More Evidence in Support of Oral Prep Safety

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The use of antiretroviral therapy as prevention in highly HIV-exposed populations has proven to be effective in protecting against HIV infection in several studies. The Partners PrEP study demonstrated the safety and efficacy of oral tenofovir disoproxyl fumarate (Viread®) alone or in combination with emtricitabine (Truvada®), both inhibitors of HIV reverse transcriptase, as compared to placebo. These drugs were tested in almost 5,000 serodiscordant couples from Kenya and Uganda. While a high protection rate was shown, a concern has been raised that the use of treatment as prevention could induce selection for resistant strains of HIV.

To address this problem, Dr. Dara Lehman from the Human Biology Division at Fred Hutch applied a very sensitive method to detect resistance-linked mutations in all subjects who seroconverted during the study or were acutely infected at the time of study randomization. A total of 122 HIV seroconversions occurred during the study, of which 18 were determined to be acute seronegative HIV infections at study enrollment. The median time between the estimated date of HIV infection and drug discontinuation, when the presence of the drug together with the virus could select for resistant strains, was 45 days. Mutations associated with resistance to the PrEP drugs were detectable in 19% of seroconverted subjects, but in the majority of these cases resistance mutations were present only at a very low frequency, less than 1% of an individual's viral population. Since resistance at <1% has not previously been associated with increased risk of treatment failure, this frequency was used as a cutoff for the study. Five seroconverters had one or more mutations associated with their PrEP regimen at a level higher than 1%: three were individuals with unrecognized acute infection at the time of PrEP randomization, and only two were subjects that became infected during the trial and had evidence of PrEP use during HIV infection.

To answer the question of whether PrEP might induce resistance in those who become infected despite its use is imperative at this time, as the FDA recently approved PrEP use outside of clinical trials, where the time between HIV tests is likely to be longer than the monthly testing that occurred during the clinical trials. Thus, in those that become infected, the coinciding presence of the drug and the virus together is likely to be longer. The data reveal that resistance to PrEP is an unlikely event in subjects receiving it as prophylaxis, but can occur both in unrecognized acute infections as well as in breakthrough infections, and more frequently when the combination of tenofovir and emtricitabine is used. The frequency of mutations leading to resistance is lower than previously

calculated with mathematical models, and, together with the data proving a low frequency of seroconversion in PrEP users, this study supports the safety of PrEP use in situations of high exposure. The conclusions of the study are summarized in Dr. Lehman's words: " The small risk of resistance must be balanced with the high number of infections averted by PrEP use, a prevention strategy safe and efficacious for situations of high exposure to HIV."

Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, Donnell D, Thomas KK, Hendrix CW, Marzinke MA, Frenkel L, Ndase P, Mugo NR, Celum C, Overbaugh J, Matsen FA, the Partners PrEP Study. 2015. Risk of Drug Resistance Among Persons Acquiring HIV Within a Randomized Clinical Trial of Single- or Dual-Agent Preexposure Prophylaxis. *J Infect Dis*. Epub ahead of print.

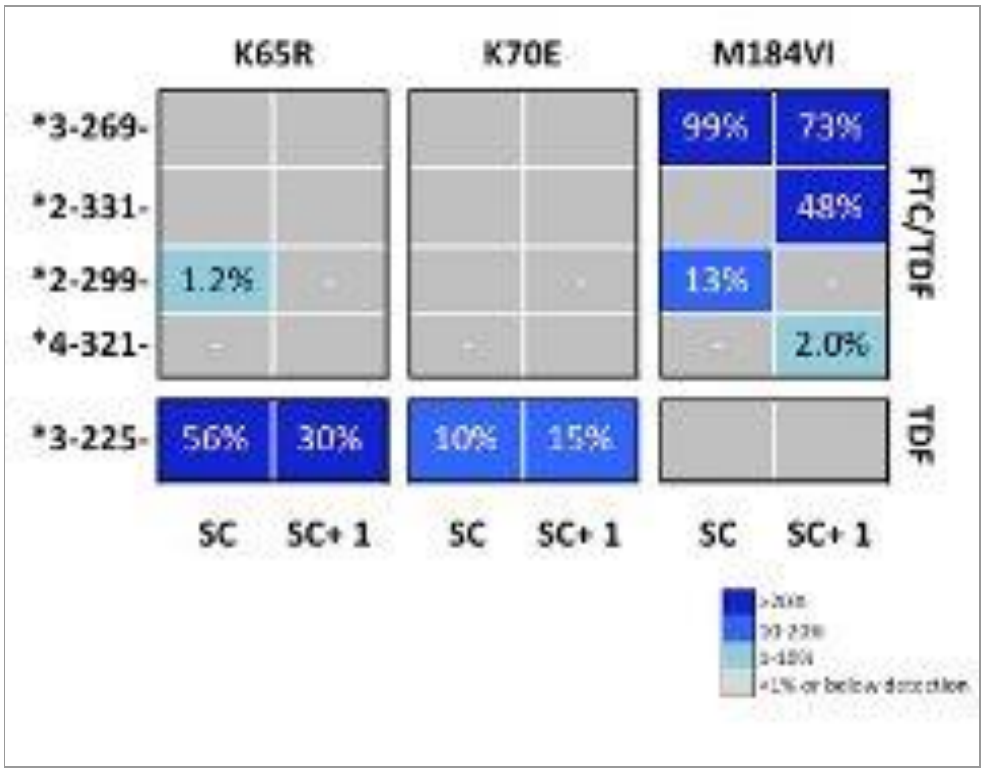

Figure provided Dr. Dara Lehman.

Frequency resistance-linked mutations in seroconverters with PrEP drugs detected during or after HIV acquisition. Higher levels are shown in darker blue colors. FTC/TDF, emtricitabine plus tenofovir disoproxil fumarate; TDF, tenofovir disoproxil fumarate alone.