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Correspondence

Topics in Antiviral Medicine welcomes editorial correspondence. Address correspondence to:

Editor, Topics in Antiviral Medicine
E-mail: journal@iasusa.org

IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

Phone: (415) 544-9400
Fax: (415) 544-9401
Website: http://www.iasusa.org

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On completion of this activity, participants will be able to:

- Describe the efficacy and safety of preexposure prophylaxis (PrEP) for HIV prevention and emerging PrEP modalities
- List methods for predicting cardiovascular disease (CVD) risk as well as complications of CVD in the context HIV infection
- Describe hot topics and emerging data in HIV research, prevention, and care

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV infection.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)-based regimens has been shown to be effective in preventing acquisition of HIV infection, with protective efficacy being dependent on adherence to treatment. Data from the PROUD (Preexposure Option for Reducing HIV in the UK) and IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) studies, the latter of which employed event-driven PrEP, showed a high rate of protective efficacy of PrEP with TDF and emtricitabine among men who have sex with men. Data from the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) study of a dapivirine vaginal ring showed a moderate rate of protective efficacy among women older than 21 years. Ongoing investigations are examining long-acting PrEP modalities and combination PrEP and contraception products. This article summarizes a presentation by Jeanne M. Marrazzo, MD, MPH, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Washington, DC, in April 2016.

**Keywords:** Adherence, dapivirine, emtricitabine, HIV, post-exposure prophylaxis, preexposure prophylaxis, PEP, PrEP, tenofovir disoproxil fumarate, tenofovir, dapivirine vaginal ring

### Efficacy and Safety of Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) is an integral part of HIV prevention. In numerous clinical trials of biomedical antiretroviral therapy–based HIV prevention, efficacy has ranged from 0% to greater than 80%. Until recently, nearly all of these studies have involved tenofovir disoproxil fumarate (TDF)-based PrEP regimens, and efficacy estimates appear to correlate very highly with adherence to these regimens.

Overall, HIV protective efficacy was 67% with TDF and 75% with TDF/emtricitabine (slash indicates a coformulation) in the Partners PrEP study, 62% in the TDF2 study, and 44% in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, while no efficacy was seen in the FEM-PrEP (Study to Assess the Role of Tenofovir/Emtricitabine in Preventing HIV Acquisition in Women) and VOICE (Vaginal and Oral Interventions to Control the Epidemic) studies; in each of these 5 studies, tenofovir was detected in 81%, 79%, 51%, 26%, and 28% of participants’ plasma, respectively.

These studies demonstrated that PrEP is highly effective with appropriate adherence, and the protective effect appears to be enduring. As an extension to the Partners PrEP study, PrEP and antiretroviral therapy were offered to high-risk HIV-serodiscordant couples. HIV-uninfected partners took daily oral TDF/emtricitabine as PrEP and continued the regimen for 6 months after their HIV-infected partners initiated antiretroviral therapy. At interim analysis, more than 95% of HIV-uninfected partners were using PrEP and 80% of HIV-infected partners had initiated antiretroviral therapy, of which more than 90% achieved viral suppression. Overall, there was a 96% reduction in expected HIV infections (39.7 expected infections vs 5.2 incidence per 100 person-years). In cases of HIV transmission, plasma tenofovir concentrations were undetectable at the time of seroconversion.

Available information continues to support the safety of TDF-based PrEP. Incidences of death, serious adverse events, and laboratory abnormalities (including renal dysfunction) are low and not statistically significantly different between persons who receive PrEP and those who receive a placebo. PrEP is well tolerated, and gastrointestinal adverse effects (eg, nausea which occurred in <10% overall and primarily during the first month of treatment) were more common among persons who received PrEP than those who received a placebo. PrEP is also safe during pregnancy and is not associated with any reductions in contraceptive efficacy.

As expected based on experience with TDF-based HIV treatment, bone mineral density (BMD) decreases over time in persons taking TDF/emtricitabine as PrEP. In the iPrEx trial, a 0.91% decrease in spine BMD (P = .001) and a 0.61% decrease in total hip BMD (P = .001) were observed at week 24 in individuals who received PrEP compared with those who received a placebo. No difference in fracture rate was observed between groups. Six months after discontinuation of treatment and by the start of the open-label extension of the trial, recovery of BMD in both hip and spine was evident, and BMD recovery continued through approximately 1.4 years after discontinuation of TDF/emtricitabine. Recovery of BMD was better in individuals younger than 25 years.

Acquired resistance to PrEP is rare, occurring in approximately 5% of individuals; approximately 12 HIV infections are averted for each case of resistance to PrEP. Resistance is usually due to the emergence of the K65R mutation after exposure to TDF or the M184V mutation after exposure to emtricitabine. However, there has been at least 1 reported case of an individual who acquired multidrug-resistant HIV infection after 2 years of daily PrEP with TDF/emtricitabine. This individual’s pharmacy records, plasma HIV RNA level, and clinical history indicated recent and long-term adherence to PrEP, and multidrug-resistant virus was likely transmitted rather than induced through prolonged exposure to tenofovir.

### Real-World Issues: PrEP and PEP

Timely initiation of PrEP represents a balance between providing protection for periods of high risk for HIV infection and...
ensuring that HIV infection has not already been established. For an individual who has initiated postexposure prophylaxis (PEP) after a high-risk exposure to HIV, continuation of PrEP depends on assessment of the person’s anticipated risk of HIV acquisition going forward. If an individual is considered to be at high risk for HIV infection, there may be an immediate transition from PEP to PrEP. In 2015, the World Health Organization provided guidance indicating that individuals can transition from taking PEP to PrEP after 28 days even if there is substantial continuing risk.12

### More Recent PrEP Studies: Real-World Effects

The PROUD (Preexposure Option for Reducing HIV in the UK) and IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) studies yielded the highest estimates thus far on the protective efficacy of PrEP. Neither study was placebo controlled; thus, participants knew the efficacy of PrEP that had been derived from the clinical trials discussed above and may have been more likely to use it based on that knowledge.

In the PROUD study, HIV-uninfected men who have sex with men (MSM) from 13 clinics in London, England, were randomly assigned to receive TDF/emtricitabine as PrEP immediately (n = 267) or to defer PrEP for 12 months (n = 256). At 60 weeks, HIV infection had occurred in 3 persons in the group that received immediate PrEP and in 19 persons in the group that received deferred PrEP. In the immediate PrEP group, there was an 86% reduction in risk (P = 0.0002), and the number needed to treat to prevent 1 HIV infection was 13.13 The data safety and monitoring board interrupted the trial and recommended that all participants be offered PrEP.

In the IPERGAY trial, HIV-uninfected MSM were randomly assigned to receive event-driven, on-demand PrEP with TDF/emtricitabine (n = 199) or a placebo (n = 201), with the event-driven design intended to replicate “real-world” scenarios. In the event-driven PrEP group, participants took 2 tablets 2 to 24 hours before sex, 1 tablet 24 hours after sex, and 1 tablet 48 hours after the first event-driven dose.14 Event-driven PrEP was associated with an 86% reduction in risk of HIV acquisition (P = .002), and the number needed to treat to prevent 1 HIV infection was 18. A median of 16 pills were taken by each participant each month in both groups, indicating a high degree of coverage of high-risk sexual acts.

These data indicate that PrEP can successfully prevent HIV acquisition in real-world settings. Additional data from Kaiser Permanente San Francisco, a large managed care organization, indicated that no new HIV infections occurred among more than 600 persons who initiated PrEP during the first year it was offered.15 Among individuals taking PrEP, 56% reported no change in condom use, 41% reported a decrease in condom use, and 3% reported an increase in condom use. After 12 months of PrEP, with a 0% incidence of HIV infection, there was a 50% incidence of any sexually transmitted infection (STI), including a 33% incidence of rectal STIs, a 33% incidence of chlamydia, a 28% incidence of gonorrhea, and a 5.5% incidence of syphilis. Based on the incidence of these STIs, the expected incidence of HIV infection would have been 8.9%—a testament to the high efficacy of TDF/emtricitabine as PrEP when the rectal mucosa is the target site of acquisition, largely owing to the high concentrations of TDF/emtricitabine that are achieved in the rectal compartment. Unfortunately, the situation differs in the cervicovaginal environment, which does not achieve protective concentrations of TDF/emtricitabine without very high adherence.16

### Beyond Oral PrEP?

Because stabilization of the HIV epidemic is likely attainable with a combination of antiretroviral therapy for treatment and PrEP for prevention, sustained delivery systems for PrEP are advancing in development, including use of drugs other than nucleoside analogue reverse transcriptase inhibitors, such as the nonnucleoside analogue reverse transcriptase inhibitor rilpivirine and the investigational integrase strand transfer inhibitor cabotegravir. Further, low rates of adherence to PrEP in some clinical trials suggest limited marketability and uptake for some nonoral formulations (eg, the tenofovir gel studied in the VOICE and Follow-on African Consortium for Tenofovir Studies [FACTS] 001 trials). However, many argue that other modalities should continue to be explored, as they may serve as a bridge to a crucial threshold of antiretroviral therapy and PrEP coverage that has yet to be achieved globally. Moreover, on-demand protection may be important to round out the PrEP portfolio, as not all individuals may have the opportunity to adequately premedicate for optimal protection—particularly women, given the pharmacokinetics of TDF-based delivery to the cervicovaginal environment. Other PrEP modalities would expand choices for personalized protection, could help individuals achieve goals of low or minimal systemic absorption and low systemic toxicity, and could offer the possibility of multipurpose prevention (eg, concomitant protection against herpes simplex virus or other STIs, and contraception).

Two trials have examined the use of a dapivirine-containing vaginal ring versus a placebo for preventing HIV infection in sexually active HIV-uninfected women in sub-Saharan Africa: the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) study and the Ring Study. The active product was a silicone elastomer vaginal matrix ring containing dapivirine 25 mg, which was inserted once every 4 weeks.17 In the ASPIRE analysis, which excluded data from 2 sites with low adherence rates, HIV infection occurred in 54 women in the group that received dapivirine compared with 85 women in the group that received a placebo, yielding HIV incidences of 2.8 per 100 person-years and 4.4 per 100 person-years, respectively, and a 37% rate of protective efficacy (P = .007). The Ring Study had similar findings; HIV incidence in the group that received dapivirine was 31% lower than in the group that received a placebo (hazard ratio, 0.69; 95% CI, 0.49-0.99).

The ASPIRE investigators further examined the disparity in efficacy by participant age (Figure). Rates of protective efficacy were less than 27% among women aged 18 to 21.
years (incidence with placebo, 5.4% per year), 56% among those aged 22 to 26 years (incidence with placebo, 6.1% per year), and 51% among those aged 27 to 45 years (incidence with placebo, 3.0% per year). Overall, protective efficacy was 56% ($P = .001$) in women older than 21 years. Although adherence was likely different across these age groups, other factors such as differential rates of STI acquisition are under investigation.

Long-acting formulations of PrEP are an active area of study. The phase IIa ÉCLAIR (Study to Evaluate the Safety, Tolerability, and Acceptability of Long-Acting Injections of the HIV Integrase Inhibitor GS1265744 in HIV Uninfected Men) study enrolled HIV-uninfected adult men at low risk of HIV infection who were then randomly assigned to receive cabotegravir 50 mg per day orally during a “loading phase” followed by a long-acting formulation of cabotegravir 800 mg intramuscularly every 12 weeks ($n = 106$) or a placebo ($n = 21$). The primary end points of the study were safety and tolerability. Study results showed that peak concentrations of long-acting cabotegravir were higher and trough concentrations were lower than predicted owing to more rapid than anticipated drug absorption and clearance after intramuscular injection; approximately 70% of individuals had trough concentrations lower than the target of 4 times the protein-binding adjusted 90% inhibitory concentration. Injection site reactions occurred in 92% of individuals who received cabotegravir and in 56% of individuals who received a placebo, and 4 individuals who withdrew consent noted injection tolerability as a reason. The HIV Prevention Trials Network 083 and 084 clinical trials will study a long-acting formulation of cabotegravir given every 8 weeks. HPTN 083 was recently launched among MSM and transgender women, and HPTN 084 will involve women.

The phase II NEXT-PrEP (Novel Exploration of Therapeutics for Pre-Exposure Prophylaxis) study examined the effect of the entry inhibitor maraviroc on HIV-uninfected men who engaged in condomless anal intercourse with at least 1 HIV-infected man or a man whose HIV serostatus was unknown in the past 90 days. A total of 406 participants were randomly assigned to receive maraviroc 300 mg ($n = 101$), maraviroc 300 mg plus a standard dose of emtricitabine ($n = 106$), maraviroc 300 mg plus a standard dose of TDF ($n = 99$), or emtricitabine plus a standard dose of TDF ($n = 100$). The incidence of grade 3 or 4 adverse events ($n = 67$), rates of discontinuation of study drug (total, 9%), and time to discontinuation were similar across groups. Five new HIV infections were reported (annual incidence, 1.4%; 4 new infections in the group that received maraviroc alone and 1 in the group that received maraviroc plus TDF), and the low incidence precluded any efficacy analysis. No transmitted drug resistance was found in cases of HIV infection.

Among other PrEP modalities in development are contraceptive vaginal rings containing sustained-release antiretroviral drugs, including a 30-day vaginal ring containing the investigational nonnucleoside analogue reverse transcriptase inhibitor MIV-150 plus zinc acetate plus levonorgestrel, a 60-day vaginal ring containing dapivirine plus levonorgestrel, and a 90-day vaginal ring containing tenofovir plus levonorgestrel. The Global Advocacy for HIV Prevention (AVAC) website provides detailed information on antiretroviral-based prevention in development.

**Conclusion**

When taken consistently, PrEP is an effective tool for preventing sexual HIV transmission. However, data on PrEP for women are still limited. Additional options for PrEP, including
long-acting antiretroviral protection and combination options (eg, antiretroviral agents combined with hormonal contraceptives) are expected to be available in the near future.


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References
Perspective
Cardiovascular Complications of HIV Infection

HIV-infected individuals are at increased risk for cardiovascular events. Widely used cardiovascular disease (CVD) risk calculators to determine indications for statin treatment are not well validated for use in the HIV-infected population. Some experts advocate including HIV infection as an independent risk factor for CVD. The effects of antiretroviral therapy on lipid profiles and the potentially increased risk for cardiovascular events must be taken into account when selecting treatment for HIV-infected individuals. There is increasing evidence that chronic immune activation and inflammation play a role in the pathogenesis of CVD in the context of HIV infection. This article summarizes a presentation by Marshall J. Glesby, MD, PhD, at the Ryan White HIV/AIDS Program Clinical Care Conference held in New Orleans, Louisiana, in December 2015.

Keywords: HIV, cardiovascular disease risk, CVD, antiretroviral therapy, statins, immune activation, inflammation

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in persons with HIV infection. Meta-analyses suggest that CVD risk is increased by approximately 1.5 to 2.0 fold among HIV-infected individuals compared with the general population. Data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study indicate that CVD accounts for approximately 11% of deaths among HIV-infected individuals, and data from the EuroSIDA study indicate that cardiovascular events account for approximately one-third of non-AIDS-defining clinical events in the HIV-infected population.

CVD Risk Prediction

A number of CVD risk calculators are available, although the most commonly used have generally not been validated for use in HIV-infected individuals. CVD risk calculators include the American Heart Association (AHA)/American College of Cardiology (ACC) 2013 pooled cohort risk calculator, the Framingham Risk Score, and the D:A:D 5-Year Estimated CVD Risk Equation, which is specific for HIV infection, but has not been validated for use outside of the dataset from which it was derived.

Management of Dyslipidemia

High- and moderate-intensity statin therapy, based on 10-year risk for first atherosclerotic cardiovascular event, using the AHA/ACC 2013 pooled cohort risk calculator are shown in Table 1. The National Lipid Association suggests that lipid goals be based on the number of risk factors present (Table 2), and has indicated that HIV infection status may be counted as a risk factor. However, the effect of antiretroviral therapy on lipids should also be considered in the context of HIV infection.

Numerous studies have shown that lipid effects vary by antiretroviral regimen. In the SWITCH-ER randomized, double-blinded, crossover study of 57 individuals receiving raltegravir or efavirenz for 2 weeks and were then switched to the opposite treatment for 2 weeks. During the 2 weeks of treatment with raltegravir, there were median reductions of 16 mg/dL in total cholesterol level (P < .001), 18 mg/dL in triglyceride level (P = .036), 8 mg/dL in LDL-C level (P = .004), and 4 mg/dL in HDL-C level (P = .005), with a 0.1 reduction in LDL-C:HDLC ratio (P = .97). Efavirenz has been shown to increase HDL-C level, whereas a decrease in HDL-C level was observed after switching to raltegravir, contributing to the lack of substantial change in LDL-C:HDLC ratio.

In the SINGLE trial of approximately 90 participants who received a regimen of abacavir/lamivudine (slash indicates a coformulation) plus dolutegravir or of tenofovir disoproxil fumarate (TDF)/emtricitabine/efavirenz, increases of 17.1 and 24.0 mg/dL, respectively, were observed in total cholesterol level; 5.2 and 7.9 mg/dL, respectively, in HDL-C level; 8.5 and 13.1 mg/dL, respectively, in LDL-C level; and 17.7 and 18.6 mg/dL, respectively, in triglyceride level, indicating greater increases in levels of atherogenic lipids as well as HDL-C in the group receiving efavirenz.

Table 1. Recommendations for High- and Moderate-Intensity Statin Therapy Based on 10-Year Risk for First ASCVD Event

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by ≥50% on Average)</th>
<th>Moderate-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by 30%-50% on Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; XL, extended release. Data compiled from the American Heart Association and the American College of Cardiology. Adults aged 40 to 75 years with an LDL-C level of 70 to 189 mg/dL, no diabetes, and an estimated 10-year ASCVD risk of 7.5% or higher should be treated with moderate- or high-intensity statin therapy.

Dr Glesby is Professor of Medicine and Healthcare Policy and Research, Associate Chief of the Division of Infectious Diseases, and Director of the Cornell HIV Clinical Trials Unit at Weill Cornell Medicine, in New York, New York. He is the Regional Clinical Director of the Northeast-Caribbean AIDS Education and Training Center.
Table 2. National Lipid Association Criteria for ASCVD Risk Assessment, Treatment Goals, and Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goala</th>
<th>Consider Drug Therapya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤1 Major ASCVD risk factor</td>
<td>non–HDL-C &lt;130 mg/dL, LDL-C &lt;100 mg/dL</td>
<td>non–HDL-C ≥190 mg/dL, LDL-C ≥160 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators, if knownb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>≥2 Major ASCVD risk factors</td>
<td>non–HDL-C &lt;130 mg/dL, LDL-C &lt;100 mg/dL</td>
<td>non–HDL-C ≥130 mg/dL, LDL-C ≥100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CKD stage 3B or 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥190 mg/dL (severe hypercholesterolemia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>ASCVD</td>
<td>non–HDL-C &lt;100 mg/dL, LDL-C &lt;70 mg/dL</td>
<td>non–HDL-C ≥100 mg/dL, LDL-C ≥70 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–1 Other major ASCVD risk factors and no evidence of end-organ damage</td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
| Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Adapted from Jacobson et al.†,‡  
*Non–HDL-C cholesterol is total cholesterol minus HDL-C.  
†HIV infection may be counted as an ASCVD risk factor.

Results from the AIDS Clinical Trials Group (ACTG) A5206 study support observations that TDF appears to reduce levels of atherogenic lipids via a mechanism that remains unclear. In the crossover study, 17 virologically suppressed participants on non–TDF-containing regimens who had some degree of dyslipidemia—defined as elevated triglyceride or non–HDL-C (total cholesterol minus HDL-C) levels—were randomly assigned to add TDF or a placebo to their existing regimen and then to receive a placebo or TDF after a washout period. During treatment with TDF compared with placebo, there were significant reductions in levels of total cholesterol (18% vs 4%; P = .01), non–HDL-C (16% vs 2%; P = .02), and LDL-C (12% vs 5%; P = .04), and nonsignificant differences in levels of HDL-C (an 8% decrease vs a 4% increase; P = .95) and triglycerides (a 4% decrease vs a 14% decrease; P = .81).

Studies comparing lipid changes during treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) and treatment with elvitegravir/cobicistat/emtricitabine/TDF indicate that increases in levels of total cholesterol, LDL-C, HDL-C, and triglycerides were statistically significantly lower with the TAF-containing than the TDF-containing regimen over 48 weeks, possibly reflecting the lower plasma concentrations of tenofovir associated with TAF use. However, there was no statistically significant difference in change in total cholesterol:HDL-C ratio.9

Questions remain regarding the association between abacavir and MI risk, but it may be reasonable to avoid use of abacavir for some individuals at high risk for cardiovascular events. There has been some concern that any increased risk for MI associated with abacavir use reflected a channeling bias in earlier observational studies10–12 in which participants at increased risk of nephrotoxic effects who might also have increased concurrent CVD risk factors were more likely to be given abacavir. However, a recent update from the D:A:D cohort indicates an approximately 2-fold increased risk of MI with current abacavir use (use within the past 6 months) after adjustment for time period and other CVD risk factors, with a rate of 0.47 per 100 person-years with current abacavir use versus 0.21 per 100 person-years with no abacavir use (relative risk, 1.98).13

A recent analysis of data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a collaboration of 6 clinical cohorts throughout North America, yielded somewhat different information. As shown in Figure 1, analysis of the full study population, including all patients on antiretroviral therapy that did not include abacavir at study entry, showed a nonstatistically significant increase in risk for MI with abacavir use.14 A replication of the D:A:D analysis adjusted for various risk factors showed a statistically significantly increased hazard ratio (HR) of approximately 1.7, although the HR was not statistically different after adjustment for additional risk factors not used in the initial D:A:D analysis. An analysis that included antiretroviral treatment–naïve persons who initiated treatment showed a statistically significantly increased HR for MI risk associated with abacavir use (which was not necessarily used in the initial regimen), after adjustment for numerous risk factors. These data have yet to be published in full.

The US Food and Drug Administration and an independent group performed a systematic review and meta-analysis that included 26 controlled trials in which patients were randomly assigned to receive abacavir, which ideally eliminates channeling bias. As shown in Figure 2, the meta-analysis found no substantial increase in risk for MI associated with abacavir use in academic center, National Institutes of Health (NIH) ACTG, or manufacturer trials, or all trials combined.15 However, the studies were generally not of long duration and the absolute number of events was relatively low.

Although a summary of all of the observational studies examining CVD risk in association with abacavir use is beyond
the scope of this article, the data are mixed, and there may never be a definitive answer to this question. Nonetheless, numerous observational studies with their inherent biases suggest that abacavir may contribute to MI risk, leading many experts to avoid its use in individuals with substantial CVD risk.

The Emerging Role of Inflammation

Unstable plaque in coronary arteries is more prone to rupture and to result in cardiovascular events than stable plaque. One study used multidetector spiral coronary computed tomography angiography among 41 HIV-infected and 101 uninfected individuals with a median age of 45 to 48 years matched for major CVD risk factors. HIV-infected individuals were significantly more likely to have high-risk plaques, including low-attenuation plaque (P = .02), which was more likely to be associated with the macrophage activation marker soluble (s)CD163.16 However, it does not appear that widely used CVD risk calculators identify individuals with high-risk morphologic features. In a study of 150 HIV-infected participants, the 2013 ACC/AHA risk calculator indicated that statin treatment was recommended for only approximately 25% of those with high-risk plaques, and the 2004 Adult Treatment Panel III cholesterol guidelines recommended treatment for only approximately 10% of those with high-risk plaques (Figure 3).17

An early indication of the potential effects of inflammation on CVD came from findings in the SMART (Strategies for Management of Anti-Retroviral Therapy) trial, in which more than 5000 participants were randomly assigned to receive continuous antiretroviral therapy or to discontinue antiretroviral therapy (drug-conservation arm) when CD4+ cell count exceeded 350/µL and then resume therapy when it fell below 250/µL.18 The study was ended early due to excess mortality and clinical events in the drug-conservation arm, including a 50% increase in cardiovascular events compared with the arm receiving continuous treatment. One analysis of participants from the drug-conservation arm showed an association between both the degree of increase of the inflammatory marker soluble interleukin-6 and the degree of decrease of HDL particle number with the magnitude of increase in HIV viral load at 1 month after interruption of antiretroviral therapy.19 Such findings suggest that increased inflammation with accompanying viremia might contribute to an increased risk for cardiovascular events.

Figure 4 illustrates the potential roles of chronic immune activation and inflammation in the pathogenesis of CVD in the context of HIV infection. Acute HIV infection results in a massive depletion of CD4+ cells throughout the gastrointestinal tract, which permits microbial translocation through the gut into the circulation, and this translocation may drive immune activation and inflammation. Other potential contributors to ongoing inflammation include low-level HIV replication during antiretroviral therapy and viral co-infection, particularly with cytomegalovirus, hepatitis B virus, or hepatitis C virus.

In a study that assessed inflammation of the arterial wall using positron emission tomography and computed tomography scans to measure uptake of tracer in metabolically active macrophages that infiltrated affected vessels, greater inflammation (measured as target-to-background ratio) was found among 27 HIV-infected participants with a mean age of 52 years than among 27 uninfected individuals with matched Framingham Risk scores and a mean age of 54 years;
inflammation in the HIV-infected group was comparable to that in the 27 uninfected individuals with established atherosclerotic CVD and a mean age of 69 years. The sCD163 marker of macrophage activation was significantly correlated with target-to-background ratio in HIV-infected individuals ($P = .03$). Such findings support the potential role of inflammation in CVD risk in the context of HIV infection.

In a study that assessed whether statin therapy might have a beneficial effect on inflammation, 40 HIV-infected individuals with subclinical coronary atherosclerosis and aortic inflammation (detected by positron emission tomography [PET] imaging) and LDL-C levels below 130 mg/dL were randomly assigned to receive atorvastatin 20 mg with dose escalation to 40 mg or placebo for 12 months. Treatment with atorvastatin did not substantially affect arterial inflammation, although data were not available for 19 participants. However, treatment with atorvastatin did reduce noncalcified plaque volume and other high-risk plaque features.

The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial is currently underway to examine the efficacy of pitavastatin in preventing cardiovascular events in asymptomatic HIV-infected individuals with no history of CVD (Figure 5). Eligible participants have an estimated 10-year risk for cardiovascular events of less than 7.5% and an LDL-C level of less than 190 mg/dL, an estimated risk of 7.5% to 10.0% and an LDL-C level of less than 160 mg/dL, or an estimated risk of 10.0% to 15.0% and an LDL-C level of less than 130 mg/dL. A target population of 6500 individuals aged 40 to 75 years are being randomly assigned to receive pitavastatin 4 mg daily or placebo, with a planned 6-year follow-up period (https://clinicaltrials.gov, NCT02344290). The composite primary end point in the REPRIEVE trial is CVD-related death, MI, unstable angina, stroke, and arterial revascularization. A mechanistic substudy is examining the effects of pitavastatin on coronary plaque, vascular inflammation, and immune activation among 800 participants.

Pitavastatin is a newer statin not thought to have interactions with antiretroviral drugs and thus far not associated with increased risk for diabetes. In a randomized trial of approximately 200 HIV-infected individuals, pitavastatin reduced total cholesterol and LDL-C levels substantially more than did pravastatin 40 mg over 12 months, without significant differences between arms in HDL-C and triglyceride levels.
With regard to CVD risk, the most important risk factor to address is smoking status. Although somewhat controversial, data from a Danish study indicated that 5 of 4 MIs among people with HIV infection were associated with ever having smoked compared with 1 of 4 MIs among matched uninfected controls. Data from the D:A:D cohort indicate that the risk of MI is lower among persons who have stopped smoking than those who currently smoke (incidence rate ratio, relative to those who never smoked, decreased from 3.73 to 3.00 within the first year after smoking cessation and to 2.07 after ≥5 years). 24

**Conclusions**

CVD risk stratification tools for the general population are generally not validated for use in the HIV-infected population. It is reasonable to use the Framingham Risk score or AHA/ACC pooled cohort risk calculator for HIV-infected individuals and to consider HIV infection a risk factor, as suggested by the National Lipid Association. Inflammation and immune activation are likely important contributors to atherosclerosis, although much remains to be learned about its pathogenesis in HIV-infected individuals. Whether statins are indicated more broadly in the HIV-infected population remains unclear, and data from the REPRIEVE trial may help to address this question.

**References**

**Special Contribution**

**2017 Update of the Drug Resistance Mutations in HIV-1**

Annemarie M. Wensing, MD, PhD; Vincent Calvez, MD, PhD; Huldrych F. Günthard, MD; Victoria A. Johnson, MD; Roger Paredes, MD, PhD; Deenan Pillay, MD, PhD; Robert W. Shafer, MD; Douglas D. Richman, MD

The 2017 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2015. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The figures are designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs and, therefore, in making clinical decisions regarding antiretroviral therapy.

The 2017 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2015. The Q148K mutation was added to the bar for the integrase strand transfer inhibitor dolutegravir, and the bars for multi-nucleoside and nucleotide analogue reverse transcriptase inhibitor (nRTI) resistance were modified to indicate specifically that thymidine analogue mutations do not affect susceptibility to emtricitabine and lamivudine.

**Methods**

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on drug resistance–associated mutations for HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV-1. This list includes mutations that may contribute to a reduced virologic response to a drug.

In addition, the group considers only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration as well as any drugs available in expanded access programs are included (listed in alphabetic order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Positions in bold generally indicate that particular caution is warranted with use of a drug. For nucleoside and nucleotide reverse transcriptase inhibitors, bold mutations indicate signature mutations selected for by particular drugs that may, alone or in combination with other mutations, result in a substantial reduction in drug susceptibility and clinical outcome. For nonnucleoside reverse transcriptase inhibitors, bold mutations indicate a substantial reduction in drug susceptibility or clinical outcome and that particular drugs should be avoided if possible. For protease inhibitors, mutations at bolded positions are associated with greater reductions in drug susceptibility and virologic responses to therapy. Certain protease inhibitors, particularly ritonavir-boosted darunavir, have high genetic barriers to resistance and may still retain considerable activity despite the presence of a mutation at a bolded position. For the entry inhibitor enfuvirtide, bold mutations may indicate a significant reduction in drug susceptibility or clinical outcome and that use of the drug should be avoided if possible. For integrase strand transfer inhibitors, bold mutations indicate a substantial reduction in drug susceptibility or clinical outcome for elvitegravir and raltegravir, and these drugs should be avoided if possible. Dolutegravir may still retain considerable activity in the presence of bolded mutations if twice-daily dosing is applied.

**Identification of Mutations**

The mutations listed are those that have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) association studies between genotype at baseline and virologic response in patients exposed to the drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in otherwise wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.
Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient’s antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance emerges most commonly to lamivudine or emtricitabine or nonnucleoside analogue reverse transcriptase inhibitors).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing and 2016 IAS–USA panel recommendations for antiretroviral therapy. Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to journal“at”iasusa.org or by fax to 415-544-9401.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and no alterations in format or content can be made.

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which you wish to reprint the material, the funding organization(s), if applicable, and the intended audience. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of the adaptation(s) and, if possible, a copy of the proposed adaptation. To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted.

Permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted at www.iasusa.org. Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact IAS–USA.

Financial affiliations in the past 12 months: The authors (listed alphabetically) disclose the following affiliations with commercial organizations that may have interests related to the content of this article: Dr Calvez has served as an advisor or consultant to and has received research grants from Bristol-Myers Squibb, Gilead Sciences, Inc, Johnson and Johnson, and Viiv Healthcare, and is a founder of SkinDermic Pharma. Dr Günthard has received grants from Gilead Sciences, Inc, has served on a data and safety monitoring board for Merck & Co, Inc, and on a consulting or advisory board for Gilead Sciences, Inc, has received travel support from Bristol-Myers Squibb, Gilead Sciences, Inc, and Janssen Therapeutics. Dr Johnson has no relevant financial affiliations to disclose. Dr Paredes has received research grants from Viiv Healthcare, and Merck, Sharp, and Dohme. Dr Pillay has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Antiva Biosciences, Chimerix, Gilead Sciences, Inc, and Monogram Biosciences, Inc. Dr Shafer has served as a consultant or advisor for Viiv Healthcare and has received grants from Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, and Vela Diagnostics. Dr Wensing has served on advisory boards for CJ&J Worldwide, Gilead Sciences, Inc, and Viiv Healthcare; has participated in the Dutch HIV Masterclass organized by Virology Education; has received travel support from Virology Education; and has received grants from Janssen Pharmaceuticals, Gilead Sciences, Inc, and Viiv Healthcare.

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References

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)

69 Insertion Complex (affects all nRTIs currently approved by the US FDA)

151 Complex (affects all nRTIs currently approved by the US FDA except tenofovir)

Thymidine Analogue-Associated Mutations (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.
### MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
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<tr>
<td>Atazanavir +/− ritonavir</td>
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<tr>
<td></td>
<td>M G I F</td>
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<tr>
<td></td>
<td>V M L Y</td>
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<td>C T V V</td>
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<tr>
<td>Darunavir/ritonavir</td>
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<td>M G I F</td>
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<td>Darunavir/ritonavir</td>
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<td>C T V V</td>
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<tr>
<td>Fosamprenavir/ritonavir</td>
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<td>C T V V</td>
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<td>Indinavir/ritonavir</td>
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### MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

<table>
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<tr>
<td>Enfuvirtide</td>
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<td></td>
<td>D V A R H T D</td>
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<td>S M E</td>
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<td>Maraviroc</td>
<td>See User Note</td>
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### MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS

<table>
<thead>
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<th>Integrase Strand Transfer Inhibitor</th>
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<tr>
<td>Dolutegravir</td>
<td>F E G Q N R</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>T E T E S Q N R</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>L E T E F E G Y Q N R</td>
</tr>
</tbody>
</table>
Data are lacking on the potential negative impact of IAS–USA.

The presence of K65R is associated with a reduced virologic response to tenofovir. A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W. The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.

There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.

Resistance to etravirine has been extensively studied only in the context of coadministration with ritonavir-boosted darunavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of effect) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.

The single mutations L100I, K101P, and Y181C/I, H221Y, F227C, and M230I/L reduce susceptibility 6 fold. A 16th mutation, Y188L, reduces susceptibility 2 fold. The combinations of reverse transcriptase–associated mutations L100I plus K101P or L100I plus Y181C/I reduce susceptibility approximately 50 fold and 15 fold, respectively, but are not commonly observed in patients receiving rilpivirine.

Mutations at position 158 (most notably 158A) may occur as natural polymorphisms, especially in non-B subtypes. Each of which reduces rilpivirine susceptibility 2.5 fold to 3 fold, occur commonly in patients receiving rilpivirine. E153K and to a lesser extent K101E usually occur in combination with the nRTI resistance–associated mutation M184I, which alone does not reduce rilpivirine susceptibility. When M184I is combined with E153K or K101E, rilpivirine susceptibility is reduced about 7 fold and 4.5 fold, respectively. The combinations of reverse transcriptase–associated mutations L100I plus K103N/S and L100I plus K103R plus V179D were strongly associated with reduced susceptibility to rilpivirine. However, for isolates harboring the K103N/R/S or V179D as single mutations, no reduction in susceptibility was detected.

Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI). In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

Resistance mutations in the protease gene are classified as “major” or “minor.” Major mutations in the protease gene (positions in bold type) are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. These mutations tend to be the primary contact residues for drug binding and may also be associated with reductions in virologic responses to therapy. Minor mutations generally emerge later than major mutations and by themselves do not have a substantial effect on phenotype. They may improve replication of viruses containing major mutations. So minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades. Mutations in gag cleavage sites may delay or prevent emergence of TAMs. This effect may be overcome by an accumulation of TAMs or other mutations.

K65R is selected frequently (4%–11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.

K65R mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo. When associated with TAMs, M184V increases abacavir resistance.

Mutations known to be selected by TAMs (ie, M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) also confer reduced susceptibility to all nRTIs currently approved by the US Food and Drug Administration (FDA) when present with 1 or more TAMs at codons 41, 210, or 215. Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI susceptibility. Patient-derived viruses with K65E and site-directed mutations replicate very poorly in vitro; as such, no susceptibility testing can be performed.

Although reverse transcriptase changes associated with the E44D and V118I mutations may lead to viral hy-
confer resistance to all PIs and may emerge before mutations in protease. A large proportion of virus samples from patients with confirmed virologic failure on a PI-containing regimen is not found to have PI resistance–associated mutations. Preliminary data from recent studies suggest that several mutations in the Gag protein\(^a\) may be responsible for reduced PI susceptibility in a subset of these patients.

r. Ritonavir is not listed separately, as it is currently used only at low doses as a pharmacologic booster of other PIs.

s. Many mutations are associated with atazanavir resistance. Their impacts differ, with 150I, 184V, and 885S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I plus L76V might increase susceptibility to atazanavir when no other related mutations are present.\(^b\)

t. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI resistance–associated mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. The negative impact of the protease mutations I47V, I54M, T74P, and 184V and the positive impact of the protease mutation V82A on virologic response to ritonavir-boosted darunavir were shown in 2 data sets independently.\(^c\) Some of these mutations appear to have a greater effect on susceptibility than others (eg, 150V vs V111). The presence at baseline of 2 or more of the substitutions V111, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.\(^d\)

u. The mutations depicted on the figure bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

v. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to ritonavir-boosted lopinavir.\(^e\)\(^f\) The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.\(^g\) However, there is emerging evidence that specific mutations, most notably I47A (and possibly 147V) and V32I, are associated with high-level resistance.\(^h\)\(^i\) The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to ritonavir-boosted lopinavir.\(^j\)

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI resistance–associated mutations.\(^k\)

x. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.\(^l\)\(^m\)\(^n\)

y. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXCR chemokine receptor 4 (CXCRI; termed dual/mixed [DM] virus) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs is frequently associated with outgrowth of DM or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism.\(^o\) There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted in the figure. Some CCR5 antagonist–resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3\(^p\), the clinical significance of such mutations is not yet known.

z. In site-directed mutants and clinical isolates, the mutation F121Y has a profound effect on susceptibility to eltegravir and raltegravir and to a lesser extent to dolutegravir. Mutation R263K can be selected in vivo during treatment with dolutegravir and raltegravir and results in a 2- to 5-fold reduction in susceptibility to dolutegravir, eltegravir, and raltegravir.\(^q\)\(^r\)

aa. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.\(^s\) Cross-resistance studies with raltegravir- and eltegravir-resistant viruses indicate that Q148H/R and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility.\(^t\)\(^u\) Reduced virologic suppression in patients.\(^v\)\(^w\)\(^x\)\(^y\)

bb. Seven eltegravir codon mutations have been observed in integrase strand transfer inhibitor treatment–naïve and –experienced patients in whom therapy is failing\(^a\)\(^b\)\(^c\)\(^d\)\(^e\)\(^f\)\(^g\)\(^h\)\(^i\)\(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\)\(^aa\)\(^bb\). The negative impact of the protease mutations I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.\(^d\)

References to the User Notes


97. Fransen S, Gupta S, Danovich R, et al. Loss of raltegravir susceptibility by human immunodeficiency virus type 1 is conferred


Special Contribution

A Conversation Among the IAS–USA Board of Directors: Hot Topics and Emerging Data in HIV Research and Care

The IAS–USA volunteer Board of Directors met in October 2016 for its annual meeting. For the second year, the Board conducted a live, hour-long, interactive, roundtable webinar covering current questions and issues in HIV research, prevention, and care. Important highlights from the Board’s discussion, which was moderated by Paul A. Volberding, MD, are included below. Members of the IAS–USA volunteer Board of Directors are Constance A. Benson, MD; Judith S. Currier, MD; Carlos del Rio, MD; Joel E. Gallant, MD, MPH; Roy M. Gulick, MD, MPH; Jeanne M. Marrazzo, MD, MPH; Douglas D. Richman, MD; Michael S. Saag, MD; Robert T. Schooley, MD; and Paul A. Volberding, MD.

Keywords: HIV, antiretroviral therapy, investigational antiretroviral drugs, cure, vaccine, preexposure prophylaxis, PrEP, infectious diseases, hepatitis C virus, HCV, opportunistic infections

Dr Volberding: I am happy to have our board together for its 25th year. Today we will be discussing current questions and issues in HIV research, prevention, and care. I hope we get to a wide range of important issues. Let us begin by discussing the antiretroviral drugs that are currently in development.

Dr Gulick: With the currently available drugs, there is only a very small number of people who have experienced virologic failure due to resistance, but they need drugs that work against drug-resistant viruses. There are a couple of compounds in development that we have our eyes on. One of them is a CD4 attachment inhibitor, fostemsavir, an investigational drug with a new mechanism of action that is in phase III testing. It specifically binds envelope glycoprotein 120 (gp120) and prevents the virus from binding to the CD4 receptor. Phase II trial results demonstrated safety and efficacy.

Phase III testing is fully enrolled for treatment-experienced patients, and we are waiting for those results.

Another new drug class in development is maturation inhibitors, which act very late in the HIV life cycle. We know that the polyproteins of HIV are cleaved by the protease enzyme, and there are many protease inhibitors (PIs). However, another mechanism is to bind the polyproteins together, and that is how this new class of maturation inhibitors works, distinct from every other drug we have. There are candidate compounds in development.

Dr Volberding: With regard to monotherapy, is using dolutegravir alone successful?

Dr Gallant: For a long time, we have been using 2 nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) plus a third agent as the preferred treatment strategy, and that has not really changed. There have been attempts to research dual therapy. Some have not been very successful, such as the use a PI plus an integrase strand transfer inhibitor (InSTI). We have seen some success with use of boosted PIs plus lamivudine, and there is a small study from Argentina looking at dolutegravir plus lamivudine. This regimen worked quite well for the 20 patients in the study, and 2 larger-scale studies of this regimen are being conducted in the United States.

It will be interesting to see what happens. If dolutegravir does have a resistance barrier as high as that of PIs, then it may be a successful strategy.

Dr Gulick: That 2-drug combination (dolutegravir and lamivudine) looks interesting. It is important to remember that it was used in a small pilot study for 20 treatment-naive patients with plasma HIV RNA levels less than 100,000 copies/mL. The AIDS Clinical Trials Group is following up with a bigger study that is enrolling people with HIV RNA levels of up to 500,000 copies/mL.

Dr Benson: The ASPIRE (Dolutegravir Antiretroviral Strategy to Promote Improvement and Reduce Drug Exposure) trial in the United States is examining people who are fully virally suppressed on their antiretroviral regimen and are then transitioned to dolutegravir plus lamivudine for longer-term maintenance therapy. So, I think there are 2 larger-scale trials underway that will better address the question of

Dr Benson is Professor of Medicine at University of California San Diego in San Diego, California; Dr Currier is Professor of Medicine at University of California Los Angeles in Los Angeles, California; Dr del Rio is Professor of Medicine and Global Health at Emory University in Atlanta, Georgia; Dr Gallant is Medical Director of Specialty Services at Southwest CARE Center in Santa Fe, New Mexico; Dr Gulick is Professor of Medicine at Weill Cornell Medicine in New York, New York; Dr Marrazzo is Professor of Medicine at University of Alabama at Birmingham in Birmingham, Alabama; Dr Richman is Professor of Pathology and Medicine at University of California San Diego and Veterans Affairs San Diego Health System in San Diego, California; Dr Saag is Professor of Medicine at University of Alabama at Birmingham in Birmingham, Alabama; Dr Schooley is Professor of Medicine at University of California San Diego in San Diego, California; Dr Volberding is Professor of Medicine at University of California San Francisco in San Francisco, California.
how effective 2-drug therapy might be with an InSTI-based regimen.

Dr Saag: In practice, I am seeing many people using dolutegravir with boosted darunavir, but am not yet aware of any data.

Dr Gallant: There was a study of boosted darunavir and raltegravir, but among those with high viral loads or low CD4+ cell counts, it did not work so well. Maybe it would work better with dolutegravir, but we do not currently have any data.

Dr Volberding: I have seen early data on dolutegravir plus cobicistat-boosted elvitegravir. That is another 2-drug combination that might be of some interest.

Dr Gallant: Coformulated (T) elvitegravir/cobicistat/tenofovir alafenamide (TAF)/emtricitabine plus darunavir 800 mg for treatment-experienced patients worked quite well, but patients could not have more than 3 thymidine analogue mutations, could not have integrase mutations, and could not have darunavir mutations. So, for that select group of treatment-experienced patients on more complex regimens, the 2-pill combination of elvitegravir/cobicistat/TAF/emtricitabine plus darunavir may be a simpler option.

There have been a surprising number of very small observational studies of dolutegravir monotherapy in people who have previously been virally suppressed. Frankly, the results, if you put them all together, are not as good as those seen with dolutegravir and lamivudine, and there have been some treatment failures with integrase resistance, something we do not see with standard 3-drug–containing dolutegravir regimens. Given the safety and low cost of lamivudine, it makes more sense to carefully study treatment with dolutegravir and lamivudine before considering the further study of dolutegravir monotherapy.

Dr Currier: Before we leave the topic of investigational drugs, the unboosted investigational InSTI bictegravir in a single-tablet regimen is currently in phase III testing, and we can expect more information about in the coming year.

Dr Gulick: We should also mention doravirine, an investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) that is in development. It has activity against NNRTI-resistant virus. We have not seen many results outside the treatment-naive population, but this drug may have some promise.

Dr Richman: It is also worth mentioning that for any patient that you are considering for a tenofovir-free regimen, you have to take into account their hepatitis B virus (HBV) serostatus.

Dr Volberding: You raise the issue of HBV infection. Do you want to comment on TAF and HBV, because we are seeing many people switching from tenofovir disoproxil fumarate (TDF) to TAF?

Dr Richman: There are data that have been presented that TAF is at least as good as TDF, and that makes sense for the pharmacology as well, and TAF has now been approved by the US Food and Drug Administration for treatment of HBV infection.

Dr Volberding: What are the latest advances with regard to preexposure prophylaxis (PrEP), including vaginal rings used for HIV prevention, and sexually transmitted infections (STIs)?

Dr Marrazzo: PrEP is being used more frequently, certainly among men who have sex with men (MSM) in the United States. I think the real advances in PrEP are the user-friendly delivery systems that people are moving toward: topical delivery (sustained vaginal ring delivery) and long-acting injectable formulations.

The investigational microbicide dapivirine in a vaginal ring was studied in the ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) study—it shares a name with but is different from the HIV treatment study referenced earlier—and The Ring Study, the results of which were published in the New England Journal of Medicine in 2016. At first glance, the results are somewhat disappointing in that overall efficacy in this study of young women in sub-Saharan Africa was only approximately 27% to 30% in those who replaced their dapivirine ring each month versus those who received a placebo. However, when the data were broken down, particularly by age group and then by adherence (presented at the 2016 International AIDS Conference), based on some very interesting modeling using residual drug levels, results looked better for women who were adherent. Estimates are that the ring may be substantially more effective if it is used consistently every day. There were no cases of resistance reported in association with the dapivirine ring, and that is important.

The dapivirine vaginal ring is promising and is moving into unblinded, open-label studies in sub-Saharan Africa. TDF-and contraception-containing rings are also in development. Multipurpose, combined prevention is probably going to be the future.

Cabotegravir, which is an investigational dolutegravir analogue, is now being examined in 2 HIV Prevention Trials Network (HPTN) studies as an injectable PrEP option, given every other month for now. The dosing interval was adjusted after data from the ECLAR (Effect of Cell Surface Markers and Lymphoid Cell Distribution on the Arterial Tissue Repair) study because the absorption was faster, trough levels were lower, and peak levels were higher than anticipated. It has been an evolving algorithm, but ultimate dosing frequency is still to be determined.

Dr Gulick: The initial hope was that cabotegravir could be dosed every 3 months, but when investigators looked carefully at the pharmacokinetics, it was changed to every 2 months. HPTN 085 is a large, placebo-controlled study among MSM in the Americas, Asia, and South Africa that will open soon; HPTN 084 is the companion study among women in Africa. One group of participants will be taking 1 pill once a day of TDF/emtricitabine or a placebo. Another group will receive injections of cabotegravir or a placebo.
Dr del Rio: That is an important point. This is the first PrEP study that will compare an active agent with a new agent, and that is a new direction.

Dr Marrazzo: It is a huge paradigm shift. There are no more placebo-controlled studies of antiretroviral PrEP. Also, in the run-in phase of the cabotegravir study, everybody will receive an oral formulation of cabotegravir, so cabotegravir toxicity can be assessed before they receive the injection. Obviously, a huge concern with long-acting injectable agents is sustained safety.

Dr Volberding: What about TAF as PrEP?

Dr Gulick: Do not use it (yet). There is a chance that the pharmacokinetics could be different, and we do not know where the active compound has to be for HIV prevention. A study of TAF for PrEP is currently enrolling participants, but we should wait for the results before recommending it.

Dr Marrazzo: I think we do not know yet. There are not any data.

Dr Benson: Before we leave the topic of pharmacokinetics, I wonder if we could go back to the dapivirine ring studies. I think the concerns are the drug elution pharmacokinetics associated with the ring and the need for tissue levels beyond just where the local elution of drug from the ring stops. One of the concerns about topical therapy is the pharmacokinetics of tissue penetration at the place where you need it.

Dr Marrazzo: This is not only a concern for topical therapy. The biggest concern for women taking oral tenofovir is that you can very quickly get much higher levels in the rectum than you can in the cervicovaginal-vulnerable tissue. This is why women cannot just start taking tenofovir, say, 4 days ago and assume there is protection in the cervicovaginal area.

Dr Gulick: It is the same issue. We do not know where or at what level the active drug has to be to achieve the desired effect.

Dr Volberding: One of the things I think is worth talking about, with regard to prevention, is the issue of transmission among people whose virus is undetectable. The evidence is clear that if one has undetectable virus one is not transmitting HIV. What about STIs and PrEP? I think some may be aware that there is an early meta-analysis suggesting a very high rate of syphilis in the context of PrEP use.

Dr Marrazzo: I will say that the data that are out there are observational. With regard to STIs, the bottom line is that we are seeing what most people would say is an explosive increase in common STIs, certainly in MSM, whether they are HIV infected or not. I do not know that PrEP is making this happen more. I do not think we can say that yet. The research you are referring to indicated that PrEP use among MSM was associated with an increase in all STIs, and in fact, syphilis was 45 times more likely. We need more-sophisticated epidemiologic analyses to confirm this. Nonetheless, practitioners should be aware that there are many STIs occurring in this new generation of MSM.

Dr Volberding: How frequently should MSM taking PrEP be screened for STIs?

Dr Marrazzo: I think it has to be tailored. I would not object to monthly screening for some men. I know the Centers for Disease Control and Prevention (CDC) recommends every 3 to 6 months, but I think 6 months is a long time. I look at provision of PrEP as an opportunity to get people in to talk about their sexual health and their primary health care.

Dr Currier: I do think that having PrEP available is bringing people into care who were previously not engaged in care, and we have really capitalized on that. We should think about the opportunities for other prevention interventions when people come in for PrEP. With the recent cases of meningococcal meningitis, we are encouraging MSM to get vaccinated.

Dr Gulick: There was a similar outbreak in New York City recently, and the Department of Health recommended that all MSM, HIV infected or not, receive the meningococcal vaccine. Now, we have not seen a case in New York for a while. In 2003, there were outbreaks in Chicago, Illinois, and Toronto, Ontario, with the same strain of meningococcal disease, again in MSM. Vaccinations were widely provided, and the outbreak stopped. However, we really do not know why these outbreaks start and stop.

Dr Marrazzo: Meningococcal meningitis may be a sexually acquired infection because it classically colonizes the oral pharynx and can also cause urethritis and cervicitis, rarely, just like gonorrhea. That may be how it is being transmitted, selectively, among MSM.

Dr Gulick: We do not know that. It could be transmitted simply through oral sex or even kissing.

Dr Marrazzo: Then why would it not be happening equally as much in heterosexual populations?

Dr Gulick: You do need prolonged contact for it to spread.

Dr Marrazzo: I agree—it may simply be close contact in nonsexual settings. In any case, meningococcal meningitis should be addressed in the MSM population.

Dr Volberding: Where is hepatitis C virus (HCV) treatment going, and are there important new drugs in development?

Dr Saag: I think the recent release of velpatasvir creates a plateau of sorts after that initial burst of new drugs.

Every HIV/HCV-coinfected patient should be evaluated for cure of their HCV infection. We should be aware of the HCV serostatus of every patient in our clinics, to know whether they have HCV infection or not. Once that has been determined, if HCV RNA is detectable, most payers will now cover hepatitis C therapy. For practitioners, using the online HCV guidance4 to decide which drugs to use is important.

The most important thing is to be aware of potential drug-drug interactions. One of the things we can and should be thinking about for new patients establishing care as we evaluate...
We are also seeing huge rates of reinfection, which ties back to the idea of using PrEP as an opportunity to think about appropriate rescreening for infections.

Dr Benson: One of the issues that is often raised clinically is how the need for a liver biopsy has been used as a barrier to initiation of HCV therapy. How has the implementation of transient elastography in clinical settings eliminated the need for liver biopsies?

Dr Schooley: I think transient elastography is one of the most important advances in terms of liver disease staging in the last decade. With transient elastography, you can very easily separate people who have early stages of fibrosis from those who have more advanced fibrosis.

Dr Volberding: What is transient elastography?

Dr Schooley: Basically, transient elastography is a variation of an ultrasound, in which you are measuring the stiffness of the liver. What this lets you do, as an infectious diseases physician or as a nonhepatologist, is perform a simple test. You can do it yourself in your office and within about 8 minutes know whether a patient has advanced liver disease. If patients do not have advanced liver disease, there is no reason to send them to a hepatologist for evaluation. If they do have advanced liver disease, many times you can treat it yourself if you are prepared to follow the patients after cure to make certain they do not have hepatocellular carcinoma (HCC). For patients who have evidence of HCC, it would be better to consider liver transplantation before you treat them for HCV infection. The reduction in risk for HCC is one of the major benefits of successful treatment of HCV infection. The risk does not go away in people with more advanced disease, and that is where transient elastography is very helpful, to segregate those people who require more ongoing follow up.

This is another reason why I think that although the agents themselves are getting simpler to use (the algorithms are getting simpler as the genotype matters less), most HCV therapy will still be prescribed by a relatively small number of practitioners because of the infrastructure required by insurance companies, the need for access to transient elastography, and the need for understanding of how to manage people after cure. So I think it is something that will remain a specialized area of care but one that more practitioners should consider.

Dr Volberding: I want to start a discussion about HIV cure. I think there was a press release about the supposed cure of another person with HIV infection. I think we all recognize and are challenged by that kind of a report.

Dr Richman: That report on the cure of someone with HIV infection who is still taking antiretroviral therapy is premature.

Dr Volberding: The person had undetectable virus but is on antiretroviral therapy.

Dr Richman: Like millions of other people. The issue of HIV cure and the issue of HIV vaccines are, I think, 2 of the most important and exciting research areas in the field.

Dr Saag: As far as new HCV drugs that are coming along, as was mentioned, everything is moving toward panenotypic agents. In the next 2 to 3 years, HCV genotype may not matter as much as it has to date. Still, I think the revolution of HCV therapy is just breathtaking.

Dr del Rio: I think we also need to remember that those who are HCV seronegative, particularly MSM, need to be tested regularly. We are seeing an epidemic of sexually transmitted HCV infection and an increase in acute HCV infection, and we are missing it.

Dr Marrazzo: We are also seeing huge rates of reinfection, which ties back to the idea of using PrEP as an opportunity to think about appropriate rescreening for infections.

Dr Schooley: You emphasize the HIV/HCV-coinfected population, but I think practitioners should think about using the same infrastructure for HCV-monoinfected patients. There is no question that the number of people with HCV infection requiring therapy is massive, and it is not going to be covered by the hepatology community.

Dr Volberding: How rapidly is HCV therapy taking off?

Dr Schooley: HCV therapy is continuing to pick up. The drugs are getting simpler and simpler to use. The costs are being covered for most patients.

I think one thing that is different about this therapeutic area is that you often find third party payers forcing you toward one drug or another. Having said that, the drugs all work very well. Some of them are more complicated than others for certain patients, but we are about to be in a situation where we have several once-a-day, single-pill regimens that work for virtually every HCV genotype.

I would encourage those working in hospitals located in 340B-eligible census tracts to review how your institutions are allocating the 340B funds awarded on the basis of your HCV program. 340B is a federal program that provides supplemental funds to institutions providing care to labor (but not procedure)–intensive patient populations, such as those with HIV infection, HCV infection, hemophilia, or cystic fibrosis. The funds are provided to eligible institutions on the basis of the number and distribution of patients under care and are intended to support the programs generating the funds. Unfortunately, a number of institutions collect the funds from the federal government and apply them to general institutional uses rather than to the programs responsible for generating them. Those taking care of these patient populations in eligible institutions should ask the hospital to review the magnitude and allocation of 340B funds. Institutions may be receiving millions of dollars for their HIV and HCV programs and allocating them to the general hospital books while maintaining that they are “losing money” in their provision of HIV and HCV care. Explicit discussions about how these funds are used should be the expectation.

Dr Saag: As far as new HCV drugs that are coming along, as was mentioned, everything is moving toward panenotypic agents. In the next 2 to 3 years, HCV genotype may not matter as much as it has to date. Still, I think the revolution of HCV therapy is just breathtaking.

Dr del Rio: I think we also need to remember that those who are HCV seronegative, particularly MSM, need to be tested regularly. We are seeing an epidemic of sexually transmitted HCV infection and an increase in acute HCV infection, and we are missing it.
Dr Volberding: How is vaccine related to cure? We think of a vaccine as prevention.

Dr Richman: HIV cure is probably one of the most exciting and important areas with regard to people who are already HIV infected, and an HIV vaccine would clearly be the most effective preventative measure for those who are not yet infected. What links them is that they are important and exciting research areas, but the prospect of actually achieving an effective HIV cure or a vaccine is quite far off. The practical issue for our patients is that those who are expecting either a cure or an easy method of HIV prevention are going to have to proceed with the understanding that they will need to use what is now available for at least the next 5 to 10 years.

Dr Saag: You are saying what Margaret Heckler said in 1985, that we would have both the cure and a vaccine within a couple of years. It has been a long “2 years” since then.

Dr Richman: It has been a long “2 years,” and my prediction is that it will take even longer.

Dr Volberding: Vaccines are now being thought of as something that might help kill HIV-infected cells or at least, maybe, control the expression of the virus. But your bottom line is, “stay tuned”?

Dr Richman: Stay tuned. It is an important research area, but it is not something that will be implemented in the near future.

Dr del Rio: There is much HIV cure research happening, and these are the early stages. People that are volunteering for cure studies are people who are doing well on their antiretroviral therapy, and they are not really getting anything out of these studies other than helping us develop a cure. The altruism that we need in volunteers for cure studies is something to keep in mind. That is also what makes research difficult, because from an ethical perspective, if somebody is doing well on their antiretroviral medications, why should they expose themselves to something potentially toxic that puts them at risk?

I really think that cure research is becoming complicated just as HIV vaccine research is becoming complicated because PrEP prevents HIV infection reasonably well. I think that research is not going to be as simple as it was in the past, but I am confident that working with volunteers, a committed community, and committed scientists will help us achieve our goals.

Dr Volberding: At some point, cure trials will require people to stop their antiretroviral therapy to determine whether a cure has been achieved, and the ethics of that are a real challenge.

Dr Gulick: Vaccine trials are getting, as was said, even more complicated, given that the standards of care now are treatment as prevention and use of PrEP. Vaccine studies will have to be enormous to show a benefit over what we offer now.

Dr Marrazzo: Well, the studies of antibody-mediated prevention that are happening right now are based on the assumption, at least in Africa, that the HIV incidence is at least 5%. If you are using PrEP regularly, you are not going to have this level of incidence. I think this is going to be a rapidly evolving and challenging field logistically and operationally and also in terms of study analysis and design.

Dr Volberding: You raise the issue of broadly neutralizing antibodies. There has been some interest in that with regard to prevention and cure.

Dr Schooley: I think these are interesting studies from a scientific perspective, but I have reservations about some of the approaches being taken, because the more efficacious antibodies are still on the shelf. VRC 007 is a better antibody than VRC 001, and I think we will learn about breakthrough. I think, in the long term, antibodies are not going to be an approach we use with PrEP, and we need studies and to be honest about how these approaches are being studied in our clinics.

Dr Saag: To put it into context, to me the antibody studies are really proof of concept that, potentially, an antibody can protect. Once that has been proven, then you can try to design a vaccine that naturally can produce those same antibodies in vivo. I do not think we will ever be able to afford an antibody infusion as PrEP.

Dr Schooley: Although these studies are interesting science, it is highly unlikely that passive immunotherapy with broadly neutralizing antibodies will ever be of use clinically in the prevention or treatment of HIV infection. Although we have a number of these antibodies in hand after 30 years of effort, we do not know how to design antigens for use in vaccines that can induce humans to make these antibodies. Rather than spending tens of millions of dollars administering these antibodies in clinical trials, we should shift our attention to more basic research focused on antigen and adjuvant design. We have few insights about what these antigens should look like to the human immune system.

Dr Volberding: We talked about treatment as prevention. What about the need, for example, for the uninfected partner in an HIV-serodiscordant couple to continue PrEP even when the infected partner is fully virally suppressed? What is your recommendation for HIV-serodiscordant couples in which 1 partner is infected and the other is not?

Dr Marrazzo: First of all, there is the individualized approach, with a very personal discussion about what the couple’s goals and feelings are. In that context, many times TDF/ emtricitabine as PrEP is seen as much as an anxiolytic as it is a biologic, and it is an expensive anxiolytic.

Often, an HIV-seronegative partner will stop taking TDF/ emtricitabine as they realize that it is probably not necessary. The data support it not being necessary: in addition to the treatment-as-prevention data there was a study of condomless sex that was just published in the Journal of the American Medical Association (JAMA) this past year.5 I believe the results were 12,000 person-years of sexual activity with absolutely no HIV transmission. However, a relatively small number of MSM were included in the study. I would say the data are
supportive but not definitive. Also, there was no real-time monitoring for STIs, and there is a lingering question about transient general shedding in the face of inflammatory STIs, particularly anorectal chlamydia and gonorrhea. I do not think so. If you look at the Kaiser data and the PrEP study that I mentioned before, there was, I think, a 25% incidence of rectal chlamydial and gonococcal infections in that study and no HIV transmissions. These data are very supportive of the protective effectiveness of treatment as prevention.

Dr Gulick: There is another caveat about that study in JAMA, which was impressive (it took place in a number of European countries): the investigators identified people in HIV-serodiscordant relationships who said that they never used condoms. That was a requirement to enroll in the study. Participants were followed prospectively to see if there was HIV transmission, and heterosexual and gay couples were included.

The caveat is that to enroll in the study, you had to say, “We haven’t been using condoms.” Does that apply to everybody, particularly people who are not in a committed couple? It is probably difficult to extrapolate information to single MSM finding new sexual partners from these data.

Dr Marrazzo: It comes back to my initial point. There should be a very individualized discussion with the couple or with the person. You can extrapolate from these data to the extent that it is helpful, but it really comes back to the individual situation.

Dr Volberding: Another way to think about treatment as prevention is to think about it at a community level. Many cities and even more resource-limited settings are using a city-level approach to treatment as prevention. Can you comment on what the 90-90-90 goals are and on the interface between public health and HIV treatment?

Dr del Rio: The 90-90-90 goals are to have 90% of HIV-infected people diagnosed, in any community; 90% of those who are diagnosed started on antiretroviral therapy; and 90% of those on antiretroviral therapy virally suppressed. Using this model, you could potentially stop transmission of HIV, and that is the ultimate goal. I think the focus on cities is because, although the HIV epidemic is everywhere, it continues to concentrate primarily in urban areas.

Dr Volberding: Except for in the Southeastern United States.

Dr del Rio: Even in the Southeast, there are big cities like Atlanta, Georgia, and Birmingham, Alabama, where the epidemic starts. I think we need to focus our efforts on cities. Many cities have made commitments to meet these goals. I think the interface between clinical care and public health is being strengthened.

In many places, our biggest challenge continues to be people dropping out of HIV care. We know from the data that most HIV transmission in the United States is among people not retained in care.

Dr Volberding: They know they are HIV infected, but they are not in care?

Dr del Rio: People are lost to care for a number of reasons. How do we create the infrastructure that can get those people back into care to achieve the 90-90-90 goals? We need to increase the number of people who are virally suppressed. As a nation, the United States is nowhere close to achieving the 90-90-90 goals. Sweden recently published that they had, as a country, achieved the 90-90-90 goals.7

Having said that, I think the proof is pending, except for the observational data from Vancouver, Canada.8 It has not been proved that achieving those goals is ending HIV transmission. I think the data from the French National Agency for AIDS Research (ANRS), for example, presented at the 2016 International AIDS Conference was very sobering.9 It clearly showed that in spite of great effort, at a community level, HIV transmission has still continued.

Dr Volberding: HIV transmissions in San Francisco, California, are down after this effort.

Dr Gulick: The same is true in New York. New HIV infections are half as many as they were before this effort.

Dr Benson: We have been discussing sexual transmission of HIV among MSM, but one of the explosive events of this past year was an outbreak of HIV infection among people who inject drugs (PWID) in suburban or smaller rural areas and not among more traditional urban PWID populations. The Indiana HIV outbreak in 2015 was a huge wake-up call to public health officials about what is happening in rural communities of PWID.10 The corollary to that has been an epidemic of HCV transmission in the same setting. I think insufficient attention has been paid to these kinds of outbreaks and to the emergence of new populations of PWID. These rural and suburban PWID do not fit the vision of disadvantaged PWID in urban areas.

Dr del Rio: The epidemic of opioid use in our country, prescription and illegal opioids, is real. There is some recent reporting in the New England Journal of Medicine that there are 2.3 to 2.4 million opioid users in this country, versus 1.2 million people living with HIV infection, and the CDC published results of a study that examined counties and states with high risk for the epidemic Dr Benson mentioned.12 The next outbreak could be happening in a nearby county, and practitioners need to be aware.

Dr Marrazzo: A very interesting parallel is increases in cases of bacterial endocarditis among younger populations.

Dr Schooley: Also, this epidemic has taught us yet again that needle-exchange programs work. In Indiana, there was a delay in the implementation of needle-exchange programs, but when they were implemented, the HIV epidemic stopped.

Dr Volberding: Coming back to HCV infection, in some places, for example Louisiana, insurance companies still require that individuals have evidence of advanced fibrosis before they are treated for their HCV infection. So, it is important to be aware of local requirements regarding HCV therapy. Can you comment on this?
Dr Schooley: There are other reasons to treat people with HCV infection besides fibrosis, non–liver-associated reasons. For example, HCV-infected women who want to become pregnant should be treated. So, do not just tell people that they are not eligible for treatment and leave it at that. Keep them in mind as more favorable treatment guidelines emerge, which they will.

Dr Gulick: Or speak to your local health officials and make the case, and show them data from other states with fewer treatment restrictions.

Dr Saag: The problem in some Southern states is that Medicaid is bankrupt.

Dr del Rio: Also, Medicaid has not been expanded in most Southern states.

Dr Volberding: What should we be continuing to think about with regard to opportunistic infections (OIs) and tuberculosis (TB) in our patients with HIV infection?

Dr Benson: Traditional OIs have become a less important consideration for HIV-infected individuals unless they are not engaged in care. Engaging HIV-infected individuals in medical care and paying attention to the risks for coinfections needs to be part of primary care.

Having said that, there have been some changes in the recommendations for OI prophylaxis. Probably the most important change is that because the rate of *Mycobacterium avium* complex (MAC) disease is now so low and the risk of acquiring it is abrogated so dramatically with antiretroviral therapy, MAC prophylaxis is likely not needed unless someone is not on antiretroviral therapy. Even in those individuals with very advanced HIV disease who present to care, it is more important to initiate antiretroviral therapy than MAC prophylaxis. The 2016 IAS–USA recommendations for prevention and antiretroviral treatment highlight that perhaps prophylaxis is no longer needed for individuals who are taking antiretroviral therapy.\(^\text{15}\)

Dr Volberding: If you cannot keep patients on antiretroviral therapy, you probably cannot keep them on prophylaxis.

Dr Benson: There is starting to be some discussion, even with regard to prophylaxis for *Pneumocystis jiroveci* pneumonia, about the preferential need for rapid initiation of effective antiretroviral therapy in those with advanced disease rather than emphasizing initiation of prophylaxis for *Pneumocystis jiroveci* pneumonia first.

TB continues to be an important OI, particularly among HIV-infected populations in resource-constrained settings and among foreign-born HIV-infected individuals in the United States. There has been a renewed emphasis by the World Health Organization (WHO) and the CDC on treating latent TB infection and new guidance from the CDC on targeted screening for latent TB infection among populations at increased risk for TB, including HIV-infected individuals.\(^\text{14,15}\)

The other area of screening that is lacking and needs to be reemphasized is screening of people who are foreign-born or who have lived in countries where there is a high background prevalence for TB, as well as people who have lived in or been exposed to TB in congregate settings, such as prisons, jails, homeless shelters, and areas where there is a high risk for transmission of TB. Those individuals should now be emphasized in terms of screening. So, screening for latent TB infection with a tuberculin skin test or an interferon-gamma release assay is an important part of primary care for HIV-infected people and those at high risk for TB.

Dr Volberding: One thing not addressed by the 90-90-90 goals is retention in care. What are some strategies to retain patients in care?

Dr Saag: If somebody does not show up for a clinic visit without calling to cancel, then that is a red flag. There are data showing that not attending clinic visits is associated with mortality compared with routinely attending clinic visits.

I think there are two things practitioners can do to address this. First, if somebody does not show up for an appointment, call them to follow up. Ask them what happened and try to reschedule. Second, provide positive reinforcement when patients do keep their clinic appointments. These things show patients that practitioners are paying attention and are a useful first step.

Dr Volberding: I think there was a study in which people were given financial incentives to stay in care, which did not improve retention.

Dr del Rio: That was the HPTN 065 study, the results of which have not yet been published but were presented at the 2015 Conference on Retroviruses and Opportunistic Infections.\(^\text{16}\)

The study used financial incentives to encourage people to get tested for HIV infection. The goal was to progress the entire treatment cascade and not just to test people and link them to care. In Washington, DC, the intervention only worked in clinics and places that were not doing well with regard to retention. So, I think these interventions can be targeted.

Again, these are not interventions that would work for everybody. Retention in care, I think, should be individualized. A needs assessment should be completed for each patient.

Another issue around retention in and linkage to care that I think is very important is the time it takes to get someone into care. The first National HIV/AIDS Strategy recommended linkage to care within 3 months of HIV diagnosis. A newer strategy recommended 1 month. Many places are now cutting that time down further. For example, in data from South Africa, Haiti, and San Francisco, immediate initiation of antiretroviral therapy was associated with better rates of retention in care.\(^\text{17-19}\)

In Atlanta, our goal is to link people to care within 72 hours of HIV diagnosis.

Dr Volberding: In San Francisco, we have a very aggressive program in which the effort is to detect cases of acute HIV infection and to find people who are newly diagnosed with HIV infection and start them on treatment the same day.

Dr del Rio: Immediate care and same-day initiation of antiretroviral therapy are improving retention in care in many settings, as can be seen in the data from South Africa, Haiti, and San Francisco.
Dr Volberding: That is the opposite of what we used to think.

Dr Marrazzo: We should also emphasize the link between public health settings and clinics where people are newly diagnosed. It would be optimal to, if needed, walk patients from an STI clinic to an HIV clinic to be enrolled in care.

Dr del Rio: It is more than just a referral.

Dr Marrazzo: There is a very narrow window of opportunity to engage with people and make them realize the importance of HIV care.

Dr Volberding: Can you comment on the increasingly convergent relationship between HIV care and public health? The relationship that treatment programs have with their health departments is crucial, especially as we explore issues related to the treatment cascade.

Dr Gulick: Young men in general, HIV infected or not, are not as engaged in health care as we would like them to be.

Dr Currier: That has been really clear in studies that look at the health of young men initiating PrEP.

I also want to follow up on something that Dr del Rio mentioned that is being discussed in the United States President’s Emergency Plan for AIDS Relief (PEPFAR) and in many limited-resource settings: the concept of a differentiated model of care. We think about that as an issue outside of the United States, but we do not think about it enough inside the United States or about how we can be more flexible in making treatment available.

Dr Volberding: We think about implementation science as being almost exclusively an issue for resource-limited settings.

Dr del Rio: Well, part of our country is resource limited. Looking at the HIV epidemic in the United States, the epidemic is disappearing in parts of the country, while it is increasing in other parts of the country—in the South, for example—as they become less developed. It is not that the HIV epidemic itself is getting worse but that worsening conditions are making the epidemic worse.

Dr Saag: I think that we have had some success, but I do not want to create the image that we have things under control. The most powerful data I saw this year indicated that MSM in the United States, over their lifetime, have a 1:6 chance of becoming HIV infected, and black MSM have a 1:2 chance. That is an overwhelming number.

Dr Volberding: Let me restate that. Half of black MSM have a lifetime risk of becoming HIV infected. That is 50%. That is a crisis.

Dr Saag: That is a crisis. The most striking thing to me is that despite the fact that we have known about HIV for more than 30 years, we are not making that much of a dent except possibly in New York and San Francisco. For the rest of the country, there is much more work to be done.

Dr Marrazzo: We have not discussed the stigma surrounding HIV infection, but this is a huge issue in some areas. Stigma is something that should not be ignored when discussing HIV infection.

Dr del Rio: Also, 40,000 to 45,000 new HIV infections per year is not acceptable. If there were 45,000 new Ebola infections per year, I think Congress would be alarmed.

Dr Benson: There was a recent report about the workforce who are taking care of HIV-infected patients,20,21 and there may be a looming crisis in terms of physicians taking care of individuals with HIV infection.

Dr del Rio: The patient population is aging but so are practitioners.

Dr Marrazzo: During the Indiana outbreak, no infectious diseases specialists were initially available.

Dr Volberding: What are some of the research questions that drive you the most right now?

Dr Richman: As already mentioned, HIV cure and vaccine are crucially important research areas. However, for objectives that can be more readily addressed right now, I think implementation science and the prospect of long-acting antiretroviral agents as a way to address adherence to antiretroviral therapy are 2 exciting areas.

Dr Saag: Implementation is a word that is frequently used, but let me define it in this context. It means identifying the barriers to accomplishing what we know works and then determining how to remove those barriers. I think we have much to learn from other parts of the world, especially sub-Saharan Africa. Also, I think implementing immediate initiation of antiretroviral therapy is something we really need to focus on.

Dr del Rio: With regard to retention in care, we do not yet know what works, and more research is needed.

In a recently completed clinical trial that focused on trying to improve retention in care and virologic suppression among HIV-infected substance users via a combination of interventions (financial incentives and the assistance of patient navigators), the interventions did not produce a different result than the standard of care.22

Dr Benson: I think we should take advantage of some of the newer technologies used for monitoring adherence to therapy and utilize those to encourage adherence and retention in care. There are now smart phone applications that can monitor pill-taking behavior or even which drugs are taken. Making use of the technology available to us, such as devices that can monitor health similar to those that monitor individual fitness parameters, may be helpful. Contacting people if they miss a visit was discussed earlier, and a smart phone application could be used to do this.

We can use more than just face-to-face interaction as people are increasingly using technology. We need more research related to better mechanisms for retaining people in care and to take advantage of some of the newer technologies to help improve retention in care and adherence to therapy.
Dr Currier: I agree with everything that has been said, but another area that we need to make more progress in is keeping people healthy on treatment as they age. Although it seems that with early antiretroviral treatment and sustained viral suppression we can substantially reduce mortality, there are still areas that need improvement. Cancer, for example, is becoming more and more of an issue, and more study is needed on how to prevent cancer in people with long-term HIV infection.

Dr Gulick: I would like to revisit a topic we talked about before, which is 2-drug antiretroviral therapy. We have been using 3-drug therapy since 1996: 2 nRTIs and a third agent. If the 2-drug combination of dolutegravir and lamivudine really works, it would be a game changer. The WHO has calculated that with use of the generic formulations of these 2 drugs, the cost of treatment would be $50 per year. If this drug combination works, it would change how we treat HIV disease.

Dr Volberding: Our board is actively thinking about many of the issues discussed, and we are always thinking about what IAS–USA can do to reach younger practitioners who will be treating HIV and other viral infections in years to come.

A link to the full recorded webinar is available on the IAS–USA website at www.iasusa.org, along with information on upcoming live webinars and courses, online continuing medical education activities, and important scientific meetings, such as the Conference on Retroviruses and Opportunistic Infections and the Ryan White HIV/AIDS Program Clinical Conference.

Financial affiliations in the past 12 months: Dr Benson serves on a data and safety monitoring board for GlaxoSmithKline/ViiV Healthcare. She has received research grants awarded to her institution from AbbVie, Gilead Sciences, Inc, and ViiV Healthcare. Information for her spouse, Dr Robert T. Schooley, is included below. Dr Currier has no relevant financial affiliations to disclose. Dr del Rio has served as a consultant for InnaVirVax. Dr Gallant has served as a consultant or advisor to Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and ViiV Healthcare/GlaxoSmithKline. He has received research grants or contracts awarded to his institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Inc, Merck & Co, Inc, Sangamo BioSciences, and ViiV Healthcare/GlaxoSmithKline. Dr Gulick has no relevant financial affiliations to disclose. Dr Marrazzo has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Antiva Biosciences, Chimerix, Gilead Sciences, Inc, and Monogram Biosciences, Inc. Dr Saag has received research grants and support awarded to his institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, and ViiV Healthcare. He has also served as a consultant for Bristol-Myers Squibb, Gilead Sciences, Inc, Teva Pharmaceutical Industries, Ltd, and Merck & Co, Inc. Dr Schooley was awarded research grants, paid to his institution, from AbbVie, Bristol-Myers Squibb, and Merck & Co, Inc. His institution has received payment for his consultative advice or data monitoring committee service from Gilead Sciences, Inc, Globimmune, and Monogram Biosciences. He serves as a consultant to Antiva Biosciences, CytoDyn, and Farmak. He has stock options from Antiva Biosciences and CytoDyn. Dr Volberding has served on data and safety monitoring boards for Merck & Co, Inc.
Suggested Readings


UPCOMING ACTIVITIES

Spring and Summer 2017

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What’s Hot From the 2017 Conference on Retroviruses and Opportunistic Infections—February 28, 2017
Presenter: Joseph J. Eron Jr, MD, University of North Carolina at Chapel Hill

The Epidemic of Opioid Use in the United States—March 23, 2017
Presenter: Glenn J. Tresman, MD, PhD, The Johns Hopkins University

Hepatology for the Nonhepatologist—April 6, 2017
Presenter: Alexander Monto, MD, University of California San Francisco

Neurology and HIV Infection—April 18, 2017
Presenter: Serena S. Spudich, MD, Yale University

Update From EASL 2017—May 4, 2017
Presenter: David L. Wyles, MD, Denver Health

Contemporary Issues in Antiretroviral Therapy—June 20, 2017
Presenter: Joel E. Gallant, MD, MPH, Southwest CARE Center

IAS–USA Live Courses

Full-day and half-day CME courses and workshops continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the fields of HIV and hepatitis C virus (HCV) medicine. Visit the IAS–USA website for updated information on live CME activities. This spring, IAS–USA live activities focusing on the management of HIV infection will be held in the following cities:

New York, New York, Full-Day HIV Course—Friday, February 24, 2017
Atlanta, Georgia, Full-Day HIV Course—Thursday, March 30, 2017
Los Angeles, California, Full-Day HIV Course—Friday, April 28, 2017
Chicago, Illinois, Full-Day HIV Course—Wednesday, May 10, 2017
Washington, DC, Full-Day HIV Course—Monday, May 22, 2017
Berkeley, California, Full-Day HIV Course—Thursday, May 25, 2017

Cases on the Web

A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for more information. Coming soon from Cases on the Web:

Initial Antiretroviral Therapy in the HIV-Infected Patient
Authors: Jameela J. Yusuff, MD, MPH, FACP, State University of New York; Katharine Kuntz, MD, State University of New York

Immunizations for HIV-Infected Persons
Authors: Brian T. Montague, DO, MS, MPH, University of Colorado; Steven C. Johnson, MD, University of Colorado

Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for e-mail updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities. Early registration for live courses is strongly recommended. These activities have been approved for AMA PRA Category 1 Credit™. Maintenance of Certification (MOC) points are available for IAS–USA activities in 2017.
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IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
E-mail: journal“at”iasusa.org

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