

**HIV Testing and Injectable Cabotegravir (CAB for PrEP) Introduction:
What are the implications for HIV prevention scale-up and the HIV response?**

AVAC/BioPIC and WHO

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Meeting Summary

Background/Rationale

With injectable cabotegravir for HIV prevention (CAB for PrEP) receiving US FDA regulatory approval and rapidly moving into implementation studies and access planning, the need to address potential challenges in roll-out has become more pressing. One challenge that has emerged is the risk of integrase inhibitor (INI) resistance arising in people who acquire HIV while taking CAB as prescribed. It is difficult to be certain of the drug resistance risk because of the small numbers of HIV infections that have occurred in the two PrEP trials (HPTN 083 and 084). Data from the small number of participants in HPTN 083 who had retrospective testing of blood samples using more sensitive diagnostics indicate that the risk of resistance may be greater when people who are in the acute phase start CAB or acquire HIV while receiving injections or early after stopping CAB use than during the pharmacologic “tail” phase after discontinuing CAB injections. However, further data from the open label extensions and implementation science projects will help to better understand and quantify these risks.

Although the number of breakthrough infections was low, initially reported as 16 (out of a study population of 4,570), these data have raised concerns around the sensitivity of HIV antibody tests which are currently used for monitoring in individuals using oral TDF/FTC and for people taking injectable CAB for PrEP. For example, the US CDC in its recent PrEP guidelines and the US FDA state the requirement for nucleic acid amplification tests (NAAT, also referred to as RNA or viral load testing) to be provided prior to initiation of CAB and prior to every CAB injection¹. However, a NAAT HIV testing protocol for CAB initiation and continuation will limit its implementation and access in low- and middle-income countries (LMICs). While NAAT are reasonably accessible and affordable in high-income settings, such testing is expensive and often limited even for treatment monitoring in many LMICs.

Experience with oral PrEP underscores that simplifying delivery and removing some monitoring requirements may increase access and decrease costs. Access to HIV testing services is needed for all people starting PrEP and periodically while taking oral PrEP and CAB. Guidance which only permits a NAAT-based testing strategy for CAB users could mean that in LMICs access to CAB could be limited in programs, reducing options for individuals and minimizing the potential impact of CAB on the HIV epidemic.

To address this emerging evidence, AVAC/BioPIC and WHO convened program implementers, testing experts, mathematical modelers, policy makers, donors and civil society for an initial think tank to: review the diagnostic landscape and current HIV testing protocols in LMICs and

¹ The FDA guidance, issued following the meeting, specifies a NAAT that is FDA cleared for diagnostics, which in practice means one of only two test brands.

the detailed analysis of the HIV infections occurring participants in the HPTN 083 trial; provide inputs into modeling assumptions based on the priorities and key questions identified by participants; learn about US CDC and WHO guideline development; and understand priorities and concerns from ministries of health and civil society representatives. The discussions underscored the implications and trade-offs for maintaining or revising current HIV testing strategies/algorithms for ARV-based HIV prevention in high-income settings and LMICs.

Topics were considered within the context of balancing what is ideal with regard to testing with what is feasible and acceptable to make CAB for PrEP implementation possible in settings with limited resources, capacity and infrastructure to conduct complex testing.

The US FDA approved CAB for PrEP on December 20, 2021, and other national medicines regulatory agencies are reviewing submissions for CAB for PrEP. As of mid-February 2022, [regulatory dossiers have been submitted for review](#) in Australia, Botswana, Brazil, Kenya, Malawi, South Africa, Uganda and Zimbabwe. [CDC announced updated guidelines for PrEP](#) on December 8; WHO is revising its PrEP implementation guidelines and will convene a guideline development committee for CAB in March 2022; and national governments will look to update guidelines in the coming months. Planning for implementation studies is underway, and they are expected to start in 2022.

WHO guidelines and the HIV testing landscape

Cheryl Johnson from WHO reviewed the types of HIV tests used in programs and research worldwide. Diagnostics are selected based on specific country contexts and the tests' operational characteristics: specimen and detection type; time to result; storage and stability; required staff and skill; equipment and consumables needed; and quality control. Other key factors include the aims of testing and the population within which they will be used; program impact; feasibility of implementation; and price and service costs. WHO guidelines include details on the characteristics and performance of specific tests. Key considerations for CAB for PrEP implementation include:

- WHO's existing guidance for establishing HIV status for oral PrEP users recommends using the same national testing strategy and algorithms for starting and continuing PrEP as is used in clinical and community HIV testing services (HTS) to maximize access and feasibility.
- Community testing and using tests that can produce rapid results can increase access and impact; both have been critical to scaling up testing in HIV programs. HIV self-testing (HIVST), which is increasingly being used in programs, is used as a first test; all reactive tests require additional testing for an HIV positive diagnosis. During COVID-19, HIVST has been used to keep PrEP monitoring going when clinic- and community-based testing was difficult.
- The "best" testing protocol for CAB for PrEP needs to balance any potential advantages of earlier HIV detection with NAT and its inherent higher costs and feasibility issues, with the cheaper, easier to perform rapid diagnostic tests (RDTs).
- Detecting all acute infections with available testing technologies is a significant challenge. None of the rapid diagnostic tests in routine use in LMICs can reliably detect acute infections before 6 weeks post exposure. Even the most sensitive NAT tests, which are not often in routine use in LMICs, cannot reliably detect HIV in the first 10-14 days.

- NAAT (viral load testing) is already limited in many LMICs and redirecting NAAT from treatment to prevention services may not be feasible or advisable. For example, within PEPFAR programs, many people on treatment receive one NAT per year to monitor treatment success. Where testing resources are limited, using NAAT capacity for PrEP monitoring will usually be a lower priority than for treatment programs.
- In the rare cases where people acquire HIV while taking PrEP, the ARVs can suppress replication of the virus and delay the production of antibodies, making these breakthrough infections hard to detect, especially with antibody RDTs. With CAB, the result of delayed diagnosis may contribute to the development of resistance associated mutations that would be expected to confer reduced susceptibility to integrase inhibitors. This is rare however, and it is not clear whether mutations will limit future treatment options.
- Working toward broader access and availability of NAT and the development of cheaper NAT technology is a current strategy for increasing effective ART monitoring and could potentially be considered for use in future long-acting (LA) PrEP programs. It has been proposed that pooled NAT sampling may be a useful tool to aid diagnosis of early breakthrough infections. This approach is currently being used for oral PrEP in Thailand.
- Any testing strategy will come with trade-offs: potentially delayed detection of HIV and possible development of drug resistance, versus curtailing access to CAB and missing the opportunity to prevent infections. It may also necessitate using non-INSTI ART to treat people who acquire HIV while taking injectable CAB. The global health community and countries need to balance the risks and benefits of specific testing protocols to maximize access and minimize the impact of possible resistance.

In depth analysis of breakthrough infections from HPTN 083

Raphael Landovitz, the HPTN 083 Protocol Chair, presented updated data from the trial. Detailed retrospective analyses of data from HPTN 083 suggest that the INI resistance occurred with breakthrough infections among participants receiving CAB oral or injections as prescribed and with CAB concentrations at concentrations that would be anticipated to be protective based on non-human primate models. Conversely, seroconversions during the tail phase when CAB drug levels were waning did not, in the very small number of infections in the trial, result in INI resistance.

In the four breakthrough infections, HIV infection in HPTN 083 would have been detected earlier with NAT testing, and details of each of these cases is available and were presented at [CROI 2022](#).

These data, while important, should be interpreted with caution as they are based on a small number of cases: both CAB and TDF/FTC were and are highly effective in preventing HIV acquisition. Similar “endpoint adjudication” for HPTN 084 is ongoing, with even smaller numbers, and were not available at the time of this meeting. The implications of these analyses for testing for CAB delivery are still being assessed, with some key takeaway points:

- Injectable CAB can delay detection of infection using standard HIV testing algorithms.

- Data are needed to evaluate the benefits of diagnostics which can detect seroconversions earlier and whether this can prevent INI drug resistance. NAT as a routine test for CAB monitoring will be assessed in HPTN 083 and 084 open-label extension studies.

Modeling Assumptions and Considerations

Modeling is a key component of building the policy and investment case for CAB for PrEP within the context of future prevention programs. Several different modeling consortia are exploring CAB for PrEP, including University College London (UCL) and the HIV Modelling Consortium, the HPTN and the Fred Hutchinson Cancer Research Center, the University of Washington, Emory University, and Massachusetts General Hospital. Andrew Phillips and Jenny Smith from UCL reviewed the status of these efforts and highlighted outstanding questions. The UCL HIV synthesis model has the capacity to focus on resistance and testing for CAB initiation and continuation in sub-Saharan Africa. Outputs from this model include INI resistance, HIV mortality, and viral load as well as HIV incidence and number of new HIV infections. It can factor in different HIV testing scenarios, for example separating people with acute HIV infection during initiation from continuation and monitoring. Priorities for follow up include:

- Generate information comparing infections averted with infections with resistant virus and the impact of different testing protocols on these outcomes.
- Model the impact of CAB for PrEP on overall resistance, comparing resistance resulting from CAB with that which would occur if people sero-convert and develop resistance while on treatment.
- Address whether earlier detection has an impact on resistance and disentangle the performance of different tests on timing of detection versus the sensitivity/specificity of detection.
- Query whether it is possible to provide CAB without NAT testing, and, if not, whether testing at initiation or during on-going monitoring while taking injections is more vital to detecting resistance. Examine tradeoffs of testing at different stages of initiation and monitoring to determine how much benefit increased frequency of testing yields in identifying resistance.
- Explore the implications for detection and cost of different testing protocols, for example using pooled samples, and 4th versus 3rd generation rapid tests.

Guidelines and HIV testing for PrEP

Dawn Smith from the US CDC previewed elements of its new guidelines for PrEP, which were [released on December 8](#), following the December 3 think tank and prior to the December 20 FDA approval. The guideline includes specific sections for oral PrEP and injectable PrEP and creates two algorithms for testing to determine HIV status, one for persons with no recent ARV exposure, and one for those with recent ARV exposure. It also includes resources for clinicians to consult on ambiguous results and to access specialized diagnostic testing for clients who acquire HIV while on PrEP. The guideline recommends HIV-1 RNA testing prior to initiating CAB injections, at one month following initiation, at each follow-up visit to receive an injection, and at quarterly visits for a year after discontinuing injections.

WHO is convening a guideline development group for CAB for PrEP in March 2022, with guidelines expected later in the year. The committee will look to make a recommendation on CAB as an additional choice for PrEP and outline implementation considerations that balance what is feasible in LMIC in terms of testing, program and service settings, providers, and other aspects.

- WHO guidelines and implementation guidance should take into account that requiring complex testing protocols may limit access to CAB in LMICs.
- The CAB for PrEP guidelines should reflect lessons from oral PrEP where WHO guidelines have sometimes been seen as overly restrictive and a barrier to PrEP use. Updated and revised oral PrEP implementation guidance will emphasize simplifying and de-medicalizing PrEP delivery and reaching users through differentiated services. These principles should be applied to CAB guidelines and implementation recommendations from the outset.

Key Considerations and Looking Ahead

- Determine whether early detection and how much earlier – will have an impact on drug resistance. Explore whether evidence from animal studies or other sources can inform understanding of the impact of delayed diagnosis on drug resistance, how critical earlier diagnosis is to prevent possible resistance, and by how long.
- Focus on practical actions to determine what works to detect acute HIV infections. Given that rapid tests cannot detect early acute infections, assess other approaches that could be used in programs to identify clients at greatest risk for acute infection and test these cases. For example, analyze existing protocols to screen out acute HIV infections for oral PrEP programs, how well they perform in detecting acute infections, and how they could be adapted or supplemented for CAB.² Explore the Thailand model of using pooled NAT sampling which may be more cost-effective in lieu of requiring NAT for each individual at initiation and during follow-up visits.
- Ensure that the suite of CAB implementation studies now being designed examines the effectiveness and acceptability of different specific testing protocols in a way that can be assessed and compared across studies. Design programs so that they can continue to assess and adapt testing protocols as implementation and roll-out ramps up.
- Analyze the performance of point of care or 4th generation rapid diagnostics (ELISA and RDTs) on detecting HIV in the stored samples from O83 and O84.
- Explore the implications of the December 2021 FDA decision and CDC guidelines for other settings.
- Advocate for expanded access to NAAT as well as more innovation and accelerating the development of new diagnostics while ensuring that NAT does not become a barrier to incorporating CAB for PrEP into prevention programs.

² A WHO systematic review identified screening tools for acute HIV infection that performed well, including their implementation in Kenya and could be a resource for CAB. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3858557

- Articulate a long-term vision and timeline for introduction of novel diagnostics and for strengthening laboratory capacity – which will require significant time and resources – to increase access to more sensitive diagnostics for future long-acting products.
- Convene targeted and ongoing meetings including:
 - Consensus for BioPIC to hold regular meetings with a core group of experts to address critical issues for CAB implementation as they arise.
 - Focused follow-up consultation with modelers to provide specific feedback on defining key outcomes and parameters for modeling resistance, including specific testing protocols to assess impact and cost-effectiveness.
 - Engage policymakers, advocates and other opinion leaders in countries to consider CAB introduction within the context of informed choice and simplified delivery approaches, including what testing strategies may be feasible within existing testing and PrEP programs and protocols. Identify questions to ensure that concerns are addressed through implementation research projects or other approaches. Work with other key actors and experts such as the African Society of Laboratory Medicine, the FIND Consortium and LSHTM in future discussions on testing and diagnostics.
 - AVAC-led consultation on HIV testing and implications for CAB with civil society advocates.

Resources

- [Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women](#) – *NEJM*, August 2021
- [CAB-LA PrEP: Early Detection of HIV Infection May Reduce InSTI Resistance Risk](#). *CROI*, February 2022.
- [Characterization of Human Immunodeficiency Virus \(HIV\) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083](#) – *JID*, August 2021
- [Enhancing HIV Prevention with Injectable Preexposure Prophylaxis](#) – *NEJM*, August 2021
- [Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring](#) – WHO, 2021
- [Consolidated guidelines on HIV testing services](#) – WHO, 2019
- [The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021. Update – A Clinical Practice Guideline](#) – CDC, 2021
- [Apretude \(injectable cabotegravir for PrEP\) Label](#) – FDA, 2021
- [Point-of-Care HIV Viral Load Testing: an Essential Tool for a Sustainable Global HIV/AIDS Response](#) – *Clinical Microbiology Reviews*, July 2019
- [Editorial: HIV prevention injection should be fast-tracked like COVID-19 vaccines](#) – *Spotlight*, South Africa
- [Implementation Science Questions for CAB-LA](#) – BioPIC, November 2021 (draft for discussion)
- [Injectable PrEP can make breakthrough infections hard to detect](#). *Aidsmap*, 10 Mar 2021
- [Advocate Primer on Injectable Cabotegravir for PrEP: Trials, Approvals, Rollout and More](#) – AVAC, February 2022