



Nicholas Cheonis

THE HIV/AIDS DRUG PIPELINE

A STATUS REPORT



While most people in the world with HIV/AIDS lack access to treatment, many of those who take anti-HIV medications are quickly exhausting the benefit of available treatment options. The problems associated with the 16 approved anti-HIV drugs—viral resistance, long-term complications and side effects, adherence issues, and high cost—are well documented. Studies have shown that the virological failure rate of highly active antiretroviral therapy (HAART) continues to be greater than 50% per year in most U.S. clinics. Yet only two genuinely new anti-HIV compounds, Kaletra (lopinavir/ritonavir) and tenofovir DF (Viread), have been approved by the U.S. Food and Drug Administration (FDA) since the beginning of 2000. A number of promising drug candidates appear to be floundering or have been discontinued. Some people fear that the research pipeline is drying up at a time when ever more individuals with HIV infection require new medications.

Despite several setbacks, however, there are imminent signs of progress in drug development. A few new agents are expected to be approved later this year. Others are becoming available, albeit in tightly restricted quantities, through expanded access programs (EAPs). Importantly, the notion of drug failure is not always well understood by people with HIV and their providers. Failure in terms of surrogate markers, such as the inability to achieve an undetectable viral load, does not necessarily translate into clinical failure, or deterioration of an individual's health. Recent studies indicate that disease progression is slowed and an immune system benefit is maintained (though not indefinitely) in people who continue to take "failing" medications. By contrast, people not taking anti-HIV therapy are more likely to have faster rates of immune system decline.

The following survey of drugs in the research pipeline is not an exhaustive list of experimental agents, but rather an outline of the major trends in current anti-HIV research. Readers should keep in mind that while advances in medicine depend on human research, transposing clinical trial data to utility in the real world is often difficult; study subjects may be more motivated, more closely monitored, and less representative of the variety of people who are likely to use the therapy under investigation.

APPROVED DRUG CLASSES

A handful of experimental therapies in the three approved classes—protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs)—may provide benefit to people who are in need of third-line therapy, that is, those whose dominant HIV isolates (strains) have become resistant to many or all of the currently available drugs. Even if these new therapies are approved, they will require continued assessment for long-term efficacy and for toxicities that emerge over time.

Protease Inhibitors

Atazanavir

Atazanavir (Zrivada, formerly known as BMS-232632) is the first PI drug likely to be taken once per day (see page 34 for the relative merits of once-daily dosing). In addition, the pill burden (requirement) of two capsules per day should be manageable, and atazanavir does not need augmentation, or boosting, with ritonavir (Norvir). Another advantage of this new PI is its reportedly neutral effect on levels of blood lipids (fats, primarily cholesterol and triglycerides). Atazanavir's lipid profile appears to be unique, as raised blood fat levels, which increase the risk of future cardiovascular events, are a major problem of the PI drug class. For more information on this topic, see "Cardiovascular Disease in People with HIV" on page 10 in this issue.

In a recent study of 85 PI-experienced subjects with viral loads between 1,000 and 100,000 copies/mL, lipid levels remained stable—and some even decreased—by week 48 in those taking atazanavir (400 mg or 600 mg) and saquinavir (Fortovase) plus two NRTIs, compared with those taking ritonavir, saquinavir, and two NRTIs. (Earlier studies have shown that atazanavir and saquinavir work synergistically, or with enhanced effects, though combining the two substantially

raises the pill burden.) For example, fasting triglyceride levels fell by an average of 27% from baseline among those in the 600 mg atazanavir arm, while they increased by an average of 93% from baseline in the ritonavir arm. Three people in both atazanavir arms (9% and 11%, respectively) discontinued the study due to treatment-related adverse events, whereas seven people (30%) did so in the ritonavir arm.

Viral load was reduced by 1.66 log copies/mL in the ritonavir arm vs a 1.44 log decrease in the 400 mg atazanavir arm and a 1.19 log decrease in the 600 mg atazanavir arm; details about which subjects achieved an undetectable viral load were not reported. (Most experts seem to agree that PIs and NNRTIs should be able to reduce viral load levels by at least 1.5 log copies/mL, or about 96%, within the first few weeks, and NRTIs, by about 1.0 log copies/mL, or 90%. See sidebar on page 35.) Other studies suggest that atazanavir has antiviral activity comparable to that of nelfinavir (Viracept). *In vitro* (test-tube) studies indicate that atazanavir should benefit people with resistance to one or two approved PI drugs, but its efficacy may be limited in people with resistance to multiple PIs.

Notably, atazanavir can increase levels of bilirubin, a pigment produced by the breakdown of hemoglobin, which at high levels can cause jaundice (yellowing of the skin and whites of the eyes) in some people. Those genetically predisposed to increased bilirubin levels one day may be detected using a screening test and advised not to take atazanavir—a potential innovation from the new field of pharmacogenomics, or individualizing drug use based on a person's genetic characteristics. Researchers have indicated that atazanavir also may cause prolongation of the QT interval, which is associated with heart arrhythmias and can lead to cardiac arrest and sudden loss of consciousness or death, particularly in children and young adults. (The QT, or QTc, interval refers to a phase in the heart's electrical impulse cycle as measured by electrocardiogram, or ECG. Women tend to have slightly

longer QT intervals than men.) Another limitation of atazanavir is the lack of data on interactions with other anti-HIV agents.

Despite these drawbacks, Bristol-Myers Squibb (BMS, based in New York City), initiated an EAP in May 2002 that provides atazanavir free of charge to limited numbers of people from two categories: those who cannot control their HIV infection using approved standard-of-care agents, and those with severe HAART-associated hyperlipidemia (high lipid levels) despite using lipid-lowering therapy. Pending ongoing research on drug interactions in treatment-naïve people, EAP enrollees may not take ritonavir or Kaletra, and should be cautious if taking indinavir (Crixivan) or any NNRTI drugs. For more information about the atazanavir EAP, call 877-7BMS-EAP (877-726-7327).

Tipranavir

Tipranavir is the first of a new class of nonpeptidic PIs, which are more easily synthesized and manufactured—and therefore potentially less expensive—than the current peptide-based PIs. (Peptides are short chains of amino acids.) Tipranavir's activity against HIV strains with decreased susceptibility to all other PIs, presumably a result of the drug's unique molecular structure, makes it highly attractive. Recent data showed that among 41 NNRTI-naïve people (nine female) without adequate viral suppression on their second PI-based regimen, only one (2%) developed high-level resistance (a greater than ten-fold increase in mutant virus) to tipranavir. Six (14%) developed mild resistance to the drug, which was associated mostly with the V82T and L33I resistance mutations. After 48 weeks of follow-up, viral load reductions from baseline were nearly identical among study subjects who had up to five or more than five PI resistance-conferring mutations (decreases of 2.39 and 2.24 log copies/mL, respectively). The most common adverse events were diarrhea and nausea within the first month; most resolved with or without treatment.

New Drugs and Reformulations Closest to Approval

DRUG NAME	DRUG CLASS	BENEFITS	DRAWBACKS	MOST LIKELY TO USE
T-20 (enfuvirtide, Fuzeon) <i>see page 36</i>	Fusion inhibitor	Effective against multidrug-resistant virus, enhances approved anti-HIV drugs	Must be injected, difficult to manufacture, potentially very expensive	People who need third-line or salvage therapy
Atazanavir (Zrivada) <i>see page 30</i>	PI	Once-daily dosing, light pill burden, neutral (possibly favorable) effect on blood fat levels	Can cause jaundice, may prolong QT interval, implications of missing once-daily dose <i>see page 34</i>	People who cannot control high blood fat levels when taking other PIs
908 (GW433908, fos-amprenavir) <i>see page 31</i>	PI	Reduces pill burden of amprenavir	Unknown	People who prefer a reduced pill burden
d4T XR <i>see page 34</i>	NRTI	Once-daily dosing	Implications of missing once-daily dose <i>see page 34</i>	People who prefer once-daily dosing
3TC QD <i>see page 34</i>	NRTI	Once-daily dosing	Implications of missing once-daily dose <i>see page 34</i>	People who prefer once-daily dosing

New Drugs in Phase II/III Studies

DRUG NAME	DRUG CLASS	BENEFITS	DRAWBACKS	MOST LIKELY TO USE
Tipranavir <i>see page 30</i>	PI	Active against PI-resistant HIV	Diarrhea and nausea	People who need third-line or salvage therapy
Emtricitabine (Coviracil) <i>see page 33</i>	NRTI	Once-daily dosing	May not enhance activity of other NRTIs, implications of missing once-daily dose <i>see page 34</i>	People who prefer once-daily dosing

Unlike atazanavir, tipranavir must be boosted with ritonavir to compensate for its relatively short half-life and poor bioavailability (the degree to which the drug is absorbed and circulated in the body). Ongoing Phase IIb studies will help determine the optimal dose of tipranavir/ritonavir, which remains problematic since the tipranavir hard capsule was reformulated into a

lower-dose (250 mg), self-emulsifying drug delivery system (SEDDS) midway through the study described above. The tipranavir/ritonavir combination is being tested in doses of 500 mg/100 mg, 500 mg/200 mg, and 750 mg/200 mg BID (twice per day). If current studies warrant long-term use of tipranavir, an EAP is expected to begin in the third quarter of 2003. Tipranavir is under

development by Boehringer Ingelheim Pharmaceuticals (Ridgefield, Connecticut).

908

908, also known as GW433908 or fos-amprenavir, is a prodrug of the approved PI amprenavir (Agenerase). A prodrug is an inactive precursor of a drug that is converted by metabolic processes in the body into the drug's

active form. Amprenavir is known to have poor bioavailability; reformulating the drug into 908 should reduce pill burden and thwart resistance by increasing levels of amprenavir in the body. The current formulation of amprenavir must be taken as eight large capsules twice per day and is not boosted with ritonavir; researchers are evaluating 908 with and without ritonavir boosting. Dosages under investigation include 1) two 908 tablets twice per day, 2) one 908 tablet with one ritonavir capsule twice per day, or 3) two 908 tablets with two ritonavir capsules once daily. Pending results of ongoing Phase III studies, Glaxo-SmithKline (GSK; Research Triangle Park, North Carolina) anticipates submitting 908 for FDA approval in the fourth quarter of 2002.

Other PIs

TMC-114 is a second-generation PI drug highly active against HIV with PI resistance mutations *in vitro*, and against HIV isolates taken from people with up to 100-fold reduced sensitivity to at least one approved PI. (Second-generation antiretroviral drugs are designed to be more potent and easier to tolerate than currently available drugs.) A Phase IIa study began enrolling in Europe in May 2002 to evaluate a new formulation of TMC-114; polyethylene glycol in the original agent had caused excessive diarrhea at higher doses. If TMC-114 is boosted with low-dose ritonavir, it may be available as one pill taken once daily. This new PI is under development by Tibotec-Virco NV (Mechelen, Belgium), which was acquired by Johnson and Johnson in early 2002.

Triangle Pharmaceuticals (Durham,

North Carolina) announced in January 2002 that development of **mozenavir** (DMP-450), an investigational once-daily PI, was suspended because of disappointing study results, including reduced activity against virus resistant to indinavir (Crixivan) and ritonavir.

Non-nucleoside Reverse Transcriptase Inhibitors

None of the experimental NNRTIs in the pipeline are beyond the early stages of development, and only a few show promising anti-HIV activity in people whose virus cannot be adequately suppressed using currently available NNRTIs. An improved resistance profile is essential for any second-generation NNRTI, as viral mutations that decrease susceptibility to one approved NNRTI are likely to confer resistance to all drugs in this class.

TMC-125

TMC-125 attracted attention at the 9th Conference on Retroviruses and Opportunistic Infections this past February when researchers reported on two Phase IIa studies showing that the drug induced rapid and impressive reductions in viral load levels in people with inadequate viral control while taking efavirenz (Sustiva) or nevirapine (Viramune) (median reduction of 0.9 log copies/mL), and in people who had never before taken anti-HIV therapy (median reduction of 1.92 log copies/mL). In people naive to therapy, TMC-125 reduced viral loads as potently as a five-drug regimen including agents from all three approved classes. TMC-

125 also raised CD4 cell counts by 119 cells/mm³, compared with 60 cells/mm³ in a comparative analysis of people starting five drugs after no previous treatment. Significantly, these viral load reductions and CD4 cell count increases were measured within the first seven days of therapy in both TMC-125 studies. Recent reports indicate that response to anti-HIV therapy within the first week may predict long-term response to that treatment.

Headache and diarrhea are the most common adverse events associated with TMC-125. Further research on this drug, developed by Tibotec-Virco, no doubt will focus on reducing the onerous pill burden of 18 tablets (900 mg) taken twice per day. Phase IIb studies will enroll people who have used agents from all three approved drug classes; drug interaction studies are ongoing.

DPC-083

BMS's **DPC-083** appears to benefit people whose HIV strains have decreased susceptibility to efavirenz and nevirapine. (The drug was originally developed by DuPont Pharmaceuticals, which was acquired by BMS in October 2001.) DPC-083 has a very long half-life—approximately 100 hours—which suggests once daily or even alternate-day dosing. (Taking a drug every other day, however, may have a negative impact on adherence.)

Fairly modest results have been achieved thus far. A recent Phase II comparison study in 134 antiretroviral-naive subjects (15% female, 17% non-Caucasian) showed similar rates of undetectable virus (fewer than 50 copies/mL) after 24 weeks among those taking one of three doses of DPC-083 (50, 100, or 200 mg once daily) plus standard efavirenz (600 mg) in an intent-to-treat analysis (all subjects were taken into account, including those who discontinued the study). Frequency of rash, a common side effect of efavirenz and other NNRTIs, in those taking DPC-083 was 15% (50 mg arm), 33% (100 mg), and 53% (200 mg), compared with 38% in the efavirenz arm. DPC-083 also may lead to central nervous system



For information about the atazanavir (Zrivada) EAP, call 877-7BMS-EAP (877-726-7327).

(CNS) side effects, although it appears to cause less dizziness than efavirenz.

Another recent Phase II study compared 100 mg and 200 mg once-daily doses of DPC-083 plus two NRTIs in people who previously had experienced viral rebound while taking nevirapine (61%) or efavirenz (39%). After eight weeks the strongest antiviral responses were found in those who not only switched their failing NNRTI to DPC-083, but also switched to at least one new NRTI. The mean decrease in viral load from baseline was 1.28 log copies/mL. These results are very preliminary and were not generated using a more useful intent-to-treat analysis, which would have taken into account the eight subjects (16% of total) who discontinued the study. Furthermore, data showing the response rate as number of subjects achieving fewer than 50 viral copies/mL, rather than 400 copies/mL as presented, would have been revealing.

Capravirine

In early studies **capravirine** (previously known as AG-1549 and S-1153) appeared to be ten times more potent than approved NNRTIs and to have activity against virus resistant to efavirenz (but not nevirapine). Phase II studies in people with NNRTI resistance and no PI experience, however, showed that those who took one of two doses of capravirine (1,400 or 2,100 mg) plus nelfinavir and two new NRTIs were no more likely to achieve viral loads of fewer than 400 copies/mL than those who took a placebo (an inactive substance). Further development of this investigational NNRTI by Agouron (a division of Pfizer, based in New York City) seemed doubtful following reports of vasculitis (blood vessel inflammation) in dogs given capravirine. However, no vasculitis has been found thus far in humans taking the drug, and studies of lower doses of capravirine (with vasculitis monitoring) are ongoing.

Other NNRTIs

Other NNRTI drugs in development include two from Sweden's Medivir company: **MIV-150**, being

codeveloped with Chiron (Emeryville, California) and soon to enter Phase II trials, and **MV026048**, which was licensed to Roche (Nutley, New Jersey) in April 2002 and is still in preclinical testing. **Calanolide A** is a naturally occurring NNRTI compound derived from a Malaysian rain forest plant and is under development by Sarawak MediChem Pharmaceuticals (Lemont, Illinois). It appears to be moving very slowly through the research pipeline. On the reformulation front, researchers at Boehringer Ingelheim are evaluating a **once-daily** version of **nevirapine**.

A number of initially promising compounds have been shelved by their developers—a common occurrence in the pharmaceutical industry, since efficacy in humans rarely matches *in vitro* potency, and drug toxicities often sink a potential candidate. **Emivirine** (Coactinon) recently was discontinued by Triangle due to inadequate potency. BMS suspended development of **DPC-961** after several study volunteers reported suicidal ideation, and **DPC-963** appears to be on hold.

Nucleoside Reverse Transcriptase Inhibitors

NRTI drugs were the first class of antiretrovirals to be approved, beginning with AZT (zidovudine, Retrovir) in 1987. As with the other two approved classes, next-generation NRTIs will require improved potency with fewer side effects and more robust resistance profiles.

Emtricitabine

Emtricitabine (Coviracil, formerly known as FTC) is a new NRTI under investigation by Triangle. Early studies have shown that a once-daily 200 mg dose is optimal and able to reduce viral load by approximately 1.7 log copies/mL in people with no previous treatment experience. Emtricitabine appears to have potency equivalent to that of 3TC (lamivudine, Epivir) in treatment-experienced people; for several years the value of emtricitabine over 3TC has been questioned. Significantly, the two drugs' similar resistance profiles

means that viral strains with reduced sensitivity to 3TC also evade the antiviral effects of emtricitabine. In addition, compared with viral resistance to 3TC, resistance to emtricitabine seems to be less associated with the M184V mutation, which confers a protective effect against AZT resistance.

If approved, emtricitabine may be desirable mainly for people who prefer once-daily dosing. Some subjects using this drug in trials have reported mild to moderate CNS symptoms, diarrhea, rashes, and biochemical abnormalities, including very high triglyceride levels. This drug also is being studied to treat hepatitis B virus (HBV) infection.

Triangle plans to submit a new drug application (NDA) with the FDA in the autumn of 2002 based on 24-week data from a third Phase III study (FTC-301). This study has enrolled approximately 560 people to compare emtricitabine with d4T (stavudine, Zerit), taken with ddI (didanosine, Videx) and efavirenz; the primary endpoint is undetectable viral load (fewer than 50 copies/mL).

Amdoxovir

Amdoxovir (formerly known as DAPD) is another NRTI being developed by Triangle. The body metabolizes the comparatively weak pill form of this drug (dioxolane purine) into a highly active form known as DXG, or D-dioxolane guanosine. Amdoxovir's unique chemical structure is believed to account for its potency against viral isolates resistant to AZT, 3TC, and abacavir (Ziagen), and some isolates with wide cross-resistance to NRTIs. Amdoxovir also appears to work against some viral strains with reduced susceptibility to certain NNRTIs (efavirenz and nevirapine). In fact, a number of resistance mutations associated with NNRTI drugs (for example, 103N, 106A, 108I, 181C, and 190A) appear to increase the efficacy of amdoxovir. Viruses with multiple mutations including K65R, F116Y, and Q151M, however, are less susceptible to amdoxovir.

This new NRTI may be especially suitable as a component of "salvage therapy," that is, for use in people

whose predominant viral isolates no longer respond to a variety of approved anti-HIV drugs—in this case, AZT and 3TC in particular. In preliminary studies, six people who added amdoxovir (500 mg twice daily) to their current, failing antiretroviral regimens experienced an average viral load reduction of 1.9 log copies/mL—significantly more impressive than the average reduction of 1.0 log copies/mL seen in those taking amdoxovir alone after a “wash-out” period of no drugs.

Amdoxovir is currently in Phase II studies. The drug’s activity, particularly against multi-NRTI-resistant viral isolates, appears to be augmented by coadministration with mycophenolate (mycophenolic acid, CellCept), an immunosuppressive drug approved for use in organ transplantation. The two drugs are expected to be studied in a Phase II study in heavily treatment-experienced people later in 2002. Mycophenolate also may enhance the activity of several other anti-HIV agents, including tenofovir DF and ddI.

Other NRTIs

A few other NRTI compounds are still in early development. Like many NRTI candidate drugs, **BCH-13520** (developed by BioChem Pharma of Laval, Quebec) appears to be active against wild-type (nonmutated) and drug-resistant HIV *in vitro*. **ACH-126443** is being developed as a therapy for both HIV and HBV infections by Achilleon (New Haven, Connecticut).

Medivir’s **alovudine** (MIV-310, FLT) resembles AZT structurally and appears effective against multidrug-resistant HIV—particularly virus highly resistant to AZT—in early studies. A Phase IIa trial of alovudine given once daily (7.5 mg) is ongoing.

GS-7340, an oral prodrug of the nucleotide analog tenofovir DF, has undergone laboratory and preliminary animal studies. Nucleotide analogs are a subset of NRTI drugs.

As with several other compounds, the progress of **D-D4FC** (Reverset, also known as DPC-817) has been a source of confusion. Although the drug (formerly developed by DuPont) was

recently discontinued by BMS because of drug toxicity, the compound now appears to be entering Phase I studies in the U.S. and Germany under the aegis of Pharmasset, Inc. (Tucker, Georgia), reportedly the drug’s original developer. A study published this past May indicates that D-D4FC is active *in vitro* against viral isolates resistant to AZT and 3TC.

Once-Daily Formulations

One busy area of activity in NRTI development involves the reformulation of currently approved drugs to allow once-daily dosing. In December 2001 BMS submitted an approval application to the FDA for its extended-release formulation of d4T known as **d4T XR**, a 100 mg capsule to be taken once per day. Notably, drug doses of both twice-daily and once-daily d4T in equivalency studies were adjusted based on the weight of study subjects, which many treatment advocates believe should be standard practice with all anti-HIV drugs in development. The potency of QD (once-daily) formulations of both 3TC and abacavir appears comparable to that of the approved twice-daily versions. **3TC QD** is already available in Europe, and is expected to be marketed in the U.S. later this year. GSK is studying a 600 mg **AZT QD** formulation as well. Not surprisingly, GSK researchers are keen on producing once-daily formulations of their three NRTIs in combination. A single **once-daily 3TC/abacavir** pill is on the horizon, and pilot studies will investigate **once-daily Combivir** (AZT/3TC) and **Trizivir** (AZT/3TC/abacavir), pending the viability of the AZT QD formulation.

While drug companies are scrambling to develop once-daily versions of many of their anti-HIV therapies, the advantages of QD regimens are not entirely clear. Certainly, reducing the pill burden and augmenting the potency (but not the toxicities) of the first generation of antiretroviral drugs remain worthy goals. “Easier, simpler regimens” has become a standard request from people with HIV and their providers. Yet some people find adhering to once-daily regimens more challenging

than taking twice-daily (BID) agents. Any impediment to adherence should be avoided, since near-perfect adherence is crucial for maintaining adequate viral suppression and immune reconstitution. Studies have shown that taking anti-HIV drugs as prescribed at least 95% of the time is necessary to maintain viral control, and that rates of viral suppression drop significantly as adherence rates decrease. In addition, missing a QD drug dose may be more detrimental than missing a BID dose, depending on the drug’s half-life. If a QD dose is missed, a full day will have gone by before the next dose is taken, potentially allowing the drug concentration to fall below an acceptable trough (lowest) level and thereby giving the virus more opportunity to flourish. Furthermore, if QD drugs must be taken at different times during the day because of dietary or other requirements, the ease of once-daily regimens may be illusory.

ENTRY INHIBITORS

Ideally, the problems of drug resistance within and across the three approved drug classes would be overcome by the creation of therapies that target HIV in novel ways. The current arsenal of approved drugs works by interfering with either protease or reverse transcriptase, two viral enzymes (proteins) that allow HIV to replicate once it has penetrated within a host CD4 (immune system) cell. Intervening at the point of viral entry would protect CD4 cells from invasion and prevent HIV from generating more copies of itself. None of the currently approved therapies target HIV before it has overtaken a host cell.

HIV enters a CD4 cell by attaching its gp120 envelope protein to the cell’s CD4 receptor as well as to a secondary chemokine receptor (usually CCR5 or CXCR4), leading to fusion of the viral and cellular membranes and penetration of HIV into the cell. Therapies that disrupt the complex process of viral entry presumably would be effective in people who do not respond adequately to current antiretroviral drugs, due either to an

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 = 3	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 = 4	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 = 5	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 = 6	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 = 7	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 = 8	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 = 9	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

overgrowth of defective, drug-resistant viral mutants in their systems (a phenomenon known as “viral escape,” which is caused by HIV’s propensity to make errors in replicating itself), or because they initially were infected with a drug-resistant strain of HIV. Therapies that protect immune system cells against infection also may cause fewer and less serious adverse effects

than currently approved drugs, and may have additive or synergistic advantages when combined with approved drug classes.

The types of entry inhibitors currently under study include fusion inhibitors, chemokine receptor antagonists (or “blockers”), and other attachment inhibitors. Research on several such therapies is slowly moving from the

laboratory to the clinic, and one (T-20, see below) may be approved late this year or in early 2003. Nevertheless, the pace of research and development must accelerate; new classes of medications are urgently needed for the growing number of heavily treatment-experienced people and those infected with drug-resistant virus.

Fusion Inhibitors

T-20

Fusion inhibitors disrupt the viral entry process by preventing the viral and human cell membranes from joining together. **T-20** (enfuvirtide, Fuzeon, previously known as pentafuside) is the most advanced of the experimental entry inhibitors. This drug prevents fusion by binding itself to HIV's gp41 accessory protein, which pierces the host cell membrane after gp120 binds to the cell's receptor sites and changes shape. T-20 is a synthetic peptide that must be self-injected subcutaneously (under the skin) twice per day. In early studies T-20 has shown activity against both wild-type virus and viral mutants that are resistant to currently available anti-HIV agents, making it particularly useful in heavily treatment-experienced people who have exhausted their other therapeutic options.

In April 2002 preliminary but encouraging results from a 48-week, Phase III study of T-20 known as TORO 1 were announced in a press release by Trimeris (Durham, North Carolina) and Roche, which are codeveloping the drug. TORO 1 enrolled 491 HIV positive study subjects in North America and Brazil who had extensive prior exposure to antiretroviral drugs and/or had developed viral resistance to all three approved anti-HIV drug classes. The median viral load at baseline was greater than 5 log copies/mL. After 24 weeks, subjects who added T-20 (90 mg self-injected twice daily) to their current antiretroviral regimens had viral load reductions significantly greater—an average of 0.93 log copies/mL—than did those who continued to take their combination regimens without T-20. According to the researchers, these results demonstrate that T-20 enhances the activity of HAART more potently than suggested in previous studies. Twenty-four-week results from TORO 2, a similar trial that enrolled 504 HIV positive people in Europe and Australia, showed that those who added T-20 to their HAART regimens had a viral load reduction an

average of 0.78 log copies/mL greater than did those who took HAART without T-20.

In TORO 1, rates of grade 3 (severe) and grade 4 (incapacitating or life-threatening) adverse events were similar in both study arms (combination therapy with vs without T-20), while in TORO 2, grade 3 abnormalities were more common in the T-20 arm and grade 4 events were more frequent in the control arm. People taking T-20 experienced more headaches, fever, dizziness, insomnia, peripheral neuropathy, and asthenia (weakness). Most subjects taking T-20 in both studies experienced a reaction at the injection site, one of the drawbacks of this mode of drug delivery, yet only 3% in both studies discontinued as a result. Discontinuation rates were similar in both arms of TORO 1 (approximately 10% discontinued overall). Discontinuation rates in TORO 2 at 24 weeks were 17% in the T-20 arm and 5% in the control arm.

T-20 also appears to work synergistically with approved anti-HIV drugs in people with less treatment experience. A recent Phase II study enrolled 71 people with significant PI experience and/or resistance but no exposure to NNRTIs. After 48 weeks, the 51 subjects receiving one of three different doses of T-20 (50, 75, or 100 mg) with a backbone of abacavir, efavirenz, and amprenavir boosted with low-dose ritonavir achieved superior viral control and immune reconstitution compared with the 19 control subjects who received the antiretroviral backbone without T-20. Subjects taking T-20 had greater reductions in viral load (decreases of between 2.10 and 2.62 log copies/mL vs a decrease of 1.87 log copies/mL in the control arm) and greater likelihood of achieving a viral load below 50 copies/mL (55% vs 37%) in an intent-to-treat analysis. Subjects taking T-20 also had greater CD4 cell count increases (an average increase of 132 cells/mm³ vs an increase of 90 cells/mm³ in the control arm). The profile of adverse events was similar to that found in the TORO 1 study.

With such promising results, T-20 is understandably appealing to the increasing number of people who are experiencing treatment failure using approved drugs. Yet T-20 has been available only in extremely limited quantities, despite the fact that it was granted fast-track status by the FDA (which means that the FDA facilitates development and expedites review of the drug). A drug like T-20 has never before been successfully developed, in part because it is so difficult to produce. The peptide molecules used in the drug require the construction of special facilities to manufacture sufficient quantities of the drug. Producing the drug involves at least 100 different manufacturing steps, far more than the number needed to produce other anti-HIV drugs.

Manufacturing obstacles are likely to make T-20 very expensive as well as continue to limit its availability. The November 2001 announcement of T20-305, an open-label study to provide expanded preapproval access to 450 people worldwide, was greeted by treatment advocates as a disturbing sign of availability problems to come; 450 open slots were not nearly adequate to cover the many thousands of people in need of the new drug. Although the EAP's 168 open positions for people in the U.S. were filled almost immediately, the number of participants will soon increase since T-20 production capacity is due to be scaled up following the recent opening of a manufacturing plant in Boulder, Colorado. Interested clinicians should call 888-722-6321 for more information. T-20 is expected to be submitted for FDA approval in the second half of 2002.

T-1249

T-1249 is another self-injected fusion inhibitor being developed by Trimeris and Roche that binds to a region of the gp41 viral envelope protein not targeted by T-20. Though it is a few years behind T-20 in the research pipeline (currently in Phase I/II trials), T-1249 appears in early studies to be effective against a broad range of HIV-1

and HIV-2 strains (unlike T-20, which is effective only against HIV-1) and potentially against virus that develops resistance to T-20. Very preliminary, 14-day data presented at this year's Retrovirus conference showed that T-1249 given as monotherapy (without other drugs) was able to reduce viral load levels from baseline by as much as 1.4 log copies/mL, and potentially could be administered once per day. The benefits of T-1249 were tempered by the occurrence of two serious side effects in the 72-person cohort: grade 4 neutropenia (an abnormally low number of neutrophils, the most common type of white blood cell) and a hypersensitivity reaction characterized by fever, oral ulcers, and rash.

As with T-20, the difficulty of manufacturing the T-1249 peptide (which also has fast-track status) is a major obstacle. However, overcoming the manufacturing challenges of T-20 may make it easier to produce a sister compound, or the drug's developers may use a less cumbersome production process than the one used to create T-20. Hope for T-1249 remains high, since it appears that the compound might be more useful overall than T-20. Some researchers have proposed using the two fusion inhibitors in tandem.

Chemokine Receptor Antagonists

The chemokine receptor (binding) site is another potential target for entry inhibitors. As mentioned previously, HIV must bind to a chemokine receptor—usually CCR5 or CXCR4—in addition to the CD4 receptor to infect a CD4 cell and begin replicating. In effect, HIV

gains access to healthy CD4 cells by placing access keys (different configurations of gp120) into two completely different locks on the cell membrane. Experimental drugs that block chemokine receptor attachment have reached Phase II testing, but their clinical utility has not yet been proven.

CCR5

Drugs that inhibit CCR5 attachment may hold more promise than those aimed at CXCR4. This past February researchers reported on a CCR5 antagonist known as **SCH-C**, or SCH 351125, that was given to 12 HIV positive adults with at least 250 CD4 cells/mm³ who were not taking any other antiretroviral therapy. SCH-C, which was given as a 25 mg pill every 12 hours for ten days, reduced the viral load in ten of the subjects by at least 0.5 log copies/mL; in four subjects, viral load was reduced by at least 1.0 log copies/mL. SCH-C tended to increase viral load levels slightly (by no more than 0.3 log copies/mL) within the first three days of administration. Viral load levels subsequently dropped and continued to remain lower a few days after the drug was stopped, then eventually rebounded to baseline measurements. This proof of concept study suggests that CCR5 antagonists one day may be used in the clinic. Problems associated with SCH-C include the fact that two of the 12 study subjects (16%) did not experience any significant viral load reduction, and a prolonged QT interval was observed in an earlier study in healthy subjects given much higher doses of the drug (single 600 mg doses or multiple 400 mg doses per day).

A report in the May 2002 issue of *Antimicrobial Agents and Chemotherapy* indicates that SCH-C works synergistically *in vitro* with antiretroviral drugs from all three approved classes as well as with T-20, raising hopes that combining chemokine antagonists and fusion inhibitors might be a future strategy for treating multidrug-resistant HIV (provided chemokine antagonists become clinically useful). Schering-Plough has another CCR5 antagonist, **SCH-D**, in early development that appears to have superior potency compared with SCH-C. HIV isolates resistant to one of the antagonists, however, become resistant to both.

PRO-140, a CCR5 antagonist under development by Progenics Pharmaceuticals (Tarrytown, New York) has lowered viral loads to undetectable levels in animal HIV models and will advance to Phase I/II human trials once a “humanized version” of the drug is developed, according to statements on the Progenics web site. In addition, Pfizer announced this past May that its CCR5 antagonist known as **UK-427,857** is a “top priority” for the company, although it is still in very early stages of research.

CXCR4

Unlike those that attach to CCR5 (known as R5 variants), HIV isolates that attach to CXCR4 (X4 variants) are associated with rapid disease progression. Reports from this year's Retrovirus conference described the difficulties of developing CXCR4 antagonists. One study showed that sensitivity of X4 variants to CXCR4 antagonists decreases over the natural course of HIV infection. The CXCR4 antagonist known as **AMD-3100**, developed by AnorMED (Langley, British Columbia) failed to adequately reduce viral load levels in a cohort of 40 subjects with viral loads greater than 5,000 copies/mL and has been discontinued. Almost all subjects in the Phase II study, however, displayed a shift in their predominant viral strain from X4 or mixed X4/R5 variants to the less virulent and more common R5



Clinicians interested in the T-20 EAP should call 888-722-6321 for more information.

variant. These proof of concept data provide some hope that CXCR4 antagonists may play a future role in HIV disease management, perhaps in combination with CCR5 antagonists to control mixed X4/R5 infections.

Attachment Inhibitors

Drugs that use other mechanisms to block HIV binding to healthy human cells fall conveniently, if imprecisely, into the broad category of attachment inhibitors. Among these is **PRO-542**, an antibody-like fusion protein being developed by Progenics. Like immune system antibodies, PRO-542 prevents HIV attachment by binding to the gp120 protein on the envelope (outer coat) of the virus. This drug has shown efficacy in HIV positive children, with viral load decreases of up to 1.5 log copies/mL in those receiving multiple doses, and appears to be well tolerated. In laboratory tests, PRO-542 works synergistically with T-20 against a diverse range of viral isolates (allowing up to 10-fold reductions in drug doses), and also when combined with both T-20 and PRO-140. PRO-542 is currently in Phase II development. In addition, at this year's Retrovirus conference researchers from BMS discussed a new orally available gp120 inhibitor, **BMS-806**, in preclinical development.

OTHER NEW MECHANISMS OF ACTION

Integrase Inhibitors

Integrase is one of three viral enzymes—together with protease and reverse transcriptase—necessary for HIV replication. Integrase inserts HIV genetic material into the normal DNA of an infected human cell. The success of drugs targeting the other two viral enzymes has encouraged researchers that a new class of integrase inhibitors may be viable anti-HIV agents, although drugs targeting integrase remain in early clinical development. **L-870,810** is a new integrase inhibitor being developed by Merck (Whitehouse Station, New Jersey). This drug appears to be potent and to have a very favorable resistance profile in preliminary studies. A Phase I trial in HIV negative volunteers is underway.

At this year's Retrovirus conference researchers from Shionogi and Company (Osaka, Japan, and Florham Park, New Jersey) announced promising data on **S-1360**. *In vitro* and animal research shows that S-1360 has similar efficacy to AZT and capravirine, and is active against both X4 and R5 HIV variants. Furthermore, S-1360 appears (*in vitro*) not only to be active against

viral mutants resistant to all three approved drug classes, but also able to work synergistically with all three classes. Excitement generated by test-tube data, however, is often short-lived.

Zinc Finger Inhibitors

So-called zinc fingers are another potential target of anti-HIV therapy. Zinc fingers refer to proteins that form finger-like loops when certain amino acids in a protein chain are pulled together by zinc atoms. Therapies involving zinc finger inhibition disrupt viral replication by targeting the finger-like HIV nucleocapsid protein, which conveys HIV genetic material to new virus that is assembled in infected cells. Early studies show that inhibiting the nucleocapsid results in the production of dysfunctional, noninfectious virions (complete virus particles). Zinc fingers also may interfere with reverse transcription, a process that allows HIV genetic material to be integrated into the genetic material of an infected cell.

This novel approach to combating HIV infection awaits a breakthrough. A recent Phase I/II study of the zinc finger inhibitor **azodicarbonamide** (ADA) showed moderately effective anti-HIV activity. However, several reported side effects, including nephrotoxicity (kidney-related toxicity) and glucose intolerance, cast doubt on the utility of this drug.

Immunomodulating Therapies

Immune modulators do not specifically target HIV cell binding or replication. Rather, they enhance the immune system to more effectively control HIV infection, much as the immune system of a healthy individual renders other pathogens, such as cytomegalovirus (CMV), harmless. Unfortunately, there is currently no validated surrogate marker for improvements in immune function, which makes it difficult to assess the utility of immunotherapies. Some experts nevertheless predict that a future treatment strategy for people whose HIV is adequately suppressed



It is not difficult to imagine a future time when currently available anti-HIV drugs will be used only for very short durations, such as to prevent mother-to-child transmission or in postexposure prophylaxis (PEP) regimens.

with antiretroviral drugs will involve going off the drugs periodically after first boosting CD4 cell levels with immunomodulating therapy.

Interleukin 2 (IL-2, Proleukin) is a cytokine, or immune system protein, that promotes TH1 immunity via the proliferation and activity of CD4 cells, cytotoxic T lymphocytes (CTLs), and natural killer (NK) cells. (TH1, or cell-mediated, immune response is especially effective against HIV-infected cells and has been associated with long-term nonprogression.) IL-2 continues to be studied in a variety of HIV-related settings, including use in recently infected populations, in various structured treatment interruption (STI) protocols, and in combination with therapeutic vaccine agents (see below). Its utility remains a matter of debate. Side effects associated with IL-2 include flu-like symptoms (fever, chills), decreased blood pressure, and anorexia.

HE2000 is among the more intriguing immune modulators being studied. This adrenal steroid appears to induce a shift from TH2 immune response (which inhibits the cell-mediated branch of the immune system and is thought to be associated with rapid disease progression) to TH1-type response. It also appears to increase levels of key immune system cells such as interleukin 10 (IL-10)-producing CD4 cells and dendritic cells. Resistance to HE2000 has not been detected in early studies, even among people taking the drug over the course of two years. A Phase II trial in the U.S. is studying HE2000 in people whose HIV has lost sensitivity to at least two HAART regimens. The drug also is being studied in South Africa to delay the onset of AIDS-related opportunistic illnesses (OIs) such as pneumonia and tuberculosis, and in Thailand both to treat and prevent malaria. HE2000 is under development by Hollis-Eden Pharmaceuticals (San Diego, California).

Therapeutic Vaccines

Unlike a preventive vaccine, a therapeutic (treatment) vaccine is given after infection and is intended to reduce or arrest disease progression

by producing or reinforcing an immune response. Therapeutic vaccination is a challenging new field. Only two therapeutic vaccines currently exist: one to treat CMV and another that controls herpes simplex virus (HSV); neither has been approved by the FDA. Preliminary studies of anti-HIV therapeutic vaccines over the years have yielded few encouraging or tangible results.

Current interest is focused on a **DNA vaccine** developed by Merck that aims to boost TH1 immune response and appeared to arrest disease progression in very small studies in monkeys. A combination **gp120 and Nef/Tat** “fusion” HIV protein vaccine candidate from GSK also has moved into human trials, although it appeared to offer conflicting results in monkey studies. Epimmune Inc. (San Diego, California) recently received FDA approval to begin a Phase I/II study of its **EP HIV-1090** therapeutic vaccine.

Interesting data on a DNA-based therapeutic vaccine called **DermaVir** were presented at the recent XIV International AIDS Conference (IAC) in Barcelona, Spain. DermaVir, which is applied to abraded (lightly scraped) skin on the hand, appeared to sharply decrease the rates of viral rebound and induce cell-mediated immune responses in a small group of macaque monkeys with symptomatic AIDS. (The macaques were chronically infected with simian immunodeficiency virus, or SIV, the so-called monkey version of HIV.) DermaVir was given to those macaques undergoing a series of STIs in which they alternately took HAART then stopped therapy in three-week cycles.

The Immune Response Corporation (Carlsbad, California) has been studying **Remune** (HIV-1 Immunogen, the Salk HIV vaccine) for several years. Data published in the May 2002 issue of *Clinical and Experimental Immunology* indicates that this therapeutic vaccine, given as an intramuscular injection at 12-week intervals, may be able to boost HIV-specific lymphocyte proliferation in people

already responding well to HAART (that is, with lower viral loads and higher CD4 cell counts). In June 2002, however, the *San Diego Union-Tribune* reported that Immune Response faces bankruptcy and that “the outlook for Remune... appears bleak.”

Successful therapeutic vaccines may work synergistically in combination, and likely will be added to antiretroviral regimens or as immune enhancement agents during treatment interruptions. Some researchers hypothesize that therapeutic vaccines may not produce adequate responses in people with low CD4 cell nadirs (lowest levels ever), such as those who start taking HAART with fewer than 200 CD4 cells/mm³, even if their CD4 cell counts subsequently rise to more normal levels.

Gene Therapy

The relatively new field of gene therapy has shown some very early, though unproven, promise. One approach involves RNA interference, or “gene silencing,” in which short interfering RNA (siRNA) disrupts viral attachment or HIV replication by inhibiting the production of certain proteins. Human trials may begin by early 2003. Other laboratory studies have shown that siRNA targeted against viral proteins such as p24 may blunt the replication ability of HIV that becomes activated after lying dormant in cells for a period of time.

One would hope that gene therapy and other novel treatments will target NK cells, nonspecific white blood cells that recently were found to be reservoirs of HIV that are beyond the reach of currently approved drugs. For more information, see “News Briefs” on page 6.

COMMENT

While the research pipeline is not as reliably bountiful as many people would like, it clearly has not dried up. Nevertheless, pharmaceutical companies must ensure a steadier stream of innovative and affordable approaches to managing HIV infection—preferably approaches that resemble a cure rather

than life-long chemotherapy. Whether these involve schemes proposed in recent months (for example, using newly identified antibodies such as X5) or other, as yet unknown mechanisms, the need for novel therapies grows daily. Based on the enormous scientific advances in HIV disease over the past several years, it is not difficult to imagine a future time when currently available anti-HIV drugs will be used only for very short durations, such as to prevent mother-to-child transmission or in postexposure prophylaxis (PEP) regimens. In an ideal scenario, today's problematic drugs will not be needed at all.

Nicholas Cheonis is associate editor of *BETA*.

Selected sources

- Bethell, R.C. and others. BCH-13520, a new heterosubstituted nucleoside analogue, is an effective inhibitor of drug-resistant HIV-1. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington. February 24–28, 2002. Abstract 386-T.
- Blakeslee, D.J. Nonpeptidic protease inhibitors. *Journal of the American Medical Association (JAMA)* Online HIV/AIDS Information Center (www.ama-assn.org/special/hiv/newsline/conferen/icaac/pi.htm). September 17, 1996.
- Borroto-Esoda, K. and others. Lower incidence of the M184V mutation in ART-naïve patients receiving combination therapy with emtricitabine (FTC) compared to lamivudine (3TC), results of a double blind equivalence trial. 1st International AIDS Society Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina. July 8–11, 2001. Abstract LB-P21.
- Borroto-Esoda, K. and others. DAPD, a novel nucleoside inhibitor of HIV-1 replication, is active against drug-resistant isolates of HIV-1 from patients failing standard nucleoside therapy. 39th Interscience on Antimicrobial Agents and Chemotherapy. San Francisco. September 26–29, 1999. Abstract 924.
- Bowonwatanuwong, C. and others. A randomized open label study to investigate abacavir (ABC) and lamivudine (3TC) as once-daily (QD) components of a triple-combination regimen (EPV40001). 1st IAS Conference. Abstract 4.
- Crabtree, P. Time running out for Salk-backed AIDS vaccine. *San Diego Union-Tribune*. June 2, 2002.
- Chen, Z. and others. HIV-1 mutants less susceptible to SCH-D, a novel small-molecule antagonist of CCR5. 9th CROI. Abstract 396-T.
- De Bethune, M. and others. TMC114, a highly potent protease inhibitor (PI) with an excellent profile against HIV variants highly resistant to current PIs. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago. December 16–19, 2001. Abstract F-1677.
- Deeks, S.G. and others. Delayed immunologic deterioration among patients who virologically fail protease inhibitor-based therapy. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco. January 30–February 2, 2000. Abstract 236.
- Eron, J. and others. A 14-day assessment of the safety, pharmacokinetics, and antiviral activity of T-1249, a peptide inhibitor of membrane fusion. 8th Conference on Retroviruses and Opportunistic Infections. Chicago. February 4–8, 2001. Abstract 14.
- Flexner, C. New drugs: attacking chemokine receptors. *The Hopkins HIV Report* (http://hopkins-aids.edu/publications/report/mar02_6.html). March 2002.
- Gazzard, B. and others. TMC125, a next-generation NNRTI, demonstrates high potency after 7 days therapy in treatment experienced HIV-1-infected individuals with phenotypic NNRTI resistance. 9th CROI. Abstract 4.
- Goebel, F.-D. and others. Phase I/II dose escalation and randomized withdrawal study with add-on azodicarboxamide in patients failing on current antiretroviral therapy. *AIDS* 15(1): 33–45. January 5, 2001.
- Haas, D.W. and others. Atazanavir plus saquinavir once daily favorably affects total cholesterol (TC), fasting triglyceride (TG), and fasting LDL cholesterol (LDL) profiles in patients failing prior therapy (trial A1424-009, week 48). 9th CROI. Abstract 42.
- Hendrix, C. and others. AMD-3100 CXCR4 receptor blocker fails to reduce HIV viral load by ≥ 1 log following 10-day continuous infusion. 9th CROI. Abstract 391-T.
- Huff, B. HAART version 2.0. *GMHC Treatment Issues* 16(3): 1–4. March 2002.
- Kessler, H. and others. Anti-HIV activity and tolerability of DAPD, a novel dioxolane guanine RT inhibitor: preliminary results of a phase I/II clinical trial. XIII International AIDS Conference. Durban, South Africa. July 9–14, 2000. Abstract TuPpA1146.
- Lalezari, J. and others. A week 48 assessment of a randomized, controlled, open-label phase II trial (T-20-206) evaluating 3 doses of T-20 in PI-experienced, NNRTI-naïve patients infected with HIV-1. 9th CROI. Abstract 418-W.
- Lee, N.S. and others. Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. *Nature Biotechnology* 20: 500–505. May 1, 2002.
- Lee, W. and others. *In vivo* and *in vitro* characterization of GS 7340, an isopropylalaninyl phenyl ester prodrug of tenofovir; selective intracellular activation of GS 7340 leads to preferential distribution in lymphatic tissues. 9th CROI. Abstract 384-T.
- Lin, P.-F. and others. Identification and characterization of a novel inhibitor of HIV-1 entry—II: mechanism of action. 9th CROI. Abstract 10.
- Liszewicz, J. and others. Novel dendritic cell-based topical DNA vaccination combined with STI-HAART induced immune control in macaques with AIDS. XIV International AIDS Conference. Barcelona, Spain. July 7–12, 2002. Abstract ThPpA2128.
- Margolis, D.M. and others. The addition of mycophenolate mofetil can induce decreases in HIV-1 RNA and intracellular deoxyguanosine triphosphate. 5th International Workshop on HIV Drug Resistance and Treatment Strategies. Scottsdale, Arizona. June 4–8, 2001. Abstract 16.
- Moss, R.B. and others. Predictors of HIV-specific lymphocyte proliferative immune responses induced by therapeutic vaccination. *Clinical and Experimental Immunology* 128(2): 359. May 2002.
- Moulard, M. and others. Broadly cross-reactive HIV-1-neutralizing human monoclonal Fab selected for binding to gp120-CD4-CCR5 complexes. *Proceedings of the National Academy of Sciences USA* 99(10): 6913–6918. May 14, 2002.
- Nagashima, K.A. and others. Human immunodeficiency virus type 1 entry inhibitors PRO 542 and T-20 are potentially synergistic in blocking virus–cell and cell–cell fusion. *The Journal of Infectious Diseases* 183(7): 1121–1125. April 1, 2001.
- Novina, C.D. and others. siRNA-directed inhibition of HIV-1 infection. *Nature Medicine* 8(7): 681–686. July 2002.
- Paterson, D.L. and others. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 133(1): 21–30. July 4, 2000.
- Polis, M.A. and others. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. *The Lancet* 358(9295): 1760–1765. November 24, 2001.
- Reynes, J. and others. SCH C: safety and antiviral effects of a CCR5 receptor antagonist in HIV-1-infected subjects. 9th CROI. Abstract 1.
- Roche Laboratories and Trimeris, Inc. Roche and Trimeris announce 24-week results from second pivotal study of HIV fusion inhibitor T-20. Press release. May 16, 2002.
- Roche Laboratories and Trimeris, Inc. Roche and Trimeris announce 24-week results from first phase III study of HIV fusion inhibitor T-20. Press release. April 18, 2002.
- Rousseau, F.S. and others. Prototype trial design for rapid dose selection of antiretroviral drugs: an example using emtricitabine (Coviracil). *Journal of Antimicrobial Chemotherapy* 48(4): 507–513. October 2001.
- Ruane, P. and others. Pharmacodynamic effects of zidovudine 600 mg once daily versus zidovudine 300 mg twice daily in therapy-naïve HIV-infected patients (COD20002). XIV IAC. Abstract LbPeB9020.
- Ruiz, N. and others. Study DPC 083-201: a phase II double-blind (DB) comparison of 3 once-daily doses of the NNRTI DPC 083 vs 600 mg efavirenz (EFV) in combination with 2 NRTIs in HIV anti-retroviral (ARV) treatment-naïve patients. 9th CROI. Abstract 7.
- Ruiz, N. and others. Study DPC 083-203, a phase II comparison of 100 and 200 mg once-daily DPC 083 and 2 NRTIs in patients failing a NNRTI-containing regimen. 9th CROI. Abstract 6.
- Russell, S. Molecular weapon may fight off HIV. *San Francisco Chronicle*. June 3, 2002.
- Sankatsing, S. and others. TMC125 monotherapy for 1 week results in a similar initial rate of decline of HIV-1 RNA as therapy with a 5-drug regimen. 9th CROI. Abstract 5.
- Sanne, I. and others. Comparative results (phase II 48-week): BMS-232632, stavudine, lamivudine as HAART for treatment-naïve HIV (+) patients (A1424-008). 41st ICAAC. Abstract I-667.