Food and Drug Administration
Center for Drug Evaluation and Research Office of Antimicrobial Products
Division of Antiviral Products/Office of Antimicrobial Products
C/o Director Debra Birnkrant, MD
10903 New Hampshire Avenue
Silver Spring, MD 20993

April 15, 2019

RE: Urgent Concerns Regarding FDA Application for Descovy (FTC/TAF) as Pre-Exposure Prophylaxis for HIV

Dear Dr. Birnkrant:

We write this letter in regard to the recently filed supplemental New Drug Application ("sNDA") by Gilead Sciences, Inc. ("Gilead") for co-formulated tenofovir alafenamide fumarate and emtricitabine ("TAF/FTC"), marketed under the proprietary name "Descovy" (NDA number 208215), for use as HIV-1 preexposure prophylaxis or "PrEP."

While we appreciate the vital public health importance of PrEP, we have significant concerns about this sNDA and strongly urge that the Antiviral Drug Advisory Committee ("ADAC") convene a public hearing to discuss this application. **This hearing must be public and include community representation.**

Gilead's sNDA for TAF/FTC PrEP is extraordinary. Only a single phase III randomized control trial ("RCT") — DISCOVER —- was performed to evaluate the efficacy of Descovy as PrEP. Previous PrEP sNDAs and future PrEP NDAs (e.g. long-acting cabotegravir[1]) rely on at least two phase III RCTs to demonstrate efficacy. The trial population of DISCOVER was primarily men who have sex with men ("MSM"), with minimal participation by transgender women.[2] There is no evidence supporting the efficacy of Descovy as PrEP in cisgender women or people who inject drugs ("PWIDs") and the makeup of the trial's study population did not reflect the communities most at risk for HIV in this country and around the world.

We are extremely concerned that Gilead, if its sNDA is approved, may overstate the value of TAF/FTC as PrEP compared to the current standard of care (i.e. tenofovir disoproxil fumarate / emtricitabine) while simultaneously understating the uncertainty of the data supporting its efficacy and safety, especially for specific populations that were not included in the DISCOVER trial.

[1] I.e. HPTN 083 and 084
[2] Hare CB et al. "The Phase 3 DISCOVER Study: Daily F/TAF or F/TDF for HIV Preexposure Prophylaxis." *CROI 2019* (Seattle, WA) Abstract No. 104.

In light of these concerns, we strongly urge the FDA to rigorously evaluate all of the clinical data and procedures, implement an sNDA review process that includes an open and transparent assessment by the Antiviral Drug Advisory Committee, and– if Gilead's sNDA is approved– ensure that a program of robust post-marketing surveillance and regulation is strictly enforced.

We have several specific recommendations for the FDA regarding the sNDA approval process:

1. **The FDA should conduct a thorough and rigorous approval process that is transparent and with opportunities for community input.**

   As stated above, we strongly urge the FDA to convene a public meeting of the ADAC regarding this sNDA.

   Community members and academic experts have been concerned by Gilead's behavior from the start of the DISCOVER trial, underscoring the necessity of transparency during the sNDA approval process.

   a. *We specifically recommend that the FDA ensure that all clinical data utilized in the sNDA be made as public as possible before any decision is made.*

   Given that a previous animal model study of TAF as PrEP failed to show efficacy,[3] it is critically important that members of impacted populations be able to closely review any and all data used in the FDA's decision-making process. This need is further compounded by the lack of any peer reviewed publications presenting data from DISCOVER and Gilead's worrisome history of opacity.[4] The AIDS Healthcare Foundation won a (qualified) victory in its earlier FOIA litigation with the FDA over the Truvada PrEP trials, establishing a clear precedent for pivotal or post-marketing trial data to be made public. We urge Gilead and FDA to turn the Descovy PrEP data over to an open data database.

   b. *The FDA should thoroughly review, and make public, the recruitment methods and trial conduct of Gilead and DISCOVER investigators.*

   A coalition of community members actually called for the trial to be halted in the fall of 2017 due to widespread reports of inappropriate recruitment methods as well as Gilead's decision to operate outside of existing trial networks with several new, inexperienced investigators. Advocates have also been concerned about a possible conflict of interest with the principal investigator– Scott McAllaster– who is an employee of Gilead. Furthermore, community members

[3] García-lerma JG, Aung W, Cong ME, et al. Natural substrate concentrations can modulate the prophylactic efficacy of nucleotide HIV reverse transcriptase inhibitors. *J Virol. 2011*;85(13):6610-7.
[4] See e.g. https://medcitynews.com/2015/11/gilead-sanofi-would-tank-in-bioethics-internationals-new-good-pharma-scorecard/).

have been informed of at least one DISCOVER trial site being shut down due to unethical recruiting practices. A full accounting of all irregularities that occurred should be made available to the FDA and for community review.

c. *The FDA should clarify what role, if any, Gilead's use of estimated background HIV incidence compared to the incidence in the two arms of the DISCOVER trial plays in the decision regarding this sNDA.*

While the Centers for Disease Control and Prevention ("CDC") worked with Gilead to estimate HIV incidence in various metropolitan statistical areas in the US which had DISCOVER trial sites, and has used these to compute alleged relative risk reductions (in incident HIV infection) for both arms of the trial, these results must be interpreted with extreme caution. Indeed, the trial population studied in DISCOVER is dramatically different than the population experiencing incident HIV infections in the US.

2. The FDA should only approve Gilead's sNDA conditionally and require that a rigorous program of post-marketing surveillance be implemented. Furthermore, the FDA should work to make the process for generic applicants for FTC/TAF seamless and clear.

a. *Gilead's activity regarding marketing Descovy as PrEP is already concerning.*

- We have reports of the company telling community advocates that Descovy is 53% better than Truvada at reducing HIV acquisition. This is false; DISCOVER was a non-inferiority trial, and no statistically significant difference in efficacy was observed.
- We are hearing reports of potential benefits of Descovy in terms of time to protection and durability of protection. We have yet to see definitive evidence on these points.

b. *If the sNDA is approved, the FDA must ensure that Gilead does not engage in off-label marketing, overstate the alleged safety benefits of Descovy, and claim other benefits that are not backed by high quality evidence.*

- Gilead is widely reporting that Descovy will be a safer PrEP. Unboosted Descovy has not been shown to be clinically safer than unboosted Truvada. Differences in bone and kidney indicators in DISCOVER did not alter clinical outcomes. Additionally, there may be safety issues not related to bones and kidneys that will need to be further assessed.
- The product label and marketing should be given careful attention; all information presented should reflect the uncertainty on whether recent data on potential benefits in short term markers would have long-term implications. As the owner of both Truvada and Descovy, Gilead stands

to benefit from sabotaging its existing product to promote a regimen with a longer patent life. This demands extra scrutiny.

c. *FDA must require and enforce post-marketing studies in neglected patient populations (trans women, cis women, people of color) and use post marketing data to ensure that TAF/FTC is as effective as TDF/FTC for PrEP. Furthermore, the results of this post marketing surveillance must be made public as soon as possible.*

- Daily Dosing vs. 2-1-1 dosing: Advocates are concerned about possible confusion over Truvada vs. Descovy for so called 2-1-1 or "on demand" PrEP dosing. At present, data on 2-1-1 dosing is only available for Truvada; the FDA and Gilead must make it clear that such dosing is not advised for Descovy unless further research is conducted.
- Seroconversion, utilization, and adherence data: given that Descovy is only supported by one RCT that did not reflect the demographics of the U.S. and global epidemics, it will be imperative that Gilead conduct extensive additional research through demonstration projects that track any differences in seroconversions, utilization, and adherence compared to Truvada and/or generic TDF/FTC. These real world implementation studies must primarily focus on communities of color.

d. *Gilead must not impede access to PrEP through unfair pricing practices, taking Truvada off the market, or frightening patients from accessing cost-effective generic versions of TDF/FTC.*

- Gilead must leave Truvada on the market even after Descovy is approved for PrEP, so that patients don't get "hopped" off Truvada before generic Truvada becomes available. Similarly, FDA should scrutinize and publicize any citizen petition filed to remove Truvada from the market and/or delay generic entry of TDF/FTC.
- Gilead has modestly undercut the price of their own product, Truvada, to gain market share for Descovy before FTC goes off patent. Given that there is no competition in this space presently, the price should be dramatically reduced and based upon the extremely cheap costs of manufacturing Descovy. Additionally, Gilead must commit to maintaining comparable co-pay assistance programs for both Truvada and Descovy as PrEP. Gilead has a particularly bad track record of prioritizing profit over access, most notably with their direct acting antivirals for hepatitis C– Sovaldi and Harvoni– which were the subject of congressional investigations due to their particularly egregious pricing. In the case of Truvada as PrEP, U.S. taxpayers put up all of the funding for PrEP research, yet the company has upped the monthly average wholesale price to over $2,000 despite having spent nothing on the trials that led to FDA approval.

- Although this is beyond the purview of the FDA, it is worth noting that the CDC already owns patents on tenofovir-containing PrEP regimens. As such, royalties from sales of Descovy as PrEP should contribute toward building an access program. Advocates are currently calling for the CDC to enforce these patents in relation to Truvada[5].

We understand that the company is feeling a sense of urgency with their patent on emtricitabine set to expire in 2021, but it is crucial that the FDA prioritize a thorough, rigorous, and transparent evaluation process over the financial interests of Gilead's shareholders. It is unfortunate that Gilead chose to intentionally delay the development of TAF-containing products by nearly a decade in order to maximize profits. However, their decision does not mean that the FDA should now rush the company's sNDA. Convening a public hearing must be a first step before this evaluation can move forward.

We look forward to your prompt response affirming that such a hearing will take place before the company's sNDA advances further and addressing the other concerns and recommendations outlined in this letter.

Respectfully yours,

James Krellenstein
Co-founder
PrEP4All Collaboration

Jeremiah Johnson
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Cc: Jeffrey S. Murray, MD, MPH, Deputy Director, Division of Antiviral Products
Kimberly Struble, PharmD, Medical Team Leader, Division of Antiviral Products

[5] Rowland C. "An HIV treatment cost taxpayers millions. The government patented it. But a pharma giant is making billions." *The Washington Post*. March 26, 2019. URL: https://www.washingtonpost.com/business/economy/pharma-giant-profits-from-hiv-treatment-funded-by-taxpayers-and-patented-by-the-government/2019/03/26/