Initial Regimens for the Treatment-Naive Patient: Current Understanding and Practice

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Since the introduction of highly active antiretroviral therapy in the mid-1990s, antiretroviral therapy (ART) options have expanded considerably to include simpler, safer, and more tolerable regimens. This has included new options for initial regimens for treatment-naive patients as well as regimens for treatment-experienced patients with extensive drug resistance. Current regimen options are easier, better tolerated, less toxic, more effective, and more durable than regimens used in the early years of the HAART era.

Over the past 2 years, most of the attention relating to new agents has been directed toward the highly treatment-experienced patient. However, approaches to initial therapy are also evolving with the accumulation of new data and novel agents. The January 2008 revision of the US Department of Health and Human Services (DHHS) guidelines reflects some of these developments (Table). The following discussion reviews the basis for the current recommended initial regimen and potential new options for treatment-naive patients.

CONSIDERATIONS IN THE SELECTION OF THE INITIAL REGIMEN

Four factors figure prominently in the selection of initial regimens: efficacy, tolerability, long-term adverse effects, and convenience.

First, suppression of the HIV RNA level to < 50 copies/mL is the expected outcome and goal of therapy. Second, regimens should have minimal adverse effects, such as nausea and diarrhea, that may compromise adherence. Third, regimens should have limited long-term complications, such as lipoatrophy, hyperlipidemia, and hepatic or renal disease. Fourth, convenience is important: once-daily regimens with low pill burdens are believed to improve adherence and may improve quality of life. In our discussion of treatment options for the ART-naive patient, it is assumed that the patient has undergone resistance testing and does not have transmitted resistance.

THE CONTINUED PRIMACY OF 2 NRTIS AND AN ADDITIONAL AGENT

From the introduction of highly active antiretroviral therapy in the mid-1990s until today, a regimen consisting of 2 NRTIs plus either an NNRTI, a protease inhibitor (PI), or a ritonavir-boosted PI (PI/r) has been recommended for initial use. Data accumulating over the past decade, including data from recent studies, demonstrate the superiority of this approach. Studies have compared combinations of 2 NRTIs plus an NNRTI or a PI with the following:

- Triple-NRTI combinations.
- 2 NRTIs plus 2 NNRTIs.
- An NNRTI plus a PI.
- 2 PIs.

Two important studies identified lower rates of virological suppression in triple-NRTI regimens. The ACTG 5095 study randomized subjects to a triple-NRTI arm using abacavir (ABC), zidovudine (ZDV), and lamivudine (3TC); an arm with 2 NRTIs plus efavirenz (EFV); and an arm using 3 NRTIs plus EFV. At 48 weeks, 83% of subjects in both of the EFV-containing arms had HIV RNA levels of < 50 copies/mL compared with only 61% of subjects in the triple-NRTI arm. Another study, ESS30009, compared the triple-NRTI combination tenofovir disoproxil fumarate (TDF)
plus ABC/3TC with a standard regimen of EFV plus ABC/3TC. ESS30009 demonstrated a poor response and was terminated early when 49% of the subjects on the triple-NRTI regimen failed to achieve a virological response compared with 5% in the EFV-containing arm.5 The absence of benefit of a third NRTI was demonstrated in the comparison of the 2 versus 3 NRTIs plus EFV arms of ACTG 5095.6

The 2NN and ACTG 384 studies evaluated the use of a second NNRTI in a 2-NRTI plus NNRTI regimen. Both studies included 3 arms composed of EFV, nevirapine (NVP), or NVP plus EFV. Each arm also included a 2-NRTI backbone.7,8 In both studies, virological suppression was similar between the EFV and the EFV plus NVP arms, but adverse effects and toxicity were greater with the use of 2 NNRTIs.

Several studies have also evaluated so-called NRTI-sparing regimens. For example, the ACTG 5142 study randomized subjects to the following 3 arms:

- EFV plus 2 NRTIs.
- Ritonavir-boosted lopinavir (LPV/r) plus 2 NRTIs.
- LPV/r plus EFV.

There was no statistically significant difference in virological suppression at 96 weeks between the LPV/r plus EFV arm and the EFV plus 2 NRTI arm. However, levels of both triglycerides and low-density lipoprotein cholesterol were higher in the LPV/r plus EFV arm. This led the authors to conclude that EFV plus LPV/r was a less desirable regimen. A previous single arm study demonstrated reasonably good suppression using EFV plus LPV/r: 69% of subjects achieved HIV RNA levels of < 50 copies/mL by an intention-to-treat (ITT) analysis.10 However, the lack of a comparator arm limits application of these results.

An earlier open-label study, ACTG 5116, randomized 236 patients who were already suppressed to receive an NRTI-sparing regimen (LPV/r plus EFV) or a PI-sparing regimen (NRTIs plus EFV).11 The number of subjects who discontinued therapy because of virological failure or adverse effects was significantly higher in the LPV/r plus EFV arm. Levels of cholesterol and triglycerides were also higher in the LPV/r plus EFV arm.

The 006 study—a naive study of an NRTI-sparing regimen that predated ACTG 5142 and ACTG 5116—randomized subjects to the following combinations:

- ZDV/3TC plus EFV.
- ZDV/3TC plus indinavir (IDV).
- IDV plus EFV.

In an ITT analysis, the group randomized to ZDV/3TC plus EFV achieved significantly better virological suppression to < 50 copies/mL at 48 weeks: 64% versus 43% to 47% among the 2 IDV-containing regimens. Because of efficacy or toxicity, studies to date do not support initial use of a regimen with only NNRTIs and PIs. However, the studies combining PIs and NNRTIs discussed above used combinations that were less convenient, more toxic, or more poorly tolerated than some that would be available today. For example, ACTG 5142 used the older, soft gel formulation of LPV/r, with an increased dosage (533/133 mg twice daily) to compensate for the reduction of LPV levels by EFV. Other, unstudied combinations of NNRTIs and PIs would be more convenient and might be less likely to cause elevations in lipid levels or GI effects.

Additional NRTI-sparing strategies include PI/r monotherapy and dual-PI/r therapy. MONARK was a multicenter, double-blind, randomized, controlled trial of ART-naive patients with baseline HIV RNA levels of < 100,000 copies/mL who were randomized to receive LPV/r monotherapy or LPV/r plus ZDV/3TC.13 By ITT analysis, 64% of the 84 subjects randomized to receive LPV/r monotherapy reached the combined primary end points of HIV RNA suppression to < 400 copies/mL at 24 weeks and < 50 copies/mL at 48 weeks, compared with 75% of the 54 subjects randomized to receive LPV/r plus 2 NRTIs. While this difference was not statistically significant (P = .19), on-treatment analysis found that a significantly lower proportion of those receiving LPV/r monotherapy reached the primary combined end points, 80% versus 98% (P = .002).

Another recently published study, the OK study, used LPV/r monotherapy as a maintenance regimen only after initial induction with combination highly active antiretroviral therapy. This is described below with induction-maintenance strategies. Boosted PI monotherapy appears to be effective in most treatment-naive patients, although the studies to date have been small and in each there has been some evidence of decreased efficacy relative to standard 3-drug regimens. In resource-limited settings, PI/r monotherapy may have a role in second-line therapy after failure of NNRTI-based regimens, although this strategy has not been studied in that setting.

The use of 2 ritonavir-boosted PIs (“dual-boosted PIs”) has also failed to show promise for first-line...
therapy. The LORAN study randomized 41 ART-naive patients to receive LPV/r plus atazanavir (ATV) and 36 patients to receive ZDV/3TC plus LPV/r. At 24 weeks, the dual-boosted PI arm had 12 failures (49% suppression) compared with 4 failures in the conventional therapy arm.\textsuperscript{14} Another study, ANRS 127, compared 2 dual-boosted PI-based regimens for ART-naive patients: ATV and ritonavir-boosted fosamprenavir (FPV/r) versus ATV and ritonavir-boosted saquinavir (SQV/r).\textsuperscript{15} There was no conventional therapy arm. At 16 weeks, 40% of patients receiving ATV plus FPV/r and 42% of those taking ATV plus SQV/r achieved an HIV RNA level of < 50 copies/mL, which is close to the 49% suppression observed for the dual-boosted PI arm of the LORAN study. Because the study lacked a conventional therapy control arm, it cannot be used to demonstrate inferiority to standard regimens. However, the low proportion of subjects with virological suppression leads to questions regarding efficacy.

In the future, combinations of newer agents may provide alternatives to the current standard of 2 NRTIs plus an agent from a second class. For example, the combination of raltegravir (RAL) plus a boosted or unboosted PI has potential for efficacy and tolerability. However, until such novel regimens have been studied, existing data support the current recommendations that initial therapy consists of 2 NRTIs plus 1 additional agent from a second class.

**THE CHOICE OF THE NRTI BACKBONE**

The choice of which NRTIs to use in the backbone has evolved considerably since the mid-1990s. The current DHHS guidelines recommend either coformulated TDF plus emtricitabine (FTC) or coformulated ABC/3TC as the preferred NRTI combination for initial therapy. 3TC, introduced in 1991, and the similar deoxycytidine analogue, FTC, introduced in 2003, are recommended components for all initial regimens in the DHHS guidelines. These 2 agents are potent, very well tolerated, and have minimal long-term adverse effects. In addition, when resistance develops to 1 of these agents, the signature M184V mutation may boost the potency of some other NRTIs (especially ZDV and TDF) and reverse the resistance caused by thymidine analogue mutations or delay their emergence.\textsuperscript{16}

It is unclear whether 3TC and FTC are equivalent, since no head-to-head studies of these 2 agents are available. However, analysis of the GS903 and GS934 studies suggests a possible difference between the 2 drugs when combined with TDF. In study GS903, patients were randomized to receive either TDF and 3TC or stavudine (d4T) and 3TC, both in combination with EFV. After 48 weeks on the initial TDF and 3TC regimen, the K65R mutation developed in 7 subjects, leading to TDF resistance.\textsuperscript{17} In contrast, GS934—a study with a TDF and FTC arm—identified no K65R mutations among subjects in whom therapy failed in the TDF and FTC arm at 48 weeks.\textsuperscript{18} These 2 studies suggest that TDF resistance may develop more slowly in the presence of FTC than 3TC.

If there is a true difference, a potential explanation is the longer plasma and intracellular half-life of FTC, 10 and 39 hours, respectively, compared with 5 to 7 and 18 to 22 hours for 3TC.\textsuperscript{19} In addition, there was less emergence of the M184V mutation in patients receiving TDF and FTC than in patients receiving ZDV/3TC in the GS934 study.\textsuperscript{20} These findings support the superiority of FTC over 3TC when paired with TDF, but they may not extend to pairing with ABC or ZDV.

In addition, in the recently presented HEAT study, the number of patients with treatment failure who had mutations at codon 184 was unexpectedly higher among those who were taking TDF than among those who were taking ABC.\textsuperscript{21} Combining either TDF or ABC with FTC or 3TC completes a preferred 2-NRTI backbone. TDF and ABC, the preferred agents in the DHHS guidelines, are potent and are significantly better tolerated, more convenient, and safer than other NRTI options—including ZDV, d4T, and didanosine (ddI). Most evidence suggests similar potency and efficacy of ABC and TDF. For example, the HEAT study randomized 688 ART-naive subjects to receive daily LPV/r with either ABC/3TC or FTC/FTC. Adverse effects, loss to follow-up, and 48-week HIV RNA level of < 50 copies/mL were similar for both arms.\textsuperscript{21} At 48 weeks, 64% of subjects in the ABC/3TC arm and 62% of those in the TDF/FTC arm achieved virological suppression to < 50 copies/mL by ITT analysis. However, a preliminary interim analysis of data from the ACTG 5202 trial yielded surprising findings.\textsuperscript{22} ACTG 5202 is an ongoing, randomized clinical trial in ART-naive subjects with 4 arms, each with approximately 400 subjects. Subjects were randomized to receive either blinded ABC/3TC or TDF/FTC combined with open-label ritonavir-boosted ATV (ATV/r) or EFV. The interim analysis revealed that subjects receiving ABC/3TC who had baseline HIV RNA levels of > 100,000 copies/mL had a lower likelihood of achieving suppression to < 1000 copies/mL at 16 weeks and < 200 copies/mL at 24 weeks when compared with those in the arms with TDF/FTC. There was no difference in viral suppression between groups among subjects with baseline HIV RNA levels of < 100,000 copies/mL. In addition, subjects receiving ABC/3TC had higher levels of cholesterol and
triglycerides and more nonspecific symptoms, such as body aches, than those receiving TDF/FTC.
Similar differences in lipid levels have been previously reported between ABC and TDF.\(^\text{23}\)
Because the analysis from ACTG 5202 is preliminary, further data will be essential to shed light on
reasons for the differences in outcomes in that study and the apparent discrepancy between results of
this and other studies—especially those of HEAT.
Despite excellent overall efficacy and safety profiles, several toxicity issues must be considered
when using either ABC or TDF. Acute renal failure has been attributed to TDF in case reports;
persons with underlying renal disease were primarily affected.\(^\text{24,25}\) TDF has also been associated with
a gradual decline in estimated glomerular filtration rate in some observational studies.\(^\text{26-28}\) High
concentrations of TDF can cause renal tubular injury. Because TDF is secreted via glomerular
filtration, impairment of renal function from other causes may lead to a decreased glomerular
filtration rate and rising tenofovir levels, leading to TDF-associated renal injury. Of greater concern is
the potential gradual loss of estimated glomerular filtration rate over time.
Several cohort studies that have included ART-experienced subjects have reported increased loss of
renal function among those receiving TDF.\(^\text{28}\) In a follow-up analysis of the Johns Hopkins HIV Clinical
Cohort Study, the greater decline in renal function seen with TDF (compared with other NRTIs)
appeared to level off after the first 6 months of therapy and was accounted for entirely by
treatment-experienced patients in the cohort.\(^\text{29}\) In some studies, this difference has been most
notable among subjects receiving TDF and a PI/r.\(^\text{30}\) Importantly, among treatment-naive patients who
were treated with TDF plus either EFV or a boosted PI in clinical trials, decline in renal function has
not been observed.\(^\text{20,21,28,31,32}\)
TDF has also been associated with decreased bone density.\(^\text{33}\) Bone demineralization was identified
in both TDF and d4T arms of the GS903 study, although vertebral demineralization was higher in the
TDF arm. However, this stabilized after week 48, and up to week 144, there were more fractures in
the d4T arm, but none were considered pathological.\(^\text{18,31}\) Despite these concerns, TDF is a
well-tolerated drug with an excellent record of safety and efficacy, especially in treatment-naive
patients.\(^\text{33}\)
The most notable toxicity of ABC is the ABC hypersensitivity reaction (HSR), a febrile illness
occurring 2 to 4 weeks after initiation of therapy among 2% to 7% of recipients. Risk for ABC HSR is
strongly associated with the presence of the HLA-B*5701 allele.\(^\text{34-37}\) The recently published PREDICT
study evaluated the use of HLA-B*5701 screening to prevent ABC HSR.\(^\text{38}\) Subjects were randomized
to prospective screening for HLA-B*5701 or to a standard-of-care with routine counseling and
monitoring for ABC HSR. Subjects in the intervention arm were only given ABC if they tested
negative for HLA-B*5701. All suspected ABC HSRs were confirmed by cutaneous delayed
hypersensitivity patch testing. A total of 803 subjects were evaluated in the prospective screening
arm and 847 in the control arm.
Among subjects in the prospective testing arm, a clinical diagnosis of ABC HSR was made in 3.5%.
However, none of those with a suspected ABC HSR in the prospective testing arm had immunological
evidence of ABC hypersensitivity on skin testing. Among the standard-of-care arm, 7.8% received a
diagnosis of ABC HSR on clinical grounds, and 2.7% had both clinical ABC hypersensitivity and
immunological evidence of hypersensitivity on skin testing. All subjects with immunologically
confirmed ABC HSR had the HLA-B*5701 allele; ABC HSR developed in nearly 50% of those with this
allele in the control arm.
One limitation of this important study was the small proportion (17%) of nonwhite subjects, among
whom other HLA alleles may also predispose to ABC HSR. However SHAPE, a smaller retrospective
study, provided strong evidence for the utility of HLA-B*5701 testing in blacks as well as whites. In
SHAPE, 69 black and 130 white subjects with suspected ABC HSR underwent skin testing to confirm
the diagnosis. All subjects, both black and white, with confirmed ABC HSR carried the HLA-B*5701
allele.\(^\text{39}\) Testing for HLA-B*5701 has become readily available and is now recommended in the DHHS
guidelines before ABC therapy is initiated.
A second toxicity of ABC may be cardiac, although results are preliminary. The international
longitudinal D:A:D cohort study team reported an association between current or recent ABC use and
myocardial infarction.\(^\text{40,41}\) In an adjusted model, among patients receiving ABC the relative risk of
myocardial infarction was 1.94 (95% confidence interval, 1.48 to 2.55). The greatest increase in
absolute risk was observed among those with the highest cardiovascular risk profile. Risk was only
found with recent or current use but not with cumulative or past use (more than 6 months ago). The
relative rate was also elevated for ddi but not for ZDV, d4T, or 3TC.
It is worth noting that although the authors did adjust for potential confounders, a much higher
proportion of persons who had recently taken ABC had a history of cardiovascular disease, diabetes,
hypertension, dyslipidemia, and a moderate to high 10-year coronary heart disease risk. Thus, it is possible that residual confounding accounts for the difference in myocardial infarction rates between NRTI groups. Further investigation is needed to better assess the cardiovascular risk of ABC; however, it is unlikely to be directly related to traditional risk factors because of the immediate onset and rapid decline of the risk when starting and stopping ABC. TDF was not included in the analysis because of limited follow-up data. Currently, the question of possible increased cardiovascular risk, the greater effects on lipid levels, and the question of lower efficacy of ABC among patients with high baseline viral loads have introduced uncertainty about the use of ABC for initial therapy. Until we learn more about cardiovascular risk and see further analysis from the ACTG 5202 study, TDF/FTC may be the preferred backbone among patients with renal disease. In the presence of renal disease and absence of the HLA-B*5701 allele, ABC/3TC remains an excellent option and is probably safer and more effective than the previous preferred backbone of ZDV/3TC. ZDV/3TC is now classified as an alternative choice because of long-term toxicity, poorer tolerability, and the need for twice-daily dosing. The combination of ddI and either 3TC or FTC is also classified as an alternative NRTI backbone, although it has not been as well studied as the other backbones. The combination of d4T and 3TC is no longer recommended because of long-term toxicity, especially peripheral neuropathy, lipoatrophy, and lactic acidosis/hepatic steatosis.

**WHAT TO USE WITH THE NRTI BACKBONE**

The DHHS guidelines recommend either EFV, ATV/r, LPV/r, or FPV/r as preferred agents to combine with the NRTI backbone. Several studies support the noninferiority or superiority of EFV compared with boosted PIs. Use of LPV/r or other boosted PIs may be considered in patients with very low baseline CD4 counts or who have poor CD4 responses to NNRTI-based regimens. Head-to-head trials have compared once-daily ATV/r with twice-daily LPV/r (among treatment-naive and treatment-experienced patients) and twice-daily FPV/r with twice-daily LPV/r (in treatment-naive patients). These comparisons have reported similar efficacy in virological suppression among these boosted-PIs.

Twice-daily FPV/r and twice-daily LPV/r have similar efficacy and adverse effects. This was demonstrated in the KLEAN study, in which twice-daily FPV/r and twice-daily LPV/r were compared, each combined with ABC/3TC. Once-daily FPV/r, once-daily LPV/r, and twice-daily SQV/r are listed as alternatives to the preferred PIs in the DHHS guidelines. The lipid profile with once-daily dosing of FPV with a lower dose of ritonavir (1400/100 mg) is better than with the standard twice-daily dose (700/100 mg). This makes it comparable to ATV/r in dosing frequency and lipid profile. This was demonstrated in the ALERT study of a comparison of daily FPV/r (1400/100 mg) with ATV/r. In ITT analysis at 24 weeks, of the 106 subjects randomized equally to the 2 arms, 79% of those receiving FPV/r and 83% of those receiving ATV/r achieved an HIV RNA level of < 50 copies/mL (not statistically different). Changes in lipid levels were similar in the 2 arms. However, the study was not powered to demonstrate noninferiority of FPV/r. The FDA recently approved FPV/r 1400/100 mg once daily for treatment-naive patients primarily on the basis of pharmacokinetic studies showing higher amprenavir levels than with standard doses of unboosted FPV, also an approved agent. Several studies have also evaluated once-daily LPV/r. The ACTG 5073 study compared once-daily dosing of LPV/r with twice-daily dosing of LPV/r. That study randomized 402 subjects to twice-daily
LVPr, self-administered once-daily LPV/r, and directly observed once-daily LPV/r. All subjects received the original soft gel formulation of LPV/r and a 2-NRTI backbone with FTC, and either TDF or d4T. Although there was no difference among the arms in the overall end point of virological suppression to < 200 copies/mL at 48 weeks, a subgroup analysis of subjects with baseline HIV RNA levels of > 100,000 copies/mL found lower rates of suppression in patients in the once-daily arms. A more recent and larger study, MOS-730, compared once-daily with twice-daily LPV/r and also compared the soft gel capsule formulation with the newer tablet formulation. That study randomized 640 patients into 4 arms in a factorial design of once-daily, twice-daily, soft gel, and tablet arms. At 48 weeks, viral suppression was not significantly different across the arms. Furthermore, half of the subjects had baseline HIV RNA levels of > 100,000 copies/mL, and there was no difference in efficacy in this subgroup.

Twice-daily SQV/r also deserves consideration. The GEMINI study compared twice-daily SQV/r with twice-daily LPV/r. Each arm also received TDF/FTC. In GEMINI, 337 ART-naive subjects were randomized equally to each arm. At 48 weeks, virological suppression to < 50 copies/mL was similar between groups: 64.7% and 63.5% in the SQV/r and LPV/r arms, respectively. The increase in cholesterol levels was also similar in the 2 groups; however, levels of triglycerides were significantly higher in the LPV/r arm. Because SQV/r requires twice-daily dosing, has the highest bill burden among the preferred or alternative PIs, and provides no clear advantage over other PI/r combinations available for ART-naive persons, it has limited application in this population.

Several new and promising considerations for initial therapy have recently emerged. These include once-daily ritonavir-boosted darunavir (DRV/r), twice-daily RAL, and twice-daily maraviroc (MVC). The ARTEMIS study compared once-daily DRV/r (800/100 mg) with either once-daily or twice-daily LPV/r among ART-naive subjects. All subjects also received TDF/FTC. The primary end point of noninferiority was met with 84% of the DRV/r arm and 78% of the LPV/r arm achieving suppression to < 50 copies/mL at 48 weeks by ITT-time to loss of virological response analysis. However, in a subgroup analysis, subjects with baseline HIV RNA levels of ≥ 100,000 copies/mL were significantly more likely to achieve virological suppression with DRV/r than with LPV/r (79% vs 67%; P < .05). A subsequent analysis found that the difference in efficacy among those with high viral loads was accounted for by use of once-daily LPV/r. However, it should be noted that the use of once- or twice-daily LPV/r and the use of soft gel capsules or tablets was not based on randomization but on drug availability and investigator choice. This limits any conclusions about superiority of DRV/r in this subgroup.

Once-daily DRV/r was well tolerated with few major adverse effects and was associated with a more favorable lipid profile than LPV/r. However, the FDA recently issued a drug warning based on postmarketing reports about increased rates of hepatitis among persons with preexisting liver dysfunction. During clinical trials, significant hepatotoxicity was rare even among patients receiving DRV/r, even those coinfected with hepatitis B virus or hepatitis C virus. The recently approved integrase inhibitor, RAL, has also been studied in treatment-naive patients. A dose-ranging study randomized 198 ART-naive subjects to receive TDF/FTC plus either EFV or 1 of 4 doses of RAL twice daily. The primary end point was 48-week suppression to < 50 copies/mL by ITT analysis. Suppression among the 4 RAL groups ranged from 83% to 88% compared with 87% for the EFV group. Virological suppression was achieved more rapidly with RAL than with EFV, although this did not lead to a significant difference in the overall results at 24 or 48 weeks. The low adverse-effect profile, the excellent tolerability, and high potency may make RAL a potential option for initial therapy in some patients despite the need for twice-daily dosing. However, further data are needed before this can be considered a recommended option.

The recently approved CCR5 antagonist, MVC, has also been studied in ART-naive subjects. There is a theoretical rationale for early use of CCR5 antagonists. Treatment-naive patients with higher CD4+ cell counts are more likely to have pure R5-tropic virus and, therefore, are more likely to be candidates for treatment with drugs in this class than are more treatment-experienced patients with more advanced disease.

The MERIT study randomized treatment-naive patients to receive MVC or EFV along with ZDV/3TC. MVC was noninferior to EFV using the < 400 copies/mL analysis, not the < 50 copies/mL analysis. EFV also outperformed MVC in patients with baseline HIV RNA levels of > 100,000 copies/mL. The differences in efficacy were accounted for by subjects who had R5-tropic virus at the screening visit but who had dual or mixed-tropic virus at baseline when starting ART: only 7% of that subgroup achieved suppression while receiving MVC. The limits in sensitivity and the high price of the currently available tropism assay, the twice-daily dosing requirement, the lack of long-term safety data for this drug with a completely novel mechanism of action, and the wealth of better-studied alternatives
make MVC a suboptimal initial option at present. Rilpivirine (TMC-278), a once-daily second-generation NNRTI, is now being compared with EFV in clinical trials for ART-naive patients. Etravirine, another new NNRTI, has already been approved. However, it is currently dosed twice daily and has only been studied and approved for treatment-experienced patients.

**INDUCTION-MAINTENANCE STRATEGIES**

An ongoing arena for research has been the use of potent 3- or 4-agent ART for induction followed by fewer agents for maintenance of suppression. A recently published study assessed the use of ZDV/3TC/ABC maintenance therapy after achieving suppression with ZDV/3TC/ABC plus either LPV/r or EFV. In that study, the triple-NRTI maintenance regimen was inferior for maintaining suppression compared with continuation of the initial 4-drug induction regimen. That finding differed from the earlier ESS40013 study, in which maintenance therapy with ZDV/3TC/ABC was comparable with continuation of an EFV-containing regimen. However, drop-out rates in that study were high, which makes interpretation of the results difficult.

Boosted-PI monotherapy has also been evaluated for maintenance therapy. LPV/r maintenance therapy after induction with 2 NRTIs plus LPV/r was noninferior to continuation of the NRTI backbone with LPV/r in the OK study. Notably, 5 of the subjects randomized to LPV/r monotherapy experienced an elevation in HIV RNA level that was successfully resuppressed by “re-intensifying” the therapy with 2 NRTIs. These 5 subjects were not classified as failures in the primary ITT end point. However, even if these 5 subjects were considered failures, the 2 arms achieved similar levels of sustained suppression. In the LPV/r monotherapy arm, 89% achieved suppressed HIV RNA levels at 48 weeks compared with 90% in the LPV/r plus 2 NRTI arm. Because LPV/r contributes much of the toxicity to the regimen, it is unclear how this would be a significant advantage for most patients. Given the heterogeneity of findings from induction-maintenance studies and the established safety and efficacy of current ART regimens, these strategies are unlikely to become recommended treatment strategies in the near future.

**CONCLUSIONS**

During the past decade, many safer, better tolerated, more convenient, and more potent agents have become available, and several new classes of agents have been developed. Nevertheless, the original paradigm of initiating ART with a combination of 2 NRTIs and 1 agent from a second class has never been improved on. This could change as we accumulate more data, especially on novel combinations that include new agents.

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Links: