

Review article

Disease Management Constructing Optimal NRTI-Based Combinations: Past, Present, and Future

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Introduction

More than a decade ago, it became apparent that treatment of HIV infection with only 1 antiretroviral agent was associated with the rapid development of resistance.[1] Clinical trials conducted at that time showed that combining 2 antiretroviral agents improved virologic and immunologic responses, compared with use of a single agent. Accordingly, 2-drug combination antiretroviral therapy became the standard of care to maintain viral suppression and minimize the emergence of resistant strains and, thereby, reduce the risk of disease progression and death. Subsequent experience and clinical trials showed that 3-drug combinations were substantially more effective than 2-drug combinations. Recommended 3-drug regimens of highly-active antiretroviral therapy (HAART) generally include 2 nucleoside or nucleotide analog reverse transcriptase inhibitors (NRTIs), plus 1 nonnucleoside analog reverse transcriptase inhibitor (NNRTI) or 1 protease inhibitor (PI).

There are 8 NRTIs, 9 PIs, 3 NNRTIs, and 1 fusion inhibitor, as well as 4 coformulated NRTI combinations, currently approved for use in the United States. The most recent US Department of Health and Human Services (DHHS) guidelines for initial therapy in HIV-infected adults and adolescents include 91 potential HAART regimens: 70 combinations of 2 NRTIs plus a PI (of which 30 combinations use a PI boosted with low-dose ritonavir), 20 combinations of 2 NRTIs plus an NNRTI, and 1 triple NRTI.[2] Of the 90 potential combinations, 6 are designated "preferred" on the basis of trial results and expert opinion (Table 1), and 84 are designated "alternative." One triple-NRTI regimen is recommended only when an NNRTI- or

PI-based regimen cannot or should not be used as first-line therapy.

This article will discuss some of these choices, focusing on the role of NRTIs when constructing HIV regimens.

Historical Overview of Antiretroviral Therapy

The NRTIs were the first class of antiretroviral agents found to be efficacious against HIV. As early as 1986, treatment with the NRTI zidovudine was reported to reduce the number of opportunistic infections, increase the CD4+ cell count, and reduce mortality in patients with AIDS.[3] Zidovudine was introduced in the United States in 1987, followed by didanosine in 1991. Initial reports indicated that monotherapy with these NRTIs was effective in patients with HIV infection.[3-7] It was observed as

Table 1: Current "Preferred" Regimens for Initial Treatment of HIV Infection in Adults and Adolescents

DHHS Recommended Regimens	
NNRTI-based	EFV* + (ZDV or TDF) + (3TC or FTC)
PI-based	LPV/r + ZDV + (3TC or FTC)

*Efavirenz is not recommended for use in first trimester pregnancy or in women who want to conceive or are not adhering to an effective contraceptive regimen.

DHHS = US Department of Health and Human Services; PI = protease inhibitor; ZDV = zidovudine; 3TC = lamivudine; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate; NNRTI = nonnucleoside reverse transcriptase inhibitor

Adapted from Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. US Department of Health and Human Services. October 6, 2005

early as 1989,[8] and confirmed between 1992[9] and 1994,[1,10] that control of HIV replication was not maintained by single-drug therapy with zidovudine[11,12] or didanosine,[13] even when these drugs were used sequentially.

Treatment regimens combining 2 NRTIs to reduce the viral burden and delay the onset of drug resistance were the subject of discussion by 1992,[14,15] when a third NRTI, zalcitabine, was introduced for use only in combination with zidovudine. Subsequently, 2 large trials, Delta[16] and the AIDS Clinical Trials Group (ACTG) study 175,[17] showed that combination therapy with zidovudine plus didanosine or zalcitabine substantially reduced the risk of clinical progression or death, compared with zidovudine alone. The majority of patients in these studies had been treated with zidovudine prior to enrollment. Another trial showed that the combination of zidovudine plus didanosine or zalcitabine may be more effective than zidovudine alone in patients with little or no previous zidovudine therapy.[18] Three controlled trials demonstrated that the combination of zidovudine and lamivudine (3TC) an NRTI introduced in 1995 for use in combination with zidovudine provided greater and more sustained increases in CD4+ cell counts and decreases in viral load than did continued zidovudine monotherapy, when the combination was used in antiretroviral-naïve patients[19] or patients previously treated with zidovudine.[20,21] A fourth NRTI, stavudine, was introduced in 1994 for use in patients who no longer responded to, or who could not tolerate zidovudine, didanosine, or zalcitabine.

Following the introduction of the first PIs saquinavir and indinavir in mid-1990s, it became apparent that 3-drug combinations further improved the long-term immunologic and virologic effects of therapy.[22-24] This led to the construction of regimens with 3 or more antiretroviral drugs to increase and prolong HIV suppression. Founded on a large number of studies, the standard of care is now a combination of 3 drugs, typically 2 NRTIs plus either a PI or an NNRTI. One such study showed that the addition of RTV to 2 NRTIs lowered the risk of AIDS-related complications and prolonged survival.[23] Another study showed that the addition of the NNRTI nevirapine to a regimen of 2 NRTIs significantly increased the CD4+ cell count and lowered the mean titer of infectious HIV-1 in peripheral blood mononuclear cells.[22]

A sixth NRTI, abacavir, was approved in 1999, in combination with other antiretroviral agents, for the treatment of HIV infection. This approval was based primarily on the results of 2 studies, which demonstrated that abacavir/zidovudine/lamivudine reduced viral loads more effectively than zidovudine/lamivudine.[25] A seventh NRTI,

tenofovir disoproxil fumarate, was introduced in 2001 and was the first nucleotide agent approved for treatment of HIV infection. Nucleoside analogs must be converted to their triphosphate form in the cell by the enzymatic addition of 3 phosphates, whereas tenofovir contains its first phosphate, and requires 2 phosphorylation steps to become active. A 3-year efficacy and safety study showed that levels of viral suppression with tenofovir were comparable to those achieved with stavudine, when both agents were given in combination with lamivudine/efavirenz.[26] Another NRTI, emtricitabine, was approved in 2003 for the treatment of HIV infection in adults in combination with other antiretroviral agents. The chemical structure of emtricitabine is nearly identical to that of lamivudine, although emtricitabine has a somewhat longer intracellular half-life than lamivudine.[27] Due to the similarities of these NRTIs, much of the long safety and efficacy experience with lamivudine has been extrapolated to emtricitabine. A recent equivalence study showed that, in patients adequately suppressed with lamivudine plus either stavudine or zidovudine, those who switched from lamivudine to emtricitabine had comparable 48-week viral suppression compared with those who remained on lamivudine.[28]

A marked decline in the progression of HIV infection to AIDS and AIDS-related death began in 1996 following the increasingly widespread use of potent 3-drug antiretroviral combinations as components of HAART.[29-33] Despite this achievement, the large number of tablets and capsules and complicated dosing schedules necessary for early, triple-drug regimens led to problems with adherence. The introduction of zidovudine/lamivudine as a combined single tablet (*Combivir*, GlaxoSmithKline) in 1997 offered a simplified regimen and the possibility of improved drug adherence. The introduction of this coformulation set the stage for the dual-NRTI coformulations of tenofovir/emtricitabine (*Truvada*, Gilead Sciences) and abacavir/lamivudine (*Epzicom*, GlaxoSmithKline), both approved on August 2, 2004. Additionally, a triple combination of abacavir/zidovudine/lamivudine in a single tablet (*Trizivir*, GlaxoSmithKline) was approved in 2000.

Present Role of NRTIs in Combination Therapy

A major goal of HAART is to suppress plasma HIV RNA below detectable levels by combining 3 or more antiretroviral agents from 1 or more classes. The use of agents from different classes lessens the development of resistance.[34] However, antiretroviral regimens containing drugs from more than 2 classes are not routinely recommended for patients who are treatment naïve, because those in whom a 3-class regimen fails may become resistant to drugs in all 3 classes, leaving them with fewer options for subsequent therapy. A HAART regimen should have acceptable short- and long-term toxicity and must fit

the patient's comorbidity profile and lifestyle.[35] Currently recommended initial HAART regimens specify the use of 2 NRTIs and either an NNRTI or a PI.[2]

The rational selection of triple-drug regimens is based primarily on the results of clinical trials, but also on the potency and durability of response, drug toxicity, drug-drug interactions, potential for resistant mutation selection, impact on future treatment, and dosing convenience of the individual agents.[2] Although indirect comparisons of controlled trials of PI- vs NNRTI-based HAART had been made,[36] until the final results of ACTG study 384 were published in December 2003, the clinical effectiveness of PI- and NNRTI-based 3-drug combinations had not been compared directly in randomized controlled studies. Because zidovudine/lamivudine and stavudine/didanosine had been compared previously in clinical trials of 2-drug regimens and because of the favorable results observed in these trials,[37,38] these NRTI combinations have been frequently used in 3-drug regimens. NRTIs such as zidovudine, which was introduced almost 2 decades ago, continue to remain reliably effective when used in current combination regimens when patients are adherent.

The following provides an update on key studies of NRTIs in combination therapy.

Zidovudine/lamivudine vs Stavudine/didanosine

ACTG 384 was a large study designed to compare different combination regimens in previously untreated patients.[39,40] The NRTI backbones were zidovudine/lamivudine or stavudine/didanosine. The first part of this study examined treatment with one of four 3-drug regimens until virologic failure, at which point patients were switched to another 3-drug regimen that included none of the first 3 drugs.[39] The second part of this study compared these four 3-drug regimens with two 4-drug regimens.[40] Patients treated with a 3-drug combination received zidovudine/lamivudine or stavudine/didanosine plus the PI nelfinavir or the NNRTI efavirenz, whereas those treated with a 4-drug combination received one of these NRTI combinations plus nelfinavir/efavirenz. The results confirmed that the efficacy of antiretroviral drugs depends on how they are combined. The combination of stavudine/didanosine was inferior to that of zidovudine/lamivudine[41] and was more toxic.[39] Compared with the other 3-drug regimens, the regimen containing efavirenz/zidovudine/lamivudine as the first regimen delayed failure of the first regimen, and using this combination as the first or second regimen delayed failure of the second regimen.[39] In addition, there was no significant difference in time to failure between a single 4-drug regimen and 2 consecutive 3-drug regimens.[40] While the 4-drug regimens were effective, the simpler 3-drug regimen

of efavirenz/zidovudine/lamivudine emerged as the optimal choice for the initiation of therapy.

Zidovudine/lamivudine/lopinavir/ritonavir

Although there are currently no published studies evaluating the efficacy of the 3-drug combination of zidovudine/lamivudine and coformulated ritonavir-boosted lopinavir for initial HAART, the tolerability of this combination was assessed in the setting of postexposure prophylaxis and then retrospectively compared with the tolerability of zidovudine/lamivudine/nelfinavir.[42] The tolerability of zidovudine/lamivudine/lopinavir/ritonavir appeared significantly better than that of zidovudine/lamivudine/nelfinavir (side effects: 64% vs 85%, respectively; $P < .003$). Currently, the DHHS guidelines designated efavirenz and lopinavir/ritonavir both combined with a dual NRTI backbone as "preferred" regimens. A large trial comparing the efficacy of lopinavir/ritonavir with that of efavirenz after initial treatment with coformulated zidovudine/lamivudine in treatment-naive patients has completed enrollment.[43] Until results are available from this randomized trial, data remain limited. An open-label study compared outcomes in 97 patients who started therapy with efavirenz and lopinavir/ritonavir, and found similar clinical outcomes between these 2 regimens at 17 months.[44]

Zidovudine/lamivudine Plus Efavirenz or Indinavir

Several studies have evaluated the NRTI backbone of zidovudine/lamivudine combined with an NNRTI or an unboosted PI. The open-label DuPont 006 study assessed the NRTI backbone of zidovudine/lamivudine plus either efavirenz or indinavir, with a third arm of efavirenz/indinavir.[45] Efficacy was similar with the NNRTI-based regimen and the PI-based regimen, although the zidovudine/lamivudine/efavirenz arm performed significantly better than the PI-containing arms with respect to the primary outcome measure of percentage of patients with suppression of plasma HIV RNA to undetectable levels.

The Merck 035 study assessed the durability of zidovudine/lamivudine/indinavir.[46] Twenty of the 30 patients receiving this combination still had a viral load < 50 copies/mL after 3 years.

Triple-NRTI Therapy

A number of studies have demonstrated that the combination of lamivudine/abacavir plus zidovudine or stavudine provides a highly effective NRTI-backbone. CNA 3014 compared coformulated zidovudine/lamivudine plus a third NRTI, abacavir with zidovudine/lamivudine plus a PI, indinavir, in an open-label study.[47] At 48 weeks, the proportion of patients with HIV RNA < 400 copies/mL and < 50 copies/mL was 64% and 59%, respectively, in the abacavir group and 50% and 48%, respectively, in the

indinavir group. The higher level of adherence among patients in the abacavir group may explain the higher degree of virologic control among patients on this regimen.

ACTG 5095 compared coformulated zidovudine/lamivudine/abacavir with 2 different NNRTI-based regimens: zidovudine/lamivudine/efavirenz and coformulated zidovudine/lamivudine/abacavir plus efavirenz.[48] Coformulated zidovudine/lamivudine/abacavir alone was less effective than the efavirenz-based regimens with respect to change in viral load. The proportion of patients with HIV RNA < 200 copies/mL at 48 weeks was 74% in the zidovudine/lamivudine/abacavir arm, compared with 89% in the pooled efavirenz arms. Entry into the triple-NRTI arm was discontinued prematurely.

In the Clinically Significant Long-term Antiretroviral Sequential Sequencing (CLASS) Study, lamivudine/abacavir were used in combination with a third NRTI, stavudine: an NNRTI, efavirenz; or a ritonavir-boosted PI, amprenavir.[49] Each regimen had similar activity based on the proportion of subjects with plasma HIV-1 RNA levels < 400 copies/mL at week 48 (80% vs 83% vs 75%, respectively). However, lamivudine/abacavir/efavirenz was more efficacious than the other combinations in a secondary analysis using a cut-off of < 50 copies/mL (62% vs 76% vs 59%, respectively for the third NNRTI, the NNRTI, and the boosted PI regimens, respectively), and it was also superior at achieving levels of < 400 copies/mL among the subgroup of participants with a baseline viral load > 100,000 copies/mL (55% vs 77% vs 53%, respectively).

Other triple-NRTI combinations are less efficacious than lamivudine/abacavir/zidovudine or lamivudine/abacavir/stavudine. High rates of early virologic failure have recently been reported among previously untreated HIV-infected patients who received lamivudine/abacavir/tenofovir as initial therapy.[50] At week 8, 11 patients (58%) failed to experience at least a 2- \log_{10} decline from baseline or had a viral rebound after initial viral suppression. In another study, 20 of 21 patients treated with the combination of lamivudine/didanosine/tenofovir experienced virologic failure (< 2 \log_{10} reduction in plasma HIV RNA level) at 12 weeks.[51] In both studies, treatment was associated with the selection of the M184V/I mutation with or without the K65R mutation (see below).

Quadruple Regimens

When given as initial HAART, 4-drug regimens have shown promising preliminary results in recently completed studies as well as ongoing, comparative trials.[40,52]

Results of the studies summarized here indicate that regimens based on a dual-NRTI backbone plus an NNRTI or a PI can be used as initial therapy for HIV infection. A triple-NRTI regimen of abacavir/zidovudine/lamivudine can be considered as an alternative under certain circumstances disfavoring the use of the "one-plus-two" regimens based on a PI or NNRTI with 2 NRTIs.

NRTI Resistance

Viral mutations decrease the susceptibility of HIV to antiretroviral agents by the selection of resistant strains. Combination therapy can block this selection process because multiple drugs suppress viral replication more effectively than single agents.[34] Although now considered suboptimal, dual-NRTI regimens do provide a higher barrier to resistance than does single-NRTI therapy,[53] and studies of 2-drug combinations permit the assessment of viral mutations without the potentially confounding effect of a third or fourth agent.

NRTIs arrest the synthesis of viral DNA by reverse transcriptase.[34] Resistance is conferred by several mechanisms, including the loss of affinity of the NRTI for the HIV reverse transcriptase. For example, the M184V mutation involves the substitution of methionine with valine at position 184 of reverse transcriptase. While M184V is the main mutation that confers resistance to lamivudine, it also increases sensitivity to zidovudine by decreasing the efficiency of excision of the incorporated drug.[54] The K65R mutation, which involves the replacement of lysine by arginine at position 65, and the L74V mutation are particularly associated with abacavir- or tenofovir-containing containing regimens and appears to confer resistance to most NRTIs with the exception of zidovudine.[53] The L74V mutation is also associated with abacavir resistance, but does not generally confer broad cross-resistance to other NRTIs. The Q151M complex of mutations, which involves the replacement of glutamine by methionine at position 151, is most often associated with the failure of regimens containing stavudine and didanosine, but can confer resistance to all NRTIs.[53]

Resistance to NRTIs is also conferred by removal of thymidine analogs such as zidovudine and stavudine from the prematurely terminated DNA chain[34]; accordingly these are called thymidine analog mutations (TAMs), although cross-resistance to other NRTIs can occur. Studies of dual-NRTI regimens, including zidovudine/lamivudine and stavudine/lamivudine, have shown that zidovudine and stavudine are similar in their tendency to select for thymidine analog mutations.[55-60] Kuritzkes and colleagues[57] observed that resistance to zidovudine and stavudine emerged at comparable rates in patients treated with either of these NRTIs, although the zidovudine/lamivudine arm showed a greater tendency toward

development of 2 or more thymidine analog mutations. Sarmati and coworkers[58] found that zidovudine-like resistance mutations in zidovudine-naive patients appeared to correlate with virologic failure during long-term stavudine therapy; among 10 patients failing treatment with stavudine/lamivudine, 9 had zidovudine-like resistance mutations. Other investigators, however, have found a relatively low incidence of zidovudine-like resistance mutations among patients treated with stavudine.[59,60]

In the ACTG 384 study, subjects in 3-drug groups who began therapy with lamivudine/zidovudine/efavirenz had fewer treatment failures with resistance to NRTIs (7.7%) than did those who began therapy with didanosine/stavudine/efavirenz (16.1%, $P = .02$); in addition, each of the 3 groups that began therapy with didanosine/stavudine had a higher incidence of serious toxic effects than the groups that began therapy with lamivudine/zidovudine.[40] Figures 1, 2 and 3 show the proportion of patients who had regimen failure with resistance to study drugs, by treatment group.

The most frequent mutations conferring resistance to NRTIs were detected at position 184 (80%), which is associated with increased sensitivity to zidovudine; mutations conferring resistance occurred with a frequency of only 3% at position 65. There were relatively few first regimen failures during the study in the group that began therapy with lamivudine/zidovudine/efavirenz.

In a dose-escalating, in vitro study of tenofovir-based 2-drug combinations, tenofovir alone selected for K65R only, while abacavir alone selected for M184V followed by K65R and other mutations (Y115F, L74V).[61] The combination of tenofovir/abacavir selected for K65R followed by another mutation (Y115F), whereas the combination of tenofovir/lamivudine selected only for K65R. These results suggest that K65R is the major mutation selected by tenofovir alone or in combination with abacavir or lamivudine.

The dual-NRTI combinations of abacavir/lamivudine, abacavir/zidovudine, and lamivudine/zidovudine with or without nelfinavir were compared in HIV-infected children in the Pediatric European Network for Treatment of AIDS 5 study.[62] Plasma HIV RNA decreased by 2.6 \log_{10} copies/mL in the abacavir/lamivudine group, compared with 1.7 and 2.2 \log_{10} copies/mL in the lamivudine/zidovudine and abacavir/zidovudine groups, respectively. M184V and thymidine analog mutations were prevalent among children receiving lamivudine/zidovudine, while abacavir/zidovudine selected for thymidine analog mutations only, and abacavir/lamivudine selected for M184V, K65R, and other mutations (Y115F, L74V).[63]

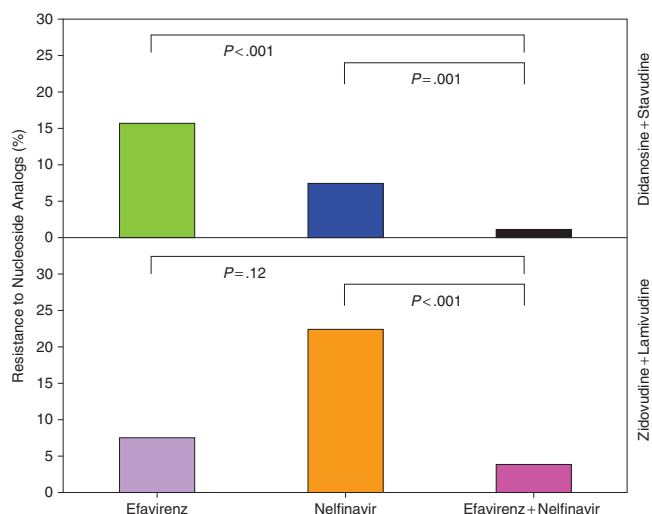


Figure 1
Percentage of subjects who had regimen failure with resistance to NRTIs according to Treatment Group. For subjects in groups 1 (initial therapy = didanosine/stavudine/efavirenz), 2 (initial therapy = didanosine/stavudine/nelfinavir), 3 (lamivudine/zidovudine/efavirenz), and 4 (lamivudine/zidovudine/nelfinavir), the bars show the cumulative percentage of subjects with drug resistance at the time of the first or second regimen failure; for subjects in groups 5 (initial therapy = didanosine/stavudine/efavirenz/nelfinavir ddI/d4T/EFV/NFV) and 6 (lamivudine/zidovudine/efavirenz/nelfinavir), the bars show the percentage of subjects with new drug-resistance mutations after the failure of their first regimen. Drug-resistance mutations were identified through the sequencing of the HIV-1 reverse transcriptase and protease of virus isolated from subjects with virologic failure or toxicity-related failure who had plasma HIV-1 RNA levels of at least 1000 copies/mL. From Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of 4-drug regimens and pairs of sequential 3-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003; 349: 2304-2315, with permission of the publisher, Massachusetts Medical Society.

In summary, these results indicate that treatment with zidovudine or stavudine plus lamivudine or emtricitabine allows the preservation of future treatment options because selection for M184V occurs first, is accompanied by the slow accumulation of thymidine analog mutations over a period of months after initial virologic failure, and rarely selects for K65R. In fact, zidovudine may actually prevent selection of K65R. In addition, the extensive resistance data available for NRTIs generally (and for older agents such as zidovudine, stavudine and lamivudine particularly) allow clinicians to anticipate outcomes and manage resistance more effectively.

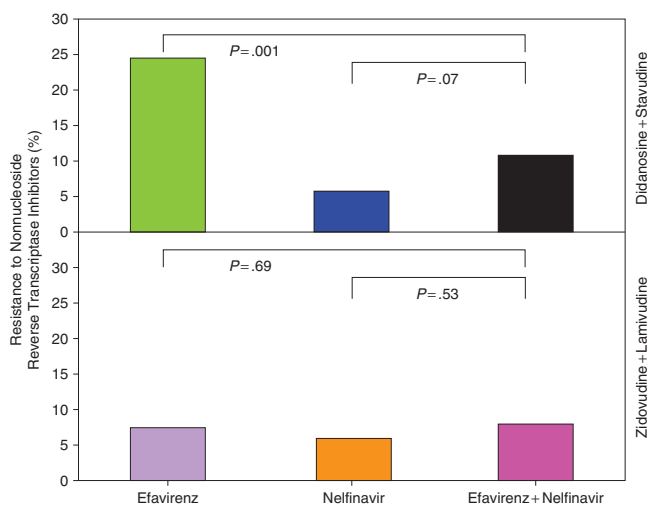


Figure 2
Percentage of subjects who had regimen failure with resistance to NRTIs according to Treatment Group.
 Percentage of subjects who had regimen failure with resistance to NNRTIs according to Treatment Group. For subjects in groups 1 (initial therapy = didanosine/stavudine/efavirenz), 2 (initial therapy = didanosine/stavudine/nelfinavir), 3 (lamivudine/zidovudine/efavirenz), and 4 (lamivudine/zidovudine/nelfinavir), the bars show the cumulative percentage of subjects with drug resistance at the time of the first or second regimen failure; for subjects in groups 5 (initial therapy = didanosine/stavudine/efavirenz/nelfinavir ddI/d4T/EFV/NFV) and 6 lamivudine/zidovudine/efavirenz/nelfinavir), the bars show the percentage of subjects with new drug-resistance mutations after the failure of their first regimen. Drug-resistance mutations were identified through the sequencing of the HIV-1 reverse transcriptase and protease of virus isolated from subjects with virologic failure or toxicity-related failure who had plasma HIV-1 RNA levels of at least 1000 copies/mL. From Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of 4-drug regimens and pairs of sequential 3-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003; 349: 23042315, with permission of the publisher, Massachusetts Medical Society.

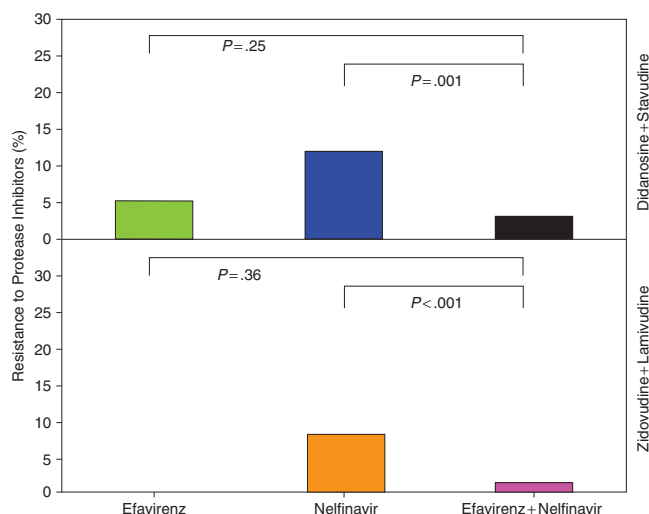


Figure 3
Percentage of subjects who had regimen failure with resistance to PIs according to Treatment Group.
 Percentage of subjects who had regimen failure with resistance to PIs according to Treatment Group. For subjects in groups 1 (initial therapy = didanosine/stavudine/efavirenz), 2 (initial therapy = didanosine/stavudine/nelfinavir), 3 (lamivudine/zidovudine/efavirenz), and 4 (lamivudine/zidovudine/nelfinavir), the bars show the cumulative percentage of subjects with drug resistance at the time of the first or second regimen failure; for subjects in groups 5 (initial therapy = didanosine/stavudine/efavirenz/nelfinavir ddI/d4T/EFV/NFV) and 6 lamivudine/zidovudine/efavirenz/nelfinavir), the bars show the percentage of subjects with new drug-resistance mutations after the failure of their first regimen. Drug-resistance mutations were identified through the sequencing of the HIV-1 reverse transcriptase and protease of virus isolated from subjects with virologic failure or toxicity-related failure who had plasma HIV-1 RNA levels of at least 1000 copies/mL. From Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of 4-drug regimens and pairs of sequential 3-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003; 349: 23042315, with permission of the publisher, Massachusetts Medical Society.

Metabolic Changes and Adverse Effects Associated With NRTI-Based Regimens

Most pharmacokinetic interactions between antiretrovirals are related to the hepatic cytochrome P450 (CYP450) enzyme system, which all NNRTIs and PIs can alter, thereby affecting drug metabolism and plasma levels.[64] NRTIs, unlike NNRTIs and PIs, are not metabolized by the CYP450 system and, with the exception of zidovudine and abacavir, undergo elimination through the renal, rather than hepatic route. Accordingly, there is little potential for interaction between NRTIs and either NNRTIs or PIs that could adversely alter the plasma concentrations of these agents. However, activity of NRTIs is dependent on the intracellular concentration of their

phosphorylated forms, and the effects of antiretrovirals or other medications on membrane transporters may lead to changes in intracellular levels.

Some adverse effects of HAART have been well described, such as the increased risk for lipoatrophy associated with thymidine analogs such as stavudine, and to a lesser extent, zidovudine. In one study, the incidence of clinical lipodystrophy (mainly lipoatrophy) was significantly greater among HIV-infected patients receiving stavudine/lamivudine/indinavir compared with those receiving zidovudine/lamivudine/indinavir.[65] Replacing stavudine with zidovudine or abacavir has been shown to improve stavudine-induced lipoatrophy while maintain-

Table 2: Selected Investigational Antiretroviral Drugs in Phase 23 Studies

Class	Agent	Manufacturer
NRTI	Alovidine (MIV-310)	Medivir
	Amdoxovir (DAPD)	RFS Pharmaceuticals
	AVX754	Avexa
	Elvucitabine (ACH-126)	Achillion
	Racivir (PSI 5004)	Pharmasset
	Reverset (D-D4FC)	Pharmasset
NNRTI	695634	GlaxoSmithKline
	Calanolide A	Sarawak MediChem
	DPC 083	Bristol-Myers Squibb
	Etravirine (TMC 125)	Tibotec
	MIV-150	Medivir
	TMC-278	Tibotec
PI	DPC-681	Bristol-Myers Squibb
	GW640385	GlaxoSmithKline
	L-756423	Merck
	RO0334649	Roche
	TMC-114	Tibotec
Fusion/Entry Inhibitor	AMD070	Anormed
	Aplaviroc*	GlaxoSmithKline
	BMS-488043	Bristol-Myers Squibb
	FP-21399	EMD Lexigen
	Maraviroc (UK 427)	Pfizer
	PRO 140	Progenics
	PRO 542	Progenics
	TNX-355	Tanox
Vicriviroc (SCH 417)	Schering	

NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor. Adapted from "2005 Antiretrovirals Pipeline," available at: <http://www.aidsinfonyc.org> (accessed December 8, 2005) and from the University of California at San Francisco Center for HIV Information, "FDA-Approved and Investigational Antiretrovirals," available at: <http://hivinsite.ucsf.edu/> (accessed December 6, 2005).

* Development halted October 2005.

ing HIV suppression.[66] In addition, switching HIV-infected patients from stavudine and/or PI-containing regimens to coformulated zidovudine/lamivudine plus abacavir was associated with objective evidence of limb fat sparing and fat restoration, while maintaining HIV suppression.[67] A combination of stavudine/lamivudine/efavirenz compared with tenofovir/lamivudine/efavirenz TDF found a higher rate of lipodystrophy in the stavudine/lamivudine/efavirenz (12% vs 1%).[68] Other potential adverse effects of antiretroviral drugs used in initial HAART regimens may necessitate careful patient monitoring. For example, a number of reports have linked renal tubular dysfunction and acute renal failure with tenofovir.[69-73]

Future Directions

Optimization of current regimens and the development of new antiretroviral agents should increase the benefits of HAART over time.

Adherence remains crucial to the long-term success of HAART. Regimens with once- or twice-daily dosing and regimens with fewer pills per day may improve adherence[74] and possibly long-term viral suppression.[75-77] The availability of simpler dosing regimens, aided by the combination of 2 or 3 antiretrovirals in a single pill, has improved adherence. With respect to combination therapy, the adherence benefit of newer, once-daily dosage formulations may be limited by the fact that other drugs in the HAART regimen still require more frequent dosing, or dosing at the same frequency but at different times secondary to food requirements or potential interactions. Furthermore, missing a once-daily dose may have a greater potential to result in suboptimal drug levels, compared with missing a single dose of more frequently administered formulations.[52]

New agents from existing antiretroviral classes, novel formulations of existing drugs, and antiretrovirals from new classes are becoming available. Many of these new options offer advantages in terms of convenience, and some retain antiviral activity against HIV strains that are resistant to other drugs.[34] Examples of such new therapy options are the PIs atazanavir (taken once daily) and fosamprenavir (taken once daily with ritonavir or twice daily with or without ritonavir), which were approved in 2003. The PI tipranavir (approved June 22, 2005), when administered with ritonavir, is active against HIV in some patients whose previous PI-based therapy has failed. Enfuvirtide, a fusion inhibitor, is an example of a new drug class offering activity against HIV resistant to other antiretroviral classes.[78,79] In addition, many promising new agents are on the horizon. Table 2 summarizes key investigational agents from existing antiretroviral classes, as

well as those from potentially novel drug classes, which are being actively investigated phase 2 or 3 studies.

Discussion

Initial antiretroviral therapy should consist of 3 agents, including 2 NRTIs/NtRTIs and a PI or an NNRTI. Use of such regimens is based on established durability, potency and efficacy, and well-characterized safety and resistance profiles. For some patients, the "preferred" regimens may not be appropriate, and alternatives, such as boosted and unboosted PI-based regimens, or triple-NRTI regimens that contain a thymidine analog (abacavir/lamivudine/zidovudine), can be considered. Although several novel regimen configurations, such as quadruple NRTIs, dual PIs, and NRTI-sparing regimens have been examined, none of these approaches has showed great promise.

Certain antiretroviral combinations should be avoided because of toxicity risks. These combinations include didanosine/stavudine and tenofovir/didanosine. In addition, efavirenz should not be used in pregnant women, women planning pregnancy, or sexually active women who are not adhering to a proven contraceptive. Triple-NRTI regimens that do not include zidovudine or stavudine should also be avoided, due to a high rate of early virologic failure and selection of resistance.

In addition to safety and efficacy concerns, different dual-NRTI backbones have unique resistance profiles that should be considered when making treatment decisions. Specifically, zidovudine plus either lamivudine or emtricitabine selects for M184V initially, and can subsequently select for thymidine analog mutations; tenofovir plus either lamivudine or emtricitabine frequently selects for M184V, and sometimes selects for M184V and K65R; abacavir plus either lamivudine or emtricitabine frequently selects for M184V and infrequently selects for M184V and L74V. These mutational patterns should inform the selection of initial and subsequent therapies. In addition to these considerations, the tactical sequencing of certain combinations may avoid class resistance and preserve future treatment options.

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