

Bulletin of Experimental Treatments for AIDS • www.sfaf.org/beta

BETA

*Summer 2005
Vol. 17, No. 4*

42
*Understanding
Clinical Studies*

20
Drug Interactions



A Publication of the San Francisco AIDS Foundation

CONTENTS

SUMMER 2005

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BETA is published biannually by the San Francisco AIDS Foundation in English (Winter and Summer) and Spanish (Spring and Autumn). Funding is provided by private and corporate donations.

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features

Drug Interactions and Anti-HIV Therapy20

LIZ HIGHLEYMAN

A Guide to Clinical Trials

Part I: Understanding Clinical Studies42

[SAN FRANCISCO AIDS FOUNDATION]

departments

NEWS BRIEFS3

LIZ HIGHLEYMAN

POLICY AND POLITICS

Medicare Prescription Drug Coverage:

Preparing for January 1, 200634

JEFFREY S. CROWLEY, MPH

DRUG WATCH

Pipeline Progress: Then and Now15

JOHN HAWES

WOMEN AND HIV

Women's Research Roundup30

KRISTEN JILL KRESGE

OPEN CLINICAL TRIALS50

NEWS FLASH

On July 1, as *BETA* went to press, Pfizer announced that it would stop clinical development of **capravirine**. Recent research showed that this experimental NNRTI did not offer a significant improvement over existing treatments, and that use of capravirine would likely be hampered by interactions with other anti-HIV therapies.

notice

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C O N F E R E N C E C O V E R A G E

The 12th Conference on Retroviruses and Opportunistic Infections, one of the two major annual meetings addressing HIV/AIDS, took place February 22–25 in Boston.

This year's conference did not feature any major breakthroughs, but included many oral and poster presentations in areas such as HIV pathogenesis, antiretroviral regimens, side effects of therapy, and experimental agents. Diverging from the usual format, the conference organizers hastily arranged a special session to discuss a case of multidrug-resistant, possibly rapidly progressing HIV that garnered extensive media attention in the weeks before the meeting (see news item below). Due to the amount of information presented, this conference summary is necessarily incomplete; for more in-depth reports, see the web sites listed below. For news related to HIV/HCV and HIV/HBV, see the coinfection item following the conference report. For Retrovirus conference coverage and other recent news related to HIV/AIDS in women—including data on the use of single-dose nevirapine (Viramune) to prevent mother-to-child HIV transmission—see “Women's Research Roundup” on page 30.

TREATMENT REGIMENS AND STRATEGIES

Looking at first-line anti-HIV regimens, data from the large international INITIO study (abstract 165LB) showed that a three-drug regimen consisting of efavirenz (Sustiva, Stocrin) plus two nucleoside reverse transcriptase inhibitors (NRTIs) is superior to two other first-line regimens. The 915 subjects were randomly assigned to receive one of three regimen sequences: 1) ddI (didanosine, Videx)/d4T (stavudine, Zerit)/efavirenz followed by AZT (zidovudine, Retrovir)/3TC (lamivudine, Epivir)/abacavir (Ziagen)/nelfinavir (Viracept) in the case of treatment failure; 2) ddI/d4T/nelfinavir followed by AZT/3TC/abacavir/nelfinavir; or 3) a four-drug regimen of ddI/d4T/efavirenz/nelfinavir. After more than three years of follow-up, in an intent-to-treat analysis, rates of undetectable viral load (below 50 copies/mL) were 74%, 62%, and 62%, respectively. There were no significant differences in terms of CD4 cell count increases, progression to new AIDS-defining illnesses or death, or rates of serious adverse events. Starting with a four-drug regimen provided no additional benefit, but was associated with more side effects. In total, more than one-third of the subjects changed their NRTI backbones, with most switching from ddI/d4T to AZT/3TC.

As the number of antiretroviral drugs has grown, it has become impossible to test all potential combination regimens against each other in clinical trials. In lieu of this, John Bartlett, MD, and colleagues (abstract 586) performed a meta-analysis (an analysis that includes data from multiple trials) of studies looking at three-drug regimens for first-line therapy. This analysis included data from 64 trials with a total of 10,559 subjects. On the whole, regimens containing either a ritonavir (Norvir)-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) performed better than regimens based on unboosted PIs or triple-NRTI regimens (undetectable viral load rates of 64%, 63%, 44%, and 51%, respectively). However, boosted PI regimens produced greater increases in CD4 cell count (209 cells/mm³) than NNRTIs (180 cells/mm³), unboosted PIs (178 cells/mm³), or triple-NRTI regimens (150 cells/mm³).

Triple-NRTI regimens have gotten bad press recently due to several studies showing that they may not be potent enough to durably suppress HIV. However, a combination of AZT/3TC/tenofovir DF (Viread) appears to work well in some individuals. An open-label French study of 36 treatment-naive subjects (abstract 599) found that 90% had viral loads below 50 copies/mL after six months on this regimen, as did 69% after 12 months. During the first year, four subjects (11%) experienced virological failure; two of these stayed on the AZT/3TC/tenofovir regimen and maintained low viral loads. Despite recent recommendations to avoid triple-NRTI regimens, the authors concluded that AZT/3TC/tenofovir “should be further evaluated.”

The DART study in Africa (abstract 22) also looked at the same triple-NRTI regimen. In a cohort of 200 symptomatic Ugandan subjects with CD4 cell counts below 200 cells/mm³, 51% achieved viral loads below 50 copies/mL and 68% below 400/copies/mL in an intent-to-treat analysis after 24 weeks; the median CD4 cell increase was 88 cells/mm³. While better outcomes would likely be achieved using PIs or NNRTIs, the researchers concluded that triple-NRTI regimens “are highly relevant in resource-limited settings.”

T-20 (enfuvirtide, Fuzeon), one of the few drugs that effectively suppress HIV in people with extensive resistance

**Even though the MI risk doubled with HAART,
the absolute number of heart attacks was
still very small.**

to the three major antiretroviral drug classes, is itself susceptible to resistance. Cecilia Cabrera and colleagues (abstract 718) studied 15 heavily treatment-experienced subjects. All initially experienced reductions in viral load after starting T-20, but HIV RNA increased soon after week 4 in 13 of the subjects. Mutations in the gp41 envelope protein developed by week 2–4 in all subjects. However, Steven Deeks, MD, and colleagues (abstract 680) reported that after 22 subjects with T-20-resistant HIV stopped taking the drug, they experienced modest viral load increases, leading the authors to conclude that T-20 continues to have “persistent low-level activity” even when resistance mutations are present. Finally, a 30-person study by George Beatty, MD, and colleagues (abstract 581) found that interrupting HAART prior to starting salvage therapy with T-20 did not lead to improved virological response at 24 weeks compared with immediate initiation of T-20, and that baseline susceptibility to T-20 did not predict treatment outcome. [Ed. note: Dr. Beatty is a member of *BETA*’s Scientific Advisory Committee.] Together, these studies indicate that when T-20 failure occurs, it happens relatively early (4–8 weeks), but that individuals who do well on the drug can expect sustained response.

Along with all the study data about specific antiretroviral regimens, researchers presented some “big picture” results. An analysis of more than 6,800 subjects in the EuroSIDA cohort by Christian Holkmann-Olsen and colleagues (abstract 601a) revealed that HAART is effective across the board, regardless of baseline CD4 cell count or viral load. During 22,766 person-years (PY) of follow-up, the researchers recorded 889 instances of new AIDS-defining illness or death (125 deaths). They found that the incidence of AIDS or death for any given CD4 cell count or viral load category was “similar regardless of specific drugs being used.” In comparison with indinavir (Crixivan)—for which clinical endpoint data are available (most newer drugs were approved on the basis of short-term laboratory marker data)—a wide variety of regimens (two NRTIs plus either an NNRTI or a boosted or unboosted PI, or abacavir plus two other NRTIs) reduced the risk of AIDS-defining illness and death to a similar degree.

CARDIOVASCULAR RISK AND HAART

As has become typical at HIV conferences, many presentations were devoted to adverse events associated with antiretroviral therapy, especially metabolic side effects. One such side effect, elevated lipid levels, is a concern because it may increase the risk of cardiovascular disease. Based on the latest data from the large D:A:D study—which includes more than 23,000 HIV positive subjects—Jens Lundgren, MD, (abstract 62) reported that use of HAART appears to

double the risk of myocardial infarction (MI; heart attack). The researchers reached this conclusion based on an analysis of data from various studies assessing arterial intima-media thickness (a marker for atherosclerosis, or “hardening of the arteries”) or presence of cardiovascular disease. The increased risk associated with HAART was similar in magnitude to that seen in tobacco smokers. Other modifiable (e.g., elevated lipid levels, hypertension) and unmodifiable (e.g., age, sex, family history) risk factors also contributed to heart attack risk. In contrast to some previous research, neither lipodystrophy (body shape changes) nor degree of immunosuppression were linked to increased MI risk.

In a related study, Wafaa El-Sadr, MD, and colleagues (abstract 42) analyzed how MI risk changes over the course of anti-HIV treatment. Data from the same cohort (median age 39 years; 76% men) were collected through February 2004. During 76,577 PY of observation, 277 first MIs were reported. The MI incidence rate was 1.39 per 1,000 PY among those not exposed HAART, 2.53 per 1,000 PY among those on HAART for less than one year, and 6.07 per 1,000 PY among those on HAART for six or more years. The researchers calculated that for each additional year on HAART, the risk of MI increased by 1.17-fold. A similar association between antiretroviral therapy and MI risk was seen in both sexes and all age groups. Interestingly, the authors noted that elevated blood lipids explained “part but not all” of the association between HAART and increased MI risk.

Importantly, even though the MI risk doubled with HAART, the absolute number of heart attacks was still very small. Lundgren emphasized that the reduction in HIV-related illness and death attributable to the use of antiretroviral therapy greatly outweighs the small additional risk of MI.

SWITCHING DRUGS TO REDUCE LIPOATROPHY

The ACTG 5116 study looked at the safety and efficacy of treatment simplification in individuals with well-controlled HIV. Margaret Fischl, MD, and colleagues (abstract 162) looked at 236 subjects who had viral loads below 200 copies/mL, had no phenotypic evidence of drug resistance (i.e., when their HIV was combined with anti-HIV drugs in the lab), and had been on three- or four-drug PI- or NNRTI-based first regimens for at least 18 months. Subjects were randomly assigned to switch to an NRTI-sparing regimen of lopinavir/ritonavir (Kaletra) plus efavirenz (Arm 1) or to substitute efavirenz if they were taking a PI while staying on their NRTIs (Arm 2); most subjects (78%) who were taking two NRTIs used

AZT/3TC. After 110 weeks, in an intent-to-treat analysis, 66% of subjects in Arm 1 had viral loads below 50 copies/mL, compared with 74% in Arm 2. In addition, 17% of subjects in Arm 1 discontinued due to adverse events (mainly elevated triglyceride levels), compared with 5% in Arm 2.

Results of this study suggest that a PI-sparing regimen including NRTIs is superior to a regimen that excludes NRTIs, but the side effect profiles of the two regimens tell a somewhat different story. Lipoatrophy (loss of peripheral fat in the face and limbs) presents a particular concern for individuals taking NRTIs, especially d4T. Pablo Tebas, MD, (abstract 40) presented data from 62 subjects in the ACTG-5125s substudy of ACTG 5116. After 48 weeks, limb fat increased significantly in the NRTI-sparing arm, but decreased in those who stayed on NRTIs. Among a subset of 46 subjects followed for a median of 104 weeks, those in the NRTI-sparing arm continued to gain limb fat while those in the NRTI arm continued to lose it. However, triglyceride and total cholesterol levels increased much more in the NRTI-sparing arm. Tebas concluded that the benefits of NRTI-sparing regimens on body fat distribution must be balanced against their inferior virological potency. This study was not powered to detect differences among specific NRTIs (only about one-quarter were taking d4T).

Switching to an NRTI-sparing regimen can reduce lipodystrophy, but it may not be necessary to exclude all drugs in this class; studies suggest that omitting only thymidine analogs (d4T and AZT) may accomplish the same goal. Robert Murphy, MD, (abstract 45LB) reported results from ACTG 5110s. In this study, 101 subjects with lipoatrophy were randomly assigned either to replace a thymidine analog (AZT 24%; d4T 76%) with abacavir, or to switch to an NRTI-sparing regimen of lopinavir plus nevirapine; 77 subjects switched immediately, while 24 controls stayed on their baseline regimen for 24 weeks and then switched. After 24 weeks, based on computed tomography (CT) scans, subjects in both the thymidine-sparing and the all-NRTI-sparing arms experienced significantly increased subcutaneous abdominal fat; visceral abdominal fat decreased in the abacavir group. Thigh fat increased significantly (by 8%) in the all-NRTI-sparing arm but not in the abacavir arm. Subjects in all groups maintained good virological control, but CD4 cell counts increased more in the all-NRTI-sparing arm. Elevated lipids were seen in the lopinavir arm and hypersensitivity reactions were seen in the abacavir arm.

For individuals who wish to stay on an NRTI-containing regimen without thymidine analogs, is it better to switch to abacavir or tenofovir? In the British RAVE study, Graeme Moyle, MD, and colleagues (abstract 44L) randomly assigned

105 subjects with lipoatrophy to switch from a thymidine analog (AZT 33%; d4T 67%) to either abacavir or tenofovir. After 48 weeks, DEXA scans showed that limb fat increased significantly, and by similar amounts, in both the abacavir and tenofovir groups. Subjects in both arms maintained good virological suppression. Looking at lipid profiles, triglycerides, total cholesterol, and LDL “bad” cholesterol decreased more in the tenofovir arm. More subjects discontinued in the abacavir arm due to hypersensitivity reactions; no differences in renal function or bone density were detected. Subjects who switched from AZT showed improvements in anemia. The researchers concluded, “While both agents maintain virological suppression, [tenofovir] is associated with fewer treatment discontinuations and greater improvements in lipid parameters than [abacavir].”

Tenofovir also received support from two Spanish studies. In the LIPOTEST study (abstract 860), 53 subjects with well-controlled HIV and lipoatrophy switched from d4T to tenofovir; other drugs in their regimens did not change. After 18 months, facial fat thickness increased significantly and blood cholesterol decreased slightly. In addition, lactic acid levels decreased significantly and mitochondrial DNA (mtDNA) in peripheral blood mononuclear cells increased slightly; both elevated lactic acid and reduced mtDNA are signs of mitochondrial toxicity. Virological control of HIV was maintained and no serious adverse side effects were reported.

In a study by A. Milinkovic and colleagues (abstract 857), 56 subjects with well-controlled HIV were randomly assigned to continue on d4T, reduce their d4T dose from 40 to 30 mg twice daily, or substitute tenofovir for d4T; other drugs were not changed. After six months, limb fat increased significantly in the dose-reduction and tenofovir arms, but continued to decrease in the full-dose d4T arm. Triglyceride and total cholesterol levels decreased somewhat in the dose-reduction arm and significantly in the tenofovir arm, but increased in the full-dose d4T arm.

Taken together, these studies suggest that substituting tenofovir or abacavir for thymidine analogs can improve lipodystrophy without sacrificing virological control. New fixed-dose combination pills have made tenofovir (in Truvada) and abacavir (in Epzicom) as convenient as Combivir and Trizivir, both of which contain AZT. D4T is clearly the major contributor to lipoatrophy; for this reason, the drug was demoted from “preferred” to “alternative” status in a recent revision of the U.S. federal HIV treatment guidelines. However, AZT also appears to play a role in lipoatrophy, and further studies will show whether it deserves to meet the same fate.

NEW ANTI-HIV AGENTS

Researchers at the Retrovirus conference presented new data on a plethora of experimental agents at different stages of the drug development process. Two presentations offered the latest data on Boehringer Ingelheim's new PI, tipranavir (Aptivus), which was granted accelerated approval by the Food and Drug Administration (FDA) in June (see news item below). Another PI in the pipeline, Tibotec's TMC-114, generated perhaps the most excitement at the conference. This and other investigational agents further along in the development process are discussed in "Drug Watch" on page 15.

Data were also presented for several agents further back in the development pipeline. One that generated some excitement was PA-457, the first HIV maturation inhibitor. PA-457 works by interfering with a protein needed to construct functional viral progeny; without it, new viral particles are incomplete and noninfectious. In a placebo-controlled single-dose study (abstract 159), 24 treatment-naïve or treatment-experienced HIV positive men received PA-457 at doses of 75, 150, or 250 mg, or placebo. The 250 mg dose reduced HIV viral load by 0.51 logs and PA-457 appeared to suppress HIV for several days. A ten-day study is underway and a Phase II trial should start by the end of the year. (For an explanation of logs, see "About Logs" on page 18.)

Susan Little (abstract 161) presented the first results using Merck's integrase inhibitor, L-870810, in 30 treatment-naïve and treatment-experienced HIV positive subjects. Ten-day monotherapy with 200 and 400 mg doses reduced HIV viral load by 1.73 and 1.77 logs, respectively; 20% and 38%, respectively, had viral loads below 400 copies/mL. Although L-870810 was well tolerated in this study and no major toxicities have been detected in humans, development has been halted due to toxicity in dogs; however, research on the related agent L-870812 is continuing. Data were also presented on BioAlliance's candidate integrase inhibitor, FZ41 (abstract 547).

GW-873140, a CCR5 coreceptor blocker, was tested in a study of 31 HIV positive and eight HIV negative subjects (abstract 77). Good viral suppression was achieved after 10 days. Researchers also found that GW-873140 appears to continue to block receptors for as long as 10 days after discontinuation, suggesting that infrequent dosing may be possible. This agent is due to enter Phase III trials later this year.

In a seven-day dose-ranging study in 27 treatment-naïve subjects (abstract 160), Tibotec's new NNRTI, TMC-278, appeared highly active against HIV that was resistant to approved NNRTIs. The median viral load decrease was about 1.2 logs, which was similar across doses (25, 50,

100, and 150 mg daily). No adverse events were detected and a Phase II trial is now starting (see "Open Clinical Trials" on page 51).

Other experimental agents to keep an eye on include Pfizer's CCR5 antagonist UK-427,857, now named maraviroc (abstracts 96, 663); Tibotec's nucleotide-competing reverse transcriptase inhibitor known as Compound-1 (abstract 156); Takeda's TAK-652, which replaces TAK-779 and TAK-220 (abstracts 541, 542); Boehringer Ingelheim's BILR-335BS (abstracts 557, 558); and NCI UIC-02031, a new nonpeptidic PI (abstract 562).

UNUSUAL NEW YORK AIDS CASE REMAINS AN ENIGMA

On February 11 New York City Department of Health and Mental Hygiene officials announced that they had discovered a case of multidrug-resistant, apparently rapidly progressing HIV in a gay man in his forties who reported crystal methamphetamine use and multiple sexual partners. The man last tested HIV negative in May 2003, was believed to have been infected in October 2004 (though possibly earlier), and developed symptoms suggestive of acute retroviral syndrome (fatigue, fever, sore throat) in early November 2004. He then tested HIV positive with an unusual multidrug-resistant strain of the virus on December 16, by which time he showed signs of advanced immunosuppression. By January his CD4 cell count had fallen to 28 cells/mm³.

The announcement set off a flurry of press coverage and discussion among medical professionals and HIV prevention workers. Some criticized New York officials for raising the alarm too soon based on a single case. In a rare move, organizers convened a special symposium to discuss the case at the February Retrovirus conference.

Genetic analysis showed that the man had a strain of subtype B HIV that had not been seen previously. Initial genotypic resistance testing indicated his HIV was resistant to the three major classes of antiretroviral drugs. Drug resistance in newly infected individuals is not uncommon, but resistance to all three classes in treatment-naïve individuals is rare (see "Transmission of Drug-Resistant HIV," below). It was later determined that the man's virus was susceptible to efavirenz as well as T-20. The man's HIV strain was also found to be dual-tropic (able to use both CCR5 and CXCR4 coreceptors to enter cells) and syncytium-inducing (causing fusion of cells). Dual-tropic, syncytium-inducing virus, which is associated with rapid disease progression, is not unknown in newly infected individuals, although it is more often seen later in the course of disease. The unusual—though not singularly unique—aspect of the New York case is the co-occurrence of multidrug

resistance and apparently rapid progression. Details of the genetic analysis were presented at the Retrovirus conference by David Ho, MD (abstract 973B) and published in the March 19, 2005 issue of *The Lancet*.

Experts emphasized that the New York man's rapid progression did not necessarily herald a "super strain" of HIV. It has long been known that a small proportion of individuals naturally progress rapidly to AIDS, and a variety of factors—including genetic variations and methamphetamine use—may have contributed to the early onset of immunosuppression in this case. Since February little new information has come to light. Despite extensive testing of more than a dozen of the New York man's sexual contacts (many of his 100 or more partners were anonymous) and retrospective analysis of stored blood samples, no similar strains have been detected; however, the investigation is ongoing. New York health officials issued a press release on March 29 stating that they were still examining data from several individuals who might be infected with related HIV strains.

TRANSMISSION OF DRUG-RESISTANT HIV: MORE OR LESS?

Concern about a growing incidence of drug-resistant (DR) HIV transmission is complicated by inconsistent data from recent small studies. According to Andrew Leigh Brown, PhD, of the University of Edinburgh (speaking at the special symposium at the Retrovirus conference; see previous item) several studies during the HAART era appear to show one of two trends: either an increase in transmission of DR HIV from 1996 to around 2000, followed by a stable or declining rate; or no increase in DR virus transmission. These outcomes might be explained by data indicating that DR HIV is less "fit," or transmissible, than wild-type (nonmutated) virus.

A picture of transmission patterns of DR HIV based on geography emerged at the 3rd European HIV Drug Resistance Workshop, held March 30–April 1 in Athens. Reported rates of DR HIV transmission ranged from 4% (Slovenia, Spain) to 17% (Belgium)—with 14.5% reported in the U.S.—in cohorts of newly diagnosed individuals. One retrospective study from Sweden showed a decline in transmission of DR virus between 1992 and 2002, attributed by researcher Jan Albert to the widespread, effective use of HAART in that country. Reports from other countries showed either a steady or increasing rate of DR HIV transmission over time. Geographical differences appeared to be regional as well as national, as two studies from Germany—one from the western Ruhr region, the other in people mostly from Berlin—showed different DR HIV

transmission rates (12% and 16%, respectively) as well as distinct trends (rising steadily from 8.4% to 14.2% between 2001 and 2004, vs peaking at 20% in 1998/1999 then stabilizing at 16% in 2001). Of note, only a tiny percentage of cases among the various studies involved dual- or triple-class drug resistance.

ON THE WEB

12TH RETROVIRUS CONFERENCE:

www.retroconference.org/2005/Home.htm

FOR MORE COMPLETE COVERAGE OF THIS AND OTHER RECENT CONFERENCES, SEE:

www.aidsmap.org

www.hivandhepatitis.com/2005icr/12croi/main.html

www.natap.org/2005/CROI/croi.htm

www.thebody.com/confs/retro2005/retro2005.shtml

DRUG APPROVALS AND WARNINGS

FDA APPROVES TIPRANAVIR

On June 22 the FDA granted Boehringer Ingelheim's nonpeptidic PI, tipranavir—which will be marketed under the brand name Aptivus—accelerated approval for treatment-experienced individuals with HIV. The approved dose is 500 mg tipranavir, which must be taken with 200 mg of ritonavir, twice daily. Studies have shown that tipranavir works against HIV that has developed resistance to other drugs in its class. Data from two large Phase III trials (RESIST-1 and RESIST-2) showed that twice-daily tipranavir boosted with ritonavir worked better than boosted comparator PIs in subjects with PI-resistant HIV. After 24 weeks significantly more subjects in the tipranavir arms achieved undetectable viral loads compared with individuals in the comparator arms. However, subjects

receiving tipranavir were more likely to experience severe (grade 3 or 4) ALT (liver enzyme) elevations than those taking other PIs (7% vs 1%, respectively).

At the February Retrovirus conference, David Cooper, MD, (abstract 560) reported that in a study of 1,159 subjects, about twice as many individuals in the tipranavir arm responded to treatment (40% vs 21%) compared with those taking lopinavir after 24 weeks. At the same meeting Jonathan Schapiro, MD, (abstract 104) presented data from genotypic resistance analyses of the same cohort showing that tipranavir worked better than comparator PIs in subsets of subjects with various patterns of PI-resistance mutations. Research suggests that tipranavir may reduce blood levels of other PIs, which could make it unsuitable for use in salvage regimens that combine multiple PIs. The most frequently reported adverse events in people taking tipranavir were gastrointestinal symptoms (e.g., diarrhea, nausea), fatigue, and headache; mild skin rash was seen more often in women than men. The most common severe laboratory abnormalities were elevated liver enzymes and blood lipid levels.

Tipranavir is currently undergoing trials in treatment-naïve individuals and in children.

ONCE-DAILY LOPINAVIR APPROVED

On May 2 Abbott Laboratories announced that the FDA approved a once-daily dosing regimen for lopinavir/ritonavir (Kaletra). A study presented at February's Retrovirus conference (abstract H-570) showed that once-daily and twice-daily lopinavir had similar efficacy when used in combination with FTC (emtricitabine, Emtriva) and tenofovir in treatment-naïve individuals. Last October the lopinavir product label was revised to include longer-term data from two trials showing that the drug was still effective after 144 and 204 weeks. Full prescribing information for lopinavir may be viewed at www.kaletra.com.

NEW HEPATITIS B DRUG APPROVALS

On March 29 the FDA approved a new antiviral agent, entecavir (Baraclude), for the treatment of adults with chronic hepatitis B virus (HBV) infection. The drug, marketed by Bristol-Myers Squibb, is an NRTI taken orally once daily. Diverging from the typical drug approval path, entecavir was approved simultaneously for use in people with hepatitis B alone and in those with HIV/HBV coinfection. The new drug is indicated for both HBV-monoinfected and HIV/HBV-coinfected individuals who have previously used 3TC (a standard therapy for HBV as well as a common component of anti-HIV regimens), and for first-line therapy in individuals with HBV alone. In clinical trials, after 48 weeks entecavir produced greater reductions in HBV viral load than 3TC in both treatment-naïve subjects

and those who had previously used 3TC (to which HBV rapidly develops resistance). In a smaller study of 68 subjects, entecavir was shown to be superior to placebo in HIV/HBV-coinfected participants who were taking an antiretroviral regimen containing 3TC. Not all people with chronic hepatitis B require treatment; entecavir was approved for individuals with actively replicating HBV and either elevated liver enzymes (ALT or AST) or histological evidence of liver tissue damage. Based on trials so far, entecavir appears about as safe as 3TC; severe hepatitis "flares" (sudden worsening of symptoms) may occur when either drug is discontinued. Full prescribing information for entecavir may be found at www.baraclude.com.

In May the FDA approved Roche's Pegasys brand of pegylated interferon alfa-2a for the treatment of chronic hepatitis B. In two large multinational Phase III trials of more than 1,500 subjects with HbeAG-negative or HbeAG-positive HBV, significantly more individuals who received Pegasys achieved sustained virological response (continued undetectable HBV viral load 24 weeks after a 48-week course of therapy) compared with subjects taking 3TC. The combination of Pegasys plus 3TC was not shown to be superior to Pegasys alone. These trials did not include HIV positive individuals, and Pegasys was not approved for HIV/HBV coinfection. The drug is already standard therapy for the treatment of chronic hepatitis C (see next item).

PEGASYS/RIBAVIRIN FOR HIV/HCV COINFECTION

On February 25 the FDA approved Pegasys plus ribavirin (Copegus) for the treatment of chronic hepatitis C virus (HCV) infection in people with HIV; this is the first and only hepatitis C therapy approved for HIV/HCV-coinfected individuals. Pegylated interferon (either Pegasys or Schering-Plough's Peg-Intron) plus ribavirin was already standard therapy for HCV-monoinfected individuals. The expanded indication was based on data from the APRICOT study, which showed that 40% of 868 HIV/HCV-coinfected subjects treated with Pegasys/ribavirin achieved sustained virological response (29% for HCV genotype 1; 62% for genotypes 2 and 3); the APRICOT results were published in the July 29, 2004 issue of the *New England Journal of Medicine (NEJM)*. In early February the European Medicines Agency also approved Pegasys/ribavirin for coinfecting individuals. Full Pegasys prescribing information may be viewed at www.pegasys.com.

SOFT-GEL SAQUINAVIR AND DDC TO BE DISCONTINUED

On March 11 Roche announced that it plans to discontinue two of its antiretroviral medications, ddC

(zalcitabine, Hivid) and the soft-gel formulation of saquinavir (Fortovase), due to lack of demand. DdC does not offer any clear benefit over ddI and is associated with a high rate of peripheral neuropathy; it is not included as a component of any of the preferred or alternative antiretroviral regimens recommended in the U.S. federal HIV treatment guidelines. Fortovase has been overshadowed by the older hard-gel formulation of saquinavir (Invirase), which is now used with a boosting dose of ritonavir. Boosted Invirase is better tolerated and more convenient than Fortovase, especially with the recent introduction of a new 500 mg Invirase tablet that allows users to take fewer pills each day. The move comes not long after GlaxoSmithKline (GSK) withdrew its PI amprenavir (Agenerase) from the market at the end of 2004—the first drug to be removed from the anti-HIV formulary. Roche said it plans to stop producing ddC and Fortovase around 2006.

HIGHER ABACAVIR HYPERSENSITIVITY RATE

The risk of hypersensitivity reactions associated with abacavir (Ziagen) may be higher than previously believed. Since the drug's introduction, most experts have put the rate of hypersensitivity reactions at around 3–5%. But two new studies suggest that the actual rate may be in the 5–10% range. In an overview of nine recent clinical trials (presented at the February Retrovirus conference, abstract 835), FDA researchers found an overall abacavir hypersensitivity rate of 8% (range 2–9%). The drug's manufacturer, GSK, conducted a similar review that included the same recent studies plus earlier clinical trials (abstract 836); this review found a hypersensitivity rate of 5.4%.

Recent research indicates that 600 mg abacavir once daily is as effective as 300 mg twice daily, but it is not yet clear whether the risk of serious hypersensitivity is greater when using the higher dose. As reported in the April 1, 2005 issue of the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, Graeme Moyle, MD, and colleagues found that in study CNA30021 (which included 770 participants) the once-daily and twice-daily arms had similar overall hypersensitivity rates (9% vs 7%, respectively), but the frequency of moderate-to-severe reactions was slightly higher in the once-daily arm. A GSK analysis of data from three large studies totaling more than 900 subjects found no greater risk of hypersensitivity with the higher dose.

Abacavir hypersensitivity may be characterized by symptoms including fever, skin rash, nausea, abdominal pain, cough, sore throat, and/or shortness of breath. Individuals who experience such symptoms while taking abacavir should contact their physicians immediately. Once the drug has been discontinued, it should not be started again. The same caution applies to the fixed-dose combination pills Trizivir and Epzicom, both of which contain abacavir.

MORE DRUG INTERACTION WARNINGS FOR RITONAVIR

In late March the FDA announced that the product labels for ritonavir (Norvir) and lopinavir/ritonavir (Kaletra) had been revised to include interactions with fluticasone (a synthetic corticosteroid that is the active ingredient in Flonase nasal spray) and trazodone (Desyrel), an antidepressant. Ritonavir interacts with many medications due to its potent inhibitory effect on the CYP450 enzyme system in the liver, which can lead to slower processing of other drugs and thus greater risk for toxicity (see “Drug Interactions” on page 20). In the case of fluticasone, use with ritonavir can lead to decreased blood levels of the hormone cortisol. In addition, the revised label for ritonavir added alfuzosin (Uroxatral), an alpha-blocker drug used to increase the flow of urine in men with benign prostate enlargement, to the drug's contraindications list. The revised package inserts for ritonavir and lopinavir may be viewed at www.norvir.com and www.kaletra.com.

OTHER HIV NEWS

TMC-114 EXPANDED ACCESS TO START THIS AUTUMN

Tibotec Therapeutics announced June 14 that it plans to start an expanded access program (EAP) this autumn for its experimental protease inhibitor, TMC-114. The company also plans to seek accelerated approval from the FDA for the agent, which has shown promise in Phase II clinical trials (see “Drug Watch” on page 15). The EAP will be open to heavily treatment-experienced HIV positive adults with CD4 cell counts below 100 cells/mm³ and viral loads above 10,000 copies/mL who need TMC-114 to construct a viable HAART regimen. Check the Tibotec web site (www.tibotec.com) for more details and contact information as the launch date approaches. Tibotec recently began an open-label Phase III study of the drug (see “Open Clinical Trials” on page 50); the EAP is for individuals who are not eligible or able to participate in the clinical trial.

SCULPTRA PHYSICIAN LOCATOR LAUNCHED

Dermik Aesthetics, which manufactures Sculptra (poly-L-lactic acid)—a recently approved cosmetic treatment for facial lipoatrophy—has launched a physician locator to help HIV positive people find providers in their area who administer the product. Dermik emphasizes that the inclusion of a physician in the database “is not intended as a recommendation, referral, or endorsement of any particular health-care provider or practice.” See www.sculptra.com/US/Locator.do.

TREATMENT GUIDELINES UPDATED FOR NPEP

In January the U.S. Department of Health and Human Services (DHHS) put forth new recommendations concerning post exposure prophylaxis (PEP) for nonoccupational HIV exposure, referred to as “NPEP” (*Morbidity and Mortality Weekly Report*, January 21, 2005). Previously the government recommended antiretroviral PEP only for occupational exposures such as accidental needlestick injuries in health-care facilities; in that setting, PEP reduces the risk of HIV infection by about 80%. According to the new guidelines, individuals should be offered a 28-day course of three-drug antiretroviral therapy if they have a “substantial risk” of HIV exposure—for example, unprotected intercourse or sharing drug injection needles with a person known to be HIV positive; NPEP must be started within 72 hours of the suspected exposure. In the case of lower risk exposures or if the partner’s HIV status is unknown, the guidelines recommend weighing the benefits and risks of NPEP on a case-by-case basis. These guidelines are intended to cover accidental or rare exposures (e.g., sexual assault, condom breakage); NPEP should not be considered a “morning after pill” to be used after habitual high-risk behavior.

“BLIPS” AND SPONTANEOUS UNDETECTABLE VIRAL LOAD

According to a study published in the February 16, 2005 issue of the *Journal of the American Medical Association (JAMA)*, transient viral load increases, or “blips,” are usually random variations and not a cause for concern. Richard Nettles, MD, and colleagues from Johns Hopkins University collected blood from ten HIV positive subjects and tested their viral loads every 2–3 days for a period of 3–4 months. All subjects were on antiretroviral therapy and had previously had undetectable viral loads for at least six months. Nine subjects (90%) experienced HIV RNA blips of 50 copies/mL or more followed by a return to undetectable levels; the average blip duration was less than three days. Blips were not associated with any demographic or clinical factors and were only marginally associated with intermittent nonadherence. Ultrasensitive genotypic testing showed that blips were not linked to the emergence of drug-resistance mutations. The researchers concluded that transient viral load increases appear to be “random biological and statistical variations” and were not clinically significant. Thus, it is important to obtain confirmatory results and not change antiretroviral therapy based on a single viral load test.

Spontaneous undetectable HIV viral load in individuals not taking antiretroviral medications may be more common

than previously believed, according to a study published in the May 1, 2005 issue of *Clinical Infectious Diseases (CID)*. Yoann Madec and colleagues from Paris found that 36 of 426 recently infected individuals (8.5%) with known seroconversion dates had sustained (two readings within 18 months) HIV RNA levels below 400–500 copies/mL with no treatment 4.6–62.8 months after seroconversion. A majority had detectable viral loads during part of the study before achieving undetectable status. According to the researchers, 6.7% of study participants still maintained viral loads below 400–500 copies/mL five years after seroconversion. Women, subjects younger than 26 years of age, individuals with lower baseline viral loads, and subjects with higher baseline CD4 cell counts were more likely to achieve spontaneous HIV clearance. During the period when viral loads were undetectable, the researchers found that subjects experienced slower CD4 cell declines than expected based on past studies of HIV disease progression. As discussed in an editorial by Elizabeth Connick, MD, and colleagues in the same issue, the French study points to the need for further studies of primary HIV infection and its treatment.

KALETRA MAINTENANCE “MONOTHERAPY”

In an effort to increase the convenience of antiretroviral therapy and reduce the risk of side effects, researchers have studied a variety of simplified regimens. In the March 4, 2005 issue of *AIDS*, R.E. Campo and colleagues reported that switching to Kaletra “monotherapy”—which is really a combination of two drugs, lopinavir plus a boosting dose of ritonavir, in a single pill—appeared to maintain virological suppression and did not encourage the emergence of resistance in individuals with well-controlled HIV. In this small pilot study, six treatment-naïve HIV positive individuals were initially treated with lopinavir plus AZT and 3TC for at least 24 weeks. After virological suppression was achieved (at least three consecutive viral load measurements below 50 copies/mL), the two NRTIs were discontinued. Four individuals (67%) maintained viral loads below 1,000 copies/mL for the duration of the six-month study. The other two subjects, who admitted poor adherence, had at least one viral load above 1,000 copies/mL. When one subject improved his adherence, his viral load fell below 400 copies/mL. No lopinavir-resistance mutations were detected in either individual.

INCREASE IN DRUG-RESISTANT STAPH INFECTION

Infection with methicillin-resistant *Staphylococcus aureus* (MRSA), once largely confined to health-care facilities such as hospitals and nursing homes, is increasingly being seen in community settings. Drug-resistant staph

infection has recently been detected among prisoners, athletes, and children. A study published in the April 7, 2005 issue of *NEJM* found that between 2001 and 2002, as many as one-fifth of MRSA infections in Atlanta, Baltimore, and Minnesota had no apparent link to health-care settings. “Community-associated MRSA infections are now a common and serious problem,” the authors concluded.

Healthy people often carry *S. aureus* on their skin and in their noses, but the bacteria may be especially likely to cause problems in immunocompromised people. According to a retrospective study reported at the February Retrovirus conference (abstract 142), 94 “clinically significant” cases of drug-resistant *S. aureus* were detected in a cohort of 3,455 HIV positive subjects between January 2000 and December 2003; 60% of the infections were community-acquired and 40% were potentially linked to hospitals. The incidence of clinically significant MRSA infection increased 6.2-fold from the first six months to the last six months of the study. The risk of MRSA was higher among individuals who acquired HIV through heterosexual sex and those with CD4 cell counts below 50 cells/mm³. Among subjects with CD4 cell counts above 50 cells/mm³, higher HIV viral load was also associated with an increased risk of MRSA infection. According to the researchers, this finding “suggests a direct effect of HIV on antistaphylococcal defenses.”

Adding to the evidence, N.E. Lee and colleagues carried out a case-control study of MRSA skin infections in 35 gay men in Los Angeles; results were published in the May 15, 2005 issue of *CID*. Most of these cases were community acquired and not associated with hospitals. MRSA skin infections (abscesses, cellulitis, boils) were linked to high-risk sexual behavior (including meeting partners in bathhouses, sex clubs, or over the internet, but not average number of sexual partners), methamphetamine use, nail-biting, close contact with customers at work, and use of a public hot tub or sauna; condoms were found to have a protective effect. In this study MRSA infection was not associated with immunosuppression or use of antiretroviral therapy. The researchers concluded that among this population, MRSA appears to be spread via direct skin-to-skin transmission or indirect transmission related to environmental exposures, and emphasized the need for increased awareness of community-acquired MRSA so that appropriate treatment can be started without delay.

HIV/HCV AND HIV/HBV COINFECTION

The problem of HIV and viral hepatitis coinfection has attracted increasing attention over the past few years, and experts have begun to accumulate enough data to make recommendations about optimal management. The May 2005 issue of the *Journal of Hepatology* featured a summary

of recommendations developed at the First European Consensus Conference on Treatment of HBV and HCV in HIV-Coinfected Patients, which took place March 1–2 in Paris. The summary includes guidelines about which coinfecting individuals are good candidates for hepatitis B or C treatment, when such therapy should be started, and which anti-HIV medications pose potential risks for individuals with liver disease.

Several researchers presented data on HIV/HCV and HIV/HBV coinfection at the February Retrovirus conference, but coinfection did not grab the headlines as it did at last year’s meeting. Mark Sulkowski, MD, and colleagues (abstract 121) presented some of the clearest evidence to date that liver damage can progress faster than expected in HIV/HCV-coinfecting individuals. In a cohort of 67 coinfecting subjects who received paired liver biopsies an average of two years apart, 28% had fibrosis scores that increased by at least two stages from one biopsy to the next. The researchers suggested that because fibrosis progresses more rapidly in coinfecting individuals, the usual recommendation that people with minimal fibrosis can “wait and watch” may not be appropriate for the coinfecting population. Sherri Stuver and colleagues (abstract 947) found that having a nadir (lowest ever) CD4 cell count below 200 cells/mm³—and especially below 100 cells/mm³—was significantly associated with fibrosis progression, but that subjects on HAART who achieved HIV viral loads below 75 copies/mL had a decreased risk of liver disease progression or death.

On the other hand, research continues to turn up contradictory data about whether HCV adversely affects HIV disease progression. A study by R.C. Hershow and colleagues reported in the March 2005 issue of *CID* looked at 625 HIV positive subjects in the Women’s Interagency HIV Study (WIHS), 190 (29%) of whom also had hepatitis C. The researchers found that the coinfecting women did not progress to AIDS-defining illnesses or death faster than those with HIV alone. HIV viral load levels were similar in both groups, but CD4 cell percentages were slightly higher among the coinfecting women.

In terms of antiretroviral therapy, Barbara McGovern and colleagues (abstract 950) found that HIV/HCV-coinfecting individuals who had been exposed to NRTIs—in particular d4T, ddI, or ddC—were at higher risk for steatosis (fatty liver), but Alison Uriel and colleagues (abstract 925) did not see a link between specific anti-HIV drugs and this condition. Sulkowski and colleagues reported in the April 8, 2005 issue of *AIDS* that steatosis was present in 40% of a cohort 112 HIV/HCV-coinfecting subjects (99% with HCV genotype 1), most of whom were taking HAART. Steatosis was more common among subjects

with advanced liver disease, those with hyperglycemia (high blood sugar), obese individuals, and those receiving d4T; only four subjects had never taken d4T, none of whom had steatosis. Finally, according to a study published in the March 2005 issue of the *Journal of Hepatology*, HIV/HCV-coinfected individuals taking HAART are more likely to develop fulminant hepatic failure (severe, rapid liver failure) than those with HIV alone. In a retrospective analysis of medical records from 11,678 veterans with HIV mono-infection and 4,761 with HIV/HCV coinfection, R.J. Kramer and colleagues determined that the cumulative incidence of fulminant hepatic failure was 1.1 per 1,000 PY in the HIV-monoinfected group compared with 2.5 per 1,000 PY in the coinfecting group. They noted that the risk of fulminant hepatitis was considerably higher since the advent of HAART, suggesting that antiretroviral drug toxicity plays a role. However, the risk of fulminant hepatitis remains low: in this study only 92 total cases were seen between 1991 and 2000.

It remains unclear how often HCV is transmitted sexually among men who have sex with men (studies consistently show very low rates of sexual transmission, in the range of 0–3%, within monogamous heterosexual couples). Marie-Laure Claire and colleagues from Necker Hospital in Paris (abstract 122) presented the latest data on a cluster of 12 HIV positive men diagnosed with acute hepatitis C; ten had the rare genotype 4d, suggesting a common source of infection. The researchers found that male-to-male sex was “the only significant risk factor” for HCV infection in this cohort. In a related study, A. Rauch and colleagues (abstract 943) studied 1,347 HIV positive heterosexual subjects and 1,542 HIV positive gay/bisexual men in the Swiss HIV Cohort. Eight heterosexuals seroconverted to HCV positive (0.2 per 100 PY), compared with 14 gay/bisexual men; among the gay/bisexual men, the rate was the same 0.2 per 100 PY for those who reported only safe sex, but 0.7 per 100 PY for those reporting unprotected sex. However, in a recent study by M. Alary and colleagues published in the March 2005 issue of the *American Journal of Public Health*, only one new HCV infection was detected among more than 1,000 gay men in Montreal during eight months of follow-up (2,653 PY), even though 63% said they had engaged in unprotected anal sex; the one infection occurred in a man who reported sharing drug injection equipment. Notably, the men in Alary’s study were HIV negative while those in the two European studies were HIV positive; research suggests that sexual transmission of HCV may be more likely in people with HIV.

PIS INCREASE HEART DISEASE RISK

Adding to the evidence from the D:A:D study presented at the Retrovirus conference, a study published in the March 1, 2005 issue of the *American Journal of*

Cardiology also found that elevated blood lipids are linked to increased risk of heart disease in HIV positive people using HAART. Steven Grover, MD, from McGill University and colleagues analyzed data from a trial that compared blood lipid changes in subjects using atazanavir (Reyataz) or nelfinavir for 32 weeks. Using coronary risk equations derived from the Framingham Heart Study (a large, long-term study of cardiovascular risk factors in the general population) and other mathematical models, the researchers estimated that the increases in total cholesterol and LDL “bad” cholesterol seen in subjects taking nelfinavir (24% and 28%, respectively) could be expected to increase the risk of heart disease by 50% over 10 years, regardless of other cardiovascular risk factors. The authors concluded, based on their model, that “minimizing dyslipidemia associated with [HAART] may preserve life expectancy.”

In a different type of analysis, U.H. Iloeje from Bristol-Myers Squibb and colleagues looked at a large database of more than 7,500 HIV positive individuals to determine whether cardiovascular events (heart attack, stroke, angina, coronary artery disease, coronary bypass or angioplasty surgery) were associated with antiretroviral therapy. Results were published in the January 2005 issue of *HIV Medicine*. A total of 127 cardiovascular events occurred during the follow-up period. While 77% of the subjects had taken PIs, 88% of the events occurred in this group. After adjusting for other risk factors, the researchers determined that the rate of cardiovascular disease was 9.8 per 1,000 PY among subjects who used PIs compared with 6.5 per 1,000 PY among the PI-naive participants. Not surprisingly, the researchers found that traditional risk factors—including smoking, diabetes, and older age—also contributed to increased heart disease risk. The authors recommended that “clinicians should evaluate the risk of [cardiovascular disease] when making treatment decisions for HIV-infected patients.”

COCAINE ALSO A CARDIAC RISK FACTOR

According to an article in the March 28, 2005 issue of *Archives of Internal Medicine*, cocaine use is associated with increased risk of heart disease in people with HIV. Shenghan Lai, MD, and colleagues from Johns Hopkins studied 224 HIV positive and HIV negative African American subjects aged 25–45 years. They found that both individuals with HIV and people who used cocaine were significantly more likely to develop coronary calcification (an early subclinical sign of atherosclerosis) and that the risk was compounded in subjects who were both HIV positive and cocaine users. Using CT scans, the researchers detected coronary calcification in 19% of HIV negative

non-cocaine users, 29% of HIV positive non-users, 30% of HIV negative cocaine users, and 38% of HIV positive cocaine users. Among the non-users, however, those with HIV were found to have more and larger areas of calcification. Higher rates of coronary calcification among the non-users were apparent even among HIV positive individuals who were not taking PIs, which can raise blood lipid levels.

SMOKING CESSATION REDUCES CARDIOVASCULAR RISK

Some studies have found that HIV positive individuals are more likely to smoke tobacco than the population at large. According to a study published in the April 29, 2005 issue of *AIDS*, smoking cessation was associated with decreased intima-media thickness (an indicator of atherosclerosis). Rodolphe Thiebaut and colleagues looked at cardiovascular risk-reduction strategies among 233 HIV positive subjects in the French Aquitaine Cohort (median age 44 years; 25% women). After 36 months of follow-up, 17% of the subjects were taking lipid-lowering statin or fibrate drugs (up from 2% at the start of the study), 60% were on PI-sparing antiretroviral regimens (up from 45% at baseline), and 49% were still smoking (down from 59%). Looking at the individual interventions, the researchers found that only smoking cessation was linked to decreased intima-media thickness. They recommended active promotion of smoking cessation to reduce the risk of cardiovascular disease among HIV positive persons.

ALENDRONATE REDUCES BONE LOSS

Alendronate (Fosomax) plus vitamin D and calcium increases bone mineral density (BMD) in HIV positive individuals with osteopenia (mild bone loss) or osteoporosis (severe bone loss), according to a study published in the April 1, 2005 issue of *JAIDS*. Previous research has shown that HIV positive people are at increased risk for bone loss, but it is not yet clear whether this is due to antiretroviral therapy, immunosuppression, or HIV itself. Kristin Mondy, MD, from Washington University in St. Louis and colleagues conducted a prospective study of 31 HIV positive subjects on HAART with low lumbar spine BMD (T-scores less than -1.0); importantly, most of the subjects (87%) were men, and studies in the general population indicate that women are more prone to bone loss. Subjects were randomly assigned to either receive or not receive 70 mg alendronate once weekly; all subjects received daily vitamin D and calcium supplements. After 48 weeks, subjects taking alendronate experienced a 5.2% increase in lumbar spine BMD, compared with a 1.3% increase among those taking supplements alone; no adverse events were seen in either arm. The authors concluded that

“alendronate, vitamin D, and calcium are safe and potentially useful in the treatment of osteopenia/osteoporosis associated with HIV infection.”

Alendronate also appears to be effective without added supplements. A Spanish study reported in the February 18, 2005 issue of *AIDS* found that in a 96-week study of 25 HIV positive subjects on HAART with osteoporosis, those receiving 70 mg alendronate once weekly plus dietary counseling experienced increased BMD, compared with no significant improvement in those assigned to receive dietary counseling alone. Increased spine BMD was apparent at 48 weeks, and improved trochanter (near ball of the hip joint) BMD was seen by the end of the study. Although subjects in this study did not receive vitamin D or calcium supplements, dietary counseling helped ensure that their daily diets contained at least 1,200 mg of calcium.

ANTIDEPRESSANTS, MEDICAL MARIJUANA IMPROVE ADHERENCE

Depression is linked to poor adherence, and use of antidepressants can help HIV positive individuals stick to their prescribed HAART regimens, according to a study published in the April 1, 2005 issue of *JAIDS*. Lourdes Yun, MD, and colleagues from the Denver Public Health Department retrospectively analyzed medical records from 1,713 HIV positive subjects attending public health clinics between 1997 and 2001. Among the 981 subjects (57%) diagnosed with clinical depression, 46% were prescribed antidepressants and 52% were prescribed HAART. About half the subjects with depression refilled their antidepressant prescriptions at least twice. The researchers found that 69% of subjects who took antidepressants regularly adhered well to HAART, compared with 31% of depressed subjects who did not take antidepressants regularly. They also found that while HAART adherence improved over time in all groups, the improvement was greatest in the subjects who took antidepressants regularly. A possible confounding factor in this study is the likelihood that some subjects might have been naturally good adherers who took both their antidepressants and their antiretroviral medications as directed. The authors concluded that “attention to diagnosis and treatment of depressive disorders in this population may improve antiretroviral adherence and ultimate survival.”

In related news, a study published in the January 1, 2005 issue of the same journal found that medical cannabis (marijuana) was associated with improved adherence to antiretroviral therapy among HIV positive subjects experiencing nausea. Nausea is a side effect of several anti-HIV drugs and has been shown to interfere with adherence. Bouke de Jong, MD, from Stanford University and

While HAART adherence improved over time in all groups, the improvement was greatest in the subjects who took antidepressants regularly.

colleagues surveyed 252 subjects about their use of cannabis and antiretroviral therapy; 69% were on HAART, 67% provided data on HAART adherence, and 24% reported using cannabis. Among the subjects as a whole, the researchers found no association between marijuana use and HAART adherence. Among a subgroup of subjects with chronic nausea, however, those who used cannabis were about three times more likely to adhere to HAART compared with non-cannabis users. In contrast, among subjects without nausea, marijuana use was associated with decreased adherence. HAART adherence was not associated with sex, race/ethnicity, or age, but was poorer among subjects who used alcohol and illegal drugs other than cannabis. The authors concluded that medical marijuana may “facilitate, rather than impede” HAART adherence for a selected group of individuals.

BENEFITS OF CASE MANAGEMENT

Case management can help newly diagnosed HIV positive people access care, according to a study published in the March 4, 2005 issue of *AIDS*. Gardner Lytt and colleagues with the Antiretroviral Treatment and Access Study (ARTAS) group looked at 273 participants from Atlanta, Baltimore, Los Angeles, and Miami who had recently been diagnosed with HIV. Half the subjects were randomly assigned to receive case management, while the other half were simply given referrals to treatment providers. The case management group had as many as five contacts with case managers over a 90-day period, during which the case managers helped clients identify and address their needs and barriers to care; case managers also helped clients contact care providers and were available to accompany them to clinic visits. The researchers found that 78% of subjects in the case management arm visited HIV clinics at least once within a period of six months, compared with 60% in the referral-only arm. Looking at those who visited clinics twice within a one-year period, the respective figures were 64% and 49%. The researchers estimated that the case management intervention cost \$600–1,200 per client. Since “a relatively modest investment” in case management was associated with “a significantly higher rate of successful linkage to HIV care,” they concluded that case management is an “affordable and effective resource” for newly diagnosed individuals.

GREATER IRIS RISK WITH ADVANCED IMMUNOSUPPRESSION

An article in the Winter 2005 issue of *BETA* discussed immune reconstitution inflammatory syndrome (IRIS) in HIV positive people whose immune systems begin to recover with effective antiretroviral therapy. A retrospective

analysis published in the March issue of *HIV Medicine* shed further light on who is most at risk for IRIS. D.J. Jevtovic and colleagues from Belgrade studied 389 subjects who started HAART between 1998 and 2003. Most (87%) had an AIDS diagnosis and 62% had CD4 cell counts below 100 cells/mm³. After 35 months, about three-quarters achieved viral loads below 50 copies/mL and 45% reached CD4 cell counts above 400 cells/mm³. The researchers found that 65 subjects (17%) experienced at least one episode of IRIS, including symptoms of herpes zoster (shingles), tuberculosis, cytomegalovirus (CMV), cryptococcosis, toxoplasmosis, hepatitis, and immune recovery vitritis (a type of eye inflammation). The risk of IRIS was highest among individuals who had more advanced immunosuppression (CD4 cell counts below 100 cells/mm³) when they started HAART. Median CD4 cell increases and viral load decreases did not differ between the IRIS and non-IRIS groups, but IRIS risk was very low among those whose CD4 cell counts increased to more than 400 cells/mm³. Previous research has shown that HAART works better when it is started before advanced immune system decline; this study suggests that doing so can also help prevent IRIS.

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Pipeline Progress: Then and Now

**John
Hawes**

The antiretroviral drug pipeline was last reviewed in *BETA* three years ago (see “The HIV/AIDS Drug Pipeline: A Status Report” in the Summer/Autumn 2002 issue). That report called on pharmaceutical companies to “ensure a steadier stream of innovative and affordable approaches to managing HIV infection.” Is this goal being achieved?

A Picture of Progress

The most obvious sign of progress is the arrival of the entry inhibitor class of drugs into the clinic with the March 2003 approval of T-20 (enfuvirtide, Fuzeon). The entry inhibitor class includes several subclasses of agents—attachment inhibitors, coreceptor antagonists, and fusion inhibitors such as T-20—that prevent HIV from gaining access to cells (see sidebar and “Newer Antiretroviral Classes,” below). The approval of the first drug in a new class of antiretrovirals is a significant step forward in treatment and a hopeful sign of future advances.

Another way to see the changes in drug development over the past few years is to look at the current status of the drugs highlighted in the 2002 report. These included new drugs or reformulations of existing drugs that were considered to be closest to approval and two new agents that had just reached the advanced clinical development stage (Phase II/III studies). (For more information on clinical trials and phases of research, see “A Guide to Clinical Trials” on page 42.)

Somewhat surprisingly, all of these drugs are now approved and all but one are in clinical use (see below). Tipranavir (Aptivus) was granted accelerated approval by the Food and Drug Administration (FDA) this past June (see “News Briefs” on page 7). Extended release d4T (stavudine, Zerit XR) was approved in December 2004 but is not yet commercially available.

Current Status of Promising Agents in 2002

- 3TC QD, once daily (lamivudine, Epivir) – NRTI
Approved June 2002
- T-20 (enfuvirtide, Fuzeon) – fusion inhibitor
Approved March 2003
- atazanavir (Reyataz) – PI
Approved June 2003
- FTC (emtricitabine, Emtriva) – NRTI
Approved July 2003
- fosamprenavir (Lexiva) – PI
Approved October 2003

- d4T, extended release (stavudine, Zerit XR) – NRTI
Approved June 2004, but not yet available for clinical use
- tipranavir (Aptivus) – PI
Approved June 2005

Often unnoticed in drug development are the compounds that never move out of preclinical research, or those that appear promising in preclinical studies but fade away in early human trials due to pharmacologic, efficacy, or safety concerns. Such was the case for many antiretroviral compounds that were alive in 2002 but are no longer being pursued. However, some candidates have survived and may progress to approval in the next few years, just as those shown above have done. In the meantime, this report provides an update on agents that have moved to the final preapproval stage of drug development (Phase III) and a list of new compounds in all stages of clinical development as of May 2005. (For recent reports on several agents further back in the development pipeline, see “News Briefs” on page 6.)

Traditional Antiretroviral Classes

Among the three traditional antiretroviral drug classes, there are 12 new compounds in more advanced clinical trials: six NRTIs, four NNRTIs, and two PIs (see page 17). The furthest along are the NRTI Reverset (formerly D-d4FC), the NNRTI capravirine (formerly AG-1549), and the PI TMC-114, all of which are in Phase III studies.

Reverset is a cytidine analog like 3TC (lamivudine, Epivir) and FTC (emtricitabine, Emtriva). As with many other investigational drugs from the three traditional classes, Reverset is being developed for use against HIV strains that are resistant to currently approved therapies as well as wild-type (nonmutated) virus. In treatment-naïve HIV positive people, once-daily Reverset alone has produced maximum reductions in HIV viral load of 1.2–2.3 logs after ten days. In another ten-day monotherapy trial,

Newer Antiretroviral Drug Classes*

ENTRY INHIBITORS

HIV entry into a CD4 cell is a three-step process:

1. HIV must attach itself to the CD4 protein receptor on the host cell surface
2. HIV must bind with a secondary coreceptor (CCR5 or CXCR4) on the cell surface
3. HIV must then fuse with the cell to enter and make copies of itself

ATTACHMENT INHIBITORS

block binding of HIV to the CD4 protein

CORECEPTOR ANTAGONISTS

block binding of HIV to the CCR5 or CXCR4 coreceptors

FUSION INHIBITORS

prevent HIV from fusing with the cell

INTEGRASE INHIBITORS

disrupt the activity of integrase, one of three HIV enzymes— together with protease and reverse transcriptase—that the virus needs to replicate

MATURATION INHIBITORS

cause HIV inside a CD4 cell to form defective, noninfectious copies of itself

** among these classes and subclasses, only one drug— a fusion inhibitor—is currently approved*

Reverset was studied in eight NRTI-experienced individuals whose current therapy was failing to suppress HIV. The mean viral load before Reverset treatment was 4.53 log copies/mL. At the end of the ten-day study, the mean viral load decrease was 0.8 logs, and four of the eight subjects achieved viral loads below 400 copies/mL.

Capravirine is an NNRTI with potent activity against HIV, including strains with the K103 mutation—the genetic change that causes resistance to the entire NNRTI class. Previously, the FDA put a hold on capravirine due to concerns about vasculitis (blood vessel inflammation), but the drug was subsequently cleared for further clinical study. Phase II research has shown that capravirine can produce durable viral suppression in some people, although a recent trial evaluating the addition of capravirine to a standard PI-based regimen did not show any significant difference between subjects who received capravirine and those who did not after 48 weeks of treatment. There was some evidence that capravirine was more effective in people with

3TC and AZT resistance, but this needs to be confirmed. Several Phase II and III trials are ongoing.

TMC-114 is a protease inhibitor with activity against PI-resistant HIV. TMC-114 appears to be effective in HIV positive people on previously failing PI regimens when it is boosted with low-dose ritonavir (TMC-114/r) to increase its potency. An interim analysis of 24-week data from two ongoing dose-ranging trials in 497 treatment-experienced subjects showed that TMC-114/r produced significantly better virological response (greater than 1.8 log viral load decrease from baseline) compared with optimized regimens containing comparator PIs. After 24 weeks, 47% of subjects receiving 600/100 mg TMC-114/r twice daily achieved viral loads below 50 copies/mL; viral suppression rates in the 400/100 mg once daily, 800/100 mg once daily, and 400/100 mg twice daily arms were 30%, 31%, and 38% respectively. Two-thirds of the TMC-114/r-treated individuals whose regimens also included T-20 achieved viral loads below 400 copies/mL. Such a regimen may be highly valuable as salvage therapy, for which there are few current options. These trials will continue through 96 weeks, and a new Phase III trial is beginning (see “Open Clinical Trials” on page 50).

Newer Antiretroviral Classes

To date, only one drug (the fusion inhibitor T-20) has been approved outside of the three traditional antiretroviral classes. Although research is ongoing to develop drugs from novel classes, most compounds that have progressed beyond early Phase I trials act as entry inhibitors, including several attachment inhibitors and coreceptor antagonists in Phase II trials. The maturation inhibitor PA-457 is also in Phase II, and in late June Gilead announced a new Phase I/II study of their integrase inhibitor, GS-9137.

The only investigational drug from a newer antiretroviral class currently in Phase III clinical development is the entry inhibitor **maraviroc** (formerly UK-427,857). Specifically, maraviroc is a CCR5 coreceptor antagonist (see sidebar) and appears to be very potent. In HIV positive people beginning antiretroviral therapy, maraviroc treatment has been associated with a viral load drop of 1.42 logs after only ten days. Other preliminary data indicate that dose adjustments will be needed when maraviroc is combined with other antiretroviral agents due to pharmacokinetic drug-drug interactions (see “Drug Interactions and Anti-HIV Therapy” on page 20).

Laboratory research has shown that HIV resistant to maraviroc appears to be susceptible to other coreceptor antagonists. Phase II/III studies of maraviroc in treatment-naïve and treatment-experienced individuals are in

Status of Investigational Antiretroviral Agents in Clinical Development

Clinical Stage	Traditional Antiretroviral Classes			Novel Antiretroviral Classes			
	NRTI	NNRTI	PI	EI*	MI	II	Other**
Phase I	D-FDOC MIV-210	695634 KP-1212 DOT (dioxolane thymidine)	GSK-640385 Ro-033-04649	AMD-070 (CA) PRO-140 (CA) BMS-378806 (AI) AMD-3100 SP01A		C-2507 GS-9137 (JTK-303)	HGTV-43 VRX-496 BAY 50-4798
Phase II	alovudine (MIV-310) elvucitabine (beta-L-Fd4C) SPD-754 (DOTC) amdoxovir (DAPD) racivir	etravirine (TMC-125) calanolide A TMC-278	AG-1859	TNX-355 (AI) BMS-488043 (AI) PRO-542 (AI) vicriviroc (SCH-D) (CA) GW-873140 (CA)	PA-457		
Phase III	Reverset (D-d4FC)	capravirine	TMC-114	maraviroc (UK-427,857) (CA)			

EI, entry inhibitor; MI, maturation inhibitor; II, integrase inhibitor.

* Entry inhibitor subclasses shown: AI, attachment inhibitor; CA, coreceptor antagonist. No compound from the fusion inhibitor subclass is in active clinical development.

** Except for the three compounds listed in Phase I, all compounds from "other" novel classes are in preclinical stages.

progress (see "Open Clinical Trials" on page 51 for two currently enrolling studies).

Commentary

Antiretroviral drug development over the past few years has led to improvements in how HIV disease is managed, with lower pill burdens, useful reformulations of older drugs, fixed-dose combination pills, and more effective therapies, especially for people without extensive treatment history. But the movement forward seems slow. After the recent approval of tipranavir, no other experimental agent is under review for FDA approval. Only one—Tibotec's TMC-114—will be available through an expanded access program (EAP) for people with few treatment options (see "News Briefs" on page 9).

And what of the innovative and affordable approaches that were called for in the 2002 drug progress report? Additional entry inhibitors may prove to be a breakthrough in the management of HIV/AIDS. Like T-20, however, they are likely to be expensive. Another answer has been increased pharmacokinetic enhancement, or boosting, of

approved PIs (see "Drug Interactions and Anti-HIV Therapy" on page 22). This approach takes advantage of drugs that are already available and about which a great deal is already known, and renders them more potent, more convenient, or both. Yet the boosted PI strategy is hampered by the present need for ritonavir (Norvir) as the boosting agent—a drug available through only one manufacturer (Abbott) that dramatically raised the price of this PI by 400% in December 2003. It had been hoped that research would have provided a cheaper and more accessible boosting alternative by now.

Although there has been progress in the pipeline since 2002, those who fund and carry out HIV research should be encouraged to "think out of the pipe," to move from better managing this infection to realizing a cure.

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ABOUT LOGS

Viral load levels are customarily expressed in one of two ways: absolute numbers (e.g., 1,000 copies/mL) or logs (e.g., 3 log copies/mL).

A **log** is a way of expressing large numbers using the logarithmic scale. Simply put, a log refers to how many times a base number—10 in the case of viral load—is multiplied by itself to produce a given absolute number. For example, 3 log is the same as $10 \times 10 \times 10$, which equals 1,000.

An easy way to remember the log system is to count the zeros in numbers that are expressed as powers of 10. The number of zeros equals the log value. For example, 1,000 (three zeros) equals 3 log, 100 (two zeros) equals 2 log, and 10 (one zero) equals 1 log. See the accompanying chart for other conversions from logs to absolute numbers.

A **log change** in viral load level reflects a 10-fold (exponential) increase or decrease. For example, a decrease in viral load from 1,000 to 100 copies/mL is a 1 log reduction, since the viral load has dropped from 3 log to 2 log copies/mL (3 log – 2 log = 1 log

change). Note that the 1 log change does not represent a decrease in absolute numbers (a mere 10 copies/mL), but rather a 10-fold decrease. An increase from 100 to 1,000 copies/mL likewise would be a 1 log change.

Using more real-world figures, a person might begin treatment with a viral load of 62,376 copies/mL. Anti-HIV therapy might then reduce that person's viral load to 471 copies/mL. In approximate log figures, that is a reduction from about 4.8 log to about 2.7 log copies/mL, or a 2.1 log decrease (4.8 log – 2.7 log = 2.1 log change).

Log changes also can be expressed in terms of **percentages**. When thinking of increases and decreases in viral load levels, it might be useful to remember the following:

- 0.5 log change = 70% change in viral load (VL)
- 1 log change = 90% change in VL
- 2 log change = 99% change in VL
- 3 log change = 99.9% change in VL

LOGS AND ABSOLUTE NUMBERS

log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL
	1.0 = 10	2.0 = 100	3.0 = 1,000	4.0 = 10,000	5.0 = 100,000	6.0 = 1,000,000
0.1 = 1	1.1 = 13	2.1 = 126	3.1 = 1,259	4.1 = 12,589	5.1 = 125,893	6.1 = 1,258,925
0.2 = 2	1.2 = 16	2.2 = 158	3.2 = 1,585	4.2 = 15,849	5.2 = 158,489	6.2 = 1,584,893
0.3 = 2	1.3 = 20	2.3 = 200	3.3 = 1,995	4.3 = 19,953	5.3 = 199,526	6.3 = 1,995,262
0.4 = 3	1.4 = 25	2.4 = 251	3.4 = 2,512	4.4 = 25,119	5.4 = 251,189	6.4 = 2,511,886
0.5 = 3	1.5 = 32	2.5 = 316	3.5 = 3,162	4.5 = 31,623	5.5 = 316,228	6.5 = 3,162,278
0.6 = 4	1.6 = 40	2.6 = 398	3.6 = 3,981	4.6 = 39,811	5.6 = 398,107	6.6 = 3,981,072
0.7 = 5	1.7 = 50	2.7 = 501	3.7 = 5,012	4.7 = 50,119	5.7 = 501,187	6.7 = 5,011,872
0.8 = 6	1.8 = 63	2.8 = 631	3.8 = 6,310	4.8 = 63,096	5.8 = 630,957	6.8 = 6,309,573
0.9 = 8	1.9 = 79	2.9 = 794	3.9 = 7,943	4.9 = 79,433	5.9 = 794,328	6.9 = 7,943,282
<i>copies/mL refers to viral load</i>						7.0 = 10,000,000

Selected Sources

Hammond, J.L. and others. Long-term virologic response to capravirine in HIV-infected, NNRTI-experienced patients. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago. September 14–17, 2003. Abstract H-871.

Hawley, P. and others. Absence of risk of vasculitis in a HIV population taking capravirine—results of an active monitoring plan. 14th International AIDS Conference. Barcelona. July 7–12, 2002. Abstract TuPeB4549.

Katlama, C. and others. Efficacy of TMC114/r in 3-class experienced patients with limited treatment options: 24-week planned interim analysis of 2 96-week multinational dose-finding trials. 12th Conference of Retroviruses and Opportunistic Infections (CROI). Boston. February 22–25, 2005. Abstract 164LB.

Muirhead, G. and others. A novel probe drug interaction study to investigate the effect of selected ARV combinations on the pharmacokinetics of a single oral dose of UK-427,857 in HIV+ subjects. 12th CROI. Abstract 663.

Murphy, R.L. and others. Tolerance and potent anti-HIV-1 activity of Reverset following 10 days of monotherapy in treatment-naïve individuals. 11th CROI. San Francisco. February 8–11, 2004. Abstract 137.

Murphy, R.L. and others. Tolerance and anti-HIV activity of Reverset following 10 days as add-on therapy to current regimens in treatment-experienced HIV-infected individuals. 44th ICAAC. Washington, DC. October 30–November 2, 2004. Abstract H-1130.

Pesano, R. and others. 24 week safety, tolerability, and efficacy of capravirine as add-on therapy to neftinavir and 2 nucleoside reverse transcriptase inhibitors in patients failing a non-nucleoside reverse transcriptase inhibitor-based regimen. 12th CROI. Abstract 555.

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Drug Interactions and Anti-HIV Therapy

Liz
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The advent of highly active antiretroviral therapy (HAART) has decreased mortality and improved the quality of life for HIV positive people, but treatment of HIV and its associated conditions remains highly complex. With some 20 antiretroviral agents, dozens of drugs for opportunistic illnesses (OIs), and additional therapies to manage associated conditions such as elevated blood fats, the potential for drug interactions is a pressing concern.

Interactions happen when one drug influences the level or activity of another. Because of the way they are processed in the body, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are especially likely to be involved. Interactions may raise blood levels of a drug, possibly causing intensified side effects, or they may decrease drug concentrations, potentially resulting in reduced effectiveness. But drug interactions are not always problematic: the PI ritonavir (Norvir) can “boost” levels of other drugs in its class, increasing their potency and allowing for more convenient dosing.

With so many drugs to consider, it is not possible to give a comprehensive listing of every possible interaction. Instead, this article will discuss how and why drug interactions occur, describe some of the important interactions commonly seen with antiretroviral therapy, and offer steps to avoid or manage them. The accompanying resource list on page 28 provides useful online drug interaction databases and tools to help determine whether specific medications are likely to interact.

HIV positive people should be aware of the potential for interactions and inform all their health-care providers about all drugs they are taking, including prescription and over-the-counter (OTC) medications, herbal remedies and supplements, and recreational or street drugs.

A Ubiquitous and Growing Problem

The antiepileptic drug phenytoin (Dilantin) can dangerously decrease levels of lopinavir/ritonavir (Kaletra). Use of the antibiotic erythromycin with PIs may increase the risk of sudden cardiac death. The new PI atazanavir (Reyataz) should not be used with omeprazole (Prilosec), a popular medication for gastroesophageal reflux. Boosted saquinavir (Invirase) can potentially cause liver toxicity when combined with rifampin, part of the standard first-line regimen for tuberculosis.

These are just a few of the interactions between anti-HIV medications and other drugs that have been announced in “Dear Doctor” advisories or described in medical journals during the past year. As novel agents are approved and additional information about existing products becomes available, new interactions continually come to light. Uncovering potential interactions is a major focus of the drug development process and—as shown by the amount of time and space devoted to the topic at professional conferences and in the medical literature—avoiding and managing drug interactions has become an increasingly important part of HIV medicine.

Today most HIV positive people receiving treatment take antiretroviral regimens consisting of three or more drugs from at least two different classes. Many also use various medications, such as antifungals and cholesterol-lowering statins, to treat associated conditions and manage side effects. OTC medications, street drugs, methadone, alternative and complementary therapies, and even certain foods may also be involved in interactions.

This exploding “polypharmacy” presents a challenge for people with HIV and their providers. While many drug interactions are of little clinical significance, others can lead to severe toxicities, loss of virological control of

HIV, and the emergence of drug-resistant virus. Fortunately, a relatively small subset of drugs is implicated in the lion’s share of interactions; often problems can be avoided by heightened vigilance and judicious substitution of effective alternatives.

Mechanisms of Drug Interactions

Drug interactions fall into two broad categories: pharmacodynamic and pharmacokinetic.

Pharmacodynamic interactions are those related to the combined clinical activity of two or more agents used together, for example, additive or synergistic side effects (see below). Pharmacokinetic interactions occur when one agent changes the blood concentration of another. The majority of clinically significant drug interactions encountered in HIV medicine are pharmacokinetic in nature.

Pharmacodynamic Effects

Some drug interactions occur when similar agents, or agents with similar effects, are used together. An additive effect refers to the combined effects of two or more agents added together (i.e., $1 + 1 = 2$). A synergistic effect occurs when the overall effect of two or more agents used together is greater than the sum of the effects the compounds would produce if used separately (i.e., $1 + 1 = 3$). An antagonistic effect happens when one agent reduces or cancels out the effects of another (i.e., $1 + 1 = 0$).

Successful HAART relies on additive effects. Not long after the advent of the first antiretroviral drugs, it became clear that single agents used alone (monotherapy) could not suppress HIV

over the long term since the virus can mutate to develop drug resistance. Therefore, multiple agents from more than one drug class are now used to construct effective regimens.

Additive and synergistic side effects are a major concern in anti-HIV therapy. When two or more drugs with overlapping toxicity profiles are used together, the combined toxicity may prove intolerable, even if the individual agents alone produce only mild side effects. For instance, the “d drugs”—ddC (zalcitabine, Hivid), ddI (didanosine, Videx), and d4T (stavudine, Zerit)—can all cause pancreatitis (inflammation of the pancreas), peripheral neuropathy (nerve damage), and mitochondrial toxicity. Thus, experts recommend that combinations of these drugs should be avoided if possible.

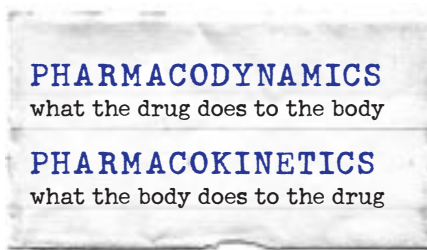
An Introduction to Pharmacokinetics

Pharmacokinetics refers to what happens to drugs in the body: their absorption, metabolism (processing), transport, distribution to tissues, and elimination.

In a nutshell, the plasma concentration of a drug varies between doses. The goal is to achieve a minimum, or trough, concentration (C_{\min}) that is effective without causing unacceptable toxicity at the highest, or peak, level (C_{\max}). The total exposure to a drug between one dose and the next is called the area under the curve, or AUC. If a drug has a narrow therapeutic range—meaning a small difference between an effective dose and a toxic one—even minor interactions may prove problematic.

Altered Absorption and Transport

Most medications are taken orally and absorbed from the stomach and intestines. Any agent that changes the gastrointestinal environment can affect drug absorption, which is why some medications have food restrictions. Many agents are better absorbed when the stomach is empty, but



some—including nelfinavir (Viracept)—are better absorbed when taken with food. Lipid-soluble (dissolvable in fat) compounds require fatty foods for optimal absorption; however, one such agent, efavirenz (Sustiva), should be taken without fat in order to slow absorption and reduce side effects.

Medications that neutralize the acidity of gastric secretions (that is, increase their pH) can interfere with the absorption of other drugs, such as atazanavir, that require an acid environment. The old formulation of ddI contained an antacid buffering agent and thus could not be taken at the same time as several other drugs; this is not a concern with the newer, long-acting enteric-coated form of ddI (Videx EC). For the same reason, certain drugs should not be taken with acid-lowering medications. In addition, some agents can combine with one another in the stomach (a process called chelation), resulting in insoluble compounds that cannot be absorbed; this can occur when some drugs are taken with certain minerals.

The initial phase of drug absorption and metabolism occurs in the intestines. Cells in the intestinal lining contain transporter proteins, called P-glycoproteins, that act as “pumps” to return drug molecules back into the intestine for excretion rather than allowing them to enter the bloodstream. P-glycoproteins also pump certain drugs out of individual cells throughout the body and are associated with drug resistance. Agents that promote P-glycoprotein activity (including some antiretroviral drugs) cause lower plasma drug concentrations, while P-glycoprotein inhibitors increase drug levels.

Once successfully absorbed, the drug enters the bloodstream. Agents are carried in the plasma in either a free (unbound) form or bound to blood proteins such as albumin; the bound form is not bioavailable and cannot enter tissues. Thus, agents that alter protein binding can affect

The Benefits of Boosting

Interactions between antiretroviral medications are not always a bad thing. In the case of ritonavir, the drug’s unique interaction profile allows it to be used to “boost,” or increase, blood concentrations of other PIs. Ritonavir works well as a pharmacological enhancer because it inhibits both the initial stages of PI metabolism in the intestines and CYP3A4 processing in the liver.

This capacity has given ritonavir a new lease on life as a low-dose (typically 100 mg) adjunct drug. At the same time, use of full-dose ritonavir has fallen out of favor because its propensity to raise levels of so many medications is more often harmful than beneficial. Low-dose ritonavir has also boosted the fortunes of other first-generation PIs (namely indinavir and saquinavir) by dramatically reducing their high pill burdens, loosening food requirements, and allowing them to be taken fewer times per day.

Today’s experimental PI candidates are routinely tested in conjunction with ritonavir. Abbott hit the jackpot with Kaletra, a combination pill containing lopinavir (a second-generation PI) plus a small dose of ritonavir. But the company raised the ire of the HIV community when it increased the price of low-dose ritonavir by 400% in December 2003—an attempt, some charged, to give Kaletra a price edge over other PIs.

Researchers are avidly searching for other drugs that can also be used as pharmacological boosters. A few of the approved PIs—including nelfinavir, which has an interaction profile somewhat similar to that of ritonavir—have been linked to increased concentrations of other PIs in some studies. But to date none has demonstrated a strong enough or consistent enough effect to give ritonavir a run for its money.

how much active drug reaches a site of action.

The CYP450 System

Drugs are metabolized, or biotransformed, into byproducts that can more easily be excreted in the feces or urine. Before it is circulated throughout the body, blood leaving the gastrointestinal tract first passes through the liver, where most drug processing occurs. One type of hepatic drug metabolism is carried out by a group of enzymes (proteins that facilitate

chemical reactions) known as the cytochrome P450 (CYP450) system. In addition to the liver, CYP450 enzymes are also present in the intestines and elsewhere in the body.

There are some two dozen CYP450 isoenzymes (specific variants), classified into families designated by numbers and letters, but a small subset carries out most drug metabolism. Many agents are metabolized by a single isoenzyme, but others are processed by more than one. The most abundant isoenzyme, CYP3A4,

is responsible for metabolizing about half of the drugs currently on the market.

Drug metabolism is limited by the quantity of CYP450 enzymes, and different agents compete for their use. Some drugs, called CYP450 inhibitors, retard the activity of these enzymes (ritonavir and erythromycin are examples of inhibitors). When an inhibitor of a specific isoenzyme is present, the processing of other drugs that require the same enzyme is slowed, causing blood concentrations of these other drugs to increase. (This is why ritonavir can be used to boost levels of other PIs; see sidebar on page 22.) Other agents, called CYP450 inducers, cause cells to produce more of a specific isoenzyme over time (rifampin and phenytoin are examples of inducers). When such an agent is present, drugs that are metabolized by the now more abundant isoenzyme are processed more rapidly, causing their blood concentration to fall.

After they are processed and distributed to tissues, drugs must be eliminated. Some drug metabolites are excreted in bile and eliminated through the feces, while others are processed by the kidneys and eliminated in the urine. Any factors that impair or inhibit the filtering activity (tubular secretion) of the kidneys can slow the processing of drugs that rely on this mechanism, again allowing them to reach higher plasma concentrations. For this reason, people with renal insufficiency (kidney dysfunction) are more prone to drug interactions and side effects.

As described by Stephen Piscitelli, PharmD, and Keith Gallicano, PhD, in an overview of antiretroviral and OI drug interactions in the March 29, 2001 issue of the *New England Journal of Medicine (NEJM)*, pharmacokinetic interactions among drugs used in HIV therapy are often “multifactorial,” involving altered drug absorption, P-glycoprotein modulation, CYP450 induction and/or inhibition, changes in renal elimination, and fluctuations in intracellular drug concentration.

Factors that Impact Drug Interactions

Drug interactions are not the same in all people. Several factors can influence pharmacokinetics, including sex, age, race/ethnicity, pregnancy, hormone levels, body size, alcohol use, and coexisting conditions such as liver or kidney dysfunction. For instance, individuals may possess genetic variations, or polymorphisms, that affect expression of specific CYP450 enzymes. A study presented at the February 2004 Retrovirus conference, for example, revealed that people of African descent are seven times more likely than white people to carry a specific variant of the gene controlling expression of the CYP2B6 isoenzyme; as a result, black people as a group eliminate efavirenz more slowly, potentially leading to more intense side effects but also greater efficacy. P-glycoprotein expression also varies by racial/ethnic group.

The impact of liver disease is of particular concern since a substantial proportion of HIV positive people have chronic hepatitis B or C coinfection, which can lead to liver damage including fibrosis and cirrhosis (scarring). When the liver is damaged—as a result of viral hepatitis, heavy alcohol use, drug toxicity, or some other cause—its ability to process drugs may be impaired, potentially leading to higher blood concentrations.

As reviewed by David Wyles, MD, and John Gerber, MD, in the January 1, 2005 issue of *Clinical Infectious Diseases (CID)*, several studies have shown that the pharmacokinetics of antiretroviral drugs may be significantly altered in HIV positive people with hepatitis B or C, and that such impairment is more pronounced in those with more advanced liver damage. For example, L. Becquemont and colleagues demonstrated that CYP3A4 and CYP2D6 isoenzyme activity decreased by 65% and 81%, respectively, in HCV-infected subjects compared with uninfected individuals. At the functional level, other research

has demonstrated impaired drug clearance in people with liver damage.

Wyles and Gerber concluded that liver dysfunction has a considerable impact on PI metabolism, but on the whole, NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) processing are minimally affected. Fortunately, altered drug metabolism in people with liver damage can often be managed by adjusting drug doses. The authors cautioned, however, that making generalized recommendations for dose reduction is difficult, “given the highly variable pharmacokinetics of PIs across the population.”

Interactions Involving Antiretrovirals

Several antiretroviral drugs are both CYP450 and P-glycoprotein substrates (targets). It is therefore not uncommon to encounter interactions among them or with agents used to treat other conditions. Drug interactions involving the NRTI, NNRTI, and PI classes are discussed below. The remaining approved anti-HIV drug, the entry inhibitor T-20 (enfuvirtide, Fuzeon), must be taken by injection because it would be destroyed by acid in the stomach. As reported by Indravadan Patel and colleagues from Roche in the February 2005 issue of *Clinical Pharmacokinetics*, T-20 has no known interactions with other antiretroviral medications.

NRTIs

NRTIs are prone to pharmacodynamic interactions such as additive and synergistic toxicities, but because they are primarily eliminated by the kidneys, not the liver, they have little impact on the CYP450 system. As such, NRTIs have few known pharmacokinetic interactions with NNRTIs or PIs. AZT (zidovudine, Retrovir) is processed by glucuronyl transferases in the liver, and agents that affect levels of these enzymes can raise or lower AZT blood levels. Abacavir (Ziagen), alone among the NRTIs, is broken down by the same enzyme that metabolizes alcohol; thus,

concurrent use of alcohol may raise abacavir levels.

Tenofovir DF (Viread), the only approved nucleotide reverse transcriptase inhibitor, has some unique interactions. Tenofovir can increase plasma levels of both buffered and enteric-coated ddI dramatically (by more than 50% in some studies). In one case, a man with pre-existing kidney dysfunction died of kidney failure and lactic acidosis (a known side effect of ddI) after taking the two drugs together. When using this combination, the ddI dose should be reduced and individuals should be monitored for ddI-related toxicities. Tenofovir can decrease blood concentrations of atazanavir, so levels of this PI should be increased through higher dosing or boosting with ritonavir. Conversely, atazanavir—as well as lopinavir—increases tenofovir levels, but dose adjustment is generally not necessary; tenofovir does not appear to interact with saquinavir, nelfinavir, or indinavir (Crixivan).

NNRTIs

All three approved NNRTIs impact the CYP450 system: nevirapine (Viramune) is a CYP3A4 inducer, delavirdine (Rescriptor) is a CYP3A4 inhibitor, and efavirenz combines both effects. The NNRTIs also induce and/or inhibit other isoenzymes that play more minor roles in drug interactions.

Nevirapine and efavirenz speed processing and reduce plasma concentrations of other drugs metabolized by CYP3A4. In particular, these NNRTIs can cause levels of some PIs to fall, necessitating higher doses and/or boosting with ritonavir. They also lower concentrations of a variety of other agents metabolized by the CYP450 system, including methadone and oral contraceptives, potentially resulting in decreased efficacy.

Efavirenz and delavirdine (which is no longer recommended for first-line therapy) can increase levels of some PIs and other types of medication metabolized by the liver. Caution

is advised when combining these NNRTIs with drug classes that can reach potentially dangerous concentrations when used with CYP450 inhibitors.

Given its mixed inducer/inhibitor effect, as well as its purported influence on other isoenzymes besides CYP3A4, efavirenz can increase nelfinavir and ritonavir levels even though it decreases concentrations of atazanavir, lopinavir, indinavir, saquinavir, and fosamprenavir (Lexiva). Efavirenz has been shown to lower atazanavir concentrations by about 75%; while its effect on other PIs is less dramatic, it should not be used with unboosted indinavir or saquinavir.

Caution is warranted when combining NNRTIs with CYP450 inducers such as rifampin, since these can lower NNRTI levels. It is also important to remember that NNRTIs have long half-lives, meaning they stay in the body for an extended period after discontinuation; this should be taken into account when stopping an NNRTI and substituting a potentially interacting drug. A final caveat with nevirapine is to avoid or use with caution other drugs that may cause skin rash or liver toxicity, due to the potential for overlapping side effects.

PIs

As a class, the PI drugs raise the most concern related to drug interactions. All approved PIs are metabolized by the CYP3A4 isoenzyme and are CYP3A4 inhibitors, but some are stronger than others and some have additional effects. A retrospective chart review conducted soon after the advent of first-generation PIs (published in the March 1997 issue of *Clinical Pharmacokinetics*) revealed that the probability of experiencing undesirable drug interactions was 31% after starting indinavir, 42% after starting saquinavir, and 77% after starting ritonavir. For subjects with CD4 cell counts below 100 cells/mm³ the risk was even greater: 55%, 63, and 93%, respectively.

Saquinavir has the mildest CYP3A4 inhibitory effect, and is therefore the least likely to affect levels of other drugs. Atazanavir, fosamprenavir, indinavir, and nelfinavir are all moderate inhibitors. In contrast, ritonavir is so potent in this respect that it can be used to boost blood concentrations of other drugs in its class (see “The Benefits of Boosting” on page 22). Unlike other approved PIs, ritonavir and nelfinavir both also induce CYP3A4, and share the interesting property of being able to induce their own metabolism. Little is known about the use of lopinavir alone, since it is coformulated with ritonavir in the Kaletra combination pill.

Like all CYP450 inhibitors, PIs slow the processing of other medications metabolized by the same isoenzymes, potentially allowing them to reach highly toxic concentrations. Full-dose ritonavir presents the greatest risk; the smaller ritonavir dose in the Kaletra pill (100 mg) or used to boost other PIs is less likely to cause problematic interactions. Some of the drugs that warrant extra caution or should be avoided altogether when used with PIs include certain statins, anticonvulsants, benzodiazepines, and calcium-channel blockers. (Problematic drug classes are discussed in more detail below.)

Because PI interaction profiles vary in some important respects, each new drug in this class must be extensively tested to determine how it will behave under “real world” conditions. For example, as reported in the January 28, 2005 issue of *AIDS*, a recent clinical trial (ACTG 5143) revealed that combining fosamprenavir plus lopinavir led to significantly reduced levels of both amprenavir (the active metabolite of fosamprenavir) and lopinavir; as a result, enrollment in the study was halted. Unlike most of its classmates, tipranavir (Aptivus), a nonpeptidic PI recently granted approval, is a CYP3A4 inducer. In a study by Sharon Walmsley, MD, and

colleagues presented at the XV International AIDS Conference in Bangkok in July 2004, tipranavir reduced minimum plasma concentrations of amprenavir (Agenerase), lopinavir, and saquinavir by 51%, 45%, and 84%, respectively. As such, tipranavir should be avoided or used cautiously in conjunction with other PIs.

Even as PIs impact levels of other drugs metabolized by the CYP450 system, they themselves are subject to alteration by CYP450 inducers and inhibitors. Inducers present the most concern since they can potentially lead to subtherapeutic PI levels, viral breakthrough (increase in viral load), and the development of drug-resistant HIV.

Interactions with Other Types of Drugs

While a complete list of known and theoretical interactions between antiretrovirals and other types of drugs is beyond the scope of this article, a few categories of medications warrant particular attention because they are commonly used by people with HIV or because their interactions are particularly frequent and/or clinically significant.

For the most part, the drugs discussed below are CYP450 substrates. To refresh, agents that inhibit CYP450 enzymes tend to increase concentrations of other drugs, while agents that induce CYP450 enzymes usually decrease drug concentrations. In actual practice, most of the following medications are of concern either because they reduce antiretrovirals to subtherapeutic levels, or because anti-HIV drugs raise them to dangerously toxic levels. However, for almost every general rule about interactions between drug classes, there are exceptions and special cases.

HIV positive individuals should educate themselves about common drug interactions and health-care professionals should keep up to date with the medical literature in this field, and especially with advisories

issued by the Food and Drug Administration (FDA) or pharmaceutical companies regarding newly discovered interactions. Monitoring for effectiveness and toxicity should be performed regularly, especially when adding or changing medications.

Drugs Used to Treat OIs

Several antifungal and antibiotic drugs used to treat OIs are prone to interactions with some PIs and NNRTIs. The "azole" antifungals are CYP3A4 and P-glycoprotein inhibitors, some of which can increase concentrations of other medications metabolized by these pathways. Conversely, CYP3A4 inhibitors can raise azole levels. Use of voriconazole (VFEND) with ritonavir (400 mg dose) or efavirenz is contraindicated. Fluconazole (Diflucan) is associated with fewer interactions than itraconazole (Sporanox) or ketoconazole (Nizoral).

Macrolide antibiotics, including erythromycin and clarithromycin (Biaxin), also inhibit both CYP3A4 and P-glycoprotein. As reported in the September 9, 2004 issue of *NEJM* (and summarized in the last issue of *BETA*), erythromycin appears to increase the risk of fatal cardiac arrhythmias (heart rhythm disturbances) when coadministered with drugs metabolized by CYP3A4. Although the authors of this study did not look at PIs specifically, they found that subjects using erythromycin along with other CYP3A4 inhibitors had a risk of sudden cardiac death five times higher than that seen in individuals not taking such a combination. A related macrolide, azithromycin (Zithromax), has a minimal effect on CYP450 enzymes and may be a suitable alternative to erythromycin or clarithromycin.

Interactions between antiretrovirals and drugs used to treat tuberculosis (TB) are a growing concern, especially in resource-limited countries where TB remains a major cause of AIDS-related death. Rifampin (known as rifampicin outside the U.S.), part of

standard first-line regimens for TB prophylaxis and treatment, is one of the most potent CYP3A4 inducers known, and can reduce PIs to subtherapeutic levels. The optimal regimen for treating active TB in people with HIV remains unclear; physicians must weigh the superior efficacy of rifampin against concerns about interactions with antiretroviral drugs.

The azoles, macrolides, and rifamycins can interact not only with antiretrovirals, but also with each other. On account of this complexity, the care of HIV positive people who require treatment for multiple OIs should be managed by experienced physicians.

Acid-Lowering Drugs

As noted previously, medications that neutralize the acidity of gastric secretions can interfere with the absorption of drugs like atazanavir that require an acid environment. Such medications are often taken to relieve gastroesophageal reflux, or "heartburn." OTC antacids (e.g., TUMS, Maalox) and buffered medications typically exert their acid-neutralizing effects for only a short time, making it possible to use them within 1–2 hours of acid-dependent drugs.

Other types of acid-lowering agents are much longer-acting. Proton pump inhibitors (e.g., omeprazole [Prilosec], esomeprazole [Nexium], lansoprazole [Prevacid]), which block the production of stomach acid, can alter gastric pH for 24 hours or longer. In December 2004 Bristol-Myers Squibb warned against the use of ritonavir-boosted atazanavir plus omeprazole after a study revealed a 76% reduction in atazanavir plasma concentrations when the drugs were coadministered. (The study used the 40 mg prescription dose of omeprazole; it is not known whether the 20 mg OTC dose would have a similar effect.) Data are forthcoming on the safety of atazanavir plus histamine-2 (H₂) receptor antagonists, another class of acid-lowering agents that includes cimetidine (Tagamet) and ranitidine (Zantac).

For further reading

Package inserts for approved drugs—included with purchased medications or available from a pharmacist or on the internet. Check pharmaceutical company web sites; most have sites for specific drugs, often with URLs that include the drugs' brand names (e.g., www.reyataz.com)

HIV Drug-Drug Interactions—The Body's listing of the latest drug interaction news, research, tools, and specific medication alerts (www.thebody.com/treat/interactions.html)

Polypharmacy Problems: Drug Interactions in the Multidrug Therapy of HIV Infection—article by Alice Pau, PharmD, and Tim Horn. *PRN Notebook*, March 2002; includes interaction charts featuring lipid-lowering agents, herbal/nutraceutical therapies, and illicit/recreational drugs (www.prn.org/prn_nb_cntnt/vol7/num1/pau_frm.htm)

What's PK Got to Do with It?—the Winter 2005 issue of *Positively Aware* features a series of articles on pharmacokinetic basics and how the three major antiretroviral drug classes work and interact (www.tpan.com/publications/positively_aware/winter_05_pk/pk_34_web.pdf)

Clinically Significant Drug Interactions Associated with Highly Active Antiretroviral Therapy—article by John Faragon, PharmD, and Peter Piliero, MD. HIV Education Prison Project, January 2004 (www.idcronline.org/archives/jan04/mainarticle.html); accompanying chart, Drug Interactions with HAART and Methadone (www.idcronline.com/archives/jan04/hiv101.pdf)

Drug Interactions: HIV Medications, Street Drugs and Methadone—article by James Learned and Maia Szalavitz. *ACRIA Update*, Spring 2005 (www.thebody.com/cria/spring05/interactions.html)

Cholesterol-Lowering Medications

As HAART extends the lives of people with HIV, elevated blood lipids (fats) associated with PIs are a growing concern because high cholesterol and triglyceride levels are linked to increased cardiovascular disease risk. As such, many people taking PI-based antiretroviral regimens are also using medications to lower their lipids.

One class of commonly used cholesterol-lowering agents, the "statins," are metabolized by the CYP450 system

and their concentrations can be increased by PIs (particularly ritonavir). But not all statins are equal. In November 2000 the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group recommended that people on HAART should start with low doses of pravastatin (Pravachol), atorvastatin (Lipitor), or fluvastatin (Lescol), which appear to interact least with antiretrovirals. The panel advised against use of lovastatin (Mevacor) or simvastatin (Zocor), which can reach dangerously

high levels when used with PIs, potentially leading to intensified side effects including rhabdomyolysis (muscle damage) and kidney failure. The interaction profile of the newest statin, rosuvastatin (Crestor), has not yet been well defined.

Medications for Psychiatric Conditions

Certain anticonvulsant or anti-epilepsy drugs—notably phenytoin (Dilantin), carbamazepine (Tegretol), and phenobarbital (Solfoton)—are potent CYP450 inducers that can potentially render some PIs and NNRTIs ineffective. Certain PIs, including lopinavir, can also decrease phenytoin levels. More suitable alternatives for use with HAART include divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), and levetiracetam (Keppra). Monitoring of antiseizure drug levels in the blood may help avoid excessive or suboptimal dosing.

Among the benzodiazepines, a class of sedatives used to treat anxiety and insomnia, midazolam (Versed) and triazolam (Halcion) may reach dangerously high concentrations when used with CYP450 inhibitors, potentially causing fatal respiratory depression. Caution is also warranted concerning alprazolam (Xanax), diazepam (Valium), and zolpidem (Ambien). Safer alternatives include lorazepam (Ativan) and temazepam (Restoril).

Among medications used to treat depression, drugs in the tricyclic antidepressant class are most likely to be involved in CYP450-mediated interactions. Levels of the more commonly used selective serotonin reuptake inhibitors (SSRIs)—including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and escitalopram (Lexapro)—may also be increased by CYP450 inhibitors; excessive SSRI levels can cause symptoms such as seizures, heart rhythm abnormalities, and coma. When taken with PIs, especially ritonavir, antidepressant doses may need to be reduced. Here again,

drug level monitoring may help avoid interaction problems.

Many people with HIV see separate providers for HIV-related and mental health care. Due to the potential for antiretroviral and psychiatric drug interactions, it is important that all providers know about all the drugs their patients are using and work together to determine appropriate regimens.

Oral Contraceptives

Agents that impact CYP3A4 can significantly reduce plasma concentrations of estrogen and other steroid hormones. In women using oral contraceptives containing ethinyl estradiol or other forms of estrogen, concurrent use of efavirenz, nevirapine, nelfinavir, ritonavir, or lopinavir may decrease hormone levels enough to cause unintentional pregnancy. HIV positive women taking these antiretrovirals should use a backup contraception method along with combination estrogen/progesterone pills, birth control pills that contain only progesterone, or a barrier method (e.g., condoms).

Erectile Dysfunction Drugs

Levels of the erectile dysfunction drugs sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) may rise when used with PIs. For example, studies have shown that sildenafil concentrations increased by more than four-fold when coadministered with ritonavir. Excessive plasma levels of these drugs may cause low blood pressure, dizziness, fainting, headaches, vision disturbances, and/or priapism (painful, prolonged erections). Men using antiretrovirals that inhibit CYP3A4 should talk to their physicians about taking erectile dysfunction agents in lower doses and/or less often.

Other Medication Classes

Pis can increase plasma levels of ergot alkaloid derivatives (e.g., Cafegot, Migranal) used to treat migraine headaches; coadministration of these drugs should be avoided.

Levels of calcium-channel blockers (e.g., diltiazem, verapamil), used to treat conditions such as angina (chest pain), high blood pressure, and cardiac arrhythmias, may also increase in the presence of CYP3A4 inhibitors.

Pis can also interact dangerously with immunosuppressive drugs (e.g., tacrolimus [Prograf]) used to prevent organ rejection after a transplant. One HIV positive liver transplant recipient at the University of Pittsburgh died from an organ rejection reaction several years ago when his hometown doctor took him off HAART, thereby causing his tacrolimus level to drop precipitously. This case illustrates the importance of physicians working together to determine appropriate medication combinations.

Recreational and Street Drugs

There have been few formal studies of interactions between antiretrovirals and recreational or street drugs, but anecdotal reports and pharmacokinetic data indicate that some such combinations may be harmful. In addition, street drugs may be cut with substances other than the advertised ingredient, which can also impact interactions.

Evidence suggests that ritonavir can increase blood concentrations of ecstasy (MDMA, "X"), which is metabolized by the CYP2D6 isoenzyme. Elevated ecstasy levels may

cause heightened agitation, seizures, increased heart rate, and/or cardiac arrest. The October 1996 death of a London man with pre-existing liver disease was widely attributed to concurrent use of ritonavir (which he had recently started) and a moderate dose of ecstasy (reportedly 2.5 tablets). Other forms of amphetamine, including crystal methamphetamine ("speed," "crank," "Tina"), share the same processing pathway and may have comparable interaction profiles. However, cocaine, also a stimulant, has not been reported to interact with antiretroviral medications.

Another worrisome party drug is gamma-hydroxybutyrate, or GHB. The combination of ritonavir, saquinavir, and modest doses of GHB and ecstasy may have been responsible for the nearly fatal respiratory arrest of a Seattle man reported in 1999. While there are minimal human data available, animal studies suggest that GHB is metabolized by the CYP450 system.

In both the London and Seattle cases, the individuals were found to have unusually high blood levels of their respective recreational drugs, but this may have been due to other factors (e.g., adulterated drugs, genetic variations in drug-processing enzymes) and cannot be definitively attributed to interactions with anti-HIV drugs.

Finally, ritonavir, other PIs, efavirenz, and nevirapine appear to

Antiretroviral drugs may interact with:*

Other anti-HIV medications	Benzodiazepines (e.g., alprazolam, midazolam, triazolam)
OI drugs (e.g., voriconazole, clarithromycin)	Oral contraceptives containing estrogen
Antituberculosis drugs (rifampin, rifabutin)	Erectile dysfunction drugs (e.g., sildenafil, vardenafil)
Antacids (e.g., omeprazole, cimetidine)	Recreational, street, or party drugs
Cholesterol-lowering statins (e.g., lovastatin, simvastatin)	Methadone
Antidepressant drugs (e.g., fluoxetine, sertraline)	Herbal remedies (e.g., St. John's wort, garlic)
Anticonvulsant drugs (e.g., phenytoin, phenobarbital)	

* not a comprehensive listing

Drug Interaction Resources

Online tools and databases:

University of Liverpool—comprehensive and frequently updated online database of antiretroviral drug interactions; includes charts in PDF format and an interactive database access tool (www.hiv-druginteractions.org)

HIV InSite—interactive tool allows searches by antiretroviral drug, interacting drug, and interacting drug class (www.hivinsite.com/arvdb?page=ar-00-02); the site also includes ARV Alert, featuring the latest safety alerts about antiretroviral drug interactions and adverse events (www.hivinsite.com/InSite?page=ar-alert)

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents—Table 19: Drugs That Should Not Be Used With PI or NNRTI Antiretrovirals; Table 20: Drug Interactions Between Antiretrovirals and Other Drugs (www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf)

AIDSmads.com—simple tool for checking antiretroviral drug interactions (www.aidsmeds.com/cmm/DrugsNewContent.asp)

Project Inform—comprehensive list of interactions by drug; also includes a glossary and information about street drug interactions (www.projectinform.org/fs/drugin.html)

Party Smarty Marty—resource on interactions between anti-HIV medications and recreational drugs sponsored by the San Francisco Community Clinic Consortium and the Haight-Ashbury Free Clinic (www.hafreeclinics.org/drugs)

Drug Digest—includes drugs for all conditions and herbs by both common and Latin names; includes food and alcohol as well as drug-drug interactions (www.drugdigest.org/DD/Interaction/ChooseDrugs/1,4109,,00.html)

Medscape HIV/AIDS Clinical Calculator—checks interactions among drugs in a regimen and suggests appropriate dosing schedules (www.medscape.com/px/hivscheduler)

reduce plasma concentrations of opiates (e.g., heroin, numerous prescription pain-relievers), which could potentially reduce the risk of overdose, but may lead to withdrawal symptoms or inadequate pain relief.

Methadone

As is true with other opiates, some anti-HIV medications can raise or lower methadone plasma concentrations. In particular, the NNRTIs efavirenz and nevirapine, both CYP3A4 inducers, may decrease methadone levels enough to cause

withdrawal symptoms (e.g., runny nose, tearing eyes, excessive perspiration, nausea, abdominal cramps, convulsions) in people receiving methadone maintenance therapy. Studies—including one by Elinore McCance-Katz, MD, reported in the August 15, 2003 issue of *CID*—indicate that lopinavir can also decrease methadone levels, even though ritonavir alone might be expected to have the opposite effect. Taking fosamprenavir (or the older version, amprenavir) with methadone can lower levels of both drugs.

Physicians and methadone maintenance program staff should be aware of this potential effect, which may take as long as two weeks to fully emerge, and be prepared to monitor methadone levels and gradually increase methadone doses enough to avoid opiate withdrawal (perhaps by 25% or so).

Herbal Remedies

There has been little formal research on interactions between antiretroviral agents and herbal therapies, but in a few instances enough data have emerged to make recommendations. St. John's wort (*Hypericum perforatum*), used to relieve depression, induces both CYP3A4 and P-glycoproteins, and was associated with significantly decreased indinavir concentrations in one study. The U.S. government's antiretroviral treatment guidelines state that St. John's wort should not be used with PIs or NNRTIs; in February 2000 the FDA issued a public health advisory with the same message.

Garlic (*Allium sativum*) inhibits CYP3A4 activity, and high-dose garlic supplements reduced saquinavir levels in one study; however, the smaller amount of garlic normally consumed in food is unlikely to cause problems. Another herbal remedy that could interact pharmacokinetically with anti-HIV medications is milk thistle (and its derivative, silymarin), used to treat liver conditions including chronic hepatitis B and C.

Grapefruit juice—not an herbal remedy but a botanical product nonetheless—received considerable attention in the late 1990s as a proposed strategy to boost plasma saquinavir concentrations. While grapefruit juice does affect CYP3A4 activity in the intestines, it does not appear to cause clinically significant interactions with approved PIs or NNRTIs.

Herbal remedies and nutritional supplements are not closely regulated like drugs, and it is not always easy to determine the exact ingredients or

People with HIV should inform their health-care team (general practitioners, specialist physicians, nurses, alternative and complementary therapy providers) about all the medicinal products they are using: prescription drugs, OTC medications, recreational or street drugs, and alternative or complementary therapies including herbs and nutritional supplements.

amounts of various substances in these products. To reduce the risk of interactions, people with HIV should inform their health-care providers about any alternative or complementary therapies they are using or considering.

Conclusion

As aptly stated in the U.S. government's anti-HIV treatment guidelines, the list of interactions involving antiretroviral drugs is "extensive and constantly expanding," presenting a daunting challenge for HIV positive individuals and their providers.

The best way to minimize the risk of drug interactions is to remain vigilant. There is no need to memorize every possible interaction—even HIV/AIDS professionals find it difficult to keep up with the ever-growing list. Instead, become familiar with how drugs are metabolized, the major interaction mechanisms, and which drug classes are most likely to cause problems. With this background, refer to databases and tools like those listed in the sidebar on page 28. When considering a regimen change, do some research and ask about potential interactions. Pharmacists, who specialize in drugs and their pharmacokinetics, can be an excellent resource.

People with HIV should inform their health-care team (general practitioners, specialist physicians, nurses, alternative and complementary therapy providers) about all the medicinal products they are using: prescription drugs, OTC medications, recreational or street drugs, and alternative or complementary therapies including

herbs and nutritional supplements. Piscitelli recommends putting all these products in a bag and bringing them along to appointments so providers can see for themselves what their patients are using. He also emphasizes the importance of reviewing an individual's complete regimen at each visit. It is good practice to consider the possibility of a drug interaction if an antiretroviral regimen does not seem to be working as well as it should (e.g., rising viral load, decreasing CD4 cell count) or if a person experiences new, unusual, or severe side effects.

HIV positive people need not despair if they must take a medication implicated in many interactions. Often, drug interactions can be overcome simply by raising or lowering doses; however, this should never be done without the guidance of a knowledgeable practitioner. In other cases, it may be possible to replace an interacting drug with a noninteracting agent that works comparably well. Any time a new or unusual interaction comes to light, it should be reported promptly to the drugs' manufacturers and the FDA so that interaction databases can be updated and other people with HIV can benefit from this increasing body of knowledge.

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Selected Sources

Back, D. and others. Pharmacokinetic drug interactions with nevirapine. *Journal of Acquired Immune Deficiency Syndromes (JAIDS)* 34 (S1): S8–S14. September 2003.

Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the

treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report* 49(09): 185–189. March 10, 2000.

De Luca, A. and others. Deep salvage with amprenavir and lopinavir/ritonavir: correlation of pharmacokinetics and drug resistance with pharmacodynamics. *JAIDS* 35: 359–66. April 20, 2004.

Dubé, M. and others. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. *Clinical Infectious Diseases* 31: 1216–1224. November 2000.

Elbekai, R. and others. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. *Current Drug Metabolism* 5(2): 157–167. April 2004.

Fichtenbaum, C. and others. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG study A5047. *AIDS* 16: 569–77. March 8, 2002.

Haas, D. and others. A common CYP2B6 variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG Study NWCS214. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco. February 8–11, 2004. Abstract 133.

Kashuba, A. and others. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 19: 145–152. January 28, 2005.

Patel, I. and others. Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clinical Pharmacokinetics* 44(2): 175–186. February 2005.

Pinzanni, V. and others. Methadone withdrawal symptoms with nevirapine and efavirenz. *Annals of Pharmacotherapy* 34: 405–407. March 2000.

Piscitelli, S. and Gallicano, K. Interactions among drugs for HIV and opportunistic infections. *New England Journal of Medicine* 344: 984–996. March 29, 2001.

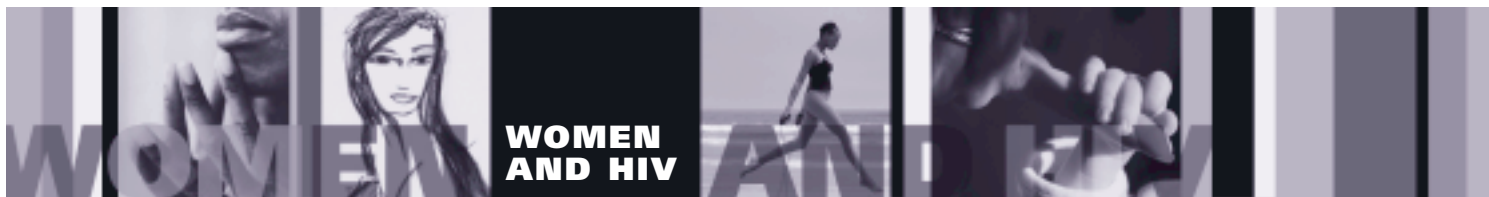
Piscitelli, S. and others. Indinavir concentrations and St. John's wort. *The Lancet* 355(9203): 547–548. February 12, 2000.

Taburet, A. and others. Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pre-treated patients infected with human immunodeficiency virus. *Clinical Pharmacology and Therapeutics* 75: 310–323. April 2004.

Vishnuvardhan, D. and others. Lopinavir: acute exposure inhibits P-glycoprotein; extended exposure induces P-glycoprotein. *AIDS* 17: 1092–1094. May 2, 2003.

von Moltke, L. and others. Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *Journal of Clinical Pharmacology* 38: 106–111. February 1998.

Wyles, D. and Gerber, J. Antiretroviral drug pharmacokinetics in hepatitis with hepatic dysfunction. *Clinical Infectious Diseases* 40: 174–181. January 1, 2005.



Women's Research Roundup

Kristen Jill
Kresge

Women with AIDS Have Lower Breast, Uterine Cancer Risk

Women with AIDS may have a lower risk of developing breast and uterine cancer, according to a study presented at the 96th annual meeting of the American Association for Cancer Research held April 16–20 in Ahaheim. James Goedert and colleagues compared data from 77,369 women with AIDS (from five years before they received an AIDS diagnosis until ten years after) with several million general-population cancer records. Among the women with AIDS, 274 developed breast cancer, 31 developed ovarian cancer, and 29 developed uterine cancer. The incidence (new cases) of breast cancer among both pre- and postmenopausal women with AIDS was 32% lower than among women at large (27% lower after adjusting for differences in childbearing); the incidence of uterine cancer was 40% lower, while the rate of ovarian cancer was similar.

The reasons for these differences are not clear, but the researchers suggested that they may be related to reduced body fat and altered estrogen and androgen (female and male hormone) levels in women with AIDS. Importantly, the difference in breast cancer rates was greatest early in the AIDS epidemic and has become very small since the advent of HAART, suggesting that antiretroviral therapy modifies whatever factors led to lower cancer rates in the pre-HAART era.

Women on HAART Still at Higher Risk for Herpes Zoster

According to a report in the December 15, 2004 issue of the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, HIV positive women are at greater risk of herpes zoster (shingles) than HIV negative women, even when receiving highly active antiretroviral therapy (HAART). Herpes zoster, caused by the varicella-zoster virus, is a common opportunistic illness (OI) associated with immunodeficiency. Although previous studies have shown an increased incidence of herpes zoster after initiating HAART, few data were available on the effect of long-term antiretroviral therapy on its occurrence.

The *JAIDS* report involved an analysis of 1,832 HIV positive and 489 HIV negative women in the Women's Interagency HIV Study (WIHS) from six research sites in Chicago, New York, Washington, DC, and California. All women were screened at six-month intervals for a follow-up period of up to 7.5 years. The study relied on self-reported diagnoses of herpes zoster; medical records were not used to verify reported cases. The majority (68%) of women with HIV started HAART during the follow-up period.

Marshall Glesby, MD, and colleagues found that in the HIV positive group, 337 women (18%) reported at least one case of herpes zoster, compared with only 7 women (1%) in the HIV negative group. HIV positive women were more likely to be diagnosed with the condition regardless of CD4 cell count. Those with CD4 cell counts below 200 cells/mm³ were nearly 25 times more likely to develop shingles than HIV negative women. HIV positive women with high CD4 cell counts (greater than 750 cells/mm³) had nearly a nine times greater risk. Similar results have been reported in men. Based on the WIHS results, the authors concluded that herpes zoster—unlike many other OIs—likely will continue to be a problem for HIV positive women on HAART.

Cervical and Anal Pap Smears Both Important Diagnostic Tools

High rates of human papillomavirus (HPV) infection have been reported in HIV positive women. HPV causes genital warts and some strains can cause cervical and anal dysplasia (abnormal tissue changes), which are precursors of cervical and anal cancer. Routine cervical Pap smears are a standard component of gynecological care, but the optimal use of anal Pap smears in HIV positive women has not been defined.

In a poster presented at the 12th Conference on Retroviruses and Opportunistic Infections this past February in Boston, Thomas Young, MS, NP, and colleagues from the University of California at San Francisco reported that cervical and anal Pap screening are both important in the care of women with HIV. Their retrospective

study (abstract 900) analyzed the results of 217 cervical and 268 anal Pap smears from 161 women screened between January 2000 and July 2004 at San Francisco General Hospital. Of these women, 41% were on continuous antiretroviral therapy. Half of the women were “white,” 29% were African American, 15% were Latina, and 4% were of Asian descent. The results of cervical and anal Pap screens were considered “paired” in women who received both tests within a six-month interval. Of these paired screens, about half (48%) provided discordant results (one normal and one abnormal), indicating that cervical disease does not predict anal disease, or vice versa. Women with normal cervical Pap results had abnormalities in the anal Pap smear in 36% of cases. A comparison of anal Pap smear and biopsy results found that the anal Pap test had a sensitivity of 94.7%, justifying more research using this important screening tool in women.

The study authors suggested that the high level of discordance in this small cohort illustrates that anal and cervical Pap smears provide independent information and that using both in routine evaluations of HIV positive women should be examined further.

HPV Viral Load Correlated with Cervical Disease

As the life expectancy of HIV positive women receiving HAART increases, it has become more important to find markers to identify and prevent cervical disorders—a necessary adjunct to improved screening tools (see previous item). Previous studies have not reached a consensus on the ability of HPV viral load to serve as a marker for cervical disease.

An Italian study reported in the February 1, 2005 issue of *Clinical Infectious Diseases* found that HIV positive women with high-grade cervical lesions have significantly higher levels of HPV in their cervix than women at high risk for HPV with no signs of cervical disease.

Flavia Lillo, MD, and colleagues analyzed 64 samples from 16 HIV positive women who had surgery to remove cervical squamous intraepithelial lesions (SIL; abnormal cell growth). These samples were compared with 44 control samples from 22 HIV positive women who were at high risk for HPV but had no signs of cervical disease. The authors reported that all women with SIL had higher HPV viral loads than those in the control group. Additionally, HPV viral loads in the women with cervical disease decreased notably after removal of the damaged tissue. This study suggests that measuring HPV viral load in the cervix could be a clinical biomarker to identify women at risk for the development of cervical cancer.

The researchers did not find a difference between the two groups in the number or subtype of HPV strains detected

in the cervix. This allowed them to conclude that measurement of single-strain HPV viral loads, which is impractical in clinical practice due to cost, may be unnecessary in predicting cervical disease risk.

In related news, researchers reported in the April 20, 2005 issue of the *Journal of the National Cancer Institute* that HPV is more likely to be reactivated in HIV positive women with advanced immunosuppression. Howard Strickler, MD, from the Albert Einstein College of Medicine and colleagues studied 1,848 HIV positive and 514 HIV negative women enrolled in the WIHS cohort. The women received cervical Pap smears and HPV viral load tests every six months for an average of seven years of follow-up (a total of 5,661 person-years).

The researchers found that CD4 cell count and HIV viral load were strongly associated with detectable HPV. A majority of the women had detectable HPV viral loads at some point during the study period. However, women with more advanced HIV disease (CD4 cell counts below 200 cells/mm³ or HIV viral loads above 100,000 copies/mL) were more likely than women with minimal immunosuppression to have subsequent HPV outbreaks after a period of undetectability. Women with more advanced immune suppression were also more likely to develop SIL.

In the cohort as a whole, the incidence of HPV infection was strongly associated with the number of recent sexual partners; however, 22% of sexually inactive HIV positive women with fewer than 200 cells/mm³ still developed detectable HPV after being undetectable, suggesting HPV reactivation rather than new infection. The researchers concluded that more frequent HPV reactivation could help explain the high rates of HPV infection seen in HIV positive women.

Many Women Stop HAART Within Five Years

A substantial proportion of U.S. women with HIV stop antiretroviral treatment within five years, according to an article in the April 1, 2005 issue of *JAIDS*. Linda Ahdieh-Grant, PhD, from Johns Hopkins University and colleagues looked at factors associated with HAART discontinuation among 936 HIV positive women in the WIHS cohort who started treatment between 1995 and 2000. Women were divided into three groups based on the date of HAART initiation: October 1995–March 1998, April 1998–June 1999, and July 1999–September 2000. All subjects received HAART for at least six months.

The researchers found that nearly one-quarter of the women (24%) discontinued therapy five years or less after they started. Women who had high HIV viral loads and

those who experienced small increases in their CD4 cell counts (both potential indicators of treatment failure) were more likely to discontinue therapy than those with undetectable viral loads and larger CD4 cell increases. Depression was also linked to early HAART discontinuation. African American and Latina women were more likely than “white” women to stop treatment during the earlier study periods, but not during the third period.

The rate of treatment discontinuation was higher among women who started therapy during the July 1999–September 2000 period, reflecting “ongoing and dynamic shifts in the approach to HAART utilization”—including a greater recognition of the long-term side effects of anti-retroviral drugs. (Previous research has shown that women are significantly more likely than men to stop antiretroviral therapy due to adverse side effects.) The authors suggested that their findings “emphasize that access to treatment for depression may have important implications for the management of HIV-infected individuals on antiretroviral therapy.”

Pregnancy Risk Category Raised for Efavirenz

In March Bristol-Myers Squibb announced that the pregnancy risk category for efavirenz (Sustiva, Stocrin) has been changed from C to D. Category C indicates that the risk of fetal harm cannot be ruled out based on available evidence, while category D denotes actual evidence of fetal risk. The change came about as a result of four case reports of neural tube defects (meningomyelocele and Dandy-Walker syndrome) in infants born to women who took efavirenz during the first trimester of pregnancy. Brain and eye malformations have also been seen in studies of the drug in monkeys. The latest U.S. federal HIV treatment guidelines recommend that women not take efavirenz during the first trimester; use later in pregnancy may be considered if there are no alternatives available and the benefits outweigh the risks. Women of childbearing potential should receive a pregnancy test before starting efavirenz and use effective contraception while taking the medication. Complete efavirenz prescribing information is available at www.sustiva.com.

Nevirapine Still at Center of MTCT Controversy

The use of a single dose of nevirapine (Viramune) to prevent mother-to-child transmission (MTCT) of HIV was thrust back into the spotlight late last year when a National Institutes of Health (NIH) whistleblower questioned how the HIVNET012 trial was conducted. This trial, which

began in Uganda in 1997, was the first to show that single-dose nevirapine given to the mother during labor and to the baby within three days of birth was effective at reducing HIV transmission. The MTCT rate after 12 months in breast-feeding women was 16% in women who received single-dose nevirapine compared with rates upwards of 25% in women who received no prophylaxis.

This finding was an important advance because a single dose of nevirapine is relatively cheap and easy to administer throughout the developing world, where the more intensive AZT-based MTCT regimen used in developing countries is not widely available. As such, news stories about the whistleblower’s claims that HIVNET012 researchers failed to report safety issues reverberated in many countries where single-dose nevirapine is the basis of MTCT programs.

The NIH maintained that “remonitoring reports of HIVNET012 found no additional serious adverse reactions related to nevirapine,” although reviews of the study did reveal problems with record-keeping that the agency said had “no bearing” on nevirapine’s safety or efficacy. A report by the National Academy of Sciences Institute of Medicine (IOM) released on April 7 stated that an independent IOM review panel found no major flaws in the study that would cast doubt on the conclusion that single-dose nevirapine is safe and effective in preventing MTCT of HIV. Despite some procedural “shortcomings,” said IOM panel chair James Ware from the Harvard School of Public Health, the HIVNET012 findings remain “sound and reliable.” Nevertheless, the ethics of using nevirapine in developing countries—where women with HIV may have severely limited access to both medications and high standards of care—remains controversial.

More Resistance in Mothers Following Single-Dose Nevirapine

At the 2005 Retrovirus conference, seasoned MTCT researcher James McIntyre, MD, of the University of Witwatersrand in Johannesburg presented a summary of nevirapine’s role in preventing MTCT. McIntyre dismissed doubts about nevirapine’s safety based on evidence in thousands of women and babies that have been studied in MTCT trials to date. However, he also emphasized that researchers have accumulated new knowledge about better ways to prevent MTCT of HIV without jeopardizing future treatment options for women. Several oral presentations and posters at the meeting highlighted the potential for women to develop resistance to the entire class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) after receiving only one dose of nevirapine during childbirth.

Single-dose nevirapine for the prevention of MTCT was previously associated with the development of NNRTI

resistance in 30% to 50% of women. Now, researchers are finding that resistance appears to be even more common. In an oral presentation at the same conference (abstract 100), Jeffrey Johnson from the U.S. Centers for Disease Control and Prevention (CDC) reported that a majority of pregnant women who receive single-dose nevirapine develop resistance.

In this study, investigators conducted genotypic resistance tests on plasma samples—taken both before and after receiving nevirapine—from 50 women who were part of a South African MTCT study. The analyses were performed using a highly sensitive assay that could detect resistance at levels as low as 0.2% for the K103N signature nevirapine-resistance mutation. Traditional assays require that the resistant variant make up at least 20% of the total virus population. Using the more sensitive method, an additional 16 women who were previously thought to have no resistance were found to have the K103N mutation. This finding suggests that conventional resistance assays identify only a portion of the women who develop resistance after single-dose nevirapine.

In another oral presentation at the Retrovirus conference (abstract 101), Sarah Palmer, PhD, of the National Cancer Institute reported on the persistence of resistance mutations following single-dose nevirapine in South African women. The first group of eight women in this study had evidence of NNRTI resistance at six weeks and at six months, but not at one year when resistance was measured using traditional genotypic tests. However, using a more sensitive resistance assay, the researchers found that seven of these women (88%) still had resistance mutations one year after taking single-dose nevirapine. In a second group of nine women, the sensitive assay detected mutations in seven women (78%) who were previously found to have no resistance at six months using standard tests.

Palmer and colleagues concluded that populations of drug-resistant HIV variants following administration of single-dose nevirapine may decline over time, but can persist for up to one year after receiving the drug. These results suggest that, whenever possible, pregnant women should receive combination antiretroviral therapy rather than nevirapine monotherapy.

Single-Dose Nevirapine Prevents MTCT in Second Pregnancies

The first study to analyze the efficacy of single-dose nevirapine in preventing MTCT during second pregnancies was presented at the February Retrovirus conference by Neil Martinson, MBBCh, MPH, of Johns Hopkins University (abstract 103). The study enrolled participants from 13 prenatal clinics in Soweto. Data were obtained from 77 mothers who had previously received single-dose nevirapine

and 140 mothers without past nevirapine exposure as controls; results from additional subjects were not available for presentation but are expected in the future.

A preliminary analysis found that eight of 77 nevirapine-experienced women (10.4%) who took the drug again during a second pregnancy transmitted HIV to their babies, compared with five of 140 women (3.6%) receiving nevirapine for the first time. While the difference between the two groups may appear large, it was not statistically significant because the study included too few participants (that is, it did not have sufficient power) to rule out the possibility that the difference was due to chance (see “A Guide to Clinical Trials” on page 45). The study team noted that the 10.4% transmission rate in the group receiving a second single dose of nevirapine was comparable to rates seen in previous studies of women receiving the drug during first pregnancies.

Researchers had suspected that resistance mutations might limit the effectiveness of nevirapine in preventing HIV transmission in subsequent pregnancies. Although the results were inconclusive, this study supports the use of single-dose nevirapine in multiple pregnancies because transmission rates were lower than rates seen in women who receive no prophylaxis.

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Medicare Prescription Drug Coverage: *Preparing for January 1, 2006*

Jeffrey S.
Crowley, MPH

After many years of effort by health advocates, Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (called the MMA) in December 2003. The law updates the benefits provided to Medicare beneficiaries by adding coverage for prescription drugs beginning January 1, 2006. Prescription drugs play a central role in modern health care, and extending drug coverage to Medicare beneficiaries is an important goal. The way in which Congress tackled this problem, however, has been highly contentious. This article will describe the law as it was passed, the issues that remain to be resolved, and what it all means for people with HIV/AIDS.

Medicare Facts

- A federal program that provides health-care coverage to retired workers and workers under age 65 who become disabled, as well as their spouses, and in some cases, dependents
- Covers 41 million people, including 5.4 million nonelderly people with disabilities
- Covers an estimated 6.4 million dual eligibles (low-income people who receive both Medicare and Medicaid); California is home to one-sixth of the dual eligible population
- The second-largest source of health-care coverage for people living with HIV/AIDS in the U.S., after Medicaid
- Serves 85,000 people with AIDS, including 55,000 dual eligibles (estimated figures); (eligibility for Medicare based on disability requires individuals to be severely disabled—in the case of HIV, this means an AIDS diagnosis)
- Annual cost: \$327 billion
- Estimated annual cost to Medicare for HIV/AIDS care: \$2.9 billion

Better than Nothing?

The absence of prescription drug coverage has made Medicare particularly deficient for people with HIV/AIDS. Therefore, the HIV community, including the San Francisco AIDS Foundation, was actively engaged in efforts to enact a Medicare prescription drug law in 2003. By the time the law was ready for passage in Congress, the HIV community joined a broad range of consumer advocacy organizations and others in opposing enactment of the MMA, believing that having no law would be better than the law that was actually passed. Groups reluctantly came to this conclusion for many reasons.

First, the MMA has the potential to leave dual eligibles—low-income people who receive both Medicare and Medicaid, who generally are sicker and poorer than other Medicare beneficiaries—with less comprehensive prescription drug coverage than they currently enjoy. Dual eligibles currently receive comprehensive prescription drug coverage through Medicaid (known as Medi-Cal in California), the government health insurance program for low-income children and families, seniors, and people with disabilities. In addition, many critical Medicaid consumer protections will not apply to Medicare drug coverage. This is of particular concern because dual eligibles will lose Medicaid drug coverage on December 31 of this year and be required to enroll in the Medicare prescription drug program for their drug coverage. Most dual eligibles will continue to receive coverage for some other health needs through Medicaid, and all Medicaid beneficiaries who are not covered by Medicare will continue to receive their prescription drug

coverage through Medicaid. (Medicaid programs are run by the states, and the federal government gives states funding for at least half of the total costs.)

Second, although savings that result from providing dual eligibles with weaker coverage were used to partially finance drug coverage for all Medicare beneficiaries, significant gaps remain in this new coverage. For example, many people feel that the cost-sharing obligations associated with the standard benefit in the new law are unreasonable and unmanageable for people with chronic illness.

Medicare prescription drug coverage will be provided through new private insurance policies that cover only prescription drugs or through private managed health-care plans that provide prescription drug coverage. Critics have argued that the private market approach to drug coverage will raise administrative costs and waste public resources that could have been used to finance more comprehensive benefits.

In addition, those plans that provide only prescription drugs and not full managed health care (stand-alone prescription drug plans) do not have a financial incentive for ensuring that people receive the drugs they need. In the private insurance market or under Medicaid, insurers know that if they are overly restrictive in providing access to prescription drugs, people will get sicker and may end up in the hospital, costing the insurers more money. Under the MMA, if people end up in the hospital or need to visit the doctor more frequently because they cannot get the drugs they need, Medicare—and not the stand-alone prescription drug plans—will pay for the increased costs. On the other hand, the managed care plans that provide both health care and prescriptions drugs (Medicare Advantage health plans) are significantly overpaid for their services to encourage participation. Critics of this incentive have pointed out that this excess payment could be used to finance more comprehensive benefits as well.

Despite such opposition, Congress passed the MMA, and Medicare drug coverage will start on January 1, 2006. The HIV community needs to move past debates over whether Congress did the right thing in passing the law and, collectively, ensure that the MMA provides comprehensive, high-quality prescription drug coverage for all Medicare beneficiaries with HIV/AIDS.

Key Features of Medicare Drug Coverage

Important features of the new Medicare drug coverage program (also known as Medicare Part D) include:

Choice of Plans

The MMA does not provide a Medicare drug benefit directly. Rather, it creates a right for Medicare beneficiaries

to purchase prescription drug coverage from a Medicare prescription drug plan. At a minimum, every Medicare beneficiary should have a choice of at least two plans. The law created special provisions if two plans are not available, but it does not appear that this will be a problem anywhere in the country. Indeed, early indications are that Medicare beneficiaries will have many choices of plans (possibly ten or more). Individuals can enroll in stand-alone prescription drug plans or in Medicare Part C managed care plans (now called Medicare Advantage health plans) that will also provide them with prescription drug coverage.

Covered Drugs

People who participate in the Medicare prescription drug program will receive coverage for prescription drugs and biological products such as insulin and related test supplies. Some drugs are excluded from coverage under the Medicare drug benefit. These include medications already covered under Medicare Parts A and B (which provide for coverage of hospital and physician services) and drugs that are designated as “excludable” by state Medicaid programs.

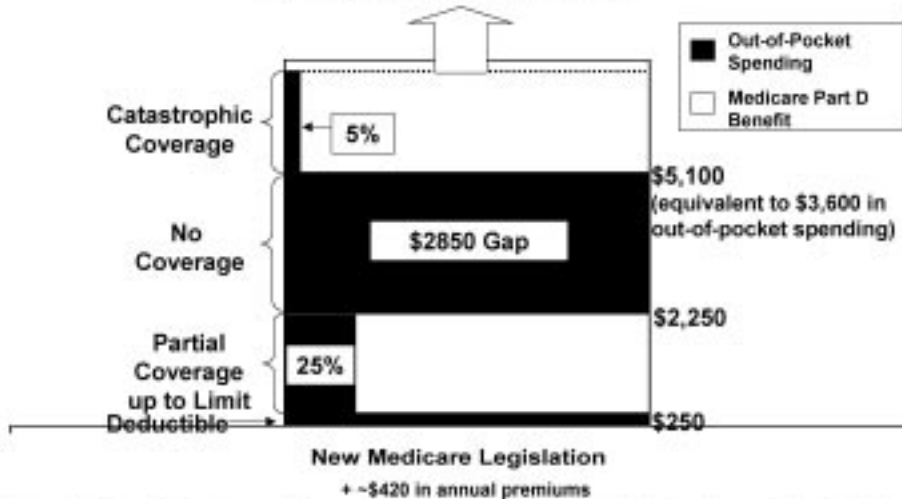
Medicare Parts A and B pay for some narrow categories of prescription drugs, such as those that must be administered in a physician’s office. These medications cannot be covered by Medicare prescription drug plans, but Medicare Parts A and B will continue to cover them.

Certain drugs are considered “excludable” because federal rules permit state Medicaid programs to decide whether to cover them. This category includes drugs that are prescribed for certain purposes (such as cosmetic purposes and weight loss or gain), over-the-counter drugs, and two specific classes of mental health drugs: benzodiazepines and barbiturates. It is important to note that drugs prescribed to treat AIDS wasting are not excludable even though the same drugs could be prescribed in other cases for weight gain. Also, although considered excludable, products to help people quit smoking may be covered by Medicare drug plans. State Medicaid programs will retain the option to cover excludable drugs for dual eligibles. They will also continue to receive federal money to match their spending on these drugs.

Beneficiary Cost

The cost of drug coverage has several components. First, individuals will be required to pay a monthly **premium** (fee paid to an insurance company to obtain drug coverage). Plans are permitted to set their own premiums. It is not yet known how much the premiums will cost and how much they will vary from plan to plan. The Congressional Budget

Summary of Out-of-Pocket Drug Spending in 2006



Note: Benefit levels are indexed to growth in per capita expenditures for covered Part D drugs. As a result, the Part D deductible is projected to increase from \$250 in 2006 to \$445 in 2013; the catastrophic threshold is projected to increase from \$5,100 in 2006 to \$9,065 in 2013. Source: Kaiser Family Foundation representation of cost-sharing requirements for standard Part D drug coverage as described in the Medicare Modernization Act.

Office has estimated that the average premium in 2006 will cost \$37 per month. Plans that participate in the Medicare prescription drug program must offer what is called standard coverage. They are also permitted, however, to offer different levels of coverage for higher premiums.

New Medicare beneficiaries must enroll in a Medicare prescription drug plan as soon as they become eligible, and current Medicare beneficiaries must enroll no later than May 2006, otherwise they will pay a premium penalty—for the rest of their lives. This premium penalty is likely to be 1% for every month that an individual delays enrollment in the drug coverage program. So, for example, people who wait one year after becoming eligible for Medicare to enroll in a prescription drug plan will be charged a premium that is 12% higher than for those who enrolled on time; people who wait five years will be charged 60% more than if they had enrolled in prescription drug coverage when they became eligible for Medicare.

The next component of the cost to beneficiaries is the **deductible**. This is the amount individuals must spend on prescription drugs each year before their drug plan starts providing coverage. Congress set the deductible at \$250 per year for 2006. This amount will increase every year based on how much per-person Medicare drug spending grows from year to year.

Then there is **cost-sharing** (also known as **copayments**), whereby beneficiaries must also pay a certain share of the cost of their drugs. This can vary depending on an individual's level of drug spending in a year. Total drug spending

from the \$250 deductible to \$2,250 in one year is called the **initial coverage period**. In the initial coverage period, individuals must generally pay 25% of the cost of their medicines. So, an individual with a \$100 prescription would pay \$25 at the pharmacy. For a \$1,000 prescription, the person would pay \$250. Prescription drug plans can charge more for certain drugs. For example, if they want individuals to use generic rather than brand-name drugs, or a preferred drug within a specific class, they can charge a lower cost-sharing fee for the preferred agent. They can also charge higher cost-sharing

fees for nonpreferred drugs. On average, however, plans must charge beneficiaries 25% of the cost of drugs in the initial coverage period.

Annual drug spending from \$2,250 to \$5,100 is called the **coverage gap**. In this period, prescription drug plans provide *no* coverage, and individuals must pay 100% of their drug costs. So, an individual with a pharmacy bill of \$100 or \$1,000 who has reached the coverage gap must pay the full bill until reaching the next level of coverage. This gap has been called the “doughnut hole” in the popular press (see the sidebar above).

For drug spending above \$5,100 in a year, individuals will have what is called **catastrophic coverage**. At this level, beneficiaries pay only 5% of their drug costs. So, someone with a \$100 pharmacy bill would pay \$5; an individual with a \$1,000 pharmacy bill would pay \$50. There is no limit on the amount of drug coverage available to each person—beneficiaries cannot “use up” their coverage because they have extensive needs for prescription medications. As with the deductible, the spending levels for the initial coverage period, the coverage gap, and catastrophic coverage will be adjusted annually as the cost of Medicare drug coverage increases.

Protections for Low-Income Beneficiaries

Recognizing that the MMA's cost-sharing structure for most Medicare beneficiaries is not affordable to low-income individuals, lawmakers created an extensive

low-income subsidy (LIS) program for people with incomes below 150% of the federal poverty level (\$14,355 for a single individual and \$19,245 for couples in 2005) and with limited resources (such as money in the bank or property, with exceptions for a person’s primary residence and primary vehicle). As federal officials begin to educate the public about the availability of the Medicare drug program, this subsidy is being called “**extra help.**” If someone receives a letter from the Social Security Administration—or reads in the press—about extra help, it refers to this assistance program for low-income Medicare beneficiaries. Anyone who might qualify should apply for this extra help to ensure that everyone who is eligible benefits from this important resource.

The level of extra assistance varies depending on income. For dual eligibles, there is no premium—as long as the plan in which they enroll is considered “cost average” (has a premium that is no more expensive than the average premium for all plans participating in the Medicare prescription drug program). For example, if the average monthly premium is \$37 in 2005, and an individual selects a plan with a premium of \$47 per month, the person must pay the difference of \$10 a month. Dual eligibles also have no deductible, meaning that their coverage begins right away (they do not have to first spend \$250 out of pocket). Depending on income, dual eligibles will pay cost-sharing of \$1 or \$2 per prescription for preferred drugs and \$3 or \$5 per prescription for nonpreferred drugs. In addition,

dual eligibles have no coverage gap—that is, there is no point when they are responsible for 100% of their drug costs. Finally, dual eligibles who reach \$5,100 of drug expenses in one year have no further cost-sharing requirements. Dual eligibles living in nursing homes or other institutions pay no cost-sharing.

People who are not dually eligible may apply to receive extra help. Unlike dual eligibles, who are deemed qualified for extra help in most cases, Medicare-only beneficiaries must apply and be qualified. The non-dual eligibles who qualify for LIS will receive different levels of assistance based on their income and assets. There is no coverage gap or “doughnut hole” for anyone who qualifies for LIS (see the chart below).

Important Policy Issues

Since Congress enacted the MMA, a number of policy decisions remain to be made that will determine whether Medicare prescription drug coverage is responsive to the needs of people living with HIV/AIDS. Key policy issues that have direct implications for Medicare beneficiaries with HIV/AIDS include:

Formulary Policies and Coverage of Necessary Drugs

The MMA included certain requirements that influence the development of plan formularies (lists of drugs that a plan will cover). The law requires plans that decide to operate a formulary (instead of simply covering all FDA-

approved prescription drugs) to cover at least two medications in each class of drugs. Plans that operate formularies must also set up a pharmacy and therapeutics (P&T) committee, consisting mostly of physicians and pharmacists, to determine which drugs are included in the formulary. At least one physician and one pharmacist on the P&T committee must be independent from the plan, and must have expertise in either the care of elderly individuals or people with disabilities.

The law also authorized the Centers for Medicare and Medicaid Services (CMS, the federal agency

Subsidies for Low-Income Beneficiaries

	Premium	Deductible	Cost-Sharing (Deductible – Stop-Loss Threshold)	Cost-Sharing (Above Stop-Loss Threshold)
Dual Eligibles Residing in Institutions	\$0 for low-cost plan, 20% of late enrollment penalty for up to 60 months	\$0	\$0	\$0
Dual Eligibles Below Poverty	Same as above	\$0	\$1/preferred + \$3/non-preferred in 2006, indexed to general inflation	\$0
Dual Eligibles Above Poverty + Non-Duals Below 135% of Poverty (Assets below \$6,000/\$9,000)	Same as above	\$0	\$2/preferred + \$5/non-preferred in 2006, indexed to per capita drug cost growth	\$0
Non-Duals Below 135% of Poverty (Assets between \$6,000-\$10,000/\$9,000-\$20,000) + Non-Duals Between 135-150% of Poverty (Assets below \$10,000/\$20,000)	Sliding Scale	\$50	15%	\$2/preferred + \$5/non-preferred in 2006, indexed to per capita drug cost growth

Source: Medicare Prescription Drug, Improvement, and Modernization Act of 2003

Key dates in the implementation of Medicare prescription drug coverage (Medicare Part D):

July 2005

Applications start being accepted for “extra help”—the low-income subsidy (LIS) program

September 2005

Centers for Medicare and Medicaid Services (CMS) announces which plans will be permitted to offer prescription drug coverage

September 2005

CMS begins to randomly assign dual eligibles to prescription drug plans (individuals selecting a plan on their own before January 1 will have their choice honored)

November 15, 2005–May 15, 2006

Initial enrollment period—all current Medicare beneficiaries must enroll in a Medicare prescription drug plan during this period to avoid a late enrollment premium penalty

December 31, 2005

Medicaid drug coverage ends for dual eligibles

January 1, 2006

Medicare prescription drug coverage begins

that administers Medicare and Medicaid) to review plan formularies and features of their benefit structure to ensure that they do not discriminate against any groups of Medicare beneficiaries. Federal officials have instructed plan administrators that they must cover the majority of drugs in six classes, including antiretrovirals. In fact, in the initial rollout of the MMA, CMS has publicly stated that they will not approve a plan formulary unless it provides coverage for every currently available antiretroviral. Plans can still limit access to certain medications by requiring medical justification before providing a drug (through a process called **prior authorization**); nonetheless, it is a significant protection that all antiretrovirals will be covered by all plans.

Since people living with HIV/AIDS depend on a range of drugs, not just antiretrovirals, and because the general standard is that plans must cover only two drugs per class, it will be especially important for HIV positive Medicare

beneficiaries to determine whether plans cover their non-HIV drugs before they enroll (unless it is medically appropriate for them to switch to one of the drugs covered by the plan). Federal officials are requiring prescription drug plans to develop a transition plan for new enrollees who are currently on a treatment regimen. CMS has suggested that plans consider covering current drugs for at least 30 days, but this is not required. Therefore, individuals should review the transition plans of individual prescription drug plans to determine whether they may be required to switch drugs or if they can continue on their present course of therapy.

It will be necessary to monitor plans to ensure that when new (and frequently costly) antiretrovirals are approved by the FDA, plans provide coverage for these drugs. Plans have been given 90 days to make coverage decisions and 180 days to include new drugs in their formularies. That wait may be too long for some people with HIV/AIDS. It will also be important to ensure that drugs prescribed for off-label purposes are covered. It has become common practice for physicians to prescribe drugs for uses other than the approved on-label use (for example, pediatric use of drugs approved only for adults); off-label prescribing has been particularly important in the treatment of HIV. CMS has not required plans to cover drugs for off-label use, but has said that it will review the request process to ensure that it is not “burdensome.”

Lastly, prior authorization and other techniques are commonly used to ensure that high-cost drugs are not provided when less costly alternatives work just as well. These strategies can also be used to improve patient care. For example, plan monitoring could ensure that prescribed antiretroviral combinations are consistent with current clinical practice standards. Nonetheless, the HIV community will need to keep track of how plans use prior authorization and other techniques to ensure that they do not inappropriately restrict access to needed medications.

Affordability

Some Medicare beneficiaries with HIV/AIDS could be better off than before because the MMA gives them prescription drug coverage for the first time. Drug coverage is only meaningful, however, if individuals are able to afford all components of the cost, including premiums, the deductible, and cost-sharing. Several aspects of the MMA may make it unaffordable for some people. Total out-of-pocket spending is beyond the means of many individuals. HIV positive Medicare beneficiaries who have incomes of 160% of the poverty level (i.e., monthly income below \$1,300), for example, qualify for no cost-sharing assistance. Such individuals would have to pay a monthly premium, their first \$250 in drug costs (the deductible),

and (in the initial coverage period) they still could easily have cost-sharing expenses of \$200–\$300 per month. They would also be hard-pressed to pay for medications during the coverage gap, when they could be expected to pay \$1,000 or more per month in drug costs. Such costs are clearly a huge burden for people at this income level.

While the low-income subsidies are fairly comprehensive, some individuals who qualify for this extra help may still find Medicare prescription drug coverage unaffordable. For low-income people, who may have incomes near or below the poverty level, even a few dollars per prescription could be a significant barrier to maintaining access to all the drugs included in an effective treatment regimen. This challenge is greatly magnified for individuals who need large numbers of drugs. Dual eligibles who currently have Medicaid coverage will also lose an important consumer protection. Under Medicaid, pharmacists must give beneficiaries their drugs even if they cannot afford to pay the cost-sharing portion. No similar protection exists under Medicare. Again, close monitoring will be necessary to ensure that these coverage gaps are eliminated or that new ways are found to assist low-income individuals.

Adequate Information to Make Enrollment Decisions

An important concept behind the structure of the MMA is that if Medicare beneficiaries are given choices among competing plans, the marketplace will weed out bad plans. While research has suggested that this model may not be appropriate for the Medicare population, it is clear that in order for it to work, individuals must have access to appropriate information to make informed enrollment choices. Many Medicare beneficiaries, including people with HIV/AIDS, may need additional support—and in some cases, one-on-one assistance—in making plan choices. During the policy development process, federal officials responded to consumer input by ensuring that plans must give Medicare beneficiaries more information when deciding on plans—if individuals know enough to ask for this information. However, it is important to note that in general, plan information will be available only online at www.medicare.gov or by calling 1-800-Medicare.

As an interim step before Medicare drug coverage could be implemented, the MMA established the Medicare drug discount card program (in effect during part of 2004 and all of 2005). Experience with this program has shown that many people were overwhelmed by the number of choices available to them, and that they did not know how to evaluate information to make an appropriate plan decision. Indeed, enrollment in the discount card program has been far lower than anticipated. Selecting a Medicare prescription drug plan is more complicated than enrolling

in a discount card program. There is widespread concern that individuals will not know what to do, or where to turn for help. Therefore, the HIV community will need to use its resources to educate and assist individuals in making appropriate plan choices and navigating the new Medicare prescription drug program.

Workable Appeals Process

Problems will result when individuals believe that they cannot obtain the services they need through any insurance program. Therefore, an important measure in evaluating the Medicare prescription drug program (or any similar program) is whether it includes a workable process for resolving complaints and appeals of coverage denials. The MMA extended many of the rules for grievances and appeals that were already in place for the Medicare Advantage program (the Medicare managed care program). This raised a serious issue in that those rules only would have required a resolution of a complaint within 30 days. While consumer advocates remain troubled by many of the final rules for the Medicare prescription drug grievance and appeal process, federal officials significantly improved this aspect of the program by setting a general standard that a dispute over coverage of a drug must be resolved within three days, and in emergencies, within one day. Also, in all cases, plans must resolve decisions as quickly as the enrollee's health requires, even if it is more quickly than these general time standards.

A potential innovation in the appeals process for Medicare prescription drug plans is the creation of an **exceptions process**. Under the exceptions process, an individual can request that a plan cover a drug at the lowest level of cost-sharing, even if the plan normally charges a higher level of cost-sharing for that drug. This process also allows individuals to obtain coverage for drugs that a plan has kept off its formulary. The exceptions process is intended to be easier than a formal appeal, which would be sought only if an individual were denied an exception. An exception requires an individual's treating physician to state that the requested treatment is needed by the patient and that less costly alternatives have not worked or are unsafe or inappropriate for that person. It will be important to monitor whether this proves to be an easy and understandable process, or whether it becomes one more barrier to keep people from getting the drugs that they need.

Getting Ready for January 1

As the start of Medicare drug coverage on January 1, 2006, approaches, the HIV community and HIV positive Medicare beneficiaries have work to do to get ready. To make the most of this new drug coverage program, high priority actions include:

Ensure that All Medicare Beneficiaries with HIV/AIDS Enroll in a Plan

Individuals who qualify for both Medicaid and Medicare (dual eligibles) will be automatically assigned to a plan in October 2005, although they may opt to change plans. If they do not choose to change their plan, they will be automatically enrolled in that plan by January 1, 2006. While some people may believe that this selection process will take into account their individual needs, the law requires that these assignments be random. And if all plans are not the same, then some will meet the needs of people with HIV/AIDS better than others. In addition, most dual eligibles will be automatically assigned to “cost average” plans, which may be less likely to meet all their needs than more expensive plans.

Moreover, some people have responded to the shortcomings of the Medicare prescription drug law by wondering whether non-dual eligibles with HIV/AIDS should enroll in this program at all. Except for people who may have benefits that count as an alternative to this coverage (such as qualified employee or retiree coverage that is equally comprehensive), it is in the best interest of every Medicare beneficiary with HIV/AIDS to enroll in a Medicare prescription drug coverage plan, if only to avoid the financial penalty associated with delayed enrollment. If there are gaps in coverage, AIDS Drug Assistance Programs (ADAPs) or Medicaid may supplement Medicare coverage, depending on the state, but they cannot simply replace the benefit. In fact, the law specifically denies Medicaid programs federal funds for filling in coverage gaps, although states may decide to do so with state-only funds. Similarly, there are strong financial incentives that will limit the willingness of many ADAPs to supplement Medicare drug coverage, because spending by ADAPs does not count toward the out-of-pocket spending that moves an individual out of the coverage gap and into the catastrophic level of coverage. While state pharmacy assistance programs have a special exception that allows their spending to count toward out-of-pocket spending that qualifies individuals for catastrophic coverage, federal officials crafted the rules to prevent ADAPs from qualifying for this exception, even if they use state general fund dollars.

Therefore, an important activity for the HIV community is to educate people about their drug coverage plan options and to provide assistance to ensure not only that HIV positive people get into the Medicare prescription drug program, but also that they select plans that meet their needs. HIV advocates can help by comparing different plans on the basis of how each one handles individuals who need to continue existing treatment regimens, whether the plan’s network includes a person’s preferred

pharmacy, and coverage of common anti-HIV drugs and drugs for opportunistic illness (OI) treatment and prophylaxis, as well as treatment for any coexisting diseases.

Ensure that All Eligible Individuals Enroll in the Low-Income Subsidy Program

Given the high cost of anti-HIV therapies and the extensive treatment regimens many HIV positive people require, it is easy to understand the importance of taking advantage of all assistance that is available. The “extra help” offered to Medicare beneficiaries below 150% of the poverty level is quite significant. Therefore, it is important to ensure that every eligible person with HIV/AIDS is signed up to receive this extra assistance. Individuals can inquire about extra help by contacting their local Social Security or Medicaid office. While Social Security is set up to handle most applications for extra help, individuals with HIV/AIDS may want to apply through a Medicaid office so that they can also be screened for Medicare Savings Programs. (Alternatively, individuals should contact a Medicaid office and ask about these programs.)

Medicare Savings Programs do not assist with prescription drug coverage, but pay Medicare Part B premiums and, depending on one’s income, also pay Medicare cost-sharing for expenses other than drugs (such as hospital stays). These programs are available to Medicare beneficiaries with incomes up to 135% of the poverty level who do not qualify for full Medicaid coverage. The savings programs are not well known in the HIV community because, without drug coverage, they were of little assistance to people with HIV/AIDS. Therefore, if individuals had too much income to qualify for Medicaid in states with programs for the medically needy, HIV benefits counselors and case managers would assist people in **spending**

Resources

GOVERNMENT AGENCIES

Centers for Medicare and Medicaid Services (CMS)

www.medicare.gov/medicarerreform/default.asp

Social Security Administration (SSA)

www.ssa.gov/organizations/medicareoutreach2

RESEARCH AND ADVOCACY GROUPS

Center for Medicare Advocacy

www.medicareadvocacy.org

Henry J. Kaiser Family Foundation

www.kff.org/medicare/rxdrugdebate.cfm

Medicare Rights Center

www.medicareriights.org

down (called a **share of cost** in California) to qualify for Medicaid coverage. While spending down will still be necessary for some people who rely on Medicaid for more than prescription drugs and cost-sharing (such as people who use long-term services or who need vision services or extensive physical or occupational therapy), some people with HIV/AIDS will find that Medicare Savings Programs can provide critical assistance without requiring that they spend down to qualify for Medicaid coverage.

Work to Establish a Transition Period

The odds of enacting legislation usually work against passage. Moreover, given the continuing controversy over the cost of the Medicare prescription drug law and the ongoing debate over whether the Secretary of Health and Human Services should be permitted to negotiate drug prices, many members of Congress are strongly opposed to enacting changes to the Medicare prescription drug law before it is implemented.

There is one issue, however, that is so important it cannot wait. The HIV community, along with a broad range of consumer advocacy groups, is deeply concerned about the impact of the transition from Medicaid to Medicare drug coverage for dual eligibles. Ideally, this change will be seamless for the vast majority of this population. It is implausible, however, that Medicaid prescription drug coverage for 6.4 million dual eligibles (the sickest and poorest group of Medicare beneficiaries) will end on December 31, and Medicare drug coverage will start on January 1, without serious problems arising. Some people may fall through the cracks and go to their pharmacies in 2006, only to be told that they do not have Medicaid or Medicare coverage. This has been called a “train wreck” scenario—and the HIV community must marshal its resources to prevent such a crash. Various proposals have been floated, including simply extending Medicaid coverage for six months as a backup, to ensure payment for critical drugs if Medicare coverage cannot be verified or if a Medicare plan denies coverage for an existing treatment regimen. The HIV community must advocate for a one-time fix to ensure that dual eligibles are protected during the transition from Medicaid to Medicare prescription drug coverage.

Conclusion

If the HIV community or the Medicare consumer community had the same level of political clout as health insurers and other corporate interests, the Medicare prescription drug law would look very different. Nevertheless, advocates are not without influence—or important allies in Congress. Indeed, some of the most significant improvements to the law were made just before it passed, including critical additions to the “extra help” LIS program.

The Medicare prescription drug law represents an opportunity. While advocates can anticipate potential problems, they also need to acknowledge that problems will likely be rare and successes common. Given the clear signal from federal officials that all antiretroviral medications must be covered, it is reasonable to approach January 1 with the mindset that most Medicare beneficiaries with HIV/AIDS will get their prescriptions filled. To promote this positive outcome, the HIV community has a role to play in educating, assisting, monitoring, and advocating on behalf of Medicare beneficiaries with HIV/AIDS.

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Thanks to Anne Donnelly for her help in preparing this article.

For More Information

FACT Sheet: Medicare and HIV/AIDS. Henry J. Kaiser Family Foundation. October 2004. Available at www.kff.org/hiv/aids/7171.cfm.

Medicare Modernization Act Final Guidelines—Formularies. Issued by the Centers for Medicare and Medicaid Services (CMS). Available at www.cms.hhs.gov/pdps/FormularyGuidance.pdf.

Medicare Prescription Drug Benefit; Final Rule. Issued by the CMS. Available at www.cms.hhs.gov/providerupdate/regs/CMS4068F.pdf.

Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Public Law 108-173. Available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ173.108.pdf.

MMA and Dual Eligibles: A Transition in Crisis. Medicare Rights Center. March 2005. Available at www.medicarerights.org/searchframeset.htm.

The New Medicare Prescription Drug Law: Issues for Dual Eligibles with Disabilities and Serious Conditions. Kaiser Commission on Medicaid and the Uninsured. June 2004. Available at www.kff.org/medicaid/7119.cfm.

A Guide to Clinical Trials

CBC (INCLUDES DIFF/PLATELET)		THOUS/MCL	3.8-10.8
WHITE BLOOD CELL COUNT	5.04	MILL/MCL	4.20-5.80
RED BLOOD CELL COUNT	15	G/DL	13.2-17.1
HEMOGLOBIN	43	%	38.5-50.0
HEMATOCRIT	86	PG	80.0-100.0
MCV	31.3		27.0-33.0
MCH			

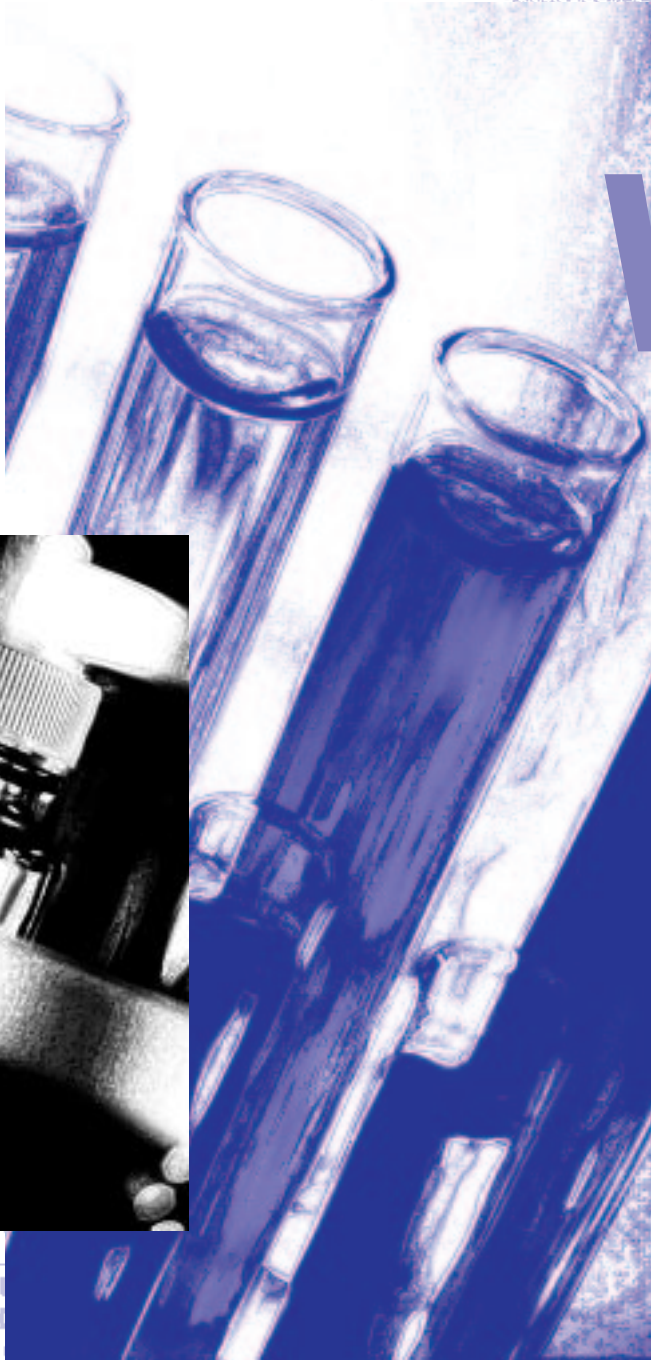
PART I:

UNDERSTANDING CLINICAL STUDIES

When a new drug, assay, device, procedure, or other potential medical innovation is developed, it must be thoroughly tested to ensure that it is safe and does what it purports to do.

Medical studies of new interventions involving human subjects are called clinical trials. Such studies test new or improved therapies in volunteer participants, first determining whether they are generally safe, then whether they are effective. Although clinical trials are governed by extensive regulations to ensure that they are ethical and as safe as possible, individuals considering clinical trials should carefully weigh the possible risks of participation against the potential benefits.

This article provides an overview of the clinical trial process. Part II will discuss interpretation of clinical study results, and will appear in the next issue of *BETA*.



HIV-1 RNA, Q
dDNA, 3RD
COPIES/ML

SAN FRANCISCO AIDS FOUNDATION

Accelerated Approval, TIND, and Expanded Access

In the early years of the AIDS epidemic, HIV positive people and their advocates pushed for new mechanisms to make experimental drugs available more quickly. The FDA may grant **accelerated approval** for agents that treat serious illnesses for which there are few or no other therapeutic options. However, the agency still requires pharmaceutical companies to complete the clinical trial process and provide longer-term data before drugs are granted final traditional approval.

Some people who would like to try not-yet-approved but potentially beneficial therapies do not meet inclusion criteria, are too ill, live too far away, or are otherwise unable to participate in clinical trials. In 1987 the FDA instituted the **Treatment Investigational New Drug (TIND)** category to provide early access to promising medications for individuals with serious or life-threatening conditions and no good treatment options. For an agent to qualify as a TIND, there must already be some evidence that it is safe and effective. In addition to enabling more people to access experimental drugs, TINDs also provide information on safety and efficacy under “real world” conditions. Participants’ regular physicians dispense the drug and provide such data to the manufacturer.

While experimental agents are actively under study in clinical trials—or when trials have been completed and drugs are awaiting approval—pharmaceutical companies may institute **expanded access programs (EAPs)**. In effect, TINDs and EAPs act as open-label studies that do not involve blinding, randomization, or matched control arms.

The Drug Development Process

The process of developing a new drug is complex, lengthy, and expensive. It may take ten years or more for a candidate to make its way from the laboratory to pharmacy shelves. (However, there are various mechanisms in place to speed things up for experimental agents for HIV/AIDS and other life-threatening illnesses; see sidebar above.) According to the U.S. Food and Drug Administration (FDA) only one of every 1,000 candidate compounds makes it from the laboratory to clinical trials, and just

one in five of these is ever approved and marketed.

Most experimental agents originate in university, government, or pharmaceutical company laboratories. Increasingly, they are designed by computers to meet certain structural or functional specifications. Promising compounds are then subjected to extensive testing. The first step involves *in vitro* (Latin for “in glass”) testing in a laboratory. For example, a potential antiretroviral compound may be added to a culture in a petri dish containing human cells and HIV to

see whether the agent slows viral replication.

But activity in a test tube does not mean an agent will work in the body (*in vivo*). Laboratory testing also cannot conclusively show that an agent is safe, although it can provide important information about its effects on cells. The next step in testing usually involves animal studies. Typically, drug candidates are first tested in mice or rats, then often in dogs, then sometimes in primates. Animals are not people, however, and many agents have been shown to be more or less safe or effective in different species.

Finally, if a candidate still looks promising after laboratory and animal studies, it may advance to testing in humans. Researchers must submit an application to the FDA, the federal agency that regulates drugs and medical devices. If approved, the experimental agent is designated an investigational new drug (IND) and may enter clinical trials.

Phases of Clinical Trials

Although the ultimate goal of the drug development process is to come up with treatments that work, researchers must first determine whether they are safe. The clinical trial process is divided into four phases, each of which includes a larger number of participants.

Phase I: The earliest safety trials of an experimental agent involve a small number of subjects (typically 10–100); these trials often use healthy volunteers without the disease under study. The aim is to detect any obvious toxicities (side effects or adverse events) before many subjects are put at risk. Usually subjects are exposed to the new agent for a short period, perhaps only a few days. These studies evaluate a compound’s **pharmacokinetics**—how it is absorbed, metabolized, processed, distributed, and eliminated by the body. At this stage researchers also try to determine an optimal amount of the agent that will offer the most benefit without unacceptable toxicity, a process

known as **dose-ranging**. While there may be some early indications that a compound works, determining efficacy is not the goal of Phase I trials.

Phase II: Once it is established that there are no major safety concerns, an agent is further tested to see whether it still appears safe in a larger cohort of people (typically 50–500) with the disease under study. These studies also provide preliminary data on a candidate’s efficacy (activity, or how well it works). Sometimes these trials are divided into Phase IIa (pilot studies) and Phase IIb (small controlled trials). The study period is longer than for Phase I trials, usually several months to two years. In an effort to speed the development process, trial stages are sometimes combined (Phase I/II or Phase II/III). This stage is where most drug candidates are weeded out; only about one-third of experimental agents successfully make it through Phase II studies.

Phase III: The goal of the third stage of human testing is to determine whether the experimental agent is effective in a still larger population, typically several hundred to several thousand. These trials usually last at least a couple of years, and often considerably longer. The most rigorous type of study is the prospective, double-blind, randomized, controlled trial (described in detail below), which compares a candidate drug against either a **placebo** (dummy drug) or a currently available therapy. During this stage, researchers continue to monitor the agent’s safety, since some toxicities may become apparent only after a drug is used in larger groups or over longer periods. Data from the final Phase III studies—called pivotal trials—may be submitted to the FDA as part of a New Drug Application (NDA) to be considered as evidence for approval.

Phase IV: After a drug has been approved and is on the market, additional studies are done to see how well it works under “real world” conditions and to determine whether its

efficacy is durable, or long-lasting. Importantly, postmarketing studies also look for uncommon or long-term toxicities that did not show up in earlier trials (as was the case for metabolic side effects associated with the first protease inhibitors). Over time, more information may be revealed about interactions with other drugs and use in different populations, such as people with coexisting conditions. Patient advocates have charged that pharmaceutical companies too often neglect postmarketing research, a problem exemplified by the recent controversy over COX-2 inhibitors (a widely used class of pain relievers) and their association with heart problems. Legislation is being considered to address this issue.

Trial Design

A good design is crucial to ensuring that a clinical trial is able to provide the answers the investigators are seeking. Each trial begins with a protocol, a written description of what hypothesis the researchers wish to test and what methods they plan to use. This includes details such as drug dosages, administration routes, schedule of clinic visits, and what monitoring tests will be performed. Often in the case of new HIV/AIDS therapies, a **Community Advisory Board (CAB)** made up of HIV positive people and their advocates may offer advice about how a trial should be conducted. All aspects of a trial should be set forth in the protocol; many of these will determine how useful the trial is and whether its results will be regarded as credible.

Who Are the Subjects?

Enrollment criteria specify who may participate in a clinical trial. Characteristics and qualifications that a prospective subject must have are known as **inclusion criteria**, while those that disqualify a subject are called **exclusion criteria**. Enrollment criteria may include demographic characteristics (e.g., sex, age), behavioral factors (e.g., injection drug use),

disease status (e.g., CD4 cell count, HIV viral load), and current or past medical history (e.g., kidney dysfunction, use of cancer chemotherapy).

Researchers may be tempted to select trial subjects who are most likely to do well on an experimental therapy. In addition, trials are regarded as “cleaner” if they eliminate any potentially confounding factors that could affect the study’s outcome. For example, many trials exclude subjects who have coexisting conditions such as active opportunistic illnesses (OIs) or chronic hepatitis C. Concurrent use of other medications is also often excluded because they might interact with the experimental agent, potentially impairing its activity or causing unforeseen side effects. Another common exclusion criterion is active substance use, since many researchers assume that alcohol and illicit drug users have chaotic lives and are less likely to achieve optimal adherence.

It is important, however, that trials include a range of participants similar to those who will ultimately use the drug in practice. Otherwise, treatments may appear much more promising when tested in an “ideal” subject population than when used under real world conditions.

Many early trials of HIV therapies were conducted mostly in gay white men, a population that was initially heavily impacted by AIDS and had a propensity to volunteer for clinical research. Since then women, people of color, injection drug users, and other marginalized populations and their advocates have pressed for broader inclusion in clinical trials, and competent researchers recognize the importance of including a representative cross-section of people affected by a disease. Recent research has shown, for example, that people of African descent as a group metabolize efavirenz (Sustiva) more slowly than white individuals, and thus achieve higher blood levels of the drug.

In the not too distant past, women “of childbearing age” were

routinely excluded from clinical trials because many experimental agents have the potential to harm fetuses or cause birth defects. More recently, a consensus has emerged that drugs should be studied in both sexes. However, pregnant and breast-feeding women are still typically excluded, unless the trial is for an immediately life-threatening condition or for a pregnancy-specific intervention. In addition, women “of childbearing potential” (meaning there is a chance they could become pregnant), as well as male partners of such women, may be required to use at least one form of effective contraception during and for some time after a trial.

Most drugs are tested in adults first, and only later—if ever—in children. A majority of HIV trials specify that subjects must be at least 13 or 18 years of age. In the meantime, many physicians use drugs approved for adults “off label” to treat pediatric patients, making educated guesses about pharmacokinetics and optimal dosing. To encourage more pediatric drug research, the federal government in 1997 passed a law granting extended patent protection for drugs tested in children. In 2000 the FDA imposed a regulation requiring that trials for certain drugs must include children. The rule was overturned in court, but some lawmakers continue to push for such legislation.

Who Else Is Involved?

The researcher in charge of a clinical trial at a specific study site is called the principal investigator. The lead researcher typically works with a team of health professionals, social workers, and others. There is often a study coordinator who oversees the administration of a trial. In many cases a study nurse will be the main person with whom trial participants interact on a regular basis.

While clinical trials typically provide excellent care and monitoring, it is important that participants continue to see their regular physicians if their providers are not part of the study

“All the progress we’ve made over the past two decades—even the past five years—has been made possible by the people who have decided to flip the coin and take the chance. Every time we’re successful, it’s because somebody went first.”

—Cal Cohen, MD (research director for the Community Research Initiative of New England)

team. This can help ensure that nothing done during the study will unexpectedly interfere with ongoing treatment, and vice versa. If possible, laboratory results obtained during the trial (e.g., CD4 cell count, HIV viral load) should be available to subjects’ regular health-care providers.

How Many Subjects?

The number of subjects in a trial is a critical factor in determining a drug’s efficacy, as well as influencing the study’s perceived credibility. While it may take only a few subjects to uncover major toxicities, many more participants are needed to determine conclusively that an agent works. With a small number of subjects, there is always the possibility that an outcome could be the result of chance rather than being a true effect of an experimental therapy. Researchers, therefore, try to include enough subjects in their trials so that the results will be considered statistically significant, or very unlikely to be due to chance alone. The ability of a study to produce statistically significant data is known as its **power**.

How Long Will It Last?

Along with the number of participants, the length of a trial is an important factor when thinking about a study’s credibility. Longer trials, not surprisingly, provide more data than shorter ones. In addition, as noted above, some adverse events show up only with prolonged use of a drug (e.g., type 2 diabetes mellitus, heart attacks). Conversely, some side effects may improve over time (e.g., gastrointestinal symptoms). In some cases, an agent may look promising at first, but

then stop working (as happened with nucleoside reverse transcriptase inhibitor [NRTI] monotherapy). On the other hand, it may take time for a drug to become effective (as is the case with some antidepressants), so it should not be rejected too soon.

As a clinical trial progresses, the investigators may report preliminary or interim results at scientific conferences or in medical journals. If preliminary data indicate that an agent is either quite harmful or very beneficial, the trial may be halted prematurely. For example, in 1986 Phase II testing of the first approved anti-HIV drug—AZT (zidovudine, Retrovir)—was halted six months after it began when 19 subjects in the placebo arm had died compared with just one in the AZT arm.

Regardless of what is specified in the study protocol, any participant in a clinical trial may withdraw at any time for any reason.

Characteristics of Clinical Trials

There are a few major types of trials for people with HIV/AIDS. **Interventional** trials test new drugs or other types of therapies, or determine whether already approved therapies can be used in new ways. **Observational** trials look at certain factors or outcomes (e.g., disease progression) over time. Other studies examine what risk factors are associated with the development of a condition.

Several characteristics influence the usefulness of a trial and the credibility of its results. As noted above, the “gold standard” for clinical trials is the prospective, double-blind,

randomized, controlled trial with clinically meaningful endpoints. Often, however, one or more of these criteria cannot be fulfilled.

Time Course

A **prospective** study is one that looks forward in time. Typically, a study cohort is selected and followed for a predefined period, sometimes several years. A **retrospective** study is one that looks backward at events that happened in the past. Such a study might, for example, analyze medical records or stored blood samples.

Control

To determine whether a new therapy is truly effective, it is important to compare it against something else. In a **controlled** trial, one group of subjects receives the agent under study (the experimental arm), while another arm does not (the control arm). Some trials have complex designs with multiple experimental arms.

Traditionally, new therapies have been tested against a placebo, an inactive mock treatment that looks or feels like the experimental agent (e.g., sugar pill, saline injection). This is done to minimize the influence of a phenomenon known as the **placebo effect**, whereby the treatment process itself—receiving a pill, injection, or other intervention—can make a person feel better or experience side effects (including changes in biological markers), even if he or she receives an agent that has no therapeutic value or toxicity.

In modern HIV/AIDS trials, it is considered unethical to give subjects a placebo when effective therapies

exist. Thus, experimental agents are now usually compared with either the standard-of-care or the best available known treatment. Often subjects in the experimental and control arms will receive multidrug regimens that are the same except for a single component (for example, AZT/3TC/nelfinavir vs AZT/3TC/efavirenz). Sometimes experimental agents are compared with a null control (for example, AZT/3TC/abacavir/efavirenz vs just AZT/3TC/abacavir).

Randomization

Another tool for assessing whether a new therapy is truly effective is to ensure that the experimental and control arms are similar in every way except for the fact that one is receiving the investigational agent and the other is not. If the experimental arm contains all women and the control group all men, for example, it would be impossible to say whether any differences in outcome were solely due to the treatment or were influenced by the sex of the participants.

Investigators ensure that trial arms are similar by employing a process called **randomization**. This means that any prospective participant has an equal chance of ending up in either arm (or in any one of multiple arms). In a two-arm trial, this would be like flipping a coin for each subject and assigning “heads” to one group and “tails” to the other. This is done to minimize **selection bias**. If it were up to investigators to choose which participants were placed in which study arm, they might, for example, tend to assign sicker subjects to receive the therapy

they think will work best; conversely, they might favor healthier participants who are likely to respond better and make the experimental agent look good. If the study population is large enough, randomization should achieve a roughly equal distribution of potentially confounding characteristics (e.g., sex, age, race/ethnicity, HIV transmission route, disease status) in all arms.

Blinding

Blinding refers to whether the researchers and the study participants know which arm the subjects are part of. In a single-blind (or simply, blind) study, the subjects do not know whether they are receiving the experimental agent, an existing standard therapy, or a placebo. In a double-blind study, the investigators do not know either.

Blinding is also done to minimize bias, which could occur—consciously or unconsciously—due to participant or researcher expectations. For example, in an unblinded study, if an investigator believes the experimental agent is superior to an existing drug, she might have a tendency to emphasize positive outcomes associated with the new therapy while minimizing negative ones. Likewise, if a subject thinks the experimental agent is more risky than standard therapy, he might tend to overreport side effects associated with the new drug or underreport those linked to the old one.

Infrequently, differences in safety or efficacy between study arms are so dramatic that the trial code is broken early and the study is unblinded, allowing researchers to determine as soon as possible which subjects received which agents.

Endpoints

Endpoints are milestones, ideally specified before a study begins, that an experimental agent must achieve or bring about in order to be considered a success. Traditionally, trials have employed clinically meaningful endpoints, for example, disease

“If it weren’t for clinical trials, we would not have any of the new, more potent therapies we have today. Treatments of the future are totally dependent on the successful conduct of clinical studies today.”

—Michael Saag, MD (director of the Center for AIDS Research at the University of Alabama at Birmingham)

resolution, progression to an AIDS-defining illness, or death.

In the case of diseases like HIV/AIDS that typically progress slowly (especially when effective therapy is used), it could take very large studies with very long follow-up periods—perhaps a decade or more—before an appreciable number of participants experience clinically apparent disease progression or death. For that reason, contemporary trials often use **surrogate markers**, which are usually laboratory findings that are assumed to predict clinical outcome.

In the case of experimental anti-HIV drugs, for example, trials typically measure whether CD4 cell counts go up and viral loads go down, although the true outcomes of interest are OIs and death. Likewise, elevated cholesterol and blood pressure are considered surrogate markers for cardiovascular disease risk, although the true outcomes of interest are heart attacks, need for cardiac surgery, and death. The FDA may approve drugs based on surrogate marker data alone.

Ethical Research

All U.S. clinical trials must include mechanisms to ensure the ethical treatment of human subjects. Before a clinical trial gets underway, its protocol must be extensively reviewed to see that its benefits outweigh its risks. Reviewers include FDA officials and **Institutional Review Boards (IRBs)**, committees at each research institution comprised of physicians, other health-care professionals, statisticians, ethicists, local community members, patient advocates, and people with the disease under study. IRBs not only approve studies before they begin, but also monitor their progress until completion. In addition to federal requirements, some states also have their own regulations governing human research. Finally, international agreements such as the Nuremberg Code, the Declaration of Helsinki, and the International Code of Medical Ethics put forth principles for conducting ethical research.

Ten Questions to Ask When Considering a Trial

- What experimental intervention is being tested?
- What is already known from earlier studies?
- Are there any known toxicities or side effects?
- What (if any) treatment will control subjects receive?
- How often are study visits and what do they involve?
- What monitoring tests will be performed and how often?
- What other treatment options are available?
- Can subjects still receive the study drug after the trial ends?
- What (if any) long-term follow-up will be done?
- Whom should subjects contact in case of problems?

Informed Consent

Before agreeing to take part in a clinical trial, prospective participants must be given information about all aspects of the study, including its risks and benefits, in language they can understand. All prospective subjects (or their parent or guardian, if the participant is a minor) must sign an **informed consent** document that describes the nature of the study, the therapy being tested, known or potential risks, the subject's rights, and who to contact in case of problems. Prospective subjects should also be informed of other options that exist if they decide not to enroll in a trial.

The document is only part of the informed consent process. The study should also be verbally explained to the subject, who should be encouraged to ask questions (see sidebar above). The prospective subject may take the document home to discuss with family and friends.

Informed consent does not end when the document is signed and the participant enters a trial. Researchers must inform subjects of any important changes in the study design or new information about the experimental agent that becomes available during

the course of the study. Importantly, an informed consent document does not waive the participants' legal or medical rights, and researchers remain liable for damages due to negligence. The informed consent document is also not a contract; participants may discontinue a study at any time for any reason.

Financial Considerations—on Both Sides

Funding for a trial may come from various sources, including the federal government (e.g., studies conducted by the National Institutes of Health or the Department of Veterans Affairs), private grants, charitable organizations, and pharmaceutical or biotechnology companies. A trial's informed consent document should disclose all funding sources. In addition, all investigators must file financial disclosure statements explaining their financial relationship with the sponsor. The federal government and some states have various laws and policies concerning conflicts of interest, for example, when a researcher leads a trial of a drug produced by a company in which he owns stock.

Traditionally, drugs used in clinical research have been provided free of charge. Many studies also cover monitoring tests and other types of medical care. However, some observational trials—including studies comparing various new dosing schedules or combinations of approved agents—do not provide free drugs. Health insurance regulations differ widely, but many insurers do not cover treatments or monitoring tests that are considered experimental.

In some cases, trials may provide a stipend to participants. These can be used to reimburse participants for expenses such as transportation or childcare, or to compensate subjects for their time and inconvenience. Some researchers provide other forms of compensation, such as bus tokens or meals, especially if they are trying to include study participants from low-income and otherwise marginalized populations. However, it is illegal and unethical to pay people to join a trial, or to use stipends to persuade unwilling subjects to enroll.

Considering a Trial

Individuals considering whether to take part in a clinical trial have many factors to weigh. How do a trial’s advantages and benefits stack up against its inconveniences, discomforts, and potential risks? Trials of new drugs—and especially novel drug classes—can offer few guarantees. Researchers cannot be sure how effective a treatment will be, nor can they rule out unforeseen toxicities and side effects.

Why Do It?

There are several reasons why clinical trials may be attractive. First, they provide early and usually free access to the newest therapies. Sometimes subjects are given continued access to experimental medications even after the study period ends. Early in the epidemic, before many antiretroviral medications were approved, trial participation was often the only way to obtain drugs. This is

Trial Pros and Cons

PROS	CONS
Early access to new therapies	Inconvenience
Free drugs and testing	Time-intensive study visits
High-quality medical care	Possible discomfort or pain
Expert doctors and leading medical centers	May not receive experimental agent
Frequent, intensive health monitoring	Experimental agent may not be effective
Satisfaction of helping others	Possible adverse side effects
Advancement of medical knowledge	Small risk of life-threatening toxicities

no longer the case, but clinical studies remain at the forefront. For individuals who have developed resistance to the three major classes of antiretroviral drugs, trials can provide the first access to agents that work by entirely different mechanisms.

Clinical trials also offer excellent medical care provided by expert physicians at leading hospitals and medical centers. In particular, trial participants typically receive frequent, intensive health monitoring using the latest testing methods (usually at minimum regular CD4 cell counts and viral load assays). Despite the institution of the AIDS Drug Assistance Program (ADAP) and other programs to help people with HIV/AIDS, too many people are still unable to access top-notch treatment and care for financial reasons, and trials may help fill this gap.

Last, but certainly not least, trial participants may get personal

satisfaction from helping others and contributing to medical science. Even if a particular experimental agent does not provide much benefit for a specific subject, the data gathered during the trial will advance the overall state of knowledge about HIV/AIDS and its treatment, to the benefit of other people with the disease.

Drawbacks and Risks

There is no denying that participating in a clinical trial can be time-consuming and inconvenient, especially for subjects who do not live close to a study site. This may be especially problematic for individuals who continue or have returned to work, and for those who must arrange for childcare. Trials may also involve a certain amount of discomfort, for example, frequent blood draws.

Of greater concern are the potential adverse effects of a new therapy. These may range from temporary

Find out about currently enrolling clinical trials from physicians, nurses, and other providers; from hospitals, universities, and medical schools; and from support groups, patient advocacy organizations, and activist groups. For online clinical trial listings and databases, see the introduction to “Open Clinical Trials” on page 50.

gastrointestinal distress to elevated blood cholesterol to life-threatening Stevens-Johnson syndrome (a type of serious hypersensitivity reaction characterized by severe rash). No matter how promising an agent looks in laboratory and animal studies, it may still cause unacceptable toxicities in humans. Some side effects may not appear right away, but only after prolonged use, and some may not diminish immediately (or ever) after a drug is discontinued. Participants in a trial should always be given information about what to do and whom to contact if they experience unexpected or serious reactions.

Another potential risk is being randomly assigned to the control arm rather than an experimental arm; often neither the subject nor the investigator will know whether this is the case. (Some study designs allow for a “cross-over” from experimental to control arms, and vice versa, or permit all participants to receive the experimental agent at the end of the study period, so even participants initially assigned to the control arm may benefit.)

Even if one is assigned to an experimental arm, it is possible that the new agent will not be effective. With the growing awareness of the importance of choosing optimal

individualized regimens, avoiding resistance, and sequencing successive regimens in order to extend effective treatment, prospective subjects may be less willing to leave their therapy to chance, and more inclined to rely on the expertise of experienced physicians and the latest treatment guidelines.

Making the Decision

When the first anti-HIV drugs were being developed, there was no shortage of eager trial volunteers. In many cases, participating in a clinical study was the only way to obtain treatment, and doing so was a matter of life and death.

But today, with some 20 anti-retroviral drugs on the market, many HIV positive people are doing well on treatment and may see little reason to put up with the inconvenience of a trial or risk unknown side effects to obtain the minimal improvement an experimental drug might provide. Also, many HIV positive people have returned to work and fuller lives since the advent of HAART, and no longer have time for extra clinic visits and meetings.

Yet the importance of clinical trials cannot be overstated. Trials still provide access to innovative treatments, including new classes of drugs

for individuals who require salvage therapy. Clinical studies also provide the information needed to make adjustments to treatment strategies—such as the shift away from the “hit early, hit hard” approach and the increasing preference for protease-sparing first-line regimens to minimize metabolic complications—that may ultimately benefit all people with HIV. Finally, clinical trials are the only way to discover better immune-based therapies and effective HIV vaccines, not to mention the ultimate achievement: a cure for AIDS.

This article was prepared for the San Francisco AIDS Foundation by Liz Highleyman.

For More Information

An Introduction to Clinical Trials

National Library of Medicine

www.clinicaltrials.gov/ct/info/whatis

What Is an AIDS Clinical Trial?

Department of Health and Human Services

www.aidsinfo.nih.gov/other/clinicaltrial.asp

Should I Join a Clinical Trial?

AidsMeds.com

www.aidsmeds.com/lessons/ClinicalTrials.htm

The Food and Drug Administration: The Process of Approval

ACRIA Update

www.acria.org/treatment/treatment_edu_fallupdate2004_fda.html

For a partial listing of currently enrolling studies, see

“Open Clinical Trials”

on pages 50–54

OPEN CLINICAL TRIALS FOR HIV/AIDS TREATMENTS

Below is a partial listing of currently enrolling clinical trials gathered from various sources. **TrialSearch**, operated by the **AIDS Community Research Initiative of America (ACRIA)**, is an extensive online database of clinical trials related to HIV/AIDS. In addition to TrialSearch, ACRIA also provides a listing of trials in the mid-Atlantic region. The University of California at San Francisco's **HIV InSite** web site features **TrialScope**, a database of organizations that conduct HIV/AIDS-related research.

The federal government's **AIDSinfo** site includes a section on clinical trials that features an introduction to HIV/AIDS research and study listings from the National Institutes of Health's **ClinicalTrials.gov** database. AIDSinfo also offers personalized advice about clinical trial participation via e-mail (ContactUs@AIDSinfo.nih.gov), an interactive web site (www.aidsinfo.nih.gov/live_help; Mon.–Fri. 9:00 am–1:00 pm PT), and a toll-free telephone service (800-874-2572, international 301-874-2572; Mon.–Fri. 9:00 am–2:00 pm PT).

The majority of U.S. government-sponsored HIV/AIDS trials are conducted by the **AIDS Clinical Trials Group (ACTG)**, a nationwide network of investigators and medical centers comprised of two branches: the Adult AIDS Clinical Trials Group (AACTG) and the Pediatric AIDS Clinical Trials Group (PACTG). The **National Center for Complementary and Alternative Medicine (NCCAM)** conducts trials of complementary therapies for conditions related to HIV and its treatment. The **HIV Vaccine Trials Network (HVTN)** is an international collaboration testing preventive HIV vaccines. **Community Programs for Clinical Research on AIDS (CPCRA)** is a nationwide network that conducts community-based clinical trials. The **Community Research Initiative of New England (CRINE)** offers a listing of trials in the Northeast. **CenterWatch** is a commercial web site that includes trial listings for all diseases including HIV/AIDS and related conditions.

The Body web site features a database of prospective clinical trial volunteers. The service collects information about participants' city, age, viral load, CD4 cell count, current and past anti-HIV therapy, and health status. Researchers can request information about prospective subjects, who will be notified if they meet a trial's enrollment criteria.

Call the telephone numbers listed for each study or see the indicated web sites for more information about

specific trials. Protocol numbers, if available, are provided in parentheses at the end of each trial description.

ACRIA: www.criany.org

Adult ACTG: www.aactg.org

AIDSinfo: www.aidsinfo.nih.gov/clinical_trials

CenterWatch: www.centerwatch.com

ClinicalTrials.gov: www.clinicaltrials.gov

CPCRA: www.cpcra.org

CRINE: www.crine.org/info/clinical.html

HIV Vaccine Trials Network: www.hvtn.org

NCCAM: www.nccam.nih.gov/clinicaltrials/hiv.htm

The Body database: <http://ssl.thebody.com/submit/?/clinicaltrials/general.html>

TrialScope: www.hivinsite.org/tscope

TrialSearch: www.acria.org/clinical_trials/index.html

TMC-114: PI in Phase III

Researchers at this past February's Retrovirus conference presented promising data on TMC-114, Tibotec's experimental protease inhibitor (PI) (see "Drug Watch" on page 16). This new open-label trial will compare the efficacy, durability, safety, and tolerability of TMC-114 boosted with low-dose ritonavir (Norvir) vs. lopinavir/ritonavir (Kaletra) in treatment-experienced individuals. Subjects will be randomly assigned to receive either TMC-114 or lopinavir, but will know which drug they are taking. The study will last about 106 weeks including screening, treatment, and follow-up.

Eligible subjects must be at least 18 years of age. They must have viral loads of at least 1,000 copies/mL and must have been treated for 12 weeks or longer with anti-retroviral regimens consisting of at least two nucleoside reverse transcriptase inhibitors (NRTIs) plus at least one non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI. They may not currently be taking other experimental anti-HIV drugs, and must not have used lopinavir, tipranavir (Aptivus), or T-20 (enfuvirtide, Fuzeon) in the past. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This trial aims to enroll 500 participants at more than 60 sites including **Atlanta** (404-355-3161), **Austin** (512-374-0677), **Berkeley** (510-204-1291), **Boston** (617-778-5454 ext. 225), **Bronx** (718-918-7232), **Chicago** (773-396-2400), **Cincinnati** (513-584-8373), **Denver** (303-315-3203),

Ft. Lauderdale (954-467-3006 ext. 224), **Lexington** (859-257-5467), **Little Rock** (501-603-0003), **Los Angeles** (310-423-3755), **Milwaukee** (414-805-6444), **Minneapolis** (954-524-2250), **Nashville** (615-936-1174), **Newark** (973-877-2663), **Philadelphia** (215-790-1788), **Phoenix** (602-307-5330 ext. 2225), **San Francisco** (415-833-3480), **San Juan** (787-723-5945), **Seattle** (206-386-2523), **West Hollywood** (310-358-2429), and **Winston-Salem** (336-716-4262); www.clinicaltrials.gov/ct/gui/show/NCT00110877. (TMC114-C214)

TMC-278: NNRTI in Phase II

Enrollment is beginning for a new study of an experimental NNRTI, TMC-278, in treatment-naive individuals. This Phase II dose-ranging study will be conducted by Tibotec, the drug's manufacturer. Subjects will be randomly assigned to receive one of three doses of TMC-278 or else efavirenz (Sustiva); all participants will also take two other backbone drugs selected by their physicians. Treatment will continue for 96 weeks.

Eligible subjects must be at least 18 years of age and have viral loads of at least 5,000 copies/mL. They must not previously have been treated with antiretroviral drugs for more than two weeks. Exclusion criteria include various medical conditions (including hepatitis B or C) or abnormal laboratory results, and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 320 participants. Trial sites include **Dallas** (214-828-4702), **Los Angeles** (323-913-1033), **Orlando** (407-647-3960 ext. 2132), **San Juan** (787-723-5945), and **Washington, DC** (202-745-6150); www.clinicaltrials.gov/ct/show/NCT00110305. (TMC278-C204)

Maraviroc: Two Studies

Two trials looking at the safety and efficacy of the investigational HIV entry inhibitor maraviroc (formerly UK-427,857) began enrolling in December 2004. Both are sponsored by Pfizer, the drug's manufacturer. Studies to date suggest that maraviroc, a reversible CCR5 coreceptor antagonist, is active against HIV, including virus that is resistant to existing antiretroviral drug classes.

I) The first Phase II/III study will compare maraviroc vs efavirenz in individuals starting anti-HIV therapy for the first time. Subjects will be randomly assigned to receive 300 mg maraviroc once daily, 300 mg maraviroc twice daily, or efavirenz; all participants will also take AZT (zidovudine, Retrovir) and 3TC (lamivudine, Epivir). Participants will have regular clinic visits, some of which

will include physical examinations, blood draws, electrocardiogram (EKG) heart rhythm monitoring, computerized tomography (CT) scans, and symptom questionnaires. Treatment will initially last 96 weeks and may be extended based on outcomes at that time.

Eligible subjects must be at least 16 years of age and have viral loads of at least 2,000 copies/mL. Exclusion criteria include various medical conditions or abnormal laboratory results, and current or prior use of certain medications (including all study drugs). Women may not be pregnant or breast-feeding and participants must use effective contraception.

This study will enroll more than 1,000 subjects at some 200 centers worldwide including **Dallas, Los Angeles, Miami, Oakland, San Francisco, and Tampa**. For more locations and contact information, call Pfizer at 734-622-7600 or send e-mail to ClinicalTrials.gov@Pfizer.com; www.clinicaltrials.gov/ct/show/NCT00098293. (A4001026)

II) The second Phase II/III study will compare maraviroc plus optimized background therapy (OBT) vs OBT plus placebo in treatment-experienced individuals. Subjects will be randomly assigned to receive 150 mg maraviroc once daily, 150 mg maraviroc twice daily, or placebo. OBT will be determined based on treatment history and resistance testing. Participants will receive regular clinic visits, some of which will include physical examinations, blood draws, and EKGs. Therapy will initially last 48 weeks and may be extended based on outcomes at that time.

Eligible subjects must be at least 16 years of age and have viral loads of at least 5,000 copies/mL. They must have been on stable HAART, or else no antiretroviral therapy, for at least four weeks. Subjects must have at least six months' experience with, or documented resistance to, the major classes of approved anti-HIV medications. Exclusion criteria include various medical conditions or abnormal laboratory results, and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 500 participants at 100 U.S. and Canadian centers including **Atlanta, Dallas, Los Angeles, Miami, New York City, Oakland, Philadelphia, Phoenix, San Francisco, and Washington, DC**. For more locations and contact information, call 734-622-7600 or send e-mail to ClinicalTrials.gov@Pfizer.com; www.clinicaltrials.gov/ct/show/NCT00098306. (A4001027)

Vicriviroc: Entry Inhibitor in Phase II

This Phase II study will examine the safety and efficacy of vicriviroc (formerly known as SCH-D and SCH-417690), a novel oral HIV CCR5 antagonist, a type

of entry inhibitor. The agent has demonstrated activity against HIV in laboratory studies to date. Treatment-experienced participants will be randomly assigned to receive one of three doses of vicriviroc (5, 10, or 15 mg daily), or else placebo, along with their current antiretroviral regimen. Subjects will have regular clinic visits, some of which include blood draws, EKGs, and tests for peripheral neuropathy. The study will last 48 weeks.

Eligible subjects must be at least 18 years of age and must have R5-tropic HIV (virus that uses the CCR5 coreceptor to enter cells). They must be experiencing virological failure (viral load of 5,000 copies/mL or greater) on a HAART regimen that contains 100–800 mg ritonavir, and must also have experienced virological failure using a previous regimen of three or more drugs. Exclusion criteria include various medical conditions (including hepatitis B or C) or abnormal laboratory results, and current or prior use of certain medications (including efavirenz or nevirapine within 30 days of study entry). Women may not be pregnant or breast-feeding.

The study aims to enroll 120 subjects at several sites including **Atlanta** (404-616-6313), **Baltimore** (410-614-2766), **Boston** (617-414-7082), **Chicago** (312-572-4545), **Cleveland** (216-844-2546), **Denver** (303-372-5535), **Galveston** (409-747-0241), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Iowa City** (319-353-8441), **Miami** (305-243-3838), **Nashville** (615-467-0154 ext. 108), **New York City** (212-746-4393), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **Stanford** (650-723-2804), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-7387); www.clinicaltrials.gov/ct/show/NCT00082498. (ACTG A5211)

GW-873140: Two Studies

Two studies are currently enrolling to examine the safety and efficacy of GW-873140, a new orally available CCR5 coreceptor blocker being developed by GlaxoSmithKline. So far the agent has demonstrated activity against HIV in laboratory studies and no major safety concerns have arisen in early clinical trials.

I) In the first open-label Phase II dose-ranging study, treatment-naïve participants will receive GW-873140 in combination with lopinavir. Treatment will last 96 weeks. Eligible subjects must be at least 18 years of age, must have HIV viral loads of at least 50,000 copies/mL, and must be starting HAART for the first time (no more than two weeks' prior use of antiretroviral drugs). They must have either R5- or R5/X4-tropic HIV, and may not have X4-tropic virus (which can enter cells using the CXCR4

coreceptor without using the CCR5 coreceptor). Exclusion criteria include various medical conditions or abnormal laboratory results, and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study will be conducted at some 40 sites including **Atlanta** (404-876-2317), **Charlotte** (704-331-9054), **Chicago** (773-388-8883), **Denver** (303-393-8050), **Ft. Lauderdale** (954-565-4899), **Houston** (713-961-7100), **Los Angeles** (323-783-7404), **New Orleans** (504-895-0361), **Philadelphia** (215-762-3251), **Phoenix** (602-307-5330), **San Francisco** (415-292-5477 ext. 480), **Santa Fe** (505-989-8200 ext. 1010), **Seattle** (206-386-2523), **Tampa** (813-875-4374), **Washington, DC** (202-822-6311 ext. 103), and **Wichita** (316-293-2655); www.clinicaltrials.gov/ct/show/NCT00102778. (100136)

II) The second open-label Phase II study is similar to the first, but subjects will receive GW-873140 plus Combivir (AZT/3TC combination pill). Eligibility criteria are the same, except that subjects must have viral loads of at least 10,000 copies/mL and R5-tropic—not R5/X4- or X4-tropic—HIV.

Study sites include **Chicago** (312-942-4810), **Dallas** (214-941-4000), **Denver** (303-764-4776), **Las Vegas** (702-383-2691), **Little Rock** (501-603-0003), **Los Angeles** (323-869-5429), **Miami** (305-243-5621), **Minneapolis** (612-863-5241), **Newark** (973-877-2663), **New York City** (212-924-3934 ext. 126), **Providence** (401-456-2437), **Rochester** (585-244-9000 ext. 409), **San Francisco** (415-565-6288), and **Washington, DC** (202-745-0201); www.clinicaltrials.gov/ct/show/NCT00104429. (102881)

Treatment Intensification with T-20

This nonrandomized open-label study will examine the benefits of intensifying therapy using T-20 for individuals with multidrug-resistant HIV. The trial will attempt to determine whether brief, aggressive treatment promotes HIV-specific immune response and lowers viral set-point. All subjects will have T-20 added to their HAART regimens (other drugs are not provided by the study). The study will last 48 weeks and there will be 17 clinic visits with blood draws.

Eligible participants must be at least 18 years of age, be on stable antiretroviral therapy, and have multidrug-resistant HIV and viral loads above 1,000 copies/mL. They may not be taking immune-modulating drugs.

The study aims to enroll 20 subjects at **San Francisco General Hospital** (415-476-4082 ext. 139); www.clinicaltrials.gov/ct/show/NCT00102934. (5R21-AI055273-02; protocol 834)

Boosted Atazanavir Maintenance Therapy

Given the long-term side effects, expense, and inconvenience associated with antiretroviral treatment, researchers are looking for ways to simplify therapy. This nonrandomized open-label pilot study will attempt to determine whether atazanavir (Reyataz) boosted with ritonavir can suppress HIV in the absence of other antiretroviral drugs. At the beginning of the study, subjects will switch from their PIs to boosted atazanavir. At week 6 they will discontinue their NRTIs and remain on atazanavir/ritonavir alone. Participants will receive EKGs at the screening visit. There will be several subsequent clinic visits that will include medication assessment, physical exams, and blood work. The study will last 54 weeks.

Eligible subjects must be at least 18 years of age and must have been on initial antiretroviral regimens including at least two NRTIs and one PI for at least 48 weeks. They must have well-controlled HIV with viral loads below 50 copies/mL and CD4 cell counts of at least 250 cells/mm³. Exclusion criteria include current or prior use of NNRTIs or certain other medications, certain PI resistance mutations, and various medical conditions (including heart rhythm abnormalities). Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 33 participants at some 20 sites including **Baltimore** (410-706-1476), **Boston** (617-732-4785), **Chapel Hill** (919-843-8761), **Cincinnati** (513-584-8373), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Iowa City** (319 353-8441), **Miami** (305-243-3838), **Minneapolis** (612-625-1462), **New York City** (212-746-4393), **Omaha** (402-559-8163), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **San Diego** (619-543-8080), **San Juan** (787-759-9595), and **Seattle** (206-731-8877); www.clinicaltrials.gov/ct/show/NCT00084019. (ACTG A5201)

SLAM-C: Pegylated Interferon Maintenance Therapy for HIV/HCV Coinfection

Past research has shown that liver damage due to hepatitis C progresses more rapidly in HIV positive people. Coinfected people do not respond as well to hepatitis C treatment as individuals with hepatitis C virus (HCV) alone, but some studies suggest that long-term interferon maintenance therapy may help slow liver disease progression even in the absence of a sustained virological response.

In this Phase II open-label study, subjects who either have never received therapy for hepatitis C or who did not clear HCV with prior treatment will receive a standard course of HCV therapy (180 mcg Pegasys brand pegylated

interferon-alfa-2a once weekly plus weight-based ribavirin daily). Subjects who respond well after 12 weeks will continue on this regimen for an additional 60 weeks. Those who respond poorly will be randomly assigned either to stop ribavirin and continue pegylated interferon for 72 weeks, or to discontinue both ribavirin and pegylated interferon. Participants will receive liver biopsies at study entry, after changing therapy, and at the end of follow-up to monitor progression of fibrosis (liver scarring). Follow-up will continue for 90–96 weeks.

Eligible participants must be at least 18 years of age and have chronic hepatitis C with elevated liver enzyme (ALT, AST, and alkaline phosphatase) levels and at least stage I fibrosis. They must have been on stable anti-HIV therapy for at least eight weeks or else off antiretroviral therapy for four weeks. They must have viral loads below 50,000 copies/mL and CD4 cell counts of at least 200 cells/mm³. They must either be naive to hepatitis C therapy or else still have detectable HCV RNA after previous treatment with standard or pegylated interferon with or without ribavirin. Exclusion criteria include various medical conditions (including decompensated liver cirrhosis, hepatitis B, autoimmune diseases, and uncontrolled depression or other psychiatric conditions) and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 180 subjects at more than 40 sites including **Atlanta** (404-616-6313), **Baltimore** (410-614-2766), **Birmingham** (205-975-7925), **Boston** (617-724-0072), **Buffalo** (716-898-3933), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cincinnati** (513-584-8373), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Galveston** (409-747-0241), **Honolulu** (808-737-2751), **Indianapolis** (317-630-6023), **Los Angeles** (310-825-1301), **Miami** (305-243-3838), **Nashville** (615-467-0154 ext. 108), **New York City** (212-746-7198), **Omaha** (402-559-8163), **Philadelphia** (215-349-8092), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **Stanford** (650-723-2804), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-7387); www.clinicaltrials.gov/ct/show/NCT00078403. (ACTG A5178; SLAM-C)

Ezetimibe Plus Statins for High Cholesterol

This study will attempt to determine whether a combination of two lipid-lowering medications, ezetimibe (Zetia) plus a drug in the statin class, can safely help reduce low-density lipoprotein (LDL, or “bad” cholesterol) levels in HIV positive people taking antiretroviral therapy. All subjects

will take HAART and statins. In addition, in this crossover study, participants will be randomly assigned to receive either daily ezetimibe followed by placebo, or else placebo followed by ezetimibe. The study will last 28 weeks and there will be nine clinic visits.

Eligible participants must be at least 18 years of age and must have an LDL cholesterol level of 130 mg/dL or higher. They must have been on stable antiretroviral regimens for at least 30 days and have been taking one of the study-recommended statins for at least three months. They must start a lipid-lowering diet and exercise program at least one month before screening and continue both for the duration of the study. Exclusion criteria include various medical conditions (including diabetes and cardiovascular disease) and current or prior use of certain medications (including ezetimibe). Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study will enroll about 40 subjects at some 15 sites including **Chicago** (312-942-4810), **Cincinnati** (513-584-8373), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Galveston** (409-747-0219), **Honolulu** (808-737-2751), **Los Angeles** (310-825-1301), **Miami** (305-243-3838), **New York City** (212-746-4393), **Philadelphia** (215-349-8092), **Stanford** (650-723-2804), and **Washington, DC** (202-687-7387); www.clinicaltrials.gov/ct/show/NCT00099684. (ACTG A5209).

Bone Mineral Density: Alendronate, Calcium, and Vitamin D

This study will examine the effects of alendronate (Fosamax), calcium, and vitamin D on bone mineral density in people with HIV. Research has shown that HIV positive individuals appear to be at greater risk for bone loss (osteopenia and osteoporosis) due to HIV itself or antiretroviral therapy. In this Phase II safety and efficacy study, participants will be randomly assigned to receive either alendronate or placebo for 48 weeks; all subjects will receive calcium and vitamin D supplements. Participants will have regular clinic visits that will include fasting blood draws and dual energy x-ray absorptiometry (DEXA) scans to evaluate bone density.

Eligible subjects must be at least 25 years of age and must have decreased bone mineral density as shown by a lumbar spine DEXA scan. Subjects must have been on stable antiretroviral therapy for at least 12 weeks prior to enrollment, and must have CD4 cell counts of at least 100 cells/mm³ and viral loads of 5,000 copies/mL or less. They must also have a serum calcium level between 8 and 11 mg/dL. Men may not have untreated hypogonadism (low

testosterone level), and women on estrogen replacement therapy and individuals taking steroids must have been on stable regimens for at least 24 weeks. Exclusion criteria include various medical conditions (including esophageal problems and past spinal fractures) and use of certain medications and supplements (including glucocorticoids, calcium, vitamin D, and high doses of vitamin A). Women may not be pregnant or breast-feeding.

This study is expected to enroll 80 participants at about 25 sites including **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cleveland** (216-778-5489), **Galveston** (409-747-0241), **Indianapolis** (317-274-8456), **Los Angeles** (310-206-8029), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 108), **New York City** (212-263-6565), **Philadelphia** (215-349-8092), **San Diego** (619-543-8080), **San Francisco** (415-514-0550 ext. 354), **Seattle** (206-731-8877), and **Washington, DC** (202-687-7387); www.clinicaltrials.gov/ct/show/NCT00061256. (ACTG A5163).

Project T: Tenofovir to Prevent HIV Infection

This study, coordinated by the Centers for Disease Control and Prevention (CDC), is part of a larger international research program to determine whether the nucleotide reverse transcriptase inhibitor tenofovir DF (Viread) can help prevent HIV infection. The drug has performed well in animal prophylaxis studies and appears to have fewer side effects than other antiretroviral medications. *The U.S. phase of the study will focus on the clinical and behavioral safety of the drug, not its effectiveness.* In particular, researchers will attempt to determine whether using a potentially preventive drug will lead to an increase in risky sexual behavior. Participants in arm A will receive either 300 mg daily oral tenofovir or placebo; those in arm B will wait nine months before starting therapy. Because it is not yet known whether tenofovir can help prevent HIV infection—and because some subjects will be taking placebo—participants should continue to practice safer sex, and will receive risk-reduction counseling and free condoms during the study. Should any participants become infected, the local research group will facilitate referrals for HIV care and treatment. The study is expected to last two years.

Eligible participants must be sexually active, HIV negative men who have sex with men between the ages of 18 and 60. The U.S. arm of the study will enroll 200 gay and bisexual men at each of two sites, **Atlanta** (404-876-2317) and **San Francisco** (415-554-8888; www.sfaidresearch.org).

BETA

is supported in part by:

- Roche and Trimeris
- GlaxoSmithKline
- Gilead Sciences
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and through the generous contributions of the many individual and institutional donors who support the San Francisco AIDS Foundation.





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- ◆ The official marathon medal
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- ◆ Bragging rights for accomplishing something others only dream about

A Training Program for Everyone

Our training programs are geared to both beginners and experienced runners. The full marathon program starts with three miles of running and walking, and gradually increases in distance each week. The half marathon program starts with just one mile. Many of our participants are first-time marathoners, and some have never run a step in their lives. But 98% of those who complete the program go on to complete the marathon.

Each weekend, you'll train with your "pace group" – other runners who share your same level of conditioning, whether fast or slow. It's a great way to get fit, have fun, and make a tremendous difference in the fight to end AIDS. It may be the best thing you do this year, and your life will never be the same.

Guided Fundraising

AIDS is now the leading cause of death among all people ages 15–69 worldwide. In San Francisco, about 1 out of every 50 people is living with HIV/AIDS. The money we raise will allow the San Francisco AIDS Foundation to provide AIDS services and prevention programs throughout the Bay Area as well as critically needed treatment access in the developing world.

In the past seven years, we've helped 17,000 people nationwide complete a marathon and raise more than \$55 million. We'll be there to help you every step of the way. You'll be surprised at how willing people are to support you. All you have to do is ask.

Training Begins September 10, 2005

Run the
**NEW ORLEANS
MARDI GRAS
MARATHON OR
HALF MARATHON**
on February 5, 2006



A Walk•The•Talk®
Production Benefiting
the San Francisco
AIDS Foundation,
Bay Area AIDS Service
Organizations, and
Treatment Access
Efforts in the
Developing World

Learn More

Visit us online at aidsmarathon.com or attend one of our free, no obligation informational meetings:

SAN FRANCISCO

San Francisco AIDS Foundation
955 Market Street, Second Floor
(corner of 6th & Market)

- Saturday, August 20 @ 1:00 pm
- Tuesday, August 23 @ 6:00 pm
- Tuesday, August 30 @ 6:00 pm
- Tuesday, September 6 @ 6:00 pm

EAST BAY

Hayward – Diablo Community College
25555 Hesperian Boulevard

- Monday, August 22 @ 6:00 pm
- Wednesday, August 31 @ 6:00 pm

Oakland – AIDS Marathon Office
2201 Broadway, Suite 103
(enter back of building on Valley Street)

- Saturday, August 20 @ 1:00 pm
- Wednesday, August 24 @ 6:00 pm
- Wednesday, August 31 @ 6:00 pm
- Thursday, September 1 @ 6:00 pm

Walnut Creek – Buena Vista School
2355 San Juan Avenue (in the Library)

- Wednesday, September 7 @ 6:00 pm

SOUTH BAY/PENINSULA

San Jose – Fairmont
170 South Market Street

- Friday, August 19 @ 6:00 pm

Burlingame – Hyatt Regency SFO Airport
1333 Bayshore Highway

- Thursday, August 25 @ 6:00 pm

San Mateo – San Mateo Community Ctr.
726 Monte Diablo Avenue

- Monday, August 29 @ 6:00 pm