetts practitioners indicated that although self-reported knowledge of PrEP seemed to be very good (92%), very few had actually prescribed PrEP (5%). Regarding the preferred type of PrEP delivery, more respondents preferred a topical microbicide (69%) over oral PrEP. The majority thought formal guidelines would be the most helpful method of increasing physician uptake of PrEP. Detailed recommendations on technical aspects of providing oral PrEP to MSM are available in the CDC interim guidance. Additionally, a recent comprehensive review of HIV prevention is available.

### Engagement in Care: Problems Along the Path to Viral Suppression

The “test and treat” strategy for HIV infection entails universal testing with immediate treatment for those who test seropositive. The efficacy of treatment as prevention demonstrated in HPTN 052 has reinvigorated the discussion over using a “test and treat” strategy to reduce the incidence of HIV infection in the United States. However, engagement-in-care research raises a note of caution regarding potential pitfalls in the effectiveness of this strategy.

The estimates published by Gardner and colleagues are helpful in understanding this issue: Figure 1 shows the estimate of 1.1 million persons being infected with HIV in the United States and then sequentially shows the use of available data to estimate where patients are lost to care at each point along the path to viral suppression. It is estimated that 21% of HIV-infected persons are currently undiagnosed. Of those who are diagnosed, losses occur at initial linkage to care and later in care such that only 50% remain in care.

Antiretroviral therapy eligibility, actual initiation, and effective antiretroviral therapy are all unique steps through which a proportion of patients do not progress, leading to the estimate of only 19% (209,773 of 1.1 million) of HIV-infected persons in the United States currently having viral load below the limits of assay detection.

Gardner and colleagues describe how maximizing only a single step in the care pathway does little to influence the final proportion of those with maximal viral suppression. For example, increasing diagnosis (as would result from an effective universal testing policy) to 90% of persons with HIV infection would only increase the percentage of persons with maximal virologic suppression by 3%. Andrews and colleagues showed a related phenomenon in a South African township in their oral abstract presentation (Abstract 148). Thus, although the efficacy of treatment as prevention demonstrated in HPTN 052 is a cause of great hope, the effectiveness of a “test and treat” strategy for lowering the incidence of HIV infection requires a strengthening of each point along the pathway to sustained viral suppression.

![Figure 1. Estimated loss of HIV-infected patients engaged in care, shown along each step in the care pathway. Gardner and colleagues calculate that only 19% of HIV-seropositive persons in the United States have a maximally suppressed viral load. Adapted from Gardner et al. by permission of Oxford University Press.](image-url)
Goetz and Rimland’s poster of Department of Veterans Affairs (VA) data shows a positive example of the care pathway (Abstract 478). In this group of 189 patients diagnosed after the VA increased HIV testing in 2005, a remarkable 71% had attained an undetectable viral load within 12 months. The authors conclude that an integrated health system such as the VA, in which each step in the care pathway can be efficiently linked, improves overall engagement in care.

**Update on Antiretrovirals**

**Searching for Rilpivirine’s Place**

An update on antiretroviral therapy was provided by Sax during the “State-of-the-Art in HIV” symposium. The US Food and Drug Administration (FDA) approval of rilpivirine in May 2011 marked the entry of a new nonnucleoside reverse transcriptase inhibitor (NNRTI). The once-daily, fixed-dose combination of rilpivirine/tenofovir/emtricitabine was approved in August 2011. The phase III studies of rilpivirine, ECHO (Efficacy Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) and THRIVE (TMC278 Against HIV in a Once Daily Regimen Versus Efavirenz), were published simultaneously in July. The trials were randomized, double-blinded studies in antiretroviral therapy-naive patients that established noninferiority of the drug compared with an efavirenz-based regimen. The trials were identical in design except for the components of the background regimens (tenofovir/emtricitabine in ECHO and variable in THRIVE). An undetectable viral load at 48 weeks was found in 85% of ECHO and 86% of THRIVE participants in the rilpivirine arms (83% and 82%, respectively, in the efavirenz groups).

Although these trials demonstrate efficacy, questions remain regarding for whom rilpivirine is best suited. Compared with efavirenz, rilpivirine had fewer central nervous system (CNS) adverse effects, rash, lipid abnormalities, and discontinuation rates. Additionally, rilpivirine is currently classified as pregnancy class B, whereas efavirenz is class D. In patients with a high plasma HIV RNA level (> 100,000 copies/mL), however, virologic failure occurred more commonly with rilpivirine than efavirenz (17% versus 7%, respectively). Resistance to rilpivirine (including the E138K mutation, also associated with etravirine resistance) largely excluded future use of the NNRTI class, whereas for those on efavirenz who developed NNRTI resistance (predominantly the K103N mutation), etravirine (and likely rilpivirine) often remained an option.

The data on tolerability and antiretroviral activity and resistance have led to rilpivirine being designated as an alternative NNRTI for treatment-naive patients in the recent Department of Health and Human Services (DHHS) treatment guidelines update. The guidelines specifically recommend caution in the use of the drug in patients with baseline plasma HIV RNA levels greater than 100,000 copies/mL. Of note, rilpivirine must be taken with a full meal and concomitant proton pump inhibitors are contraindicated. Finally, “switch” studies are under way evaluating a rilpivirine-containing regimen for patients currently virologically suppressed on regimens that contain ritonavir-boosted (r) protease inhibitors or efavirenz. In summary, rilpivirine is an efficacious NNRTI for treatment-naive patients, but has some limitations. Its long-term place amongst possible anchor drugs in initial regimens (ie, efavirenz, atazanavir/r, darunavir/r, or raltegravir) remains to be determined.

**Comparing nRTI Backbones**

Sax also discussed the final results of the AIDS Clinical Trials Group (ACTG) 5202 study. This was a US-based, prospective, randomized equivalence trial of 4 initial once-daily antiretroviral therapy regimens: dual nucleoside analogue reverse transcriptase inhibitor (nRTI) backbones abacavir/lamivudine or tenofovir/emtricitabine (blinded) with either efavirenz or atazanavir/r (open label). The trial enrolled 1858 persons and stratified patients based on high (≥ 100,000 copies/mL) or low (< 100,000 copies/mL) plasma HIV RNA level. Regarding efavirenz versus atazanavir/r, results published in February 2011 (a median 138 weeks of follow-up) show similar virologic efficacy. Regarding the comparison of nRTI backbones, an interim review in 2008 (a median 60 weeks of follow-up) led the data and safety monitoring board to recommend stopping the abacavir/lamivudine arm in the high viral load group because of statistically significant higher occurrences of virologic failures (14% versus 7%) than in the tenofovir/emtricitabine arm.

In October 2011, results from the study arm with lower initial HIV RNA level (< 100,000 copies/mL) were published and the time to virologic failure for abacavir/lamivudine versus tenofovir/emtricitabine was found to be similar in this subgroup of patients. These findings are in line with the DHHS guidelines, which recommend tenofovir/emtricitabine as the preferred dual-nRTI backbone and abacavir/lamivudine as the alternative choice to be used with caution in patients with greater than 100,000 HIV RNA copies/mL of plasma at baseline.

The search for an nRTI-sparing regimen continues to be evasive. The ACTG 5262 single-arm open-label study of 118 antiretroviral therapy-naive patients receiving twice-daily raltegravir plus once-daily darunavir/r reported that rates of virologic failure at 48 weeks were 26% overall, including 43% in those with more than 100,000 HIV RNA copies/mL. The reason for these high rates of virologic failure is not clear, and the study lacked a comparator arm. This regimen (raltegravir and darunavir/r) is being compared in a larger European study with a regimen of tenofovir/emtricitabine and darunavir/r.

**Update on HIV Primary Care**

**The Value of Triglyceride Treatment Scrutinized**

The proper management of elevated triglyceride levels in HIV-infected patients was discussed by Sax in the
HIV infection itself and antiretroviral drugs may negatively affect bone health, but traditional risk factors must not be forgotten. This was demonstrated in a large VA cohort study of 11,931 patients that compared fracture risk in HIV-infected and -uninfected patients. HIV infection itself was associated with an increased relative risk of fractures in the unadjusted comparison. However, the additional risk was negated after adjusting for traditional factors including certain demographics or comorbid diseases, smoking, alcohol abuse, and body mass index.

Regarding the effects of individual antiretroviral drugs on bone health, data were available from a substudy of ACTG 5202. In the prospective substudy, 259 persons were randomly assigned to 1 of 4 initial once-daily regimens: abacavir/lamivudine or tenofovir/emtricitabine (blinded) with either efavirenz or atazanavir/r (open label). Sequential bone density results were recorded with the primary outcome being hip and spine bone changes at week 96.

Although there was no difference in bone fractures between the groups, there was a general decrease in BMD in all groups. Similar to other studies, the decrease was similar in magnitude to that seen in the immediate postmenopausal years. Decreases in BMD were greater with tenofovir- than abacavir-containing regimens, and greater with atazanavir/r- than efavirenz containing regimens. The decrease occurred in the first 48 weeks of therapy, after which BMD plateaued.

An important cause of poor bone health is low vitamin D level, which is common in HIV-infected persons. Supplementation is recommended for those with a serum 25-hydroxyvitamin D level below 30 ng/mL. There is concern that vitamin D deficiency may have detrimental effects beyond those on bone health. An intriguing observational study found that severe vitamin D deficiency was independently associated with death and AIDS events. Ongoing investigations of bone health and vitamin D continue, including in ACTG 5280. This is a 48-week study in which efavirenz, with or without vitamin D and calcium supplementation, is compared with bone health as the primary outcome.

**Update on HIV/TB Coinfection: Initiating Antiretroviral Therapy at the Right Time**

Tuberculosis (TB) was excluded from the 2009 ACTG A5164 trial that showed a mortality benefit when antiretroviral therapy was initiated within 14 days of diagnosis of an opportunistic infection. Now, 3 trials investigating the optimal timing of antiretroviral therapy initiation in patients on TB therapy have been simultaneously published in the *New England Journal of Medicine*. The publication of these trials coincided with the first day of the IDSA 2011 meeting and was included in Currier’s presentation as one of the year’s most important findings. The 3 international trials randomly assigned patients on TB treatment to either early antiretroviral therapy initiation (mean 10-21 days after starting TB therapy) or late antiretroviral therapy initiation (mean 56-97 days after starting TB therapy).

The results of the trials showed a mortality benefit with early antiretroviral therapy initiation in those patients with severe immunosuppression (CD4+ cell count < 50/μL), but not in those with higher CD4+ cell counts. Additionally, there were more cases of immune reconstitution inflammatory syndrome (IRIS) in the early initiation group at all CD4+ cell counts. Hence, the conclusion is that for those with advanced AIDS (CD4+ cell count < 50 μL), it is beneficial to initiate antiretroviral therapy within 2 weeks of starting TB therapy. For those with higher baseline CD4+ cell counts (> 50/μL), it seems beneficial to wait until the beginning of the continuation phase (8 weeks from starting TB therapy) to initiate antiretroviral therapy. Dr Currier emphasized that most of the patients in these studies had pulmonary TB. Other forms of TB may behave differently.

Timing of antiretroviral therapy initiation in 253 Vietnamese patients...
with TB meningitis has recently been reported.\textsuperscript{30} The patients were largely young male injection drug users with advanced immunosuppression (mean CD4+ cell count, 41/µL). The study randomly assigned patients to early (7 days) versus late (2 months) antiretroviral therapy initiation. Death rates were high in both groups (greater than 50%) and no mortality benefit was shown in the early initiation group. Additionally, a higher rate of severe adverse events occurred in the early initiation group. Hence, the recommendation from this study is to initiate antiretroviral therapy in patients with TB meningitis after completion of 2 months of TB therapy.

**Update on HIV/HCV Coinfection: Good News Thus Far**

The approval in May 2011 of direct-acting antiviral drugs for chronic hepatitis C virus (HCV) infection was among the top innovations in medicine this year.\textsuperscript{31,32} The trials on which the drug approvals were based excluded subjects coinfected with HIV, but promising data for these patients are beginning to accumulate. Interim data from prospective trials of coinfectected patients receiving telaprevir or boceprevir were presented at this year’s Conference on Retroviruses and Opportunistic Infections (CROI) and IDSA meeting, respectively. These preliminary results showed a 68% early virologic response to a telaprevir-containing regimen at 12 weeks, compared with 14% on pegylated interferon alfa–ribavirin alone.\textsuperscript{33} The interim results of the boceprevir trial showed a 58% early virologic response at 12 weeks compared with a 25% response in those on pegylated interferon alfa–ribavirin alone (Abstract LB-37).\textsuperscript{34} The response rates are similar to those seen in HCV monoinfected patients.

The IDSA meeting featured an “HIV Challenges and Complications” session with expert discussion on many aspects of care for the HIV/HCV coinfected population. The topic of coinfection has also recently been reviewed.\textsuperscript{35} Important considerations for using the new HCV drugs in HIV-infected patients also on HIV therapy, including potential drug interactions and overlapping toxic effects, were highlighted.

Telaprevir is a cytochrome P450 5A4 and P-glycoprotein substrate and inhibitor. In the previously mentioned ongoing study of telaprevir in coinfectected patients, the participants were receiving tenofovir/emtricitabine/efavirenz or tenofovir/emtricitabine/atazanavir.\textsuperscript{r} The investigators increased the dose of telaprevir in the efavirenz group, and used standard telaprevir doses for those on the atazanavir\textsuperscript{r} regimen. The coadministration of the HCV and antiretroviral regimens was well tolerated. Another consideration for the clinician is that tenofovir concentrations can increase in patients using telaprevir and hence renal function should be monitored vigilantly.

In the ongoing boceprevir trial, coinfectected patients on efavirenz were excluded because of concerns about reduced drug levels of efavirenz. Participants were receiving a variety of ritonavir-boosted protease inhibitor regimens and neither the HCV nor HIV drug doses required adjustment. Numerous new medications for HCV infection are in various stages of development. Staying abreast of issues related to the treatment of HIV/HCV coinfectected patients will be of vital importance for providers in this rapidly evolving field.

**Summary**

In summary, the IDSA 2011 meeting provided a rich opportunity for clinicians to hear a review of the major findings of the previous year. Much investigation is ongoing, making the 2012 conference likely to be a similarly stimulating occasion. Next year, the conference will undergo much innovation and will have the new title, “ID Week.” This conference will be held from October 17 to 21, 2012, in San Diego, CA, and will be a joint meeting of IDSA, the Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS).

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**References**

* Indicates an IDSA 2011 conference abstract.

13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for