CONFERENCE COVERAGE

The 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) took place July 17–20 in Rome. Alternating every other summer with the International AIDS Conference, the IAS meeting focuses primarily on the medical aspects of HIV prevention and treatment, and management of associated conditions. This year the meeting’s key theme was the convergence of treatment and prevention, with studies showing that prompt antiretroviral therapy dramatically reduces the risk of HIV transmission.

Other conferences featuring HIV research since the last issue of BETA include the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC; Chicago, September 17–20), the European AIDS Clinical Society’s 13th European AIDS Conference (EACS; Belgrade, October 12–15), the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA; Boston, October 20–23), and the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD; San Francisco, November 4–8).

Selected reports from these conferences are included below, along with recent news from medical journals and other sources.

ON THE WEB

IAS 2011
www.ias2011.org

ICAAC 2011
www.icaac.org

EACS 2011
www.eacs-conference2011.com

IDSA 2011
www.idsa2011.org

AASLD 2011
www.aasld.org/LM2011

DRUG APPROVALS, WARNINGS, AND GUIDELINES

UPDATED HIV TREATMENT GUIDELINES

On October 14, 2011, the U.S. Department of Health and Human Services (DHHS) issued revised Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. EACS released revised European guidelines the same day at its meeting in Belgrade.

The updated DHHS guidelines keep the CD4 T-cell threshold for treatment initiation at 500 cells/mm³. The EACS guidelines are more conservative, recommending treatment at a threshold of 350 cells/mm³, although antiretroviral therapy (ART) is advised below 500 cells/mm³—or even earlier for several patient groups, including pregnant women and people with HIV-associated kidney disease, neurocognitive impairment, human papillomavirus-associated cancer, or hepatitis B or C.

The key DHHS changes focus on which drugs to include in a first-line regimen. Efavirenz (Sustiva) plus tenofovir/emtricitabine, available as a single-tablet regimen (Atripla), remains the sole “preferred” first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen, except for women during the first trimester of pregnancy. Regimens containing nevirapine (Viramune) are now classified as “acceptable” for appropriate patients. The recently approved NNRTI rilpivirine (Edurant) was added as an “alternative.”
The new EACS guidelines rate efavirenz and nevirapine equally, but do not yet include rilpivirine.

The DHHS recommends once-daily ritonavir-boosted atazanavir (Reyataz) and boosted darunavir (Prezista), both with tenofovir/emtricitabine (the drugs in Truvada), as “preferred” protease inhibitor options. Darunavir plus abacavir/lamivudine (the drugs in Epzicom) was reclassified as an “alternative.” Unboosted fosamprenavir (Lexiva) was removed due to inferior potency. The preferred protease inhibitor regimen for pregnant women is lopinavir/ritonavir (Kaletra) plus zidovudine/lamivudine (the drugs in Combivir). The new EACS guidelines recommend boosted atazanavir, boosted darunavir, or lopinavir/ritonavir, all combined with either tenofovir/emtricitabine or abacavir/lamivudine.

The sole approved integrase inhibitor, raltegravir (Isentress), plus tenofovir/emtricitabine remains a DHHS “preferred” regimen, while raltegravir plus abacavir/lamivudine was upgraded to an “alternative.” EACS recommends raltegravir only with tenofovir/emtricitabine.

Turning to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), tenofovir/emtricitabine remains the sole DHHS “preferred” option, except for pregnant women, for whom zidovudine/lamivudine is recommended to prevent perinatal HIV transmission. Abacavir/lamivudine remains an “alternative.”

DHHS demoted abacavir/lamivudine from “preferred” to “alternative” in 2008 due to concerns that abacavir might increase the risk of cardiovascular problems and may not be as effective for people with high viral load; however, numerous studies since then have produced conflicting data. Abacavir/lamivudine “remains a good alternative dual-NRTI option for some ART-naive patients,” according to DHHS, and the EACS guidelines recommend tenofovir/emtricitabine and abacavir/lamivudine equally.

In September DHHS also updated its Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

The revision includes updated findings from international trials of antiretroviral drugs to reduce perinatal HIV transmission during breastfeeding. Tenofovir was upgraded to an “alternative” drug for pregnant women, and “preferred” for those with HIV and hepatitis B coinfection.

Finally, in August DHHS issued the latest revision of its Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Among the notable changes, the panel increased the treatment initiation threshold for asymptomatic children age 5 and older from 350 cells to 500 cells/mm³, matching the current adult guidelines.

DHHS guidelines are available online at http://aidsinfo.nih.gov/guidelines. The EACS guidelines are online at www.europeanaidsclinicalsociety.org.

NEW COMPLERA SINGLE-TABLET REGIMEN

People starting HIV treatment for the first time now have another one-pill, once-daily antiretroviral therapy option.

On September 10, 2011, the U.S. Food and Drug Administration (FDA) approved Complera, a single-tablet regimen combining Janssen/Tibotec’s next-generation NNRTI rilpivirine plus tenofovir/emtricitabine; rilpivirine (formerly TMC278) was approved as a single agent in May (marketed as Edurant). See “Drug Watch,” page 14, for details on these new treatment options.

The Phase III ECHO and THRIVE trials showed that rilpivirine/tenofovir/emtricitabine worked as well as efavirenz/tenofovir/emtricitabine (Atripla) but caused fewer side effects, especially neuropsychiatric symptoms. At 48 weeks, 83% of participants taking rilpivirine and 81% of those taking efavirenz achieved undetectable viral load.

Data presented at the IAS conference showed continued rilpivirine efficacy at 96 weeks. At EACS, Cal Cohen reported that 50 trial participants with undetectable HIV RNA who switched single-tablet regimens from Atripla to Complera maintained viral suppression with no unexpected adverse events.

Complera should be taken once-daily with a meal; it is not yet approved for treatment-experienced HIV patients. Because tenofovir has been linked to kidney problems, it should not be prescribed for people with moderate-to-severe kidney impairment. Tenofovir and emtricitabine are active against hepatitis B virus (HBV) as well as HIV, but the safety and efficacy of Complera have not been established for HIV/HBV coinfected patients. Full prescribing information for Complera is available at www.Gilead.com.

QUAD PILL SUBMITTED FOR APPROVAL

In late October Gilead announced that it has requested FDA approval of its four-in-one “Quad” single-tablet regimen, which combines the novel integrase inhibitor elvitegravir, the new boosting agent cobicistat, and tenofovir/emtricitabine; the New Drug Application had initially been planned for early 2012.

Results from a Phase III trial (Study 102) announced by Gilead in August showed that the Quad pill worked as well as Atripla for treatment-naive patients, with 88% and 84%, respectively, achieving undetectable HIV RNA (< 50 copies/mL). The overall frequency of serious adverse events and laboratory abnormalities was similar in both arms, but Quad recipients reported fewer neuropsychiatric symptoms.
The following month the company announced final data from another Phase III pivotal trial (Study 103), indicating that the Quad was non-inferior to boosted atazanavir plus tenofovir/emtricitabine. Viral suppression rates at 48 weeks were 90% and 87%, respectively, but fewer people discontinued the Quad due to adverse events.

In the September 24, 2011, issue of *AIDS*, Richard Elion and fellow investigators with the GS-US-216–0105 Study reported that cobicistat—which is not itself active against HIV—worked as well as ritonavir as a booster for atazanavir combined with tenofovir/emtricitabine; viral suppression rates at 48 weeks were 82% and 86%, respectively. In early December Gilead reported similar findings from the larger Phase III Study 114 (692 participants), which saw virological response rates of 85% with cobicistat vs. 87% with ritonavir.

In these studies cobicistat was associated with a greater mean decrease in estimated glomerular filtration rate (GFR), a potential indicator of impaired kidney function, soon after starting the drug, but this stabilized by 24 weeks. Gilead scientists presented two posters at ICAAC suggesting that cobicistat affects creatinine secretion in the proximal renal tubules—which leads to higher serum creatinine and corresponding decreases in estimated GFR—but does not appear to affect actual GFR.

In addition, Gilead and Bristol-Myers Squibb recently announced that they will collaborate to develop a once-daily, fixed-dose coformulation containing atazanavir plus cobicistat. And in November, Gilead said it will collaborate with Tibotec/Janssen to develop yet another single-tablet regimen containing darunavir, cobicistat, emtricitabine, and the tenofovir pro-drug GS 7340.

**REVISED RALTEGRAVIR WARNING**

In early November the FDA announced that product label information for raltegravir (brand name Isentress) has been revised to include new warnings about potential adverse events.

Raltegravir is among the most well-tolerated antiretroviral drugs, but in postmarketing experience it has been associated with severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and other symptoms of hypersensitivity including liver toxicity.

The updated package insert states that patients should discontinue raltegravir and other suspect drugs immediately and contact their health-care provider if they develop hypersensitivity symptoms, including severe rash, rash accompanied by fever, malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial swelling, difficulty breathing, or liver inflammation (indicated by jaundice, nausea, loss of appetite, and upper abdominal pain). Delay in stopping raltegravir after the onset of severe rash, the insert warns, “may result in a life-threatening reaction.”

**EXPERIMENTAL HIV THERAPY**

At recent conferences researchers have presented data on several candidates in the HIV drug development pipeline, both new agents in existing antiretroviral classes and agents that work by novel mechanisms.

**ELVITEGRAVIR**

The experimental HIV integrase inhibitor elvitegravir is as effective as raltegravir for treatment-experienced patients with extensive drug resistance, according to a study presented at IAS 2011 (abstract WELBB05).

Elvitegravir can be taken once-daily, compared with twice-daily for raltegravir, but it must be used with a boosting agent—either ritonavir or the new pharmacoenhancer cobicistat—to maintain adequate drug levels; elvitegravir and cobicistat are both included in the single-tablet Quad coformulation.

Jean-Michel Molina from Hôpital Saint Louis in Paris reported findings from the Phase III Study 183-0145, a head-to-head comparison of elvitegravir vs. raltegravir in 702 treatment-experienced patients. The mean CD4 count was 260 cells/mm³ and about 25% of participants had high HIV viral load ( >100,000 copies/mL); about two-thirds were resistant to two or more antiretroviral drug classes.

Participants were randomly assigned to receive either 150 mg elvitegravir once daily or 400 mg raltegravir twice daily, both in combination with a fully active ritonavir-boosted protease inhibitor and an active third agent; ritonavir served as a booster for elvitegravir as well as the protease inhibitor.

Elvitegravir and raltegravir were equally effective at 48 weeks, with virological response rates of 59% and 58%, respectively (HIV RNA <50 copies/mL). Approximately one in five participants in both arms experienced virological failure, and about 20% of those who did showed evidence of integrase resistance mutations. CD4 cell gains were similar, approximately 140 cells/mm³ in both groups.

Both drugs were generally well tolerated and few people discontinued therapy due to adverse events (3% in elvitegravir arm vs. 4% in raltegravir arm). The types and frequencies of side effects and laboratory abnormalities were generally similar, although more elvitegravir recipients reported diarrhea (12% vs. 7%, respectively).

The investigators concluded that elvitegravir was non-inferior to raltegravir when given with an active boosted protease inhibitor. Due to cross-resistance, elvitegravir is not expected to work well for people with raltegravir-
resistant virus, but if approved it will offer another option in a drug class that is well tolerated and so far has not been associated with long-term toxicities.

**Dolutegravir**

The next-generation integrase inhibitor dolutegravir (formerly S/GSK1349572; developed jointly by Shionogi and ViiV Healthcare) suppresses HIV in treatment-naive patients as well as efavirenz but with fewer side effects, according to findings from the SPRING-1 study presented at this summer’s IAS conference (*abstract TUAB0102*).

This multinational Phase IIb trial included 205 participants starting HIV treatment for the first time; the mean CD4 count was 324 cells/mm$^3$ and about 20% had high baseline viral load. Patients were randomly assigned to receive 10, 25, or 50 mg once-daily unboosted dolutegravir or 600 mg once-daily efavirenz, both in combination with tenofovir/emtricitabine or abacavir/lamivudine. (The 50-mg once-daily dose has since been selected for further testing in treatment-naive people.)

Data from a planned 48-week interim analysis of this 96-week study were presented in Rome. By 16 weeks—a time point not usually reported—dolutegravir produced rapid HIV suppression, with 90% to 96% of dolutegravir recipients achieving undetectable viral load compared with 58% of efavirenz recipients. Over time, participants in the dolutegravir arms maintained viral suppression while efavirenz recipients caught up, resulting in similar response rates at 48 weeks: 88% to 91% in the dolutegravir arms vs. 82% in the efavirenz arm.

Three participants experienced virological failure on dolutegravir through week 48, but none showed evidence of integrase resistance mutations. There was a trend toward larger CD4 cell gains in the dolutegravir arms, but the difference did not reach statistical significance.

The difference in efficacy was largely driven by better tolerability of dolutegravir. Overall, dolutegravir recipients experienced fewer moderate-to-severe side effects than efavirenz recipients (8% vs. 20%, respectively); the difference was most pronounced for neuropsychiatric symptoms (0% vs. 6%, respectively). Two dolutegravir recipients (1%) and four efavirenz recipients (8%) discontinued therapy due to adverse events.

Some participants taking dolutegravir experienced small changes in serum creatinine (a potential indicator of kidney toxicity), but there was no difference in GFR. Blood lipid profiles were more favorable among dolutegravir recipients, with lower LDL ("bad") cholesterol and triglyceride levels.

At the EACS meeting in October, researchers presented data from the VIKING study (*abstract PS1/2*) indicating that 50 mg twice-daily dolutegravir is more effective than once-daily dosing for highly treatment-experienced patients with pre-existing resistance to raltegravir and other antiretroviral classes. Twice-daily dosing will be further evaluated in a Phase III trial and an expanded access program is expected to begin in early 2012.

**BI 224436**

Another experimental integrase inhibitor, BI 224436, demonstrated good pharmacokinetics and potent activity against raltegravir-resistant HIV in a series of early studies presented at ICAAC.

Researchers at Boehringer Ingelheim used a high-throughput screening assay to identify a set of compounds known as non-catalytic site integrase inhibitors (NCINIs). These agents work by a different mechanism than raltegravir—the sole approved drug in its class—and are therefore less likely to be cross-resistant.

Laboratory studies (*abstracts F1-1369 and F1-1370*) showed that BI 224436 was active against recombinant viruses carrying integrase enzymes from HIV isolates obtained from 200 treatment-naive and 40 raltegravir-resistant patients.

The first study in humans was a Phase Ia trial of BI 224436 oral solution administered to 48 healthy male volunteers (*abstract AI-1725*). Participants were randomly allocated to receive a single dose of the study drug (6.2, 12.5, 25, 50, 100, or 200 mg) or placebo. BI 224436 demonstrated a favorable pharmacokinetic profile. It was generally well-tolerated with no clinically relevant changes in vital signs or laboratory parameters.

The 100-mg dose of BI 224436 has been selected for further trials. Boehringer Ingelheim and Gilead recently announced that Boehringer has granted Gilead exclusive worldwide rights to develop and commercialize BI 224436 and its other NCINI candidates.

**Lersivirine**

Lersivirine (formerly UK-453061), an investigational NNRTI being developed by ViiV Healthcare, worked about as well as efavirenz in a study of treatment-naive people, researchers reported at the IAS conference (*abstract TUAB0101*). With its unique binding pattern to HIV reverse transcriptase, lersivirine remains active against virus with certain NNRTI resistance mutations, including Y181 changes.

Investigators with the multinational Phase IIb A5271015 trial compared lersivirine vs. efavirenz for first-line therapy. A total of 195 participants with no reverse transcriptase resistance mutations at baseline were randomly assigned to received 500 or 750 mg lersivirine or placebo once daily, in combination with tenofovir/emtricitabine;
about one-third were in South Africa, with the remainder in Europe, North and South America, and Australia.

In an intent-to-treat analysis at 48 weeks, 79% of participants in the combined lersivirine arms achieved HIV RNA below 50 copies/mL, compared with 89% of those taking efavirenz, which was not a significant difference.

Overall, the 500-mg and 750-mg doses of lersivirine did not work as well as efavirenz for people with pre-treatment viral load above 10,000 copies/mL (75% vs. 62% vs. 82%, respectively). However, further analysis showed that this difference was significant only among South African participants; researchers suggested suboptimal adherence may play a role.

Lersivirine was somewhat better tolerated than efavirenz. Serious adverse events and discontinuations due to side effects were uncommon and occurred with similar frequency across arms. Lersivirine recipients reported fewer neuropsychiatric symptoms but more nausea. Lersivirine was also associated with more favorable blood lipid profiles.

IBALIZUMAB

A monoclonal antibody now known as ibalizumab (formerly TMB-355 and TNX-355) was well tolerated and significantly reduced HIV viral load when added to optimized background therapy for treatment-experienced patients, researchers reported at ICAAC.

Stanley Lewis of TaiMed Biologics USA and colleagues conducted a randomized, double-blind trial (TMB-202) to determine an optimal dosing regimen for ibalizumab (abstract H2-794b). This humanized monoclonal antibody binds to the CD4 receptor and prevents HIV from entering host cells, but its mechanism of action is not fully understood.

Data from a prior Phase IIa trial, presented in 2006, showed that weight-adjusted doses of ibalizumab produced significantly greater viral load reduction than placebo. In this Phase IIb study, participants were randomly assigned to receive intravenous infusions of either 800 mg ibalizumab every 2 weeks or 2,000 mg every 4 weeks, both for 24 weeks. All patients also received an optimized background regimen that contained at least one active agent.

The analysis included 113 highly treatment-experienced patients with high mean viral load (>100,000 copies/mL) and low average CD4 count (109 cells/mm$^3$); they had been HIV positive for an average of 17 years and had documented resistance to three antiretroviral drug classes.

Both doses of ibalizumab significantly reduced HIV RNA over 24 weeks, with 44% in the 800-mg arm and 28% in the 2,000-mg arm achieving undetectable levels (<50 copies/mL); mean viral load reductions were 1.6 and 1.5 log, respectively. After primary endpoint data were collected, participants had the option to continue ibalizumab with further monitoring; extended follow-up showed durable virological response.

Ibalizumab was generally well tolerated, with no drug-related serious adverse events or premature treatment discontinuations. The most common side effects were skin rash, diarrhea, headache, nausea, and upper respiratory symptoms—all mostly mild-to-moderate—with no significant differences between dose arms.

Although fewer than half of participants achieved undetectable viral load, ibalizumab could be an important new option for heavily treatment-experienced patients, as combining it with other active agents may provide additive potency otherwise unavailable to people with highly resistant HIV. A new formulation that may allow subcutaneous rather than intravenous administration is now being studied.

APPROVED HIV THERAPY

WHEN TO START ART

When to start antiretroviral treatment continues to be a subject of controversy, with recently reported studies adding to the growing body of conflicting evidence. (See “When to Start Antiretroviral Treatment: A Changing Equation,” BETA, Summer/Fall 2008.)

As described in the September 26, 2011, Archives of Internal Medicine, an analysis from the large CASCADE cohort found that ART initiation at CD4 cell counts between 350 and 499 cells/mm$^3$ predicted slower HIV disease progression, but a similar benefit was not apparent for people with 500 to 799 cells/mm$^3$.

This analysis included 9,455 participants in 23 clinical cohorts in Europe, Australia, and Canada, who collectively contributed 52,268 person-years (PY) of follow-up data. The researchers constructed monthly sequential subcohorts (for January 1996 through May 2009) that included all treatment-naive, ART-eligible individuals without AIDS who had a CD4 count less than 800 cells/mm$^3$. They compared time to AIDS diagnosis or death between patients who initiated ART in a given month and those who remained untreated.

Overall, 812 participants (8.6%) developed AIDS and 544 people (5.8%) died. Patients who started ART with CD4 counts of 200 to 349 cells/mm$^3$ had about a 40% reduction in the risk of AIDS or death relative to untreated people (hazard ratio [HR] 0.59). Those who started treatment within the 350 to 499 cells/mm$^3$ range—as recommended by U.S. treatment guidelines—reduced their risk by 25% (HR 0.75). But those who started ART with CD4 counts between 500 and 799 cells/mm$^3$ saw no significant decrease in risk (HR 1.10).
Looking at “number needed to treat,” 21 people with 200–349 cells/mm³ or 34 people with 350–499 cells/mm³ would have to start ART to prevent a single AIDS diagnosis or death within three years.

Another study with a very different patient population also confirmed the benefits of starting ART when the CD4 count falls below 500 cells/mm³, though this analysis did not include people with higher levels.

The HPTN 052 trial made headlines at the July IAS conference with its finding that early ART initiation reduced the risk of HIV transmission by nearly 100% (see “Treatment is Prevention,” page 10), but it also offers evidence about timing of ART initiation (abstract MOAX0105).

In this study, which included 1,763 mostly heterosexual serodiscordant couples in nine countries, HIV positive participants with CD4 counts between 350 and 550 cells/mm³ were randomly assigned to either start ART immediately or defer therapy until their CD4 count fell below 250 cells/mm³ or they developed an AIDS-related illness.

About 20% of HIV positive participants in the deferred treatment group needed to start therapy during follow-up, usually due to a falling CD4 cell count. More than 90% of people who started either early or deferred ART achieved undetectable viral load.

Overall, there were 41% fewer clinical events in the immediate treatment group; incidence rates were 4.0 per 100 PY in the deferred arm vs. 2.4 per 100 PY in the immediate arm. Most strikingly, there were 17 new cases of extrapulmonary tuberculosis among participants who deferred treatment but only three cases among people who started ART immediately. The number of deaths was similar, however, with 13 in the deferred therapy group and ten in the immediate group.

In an editorial accompanying the CASCADE report, Daniel Kuritzkes from Brigham and Women’s Hospital said that the results confirm the validity of the current treatment guidelines threshold, but support continuation of the START trial—which will randomly assign participants with high CD4 counts to either start therapy immediately or wait—to get more definitive data about optimal timing of treatment initiation.

**LONG-TERM RALTEGRAVIR**

The HIV integrase inhibitor raltegravir remains safe and effective after four years, researchers reported at the October EACS conference.

Jürgen Rockstroh from the University of Bonn presented findings from a pre-specified subgroup analysis of the Phase III STARTMRK trial, which compared first-line therapy with 400 mg twice-daily raltegravir vs. 600 mg once-daily efavirenz, both in combination with coformulated tenofovir/emtricitabine. The trial included 563 treatment-naive participants with an average CD4 count of approximately 200 cells/mm³.

This study was designed to follow participants on blinded therapy for five years, longer than most randomized trials. As previously reported, the primary analysis at 48 weeks showed that raltegravir worked as well as efavirenz but caused fewer side effects, especially central nervous system symptoms.

The 192-week analysis included 420 participants, after 21% of people assigned to raltegravir and 30% assigned to efavirenz had dropped out. In a non-completer-earns-failure analysis, 76% of raltegravir recipients and 67% of efavirenz recipients had undetectable viral load (<50 copies/mL). Response rates were higher (91% vs. 85%, respectively) if patients who quit for reasons other than treatment failure were excluded.

While the study was only designed to evaluate non-inferiority, raltegravir appeared somewhat more effective than efavirenz by week 192, as the confidence interval for the difference no longer included zero (suggesting the drugs were no longer equivalent). CD4 cell gains were 360 cells/mm³ in the raltegravir arm and 301 cells/mm³ in the efavirenz arm. Virological and immunological responses did not differ according to patient sex, age, race/ethnicity, hepatitis B and C coinfection status, HIV clade, or baseline viral load.

Raltegravir continued to be well tolerated during extended follow-up. The overall rate of drug-related adverse events was lower in the raltegravir arm compared with the efavirenz arm (50% vs. 80%, respectively), but there were few serious clinical adverse events or deaths in either group. No signal of raltegravir liver toxicity was observed with long-term use.

**STOPPING INACTIVE NRTIS**

Treatment-experienced people with HIV may be able to simplify their antiretroviral therapy by discontinuing inactive NRTIs without loss of virological control, according to a study presented at ICAAC (abstract H2-787).

People with extensive treatment experience and highly resistant HIV may use “salvage” regimens that contain multiple drugs with varying degrees of efficacy. Treatment guidelines do not take a position on keeping inactive drugs in a regimen that is working well—and many clinicians and patients are hesitant to fix something that’s not broken—but continuing inactive drugs can add toxicities, contribute to drug interactions, and increase cost.

Benoit Trotier and colleagues from Clinique Médicale l’Actuel in Montreal performed a prospective study of people with multiddrug-resistant HIV who had undetectable
viral load (<50 copies/mL) on a stable ART regimen containing at least one nonactive NRTI.

The trial enrolled 31 men who had been on treatment for an average of 14 years; the median nadir (lowest-ever) CD4 count was 158 cells/mm³, indicating serious past immune deficiency, but the current median was relatively high at 525 cells/mm³.

At study entry, 22 participants were taking regimens containing four antiretroviral agents and nine people were taking five drugs. Most patients (94%) removed inactive lamivudine (3TC; Epivir) or emtricitabine (FTC; Emtriva) from their regimen, while one discontinued zidovudine (AZT; Retrovir) and one stopped tenofovir (Viread).

After 24 weeks on the simplified regimen, all participants maintained undetectable viral load. CD4 counts continued to rise, with an average gain of 13 cells/mm³, and none of the patients saw their count fall below 200 cell/mm³. There were no deaths and no new serious adverse events or laboratory abnormalities.

The researchers concluded that removing nonactive NRTIs from a regimen with four or more antiretroviral drugs in patients with suppressed viral load “appears to be safe” and “did not affect the ability of the regimen to maintain the viral load under the limit of detection through 24 weeks.”

ASSOCIATED CONDITIONS

HEPATITIS C TREATMENT FOR COINFECTED PEOPLE

As reported in the Winter/Spring 2011 issue of BETA, the first direct-acting antiviral agents for treatment of hepatitis C virus (HCV) infection—boceprevir (Victrelis) and telaprevir (Incivek)—were approved by the FDA this past May.

These two HCV protease inhibitors, when added to pegylated interferon plus ribavirin, significantly improved sustained virological response (SVR) rates for previously untreated and treatment-experienced patients with hard-to-treat HCV genotype 1.

The new drugs were approved for HIV negative people, but they are also expected to increase the likelihood of an HCV cure for HIV/HCV coinfected individuals. The first data from coinfection studies of both drugs were presented this year.

Briefly, in an interim analysis at 24 weeks, 71% of coinfected patients taking boceprevir plus pegylated interferon/ribavirin achieved undetectable HCV RNA, compared with 34% of those on standard therapy alone. Interim 24-week results were similar for coinfected people taking telaprevir plus pegylated interferon/ribavirin: 71% vs. 55%, respectively.

See page 30 in this issue of BETA for an extensive review of HIV/HCV coinfection and its treatment.

BONE LOSS AND FRACTURES

People with HIV appear to be more susceptible—and at younger ages—to a variety of progressive non-AIDS conditions, including osteopenia (low bone mineral density) and osteoporosis (more extensive bone loss). This may be attributable to long-term HIV infection itself, use of specific antiretroviral drugs, or a combination of factors.

A meta-analysis of nearly 40 studies published in the September 2011 Journal of Clinical Endocrinology and Metabolism found that HIV positive people may experience bone loss soon after starting antiretroviral treatment, but the decline reaches a plateau after about one year and remains generally stable thereafter.

Mark Bolland from the University of Auckland and colleagues searched medical databases for published reports and conference abstracts regarding bone mineral density changes over time. The primary analysis included six studies that compared HIV positive adults with HIV negative control groups, and 31 uncontrolled studies were included in a secondary analysis.

The primary analysis showed no significant differences between HIV positive and HIV negative participants in percentage change from baseline in total hip or femoral neck bone density, but spine density decreased in HIV positive participants.

Looking at all 37 studies together, treatment-naive people with HIV showed bone mineral loss ranging from 2.1% to 3.2% one year after starting ART, and 2.4% to 4.4% two years after treatment initiation.

However, the annualized rate of bone density change was greatest at one year and declined thereafter. Looking at HIV positive people who were already on ART at baseline, bone mineral density was stable or increased slightly after one year, stable or decreased slightly after two years, and stable at two and a half years or later.

The study authors concluded that bone mineral density is stable in HIV positive cohorts established on ART, whereas cohorts initiating ART have short-term accelerated bone mineral loss followed by a longer period of stability or even increases.

A limitation of this meta-analysis is that only three studies included patients taking tenofovir—now one of the most widely used antiretroviral drugs—which has been linked to bone loss in some studies.

“[O]ur results suggest that low bone mineral density should not be a concern for the majority of younger and middle-aged individuals with HIV, who are adequately treated with antiretroviral therapy and well nourished,”
The investigators concluded, but “[d]etermining whether this also applies to older cohorts of HIV-infected people is an important question to be addressed.”

The major threat with bone loss is that it may lead to fractures, which can be life-threatening, especially for older individuals. A retrospective study presented at IAS 2011 (abstract MOAB0101) looked at fracture rates in a cohort of more than 56,000 HIV positive U.S. military veterans receiving care between 1988 and 2009.

The incidence of fractures increased overall after the introduction of effective combination ART (from 1.61 to 4.06 events per 100 PY), but the researchers suggested this could be because treatment enabled more people to survive to older ages.

Looking only at people treated after the advent of combination therapy in 1996, bone loss was significantly associated with use of tenofovir or lopinavir/ritonavir (Kaletra)—though not ART overall—but traditional risk factors such as cigarette smoking and diabetes were more important.

**Tuberculosis Treatment**

A trio of studies published in the October 20, 2011, *New England Journal of Medicine* showed that the optimal time for HIV positive people with tuberculosis (TB) to start antiretroviral treatment varies according to immune system health.

Prior research has conclusively shown that HIV positive people with TB benefit from ART, but the optimal time for ART initiation has been unclear. Starting antiretroviral and anti-TB drugs around the same time raises concerns about drug interactions and additive toxicities and increases the risk of immune reconstitution inflammatory syndrome (IRIS), or worsening of symptoms as the immune system recovers.

The CAMELIA (Cambodian Early versus Late Introduction of Antiretrovirals) study looked at the link between ART timing and mortality among 661 previously untreated adults with advanced immune deficiency who were newly diagnosed with TB; all had CD4 counts below 200 cells/mm³, with a very low median of 25 cells/mm³.

Participants began a standard six-month course of TB treatment, then were randomly assigned to start ART after either two or eight weeks. After a follow-up period of about 25 months, the risk of death was significantly lower in the group that started ART earlier (18% vs. 27%, respectively). But the risk of IRIS was more than twice as high in the earlier ART group. By 50 weeks, both the earlier and later ART groups were doing well, with 95% achieving undetectable HIV viral load and a median CD4 cell gain of more than 100 cells/mm³.

The second study, ACTG A5221, also compared earlier (within two weeks) vs. later (after 8 to 12 weeks) ART initiation after starting TB treatment. This trial included 809 participants, mostly in Africa, with CD4 counts below 250 cells/mm³ (median 77 cells/mm³).

Fewer people in the earlier ART group developed new AIDS-defining illnesses or died by 48 weeks (13% vs. 16%), but the difference did not reach statistical significance. Looking only at participants with CD4 counts below 50 cells/mm³, however, significantly fewer people in the earlier ART group developed AIDS or died (16% vs. 27%). Again, IRIS was significantly more common in the earlier ART group (11% vs. 5%).

Finally, the SAPI (Starting Antiretroviral Therapy at Three Points in Tuberculosis) study looked at integration of ART and TB treatment in South Africa. This trial included 642 HIV positive TB patients with CD4 counts below 500 cells/mm³ (median 150 cells/mm³).

After a median 18 months of follow-up, 8% of participants who started ART earlier (within four weeks after beginning TB treatment) and 9% who initiated ART later (four weeks after the eight-week intensive phase of TB therapy) progressed to AIDS or died, not a significant difference (6.9 vs. 7.8 events per 100 PY).

But here again, among people with CD4 counts below 50 cells/mm³, the difference was significant in favor of the early ART strategy (8.5 vs. 26.3 events per 100 PY). Patients in the early ART group, however, were more likely to develop IRIS (20.1 vs. 7.7 cases per 100 PY) and had a higher rate of adverse events that required switching antiretroviral drugs.

“Early initiation of ART in patients with CD4 T-cell counts of less than 50 [cells/mm³] increased AIDS-free survival,” the researchers concluded. “Deferral of the initiation of ART to the first four weeks of the continuation phase of tuberculosis therapy in those with higher CD4 T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death.”

“We found that recommendations by the World Health Organization to start ART as soon as possible after initiation of tuberculosis treatment for patients with very low T-cell counts were in line with our findings,” said lead investigator Salim Abdool-Karim in a press release issued by Columbia University’s Mailman School of Public Health. “However, the results for patients with tuberculosis and HIV who have a higher T-cell count call for a different approach” and “WHO recommendations may need to be revisited.”

**Transmission and Prevention**

**Treatment Is Prevention**

One of the major stories at this summer’s IAS conference was incontrovertible evidence that early antiretro-
viral treatment can reduce the risk of HIV transmission to nearly zero, while at the same time reducing disease progression.

Myron Cohen from the University of North Carolina (abstract MOAX0102) presented results from HIV Prevention Trials Network (HPTN) Study 052—first announced this past May—which enrolled 1,763 mostly heterosexual serodiscordant couples in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, Zimbabwe, and the U.S.; about half the couples had HIV positive women while the rest had HIV positive men.

HIV positive partners with CD4 counts between 350 and 550 cells/mm³—above the recommended treatment initiation threshold at the time—were randomly assigned to either start a three-drug antiretroviral regimen immediately or defer treatment until their CD4 count fell below 250 cells/mm³ or they developed AIDS-related illnesses. All received safer sex counseling, free condoms, regular HIV testing, and screening and treatment for other sexually transmitted infections.

In an interim analysis after a median follow-up period of 20 months, HIV positive men and women who started ART early were significantly less likely to transmit the virus to their partners. There were 39 new infections in the untreated group compared with four in the immediate treatment group (27 and one, respectively, were genetically linked to the partner’s HIV strain), reflecting a 96% reduction in the risk of transmission.

“There is a clinical benefit for the patient and a dramatic, nearly 100% reduction in transmission,” said Cohen. “We can’t get much better.”

The overall rate of new infections was 2.2 per 100 person-years (PY) in the deferred treatment arm compared with 0.3 per 100 PY in the immediate ART arm (1.7 vs. 0.1 per 100 PY, respectively, for genetically linked infections). Nearly two-thirds of all cases involved transmission from women to men.

Based on these findings, an independent data and safety monitoring board (DSMB) recommended that the trial be stopped early and all HIV positive participants be offered treatment.

The HPTN 052 findings confirm that HIV treatment that suppresses viral load can dramatically reduce the risk of transmission, adding support to efforts to expand global access to antiretroviral drugs.

“These results are a real scientific breakthrough and a game changer in the response to HIV,” said UNAIDS Executive Director Michel Sidibé. “We must embrace treatment as prevention as part of a combination prevention strategy to achieve our collective vision of zero new infections and zero AIDS-related deaths.”

Given that HPTN 052 enrolled mostly heterosexual couples, its results cannot yet be generalized to men who have sex with men (MSM) or other risk groups. Furthermore, the study showed that HIV transmission does occur rarely even when the positive partner is on effective ART, so unprotected sex in this setting cannot be considered risk-free.

**PREP: MORE QUESTIONS THAN ANSWERS?**

If early ART for HIV positive people has proven to be a resounding prevention success, the benefits of antiretroviral drugs for HIV negative people hoping to avoid infection are less clear, with some studies demonstrating a large reduction in risk and others showing little or no effect.

As reported in the Winter/Spring 2011 issue of BETA, the iPrEx study (described in the December 30, 2010, *New England Journal of Medicine*) demonstrated that pre-exposure prophylaxis (PrEP) using oral tenofovir plus emtricitabine—along with regular HIV testing, risk-reduction counseling, and free condoms—dramatically reduced the risk of infection.

Robert Grant from the Gladstone Institute at the University of California, San Francisco, presented further iPrEx findings at the IAS meeting (abstract WELBC04). In this analysis of nearly 2,500 high-risk men who have sex with men and transgender women randomly assigned to receive daily oral tenofovir/emtricitabine or placebo, HIV incidence fell by 42% overall among tenofovir/emtricitabine recipients, by 73% among participants who reported good tenofovir/emtricitabine adherence, and by 92% among people who had measurable levels of the drugs in their blood.

While the reduction in relative risk is impressive, it is important to note that the absolute number of infections prevented was small; the 42% relative risk reduction, for example, reflects a decrease in absolute risk from about 5% to about 3%.

In contrast with iPrEx, the FEM-PrEP trial failed to show a prevention benefit for women. This study evaluated daily oral tenofovir/emtricitabine in 1,951 HIV negative heterosexual women in Kenya, South Africa, and Tanzania. This past April, Family Health International stopped a trial early after an interim review found about the same number of new HIV infections in the tenofovir/emtricitabine and placebo arms, indicating that the study was “highly unlikely” to show a statistically significant risk reduction.

The tables turned again this summer in Rome, when researchers presented data from two other studies showing that oral PrEP could in fact reduce the risk of infection for heterosexual women and men.

The Partners PrEP trial enrolled 4,758 serodiscordant heterosexual couples at nine sites in Kenya and Uganda. HIV positive partners were randomly assigned to take oral

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tenofovir alone, tenofovir plus emtricitabine, or placebo once daily. Again, all participants also received a comprehensive package of HIV prevention services and support.

Interim data presented by Jared Baeten from the University of Washington (abstract MOAX0106) showed that tenofovir alone reduced the risk of HIV infection by 62%, while the tenofovir/emtricitabine combination lowered it by 73% (not a statistically significant difference). No safety issues were identified in the two PrEP arms.

The TDF2 trial included 1,200 HIV negative heterosexual women and men in Botswana. Participants were randomly assigned to take either daily oral tenofovir/emtricitabine or placebo, and all received free condoms and counseling about safer sex and drug adherence.

Michael Thigpen from the Centers for Disease Control and Prevention (abstract WELBC01) reported that, here too, tenofovir/emtricitabine reduced the risk of acquiring HIV by 63% overall, with nine new infections in the PrEP group vs. 24 in the placebo group. Risk reduction reached 78% among participants who were infected while the drugs were most likely to be active (within 30 days of their last medication visit). Interestingly, PrEP was less effective for women overall (49% risk reduction), though the efficacy was similar within the 30-day period (76% risk reduction). Serious adverse events were uncommon and occurred with similar frequency in both arms.

The reassurance provided by Partners PrEP and TDF2 again gave way to confusion when investigators with the VOICE trial announced in September that they would halt a study arm testing oral tenofovir monotherapy as PrEP, after an interim analysis found that the trial would be unable to demonstrate that the drug works better than placebo.

VOICE (MTN-003), conducted by the Microbicide Trials Network, enrolled more than 5,000 sexually active HIV negative women in South Africa, Uganda, and Zimbabwe. They were randomly assigned to receive oral tenofovir alone, oral tenofovir/emtricitabine, a placebo tablet, 1% tenofovir vaginal gel microbicide, or placebo gel, all administered daily.

The disappointing news continued in November, when an independent DSMB recommended that the tenofovir and placebo microbicide arms should also be discontinued, again because an interim review found that tenofovir gel was not more effective than placebo gel, with an HIV incidence rate of 6% in both arms.

These findings are in conflict with those of the CA-PRISA 004 trial—reported with much fanfare at the 2010 International AIDS Conference in Vienna—which showed that 1% tenofovir gel applied vaginally before and after intercourse (rather than every day) reduced the risk of HIV infection by 39% overall and by 54% among women with good adherence.

Although the VOICE trial has been greatly reduced in size, the study arm testing the oral tenofovir/emtricitabine combination is continuing; follow-up is expected to be completed in June 2012. The DSMB has identified no safety concerns related to either oral or vaginal administration of tenofovir.

The reasons for the discrepant results in these studies is not yet clear. The iPrEx study showed good efficacy among mostly gay men, and Partners PrEP and TDF2 showed risk reduction in a mixed population of men and women, but the two studies of only women—FEM-PrEP and VOICE—have so far not demonstrated efficacy. Some researchers have hypothesized that tenofovir may reach higher concentrations in rectal tissue compared with vaginal tissue.

VOICE results to date suggest that tenofovir/emtricitabine may be more effective than tenofovir alone, given that the oral combination arm has been allowed to continue; however, tenofovir/emtricitabine was not shown to be effective in FEM-PrEP, and oral tenofovir monotherapy was nearly as effective as the combination in Partners PrEP.

Adherence clearly has a major influence; all studies in which PrEP demonstrated a beneficial effect found a strong association between efficacy and adherence, while also showing that achieving good adherence was difficult for many participants for reasons that are not fully understood.

Importantly, all studies have tested PrEP in combination with comprehensive prevention support, and it remains to be seen whether these outcomes can be matched in “real world” settings. Reassuringly, though, studies have not revealed “behavioral disinhibition,” or the tendency to forego safer sex practices if people think they are protected by drugs or microbicides.

Results from an online survey of 1,333 gay and bisexual men, presented at the National HIV Prevention Conference in August, showed that nearly half said they would be very likely or extremely likely to use PrEP after being told about the iPrEx findings.

While some advocates urge rapid implementation of PrEP—San Francisco is already launching a pilot project—others have expressed concerns about the spread of drug-resistant HIV, long-term drug toxicities in people who are not sick, and the potential for coercion to use drugs for public health rather than personal benefit; issues of cost and access are also critical.

“The past 30 years have shown that reductions in HIV transmission and the burden of AIDS rely on a combination of approaches that need to be tailored, adapted, and selected on the basis of the specific situations and populations,” wrote the authors of an editorial in the September 2011 issue of The Lancet, reflecting on the prevention data presented at the IAS meeting.
“Integration of antiretroviral prophylaxis into HIV prevention strategies must not be at the expense of tried and tested behavioral interventions, and care must be taken to safeguard the usefulness of these drugs for treatment in the future and to encourage a healthy drug-development pipeline,” they continued. “The fight against HIV/AIDS is a long-game, and current enthusiasm for positive results must lead to approaches that are sustainable in the long-term.”

HORMONAL CONTRACEPTION AND HIV RISK

Hormonal contraceptives may significantly increase the risk of HIV infection for both women and men, according to a study presented at the IAS conference (abstract WEAX0206) and described in the October 4, 2011, advance online edition of The Lancet Infectious Diseases.

Jared Baeten and fellow investigators with the Partners in Prevention HSV/HIV Transmission Study (originally designed to determine whether treating herpes simplex virus could help prevent HIV infection) looked at the association between hormonal contraception and women’s risk of HIV acquisition, as well as transmission from HIV positive women to their male partners. Prior human and animal studies have indicated that hormonal contraceptives may increase infection risk, but findings have been inconsistent.

This prospective analysis included 3,790 heterosexual serodiscordant couples participating in two longitudinal studies in nine African countries. About 11% used hormonal contraceptives, most frequently depot medroxyprogesterone acetate (DMPA or Depo Provera), an injection given once every three months; couples were counseled to use condoms along with their hormonal method. Follow-up continued for approximately 18 months.

Among 1,314 couples with an initially HIV negative woman, the HIV incidence rate was significantly higher for those who used hormonal contraceptives (adjusted HR 1.98, or nearly double the risk). Among 2,476 couples with an initially HIV negative man, the infection rate increased to a similar extent when his partner used hormonal contraceptives (adjusted HR 1.97).

Looking only at women who used oral hormonal contraceptives, the increased risk of HIV infection did not reach statistical significance, but the number of women using pills was too small to draw definitive conclusions.

While the observed increases in relative risk of HIV acquisition appear dramatic, it is important to note that the absolute number of new HIV infections was small: ten among DMPA users and three among oral contraceptive users.

“Our findings provide new data that show that contraception might increase a woman’s risk of acquiring HIV-1, and they are consistent with longitudinal studies of sex workers in Kenya and family planning attendees from Uganda and Zimbabwe,” the study authors wrote.

The biological mechanisms underlying these findings are fully not understood, but they may include changes in vaginal tissue, cytokine regulation, CCR5 coreceptor expression, or shedding of HIV in cervical/vaginal secretions. The study found higher HIV RNA levels in cervical secretions from women using injectable hormonal contraceptives, even while plasma viral load was similar. The study did not follow HIV positive partners after they started ART, which reduces the amount of virus in genital fluids.

In an accompanying editorial, Charles Morrison and Kavita Nanda from the non-profit global development organization FHI 360 emphasized that use of effective contraception to prevent unintended pregnancies has “unequivocal benefits” that must be weighed against the small increase in HIV risk, including reduced maternal mortality, increased socioeconomic status of women, and improved health of children spaced further apart.

“Active promotion of DMPA in areas with high HIV incidence could be contributing to the HIV epidemic in sub-Saharan Africa, which would be tragic,” they wrote. “Conversely, limiting one of the most highly used effective methods of contraception in sub-Saharan Africa would probably contribute to increased maternal mortality and morbidity and more low-birthweight babies and orphans—an equally tragic result.”

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