

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

The Choice of the Nucleoside Backbone in Initial Therapy

By Joel E. Gallant, M.D., M.P.H.

The recent approval of two fixed-dose coformulated nucleoside analog reverse transcriptase inhibitor (NRTI) combinations, *Truvada* (tenofovir DF + emtricitabine) and *Epzicom* (abacavir + lamivudine), has probably succeeded in narrowing rather than expanding options for initial therapy in treatment-naïve individuals. There is now little reason to start therapy with an NRTI backbone other than *Combivir* or one of these two newer fixed dose combinations (FDCs). This article will discuss the pros and cons of these three FDCs in patients starting therapy for the first time.

Combivir

Efficacy: The combination of zidovudine (AZT) and lamivudine (3TC) has been a gold standard now for many years, with a wealth of clinical data and clinical experience supporting its use. A review of the multiple clinical trials demonstrating the efficacy of this combination is beyond the scope of this review, but it has been studied in combination with multiple third agents, demonstrating efficacy, durability, and safety.

Pharmacology: 3TC is now approved for once-daily administration, but AZT has a relatively short intracellular life, which requires that *Combivir* be administered twice a day. There are no significant interactions involving AZT or 3TC.

Convenience: For many years, *Combivir*, the first coformulated NRTI combination, was the most convenient of the NRTI backbones. This has changed, however, with the approval of *Truvada*

and *Epzicom*, which are both dosed with a single tablet once a day without food restrictions. *Combivir* is taken as a single tablet twice a day, and while there are no actual food restrictions, many patients find AZT difficult to take on an empty stomach.

Tolerability: *Combivir* is not as well tolerated as *Truvada* or *Epzicom*, especially over the short-term. In the CNA30024 trial, comparing ABC + 3TC vs AZT/3TC, both given in combination with efavirenz (EFV) [DeJesus E, et al. Abstract H-446, 43rd ICAAC, Chicago 2003], patients in the AZT arm experienced more nausea, vomiting, fatigue and anemia than those taking abacavir (ABC), while not surprisingly, those taking ABC were more likely to develop hypersensitivity reactions. More recently, Gilead Sciences presented preliminary 24-weeks results from the GS 934 study comparing AZT/3TC vs tenofovir DF (TDF) + emtricitabine (FTC), both given in combination with EFV, in 487 treatment-naïve patients [Gazzard B, et al. Abstract H-1137C, 44th ICAAC, Washington, DC, 2004]. By an intent-to-treat analysis, 88% of those in the TDF/FTC arm achieved an HIV RNA <400 c/mL compared to 80% in the AZT/3TC arm. This difference was due to a higher rate of adverse events in the AZT/3TC arm: 9% discontinued the study due to adverse events, compared to 3% in the TDF/FTC arm (P=0.01), and grade 3/4 adverse events were experienced by 15% and 9%, respectively. Of course, these differences are more relevant to patients starting therapy than to those who have



"Museum of Industry, Baltimore"
photograph by Joel Meneses

been taking and tolerating a *Combivir*-based regimen for a long time. Nevertheless, it is not uncommon for patients who appear to be tolerating AZT to report an improvement in energy level or a decrease in low-level malaise after discontinuing it or switching to another NRTI.

Toxicity: *Combivir* also has more long-term toxicity than the other two FDCs. In addition to causing macrocytic anemia and leukopenia, AZT is associated with mitochondrial toxicity, though to a lesser degree than stavudine (d4T). This was most clearly demonstrated in ACTG 5005, a substudy of ACTG 384, which compared AZT/3TC vs didanosine (ddI) + stavudine (d4T), given in combination with EFV, nelfinavir (NFV), or both. In the 156 patients involved in the substudy, a progressive loss of limb fat was apparent in AZT/3TC-treated patients, though it was delayed compared to those taking ddI + d4T [Dube M, et al. Abstract 27, 4th Lipodystrophy Workshop, 2002]. Lactic acidosis and hyperlactatemia can

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also occur in patients taking AZT. Skeletal muscle myopathy and cardiomyopathy are specifically associated with AZT, though they were seen more frequently during the late 1980's, when AZT was used at much higher doses.

Resistance: Resistance patterns with *Combivir* failure differ significantly from those seen with either of the other FDCs. Patients failing a *Combivir*-based regimen typically develop the M184V mutation first, which causes high-level 3TC resistance but which also helps to increase AZT susceptibility and delay the emergence of thymidine analog mutations (TAMs). With continued therapy in the setting of viral replication, TAMs will eventually develop, though they occur gradually and sequentially. The degree of resistance to AZT and of cross-resistance to other NRTIs will depend on both the number of TAMs that emerge and the TAM pathway that the virus follows. The 41L/210W/215Y is associated with greater NRTI resistance compared to the 67N/70R/219 pathway. Neither the K65R nor the L74V mutation is likely to occur in patients taking *Combivir*, even when it is combined with TDF or ABC, as the presence of AZT typically prevents these mutations from emerging. It has been argued that AZT should be included in ABC/3TC- or TDF/FTC-containing regimens to prevent emergence of these mutations, which can occur more rapidly than TAMs and cause varying degrees of NRTI cross-resistance. However, this would add needless cost, dosing complexity, and toxicity to regimens that are highly potent, convenient, and well tolerated, in order to prevent resistance in the relatively small proportion of those who fail them.

Epzicom

Efficacy: The combination of twice-

daily ABC + 3TC has been studied as an NRTI backbone in a number of trials using a variety of 3rd agents, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), boosted and unboosted protease inhibitors (PIs), and other NRTIs. It has been compared head-to-head with AZT/3TC in the CNA30024 trial, discussed above, demonstrating not only better tolerability but also a better CD4 response to therapy. The latter could not be explained solely on the basis of AZT-associated bone marrow suppression, since the rise in CD4 percent was also greater in the ABC-containing arm. Once-daily ABC + 3TC has been compared with twice-daily ABC + 3TC (both in combination with EFV) in the ZODIAC trial, and both arms were similar with respect to virologic suppression and CD4 response [Gazzard B, et al. Abstract H-1722b, 43rd ICAAC, Chicago, 2003].

Pharmacology: Both ABC and 3TC are approved by the FDA for once-daily administration. The intracellular half-life of carbovir triphosphate, the active metabolite of ABC, has ranged from 12 to 20 hours in various studies [Pillero P, et al. Abstract A-1797, 43rd ICAAC, Chicago 2003; Hawkins T, et al. Abstract 2.4, 5th International Workshop of Clinical Pharmacology of HIV Therapy, Rome, 2004], and clinical trials have supported once-daily dosing as well [see ZODIAC trial discussed above]. The intracellular half-life of 3TC is similar to that of ABC. There are no significant drug interactions involving ABC or 3TC.

Convenience: *Epzicom* is taken as a single pill given once a day without food restrictions.

Tolerability: *Epzicom* is well tolerated. It is associated with fewer short-term side effects than *Combivir*. The most important side effect is the ABC

hypersensitivity reaction (HSR), which occurs in 8% of patients taking ABC, according to the most recent labeling information. This reaction typically occurs during the first few weeks of therapy and is characterized by progressively severe systemic symptoms, typically including fever, malaise, myalgias, and other flu-like symptoms. Patients may also experience a rash, gastrointestinal symptoms, and respiratory symptoms. The symptoms typically get worse with each dose and resolve rapidly with discontinuation of the drug. Patients who are suspected of having had an ABC HSR should never be given ABC again in any form (*Ziagen*, *Trizivir*, or *Epzicom*), as rechallenge has been associated with severe and even fatal reactions.

Toxicity: Neither ABC nor 3TC is thought to cause significant long-term toxicity, and neither has been associated with mitochondrial toxicity in *in vitro* studies or clinical trials. In fact, a gradual increase in limb fat has been observed in patients switching from d4T or AZT to ABC in the Mitox study, which makes it unlikely that fat loss would occur as a result of this drug [Martin A, et al. Abstract 16, 5th International Workshop on Adverse Drug Reactions and Lipodystrophy, 2003].

Resistance: Patients failing an ABC/3TC-containing regimen that does not include a thymidine analog typically develop the M184V mutation first, which causes high-level resistance to 3TC and a modest decrease in susceptibility to ABC. M184V may be followed quickly by an ABC-selected mutation. ABC can select for either K65R or L74V, but in the ZODIAC trial, the latter was far more common. L74V causes decreased susceptibility to ABC and didanosine (ddI), but susceptibility to TDF and AZT is retained or even increased. K65R causes



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decreased susceptibility to TDF, ddI, and ABC, and retained or increased susceptibility to AZT.

Truvada

Efficacy: The combination of TDF + FTC has not been extensively studied. It was used as the NRTI backbone in a comparison of once- vs twice-daily lopinavir/ritonavir (LPV/r) [Gathe J, et al. Abstract 570, 11th CROI, San Francisco, 2004]. Both arms performed well at 48 weeks, and there was no significant NRTI toxicity, despite the fact that tenofovir levels are increased

when TDF is coadministered with LPV/r. TDF + FTC has also been compared with AZT/3TC (in combination with EFV) in the GS 934 study (see “*Combivir*,” p 1) and was associated with improved efficacy at 24 weeks because of greater discontinuation due to adverse events in the AZT/3TC arm. The approval of *Truvada* was based primarily on extrapolations from data on the combination of TDF + 3TC and on the apparent similarities between 3TC and FTC with respect to tolerability, toxicity, resistance, and efficacy. GS 903 was a

large, 3-year, randomized, double-blind, placebo-controlled trial comparing TDF + 3TC vs d4T + 3TC, both given in combination with EFV [Gallant JE, et al. *JAMA* 2004;292:192-201]. Both regimens performed extremely well from a virologic and immunologic standpoint, but patients in the TDF + 3TC arm experienced less neuropathy, hyperlipidemia, and investigator-defined lipodystrophy than those in the d4T + 3TC arm. FTC appeared to be more potent than 3TC in early

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monotherapy studies, but it is not clear whether this translates into a clinical advantage. The efficacy of the two drugs in combination therapy is comparable in clinical trials.

Pharmacology: TDF and FTC both have long intracellular half-lives. In one study, the intracellular half-life of tenofovir diphosphate (TDF-DP), the active metabolite of TDF, was over 60 hours, and all six patients who discontinued TDF had detectable TDF-DP levels 60 to 72 hours after their last dose [Hawkins T, et al. Abstract 2.4, 5th International Workshop of Clinical Pharmacology of HIV Therapy, Rome,

2004]. The intracellular half-life of FTC triphosphate is approximately 39 hours, significantly longer than the 22 hour half-life of 3TC [Wang LH, et al. Abstract TuPeB4546, XIV IAC, Barcelona, 2002; Anderson PL, et al. *AIDS* 2003;17:2159-68]. The pharmacokinetics of the two drugs are complementary and clearly support once-daily dosing. There are several significant interactions to be aware of when using TDF. TDF increases ddI levels, which could potentially result in increased ddI toxicity. When the two drugs are coadministered, the dose of ddI should be reduced, but the two drugs can be taken together, with or without food. TDF also decreases atazanavir (ATV) levels, though this interaction is more than offset by boosting ATV levels with ritonavir. Tenofovir levels are increased when TDF is coadministered with LPV/r, though this has not been associated with increased TDF toxicity in clinical trials.

Convenience: *Truvada* is taken as a single tablet given once a day without food restrictions.

Tolerability: Both TDF and FTC are well tolerated. In early clinical trials, the only adverse event that occurred more often with TDF than with placebo was flatulence. FTC is generally similar to 3TC with respect to tolerability, though hyperpigmentation, generally involving the palms and soles, has been described in FTC-treated patients. It is typically mild and non-progressive, and has not resulted in discontinuation in clinical trials. It may be more common among dark skinned individuals, and in some cases has resolved with continued therapy.

Toxicity: Neither TDF nor FTC is believed to cause mitochondrial toxicity based on both *in vitro* studies and data from clinical trials such as GS 903. Data on the potential for nephrotoxicity

with TDF are conflicting. Nephrotoxicity has not been observed in clinical trials, though patients with abnormal renal function at baseline were generally excluded from participation. Data from observational studies show mixed results, with some showing no changes in renal function over time and others showing a modest association with decline in renal function, especially in patients with pre-existing renal dysfunction or with other medical conditions (e.g. diabetes or hypertension) that predispose to renal dysfunction. The dosing interval for TDF and FTC should be increased in patients with calculated creatinine clearance less than 50 mL/min. Decreased bone density was observed in both the TDF and d4T arms of the GS 903 study, though changes in lumbar spine density were significantly greater in the TDF arm. The magnitude of the decline was small, however, and of unclear clinical significance. There were no non-traumatic fractures in the TDF arm, and the decline in bone density tended to stabilize after the first 24 to 48 weeks in both arms.

Resistance: Resistance profiles associated with failure of TDF + 3TC have been well characterized, primarily from the GS 903 study. It is assumed that they would be similar with TDF/FTC, though there are some data suggesting a lower rate of emergence of M184V/I in FTC-treated patients than in 3TC-treated patients [Sanne I, et al. Abstract I-868, 43rd ICAAC, Chicago, 2003]. The first NRTI mutation to emerge in patients failing TDF + 3TC is M184V, but this can be quickly followed by K65R. K65R alone causes variable loss of susceptibility to TDF, ddI, and ABC, though it would rarely be seen alone in patients failing a TDF + 3TC or TDF/FTC-containing combination. When combined with M184V, a far

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more common scenario, there is partial restoration of susceptibility to TDF, and susceptibility to ABC or ddI would be further decreased. Both K65R and M184V increase susceptibility to AZT.

Other NRTI Backbones

The three coformulated backbones discussed above are not the only NRTI backbones available, but they're the ones we're most likely to be using in our patients beginning initial therapy. The advantages and disadvantages of the other combinations are discussed briefly.

d4T + 3TC: This is an effective combination that has been extensively studied and widely prescribed. Enthusiasm for this combination has waned, however, because of the mitochondrial toxicity associated with d4T. Nevertheless, most patients will need to take a thymidine analog at some point, and d4T + 3TC is an excellent alternative to *Combivir* for those who cannot tolerate AZT.

AZT + ddI: This was widely used as a dual-NRTI combination in the pre-HAART era, but it has not been well studied or widely used as a component of HAART. Dosing is awkward, since ddI must be given on an empty stomach, while AZT is better tolerated with food. In the pre-HAART era, the use of AZT + ddI was associated with development of TAMs as well as multinucleoside resistance mutations.

ddI + d4T: This is another widely used and well studied combination, but one that is no longer recommended due to increased risk of mitochondrial toxicity. Resistance concerns are similar to those for AZT + ddI.

ddI + 3TC or ddI + FTC: These are convenient once daily regimens that have been studied in some clinical trials, though not in comparison with the standard NRTI backbones in use today. The lack of controlled data, the lack of

coformulation, and the potential for pancreatitis and mitochondrial toxicity with ddI make these less desirable than the FDCs discussed in this article for initial therapy.

ABC + TDF, TDF + ddI, ABC + ddI:

These are convenient and tolerable once-daily backbones, but their use cannot be recommended in NRTI-naïve patients. Clinical trials involving the triple-NRTI combinations of ABC + 3TC + TDF and ddI + 3TC + TDF were associated with unacceptably high rates of virologic failure and drug resistance, which may have been due to increased selective pressure on the K65R mutation by these combinations. While combinations of one of these dual-NRTI backbones with a more potent 3rd agent may be more effective, the resistance issue is still a concern. Given the paucity of data on these backbones, there is no reason to choose them over the standard 3TC- or FTC-containing combinations. However, these combinations may be acceptable in NRTI-experienced patients as guided by resistance tests.

Triple-NRTI Backbones: Triple-NRTI combinations are generally considered suboptimal due lower efficacy compared to the preferred HAART regimens, and triple-NRTI combinations that do not include a thymidine analog should not be used at all for the reasons mentioned above. However, it is possible that 3 NRTIs plus an NNRTI, a boosted PI, or even another nucleoside or nucleotide analog might be more effective than a standard 3-drug combination containing a dual-NRTI backbone, especially in patients with high baseline viral loads and/or low baseline CD4 counts. The study best designed to answer this question is ACTG 5095, which is now comparing *Combivir* + EFV vs *Trizivir* + EFV. Until the results of that study are

presented, it is not known whether there is any benefit to addition of a third NRTI to a potent 3-drug HAART regimen.

Summary: Choosing the NRTI-Backbone

Efficacy: From an efficacy standpoint, you can't go wrong with any of these combinations. When combined with an effective 3rd agent such as EFV or a boosted PI, they all would be expected to provide potent and durable anti-retroviral activity. However, clinical trial data suggest that patients starting with *Combivir* may be more likely to have to switch drugs due to toxicity than those starting with *Epzicom* or *Truvada*. In the current DHHS guidelines (October 2004) AZT/3TC is currently listed as a preferred NRTI backbone for use with both NNRTIs and PIs. Both TDF/3TC and TDF/FTC are now categorized as preferred backbones when combined with EFV. ABC/3TC is categorized as an alternative dual-NRTI backbone, primarily because of concerns about the hypersensitivity reaction.

Pharmacology: The active metabolites of TDF and FTC have the longest intracellular half-lives, followed by ABC and 3TC. Both have the advantage over *Combivir*, which must be given twice daily. Drugs with longer half-lives are potentially more "forgiving" of delayed or missed doses, as therapeutic drug levels are maintained long after the 24-hour dosing interval. Using NRTIs with long intracellular half-lives is theoretically beneficial in patients taking NNRTI-based regimens. The long half-lives of NNRTIs may increase the risk of NNRTI resistance in patients who miss multiple doses or discontinue therapy altogether, especially if the NNRTI is combined with NRTIs with

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short half-lives, which quickly leave the NNRTI “unsupported.” On the other hand, a long half-life could be disadvantageous for patients who frequently go for long periods of time without medications, since they would spend more time with subtherapeutic drug levels. Of the three FDCs, *Truvada* is the only one associated with relevant drug interactions. However, the most significant interaction, the increase in ddI levels, is potentially advantageous, since it allows use of lower doses of ddI and administration with food. The reduction in ATV levels by TDF is readily countered by ritonavir boosting, which has become a common way to administer ATV even when it is not combined with TDF.

Convenience: Both *Epzicom* and *Truvada* win on this count, being dosed with a single pill once daily without food restrictions. There is no significant difference between the two, though the longer half-lives of TDF and FTC may allow *Truvada* to be taken with less regard for the actual dosing interval.

Tolerability: *Combivir* is the least tolerable of the three FDCs, as it is associated with more gastrointestinal side effects, fatigue, and anemia than *Truvada* or *Epzicom*. I will discuss abacavir HSR as a tolerability issue, because it occurs early in the course of therapy, in contrast to the long-term complications discussed under “toxicity.” When HSR is viewed in this light, *Truvada* comes out ahead in terms of tolerability. *Epzicom*, while very well tolerated for most patients, causes hypersensitivity in a small proportion. This is especially relevant for patients who are also being treated with NNRTIs, since they can also cause hypersensitivity reactions. Clinicians should remember that NNRTI hypersensitivity is common and typically consists of an isolated rash, with or

without hepatotoxicity. In contrast, ABC hypersensitivity is less common and is characterized by a syndrome consisting of systemic symptoms. When there is doubt as to whether the patient is experiencing ABC HSR, it is sometimes better to continue the drug with close observation (daily telephone contact at a minimum) until the diagnosis is certain, in order to avoid unnecessarily discontinuing the drug and eliminating its use in the future. Experienced clinicians have become accustomed to managing patients taking twice-daily ABC through ABC HSR reactions; whether continued therapy in the setting of a possible HSR is equally safe with once-daily dosing has not been determined. Because of ABC HSR, clinicians prescribing *Epzicom* or other ABC-containing combinations must spend more time in patient education than they would when prescribing *Combivir* or *Truvada*, and it is critical that they have a system in place to allow rapid evaluation of patients experiencing symptoms suggestive of ABC HSR. A small proportion of patients taking *Truvada* may develop FTC-related hyperpigmentation, which is generally mild and did not result in discontinuation of therapy in clinical trials.

Toxicity: Both *Epzicom* and *Truvada* appear to be relatively free of significant long-term toxicity, especially the mitochondrial toxicity that until recently had been viewed as an almost inevitable consequence of NRTI therapy. It remains to be seen whether TDF causes significant nephrotoxicity. There is certainly no contraindication to use of TDF in patients with a creatinine clearance >50 mL/min, but it should be prescribed with caution and with the appropriate dosing interval adjustments to those with poorer renal function. Patients with other conditions that predispose to renal dysfunction should

also be monitored more closely, and clinicians should remember that subsequent changes in renal function, even when not due to TDF, may require dosing interval adjustment. A decrease in bone density may occur early in the course of therapy with any antiretroviral regimen; whether it is more common with TDF than with other NRTIs remains unclear. There are no current guidelines with respect to assessment of bone mineral density, though this may someday become standard practice in HIV-infected patients.

Resistance: It is hard to choose one FDC over another in terms of resistance issues. Each has its advantages and disadvantages, and the differences are sometimes subtle. *Combivir* has the advantage of gradual resistance. While patients with multiple AZT-selected TAMs have extensive cross-resistance within the NRTI class, it takes time to develop multiple TAMs, and continued therapy despite ongoing viral replication is no longer felt to be acceptable practice in patients on an initial regimen. By intervening early in the course of virologic failure, it is possible to stop the evolution of resistance before TAMs have emerged. The gradual as opposed to early emergence of resistance may be especially beneficial in patients with poor adherence, who are most likely to develop resistance. On the other hand, this advantage may be offset by the requirement for twice-daily dosing with *Combivir*. *Epzicom* has a hypothetical advantage over *Truvada* in that the K65R mutation occurs less often than the L74V mutation, which should leave both AZT and TDF as effective agents. However, these data should be viewed with caution, as the history of antiretroviral therapy is littered with discarded sequencing strategies that

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HIV in Patients Over 50: An Increasing Problem

By Kelly A. Gebo, M.D., M.P.H.

HIV is primarily thought of as a young person's disease; however, the prevalence of HIV infection in people over the age of 50 years is growing. The reasons for this change include increased longevity due to HAART as well as a growing number of older patients becoming infected with HIV through high risk exposures. The number of AIDS cases reported in adults 50 years and over quintupled between 1990 and 2001 from 16,288 to 90,513. As a result, the number of HIV-infected persons over 65 years has grown 10-fold in the past 10 years.

Occult HIV infection is a problem in older adults, because physicians are less likely to ask older patients about high risk behaviors or to suspect HIV in older patients. In addition, older patients may be less likely to admit to high risk sexual activity or injection drug use because of social norms. It is essential to ask all patients about HIV risk behaviors in a non-judgmental manner, regardless of age.

Consistent with the general trend in the AIDS epidemic, an increasing number of older women and minority adults are being infected by HIV. This is particularly concerning, given that these groups are more likely to be disadvantaged and more likely to suffer from lower levels of physical functioning and emotional support than their younger counterparts.

Morbidity and Mortality

In the pre-HAART and early HAART eras, numerous studies demonstrated that older patients had higher mortality and decreased AIDS-free survival compared to younger patients. AIDS-related illnesses have been shown to occur at higher CD4 cell counts in patients over the age of 30 years than in younger patients, and older AIDS patients have worse outcomes with

AIDS-related conditions than younger patients. Prior to 2003, the principal clinical AIDS defining conditions were *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, Kaposi's sarcoma, and *Mycobacterium avium* complex. More recently, multiple groups have reported a lower incidence of these diseases and higher rates of other conditions, including neurologic complications, malignancies, and bacterial pneumonia which are more common in older people.

Response to HAART

HAART is effective at reducing HIV viral load and increasing CD4 cell counts. However, data regarding clinical, immunologic, and virologic benefit in older patients treated with HAART have been mixed (Table 1, p 11). Some investigators have hypothesized that the degree of immune recovery after treatment with HAART may be dependent on the thymus, which loses function with advancing age [Douek DC, et al. *Nature* 1998;396:690-695; Haynes BF, et al. *Annu Rev Immunol* 2000;18:529-60; Mackall CL and Gress RE, *Immunol Rev* 1997;160:91-102; Zhang L, et al. *J Exp Med* 1999;190:725-32; Jamieson BD, et al. *Immunity* 1999;10:569-75]. Data from the early HAART era suggested that the speed of immune recovery after initiation of HAART is inversely proportional to age and that older patients did not respond as well as younger patients [Manfredi R and Chiodo F, *AIDS* 2000;14:1475-77; Viard JP, et al. *J Infect Dis* 2001;183:1290-1294; Yamashita TE, et al. *AIDS* 2001;15:735-46]. Some studies have suggested that older patients are less likely to achieve virologic suppression than younger patients [Manfredi R, et al. *J Acquir Immune Defic Syndr* 2003;33:112-14; Goodkin K, et al. *AIDS* 2004;18 Suppl 1:S87-S98;

Knobel H, et al. *AIDS* 2001;15:1591-93], while others have suggested the opposite [Manfredi R and Chiodo F, *AIDS* 2000;14:1475-77; Yamashita TE, et al. *AIDS* 2001;15:735-46]. One study demonstrated a decreased 3-month CD4 cell count response to HAART in patients over 45 years, but this effect was not sustained at 6 months [Yamashita TE, et al. *AIDS* 2001;15:735-46]. A consistent finding across studies, however, has been a smaller CD4 cell count increase in older patients compared to younger patients treated with HAART [Manfredi R and Chiodo F, *AIDS* 2000;14:1475-77; Viard JP, et al. *J Infect Dis* 2001;183:1290-1294; Knobel H, et al. *AIDS* 2001;15:1591-93]. All of these trials were relatively small, however, with fewer than 400 patients over the age of 50 years.

Data regarding the impact of age on HIV progression and mortality in the HAART era have also been conflicting. A study of an urban cohort by Perez and Moore demonstrated a benefit to HAART in patients over 50, with no difference in 3-year survival in older and younger patients treated with HAART [*Clin Infect Dis* 2003;36:212-18.]. In contrast, Anastos and colleagues recently found an increased hazard of death and of new OIs in older women followed in the Women's Interagency Health Study (WIHS) after HAART initiation. [*Ann of Intern Med* 2004;140:256-64]. Age above 50 was also found to be a risk factor for AIDS progression and death in the EuroSIDA Study [Egger M et al., *Lancet* 2002;360:119-29].

Conclusions regarding choice of HAART regimen in older patients are limited; most data come from small non-randomized trials. Larger obser-

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vational studies or controlled trials involving older patients are needed to evaluate the efficacy of various anti-retroviral regimens in this population, as measured by virologic suppression, CD4 cell count response, HIV disease progression, and mortality.

Comorbidities

Adults with HIV infection are now surviving long enough to experience HIV as a chronic disease and are suffering from other medical comorbidities that they previously did not live long enough to endure, including liver disease, cancer, and vascular disease.

Liver disease from hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol abuse has become a common cause of hospitalization, morbidity and mortality in HIV-infected individuals. In addition, there is an increased rate of liver toxicity due to use of multidrug HAART and lipid lowering agents in HIV patients coinfecting with hepatitis. Older people are more likely to have end-stage liver disease than younger adults, due either to a longer or more rapid course of hepatitis. As a result, end-stage liver disease mortality has increased dramatically in the past 10 years, and hepatitis has become an important predictor of mortality in the HIV-infected population. It is unclear whether HIV/HCV-coinfecting older patients will experience more rapid HIV disease progression than HIV mono-infected older patients, or whether HIV/HCV-coinfecting older patients will have different rates of HIV disease progression or HCV mortality than HIV/HCV-coinfecting younger patients.

HIV infection increases the risk for some tumors, particularly Kaposi's sarcoma and non-Hodgkin's lymphoma. HIV infection is also associated with increased risk of certain cancers, such as

cervical cancer and hepatocellular carcinoma, due to coinfection with other viruses, including human papilloma virus (HPV), HBV, and HCV. In addition, the risk of certain cancers, particularly lung, breast, colon, and prostate, are known to increase with age. Recent data from the Women's Interagency HIV Study suggested an increased risk of lung cancer in HIV-infected women compared to national controls [Hessol NA, et al. *J Acquir Immune Defic Syndr* 2004;36:978-85]. Other data have shown decreased rates of prostate cancer in HIV-infected men compared to age matched HIV seronegative male controls [Biggar RJ, et al. *J Acquir Immune Defic Syndr* 2004; 36:861-68]. Data from observational cohorts with more clinical information are needed to assess differences in incidence rates between HIV-infected older and younger patients as well as comparison to age-matched HIV-negative historical controls. Appropriate cancer screening, including Pap smears and colonoscopy, is an essential component of primary HIV care, especially in older patients.

The potential increased risk of cardiovascular and cerebrovascular disease with age is particularly relevant for HIV-infected patients. Age is an independent risk-factor for cardiovascular disease (CVD). While age in itself does not cause CVD, it may reflect the accumulation of atherosclerosis, the severity of which predicts the likelihood of suffering a major CVD event [Smith SC, Jr., et al. *Circulation* 2004;109: 3112-21]. Numerous studies have demonstrated an increased risk of cardiovascular and cerebrovascular events in HIV-infected patients, and several have found an association with HAART; it is unknown how much of the increased risk is attributable to age compared to HIV and/or use of

HAART. Future work is needed to compare the rates of cardiovascular disease in older HIV-infected patients to age matched HIV-negative historical controls. Appropriately managing cardiovascular risk factors, including hypertension, lipid and glucose abnormalities, and tobacco abuse are essential for reducing the risk of cardiovascular disease from HAART in older HIV-infected patients.

Comorbidities will complicate management of the HIV-infected older patient. It is unclear whether HIV-infected older patients will have higher rates of these comorbidities than younger HIV-infected patients or HIV-negative age-matched controls. In addition, it is currently uncertain whether these comorbidities will have a synergistic effect with HIV in older adults. Therefore, it will be important to evaluate how HAART may interact with these comorbidities in future studies.

Drug Toxicities

Metabolic toxicities related to HAART are a prominent consideration in HIV clinical practice and may be more common among older patients. Many of these complications are associated with both age and antiretroviral therapy, including disorders of lipid and glucose metabolism, cardiovascular disease, osteopenia, and osteoporosis.

Treatment with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been associated with several metabolic disorders, including dyslipidemia. Protease inhibitor-based regimens have been associated with increased triglycerides, total cholesterol, and LDL levels, and several studies suggest that the metabolic disturbances vary depending on the drug used. In addition, NNRTI-based HAART regimens and d4T may also



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increase total cholesterol and LDL levels, though often with a concomitant increase in HDL. These lipid abnormalities in older patients may be more dangerous than in younger patients because of increased risk of vascular disease and pancreatitis. Studies have not yet fully evaluated the independent effects of age and drug toxicity on this increased risk of vascular disease. Studies are needed identify the effects of particular drug combinations and age on the risk of vascular disease.

HIV-infected patients with renal or hepatic insufficiency deserve special attention when choosing antiretroviral regimens. Tenofovir DF and indinavir can be associated with nephrotoxicity and may be more dangerous in elderly patients, who typically have a lower creatinine clearance than younger patients. In addition, most protease inhibitors and NNRTIs can exacerbate hepatic insufficiency in those with pre-existing liver disease. Unfortunately, little data exist on dosing of these drugs in older patients with impaired renal or hepatic clearance. Close monitoring in some circumstances may be warranted. Interactions among antiretroviral agents are common and have been used to improve activity of some HAART regimens, as when ritonavir is used to improve the pharmacokinetics of other protease inhibitors. However, little data exist on the pharmacokinetics of these drugs in older patients, who may be more likely to experience drug-drug interactions. Therapeutic drug monitoring (TDM) may be useful in patients who are at high risk of adverse events and may be used to confirm therapeutic drug levels.

Pharmacologic interactions between antiretroviral agents and other drugs used in the elderly are common as well (Table 2, p 11). Toxic levels of the lipid lowering agents, lovastatin and

simvastatin, may occur when they are coadministered with protease inhibitors, and these drugs are therefore contraindicated. Alternative agents including, pravastatin and lower doses of atorvastatin may be better choices. Cispride is contra-indicated with all protease inhibitors due to the potential for cardiac arrhythmias. Drugs for erectile dysfunction, such as sildenafil, should be used with caution in patients taking protease inhibitors or NNRTIs because of the potential for increased levels of sildenafil. Benzodiazepines and antiretrovirals also interact. Agents such as temazepam, oxazepam, and lorazepam are better choices than midazolam and triazolam, which are generally contraindicated. Proton pump inhibitors are contra-indicated in patients taking atazanavir and delavirdine. Finally, concomitant use of herbal medications and antiretroviral therapy is currently under study, but echinacea and St. Johns' wort are known to interact with anti-retrovirals, and patients should be warned of these interactions.

In summary, there is a need for information about treatment tolerability, drug-drug interactions, short- and long-term toxicity, and interactions with underlying comorbidities and their therapies in older patients. Most randomized, controlled trials evaluating new antiretroviral drugs or chemoprophylaxis of HIV-related complications have excluded older patients and/or patients with concurrent disorders. Few studies have presented sub-analyses comparing outcomes of older patients with younger ones. Toxicities and long term consequences of treatment are critically important in older HIV-infected patients. The role of age in the development of HIV-associated complications and drug toxicities needs to be studied.

Conclusions

HIV infection in adults over the age of 50 has been relatively ignored until recently. Controlled trials on the epidemiology, pathogenesis, and therapeutic and clinical outcomes of older HIV-infected patients are needed. As the HIV-infected population ages, there is a growing need to better determine the effectiveness of HAART in older patients, and to investigate factors associated with a more rapid course of HIV infection in patients over the age of 50. Older adults clearly have more comorbidities than younger patients, and the effect of these comorbidities on HIV progression is unknown. Drug toxicity due to HAART is significant, and these toxicities may be exacerbated in older patients. Research will be needed to document the safety, tolerability, and efficacy of HIV medications in older patients.

With the increased life expectancy of HIV-infected patients in the past ten years, the number of older patients with HIV infection is likely to continue to increase in the next decade. The significant decreases in HIV-associated morbidity and mortality may be partially tempered by the emergence of drug-resistant HIV and long-term toxicities from antiretroviral therapy. In addition, the growing number of patients with other comorbidities requiring pharmacologic treatment will make drug-drug interactions far more complicated. Future research evaluating drug toxicity in older patients will be essential for developing accurate treatment recommendations in older patients. ▲



The Choice of the Nucleoside Backbone in Initial Therapy

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were based on solid resistance data. To date we have no clinical data on the efficacy of TDF after failure of ABC. Moreover, patients with K65R + M184V still have good NRTI options: their virus should be hypersusceptible to AZT, susceptible to d4T, and TDF may retain partial activity. The bottom line is that NRTI resistance issues, while fascinating, are ultimately of less importance than issues of convenience,

tolerability, and toxicity, in part because the regimens in use today are so likely to succeed. For example, while emergence of K65R and M184V is an undesirable outcome of therapy with TDF + 3TC or TDF/FTC, K65R was seen in less than 3% of the patients in the GS 903 study who were randomized to the TDF arm. The ongoing GS 934 study will hopefully shed light on differences in resistance patterns between *Truvada* and

Combivir, and studies comparing *Truvada* with *Epzicom* are now being planned. In the meantime, it's comforting to know that we have several easy, safe, and effective options for initial therapy. It is no longer necessary to sacrifice potency for convenience and tolerability. Physicians can now choose from several highly potent NRTI backbones that their patients are likely to take. ▲

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Table 1. Studies Evaluating Immunologic and Virologic Responses to HAART, Stratifying by Age

Author, Journal, Year	Study Design	Follow-Up	N	Age Group	CD4 Increases	Viral Load After Treatment	Survival of Those on HAART (3 yr)	Adverse Events
Manfredi R and Chiodo F, <i>AIDS</i> 2000;14(10):1475-77	Case control	12 months	84 21	≤35 ≥55	CD4 [↑] ≤200 cells/mm ³ or ≤10% vs baseline	4.8% 23.8%	≤50 c/mL 73.8% 71.4%	15.5% 14.3%
Viard JP, et al. <i>J Infect Dis</i> 2001; 183(8):1290-1294	Cohort	24-36 months	1956 (total)	<33 ≥45	Time to CD4 [↑] by >200 cells/mm ³	Rel Hazard 1.00 0.78 (0.7, .92)		
Knobel H, et al. <i>AIDS</i> 2001;15(12):1591-93	Cohort	24 months	671 28	≤40 >60	Mean increase (SD) 196 (100) 228 (145)	<50 c/mL 51% 67%		35% 64%
Yamashita TE, et al. <i>AIDS</i> 2001;15(6):735-46	Cohort	3-33 months	397	<45 ≥45	Decreased 3 month CD4 response in those over 45, no effect of age on 6 month CD4 count	<400 c/mL No difference by age group		
Manfredi R, et al. <i>J Acquir Immune Defic Syndr</i> 2003;33(1):112-14	Cross-sectional	All on HAART ≥12 months	44 13	55-65 >65		-1.0 log ₁₀ -0.5 log ₁₀		
Perez JL, Moore RD, <i>Clin Infect Dis</i> 2003;36(2):212-18	Cohort	3 years	535 253	<50 ≥50			89% 83%	
Goodkin K, et al. <i>AIDS</i> 2004;18 Suppl 1S87-S98	Cross-sectional	Adjusted for HAART	63 72	18-39 ≥50		≥50 31.8% 50.0%		



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Table 2. Common Drug-Drug Interactions by Drug Class for Compounds Often Used in the Elderly
When using the antiretroviral listed in the left column do not coadminister with the drugs listed in the other columns.

Antiretroviral	Antimicrobials	GI Drugs	Cardiovascular Agents	Anti-neoplastic Agents	Lipid Lowering Agents	Neurologic Drugs	Antihistamines	Other
Amprenavir	Rifampin Rifapentene	Cisapride	Beperidil		Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Atazanavir	Rifampin Rifapentene	Cisapride Proton Pump Inhibitors	Beperidil	Ininotecam	Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Fos-Amprenavir	Rifampin Rifapentene	Cisapride	Flecainide Propafenone		Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Indinavir	Rifampin Rifapentene	Cisapride			Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Lopinavir/ Ritonavir	Rifampin Rifapentene	Cisapride	Amiodarone Flecainide Propafenone Quinidine		Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Nelfinavir	Rifampin Rifapentene	Cisapride			Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Ritonavir		Cisapride	Amiodarone Beperidil Flecainide Propafenone Quinidine		Lovastatin Simvastatin	Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Saquinavir	Rifampin Rifabutin Rifapentene	Cisapride				Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Delavirdine	Rifampin Rifabutin Rifapentene	Cisapride H ₂ Blockers Proton Pump Inhibitors				Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Efavirenz		Cisapride				Midazolam Triazolam Ergot alkaloids Pimozide	Astemizole Terfenadine	St. John's wort
Nevirapine	Rifampin Rifapentene					Pimozide		St. John's wort

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