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INFECTIOUS DISEASE

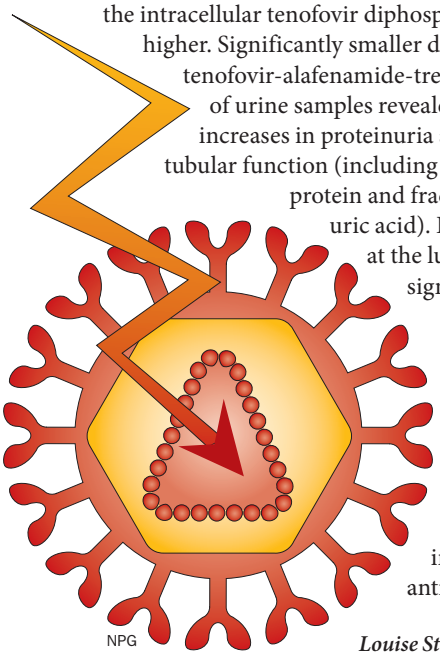
New HIV-1 prodrug shows promise in phase III trials

The results of two randomized, double-blind, phase III, noninferiority trials show that a novel prodrug for initial HIV-1 treatment—tenofovir alafenamide—has similar virological suppression to tenofovir disoproxil fumarate, with fewer adverse events. Tenofovir disoproxil fumarate is already approved as part of a coformulated, single-tablet regimen; however, treatment with this prodrug often leads to renal toxicity and greater reductions in bone mineral density than other forms of retroviral therapy, owing to high circulating plasma concentrations.

Previous investigations of tenofovir alafenamide therapy have shown higher intracellular concentrations of the active metabolite (tenofovir diphosphate) than in patients treated with tenofovir disoproxil fumarate, enabling greatly reduced doses—leading to lower plasma concentrations. Phase II trials of tenofovir alafenamide have also shown encouraging results regarding effects on glomerular filtration rate, tubular proteinuria and bone mineral density. The two recent phase III multicentre trials enrolled a total of 1,733 treatment-naive patients with HIV-1 to confirm these favourable toxicity profiles.

Participants were randomized 1:1 to receive a coformular of 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine and either 10 mg tenofovir alafenamide or 300 mg tenofovir disoproxil fumarate. Overall, 866 participants received tenofovir alafenamide and 867 were treated with tenofovir disoproxil fumarate, both formulations resulted in robust virological-supression, defined as HIV-1 RNA levels <50 copies/ml, at 48 weeks (92% and 90%, respectively). A subset of 65 patients took part in the intensive pharmacokinetic study, and 35 of these also participated in the peripheral blood mononuclear cell sampling substudy of intracellular tenofovir diphosphate concentrations. Plasma tenofovir exposure was 91% lower in samples from tenofovir-alafenamide-treated patients than in those who received tenofovir disoproxil fumarate, and the intracellular tenofovir diphosphate concentration was 4.1 times higher. Significantly smaller decreases in glomerular filtration rate in tenofovir-alafenamide-treated patients were observed. Analysis of urine samples revealed reduced or significantly smaller increases in proteinuria and other measures of proximal renal tubular function (including levels of albumin, retinol binding protein and fractional excretion of phosphate and uric acid). Decreases in bone mineral density at the lumbar spine and hip were also significantly smaller in participants who received tenofovir alafenamide than in tenofovir-disoproxil-fumarate-treated patients.

These trials were not powered to assess clinical safety events; however, these initial results suggest tenofovir alafenamide has a favourable renal and bone safety profile and could translate into an improved tenofovir-based antiretroviral therapy.



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Original article Sax, P. E. *et al.* Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* doi:10.1016/S0140-6736(15)60616-X