Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

DISCOVER: much accomplished, but not yet for all

Mikkel Ostergaard/Panos

See Articles page 239

Since the initial studies of pre-exposure prophylaxis (PrEP) a decade ago, multiple clinical trials in all key populations worldwide have confirmed the efficacy and safety of emtricitabine combined with tenofovir disoproxil fumarate (F/TDF) for HIV prevention.[1,2]

In *The Lancet*, Kenneth Mayer and colleagues[3] report the primary results of the DISCOVER trial, an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority clinical trial evaluating the efficacy and safety of F/TDF versus emtricitabine and tenofovir alafenamide (F/TAF; TAF is another tenofovir prodrug) for HIV prevention. F/TAF is already being widely used as part of HIV combination treatment regimens because of its favourable pharmacological profile. The study enrolled 5387 participants (including 5313 adult cisgender men who have sex with men [MSM] and 74 transgender women who have sex with men) at 94 sites in Europe and North America.[3] Participants were randomly assigned (1:1) to receive either emtricitabine (200 mg) and TAF (25 mg) tablets daily, with matched placebo tablets (F/TAF group; n=2694), or emtricitabine (200 mg) and TDF (300 mg) tablets daily, with matched placebo tablets (F/TDF group; n=2693). The primary efficacy outcome was incident HIV infection. After 8756 person-years of follow-up, 22 participants were diagnosed with HIV, seven of whom were in the F/TAF group (0·16 infections per 100 person-years [95% CI 0·06–0·33]), and 15 of whom were in the F/TDF group (0·34 infections per 100 person-years [0·19–0·56]). Minor increases in weight and blood lipid concentrations over the course of the study were more common in the F/TAF group than in the F/TDF group consistent with the known modest lipid-lowering effects of TDF. By contrast, decreases in bone mineral density, particularly in younger participants (ie, those aged ≥18 to <25 years), have been corroborated by the DISCOVER week 96 safety data in the F/TDF group.[4] Measurements of the urine protein to creatinine ratio and selected biomarkers for proximal tubular injury, as indicators for renal toxicity, favoured the F/TAF group over the F/TDF group. Also from the week 96 safety data, renal toxicity was accentuated in older participants (ie, those aged >50 years) and in participants with impaired renal function at baseline; however, the clinical significance of these findings remains to be shown.[4]

The clinical trial[3] was well conducted according to the protocol. The conclusion that daily F/TAF showed non-inferior efficacy to daily F/TDF for HIV prevention, with similarly low numbers of clinical adverse events reported in both groups, is supported by a robust analysis of the data.

The limitations of the DISCOVER trial[3] are the restricted eligibility, as cisgender women, people who inject drugs, and adolescents were excluded. Further, participation of transgender women was low (74 [1%] of 5387 participants), and only 9% of participants (n=474) were Black or mixed Black race.

On the basis of the primary efficacy data from the DISCOVER trial,[3] the US Food and Drug Administration (FDA) approved F/TAF for HIV PrEP on Oct 3, 2019, but limited its approval to men and transgender women who have sex with men, thus excluding individuals at risk of HIV-1 infection from receptive vaginal intercourse, since the effectiveness of F/TAF in this population had not been evaluated.

According to a recent UNAIDS report (March, 2020),[5] in 2018, approximately 52% of people aged 15 years or older living with HIV were female, 64% of whom were living in resource-limited settings in eastern and southern Africa. There is a clear need for affordable PrEP that can serve all key populations.

Among the strengths of F/TDF for PrEP is the proven effectiveness of this regimen in a wider range of key populations, both within the USA and internationally. Additionally, it is the only PrEP combination regimen that has been evaluated and shown to be effective for on-demand use in MSM.

As part of its PrEP postmarketing commitment to the FDA, Gilead (the company producing F/TAF) is now planning to conduct a randomised, comparative trial to evaluate the safety and efficacy of F/TAF for HIV PrEP in cisgender women and adolescent girls weighing at least 35 kg who are at risk of HIV infection. The clinical trial is expected to be completed as early as 2024.

Although much needed attention is on the effective response to the COVID-19 pandemic at present, all efforts to also end the HIV pandemic are continuing. There remains an urgent need to increase the integration of PrEP into the global HIV prevention effort, and to secure reliable access to affordable

PrEP for all populations at risk. A well designed pharmacokinetic study of F/TDF for PrEP in pregnant adolescents and young women in Africa, completed in early 2020, showed that tenofovir diphosphate concentrations, measured in dried blood spots, were lower during pregnancy than post partum.[6] Although there is no evidence that PrEP during pregnancy is not protective, few data correlating protection against HIV infection with tenofovir diphosphate concentrations are available for women at risk. The safe inclusion of women and pregnant women in studies of new promising PrEP combinations should be a priority.

The DISCOVER trial[3] confirmed the more efficient loading of peripheral blood mononuclear cells (PBMCs) with tenofovir diphosphate by F/TAF compared with F/TDF, resulting in trough tenofovir diphosphate concentrations above the 90% effective concentration for HIV prevention in 155 (98%) of 158 participants in the F/TAF group, and 6·3 times higher steady-state tenofovir diphosphate concentrations in PBMCs than in the F/TDF group. This higher concentration could potentially result in better protection during pregnancy, if the drug combination is first shown to be safe in women.

Based on extrapolation of the data[3] to adolescents younger than 18 years and weighing at least 35 kg, supplemented by clinical trial data for F/TAF-containing HIV treatment regimens for adolescents, the FDA has approved F/TAF for PrEP in adolescents, excluding those at risk of HIV from vaginal intercourse. Further assessment of safety, acceptance, efficacy, and effectiveness of F/TAF for PrEP in this key population is urgently needed, as we continue the roll-out of adolescent supportive adherence programmes for PrEP.[7-9]

Globally, we need to expedite the continued scale-up of effective, safe, and affordable PrEP, which will also include long-acting systemic and possibly topical PrEP. Generic oral F/TDF for PrEP is already available in more than 30 countries worldwide,[10] and the patent for this regimen will expire in the USA later this year. To achieve effective global HIV prevention, it is not only crucial that no one is left behind because of PrEP access barriers, but also that we strive to make the most acceptable, safest, and effective HIV PrEP available to all key populations.

I declare no competing interests. I thank David Burns and Patrick Jean-Philippe for their review and helpful comments. The views expressed in this Comment are my own and do not necessarily reflect the views of the National Institutes of Health.

Hans M L Spiegel
hans.spiegel@nih.gov

Kelly Government Solutions, Contractor to the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Rockville, MD 20852, USA

1 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.
2 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV-1 prevention among heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.
3 Mayer K, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide *vs* emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet* 2020; **396:** 239–54.
4 Onyema O, Podzamczer D, Salazar LC, et al. Longer term efficacy and safety of F/TAF and F/TDF for HIV PrEP: DISCOVER trial week 96 results. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 8–11, 2020 (abstr 92).
5 UNAIDS. We've got the power: women, adolescent girls and the HIV response. Geneva: Joint United Nations Programme on HIV/AIDS, 2020.
6 Anderson PL, Stranix-Chibanda L, Huang S, et al. TFV-DP in DBS for pregnant/postpartum adolescent and young women on PrEP in Africa. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 8–11, 2020 (abstr 980LB).
7 Hosek S, Celum C, Wilson CM, Kapogiannis B, Delany-Moretlwe S, Bekker LG. Preventing HIV among adolescents with oral PrEP: observations and challenges in the United States and South Africa. *J Int AIDS Soc* 2016; **19:** 21107.
8 Gill K, Dietrich J, Gray G, et al. Pluspills: an open label, safety and feasibility study of oral preexposure prophylaxis (PrEP) in 15-19 year old adolescents in two sites in South Africa. 9th International AIDS Society Conference on HIV Science; Paris, France; July 23–26, 2017 (abstr TUAC0207LB).
9 Tanner MR, Miele P, Carter W, et al. Preexposure prophylaxis for prevention of HIV acquisition among adolescents: clinical considerations, 2020. *MMWR Recomm Rep* 2020; **24:** 1–12.
10 PrEP Watch. Global PrEP tracker. 2020. https://www.prepwatch.org/resource/global-prep-tracker/ (accessed July 9, 2020).

Abrocitinib for atopic dermatitis: a step forward

See **Articles** page 255

Atopic dermatitis is one of the most common chronic inflammatory skin diseases worldwide with a global annual prevalence of 3–4%.[1] Few data are available on disease activity strata, but in a 2018 multinational survey between 10% and 20% of adults with incident atopic dermatitis reported severe disease.[2] Atopic dermatitis pathophysiology is characterised by epidermal dysfunction and T-cell-driven inflammation, with increased production of inflammatory cytokines, in particular type 2 cytokines such as interleukin (IL)-4,