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Greetings,

Maine has been spared from a high burden of HIV, making transmission among people who inject drugs (PWID) relatively uncommon. However, things can change quickly. With this year’s HIV cluster in Penobscot county (<https://www.maine.gov/dhhs/mecdc/infectious-disease/epi/hiv-cluster.shtml>) we are reminded of the need to be making PrEP recommendations to any of our patients who inject drugs - as well as to any patient at risk of sexual transmission. The chart below describes PrEP options available now and in the pipeline. A major decision point for most patients is whether to use oral or injectable medication. The former is far more likely to fail due to barriers to taking daily meds, but the latter carries a small risk of resistance to integrase inhibitors – which are common in first line HIV treatment. That resistance can occur with perfect administration but can also occur with missed injections and in the one year “tail” period after discontinuation. As such, a supportive system to keep patients engaged and medication consistently available is essential for taking advantage of the injectable option.

Read on to look briefly at a seminal study comparing oral versus long-acting injectable PrEP and the impact of delayed dosing on resistance. I hope it will help you to become more comfortable talking to patients about HIV PrEP.

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| Drug                                                                                        | Type       | Populations                                                                                                           | Medical considerations                                           |
|---------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <b>TDF</b><br><br>emtricitabine/tenofovir<br>disoproxil fumarate<br><br>Trade name: Truvada | Daily oral | Preferred for all<br>populations, only one<br>studied in PWID                                                         | Need CrCl>60, avoid if<br>osteopenia/porosis<br><br>Follow creat |
| <b>TAF</b><br><br>emtricitabine/tenofovir<br>alafenamide<br><br>Trade name: Descovy         | Daily oral | NOT for receptive<br>vaginal sex<br><br>Preferred daily option if<br>renal or bone disease<br><br>Not studied in PWID | Need CrCl >30<br><br>Follow lipids and creat                     |

|                                                            |                                       |                                                                                             |                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CAB</b><br><br>cabotegravir<br><br>Trade name: Apretude | Injectable,<br>q1mo x2, then<br>q2mos | Not RCTs in PWID but<br>some real-world data to<br>support use; Not studied<br>in pregnancy | <u>Risk of resistance</u> – requires<br>adherence to injection schedule ,<br>monitoring with HIV RNA, and one-<br>year oral PrEP after discontinuation<br>if ongoing risk.<br><br>Risk of hyperlipidemia, ?slight wt<br>gain; more study needed to<br>understand long term SEs |
|------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### In the pipeline:

Injectable lenacapavir SQ q6months – *the ID world is looking forward to this!* Obviates many of the resistance risks.

Monthly dapivirine vaginal ring for those exposed through vaginal sex only

**Title:** Though both are effective, injectable cabotegravir (CAB) is more effective than daily oral tenofovir disoproxil fumarate (TDF) to prevent HIV infection in cisgender men and transgender women who have sex with men.

#### Citation:

Landovitz, et al & HPTN 083 Study Team (2023). Efficacy and safety of long acting cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV infection in cisgender men and transgender women who have sex with men 1 year after study unblinding: a secondary analysis of the phase 2b and 3 HPTN 083 randomized controlled trial. *The lancet. HIV*, 10(12), e767–e778. [https://doi.org/10.1016/S2352-3018\(23\)00261-8](https://doi.org/10.1016/S2352-3018(23)00261-8)

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## Background

Use of long acting cabotegravir (CAB) for PrEP was approved in 2021. It was compared to oral PrEP with TDF in two large, 3-year randomized controlled trials. One (HPTN 083), was conducted in cisgender men and transgender women who have sex with men. It showed a 66% reduced risk of HIV acquisition for CAB compared with TDF (0.41% CAB vs 1.22% TDF). The other trial was conducted among cisgender women in high incidence African countries and showed an 89% risk reduction (0.21% vs 1.79%). Efficacy of TDF is directly linked to adherence. The trial here looks at data from HPTN 083 in its first year after unblinding.

## METHODS

Patients 18yo and in good health were initially enrolled if they were HIV negative as assessed by negative HIV rapid and Ab/Ag testing at screening and study entry and a negative RNA test  $\leq 14$  days prior to study entry. Excluded were people using drugs, those with coagulopathy, buttock implants or fillers, a seizure disorder, QTc  $> 500$  ms, hepatitis B sAg+, or hepatitis C positive. Participants were from 43 sites across the world including the US.

Patients were randomized to injectable CAB vs daily TDF. Those getting injectable had daily oral cabotegravir lead in x 5wks. This study reports data from HIV infections “that occurred during three periods: the blinded phase (infections that occurred before May 15, 2020 [when study was stopped early due to meeting noninferiority criteria]); the first unblinded year (infections that occurred between May 16, 2020, and May 15, 2021, limited to infections that were detected by study sites before Nov 15, 2021); and the combined period (blinded phase plus first unblinded year).”

Though this report presents somewhat confusing statements about medication assigned in this year after the initial three-year trial<sup>1</sup>, the abstract, discussion, and other sources relate that in this year, while waiting for the open label extension, patients were unblinded but stayed on their originally assigned medications.

The primary outcome was incident HIV infection. This was originally assessed by rapid HIV and HIV Ag/Ab only, though samples were collected and retrospectively used for RNA assays and resistance testing. Infections were classified and examined in various groups depending on timing and relationship to any missed injections. Cases were excluded if they occurred more than 3yrs after study initiation.

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<sup>1</sup> In one place it says placebos were stopped and patients continued on their originally assigned medication. In another it says patients were transitioned to oral TDF for one year and then entered into open label extension (OLE) where they could choose CAB vs oral TDF.

## MAIN RESULTS

4566 participants enrolled (88% cisgender MSM, 13% transgender women who have sex w men). 4488 contributed to the blinded analysis and 3290 contributed to the first year of unblinded follow-up. Average follow up time for the blinded period was 1.4 years with 85% of patients retained.

Table 1 (from the paper's Table 1, appendix) shows a summary of incident infections:

|                          | Total # cases | # incident cases | # cases included in the HIV incidence assessment <sup>†</sup> |
|--------------------------|---------------|------------------|---------------------------------------------------------------|
| Blinded phase (updated)  |               |                  |                                                               |
| CAB arm                  | 17            | 13 <sup>¶</sup>  | 13 <sup>¶</sup>                                               |
| TDF/FTC arm              | 44            | 41               | 41                                                            |
| First unblinded year     |               |                  |                                                               |
| CAB arm                  | 17            | 17               | 12 <sup>‡</sup>                                               |
| TDF/FTC arm              | 32            | 32               | 32                                                            |
| Total (updated analysis) |               |                  |                                                               |
| CAB arm                  | 34            | 30               | 25 <sup>‡</sup>                                               |
| TDF/FTC arm              | 73            | 73               | 73                                                            |

<sup>†</sup> This group is limited to incident infections that occurred <3 years after study initiation.

<sup>‡</sup> Excludes five infections that occurred >3 years after study initiation.

<sup>¶</sup> One prevalent (baseline) infection in the CAB arm was initially characterized as an incident infection and was included in the HIV incidence assessment in the primary study report; that case is not included here.

The annual incidence rates for the unblinded period were 2.2% for TDF and 0.76% for CAB, approximately 70% higher than in the blinded study. However, the hazard ratio for CAB vs TDF was similar over the two periods: 0.31 (0.17-0.58,  $p < 0.003$ ) for the blinded period, 0.35 (0.18-0.6,  $p < 0.021$ ) for the unblinded period, and 0.34 (0.22-0.53,  $p < 0.001$ ) for the combined period. Note that five CAB arm cases were excluded from the unblinded period for occurrence >3yrs after study initiation.

Overall, there were 25/2244 cases of breakthrough infection on CAB for the combined period. Most of these infections are explained by treatment delays and tail infections (here defined as time from last CAB btwn 10wks and 66wks) though 7 cases were discovered in those without such lapses. Of those 7 without lapses who developed infection, 1 started CAB in the setting of initially undetected acute HIV, 2 converted during the oral lead in and 4 converted in spite of on time injections. All seven of these had INSTI resistance.

INSTI resistance and breakthrough infections may have been avoided with the use of HIV RNA testing to catch earlier infection before it had time to become resistant. This is now recommended by the CDC at initial and fup visits. (Note though that some HIV RNA presence was so low it would not have been picked up with RNA standard testing).

Those who were infected due to delayed administration or during the tail period did not demonstrate INSTI resistance. (This was also true in the trial on cisgender women (Landowitz, 2022)). In addition, among those with infection more than 6months after last injection, there was also no INSTI resistance.

Based on these small numbers (n=7) the risk of INSTI resistance was high when it occurred in the setting of a breakthrough infection during good adherence, (risk =0.17% overall in the trial, but in 4/4 cases here). When starting or restarting treatment in undiagnosed HIV infection there was a 1/3 chance of resistance and when breakthrough occurred with erratic adherence or during tail period, there was no resistance.

Additional things to note but without describing in detail (please see text): TDF serum levels supported the prior evidence that breakthrough infection in the TDF group were almost entirely attributable to suboptimal adherence. Slight weight loss in the TDF group (<1kg) drove a small difference in weight between the two arms. INSTIs are known to affect lipids and glucose and indeed here there was a slight increase in total cholesterol and BP compared with TDF.

## **CONCLUSION**

Injectable CAB is superior to oral TDF for prevention of HIV in cisgender men and transgender women who have sex with men. Similar findings were demonstrated in trials for cisgender women in Africa and make injectable medication addition to the HIV prevention arsenal. Breakthrough infections with CAB are most common with treatment delay and only rarely occur with perfect adherence. The risk of INSTI resistance is very low and as with breakthrough may be mitigated through adherence support and use of HIV RNA testing to detect infection at earlier stages. Addressing system and patient barriers to adherence will be critical to supporting effectiveness and minimizing resistance as treatment moves into real world settings.

## **LIMITATIONS AND ADDITIONAL CONSIDERATIONS**

This study supports higher efficacy of injectable CAB to daily oral TDF. The exclusion of five cases in the unblinded period was done to follow preplanned protocol. Their inclusion would have reduced the degree of CAB superiority but probably not the overall findings. Still curious that the authors did not at least provide a point estimate if they were to include those cases. Also, we are not told who dropped out for the unblinded portion of the study. One might assume that dropouts select for more adherent individuals, but it could also select for people who could not afford treatment without a study. This may indeed be the case as in the blinded study, 47% of participants were in the US and 32% in Latin America while in the open-label phase, 22% were in the US and 54% in Latin America. (Cairns, 2022)

This leads to the most important consideration about translating this information to real life – adherence. Even in this trial, adherence to injectable and oral treatment waned over time. Though this may have been influenced by a high non-adherence rate in Peru where the COVID 19 pandemic hit with particularly severity, it is typical that transition to real world settings enhances logistic hurdles.

In insured populations practical considerations include prior authorizations to obtain medication (Koss, et al 2024). And for all groups, there is the need for more frequent visits and more expensive testing compared with oral therapy, all of which may threaten access to treatment.

Linked [here](#) is an abstract describing how low barrier implementation of injectable PrEP and ART can be feasible even in the most vulnerable populations. It speaks to the need for an organized system with dedicated time to program administration as well as incentives for adherence (\$10 per visit attended), and creative outreach to patients who do not follow up and may have inconsistent phone access (ie, street outreach, multiple collateral contacts).

On the whole, the most important takeaway from this study and its partner is that there is a new and very effective option to prevent HIV transmission in high-risk individuals. Experts share that as with contraception, having options is key to uptake. Because there is the likelihood of lower adherence with less structure and support, it will be important to garner sufficient staffing and system resources to adequately support patients and providers in taking advantage of this therapeutic option.

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