



Commentary

Beyond Undetectable Viral Load: Effect of Nucleotides on Inflammation

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Antiretroviral therapy (ART) is among the greatest successes of modern medicine. The vast majority of patients taking ART will successfully control HIV replication, with the subsequent immunological recovery and an uneventful clinical course in most patients. Moreover, safety of the new drugs currently in use has been improved so that discontinuations due to adverse events have been minimized. Many studies suggest now that the lifespan of HIV-infected persons on ART might equal that of the non-HIV infected population. Only an excess morbidity and mortality associated to the development of the so-called non-AIDS events remains as a significant clinical problem (Rasmussen et al., 2015; Marcus et al., 2016).

It has been well demonstrated that non-AIDS events, including cardiovascular disease, non-AIDS cancers, osteoporosis, liver failure, renal failure, neurocognitive impairment, and frailty, as well as overall-mortality in HIV-infected patients on otherwise successful ART are related with persistent inflammation and immune activation (Kuller et al., 2008; Borges et al., 2013; Hunt et al., 2016). The ultimate cause of this residual inflammation is not well understood, but persistent HIV-replication, bacterial translocation, aging, lifestyle factors, and coinfections, among others, have been advocated as contributors (High et al., 2012). Since the relationship between inflammation and non-AIDS morbidity and mortality was established, there have been multiple attempts to find strategies that could help improve the situation. As the direct impact of any strategy on clinical endpoints requires large numbers of patients and long follow-up, most clinical trials and studies have evaluated the impact on markers of inflammation/immune activation previously shown to be associated with clinical outcomes. Early initiation of ART has been associated with a significant decrease in the number of non-AIDS events in a large clinical trial (Lundgren et al., 2015), but no other studies with different strategies have offered similar results.

Antiretroviral drugs have also been a focus of attention for this purpose. A differential impact of drug families and individual drugs has

been the hypothesis for some analysis of randomized clinical trials. Information on the impact of different ART regimens on inflammatory biomarkers linked with mortality remains, however, very limited. Recently, integrase inhibitors have shown to improve inflammation or immune activation markers when compared to non-nucleoside reverse transcriptase inhibitors. In particular, when compared to efavirenz, raltegravir normalized the CD4/CD8 ratio faster than efavirenz (Serrano-Villar et al., 2016), and elvitegravir/cobicistat induced larger decreases of markers of monocyte activation (sCD14), systemic (hsCRP) and vascular inflammation (Lp-PLA2) (Hileman et al., 2015). No such analysis has been performed so far with the nucleos(t)ide reverse transcriptase inhibitors (NRTIs) which are included in all the recommended regimens for treatment initiation of HIV-infection.

For this reason, the article by Funderburg et al. in this issue of *EBioMedicine* (Funderburg et al., 2016) is especially pertinent. Based on a large, double-blind clinical trial, this substudy examines changes in different biomarkers of local and systemic inflammation, comparing tenofovir alafenamide (TAF) with tenofovir disoproxil fumarate (TDF) both in combination with emtricitabine and elvitegravir/cobicistat. TAF is a new prodrug of tenofovir diphosphate that has been shown to have an efficacy similar to TDF while improving the renal and bone toxicity in clinical trials. However, information on the changes in markers of inflammation is lacking. The results show that, as expected, there were significant declines of most markers from baseline in both arms, and that TAF is as effective as TDF at reducing markers of immune activation and inflammation associated with the development of non-AIDS events and all-cause mortality.

In addition to being the first report on the impact of different NRTIs in the changes in inflammation biomarkers, the information provided in this article is relevant for several reasons. Tenofovir-based regimens are the preferred choice for most patients throughout the world, so any new information on the drug will have an impact on a large number of persons. In the near future, many patients will begin therapy with or will be switched to a TAF-based regimen, based on the good efficacy and safety profile of the drug compared to TDF. So, providing information supporting a beneficial anti-inflammatory profile is reassuring for both physicians and patients. Even if we have learnt that TAF does not outperform TDF at this regard, we can inform our patients now about the lack of any potential loss of previous benefit with TAF-based regimens, at least in the short term.

We have reached nearly optimal levels in individual antiretroviral drugs and in combination therapies. The goal of achieving durable suppression of HIV replication and long-standing undetectable viral load, with a well-tolerated, non-toxic regimen is now an accessible task for

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most physicians in the world. But persistent immune activation and inflammation despite virological control still persists, as do the associated clinical events that determine the long-term morbidity and mortality of treated patients. Information on the effect of antiretroviral drugs and regimens on these important effects are needed. Practicing physicians will certainly welcome it.

Disclosure

The authors declare no competing interests.

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