Coordinating Implementation Science for CAB for PrEP: HIV Testing

AVAC/BioPIC and WHO

5 June 2024, 8am EDT

Background/Rationale

In December 2021, following the first regulatory approval of cabotegravir (CAB) for PrEP by the US Food and Drug Administration, AVAC and WHO convened a Think Tank to explore issues relating to CAB for PrEP testing algorithms, seeking to balance concerns around a potential increase in integrase strand transfer inhibitor (INSTI) resistance with CAB for PrEP accessibility in contexts where RNA tests- the most highly sensitive tests with the shortest time to detection- are not widely available. To further explore a possible association between CAB for PrEP introduction and increased INSTI resistance, members of the HIV Modelling Consortium undertook a modelling exercise, presented at a webinar in April 2022, which concluded that whilst exclusive use of RNA testing for CAB for PrEP would reduce the projected rate of INSTI resistance, this would not necessarily lead to an overall reduction in HIV-related mortality. The models further concluded that HIV rapid diagnostic test (RDT)-based algorithms did appear to be sufficient for implementation and were more feasible and affordable. Further analyses undertaken using other models came to similar conclusions, and additionally found that CAB for PrEP could never be as cost-effective as oral PrEP if RNA testing was required. Based on the available evidence, and further in-depth discussions during a WHO-hosted Think Tank in June 2022, WHO officially recommended using national testing algorithms composed of quality-assured rapid diagnostic tests and enzyme immunoassays for initiation and continuation in their CAB for PrEP guidelines released in July 2022.

As of June 2024, 11 implementation science studies had started delivering CAB for PrEP via a variety of service delivery channels across Botswana, Brazil, Kenya, Lesotho, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. In addition, Malawi, Zambia, and Zimbabwe had begun integrating CAB for PrEP into their national PrEP programmes. As CAB for PrEP delivery began, several implementers observed challenges with HIV testing, specifically:

- Cases of early HIV infection identified through CAB programmes, sometimes not identified before CAB administration.
- Some negative rapid tests discrepant with RNA test results.
- Some positive rapid tests discrepant with RNA test results.
- Some cases of potential HIV acquisition and seroconversion while on CAB for PrEP.
- Some cases of suspected long-acting early viral inhibition (LEVI) syndrome, with users who are on CAB for PrEP showing very low viral loads after multiple negative tests.

As CAB for PrEP begins to scale up, there is a need to ensure that the field is addressing emerging issues with HIV testing while balancing public health benefits with accessibility, feasibility, and cost. This think tank provided an opportunity for CAB for PrEP implementers from both implementation studies and national programs, alongside WHO technical experts on HIV testing, to convene, discuss the emerging testing issues considering current guidelines, and come up with recommendations on a way forward.

Meeting Objectives:

1. Review HIV testing algorithms currently in use for CAB for PrEP initiation and continuation to understand and document challenges faced by implementers.
2. Ensure current WHO recommendations for CAB for PrEP testing are understood, and CAB for PrEP implementers are able to manage risks and complex cases without restricting access while finding the right public health balance.

Key Takeaways

RDTs are sufficient for use with CAB for PrEP initiation and continuation and in line with a public health approach to testing.

- The absolute number of discrepant test results observed so far in implementation studies and programmatic rollout has been small, though the rollout of CAB for PrEP is still in its early stages.
- According to a systematic review assessing turnaround times of viral load in LMIC , the median turnaround time was 35 or more days, meaning it is likely not a feasible testing strategy for PrEP initiation or continuation at this time.
- Implementers recognise that requiring RNA testing for CAB for PrEP initiation and continuation is a potential barrier to access, so a public health approach would not include RNA testing requirements for certain populations, such as pregnant and lactating people.
- Continuing to closely monitor the outcomes of HIV testing algorithms for CAB for PrEP will be critical particularly as in-country guidance for providers is being drafted.

Currently, there are no known advantages to using fourth generation rapid tests over third generation rapid tests for PrEP initiation and continuation.

- WHO has no recommendations or guidance on generation of test. A list of prequalified products is available and WHO recommends countries adhere to the general principles and testing strategies and algorithms outlined in their guidance.
- An analysis of evidence from the HPTN-083 trial of CAB for PrEP concluded that two rapid tests conducted together have sufficient positive predictive value to be used for CAB for PrEP initiation and continuation.
- Fourth generation rapid tests are highly sensitive, however evidence reviewed by WHO did not demonstrate that they detect acute HIV infection, nor did it suggest a substantial public health impact or benefit compared to other quality and prequalified tests. WHO is conducting a systematic review of fourth generation tests and nucleic acid testing (NAT) techniques, including their ability to detect acute infection, with a report expected in late 2024. A scoping review on the use of multiplex testing is also underway and will have a report around the same timeline to inform future guideline development plans.
- NAT techniques can be complementary and help rule-in acute HIV, though as incidence declines, cases of acute infection will continue to become rarer.
- Costs of tests vary by setting. An additional cost consideration of using fourth generation rapid tests is the increased complexity, training, and resources needed when dealing with antigen reactive and/or antigen reactive/antibody negative results as these require further testing to establish an HIV infection. Without immediate confirmation testing and treatment access available there would be limited value. Currently countries looking for evidence on which test to use as the first test in their algorithm are considering multiplex rapid tests – such as the dual HIV/syphilis RDT which is recommended in antenatal care, with male partners, key populations, in network testing, and with PrEP services, as this has evidence showing public health impact, cost-effectiveness, and cost-savings for HIV and syphilis and contributes to broader triple elimination goals. According to WHO technology landscaping, more multiplex tests are in the pipeline, making this is an emerging trend for consideration.

Addressing questions relating to CAB for PrEP and HIV testing may provide an opportunity to review HIV testing guidelines generally.

- HIV self-testing (HIVST) is currently under review by WHO for use with CAB for PrEP initiation and continuation. Even if not used for this purpose, HIVST has an important role to play in mitigating the risk of delivering CAB for PrEP to a user in the acute phase by increasing the frequency of testing.
- Governments would benefit from updated WHO guidance on diagnosis, which is often tied to access to publicly funded antiretroviral treatment.
- The use of self-testing is important to understand as other long-acting PrEP interventions enter the market and self-management and self-injection becomes feasible. It will be important to think of the future use cases and prepare evidence for future implementation priorities.

Actions and Next Steps

- WHO is releasing a new Consolidated Guidelines on Differentiated HIV Testing Services at AIDS 2024. This guidance reiterates that there are no recommendations for using fourth generation rapid tests and that there is no evidence of public health impact at this time.
- AVAC will schedule an in-person meeting at AIDS 2024 to follow up on testing issues with implementers and programmes rolling out CAB for PrEP.
- AVAC and WHO will ensure the conversation on testing continues in order to facilitate achieving the right balance between public health and scaling up. All implementers and programmes rolling out CAB for PrEP should share case reports relating to testing issues with Cheryl Johnson, copying Catherine Verde Hashim.

Additional Resources:

- WHO Consolidated Guidelines on Differentiated HIV Testing Services (July 2024)
- CAB for PrEP Integrated Study Tracker
- HIV Testing and Injectable CAB for PrEP Introduction: What are the implications for HIV prevention scale-up and the HIV response? (BioPIC Think Tank, December 2021)
- Modelling the impact of CAB for PrEP on INSTI resistance (BioPIC webinar, April 2022)
- What can modelling tell us about the scale-up of CAB for PrEP? (BioPIC factsheet, November 2023)
- Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study (The Lancet HIV, January 2023)
- High Rates of Missed HIV Testing Among Oral PrEP Users in the United States From 2018–2021: A National Assessment on Compliance With HIV Testing Recommendations of the CDC PrEP Guidelines (Open Forum Infectious Diseases, May 2024)
- WHO CAB for PrEP Guidelines (July 2022)
- The LEVI Syndrome: Characteristics of Early HIV Infection with CAB for PrEP (CROI 2023)
- Site-Based HIV Testing Assay Performance for Cabotegravir and TDF-FTC PrEP Failure in HPTN 083 (CROI 2024)
- The clinical effect of point-of-care HIV diagnosis in infants: a systematic review and meta-analysis (The Lancet, September 2022)