The efficacy of combination antiretroviral therapy in achieving sustained suppression of plasma human immunodeficiency virus (HIV) RNA levels to below the level of detection, (partially) restoring immunity, and preventing AIDS has markedly improved over the past decade. In addition, thanks to continued drug development, physicians and patients alike have an ever-expanding spectrum of, broadly speaking, equally effective regimens to choose from.

Not surprisingly, therefore, issues concerning both short- and long-term tolerability and toxicity of regimens have come increasingly to the foreground in driving the choice of what are to be considered preferred combination antiretroviral therapy regimens. Clearly, affordable regimens that combine sustained potency with the best tolerability and least toxicity should be at the top of the wish list.

In those parts of the world where cost is less of an issue, a major advance in improving long-term safety has been the move away from thymidine-analog reverse-transcriptase inhibitors (RTIs) as the backbone of combination antiretroviral therapy regimens, particularly because of their association with largely irreversible progressive loss of subcutaneous adipose tissue (peripheral lipodystrophy) and other metabolic complications. They have mostly been replaced by 1 of 2 alternative nucleoside/nucleotide RTIs, abacavir (ABC) or tenofovir (TDF), which are currently mainly used in fixed-dose combinations with lamivudine (3TC) and emtricitabine (FTC), respectively. Whereas ABC and TDF have not been associated with demonstrable peripheral lipodystrophy development and have, overall, been found to be quite well tolerated, each have become associated with distinct but different potential toxicities, in what so far seems to be a small proportion of patients. Whereas ABC has been associated with potentially life-threatening hypersensitivity in genetically predisposed individuals and, more recently, with an increased cardiovascular risk, TDF may result in renal and bone toxicity [1]. Restricting the use of ABC to patients who have negative screening results for the HLA-B*5701 allele has largely eliminated the risk of ABC hypersensitivity [2].

Given the widespread use of ABC-3TC and TDF-FTC fixed-dose combinations as part of currently preferred combination antiretroviral therapy regimens, the results of the Simplification of Antiretroviral Therapy with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) trial reported in this issue of *Clinical Infectious Diseases* are both timely and informative [3]. In this open-label, 96-week trial, adults with HIV loads <50 copies/mL were randomized to substitute ABC-3TC or TDF-FTC fixed-dose combinations for the nucleoside RTIs in their baseline regimen, while continuing to receive any baseline non-nucleoside RTIs or protease inhibitors. Of note, prior use of individual fixed-dose combination components was allowed, and 20% and 30% of participants were already receiving ABC or TDF at trial entry, respectively. Importantly, all patients who entered the study were HLA-B*5701 negative, except 1 who was already receiving ABC at entry and tolerating the drug without problems.

Although the primary end point of the trial was virological failure, the investigators put great effort toward comprehensively assessing a wide range of possible toxicities as well as the occurrence of both AIDS and serious non-AIDS events as secondary outcomes. Although both treatment strategies, analyzed in a variety of ways, were found to have similarly sustained virological efficacy over the 96...
weeks of follow-up, what distinguished them were their toxicity profiles and the rates of occurrence of serious non-AIDS events.

Of note, and consistent with what has been found in other studies, neither strategy was associated with lipoatrophy development. Limb-fat mass increased similarly in both groups, and markers of glucose metabolism remained stable throughout follow-up. Use of TDF- FTC but not ABC-3TC was associated with early increase in serum alkaline phosphatase level, reduced bone mineralization at the level of both the spine and the hip, and a greater rate of new onset osteopenia/osteoporosis or use of antiresorptive therapy. Few fractures were reported in either group. In this population of patients with preserved renal function at baseline, which excluded patients with prior intolerance to TDF, glomerular function remained stable during follow-up in both groups. Proximal renal tubular dysfunction was not formally assessed, but hypophosphatemia was rare and not different between treatment arms. Lipid-level changes were less favorable for patients randomized to receive ABC-3TC, especially when one considers that significantly more patients in that group commenced lipid-lowering therapy during the course of the trial. ABC-3TC recipients experienced significantly greater increases in total, low-density lipoprotein, and high-density lipoprotein cholesterol levels, and their ratio of total to high-density lipoprotein cholesterol at least transiently increased, compared with that in TDF- FTC recipients. Of note, all changes in lipid levels were clinically moderate with either treatment. The average 10-year risk of a fatal or non-fatal myocardial infarction, among the 281 of 357 patients for whom it could be estimated using the Framingham equation, was similar and relatively low in both treatment arms at baseline and barely changed over the 2 years of follow-up in either group. Against this background, the reported higher rate of serious non-AIDS events, the majority of which were atherosclerotic vascular events, in patients randomized to receive ABC-3TC, is all the more striking. Although a higher proportion of patients allocated to ABC-3TC were current smokers when entering the trial, adjustment for this imbalance, as well as for duration receiving assigned treatment, did not change the results. In spite of the small absolute number of events observed (8 and 1 events among those assigned to ABC-3TC and TDF- FTC, respectively), these results from a randomized, comparative clinical trial seem to confirm the recently reported increased risk of myocardial infarction and possibly a wider range of cardiovascular events associated with ABC use in 2 observational cohorts [4, 5] and the viral suppression arm from the SMART trial [6], respectively. The association between ABC and an increased cardiovascular risk was not confirmed in an analysis of coronary artery disease events in an aggregated clinical trials database of all manufacturer-sponsored ABC trials, conducted by the manufacturer of ABC [7]. Likewise, no association was found in an analysis conducted within the AIDS clinical trials group Longitudinal Linked Randomized Trials (ALLRT) cohort [8]. Several possible explanations for the discrepancy be-
tween studies can be entertained. Studies that did find an effect can be characterized by a superior quality of (largely prospective) ascertainment of relevant endpoints, which provides an important argument in favor of the robustness of their findings. Also, these studies were conducted in populations of patients who were approximately 7–10 years older than those in the studies that showed no association. Higher underlying cardiovascular risk as a result of increased age may have made patients more prone to any additional risk exerted by ABC. Although the pathogenic mechanism by which ABC may affect cardiovascular risk remains to be elucidated, it has been suggested that this may involve a proinflammatory effect [4, 6], which could be expected to promote various aspects of the atherothrombotic process. Given the reported association with current (or recent within the past 6 months) but not past or cumulative use of ABC, a (sub)acute effect on late steps in the atherothrombotic process (eg, steps involving plaque stability, rupture, or thrombosis) seems to be more likely than a chronic effect involving atheromatous plaque formation and growth. This would also be compatible with the observation of older individuals with more advanced atherosclerosis being at higher risk of this potential adverse effect of ABC.

The results of the STEAL trial also serve to stress that, in spite of our increasing ability to obtain long-term control of HIV in our patients, they may remain at a higher risk of a wide range of clinical morbidities than uninfected individuals of similar age. This has led to speculation that normal aging might be accelerated in these patients, even if HIV is optimally controlled according to our current standard of care [9, 10]. Further research is needed to address this hypothesis and to dissect the contribution not only of any untoward effects of antiretroviral drugs but also of issues such as persistent low-grade immune activation and inflammation and ongoing or intermittent low-grade viral replication (Figure 1) [9, 11, 12]. Finally, our patients’ underlying (risk of) comorbidities should be reflected not only in the choice between equally suppressive antiretroviral regimens with different toxicity profiles but also in the appropriate identification and management of comorbidities and their traditional underlying risk factors. This can be expected to benefit the quality of patients’ lives and help ensure the remarkable gains in survival as a result of modern treatments for HIV infection. In view of the increasing burden of chronic noncommunicable diseases, principally cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases, in low- and middle-income countries [13], it is appropriate to advocate for these principles to be reflected in the expanding and maturing HIV treatment programs in those countries.

Acknowledgments

Potential conflicts of interest. P.R. has received grants from, served an advisor to, or spoken at events sponsored by Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffmann LaRoche, Merck, Pfizer, Theratechnologies, and Tibotec.

References