The 17th International AIDS Conference (AIDS 2008)—the world’s largest meeting focused on all aspects of the epidemic—took place August 3–8 in Mexico City. The 48th Annual Interscience Conference on Antiretroviral Agents and Chemotherapy (ICAAC) this year was held jointly with the Infectious Diseases Society of America (IDSA) annual meeting on October 25–28 in Washington, DC. This meeting was soon followed by the 9th International Congress on Drug Therapy in HIV Infection (HIV9), held November 9–13 in Glasgow, Scotland. Finally, the 16th Conference on Retroviruses and Opportunistic Infections (CROI) took place in Montreal February 8–11. Highlights from these meetings are reviewed below, along with recent news from medical journals and other sources.

TREATMENT GUIDELINES UPDATED
On November 3, the U.S. Department of Health and Human Services (DHHS) published the latest revision of its Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. The new version includes updated information on preferred antiretroviral drugs for treatment-naive patients, regimen simplification, treatment of special populations, and laboratory and therapeutic drug monitoring. Drug resistance testing is now recommended for people with HIV RNA levels above 500 (rather than 1,000) copies/mL.

Perhaps the most significant changes are the addition of once-daily darunavir (Prezista), boosted with ritonavir (Norvir), as a preferred protease inhibitor (PI) and the removal of the abacavir (Ziagen)/3TC (lamivudine; Epivir) coformulation (Epzicom) as a preferred nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone for people starting treatment for the first time.

Abacavir/3TC was promoted to “preferred” status in the December 1, 2007, guidelines, thanks to the new HLA-B*5701 test, which can screen out individuals who are genetically susceptible to abacavir hypersensitivity reactions.

With the latest revision, however, the drug was returned to “alternative” status due to ongoing concerns about cardiovascular risk and suboptimal antiretroviral efficacy in patients with high baseline viral load (see news item below).

Federal Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection also were recently updated, on July 29. The new version includes revised recommendations for initial antiretroviral regimens. It also reinstates the “alternative” PI status of nelfinavir (Viracept), due to the resolution of concerns about the chemical contaminant ethyl methane sulfonate (see Summer 2008 “News Briefs”). The guidelines are available online at www.aidsinfo.nih.gov/Guidelines. Changes are summarized in the “What’s New in the Document?” section of the adult/adolescent guidelines, and highlighted in yellow throughout the text and tables of both documents.

ATAZANAVIR, DARUNAVIR, MARAVIROC, RALTEGRAVIR RECEIVE EXPANDED APPROVAL
On October 1, the U.S. Food and Drug Administration (FDA) approved Bristol-Myers Squibb’s PI atazanavir (Rey-
In August, Gilead Sciences’ NRTI tenofovir (Viread, also a component of the Truvada and Atripla combination pills), one of the most widely prescribed anti-HIV medications, also received approval as a once-daily treatment for chronic hepatitis B virus (HBV) infection.

Two Phase III clinical trials (Studies 102 and 103) showed that tenofovir suppressed HBV better than adefovir (Hepsera) in both hepatitis B “e” antigen (HBeAg) negative and HBeAg positive patients at 48 weeks, and demonstrated good safety through 96 weeks. Several studies presented at this fall’s annual meeting of the American Association for the Study of Liver Diseases showed good outcomes in HIV/HBV coinfected individuals, as well.

Of the five approved drugs that directly target HBV, tenofovir and 3TC also have potent activity against HIV; maraviroc (Baraclude) inhibits HIV to a lesser extent. Another dually active drug, emtricitabine (Emtriva), is approved for HIV treatment and under study for hepatitis B.

Current DHHS antiretroviral treatment guidelines recommend that all HIV/HBV coinfected patients who require treatment for hepatitis B should receive a complete HAART regimen that includes dually active drugs. Use of these drugs as monotherapy can lead to resistance mutations in both viruses.

Updated international guidelines for the care of HIV positive individuals with chronic hepatitis B—including information on new diagnostic tools, hepatitis B treatment, drug resistance, HBV vaccination, and hepatotoxicity of antiretroviral drugs—were published in the July 31, 2008, issue of *AIDS*. A letter to the editor in the November 30, 2008, issue of the same journal discusses optimal management of HIV/HBV coinfected patients with high CD4 cell counts who do not yet require antiretroviral therapy.

**ABACAVIR EFFICACY AND CARDIOVASCULAR RISK**

As noted above, the latest version of the DHHS antiretroviral treatment guidelines removes coformulated abacavir/3TC (Epzicom) from the list of preferred dual NRTIs for first-line therapy. This decision was based on recent study findings indicating that abacavir may not suppress HIV as well as tenofovir/emtricitabine (Truvada) in people with high baseline viral load, and that abacavir is associated with increased risk of cardiovascular events. Data are conflicting in both areas, however, and the benefits and risks of abacavir are the subject of ongoing debate.

**HIV SUPPRESSION AND BASELINE VIRAL LOAD**

As reported in the Summer 2008 “News Briefs,” ACTG study 5202 was modified in March after interim results showed that treatment-naive patients with baseline HIV RNA above 100,000 copies/mL taking abacavir/3TC were more likely to experience virological failure than those taking tenofovir/emtricitabine, when combined with efavirenz (Sustiva) or boosted atazanavir. Unblinded data from these...
patients were presented in Mexico City (AIDS 2008 abstract THAB0303); the trial is continuing with the low viral load group.

The study enrolled 1,858 treatment-naive participants, of whom 797 had high baseline viral load. Within the latter group, in an intent-to-treat analysis, time to virological failure was significantly shorter in the abacavir/3TC arm compared with the tenofovir/emtricitabine arm. In addition, more patients in the abacavir/3TC arm modified their regimen, and grade 3–4 adverse events emerged sooner (participants were not prescreened for abacavir hypersensitivity).

In related research presented at ICAAC (abstract H-1254), investigators from the U.K. and Thailand performed a meta-analysis of prior clinical trials comparing abacavir/3TC and tenofovir/emtricitabine in first-line regimens containing a boosted PI. A MEDLINE search identified 12 relevant trials with a total of 4,896 treatment-naive participants. Among patients with baseline HIV RNA below 100,000 copies/mL, 79% taking tenofovir/emtricitabine and 70% taking abacavir/3TC achieved viral suppression below 50 copies/mL; for those with baseline viral load above 100,000 copies/mL, the corresponding rates were 71% and 66%. Tenofovir/emtricitabine produced higher rates of viral suppression when combined with lopinavir/ritonavir, boosted fosamprenavir, or boosted atazanavir.

The researchers concluded that these findings suggest higher efficacy for first-line tenofovir/emtricitabine relative to abacavir/3TC in patients with both high and low baseline viral loads. However, they noted that a majority of intent-to-treat failures were attributable to discontinuation for reasons other than poor virological response; since most studies did not include HLA-B*5701 screening, the results might reflect a higher drop-out rate in the abacavir/3TC arms due to suspected hypersensitivity reactions.

In response to the ACTG 5202 findings, abacavir manufacturer GlaxoSmithKline (GSK) performed an analysis of other clinical trials of abacavir/3TC regimens that employed the same efficacy endpoints (AIDS 2008 abstract THAB0304; ICAAC abstract H-1251). The analysis included six studies with a total of 2,940 treatment-naive participants, stratified by baseline HIV RNA level. Virological response and safety outcomes did not differ significantly in the abacavir/3TC and tenofovir/emtricitabine arms, regardless of initial viral load.

GSK’s HEAT study compared the Epzicom and Truvada coformulation pills, both combined with lopinavir/ritonavir, in 688 treatment-naive participants, again stratified by initial viral load; in this trial, patients underwent HLA-B*5701 screening for hypersensitivity, and susceptible individuals were not given abacavir. At 96 weeks, Epzicom and Truvada were similarly effective (60% vs 58%, respectively, with HIV RNA below 50 copies/mL) and side effects were comparable in both arms (AIDS 2008 abstract LBPE1138; ICAAC abstract H-1233).

In the open-label ARIES study, 515 HLA-B*5701 negative treatment-naive participants started abacavir/3TC plus 300/100 mg atazanavir/ritonavir. At week 36, they were randomly assigned to stay on this regimen or simplify therapy by switching to 400 mg/day atazanavir and stopping ritonavir.

In a planned week-36 interim analysis reported at ICAAC (abstract H-1250a), 80% of patients achieved HIV RNA below 50 copies/mL, with similar response rates in those with high and low baseline viral load (76% vs 84%, respectively); 4% and 2%, respectively, experienced virological failure. Rates of viral suppression below 400 or 200 copies/mL were closer in the high and low viral load groups, leading the researchers to suggest that while patients with high baseline HIV RNA might be slower to respond, most ultimately achieve full suppression.

Finally, three cohort analyses presented at the Glasgow conference also demonstrate similar efficacy of abacavir/3TC compared with tenofovir/emtricitabine. In the German STAR cohort, 113 treatment-naive patients started Epzicom and 563 started Truvada, all with lopinavir/ritonavir (HIV9 abstract P7). Among participants with baseline HIV RNA above 100,000 copies/mL, the likelihood of viral suppression below 50 copies/mL at 24 weeks was similar in the Epzicom and Truvada arms, in both intent-to-treat (57% vs 51%) and as-treated (57% vs 54%) analyses.

In the U.K. TEAL study, 120 patients started abacavir/3TC, while 140 started tenofovir/emtricitabine, usually with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (HIV9 abstract P79); there were substantially more patients with high baseline viral load in the latter arm. Among treatment-experienced patients, similar proportions in the two treatment arms achieved HIV RNA below 50 copies/mL at 48 weeks in a intent-to-treat “missing = failure” analysis (87% vs 76%; not a statistically significant difference).

Among treatment-naive participants, the intent-to-treat response rate was significantly higher in the tenofovir/emtricitabine arm (94% vs 76%). Rates were similar in an as-treated analysis, reflecting more discontinuations in the abacavir/3TC arm. Virological failure occurred in 4% of treatment-naive patients in both arms.

Another U.K. study looked at 87 treatment-naive patients starting Epzicom or Truvada with an NNRTI (usually efavirenz) or a PI (usually atazanavir/ritonavir or lopinavir/ritonavir) (HIV9 abstract P14). At 24 weeks, as-treated response rates were similar in the Epzicom and Truvada arms among participants with baseline HIV RNA
CARDIOVASCULAR RISK

As discussed in the Summer 2008 issue of BETA, researchers with the large D:A:D study reported at the 2008 Retrovirus meeting (and in the April 26, 2008, issue of The Lancet) that use of abacavir within the prior six months was associated with a 1.9-fold increased incidence of myocardial infarctions (MIs); ddI (didanosine; Videx) was associated with a smaller increased risk (48%).

Longer-term data—encompassing 33,308 HIV positive participants contributing 178,835 person-years of follow-up—were presented at the 2009 Retrovirus meeting (CROI 2009 abstract 44LB). The D:A:D investigators continued to observe an association between recent abacavir use and MIs, this time a 68% increase in risk. Similarly, ddI was associated with a 41% increase in MI risk, but no link was found with other NRTIs, including tenofovir (which was not included in the earlier analysis).

Presenter Jens Lundgren of the D:A:D Study Group noted that if “channeling bias” (the tendency to prescribe perceived-safer drugs for patients with pre-existing cardiovascular disease) influenced the abacavir findings, it should have also disfavored tenofovir, which was not the case. After the unexpected D:A:D findings were first reported, other research teams performed similar analyses of drug-related cardiovascular risk—either clinical events or biomarkers—in their studies.

Further, participants who had used abacavir in the past but stopped before one year had a slight but non-significant increase in risk, but this was not seen among people who remained on the drug. The French investigators concluded that “initiating abacavir was...associated with an increased risk of MI while longer exposure to abacavir was not.”

In the Australian STEAL study, investigators studied 360 participants who simplified treatment by switching from individual NRTIs to either the Epzicom or Truvada combination pills (CROI 2009 abstract 576). Those taking the abacavir-containing pill had a higher rate of cardiovascular disease events (seven total events, including three MIs and one stroke) than those taking the tenofovir-containing pill (one event), though the difference did not reach statistical significance due to small numbers.

Constance Benson and colleagues likewise conducted an analysis of cardiovascular events in the AIDS Clinical Trials Group ALLRT (ACTG Longitudinal Linked Randomized Trials) study, also known as ACTG A5001 (CROI 2009 abstract 721). This analysis included 3,205 HIV positive patients who initiated first-line treatment in five randomized clinical trials of antiretroviral therapy, including 781 who started a regimen containing abacavir. “In contrast to D:A:D and SMART,” they stated, “we did not find a significant association between recent abacavir use and MI or severe cardiovascular disease risk for [antiretroviral therapy]-naive patients randomized to an initial abacavir regimen.”
In light of the D:A:D findings, GSK performed a retrospective pooled analysis of data from 54 previous clinical trials that included a total of 14,683 participants, of whom 9,639 took regimens containing abacavir (AIDS 2008 abstract THAB0305). The meta-analysis did not find an increased risk of MIs or other cardiovascular events among patients taking abacavir compared with other NRTIs (2.04 vs 2.34 MIs per 1000 person-years; not a statistically significant difference).

Since they were not designed to look at cardiovascular outcomes, these trials did not measure relevant biomarkers. However, in an analysis of 476 participants in the HEAT study (described above), levels of hsCRP, IL-6, and another inflammatory marker, sVCAM-1, decreased in both the Epzicom and Truvada arms after starting therapy, but did not differ significantly between the two groups.

At the Retrovirus meeting, Frank Palella presented results from a combined analysis of 197 HIV positive women in the Women’s Interagency HIV Study (WIHS) and 129 men in the Multicenter AIDS Cohort Study (MACS) who either included abacavir in their first-line regimen or switched to it later, matched with an equal number who did not use abacavir (CROI 2009 abstract 150LB). Over a mean four years of follow-up, IL-6 and D-dimer levels fell overall, but did not differ significantly between the abacavir recipients and non-recipients; hsCRP levels also decreased in both arms, but more so in participants who did not take abacavir. The investigators concluded, “Abacavir use was not independently associated with elevated plasma levels of hsCRP, IL-6, and D-dimer.”

Likewise, a small longitudinal analysis of cardiovascular disease–associated biomarkers by Simon Mallal’s group in Australia (reported in the November 30, 2008, issue of AIDS) found that, overall, “inflammatory and metabolic indicators were not significantly worse on abacavir-based therapy,” and the researchers did not detect a consistent effect of abacavir in either treatment-naive or treatment-experienced participants.

On the other hand, a laboratory analysis of platelet function in samples from 30 abacavir recipients and 28 patients taking other NRTIs at a hospital in Dublin, Ireland (CROI 2009 abstract 151LB), found that while platelet hyper-reactivity was present in HIV positive individuals overall compared with general population norms, the increase was greater in those who took abacavir. The researchers suggested that enhanced blood clotting due to platelet hyper-reactivity might help explain increased cardiovascular risk associated with abacavir.

Concluding a session on HIV complications at the Retrovirus conference, Peter Reiss from the University of Amsterdam attempted to make sense of the conflicting data (CROI 2009 abstract 152). Across the various studies, he noted, increased cardiovascular disease risk associated with abacavir seems to be more apparent in people who switch to the drug after HIV is already suppressed than in those starting treatment for the first time. Furthermore, he said, the data suggest an acute (possibly inflammatory) process such as rupture of arterial plaques or subsequent thrombosis (clotting), rather than a chronic process such as initial plaque buildup.

While studies continue, Reiss concluded, “it seems prudent to withhold abacavir from patients with high underlying cardiovascular disease risk if suitable alternative regimens are available. If not, patients’ absolute cardiovascular disease risk in the presence of abacavir should be minimized by aggressive management of traditional cardiovascular risk factors.”

**MORE EVIDENCE FAVORS EARLY TREATMENT**

Evidence continues to accumulate supporting the benefits of earlier treatment for HIV (see “When to Start Antiretroviral Treatment: A Changing Equation,” BETA, Summer 2008). Current U.S. and European guidelines recommend that asymptomatic individuals start antiretroviral therapy when their CD4 count falls below 350 cells/mm$^3$, but recent findings suggest that starting sooner may be better.

At ICAAC, researchers with the North American ACORD trial presented data from more than 8,000 treatment-naive participants in several U.S. and Canadian cohorts (abstract H-896b). About 30% started HAART early, when their CD4 count was between 351 and 500 cells/mm$^3$ (median 420 cells/mm$^3$). The remainder deferred therapy, starting with a median count of 275 cells/mm$^3$; this group included patients who initiated HAART as soon as their CD4 count fell to 350 cells/mm$^3$, those who waited longer, and those who died without ever starting treatment.

During follow-up, 8.9% of participants who started HAART with 351–500 cells/mm$^3$ died of any cause, compared with 7.6% in the deferred therapy group. After adjusting for cohort and calendar year, patients who deferred treatment had a 71% higher risk of death than those who started with 351–500 cells/mm$^3$, and the risk rose by about 10% as the CD4 count at treatment initiation fell by 100 cells/mm$^3$.

At a press conference discussing these findings, presenter Mari Kitahata said the data “strongly support the use of antiretroviral treatment for patients at a CD4 count of 500 and below, regardless of the presence of symptoms.”

Kitahata presented further findings at the Retrovirus conference looking at even earlier treatment initiation (CROI 2009 abstract 71). This analysis assessed mortality among 2,620 individuals who initiated therapy with a CD4 count greater than 500 cells/mm$^3$ (median 674 cells/mm$^3$) compared with people who started in the 350–500 cells/mm$^3$
range (median 435 cells/mm³). After controlling for potential confounding factors, the risk of death was 60% lower in the very early treatment group than in the later group, but above 500 cells/mm³ the risk of death did not continue to decrease in a linear manner.

However, an analysis of more than 21,000 participants in multiple North American and European cohorts participating in the ART Cohort Collaboration (the When to Start Consortium) did not find very early treatment to be similarly advantageous (CROI 2009 abstract 72LB). Jonathan Sterne and colleagues found that while people who deferred treatment until their CD4 count fell within the 251–350 cells/mm³ range had a 28% higher rate of AIDS or death than those who started with 351–450 cells/mm³, earlier treatment had a decreasing benefit at higher CD4 counts, and conferred no significant additional advantage above about 400 cells/mm³.

Sterne emphasized in a press conference that while earlier treatment above 350 cells/mm³ may be beneficial, these findings also underline the importance of testing, diagnosing, and getting people on treatment when they can benefit most, before their CD4 count falls below 250–300 cells/mm³.

Turning to immunological response, a study presented at the Glasgow meeting found further evidence that earlier treatment promotes more complete CD4 cell recovery after starting antiretroviral therapy (HIV9 abstract P10). Italian investigators retrospectively assessed immunological outcomes for up to eight years in 352 patients with sustained viral suppression on HAART.

After five years of treatment, 82% of patients who started therapy with more than 350 cells/mm³ achieved a CD4 count of 500 cells/mm³—the lower end of the normal range for HIV negative people. A majority (69%) of those who started treatment with 200–350 cells/mm³ also attained 500 cells/mm³, but only 29% of those who started with fewer than 200 cells/mm³ did so. While people who started treatment with more than 350 cells/mm³ reached a plateau after four years on suppressive HAART, those who started with fewer than 200 cells/mm³ continued to experience a CD4 cell increase even after eight years, but many still never managed to achieve full immunological recovery.

In a related study reported in the February 1, 2009, issue of Clinical Infectious Diseases, Gregory Robbins and colleagues with the ACTG 384 study team also found that people who start treatment above the currently recommended threshold are more likely to achieve full immunological recovery.

After nearly three years on HAART, individuals at all baseline CD4 count strata experienced similar CD4 cell gains (about 300 cells/mm³), but only those who started therapy with more than 350 cells/mm³ achieved normal levels. Furthermore, ratios of naive to memory CD4 cells and CD4 to CD8 cells were reduced in people who started treatment later, indicating poorer immune function.

These results “support current guidelines to start antiretroviral therapy at a threshold of 350 cells/mm³ and suggest that there may be immunological benefits associated with initiating therapy at even higher CD4 cell counts,” the investigators concluded.

**TREATMENT INTERRUPTION REVISITED**

Interruption of antiretroviral therapy has fallen out of favor in recent years due to mounting evidence, including data from the large SMART trial, indicating that the strategy has more risks than benefits (see “News Briefs,” BETA, Summer 2008). But two studies presented in Glasgow suggest that treatment interruption may be feasible for carefully selected cases.

Unlike SMART—in which patients interrupted and resumed therapy based on CD4 cell count—the FOTO (Five On, Two Off) trial looked at short-cycle treatment interruptions on a fixed schedule (HIV9 abstract O19). The study included 60 participants with well-controlled HIV taking tenofovir, emtricitabine, and efavirenz (the drugs in the Atripla pill). All had a CD4 count above 200 cells/mm³ (mean about 670 cells/mm³) and sustained viral suppression. They were randomly assigned to either continue daily therapy or switch to alternating five consecutive days on treatment followed by two days off (most took weekend breaks).

At 24 weeks, 53 participants had completed the study, and none in either arm experienced virological failure (confirmed HIV RNA greater than 400 copies/mL). In an intent-to-treat analysis, 83% of participants in the FOTO arm and 80% in the daily therapy arm had HIV RNA less than 50 copies/mL, not a statistically significant difference. Ten participants in the FOTO arm and eight in the daily therapy arm experienced viral load “blips” (transient increases to 50–500 copies/mL), but CD4 cell counts remained high and no AIDS-related events occurred in either arm.

The researchers are continuing follow-up to assess whether short-cycle treatment interruption provides durable viral suppression over a longer term. If it continues to demonstrate good results, this strategy not only would offer improved convenience for individuals in wealthy countries, but also could reduce drug costs in resource-poor areas.

A longer fixed-length cycle, however, did not perform as well. As reported in the January 1, 2009, issue of the Journal of Infectious Diseases, 435 HIV positive adults in Côte d’Ivoire who were on successful antiretroviral therapy were randomly assigned to either stay on continuous therapy or switch to a two-months-on, four-months-off sched-
ule. After 24 months, 14.6% of patients in the cyclical therapy arm had a CD4 count below 350 cells/mm$^3$, compared with 5.6% in the continuous therapy arm, which did not quite reach a predetermined threshold for non-inferiority. NNRTI resistance mutations, however, were 20% more common in the cyclical arm.

In a study of CD4-guided interruption as opposed to fixed-length cycles (HIV9 abstract O18), investigators with the Italian LOTTI trial prospectively compared continuous HAART to CD4-guided treatment interruption in 329 patients. Overall, participants were healthier than those in SMART, with viral load below 50 copies/mL, baseline CD4 count above 700 cells/mm$^3$, and a nadir (lowest-ever) CD4 count that had never fallen below 200 cells/mm$^3$.

LOTTI also used a higher CD4 cutoff for interrupting and resuming therapy. Patients were randomly assigned to either stay on continuous therapy, or else stay off treatment while their CD4 count remained above 700 cells/mm$^3$, resuming when it fell to 350 cells/mm$^3$. (In SMART, participants stopped therapy when their CD4 count was above 350 cells/mm$^3$ and did not resume until it fell to 250 cells/mm$^3$.)

After four years of follow-up, about 12% of participants in both the treatment interruption arm and the continuous therapy group experienced progression to AIDS (any opportunistic illness), death from any cause, or non-opportunistic diseases requiring hospitalization.

Serious adverse events were only slightly less likely in the treatment interruption arm compared with the continuous therapy arm (21% vs 27%), but significantly more patients in the continuous arm developed primary or secondary cardiovascular or metabolic side effects (1% vs 11%). Furthermore, no patients in the treatment interruption arm experienced major cardiovascular events or developed diabetes, compared with four and six cases, respectively, in the continuous therapy arm. The major hazard in the treatment interruption group was bacterial pneumonia in seven patients, compared with none in the continuous therapy arm.

Over the entire follow-up period, the average daily cost of therapy was less than half as much in the treatment interruption arm compared with the continuous therapy arm (9 vs 20 Euros, or about $11 vs $25).

Regarding the reduction in cardiovascular and metabolic side effects—which was not seen in SMART—presenter Franco Maggiolo suggested that it may take time for these benefits to show up, and SMART was halted after just one year, compared with four years of follow-up in LOTTI.

In a related study reported in the December 1, 2008, issue of the Journal of Acquired Immune Deficiency Syndromes, Daniel Skiest and colleagues assessed quality of life, symptoms, blood lipid levels, and body measurements in 167 ACTG 5170 participants with CD4 counts above 350 cells/mm$^3$ (current median 833 cells/mm$^3$, nadir median 436 cells/mm$^3$) who underwent prolonged treatment interruption for up to 96 weeks.

Self-reported quality of life scores were high while the participants were still on therapy, and remained so after treatment interruption. The mean number of symptoms decreased significantly, from 8.2 to 7.0. Levels of total cholesterol, low-density lipoprotein (LDL or “bad”) cholesterol, high-density lipoprotein (HDL or “good”) cholesterol, and triglycerides decreased at weeks 12 and 24 after treatment interruption. Measurements of arm, waist, hip, and mid-thigh circumference increased (most patients had been taking thymidine analog NNRTIs).

Essentially, the LOTTI and ACTG 5170 studies demonstrated that most people who started treatment “too early” according to the current guidelines (i.e., with more than 350 cells/mm$^3$) can safely stop until they reach that level. However, there is increasing evidence that ongoing HIV replication has previously unrecognized harmful effects, such as immune activation and systemic inflammation, leading many experts to recommend that patients remain on treatment even with a high CD4 count.

**WOMEN BENEFIT FROM TREATMENT AS MUCH AS MEN**

While some earlier studies suggested that women might not respond as well as men to antiretroviral therapy, later research has indicated that this was likely a reflection of poorer access to care and other socioeconomic factors. At the Retrovirus conference, Kimberly Struble from the FDA’s Center for Drug Evaluation and Research presented results from a large meta-analysis of sex differences in registrational trials of antiretroviral drugs conducted over nearly a decade (CROI 2009 abstract 987b).

Using information submitted to the FDA to support drug approval, the investigators constructed a database that included 17,826 participants in 38 randomized, controlled trials of 14 antiretroviral agents. They found no clinically or statistically significant differences between women and men in 48-week efficacy outcomes. This held true for both treatment-naive and treatment-experienced patients, and for all antiretroviral drug classes analyzed.

**MARAVIROC LOOKS BETTER WITH NEW TROFILE TEST**

The first-in-class CCR5 antagonist maraviroc (Selzentry), which recently received full FDA approval for treatment-experienced patients, has also been tested as first-line therapy. Drugs in this class interfere with CCR5, one of the core-
CEPTORS HIV USES TO ENTER CELLS; ONLY INDIVIDUALS WITH EXCLUSIVELY CCR5-TROPIC VIRUS (RATHER THAN CXCR4-TROPIC OR DUAL/MIXED STRAINS) ARE CONSIDERED ELIGIBLE TO USE MARAVIROC.

The Phase III MERIT study, which included more than 700 participants, failed to show that maraviroc worked as well as efavirenz in treatment-naive patients. While the overall percentages of participants achieving HIV RNA below 50 copies/mL were similar in both arms at 48 weeks (65% vs 69%), among patients who started with a high baseline viral load (100,000 copies/mL or higher), maraviroc did not perform as well as efavirenz (60% vs 67%).

Further analysis showed that nearly half the patients who experienced virological failure on maraviroc had CXCR4-tropic HIV that might have gone undetected at screening. Therefore, researchers reanalyzed the MERIT data, testing stored blood samples using the more sensitive enhanced Trofile HIV tropism assay that became commercially available this summer (it is now the only version on the market).

As reported at ICAAC (abstract 1232a), about 15% of participants who initially were classified as having exclusively CCR5-tropic HIV turned out to have dual/mixed virus using the newer test. Added to the earlier exclusions, a total of 52% of treatment-naive patients screened had CXCR4-tropic or dual/mixed HIV.

After excluding these additional individuals, 68% of patients in both the maraviroc and the efavirenz arms achieved HIV RNA below 50 copies/mL at 48 weeks. Virological response was also similar in the subgroup with high baseline viral load (64% vs 63%, respectively). In the maraviroc arm, the proportion of patients who discontinued therapy due to lack of efficacy fell to 9% from 12% in the earlier analysis (compared with 4% in the efavirenz arm).

Like the original analysis, the reanalysis also showed that people taking maraviroc had a larger increase in CD4 cells (174 vs 144 cells/mm³, respectively). Another post hoc analysis (ICAAC abstract H-1248) found that maraviroc led to faster CD4 cell recovery—as well as rapid CD8 cell gains—during the first four weeks of therapy, and that patients in the maraviroc arm were less likely to experience discordant virological and immunological response. And among patients who did not achieve full viral suppression, significantly fewer maraviroc recipients experienced AIDS-defining events (1% vs 9%).

**RALT EGRAVIR AS FIRST-LINE THERAPY**

The integrase inhibitor raltegravir is another first-in-class drug approved for treatment-experienced patients and undergoing evaluation for people starting first-line therapy. At ICAAC, researchers presented data from the STARTMRK trial, which included 563 treatment-naive patients randomly assigned to start treatment with either raltegravir or efavirenz, both in combination with tenofovir/emtricitabine (abstract H-896a).

After 48 weeks, raltegravir was found to be non-inferior to efavirenz. In an intent-to-treat analysis, 86% of patients in the raltegravir arm achieved HIV RNA below 50 copies/mL, compared with 82% in the efavirenz arm. Furthermore, time to virological response was significantly shorter in the raltegravir arm. CD4 cell gains were statistically similar in both arms (189 vs 163 cells/mm³, respectively).

However, drug-related clinical adverse events—especially central nervous system symptoms—were significantly less frequent in the raltegravir arm. The rate of serious adverse events was 10% in both arms. Only one patient taking raltegravir developed cancer, compared with nine efavirenz recipients (this was a concern since an earlier study suggested a higher rate of cancer among raltegravir recipients, likely due to chance). Raltegravir recipients experienced significantly smaller increases in total cholesterol, LDL (“bad”) cholesterol, and triglycerides, while those taking efavirenz had a larger increase in HDL (“good”) cholesterol.

At the Mexico City conference, researchers reported longer-term data, through 96 weeks, from another raltegravir study (AIDS 2008 abstract TUAB0102). In this Phase II trial, 198 treatment-naive participants were randomly assigned to receive 100, 200, 400, or 600 mg twice-daily raltegravir or once-daily efavirenz, all combined with tenofovir/3TC. After the 48-week analysis, all raltegravir recipients were given the 400-mg dose, since there was little difference in response or adverse events across doses.

In an intent-to-treat analysis at 96 weeks, the regimens were equivalent in terms of virological efficacy, with 83% in the raltegravir arm and 83% in the efavirenz arm achieving viral suppression below 50 copies/mL. Again, CD4 cell increases were similar in the two arms, but raltegravir recipients experienced fewer adverse side effects. Even after 96 weeks, no known raltegravir resistance mutations were observed.

**COMBINING NEW DRUGS**

The recent approval of two new drug classes—CCR5 antagonists and integrase inhibitors—that so far have demonstrated potent antiviral activity with few side effects opens the door for combination regimens that exclude two, and potentially all three, of the older antiretroviral classes, with their associated problems of side effects and drug resistance in treatment-experienced patients.

Early results from one of the first studies of a PI- and NRTI-sparing regimen were presented at the Glasgow meeting (HIV9 abstract P45). This non-randomized trial includ-
ed 95 patients on failing triple-class regimens treated at San Raffaele Hospital in Milan, Italy. Using expanded access programs, participants took regimens containing raltegravir plus maraviroc plus the new NNRTI etravirine (Integrit); raltegravir plus either maraviroc or etravirine plus PI-sparing optimized background therapy; raltegravir plus either maraviroc or etravirine plus PI-containing background therapy, which usually included ritonavir-boosted darunavir; or raltegravir plus PI-containing background therapy with neither maraviroc nor etravirine.

After 24 weeks, 86% of patients taking raltegravir/maraviroc/etravirine had HIV RNA below 50 copies/mL; for the other three arms, response rates were 90%, 79%, and 79%, respectively. Participants taking only the three new drugs experienced the largest CD4 cell increase, at 217 cells/mm³ (compared with about 90–115 cells/mm³ in the other three arms). The raltegravir/maraviroc/etravirine regimen was, according to the investigators, “very well tolerated,” although it required a large number of pills per day.

Further research is needed to determine the risks and benefits of novel antiretroviral regimens that depart from the familiar standard of care of a PI or NNRTI plus a dual NRTI backbone. These data suggest that effective, tolerable therapy is feasible without the adverse effects associated with the NRTI and PI classes.

**IL-2 CONFERS NO LONG-TERM BENEFITS**

Some people do not achieve adequate CD4 cell recovery using antiretroviral therapy alone, and researchers have investigated several strategies for immune restoration, including interleukin 2 (IL-2; Proleukin), a cytokine produced by immune cells that stimulates CD4 cell production and maturation.

Results from two large international Phase III studies of IL-2 were presented at the Retrovirus conference. ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) enrolled 4,111 participants from 252 clinical sites in 25 countries (CROI 2009 abstract 90aLB). Participants had relatively well-preserved immune function, with a CD4 count of at least 300 cells/mm³ (median at study entry 457 cells/mm³, median nadir 197 cells/mm³). Half received subcutaneous injections of IL-2 in addition to antiretroviral therapy, while half received antiretroviral therapy alone. The median duration of follow-up was 6.9 years.

SILCAAT (Subcutaneous IL-2 in patients with Low CD4 Counts under Active Antiretroviral Therapy) enrolled 1,695 participants from 114 clinical sites in 11 countries. This group had more advanced immune suppression, with a CD4 count of 50–299 cells/mm³ (median at entry 202 cells/mm³, median nadir 60 cells/mm³). Again, half received IL-2 injections plus antiretroviral therapy and the rest received antiretroviral therapy alone. The median duration of follow-up was 7.6 years when a Data Safety Monitoring Board stopped the trial.

In both studies, IL-2 injections raised CD4 cell counts above the levels attained by participants receiving only antiretroviral therapy (153 extra cells/mm³ in ESPRIT, 57 cells/mm³ more in SILCAAT). Furthermore, while individuals taking antiretroviral therapy alone experienced a slow, steady CD4 cell increase, those taking IL-2 experienced a faster increase during the first year before reaching a plateau.

But these CD4 cell increases did not translate into clinical benefits after seven years. Rates of AIDS-defining illnesses, serious illness not traditionally considered HIV-related, and death due to any cause were similar for IL-2 recipients and non-recipients. In addition, IL-2 was associated with adverse events, including gastrointestinal symptoms and psychiatric side effects. Deep vein thrombosis (blood clot) was the most frequent life-threatening adverse event in both trials.

In a press conference discussing these findings, SILCAAT investigator Yves Levy suggested that the additional CD4 cells resulting from IL-2 stimulation may not be functionally equivalent to CD4 cells that are produced naturally. Also, an additional 60–160 CD4 cells may not be enough to significantly affect clinical outcomes in people on suppressive antiretroviral therapy.

In the end, Levy elaborated in a NIAID press release, “the results of these two studies indicate that although a person’s number of CD4 T-cells is a key measure of success in the treatment of HIV with antiretroviral drugs, we can’t rely on CD4 T-cell counts to predict whether immune-based therapies such as IL-2 will improve the health of HIV-infected individuals.”

**NEW PHARMACO-ENHANCERS**

A small dose of ritonavir is often used to boost plasma levels of other protease inhibitors, leading to more effective antiretroviral therapy and greater convenience (lower pill burden and less frequent dosing). Ritonavir has its disadvantages, however, including metabolic side effects and the fact that a single company, Abbott Laboratories, controls how it can be used. At the Retrovirus conference, two research teams presented early data from studies of new “pharmaco-enhancer” agents that work like ritonavir to raise levels of other drugs in the body by interfering with their processing by the cytochrome P450 3A (CYP3A) enzyme.

Brian Kearney from Gilead Sciences presented early data on GS 9350, which affects CYP3A but is not active against HIV (CROI 2009 abstract 40). In preclinical studies,
GS 9350 appeared to be a more specific CYP3A inhibitor than ritonavir, with less effect on other CP450 enzymes. In addition, it did not cause lipid accumulation in fat cells and only minimally interfered with glucose uptake. In a Phase I trial of healthy HIV negative volunteers, GS 9350 at doses of 100 and 200 mg inhibited clearance of midazolam (used as a “probe” to assess CYP3A inhibition) by 92% and 95%, respectively, compared with 95% for ritonavir.

After these promising proof-of-concept results, Gilead researchers created “quad” coformulation pills containing 100 or 150 mg GS 9350 plus Gilead’s integrase inhibitor candidate elvitegravir along with tenofovir and emtricitabine—a complete once-daily regimen in a single pill. In another Phase I study of 44 HIV negative volunteers, both the 100 mg and 150 mg GS 9350 coformulations boosted plasma concentrations of elvitegravir to therapeutic levels. GS 9350 was generally well tolerated, with no severe drug-related laboratory abnormalities or clinical adverse events.

Gilead plans to start a Phase II head-to-head trial of the GS 9350 quad coformulation versus Atripla in treatment-naive HIV positive patients.

In the second presentation, Robert Guttendorf from Sequoia Pharmaceuticals reported preclinical and Phase I clinical data for that company’s pharmaco-enhancer candidate, SPI-452 (CROI 2009 abstract 41). In laboratory studies using human liver cells, SPI-452 inhibited metabolism of all HIV protease inhibitors as well as the investigational hepatitis C virus protease inhibitor boceprevir, with no antiviral activity of its own. In rats and dogs, SPI-452 potently inhibited CYP3A and boosted plasma levels of saquinavir (Invirase), lopinavir, and atazanavir.

In the first clinical trial of SPI-452 in 58 healthy HIV negative volunteers, the drug successfully boosted saquinavir levels. In a Phase I proof-of-concept trial of 67 HIV negative volunteers, SPI-452 increased plasma concentrations of darunavir by up to 37-fold and atazanavir by up to 13-fold. SPI-452 was generally well tolerated with no severe adverse events and no significant changes in liver function, heart rhythm, or blood lipid levels.

**CANCER AND IMMUNE DEFICIENCY**

Several recent studies have looked at AIDS-defining and non-AIDS-defining cancer in people with HIV. In the October 18, 2008, issue of AIDS, Antonella d’Arminio Monforte and colleagues with the D:A:D study reported on the link between immune suppression and malignancies. Looking at 23,437 HIV positive participants from the U.S., Europe, and Australia prospectively followed for a total of 104,921 PY, the investigators analyzed deaths due to AIDS-defining—that is, Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer—and non-AIDS-defining cancers and their association with CD4 cell count.

During the follow-up period, 305 participants died due to any type of malignancy. NHL accounted for the largest number of AIDS-defining cancer deaths (82), followed by KS (28) and cervical cancer (2). Of the non-AIDS-defining malignancies, lung cancer was the most frequent cause of death (62), followed by gastrointestinal cancers (25) and hematological malignancies (22). Anal cancer, caused by the same strains of human papillomavirus (HPV) as cervical cancer, accounted for 20 deaths, reflecting the fact that regular anal Pap tests are not part of the standard of care like cervical Pap smears. Liver cancer, a potential outcome of chronic hepatitis B or C, accounted for 16 deaths.

Further analysis revealed that the overall mortality rate for non-AIDS-defining cancer exceeded the rate for AIDS-defining cancer for all patients except those with a CD4 count below 50 cells/mm³. Mortality due to AIDS-defining malignancies decreased from 20.1 per 1,000 PY when the most recent CD4 count was less than 50 cells/mm³ to 0.1 per 1,000 PY when it was greater than 500 cells/mm³. Non-AIDS-defining malignancies had a smaller but still significant association with immune suppression, with mortality decreasing from 6.0 per 1,000 PY when the latest CD4 count was below 50 cells/mm³ to 0.6 per 1,000 PY when it was above 500 cells/mm³. This association remained when anal cancer and Hodgkin lymphoma (malignancies with known infectious causes) were excluded. Surprisingly—and in contrast to hepatitis B—hepatitis C coinfection was not linked to non-AIDS-defining malignancies in this study.

“The severity of immunosuppression is predictive of death from both AIDS-defining malignancies and non-AIDS-defining malignancies in HIV-infected populations,” the researchers concluded, adding that “improvements to patients’ immune systems following the use of combination antiretroviral therapy may be expected to have a positive impact on the risk of death from non-AIDS-defining malignancies.” They also recommended other cancer prevention strategies, including smoking cessation and hepatitis B vaccination.

In a related study described in the January 2, 2009, issue of AIDS, Nancy Crum-Cianflone and colleagues retrospectively analyzed cancer incidence in a cohort of 4,498 HIV positive U.S. military personnel with a total 33,486 PY of follow-up. Unlike D:A:D, which started in the HAART era (2000), this study extended back to the early years of the epidemic (1984). Overall, 10% of cohort participants developed cancer of any type. Across the entire study, KS was the most common cancer, followed by NHL. The rate of AIDS-defining cancer increased from 7.6 cases per 1,000 PY in the early pre-HAART period (1984-1990) to 14.2 per 1,000 PY in the late pre-HAART period (1991-1995), but then declined to 5.4 per 1,000 PY in the early post-HAART era (1996-2000) and further to 2.7 per 1,000 PY in the late
post-HAART period (2001-2006). The most common non-AIDS-defining cancers were non-KS skin cancers and anal cancer. Rates of non-AIDS-defining cancers rose in the post-HAART periods as HIV positive people lived longer due to effective treatment (2.9, 2.8, 4.2, and 6.7 cases per 1,000 PY, respectively). During the most recent period, 71% of all cancers were non-AIDS-defining.

Low CD4 cell count was a predictor of AIDS-defining malignancies, but this study did not find an association with non-AIDS-defining cancers (for which the only independent predictors were older age and white race, due to higher risk of skin cancer). HAART was protective against AIDS-defining malignancies, but did not have a significant effect on non-AIDS-defining cancers. Most people with non-AIDS-defining cancers had relatively well-preserved immune function (median CD4 count of 430 cells/mm³), leading the researchers to suggest that “strategies beyond achievement of high CD4 cell counts may be necessary for reduction in [non-AIDS-defining cancers].”

At the Retrovirus conference, Michael Silverberg presented an analysis of infection-related cancers at California Kaiser Permanente health facilities (CROI 2009 abstract 30). This study included 18,890 HIV positive patients, each matched with ten HIV negative members, followed from 1996 through 2006. In addition to anal cancer, liver cancer, and Hodgkin’s lymphoma, head and neck cancer was also classified as infection-related due to its association with HPV (though it can also be caused by non-infectious causes such as smoking).

A total of 482 non-AIDS-defining cancers were identified in the HIV positive group, 220 infection-related and 269 infection-unrelated (seven people had both). The rate of infection-related but non-AIDS-defining cancers was about seven times greater in the HIV positive compared with the HIV negative group (29.7 vs. 4.4 per 10,000 PY). Specifically, HIV positive individuals had an 81-fold higher risk of anal cancer, a 17-fold higher risk of Hodgkin’s lymphoma, and double the risk of head and neck cancers. The rate of infection-unrelated malignancies was also higher in the HIV positive group, but the difference was nowhere near as large (36.4 vs. 30.6 per 10,000 PY), and was only statistically significant for the most recent time period (2004-2006).

Looking at specific malignancies, HIV positive people had an 80% higher risk of kidney cancer and a 70% higher risk of both lung cancer and skin cancer, but a lower risk of prostate cancer. EuroSIDA investigators also looked at the link between CD4 count and non-AIDS-defining cancer after accounting for other risk factors (CROI 2009 abstract 860a). This analysis included 12,865 HIV positive participants with a combined 75,234 PY of follow-up. A total of 317 non-AIDS-defining cancers were diagnosed in 309 patients, an incidence rate of 4.2 per 1000 PY: 58 anal, 24 lung, 60 hematological, 48 Hodgkin’s lymphoma, 40 genitourinary, 55 digestive, and 80 other. Compared to participants with more than 500 cells/mm³, those with fewer than 50 cells/mm³ had a 76% higher risk of non-AIDS-defining cancers, those with 51–200 cells/mm³ had a 82% higher risk, and those with 201–350 cell/mm³ had a 43% higher risk; there was no significant difference for people with 351–500 cells/mm³. Other significant cancer predictors besides CD4 count were older age, AIDS diagnosis, previous history of non-AIDS-defining cancer, time on antiretroviral therapy, and hepatitis B (but again, not hepatitis C). “Immunosuppression was associated with an excess risk of [non-AIDS-defining cancers],” the researchers concluded.

Looking specifically at liver cancer, Gary Clifford and colleagues conducted a case control study of 26 patients with hepatocellular carcinoma (HCC, a type of primary liver cancer) and 251 matched control subjects without HCC in the Swiss HIV Cohort Study. As reported in the October 18, 2008, issue of AIDS, all individuals with HCC had either hepatitis B (11 cases), hepatitis C (12 cases) or both (12 cases). Most recent CD4 cell count was significantly associated with development of HCC (33% increased risk per 100 cells/mm³ lost)—an effect that was particularly pronounced for people with hepatitis B who were not injection drug users. Use of antiretroviral therapy, however, did not significantly reduce HCC risk.

Given the conflicting data produced by research to date, Meredith Shiels and colleagues performed a meta-analysis of 11 studies, with a total of 2,100 cancer cases, comparing rates for HIV positive individuals and for the general HIV negative population as determined from cancer registries; results were presented at the 7th Annual American Association for Cancer Research International Conference on Frontiers in Cancer Prevention Research in November (abstract A117). Overall, people with HIV had about twice the risk of cancer compared with HIV negative individuals; this was more pronounced in HIV positive men (about twice the risk of HIV negative men) than in HIV positive women (50% higher risk than HIV negative women).

Malignancies that occurred more often in the HIV positive group included head and neck, lung, and liver cancer. Inexplicably, in this analysis cancer rates were similar in people diagnosed with AIDS (that is, AIDS-defining illnesses or CD4 count below 200 cells/mm³) and in those with fairly well-preserved immune function. This study adds to the growing body of evidence suggesting that HIV has detrimental effects beyond immune suppression as indicate by CD4 cell count. Here, too, the researchers emphasized the importance of addressing modifiable cancer risk factors such as smoking.
Peripheral lipatrophy (fat loss) of the limbs, buttocks, and face is a recognized adverse effect of the thymidine analog NRTIs AZT and d4T, and possibly of HIV infection itself. As reported at the Retrovirus conference (CROI 2009 abstract 42LB), Marisa Tungsiripat and colleagues evaluated the diabetes drug rosiglitazone (Avandia) as a treatment for limb lipatrophy in 71 HIV positive patients (85% men) on HAART who had used thymidine analog NRTIs for at least 12 months in the past (median four years), but not for at least six months prior to study enrollment. They did not assess facial fat loss, which many patients find a more distressing symptom. Participants generally had well-controlled HIV disease, with a mean CD4 count of about 650 cells/mm$^3$ and 90% with viral load below 400 copies/mL. About one-third had insulin resistance, but people with diabetes were excluded.

Participants were randomly assigned to receive 4 mg twice-daily rosiglitazone or placebo for 48 weeks in addition to their antiretroviral therapy. Limb fat increased in both groups by 48 weeks, as would be expected after discontinuing thymidine analog NRTIs. However, mean limb fat gain was significantly greater in the rosiglitazone arm compared with the placebo arm in terms of both absolute amount (about 900 vs 300 grams) and percentage increase (15% vs 5%). Insulin resistance (measured using the HOMA-IR method) and insulin levels decreased in the rosiglitazone arm, while slightly increasing in the placebo arm. However, mean increases in total cholesterol and non-HDL (“bad”) cholesterol were significantly larger in the rosiglitazone group; triglycerides showed a similar trend, though the difference did not reach statistical significance, and HDL (“good”) cholesterol did not change significantly in either arm. Body mass index and bone mineral density did not change significantly in either group. Rosiglitazone was generally well tolerated, with a similar number of participants discontinuing therapy in both arms.

The investigators concluded that among HIV positive individuals who stopped taking thymidine analog NRTIs, rosiglitazone “significantly improves peripheral lipatrophy even in subjects without insulin resistance.” Past studies of rosiglitazone or pioglitazone (Actos) that did not show similar improvements typically included patients still taking AZT or d4T. Due to their side effects, these drugs are no longer listed as preferred HAART components in the current DHHS treatment guidelines, but they are still widely used in resource-limited countries.

**CANNABIS RELIEVES NEUROPATHY PAIN**

Peripheral neuropathy (nerve damage) affecting the feet and hands is a side effect of certain antiretroviral drugs that can cause persistent pain and impaired daily functioning. As reported in the February 2009 issue of Neuropsychopharmacology, Ronald Ellis and colleagues conducted a controlled clinical trial to evaluate the pain-relieving effect of smoked medical cannabis in people with HIV-associated distal sensory predominant polyneuropathy (DSPN).

The double-blind trial included 34 HIV positive patients with neuropathy pain that was not adequately controlled with two or more classes of analgesic medications. Participants continued their pre-study analgesic regimens throughout the trial. In addition, they were randomly assigned to use smoked cannabis (ranging from 1% to 8% THC) or placebo “joints” four times daily for five days under direct observation in a hospital; after a two-week washout period, they crossed over to the other assignment.

Among the 28 patients who completed the entire study, pain relief was greater with cannabis than with placebo. Nearly half (46%) achieved at least 30% pain reduction while using cannabis compared with 18% while using placebo. Mood and daily functioning improved to a similar degree during both treatment assignments. Side effects were generally mild and self-limited. “Smoked cannabis was generally well-tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV DSPN,” the investigators concluded.

**TREATMENT AS PREVENTION**

HIV transmission could potentially be eliminated worldwide if universal testing were implemented and all people who test positive received prompt treatment, according to a new mathematical model by researchers from the World Health Organization (WHO).

Since effective antiretroviral therapy suppresses HIV viral load and thereby dramatically reduces the risk of transmission, some experts have suggested that more widespread treatment might serve as a prevention strategy. Earlier this year, a model by Julio Montaner and colleagues showed that treating all people with HIV according to current guidelines could produce a steep reduction in the rate of new infections in British Columbia, Canada (see “News Briefs,” BETA, Summer 2008).

But people can transmit the virus long before their CD4 count falls to 350 cells/mm$^3$ (the current guidelines’ threshold for starting therapy) or 200 cells/mm$^3$ (a common practical threshold in resource-limited areas). The new model, described in the November 26, 2008, electronic issue of The Lancet, suggests that universal testing and treatment before it is clinically necessary would have a major effect on the epidemic in sub-Saharan Africa.

The WHO researchers used data from South Africa as a test case. The model assumed a high (16%) HIV preva-
VIRAL LOAD AND HIV TRANSMISSION RISK

A January 2008 statement by the Swiss Federal AIDS Commission sparked considerable controversy, suggesting that HIV positive individuals on antiretroviral therapy who are fully adherent, maintain an undetectable viral load (below 40 copies/mL) for at least six months, and have no concurrent sexually transmitted infections are “not sexually infectious” (at least via heterosexual vaginal intercourse).

At the Mexico City conference, commission president Pietro Vernazza maintained that under the specific circumstances described, unprotected sex with a person with undetectable viral load carried a risk similar to that of sex using a condom: not 100% safe, but within a “comfortable range.”

But the risk is not non-existent, given that people on effective therapy may experience occasional transient viral load increases, or “blips,” and that HIV may be present in genital and anal secretions even if it is undetectable in the blood.

As described in the July 26, 2008, issue of The Lancet, Australian researchers used a mathematical model to quantify the small transmission risk under the circumstances described in the Swiss statement. Assuming that each couple engaged in 100 sexual acts per year, they calculated the cumulative annual probability of transmission as .22% for female-to-male transmission, .43% for male-to-female transmission, and 4.3% for male-to-male transmission. In a population of 10,000 serodiscordant couples, this would translate to 215 expected instances of female-to-male transmission, 425 instance of male-to-female transmission, and 3,524 instances of male-to-male transmission—about four times greater than the risk when using condoms.

“Although we agree that effective antiretroviral treatment which leads to undetectable viral load is likely to have a substantial effect on reducing infectiousness,” the researchers concluded, “our analyses suggest that it should not replace condoms.”

Along similar lines, researchers at the University of Bern set out to conduct a systematic review of medical literature to verify the Swiss statement (AIDS 2008 abstract THAC0505). Looking at more than 200 published articles and 100 abstracts, they found none that exactly mirrored the conditions described in the statement. In the one study that included treated patients with undetectable viral load, no cases of HIV transmission were reported. In four studies of untreated patients with HIV RNA below 400 copies/mL, only one transmission occurred (from an individual with a viral load of 362 copies/mL). No transmissions were identified from individuals with HIV RNA below 40 copies/mL.

At the Retrovirus conference, Steven Reynolds from NIAID presented findings from an analysis of 205 serodiscordant heterosexual couples in Rakai, Uganda (CROI 2009 abstract 52a). Participants were eligible for free antiretroviral therapy if they had a CD4 count below 250 cells/mm³ or advanced immunocompromise according to WHO disease-stage criteria; 12 HIV positive men and eight women started treatment. During 396 person-years (PY) of follow-up prior to treatment initiation, 34 cases of HIV transmission occurred, for an incidence rate of 8.6 per 100 PY. No transmissions occurred during 25 PY of follow-up while the positive partner was on therapy.

In a similar but larger study, Patrick Sullivan and colleagues followed 2,993 serodiscordant heterosexual couples in Kigali, Rwanda, and Lusaka, Zambia, from 2002 to 2008 (CROI 2009 abstract 52bLB). HIV positive partners started antiretroviral therapy when their CD4 count dropped below
200 CD4 cells/mm³ or they developed moderate or advanced disease (again according to WHO criteria).

During a median 17 months of follow-up, 175 cases of HIV transmission occurred, 171 from untreated partners (3.4% per 100 PY) and four from treated partners (0.7% per 100 PY). Couples in which the HIV positive partner was on antiretroviral therapy were actually less likely to engage in high-risk sex, leading the researchers to conclude that the reduced risk was likely due to a combination of antiretroviral therapy and reduced risk behaviors.

In additional to mathematical models and epidemiological studies, researchers have also measured HIV shedding in semen as a predictor of potential transmission.

In a letter in the September 12, 2008, issue of AIDS, French researchers described a man with persistent HIV RNA shedding into his semen despite his blood viral load being fully suppressed on HAART. The man’s initial antiretroviral regimen brought his blood viral load to undetectable within four months (indicating good adherence), but his semen viral load remained unchanged. After a year, he switched drugs to try to reduce HIV shedding in his semen. His blood viral load remained undetectable, but his semen viral load did not begin to decrease until six months later, and did not fall below 400 copies/mL until 11 months after the switch—or 22 months after first starting HAART.

In the August 20 issue of AIDS and at the Retrovirus Conference (CROI 2009 abstract 51) another French team reported data from an analysis of paired blood plasma and semen samples from 145 HIV positive men with negative female partners enrolled in an assisted reproduction program that used “sperm washing” to enable conception without putting the woman at risk. They found that 5% of the men had detectable virus in their semen despite being on antiretroviral therapy and having a blood viral load less than 40 copies/mL (conversely, 6% had detectable HIV in their blood but not in their semen). All of these men had some semen samples with undetectable HIV, indicating that levels fluctuated over time and a single test might miss potentially infectious virus.

Similarly, Prameet Sheth reported on a study comparing 25 HIV positive Toronto men who were starting antiretroviral therapy and 13 who had been on suppressive therapy for at least four years (CROI 2009 abstract 50). In all of the newly treated men, plasma HIV RNA became persistently undetectable (below 50 copies/mL) by week 16. While 70% had undetectable semen viral load (below 300 copies/mL) by week 4, some still had detectable HIV RNA in their semen at 24 weeks. Even more (48%) had at least one detectable semen viral load test after starting therapy; 14% of the time HIV RNA was detectable in semen but not blood plasma.

Among the men on long-term treatment, about one-third had detectable semen HIV RNA. This was more likely to occur in men with higher baseline semen viral load, but baseline plasma viral load, CD4 cell count, and herpes simplex virus status did not predict HIV shedding in semen.

“Although effective HAART often eliminated HIV RNA from the semen, isolated HIV semen shedding was common, even after extremely prolonged suppression of blood viral load,” the investigators concluded. “Public health messages and policy must be tailored carefully to reflect this reality.”

Finally, a study looking at stable male-male couples in which the negative partner was recently infected, genetic testing of viral strains in both partners showed that infectious HIV may be free-floating in the seminal fluid, not just sequestered as cell-associated DNA in infected semen lymphocytes (CROI 2009 abstract 49LB).

Taken together, these findings indicate that while antiretroviral treatment clearly lowers the risk of HIV transmission and may play a role in reducing the scope of the epidemic, it is not a guarantee against infection in individual cases.

**TRANSMISSION VIA ORAL SEX?**

The risk of HIV transmission through oral sex has been a subject of debate since the early years of the epidemic. But the issue is difficult to resolve based on epidemiological studies, since most people do not limit themselves to a single sexual practice. As described in the December 2008 issue of the International Journal of Epidemiology, researchers from Imperial College in London undertook a systematic review to assess the risk of HIV transmission via “orogenital intercourse,” both fellatio (on a man) and cunnilingus (on a woman).

The authors searched the PubMed database and bibliographies of relevant articles through July 2007. Out of the 56,214 titles searched, they identified ten potentially appropriate studies. Two additional studies were identified through bibliographies, and one was found through discussions with experts.

Ten studies, all from North America or Europe, provided estimates of HIV transmission probabilities per partner, incidence per partner, incidence per study participant, and incidence per sex act. Only three were conducted after the advent of HAART, which suppresses viral load and therefore reduces transmission risk. Given the small number of studies, they did not consider a meta-analysis (in which data from all studies are pooled) appropriate.

Six studies reported no instances of transmission via oral sex. The four studies that reported non-zero estimates included per-partner estimates of 20% (in a small study with only ten participants) and 1%, one per-study-participant estimate of 0.37%, and one per-act estimate of 0.04%.

“There are currently insufficient data to estimate precisely
There is a clear need for effective, woman-controlled HIV prevention methods, but trials of microbicides—gels or other products that protect against vaginal or rectal infection—have been frustratingly inconclusive. (See “Microbicide Development: Positive Women’s Concerns,” page 45, for more information.) Two recent studies have produced more definitive findings, disappointing in one case, promising in the other.

In the December 6, 2008, issue of The Lancet, Stephanie Skoler-Karpoff and colleagues reported on a large randomized trial comparing Carraguard gel (a carrageenan seaweed compound being developed by the Population Council) versus a placebo gel in more than 6,000 sexually active HIV-negative women at three sites in South Africa. Participants were instructed to apply the gel inside the vagina before each act of intercourse, but were also advised to use condoms.

After two years of follow-up, the HIV incidence rate among Carraguard users was 3.3 per 100 PY (134 new infections) compared with 3.8 per 100 PY (151 infections) in the placebo arm, which was not a significant difference in an intent-to-treat analysis. While self-reported adherence was high, further testing revealed that gel was used for only about 40% of sex acts in both arms.

“Carraguard is unlikely to have a meaningful protective effect as used by study participants,” the investigators stated. Given the low rate of adherence actually obtained, they added, “even a highly efficacious coitally dependent product will have insufficient effectiveness in real-life settings.”

But late-breaking data presented at the Retrovirus conference were more encouraging. Salim Abdool Karim from the Center for the AIDS Programme of Research in South Africa described findings from the HPTN 035 trial, which enrolled 3,099 women at six sites in four African countries (Malawi, South Africa, Zambia, and Zimbabwe) and one site in the U.S. (CROI 2009 abstract 48LB). This study compared two microbicide gel candidates: PRO 2000, which inhibits HIV entry into cells, and BufferGel, which boosts the acidity of the vagina to inactivate HIV and other pathogens.

A total of 194 women were newly infected after a mean follow-up period of 20 months. Of these infections, 36 occurred in the PRO 2000 group, 54 in the BufferGel group, 51 in the placebo gel group, and 53 in a group that did not use any gel. While BufferGel was no more effective than placebo or no gel, PRO 2000 was associated with a 30% lower rate of infection, which did not quite reach statistical significance.

However, in an as-treated analysis that excluded periods when the product was not used (e.g., due to pregnancy), PRO 2000 reduced the risk of infection by 36%. Both microbicides were found to be safe, and women reported high rates of adherence. Furthermore, when the researchers looked only at women who were trying to conceive, and therefore not using condoms, the gel was 78% effective. However, the numbers were too small to allow for statistical significance.

This was the first large-scale clinical trial to produce data suggesting that a microbicide can potentially reduce the risk of HIV infection. Another large Phase III study involving nearly 9,400 women is currently underway and is scheduled to conclude in August 2009.

“The study, while not conclusive, provides a glimmer of hope to millions of women at risk for HIV, especially young women in Africa,” Karim stated in an NIAID press release. “It provides the first signal that a microbicide gel may be able to protect women from HIV infection.”

In a related presentation, Peter Anton and colleagues reported the first findings from an early Phase I trial looking at the safety and acceptability of a gel containing the UC781, an investigational NNRTI, used as a rectal microbicide (CROI 2009 abstract 1066). A total of 36 HIV-negative volunteers (26 men and ten women) were enrolled and all completed the study.

Reported adherence was high and the gel was generally well-tolerated. Five participants reported adverse events, including three cases of mild-to-moderate diarrhea considered possibly related to the product. Rectal tissue biopsies and biomarker analyses indicated that participants who received active UC781 gel at concentrations of 0.1% or 0.25% had no more evidence of rectal mucosal damage or immunotoxicity than placebo recipients.

Given prior experience with nonoxynol-9—which was

the risk from orogenital intercourse exposure,” the investigators concluded. “The low risk of transmission evident from identified studies means that more and larger studies would be required to provide sufficient evidence to derive more precise estimates.”

In a related study reported in the January 28, 2009, issue of AIDS, Swedish researchers sought to determine whether exposure to HIV via oral sex results in HIV-neutralizing antibody activity in the saliva. Saliva samples were collected from 25 HIV-negative gay/bisexual men with positive male partners and from 22 low-risk HIV-negative healthy male control subjects; 21 of the 25 HIV-exposed but uninfected individuals reported unprotected receptive oral sex and three reported unprotected receptive anal intercourse.

Saliva from both exposed uninfected individuals and low-risk control subjects exhibited HIV-neutralizing activity. However, a significant difference was seen for immunoglobulin A1 (IgA1), with 13 of 25 exposed uninfected individuals—but none of the 22 presumably unexposed control subjects—exhibiting HIV neutralization. Based on these findings, the researchers concluded, “Unprotected oral sex evokes a salivary IgA1-mediated HIV-neutralizing response that persists over time during continuous exposure in uninfected male partners of infected men.”

**MICROBICIDES: FAILURE AND SUCCESS**

There is a clear need for effective, woman-controlled HIV prevention methods, but trials of microbicides—gels or other products that protect against vaginal or rectal infection—have been frustratingly inconclusive. (See “Microbicide Development: Positive Women’s Concerns,” page 45, for more information.) Two recent studies have produced more definitive findings, disappointing in one case, promising in the other.

In the December 6, 2008, issue of The Lancet, Stephanie Skoler-Karpoff and colleagues reported on a large randomized trial comparing Carraguard gel (a carrageenan seaweed compound being developed by the Population Council) versus a placebo gel in more than 6,000 sexually active HIV-negative women at three sites in South Africa. Participants were instructed to apply the gel inside the vagina before each act of intercourse, but were also advised to use condoms.

After two years of follow-up, the HIV incidence rate among Carraguard users was 3.3 per 100 PY (134 new infections) compared with 3.8 per 100 PY (151 infections) in the placebo arm, which was not a significant difference in an intent-to-treat analysis. While self-reported adherence was high, further testing revealed that gel was used for only about 40% of sex acts in both arms.

“Carraguard is unlikely to have a meaningful protective effect as used by study participants,” the investigators stated. Given the low rate of adherence actually obtained, they added, “even a highly efficacious coitally dependent product will have insufficient effectiveness in real-life settings.”

But late-breaking data presented at the Retrovirus conference were more encouraging. Salim Abdool Karim from the Center for the AIDS Programme of Research in South Africa described findings from the HPTN 035 trial, which enrolled 3,099 women at six sites in four African countries (Malawi, South Africa, Zambia, and Zimbabwe) and one site in the U.S. (CROI 2009 abstract 48LB). This study compared two microbicide gel candidates: PRO 2000, which inhibits HIV entry into cells, and BufferGel, which boosts the acidity of the vagina to inactivate HIV and other pathogens.

A total of 194 women were newly infected after a mean follow-up period of 20 months. Of these infections, 36 occurred in the PRO 2000 group, 54 in the BufferGel group, 51 in the placebo gel group, and 53 in a group that did not use any gel. While BufferGel was no more effective than placebo or no gel, PRO 2000 was associated with a 30% lower rate of infection, which did not quite reach statistical significance.

However, in an as-treated analysis that excluded periods when the product was not used (e.g., due to pregnancy), PRO 2000 reduced the risk of infection by 36%. Both microbicides were found to be safe, and women reported high rates of adherence. Furthermore, when the researchers looked only at women who were trying to conceive, and therefore not using condoms, the gel was 78% effective. However, the numbers were too small to allow for statistical significance.

This was the first large-scale clinical trial to produce data suggesting that a microbicide can potentially reduce the risk of HIV infection. Another large Phase III study involving nearly 9,400 women is currently underway and is scheduled to conclude in August 2009.

“The study, while not conclusive, provides a glimmer of hope to millions of women at risk for HIV, especially young women in Africa,” Karim stated in an NIAID press release. “It provides the first signal that a microbicide gel may be able to protect women from HIV infection.”

In a related presentation, Peter Anton and colleagues reported the first findings from an early Phase I trial looking at the safety and acceptability of a gel containing the UC781, an investigational NNRTI, used as a rectal microbicide (CROI 2009 abstract 1066). A total of 36 HIV-negative volunteers (26 men and ten women) were enrolled and all completed the study.

Reported adherence was high and the gel was generally well-tolerated. Five participants reported adverse events, including three cases of mild-to-moderate diarrhea considered possibly related to the product. Rectal tissue biopsies and biomarker analyses indicated that participants who received active UC781 gel at concentrations of 0.1% or 0.25% had no more evidence of rectal mucosal damage or immunotoxicity than placebo recipients.

Given prior experience with nonoxynol-9—which was
found to damage the rectal lining even though it appeared safe in several studies of vaginal use—the investigators stressed the importance of testing microbicide candidates for both vaginal and rectal use, since any approved vaginal product will inevitably also be used for anal sex.

**PRE-EXPOSURE PROPHYLAXIS**

Another line of promising prevention research discussed at the Retrovirus conference involved pre-exposure prophylaxis, or PrEP. Researchers are currently studying PrEP using tenofovir with or without emtricitabine (the drugs in the Truvada combination pill) in various high-risk populations (including men who have sex with men, injection drug users, and female sex workers), but efficacy data are currently only available from animal studies.

Gerardo Garcia-Lerma from the Centers for Disease Control and Prevention (CDC) reported findings from a study in which male macaque monkeys received oral tenofovir plus emtricitabine, at doses similar to those used in humans, before and after rectal exposure to a hybrid human/simian immunodeficiency virus (SHIV) (CROI 2009 abstract 47). This type of intermittent PrEP would be more practical (less expensive, more convenient) than daily therapy, and potentially less risky in terms of side effects and drug resistance.

A total of 24 macaques received oral tenofovir/emtricitabine on varying schedules: two hours before and 22 hours after exposure, 22 hours before and two hours after exposure, 72 hours before and two hours after exposure, 168 hours (seven days) before and two hours after exposure, or two and 26 hours after exposure with no advance use. In addition, a similar number of untreated monkeys served as controls.

The macaques in all five treated groups had significantly lower rates of infection than the untreated animals. Furthermore, administering tenofovir/emtricitabine one to seven days prior to exposure was significantly more effective than administration immediately before exposure or only after exposure. Monkeys were about 17 times less likely to become infected if treated either 22 hours or seven days prior to exposure and 14 times less likely if treated three days in advance, but only four times less likely if treated two hours before or only after exposure.

In related research, Charles Dobard and colleagues, also from CDC, tested a vaginal microbicide gel containing tenofovir with or without emtricitabine (CROI 2009 abstract 46). In this study, 12 macaques received either tenofovir-only gel or tenofovir/emtricitabine gel 30 minutes prior to vaginal exposure to SHIV; in addition, nine control monkeys received placebo gel and two received no treatment.

None of the 12 macaques receiving active gel (tenofovir alone or the combination) were infected after 20 vaginal exposures, while 10 of 11 untreated macaques (91%) were infected after a median of four exposures.

Two human clinical trials of tenofovir vaginal gel versus tenofovir-based oral PrEP are currently underway, and two studies looking at the safety of a tenofovir rectal gel are in the planning stages.

**NEW CDC ESTIMATES INDICATE HIGHER HIVINCIDENCE**

On August 2, at the start of the Mexico City conference, the Centers for Disease Control and Prevention (CDC) released revised U.S. HIV incidence figures showing that the number of new annual infections is about 40% higher than previously believed; the findings were also published in the August 6, 2008, issue of the Journal of the American Medical Association.

Standard HIV screening tests detect whether a person has antibodies indicating infection with the virus, but they do not determine how recently infection occurred; such tests are useful for estimating prevalence, or total cases in a population, but not incidence, which only counts new cases occurring within a given period of time.

For the revised estimates, CDC researchers employed a new method—dubbed Serologic Testing Algorithm for Recent HIV Seroconversions (STARHS)—that uses a modified antibody test that can tell whether infection occurred within the past five months. Furthermore, the new estimate incorporates data from some states that only recently began reporting HIV infections by name.

The CDC has stated for several years that the annual number of new HIV infections in the U.S. was 40,000. But the improved testing methodology and more extensive data raised that number to 56,300 infections in 2006 for all 50 states and Washington, DC.

Rates of new infections varied dramatically among different population subgroups, as described in further detail in the September 12, 2008, issue of Morbidity and Mortality Weekly Report.

More than half of all new infections (53%) occurred in men who have sex with men (MSM), a group that has recently experienced an increase in incidence (see “News Briefs,” BETA, Summer 2008). Conversely—thanks in part to prevention efforts such as needle exchange programs—incidence has declined among injection drug users, who in 2006 accounted for 12% of new infections. Just over one-quarter (27%) of all newly infected people were women.

Though they make up just 12% of the total U.S. population, blacks accounted for about 45% of all new infections, compared with 35% for whites and 17% for Latinos/Hispanics. Among women, about 60% of new infections occurred among blacks, compared with 23% for whites and 16% for Latinas/Hispanics.
CDC officials emphasized that the latest incidence estimates do not reflect an actual increase in the number of new infections. Rather, using back-calculation methods, researchers determined that the earlier figures were too low. They now think the annual number of new infections probably peaked at around 130,000 in the mid-1980s, fell to a low of about 49,000 in the early 1990s, rose to around 58,000 in the late 1990s, then declined slightly and have remained stable at around 55,000 since 1999.

Updated data on HIV prevalence—or total infections—also indicate similar disparities across population groups. As reported in the October 3, 2008, issue of Morbidity and Mortality Weekly Report, an estimated 1,106,400 U.S. adults and adolescents were living with HIV or AIDS at the end of 2006, representing a prevalence rate of 447.8 cases per 100,000 persons (counting HIV data from states with consistent name-based reporting plus AIDS data from all 50 states and Washington, DC).

Again, MSM made up about half (48%) of people living with HIV/AIDS. Women accounted for one-quarter of cases, and within this group, 72% of infections were attributed to heterosexual transmission. Similar to the incidence figures, blacks accounted for 46% of all people living with HIV/AIDS, compared with 35% for whites, 18% for Latinos/Hispanics, and 1.4% for Asian/Pacific Islanders. The HIV prevalence rate among black women was nearly 18 times higher than that of white women, while black men were six times more likely to be infected than white men.

Higher HIV prevalence is not entirely bad news, since it indicates a growing number of people are living with—rather than dying rapidly from—HIV/AIDS. But it does underline the need for more resources for improved testing, prevention, treatment, and other services.

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### HIV Testing and HIV Health Resources

Knowing your HIV status is the first step toward staying healthy with HIV or remaining negative. As a BETA reader, chances are that you already know your HIV status—but do your friends and family members know theirs? Not everyone knows that they may be at risk for HIV, let alone that they may already have the virus. And not everyone knows where and how to get tested, and what to do if they find out they have HIV.

Please take advantage of these resources—all available in English and Spanish—to help keep you and those you care about safe and healthy.

The following hotlines offer information and anonymous counseling about HIV testing, transmission, prevention, and health.

**AIDS in Prison Hotline**
1-718-378-7022 (U.S.; all collect calls accepted)
Hours: Tuesday, Wednesday, Thursday, 3 pm to 8 pm ET
809 Westchester Ave.
Bronx, NY 10455
www.osborneny.org/aids_in_prison_project.htm

**California HIV/AIDS Hotline**
1-800-367-AIDS (Toll-free within California)
1-415-863-AIDS (In San Francisco and outside California)
1-888-225-AIDS (TTY for the hearing impaired)
Hours: Monday, Wednesday, Thursday, Friday, 9 am to 5 pm PT; Tuesday 9 am to 9 pm PT
995 Market St. #200
San Francisco, CA 94103
www.aidshotline.org

**GMHC AIDS Hotline**
1-800-AIDS-NYC (1-800-243-7692)
1-212-645-7470 (TTY)
1-212-807-6655 (International)
Hours: Monday through Friday, 10 am to 9 pm ET; Saturday, 12 pm to 3 pm ET
www.gmhchotline.html

**National AIDS Hotline**
1-800-CDC-INFO (1-800-232-4636)
1-888-232-6348 (TTY)
1-888-232-6348 (TTY)
Hours: 24 hours a day, 7 days a week

**Women Alive**
1-800-554-4876 (U.S.)
1-323-965-1564 (International)
Hours: Monday through Friday, 11 am to 6 pm PT
1566 Burnside Ave.
Los Angeles, CA 90019
www.women-alive.org/index.htm

The National Prevention Information Network, part of the U.S. Centers for Disease Control and Prevention (CDC), can help you or someone close to you find an HIV testing site, and can help answer questions about HIV testing and HIV prevention.

**CDC National Prevention Information Network**
1-800-458-5231 (U.S.)
1-404-679-3860 (International)
Hours: Monday through Friday, 9 am to 6 pm ET
P.O. Box 6003
Rockville, MD 20849
www.hivtest.org/contact.cfm