Optimizing Initial Therapy for HIV Infection

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(See the article by Sax et al, on pages 1191–201.)

Antiretroviral therapy guidelines have evolved considerably over the last 6 years, particularly as they relate to the expansion of the eligibility criteria for initiation of combination antiretroviral therapy (cART). Similarly, there has been an expansion in the preferred first-line recommended regimens, which now include nonnucleoside reverse transcriptase inhibitor (NNRTI), ritonavir-boosted protease inhibitor (PI/r), and integrase strand transfer inhibitor (INSTI) based regimens [1–3]. Each of the above is combined with a backbone consisting of a nucleotide and a nucleoside reverse transcriptase inhibitor (NRTI) or 2 NRTIs. In clinical practice, once daily fixed-dose combinations of NRTIs, most commonly tenofovir disoproxil fumarate (DF)/emtricitabine or abacavir/lamivudine, with efavirenz or ritonavir-boosted atazanavir, are often favored [4, 5]. In this context, the results of the ACTG 5202 study provide additional valuable insights regarding the 4 once daily regimens most frequently used as initial therapy in clinical practice today. Of note, this was an adequately powered (n = 1857) 96-week study, with a factorial design that allowed for the blinded comparison of abacavir/lamivudine versus tenofovir/emtricitabine, and the open label comparison of efavirenz versus ritonavir boosted atazanavir [6–8]. The primary efficacy endpoint in ACTG 5202 was time to virologic failure, defined in this study as a plasma HIV-1 RNA viral load >1000 copies/mL at or after 16 weeks and before 24 weeks, or a viral load >200 copies/mL at or after 24 weeks. Safety and tolerability of each combination were evaluated as additional primary endpoints of the trial (time to regimen modification or first occurrence of a grade 3 or 4 sign or symptom, or laboratory abnormality at least 1 grade higher than baseline). The trial was designed as an equivalence study, with an a priori definition of equivalence being met if the bounds of the 2-sided 95% confidence interval (95% CI) for the hazard ratio of virologic failure fell between 0.71 and 1.40.

Study participants were stratified by baseline viral load at the 100 000 copies/mL threshold. A planned interim review by a data safety and monitoring board found an increased risk of virologic failure when abacavir/lamivudine was used among those with baseline plasma viral load >100 000 copies/mL (hazard ratio [HR], 2.33; 95% CI, 1.46–3.72), leading to study unblinding in this group. The atazanavir/r and efavirenz arms of ACTG 5202 were found to have comparable efficacy (hazard ratios for time to virologic failure: 1.13 [95% CI, .82–1.56] and 1.01 [95% CI, .70–1.46], respectively) [7], although this did not meet the prespecified definition of equivalence.

The additional ACTG 5202 results presented in this issue of the *Journal* show that abacavir/lamivudine and tenofovir/emtricitabine have comparable efficacy (hazard ratios for time to virologic failure: 1.25 [95% CI, .76–2.05] and 1.23 [95% CI, .77–1.96], when used with boosted atazanavir and efavirenz respectively) among those participants whose baseline plasma viral load was <100 000 copies/mL [8]. Of note, analysis of emerging resistance mutations following virologic failure did not identify statistically significant differences in the nature of resistance mutations for those receiving abacavir/lamivudine or tenofovir/emtricitabine in combination with either atazanavir/r or efavirenz. Mutations identified were most commonly the M184V mutation associated with lamivudine resistance, and the K103N mutation conferring first-line NNRTI resistance in those failing efavirenz-based regimens. No protease inhibitor mutations were identified. In contrast, analysis of the virologic outcomes for those within the higher viral load stratum (at the time of the DSMB review) identified shorter time to virologic failure with abacavir/lamivudine when used with either atazanavir/r (HR, 2.22; 95% CI, 1.19–4.14) or efavirenz (HR, 2.46; 95% CI, 1.20–5.05) compared with tenofovir/emtricitabine; however, major NRTI resistance mutations occurred more

Received 23 June 2011; accepted 23 June 2011.

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The Journal of Infectious Diseases 2011;204:1154–6

0022-1899 (print)/1537-6613 (online)/2011/2048-0002$14.00
DOI: 10.1093/infdis/jir506

commonly among those receiving abacavir/lamivudine in conjunction with efavirenz than boosted atazanavir ($P = .03$ for failures). In this stratum, for those with virologic failure, NRTI mutations included both M184V and K65R mutations.

Primary safety and tolerability outcomes for those in the low viral load stratum showed that use of abacavir/lamivudine was associated with a shorter time to regimen modification for both atazanavir/r and efavirenz groups, including analysis for first modification of the NRTI component. As this study was conducted prior to the wide-spread use of the HLA B*5701 allele for screening for abacavir hypersensitivity, it is relevant to point out that when the analysis was restricted to regimen modification for reasons other than suspected hypersensitivity reactions, abacavir/lamivudine still remained associated with shorter time to modification among those receiving efavirenz, but not atazanavir/r. The most common reasons for modification were clinical or toxicity concerns. This may also be reflected in the safety analysis, where again the abacavir/lamivudine/efavirenz combination had a shorter time to safety event (HR, 1.38; 95% CI, 1.03–1.85) compared with tenofovir/emtricitabine given in combination with efavirenz. The safety analysis reflects, in part, greater cholesterol abnormalities with abacavir/lamivudine, regardless of the third agent.

Efavirenz has become one of the primary antiretroviral agents used today, with extensive evaluations in combination with tenofovir/emtricitabine [9, 10]. Efavirenz has demonstrated superior virologic efficacy when compared with the older protease inhibitor lopinavir-ritonavir [11, 12]. Boosted atazanavir has been shown to be noninferior to lopinavir-ritonavir in terms of virologic efficacy, with a better metabolic profile [13]. The NRTI combinations abacavir/lamivudine and tenofovir/emtricitabine have also been compared directly, in combination with lopinavir-ritonavir [14]. The ACTG 5202 study completes the final outstanding randomized comparisons of these 4 common first-line regimens. Although statistically nonequivalent according to the trial's prespecified criteria, the similar high rates of virologic suppression seen for both atazanavir/r and efavirenz should be reassuring to clinicians [7]. These outcomes are also consistent with those of the smaller, open-label, Altair study [15].

Comparisons of the NRTI backbone has yielded different results in various studies. Abacavir/lamivudine and tenofovir/emtricitabine have both been shown to be noninferior (and in the case of tenofovir, superiority was established) when compared with the fixed dose combination zidovudine/lamivudine in conjunction with efavirenz [9, 16]. Similarly, when compared directly in combination with lopinavir-ritonavir (HEAT trial), virologic suppression was noninferior between arms at 96 weeks [14]. In contrast to ACTG 5202, there were no differences noted in the HEAT trial for those with viral loads >100 000 copies/mL, although in the latter study, the primary outcome was virologic suppression (<50 copies/mL) at 48 weeks rather than detectable viral load at 16 and 24 weeks [6, 14]. Whether the difference seen in the high viral load stratum occurred because of pharmacokinetic reasons, lower potency, or a statistical difference in adherence among those receiving abacavir, or a combination of these factors, remains unclear [8]. When compared in the open-label ASSERT trial, where all participants received efavirenz, a lower proportion of those receiving abacavir/lamivudine achieved virologic suppression (plasma viral load <50 copies/mL) at 48 weeks [17]. Another limitation of ACTG 5202 was the lack of universal baseline testing for resistance, which may have played a differential role regarding the more fragile NNRTI-based regimens.

In the results presented in this issue of the *Journal* [8], use of abacavir was associated with a shorter time to regimen modification, particularly when combined with efavirenz, driven in part by metabolic derangements and clinical toxicity. This is consistent with the results of the HEAT [14] and ASSERT trials [17]. Increased risk of cardiovascular events has been associated with the use of abacavir in some studies [18, 19], but this remains controversial. Cardiovascular events in ACTG 5202 were infrequent, and these were not statistically greater with abacavir use.

The ACTG 5202 results also point to the growing concern regarding tenofovir exposure and renal impairment and, in particular, the possible additive effect of receiving tenofovir in conjunction with a protease inhibitor [20, 21]. Although there was not a difference in the actual number of cases of renal failure between arms, there was a statistical difference in creatinine clearance changes in those receiving tenofovir and ritonavir boosted atazanavir. A subsequent substudy of ACTG5202 has also documented changes in bone mineral density among those receiving tenofovir or atazanavir, although again no difference in overall fracture rates were noted [22]. The clinical significance of these changes is still uncertain, and further long-term evaluation is required.

In summary, ACTG 5202 provides strong evidence to support current therapeutic recommendations for the preferential use of efavirenz and boosted atazanavir in combination with tenofovir/emtricitabine as initial therapy. Abacavir/lamivudine remains a preferred alternative backbone for use among individuals with baseline plasma viral load <100 000 copies/mL. These recommendations are based primarily on the increased risk of virologic failure when abacavir/lamivudine is used in individuals with baseline plasma viral load >100 000 copies/mL, and to a lesser extent because of the increased frequency of regimen modification and safety events. On the other hand, continued vigilance regarding emerging both renal and bone health issues with

long-term tenofovir-based regimens remains important.

Notes

Financial support. M. W. H. is supported by a grant from the National Institute of Drug Abuse, US National Institutes of Health (1-RO1DA031043-01). J. S. G. M. is supported by the Ministry of Health Services and the Ministry of Healthy Living and Sport, from the Province of British Columbia; through a Knowledge Translation Award from the Canadian Institutes of Health Research (CIHR); and through an Avant-Garde Award (1DP1DA026182-01) from the National Institute of Drug Abuse, US National Institutes of Health.

Potential conflicts of interest. Potential conflicts of interest: M. W. H. has received speakers honoria from Bristol-Myers Squibb, Merck, Gilead, and Ortho-Janssen. J. S. G. M. has received grants from Abbott, Biolytical, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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