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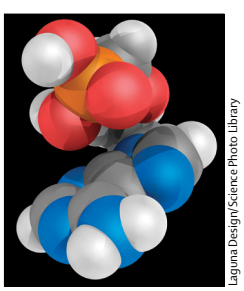
Tenofovir alafenamide for HIV infection: is less more?

Since the late 1980s, progressive development of antiretroviral drugs has revolutionised care for people with HIV infection. Early generation antiretrovirals saved the lives of patients dying from AIDS, in exchange for a high pill burden and substantial morbidity. However, such treatment was susceptible to treatment failure, especially before the introduction of combination antiretroviral therapy in the mid-1990s, but also later because of poor tolerability and adherence challenges. More recently, antiretroviral drug development has evolved towards drugs that are easier to take, resulting in improved adherence and clinical benefits. The well-tolerated, once a day, mostly single-pill regimens available for the past decade have transformed HIV into largely a chronic disease, allowing for earlier treatment initiation and expected near-normal lifespans.[1,2]

In *The Lancet*, Paul Sax and colleagues[3] report the combined results of two phase 3, non-inferiority studies comparing the safety and effectiveness of the new antiretroviral agent tenofovir alafenamide with the approved tenofovir disoproxil fumarate, both co-formulated into one, once a day pill with elvitegravir, cobicistat, and emtricitabine. In the combined analysis of 866 patients randomly assigned to the regimen containing tenofovir alafenamide and 867 patients to that containing tenofovir disoproxil fumarate, non-inferiority was established in terms of the proportion of patients achieving the primary endpoint of HIV-1 RNA less than 50 copies per mL at week 48 (800 [92%] patients *vs* 784 [90%] patients, respectively, adjusted difference 2·0% [95% CI −0·7 to 4·7], within the prespecified non-inferiority margin of 12%). In addition to addressing the efficacy of the tenofovir alafenamide-containing regimen, the data suggested an improved safety profile, with smaller decreases in creatinine clearance and bone mineral density, and smaller increases in proteinuria.

Despite substantial progress in the development of new drugs during the past decade, antiretroviral treatment remains associated with important morbidity risks. Although highly potent, safe, and widely used, tenofovir disoproxil fumarate causes proximal tubular injury in a small but clinically relevant minority of patients, and long-term use has been associated with small risks of decreased kidney function, chronic kidney disease, and decreased bone mineral density.[4-6] Both tenofovir alafenamide and tenofovir disoproxil fumarate are prodrugs of tenofovir, which is phosphorylated intracellularly into its active antiretroviral form. Tenofovir alafenamide has been hypothesised to reduce important risks of toxic effects because it achieves high concentrations of tenofovir in HIV-relevant immune cells with substantially lower plasma concentrations than tenofovir disoproxil fumarate, and consequently lower accumulation in tubular epithelial cells because tenofovir is cleared by glomerular filtration and tubular secretion. The small but significant difference in creatinine clearance decline recorded with tenofovir alafenamide versus tenofovir disoproxil fumarate is reminiscent of the small differences recorded when tenofovir disoproxil fumarate was compared with alternative antiretrovirals.[7] In pre-marketing studies of tenofovir disoproxil fumarate, these small differences in creatinine clearance were the only signal that the drug might share the nephrotoxic potential of related agents like cidofovir; it was not until tenofovir disoproxil fumarate was used widely that cases of overt kidney injury were reported.

It remains to be seen whether the small differences in creatinine clearance decline and bone mineral density



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Tenofovir

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loss reported between the two drugs will translate into clinically meaningful differences in kidney and bone health. If post-marketing experience confirms the improved safety profile suggested by the pharmacology and phase 3 trials, this would have implications for HIV treatment. A safer drug would reduce costs related to toxic effect monitoring and adverse event management. These cost savings could be magnified by reduced manufacturing costs because tenofovir alafenamide is effective at doses of 10–25 mg of the active pharmaceutical ingredient, compared with the standard tenofovir disoproxil fumarate dose of 300 mg per day. If lower manufacturing costs translate into lower drug costs, this would have significant implications for HIV treatment programmes, especially in resource-limited settings.[8] It is notable that both treatment groups in the present study achieved viral suppression rates of higher than 90%, a testament to the high potency, tolerability, and acceptability of contemporary antiretroviral treatment. Therefore, tenofovir alafenamide might signal yet another evolution in treatment—ie, toward regimens designed for lifelong use, achieving maximum adherence and minimum toxic effects.

Beyond the potential implications for people with HIV, a safer and less expensive tenofovir prodrug could also offer benefits for the treatment of hepatitis B virus infection and the prevention of HIV infection in high-risk populations. Tenofovir disoproxil fumarate is central to hepatitis B virus treatment, and clinical trials are assessing the efficacy of tenofovir alafenamide for hepatitis B virus treatment. Tenofovir disoproxil fumarate, in combination with emtricitabine, has also gained attention recently as the first drug to achieve regulatory approval for the prevention of sexual acquisition of HIV when used by at-risk HIV-uninfected people as pre-exposure prophylaxis.[9,10] Tenofovir disoproxil fumarate-containing pre-exposure prophylaxis has been associated with small but significant decreases in kidney function similar to those recorded in pre-marketing clinical trials of tenofovir disoproxil fumarate for HIV treatment, without overt toxicity.[11] Safety and cost are key considerations for the widespread implementation of pre-exposure prophylaxis, and whether tenofovir alafenamide-containing pre-exposure prophylaxis could be successful for HIV prevention, which is currently unknown, is potentially an important next question.

Tenofovir alafenamide is effective for the treatment of HIV infection. Researchers are currently investigating the effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on markers of kidney and bone health in people with HIV, and assessing other uses of this new antiretroviral agent (NCT02345252 and NCT02345226). Real-world clinical experience will ascertain whether tenofovir alafenamide offers meaningful safety or cost benefits over currently approved treatment.

*Christina Wyatt, *Jared M Baeten*
Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA (CW); and Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA 98104, USA (JMB)
jbaeten@uw.edu

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