

## Perspective

# Nucleoside Analogue Reverse Transcriptase Inhibitor Options: A Re-examination of the Class

The main options for dual nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (nRTIs) as a component of initial antiretroviral therapy regimens are tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine as fixed-dose combinations. Resistance to nRTIs can limit usefulness of many of the drugs in the class. Investigation of triple nRTI regimens has shown that zidovudine/lamivudine/abacavir does not provide benefits compared with dual nRTIs plus efavirenz and that others (tenofovir/lamivudine/abacavir and didanosine/lamivudine/abacavir) are associated with very high virologic failure rates. Further, 4-nRTI regimens are under investigation. The article summarizes a presentation on nRTIs made by Scott M. Hammer, MD, at the International AIDS Society–USA course in New York in March 2006. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).

## Dual nRTIs in Initial Treatment

The audience at the International AIDS Society–USA course in New York in March 2006 was posed the following question: When initiating therapy in an antiretroviral therapy-naïve person with no other illnesses, and with normal laboratory results and drug-susceptible virus, which of the following dual nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) components (to be combined with nonnucleoside reverse transcriptase inhibitors [NNRTIs] or a protease inhibitor [PI]) do you choose:

- (1) zidovudine/lamivudine as a fixed-dose combination (FDC)
- (2) abacavir/lamivudine FDC
- (3) tenofovir/lamivudine
- (4) tenofovir/ didanosine
- (5) tenofovir/emtricitabine FDC
- (6) stavudine/didanosine
- (7) abacavir/tenofovir
- (8) zidovudine/didanosine

The majority of audience responders selected tenofovir/emtricitabine as an FDC (57%) and most of the remainder (28%) selected zidovudine/lamivudine, with these choices being fairly representative of current use patterns in US treatment centers. The use of tenofovir/emtricitabine as a compo-

nent of initial treatment has been partly motivated by results of the Gilead 934 trial (Gallant et al, *N Engl J Med*, 2006). The trial showed that tenofovir/emtricitabine/efavirenz (n = 244) was associated with a significantly greater rate of reduction of plasma HIV RNA level to below 400 copies/mL at 48 weeks than zidovudine/lamivudine/efavirenz (n = 243; 84% vs 73%, respectively,  $P = .002$ ).

Findings of interest with regard to resistance in this trial included the absence of the characteristic K65R tenofovir-associated resistance muta-

tion in the tenofovir/emtricitabine group. It is also of interest that the characteristic M184V/I lamivudine-associated resistance mutation, which also occurs with emtricitabine, was less common in the tenofovir/emtricitabine group, adding to other observations that there is a lower frequency of M184V mutations with emtricitabine versus lamivudine in the setting of early virologic failure. It is very likely that the difference in virologic outcome with the 2 regimens is not related to any difference in intrinsic potency, but rather to better tolerability of the tenofovir/emtricitabine/efavirenz regimen, resulting in a smaller proportion of patients being discontinued from study treatment due to adverse events.

Discontinuation due to adverse events occurred in 4% of the tenofovir/emtricitabine arm versus 9% of the zidovudine/lamivudine arm, with anemia alone resulting in discontinuation of 6% of patients in the zidovudine/lamivudine arm. A nonrandomized substudy of this trial also showed greater loss of limb fat in the zidovudine/lamivudine group.

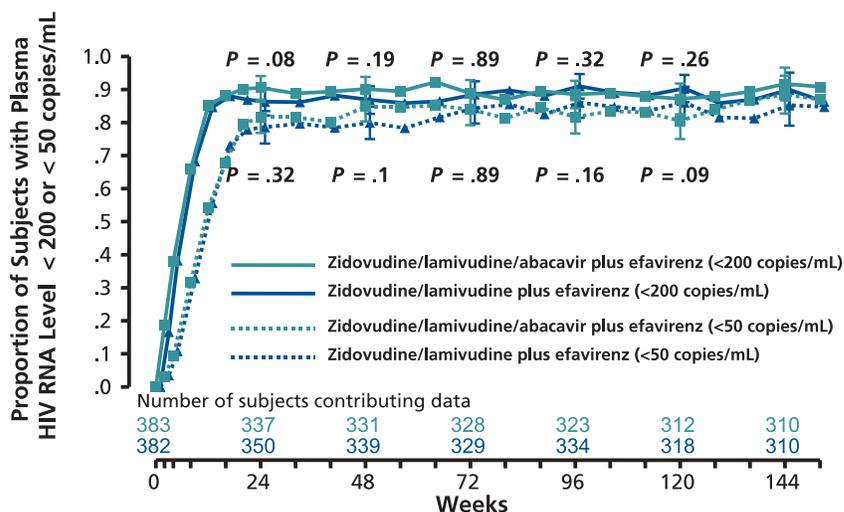


Figure 1. Proportions of patients with suppression of plasma HIV RNA level to less than 200 copies/mL and less than 50 copies/mL by treatment on intent-to-treat analysis in ACTG A5095. Adapted from Gulick et al, *JAMA*, 2006.

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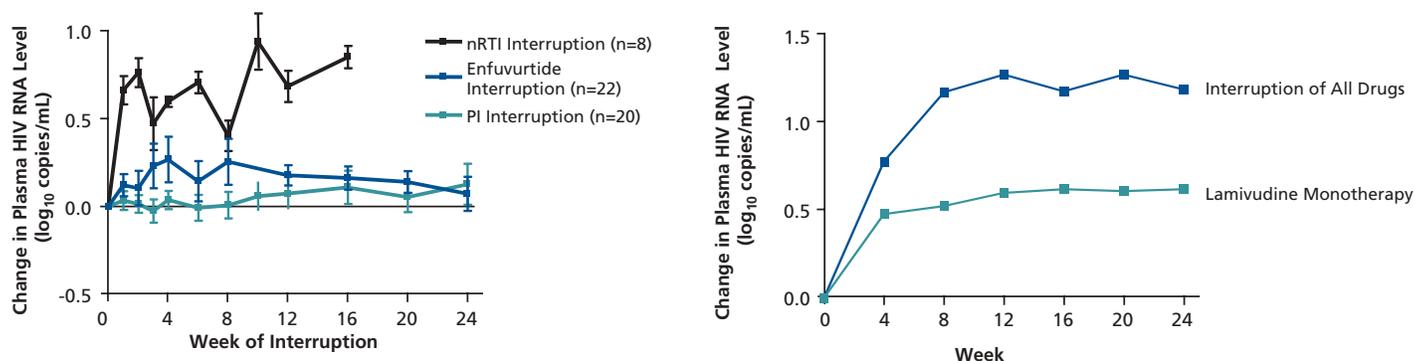


Figure 2. Effect of partial treatment interruptions (n=53) on viral load in patients with resistance to interrupted drugs (left). Adapted from Deeks et al, *J Infect Dis*, 2005. Complete treatment interruption vs continuation of lamivudine alone in patients (n=50) with multi-drug resistant virus (right). Adapted from Castagna et al, *AIDS*, 2006. nRTI indicates nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; PI, protease inhibitor.

### nRTI Resistance

Resistance mutations selected by nRTIs are listed in the International AIDS Society–USA Drug Resistance Mutations summary (Johnson et al, *Top HIV Med*, 2006). There is a high degree of cross-resistance within the nRTI class. For example, the K65R mutation is associated with cross-resistance among all the current nRTIs except zidovudine, and the thymidine analogue-associated mutations (TAMs) associated with zidovudine resistance, the codon 69-insertion complex, and the codon 151-complex can each confer cross-class resistance.

There are 2 principal mechanisms of nRTI resistance, and these mechanisms can interact to further alter susceptibility patterns (Clavel and Hance, *N Engl J Med*, 2004). In brief, nRTI resistance can occur via mutations in reverse transcriptase that interfere with the incorporation of the active nucleoside analogue form into the growing DNA; such mutations include

the M184V or I and K65R mutations. Resistance can also occur via adenosine triphosphate (ATP)-mediated excision of the anti-retroviral nucleoside that would otherwise terminate elongation of the viral DNA chain. TAMs permit ATP to bind to reverse transcriptase, where the ATP molecule can excise the incorporated nucleoside analogue from the viral DNA. As noted in Table 1, the presence of TAMs can antagonize the K65R mutation, whereas the presence of M184V or K65R mutations, which result in decreased analogue incorporation, results in reduced zidovudine monophosphate excision and reduced zidovudine resistance.

### Other Distinguishing Features of Dual nRTIs

Table 2 lists some defining characteristics of 3 commonly used dual nRTI options for combination with a PI or NNRTI in initial treatment. With regard

to the inclusion of zidovudine/lamivudine given the results of Gilead 934, the combination continues to be widely used on the basis of individual choice and on the strength of the wealth of experience in using the combination. Advantageous features of the 3 combinations listed include the fact that each is available as an FDC. The tenofovir/emtricitabine combination is active against hepatitis B virus, providing an advantage in coinfecting patients.

There has been concern about cumulative renal toxicity with tenofovir, especially given the serious toxicity observed with its related forerunner adefovir when given at high doses. Although serious renal toxicity concerns with tenofovir have not been raised by clinical trial data, there have been reports of tenofovir-related renal dysfunction in clinical experience and in Investigational New Drug (IND) safety reports. It is now recommended that calculated creatinine clearance and urinalysis results, as well as serum-creatinine level, be obtained at baseline in any patient starting tenofovir. In addition to decreased renal function at baseline, risk factors for renal dysfunction in patients receiving tenofovir include diabetes and lower CD4+ cell count.

With regard to nRTI-associated mitochondrial toxicity, the results of a recent study in a transgenic mouse model in cardiac tissue showed mitochondrial damage with zidovudine and stavudine and not with lamivu-

Table 1. Mechanisms of nRTI Resistance

TAMs: M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N	M184V	K65R
Confer zidovudine resistance via zidovudine monophosphate excision	Confers lamivudine resistance via decreased lamivudine triphosphate incorporation	Confers nonzidovudine nRTI resistance via decreased analogue incorporation
Antagonize K65R	Decreases zidovudine resistance via decreased zidovudine monophosphate excision	Decreases zidovudine resistance via decreased zidovudine-monophosphate excision

nRTI indicates nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; TAMs, thymidine analogue-associated mutations.

dine (Lewis et al, *AIDS*, 2006). The deoxynucleotide-carrier molecule that is responsible for normal transportation of nucleotide triphosphates into mitochondria was overexpressed in the mouse model, resulting in reduplication of mitochondrial cristae. The addition of zidovudine or stavudine resulted in loss of cristae, amorphous deposits, and destruction of the mitochondria, whereas no such damage was observed when lamivudine was added. These findings indicate that selective transport of zidovudine and stavudine triphosphates into the mitochondria may be responsible for the greater toxicity observed with these 2 nRTIs. Abacavir has been discontinued in 5% to 8% of patients because of hypersensitivity in clinical trials. The hypersensitivity reaction is associated with the human leukocyte antigen (HLA)-B5701 haplotype.

### Triple or Quadruple nRTIs?

Available data do not indicate that use of triple nRTIs is a beneficial strategy for initial treatment. The results of AIDS Clinical Trials Group (ACTG) A5095 showed that the combination of zidovudine/lamivudine/abacavir was inferior to dual-nRTI-plus-efavirenz regimens. However, the zidovudine/lamivudine/abacavir regimen is still considered an alternative in such settings as intolerance of or resistance to PIs or NNRTIs. The trial also showed no difference in virologic response between the regimens of zidovudine/lamivudine/abacavir plus efavirenz and zidovudine/lamivudine plus efavirenz, with no differences being observed in proportions of patients with suppression of plasma HIV RNA level to less than 200 copies/mL or less than 50 copies/mL (Figure 1) or time to first virologic failure among all patients or among those with baseline plasma HIV RNA level above or below 100,000 copies/mL (Gulick et al, *JAMA*, 2006).

Other studies have shown very high virologic failure rates (eg, 50% to 90%) with the triple nRTI regimens of tenofovir/lamivudine/abacavir and didanosine/lamivudine/abacavir. These regimens should not be used.

The high virologic failure rates are not related to such factors as antagonism at the reverse transcriptase activity level, pharmacokinetic interactions affecting serum drug levels, or interference in intracellular phosphorylation of 1 or more of the nRTIs. Rather, failure is related to a low genetic barrier to resistance and increased likelihood of “convergent” resistance involving mutations to the component drugs, with the mechanism appearing to be lack of uniform distribution of the different drugs to target cells. This finding emphasizes the importance of achieving rapid, profound suppression of viral replication with drug combinations and of ascertaining such an effect in vivo. A study of the evolution of the M184V and K65R mutations in patients receiving tenofovir/lamivudine/abacavir in the TONUS trial used both bulk sequencing and clonal sequencing to detect minor variants in the viral population (Delaunay et al, *J Virol*, 2005). The study showed that: (1) M184V evolves more quickly than K65R; (2) the 2 mutations first appear on separate viral genomes on clonal analysis; and (3) the mutations converge on the same genomes over time. The findings emphasize that bulk sequencing cannot be relied upon to provide a complete picture of viral resistance, with minor variant detection being essential to understanding the dynamics of resistance mutation evolution within the total viral population.

lution within the total viral population.

The potential use of quadruple nRTI regimens remains under investigation. A recent small study comparing the quadruple nRTI regimen of zidovudine/lamivudine/abacavir/tenofovir with zidovudine/lamivudine/efavirenz showed similar rates of viral suppression to less than 50 copies/mL at 48 weeks in intent-to-treat analysis (67% vs 68%) and in on-treatment analysis (100% vs 98%; Moyle et al, *Antivir Ther*, 2006).

### Residual Activity of nRTIs in the Context of Resistance: Treatment Interruption Studies

Recent findings on the strategy of structured treatment interruption (STI) of antiretroviral therapy are reviewed in the contribution by Dr Benson in this issue. In brief, STIs should not be part of antiretroviral therapy strategies in most settings according to currently available data.

Data from studies of nRTI interruption indicate that the agents possess residual activity in vivo despite the presence of nRTI resistance mutations, supporting the rationale for continuing treatment with or recycling these agents at later stages of treatment when full viral suppression cannot be achieved with available options.

For example, as shown in Figure 2,

**Table 2. Characteristics of Recommended Dual nRTI Options in Initial Antiretroviral Therapy**

Regimen	Features	Differential toxicity concerns	Resistance mutations
Tenofovir/emtricitabine	FDC, once daily Both drugs active against HBV	Renal dysfunction — increased risk with diabetes, lower CD4+ cell count, or decreased renal function at baseline	M184V, K65R
Zidovudine/lamivudine	FDC, twice daily	Anemia, mitochondrial dysfunction	M184V, TAMs
Abacavir/lamivudine	FDC, once daily	Hypersensitivity reaction (HLA-B5701)	M184V, K65R

FDC indicates fixed-dose combination; HBV, hepatitis B virus; HLA, human leukocyte antigen; nRTI, nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; TAMs, thymidine analogue-associated mutations.

cessation of nRTI treatment in the setting of nRTI resistance nevertheless resulted in a marked increase in viral load, whereas discontinuation of the entry inhibitor enfuvirtide or PI treatment in the context of resistance had little effect on viral load.

As also shown in Figure 2, the continuation of lamivudine alone while stopping all other drugs in patients with resistance including the M184V lamivudine resistance mutation nevertheless resulted in a markedly smaller increase in viral load than did the stopping of all drugs, likely reflecting residual antiviral activity or a viral fitness defect conferred by the M184V mutation.

## Conclusion

The leading dual nRTI options as components of NNRTI- or PI-based regimens (in the absence of drug resistance) are tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine as FDCs. Triple nRTI regimens are not recommended, but zidovudine/lamivudine/abacavir can be considered in select circumstances and zidovudine/lamivudine/tenofovir is under study. The observation of very high virologic failure rates with some triple nRTI combinations underscores the need to understand the complexity of in vivo evolution of resistance. Quadruple nRTI regimens remain experimental.

*Presented by Dr Hammer in March 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Hammer in October 2006.*

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## Suggested Reading

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