

ANTIRETROVIRAL UPDATE: NEWER INVESTIGATIONAL DRUGS

Characteristics of selected new drugs from established and novel classes of antiretrovirals were discussed at the Chicago course by Roy M. Gulick, MD, MPH.

As of mid-1999, 14 antiretroviral drugs have been approved for use in treating HIV-1 infection. A large number of newer, investigational drugs representing established and novel classes are at varying stages of development (Table 1). Some of these drugs may prove to provide partial remedies to limitations of current regimen options, including problems with adverse effects and tolerability, pharmacokinetic interactions, adherence, and resistance and cross-resistance. Dr Gulick described the characteristics of selected investigational drugs from each antiretroviral class: the nucleoside reverse transcriptase inhibitor (nRTI) emtricitabine, the nucleotide reverse transcriptase inhibitor (nRTI) adefovir, the nonnucleoside reverse transcriptase inhibitor (NNRTI) emivirine, the protease inhibitors amprenavir (recently approved) and lopinavir, and the fusion inhibitor pentafuside.

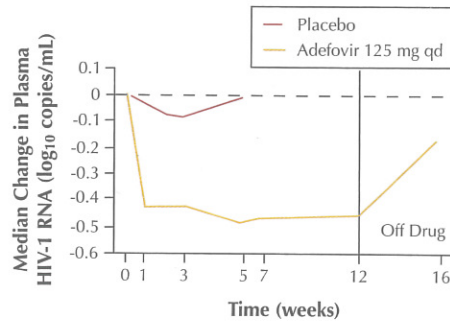


Figure 1. Median change in plasma HIV-1 RNA level during adefovir monotherapy. Adapted from Deeks SG, et al. *J Infect Dis.* 1997;176:1517-1523.

EMTRICITABINE (FTC)

The nRTI emtricitabine (FTC) exhibits anti-HIV-1 potency in vitro 4 to 10 times greater than the related drug lamivudine and also exhibits activity against hepatitis B virus. The proposed dosage of the drug is 200 mg once a day; didanosine is the only currently-approved nRTI routinely given on a once-daily schedule. Phase III

studies of emtricitabine are under way. Adverse effects have been uncommon, consisting primarily of gastrointestinal tract effects and headache. The drug is eliminated largely via renal mechanisms. Resistance in vitro is conferred by the reverse transcriptase M184V mutation associated with lamivudine resistance, indicating cross-resistance between the 2 drugs. In a Phase I dose-escalation study of emtricitabine, 200 mg once a day or twice a day exhibited a trend toward greater reduction of serum viral load, achieving maximal reductions of greater than 1.5 log. Data from a subsequent Phase II/III study indicate similar degrees of effect of once-daily dosing of 25, 100, or 200 mg emtricitabine and 150 mg twice a day of lamivudine.

ADEFOVIR DIPIVOXIL

The nRTI adefovir dipivoxil is in Phase III studies and studies in antiretroviral-experienced patients and currently is available through an expanded access program. Adefovir exhibits in vitro potency against HIV-1 (90% effective dose [ED₉₀] of 0.007-7 μM), as well as against cytomegalovirus and hepatitis B virus. The proposed dosage is 60 mg once a day; there are no food restrictions with usage. The drug undergoes renal excretion. Adverse effects include gastrointestinal tract effects, carnitine depletion, and proximal renal tubular dysfunction. In vitro resistance mutations have been detected at reverse transcriptase codons 70, 69, and 65. The emergence of mutations in vivo has been uncommon to date. Figure 1 shows degree of reduction in viral load in a Phase I study with an initial formulation equivalent to the current 120 mg dose. In a virologic substudy of a Phase II study in which adefovir was added to existing regimens, it was observed that a greater decrease in plasma HIV-1 RNA level (0.94 log) occurred in patients exhibiting the M184V lamivudine-associated resistance mutation than

TABLE 1. SELECTED INVESTIGATIONAL ANTIRETROVIRAL DRUGS

Class	Investigational Drugs
Nucleoside reverse transcriptase inhibitors	emtricitabine (FTC), lodenosine (FddA), BCH-10652 (dOTC), DAP/DXG
Nucleotide reverse transcriptase inhibitors	adefovir dipivoxil, PMPA
Nonnucleoside reverse transcriptase inhibitors	emivirine (MKC-422), AG1549 (S-1153), PNU-142721, DMP-961, DMP-963, GW420867X
Protease inhibitors	lopinavir (ABT-378), tipranavir, L-756, 423, BMS-232, 632, AG1776 (JE-2147), DMP-450, PD-178390
Fusion inhibitors	pentafuside (T-20), FP-21399, T-1249

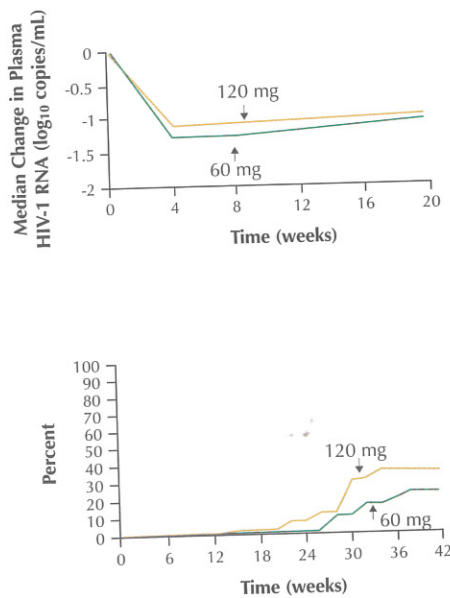


Figure 2. Top: Mean change in plasma HIV-1 RNA in patients receiving adefovir 120 or 60 mg plus nelfinavir and/or saquinavir soft-gel capsule. Bottom: Time to development of serum creatinine level at least 0.5 mg/dL above baseline according to adefovir dosage group ($P=0.05$). Courtesy of C Brosgart, MD, Gilead Sciences, Foster City, CA.

in those patients with wild-type virus (0.65 log). The decrease in viral load level was also greater in the setting of both lamivudine- and zidovudine-associated resistance than with zidovudine-associated resistance alone.

The proposed dosage of the drug has been decreased from 120 mg to 60 mg on the basis of data indicating comparable virologic effect when used in potent combination regimens and a potential reduction in incidence of proximal renal tubular dysfunction. Proximal renal tubular dysfunction associated with adefovir is characterized by delayed onset. In a Phase II study of the 120 mg dose, 1% of patients receiving adefovir developed the adverse effect by 24 weeks and 38% developed it by 100 weeks; the median time to onset was 28 to 32 weeks. The effect was largely reversible with drug discontinuation, with a median time to resolution of 8 to 12 weeks. In a study comparing the 60 and 120 mg doses in combination with nelfinavir and/or soft-gel saquinavir in protease inhibitor-naïve

patients, decreases in viral load were comparable in the 2 groups, and a reduced incidence of increases in serum creatinine of at least 0.5 mg/dL over 42 weeks was reported with the 60 mg dose (Figure 2). Given its apparent absence of cross-resistance with other drugs but relatively modest virologic effect and the concern over toxicity, adefovir may be best suited for use by antiretroviral-experienced patients with limited therapeutic options. It currently is being evaluated in a large number of studies of patients in whom protease inhibitors have failed.

EMIVIRINE (MKC-442)

The NNRTI emivirine (MKC-442), a uracil analogue that has the chemical structure of a nucleoside, is highly potent against HIV-1 in vitro (90% inhibitory concentration [IC_{90}] of 10-98 nM). The proposed dosage is 750 mg twice a day (no food restrictions), and the drug is metabolized primarily by the cytochrome P450 3A4/5 isoenzyme system and partially by the cytochrome P450 1A2 system. Penetration of the drug into the central nervous system has been observed in animal studies. The drug currently is in Phase II/III evaluation. Adverse effects have included nausea, headache, dizziness, diarrhea, and rash, the latter of which has been observed in approximately 10% of patients. Figure 3 shows the effect of emivirine monotherapy on viral load in a dose-escalation study, indicating a decrease of approximately 1.5

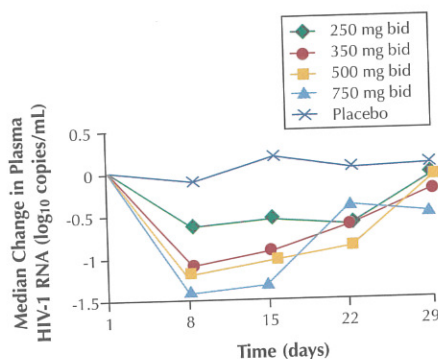


Figure 3. Median change in plasma HIV-1 RNA according to emivirine dosage. Courtesy of CP Moxham, PhD, Triangle Pharmaceuticals, Durham, NC.

log with the 750 mg twice-daily dosage. Genotypic analysis has indicated that resistance to emivirine is in some patients associated with mutation at reverse transcriptase K103N, suggesting the likelihood of cross-resistance with other NNRTIs. Patients taking MKC-442 who do not develop the K103N mutation, however, retain susceptibility to other NNRTIs. The optimal sequencing of NNRTIs requires further study.

AMPRENAVIR

The protease inhibitor amprenavir was recently approved for use at a dose of 1200

*Mutations associated
with resistance to
amprenavir
in vitro may differ
from those associated
with resistance to
other PIs*

mg (eight 150 mg capsules) twice a day. It is the first approved protease inhibitor that does not require food restrictions. The drug is metabolized via the cytochrome P450 3A4 isoenzyme system, and like indinavir and nelfinavir, it is a cytochrome P450 3A4 inducer. The most common adverse effects of amprenavir are rash and gastrointestinal tract effects. Mutations associated with resistance in vitro occur at the protease codons 50, 46, and 47, mutations that have generally not been described for other protease inhibitors; resistance mutations have also been detected at *gag* cleavage sites and described in the clinical setting.

Amprenavir is potent in vivo as a single drug, resulting in initial reductions in viral load of approximately 1.5 log; as with other single drugs, viral breakthrough occurs fairly rapidly after

Resistance mutations associated with lopinavir in vitro have not included the characteristic protease codon 82 mutation

this study show good antiviral activity of the regimen, suggesting at least the potential for replacement of failing amprenavir-containing regimens with indinavir-containing regimens.

A small open-label evaluation of the combination of amprenavir and the nRTI abacavir has suggested a durable effect on viral load of this double combination. Approximately 90% of patients exhibited reduction in plasma HIV-1 RNA to below 500 copies/mL, with approximately 80% exhibiting reductions to less than 50 copies/mL over the course of extended follow-up. These findings suggest that additional investigation of double combinations of potent drugs may be warranted.

ACTG 398 is a large study that should provide guidance on the potential role of amprenavir in regimens for patients in whom initial protease inhibitor therapy has failed. In this study 481 patients with more than 4 months of treatment with up to 3 protease inhibitors and plasma HIV-1 RNA levels of at least 1000 copies/mL are being treated with a regimen of amprenavir/abacavir/efavirenz/adefovir plus either saquinavir soft-gel capsule, indinavir, nelfinavir, or matching placebo. Treatment is to continue for at least 72 weeks. Results are

expected to provide some idea of the potential of such a regimen to exert antiretroviral activity in the context of prior protease inhibitor failure.

Findings suggest additional investigation of double combinations of potent drugs may be warranted

initiation of treatment (Figure 4). The AIDS Clinical Trials Group (ACTG) 347 study compared amprenavir alone with amprenavir/zidovudine/lamivudine. The amprenavir monotherapy arm was discontinued early due to viral breakthrough. A subset of patients from this arm has been enrolled in ACTG 373, which is evaluating the effects of a subsequent regimen of indinavir/nevirapine/stavudine/lamivudine. Preliminary results of

LOPINAVIR (ABT-378)

The protease inhibitor lopinavir (ABT-378) is a potent inhibitor of HIV-1 in vitro (IC₉₀ of 0.07 μM). The proposed dose of the drug is 400 mg twice a day to be administered with ritonavir 100 mg twice a day; like saquinavir, lopinavir levels are markedly increased in the presence of small concentrations of ritonavir due to their pharmacokinetic interaction. The drug will be formulated as capsules containing 133 mg of lopinavir and 33 mg of ritonavir, and should be taken with food. As with other protease inhibitors, the drug is metabolized by the cytochrome P450 3A4 isoenzyme system. Lopinavir currently is being evaluated in Phase III studies and studies in antiretroviral-experienced patients. The most common adverse effects have been abnormal stool consistency and diarrhea. The drug was designed with the aim of avoiding the characteristic protease inhibitor-associated resistance mutation at protease codon 82; resistance mutations in vitro have occurred first at codon 84 and then at other sites, as well as at gag cleavage sites. Figure 5 shows virologic response in a study of lopinavir/ritonavir

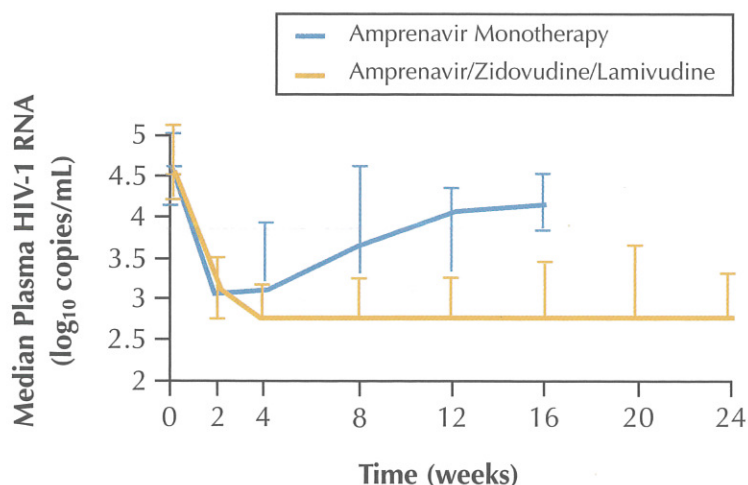


Figure 4. Median plasma HIV-1 RNA levels in patients receiving amprenavir alone or amprenavir/zidovudine/lamivudine in the AIDS Clinical Trials Group 347 study. The monotherapy arm was discontinued at 16 weeks due to viral breakthrough. Adapted from Murphy RL, et al. *J Infect Dis.* 1999;179:808-816.

twice a day plus stavudine and lamivudine. Suppression of viral load has been maintained over 6 to 9 months, with more than 90% of patients achieving HIV-1 RNA levels of less than 400 copies/mL.

An ongoing trial is evaluating the effects of lopinavir in 70 protease inhibitor-experienced patients. Patients have more than 12 weeks of protease inhibitor treatment and are nRTI-experienced, but are NNRTI-naive and have plasma HIV-1 RNA levels of 1000 to 100,000 copies/mL. Patients are receiving lopinavir/ritonavir 400 mg/100 or 200 mg twice a day, nevirapine, and a new nRTI. Recently reported results show that 84% of patients reduced their viral load levels to below 500 copies/mL at 24 weeks in an on-treatment analysis. Further follow-up results are forthcoming.

PENTAFUSIDE (T-20)

Pentafuside (T-20) is a viral fusion inhibitor that blocks interaction of the viral envelope gp41 with the target cell membrane during the fusion process. (Please see accompanying article, page 4). The drug exhibits an IC₅₀ of 1.7 ng/mL against HIV-1 in vitro. The proposed dosage of pentafuside currently is uncertain, although as a peptide the drug requires intravenous or subcutaneous ad-

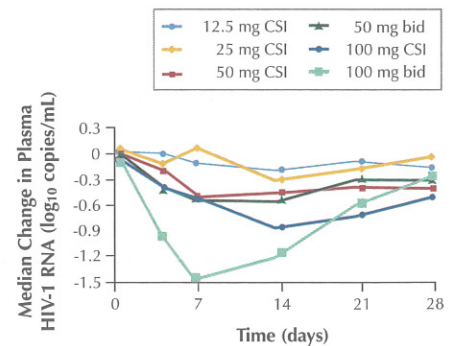
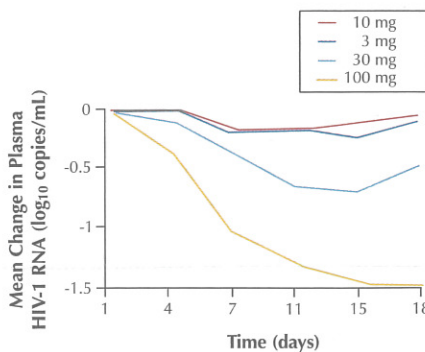


Figure 6. Left: Mean change in plasma HIV-1 RNA according to pentafuside intravenous dosage. Adapted from Kilby JM, et al. *Nat Med* 1998;4(11):1302–1307. Right: Median change in viral load according to continuous infusion (CSI) dosage or subcutaneous twice-daily dosing. Courtesy of J Lalezari, MD, San Francisco, CA.

ministration. Dose-escalation studies indicate a potent virologic effect at intravenous doses of 100 mg twice a day; subsequent study of continuous infusion and subcutaneous administration indicate a superior effect with subcutaneous administration of 100 mg twice a day (Figure 6). The route of metabolism of pentafuside currently is unclear, and adverse effects have not been well characterized, with some patients in early studies reporting fever or headache. Pentafuside-associated resistance mutations in the viral gp41 have been observed both in vitro and in vivo, ac-

counting for the rebound of viral load levels over a few weeks when the drug is used singly.

A second fusion inhibitor, T-1249, is in early clinical development. This peptide compound appears to demonstrate activity in vitro against pentafuside-resistant virus.

CONCLUSIONS

Much progress has been made in the treatment of HIV infection over the last few years by the development and widespread use of potent antiretroviral regimens. However, current regimens are limited by inconvenience, adverse effects, and resistance and cross-resistance. Newer drugs in development include new members of existing classes of drugs (nRTIs, NNRTIs, protease inhibitors) and new classes of drugs (nRTIs, fusion inhibitors). These newer drugs include those that can be dosed once or twice daily, with different adverse effect profiles and, in some cases, with demonstrated activity against resistant virus. Further progress in the field will stem from continued research and development of newer antiretroviral drugs.

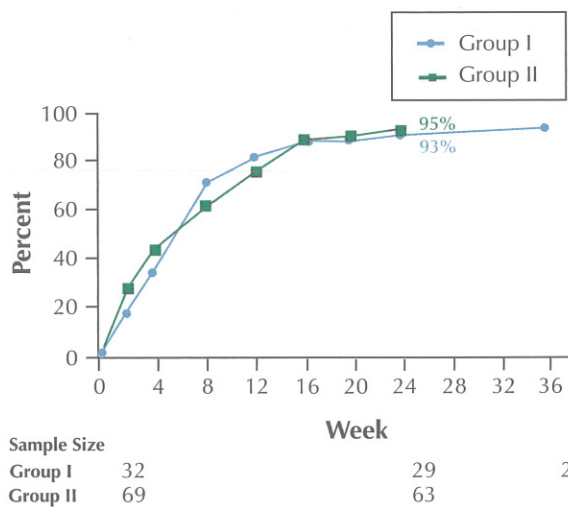


Figure 5. Proportion of patients receiving lopinavir/ritonavir twice a day plus stavudine and lamivudine with plasma HIV-1 RNA level less than 400 copies/mL. Courtesy of SC Brun, MD, Abbott Laboratories, Abbott Park, IL.

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