Coordinating Implementation Science for CAB for PrEP: Bridging from the HPTN 083 and 084 Open Label Extensions to Implementation

AVAC

AVAC/BioPIC and WHO

Tuesday, 14 March 2023, 9am - 11am EDT | Meeting Summary

Introduction

As plans for injectable cabotegravir (CAB) for PrEP implementation science studies begin to take shape, the BioPIC collaborative continues to foster coordination across projects, donors and regions, providing a platform for sharing and learning. This meeting was part of an ongoing series of BioPIC Think Tanks, started in September 2021. It focused on WHO's research priorities for CAB for PrEP, presented by Robin Schaefer (WHO), and emerging lessons from the ongoing HIV Prevention Trials Network (HPTN) 083 and 084 Open Label Extension (OLE) studies, presented by Raphael Landovitz (UCLA) and Sinead Delany-Moretlwe (University of Witwatersrand), to create an effective bridge from CAB for PrEP trials to implementation.

Meeting Objectives:

1. Share insights from HPTN 083 and 084 on CAB for PrEP patterns of use, the choice process, and provider and user perspectives during the transition from trial to OLE
2. Identify lessons from HPTN 083 and 084 OLE that may be applied in CAB for PrEP Implementation studies

Context

Each new HIV biomedical prevention tool that becomes available carries trade-offs between efficacy, safety, convenience, side-effects, and acceptability. For users that may find taking a daily pill challenging, the development of longer acting options, including injectables, which are more discreet than pills, could increase prevention choices and increase acceptability. To respond to the need for longer acting options, two randomised control trials were conducted to evaluate the effectiveness of injectable CAB for PrEP vs tenofovir disoproxil fumarate (TDF)-based oral PrEP.

The HPTN 083 study compared CAB for PrEP to daily oral PrEP use by cisgender gay and bisexual men and transgender women who have sex with men, and found risk of HIV acquisition reduced by 66 percent in the group taking CAB compared to those taking oral PrEP. Similarly, the HPTN 084 study compared CAB for PrEP to daily oral PrEP use among individuals assigned female at birth and found risk of HIV reduced by 89% in the group taking CAB. Both CAB and oral PrEP were found safe and effective in reducing HIV acquisition in these trials and the higher risk of HIV acquisition among those in the oral PrEP group was at least partly due to the adherence advantage conferred by CAB. Both trials were unblinded early based on recommendations from their Data Safety and Monitoring Board, while an amendment was sought and approved to transition to an OLE, where participants were given the option to remain on or switch to either oral PrEP or CAB for PrEP. This OLE has allowed investigators to collect information on method preference, use patterns, and user perspectives, as well as additional safety information. As investigators prepare to start CAB for PrEP implementations studies, there is an opportunity to garner insights from the OLE phase of the HPTN 083 and 084 trials, to provide valuable lessons on how to create an effective bridge from CAB for PrEP trials to implementation.

WHO Research Priorities for CAB for PrEP:

- Risk of HIV drug resistance (including impact on treatment efficacy) and optimal HIV testing approaches (WHO guidelines state that programmes can use current national HIV testing strategy/algorithm).
- Safety of CAB for PrEP during pregnancy and the post-partum period and how to deliver CAB for these populations.
- Implementation of CAB for diverse populations, particularly key populations not specifically included in trials.
- Implementation of multiple PrEP products, including ensuring informed choice and examining patterns of uptake, switching, and use of different PrEP products.
- Integration of CAB into differentiated service delivery models, including where and how to deliver services.
- Impact, costs and cost-effectiveness of delivering CAB for PrEP.

Key Highlights from HPTN 083 and 084 OLEs

- Implementation of CAB for PrEP must balance public health benefits with accessibility and affordability of services.
- The overwhelming majority of OLE participants chose CAB for PrEP over oral PrEP; however, this may not be representative of the population as a whole as participants had joined the trials specifically because they were interested in an injectable method.
- Users have complex reasons behind why they choose their preferred method that often go beyond efficacy. These may include comfort with taking daily pills, being in a serodifferent relationship where their partner takes daily pills, a dislike of injections, or the influence of providers or those in their social network; understanding these motivations will be critical to designing effective demand generation strategies.
- More data are needed on acceptability and use of CAB for PrEP in diverse populations, including adolescents, sex workers, people who inject drugs, and trans and gender diverse people. More data are also required for CAB for PrEP in pregnant and lactating people, including safety of CAB for PrEP in these populations.
- Both the 083 and 084 trials examined clinic-based delivery models only, but other service delivery models will be tested in upcoming implementation research studies.
- Cost-effectiveness studies using evidence from HPTN 083 and 084 suggest that CAB for PrEP can be cost-effective, particularly if priced one to two times the cost of oral PrEP, although uncertainty remains around these estimates and more studies are required across settings and populations. Further information on cost and cost effectiveness will be generated from ongoing and planned implementation research and modelling studies.

Mapping Research Priorities

The HPTN 083 and 084 trials and OLEs have begun to answer many of the priority research questions on CAB for PrEP; however, gaps remain. The table below maps out priority research questions against currently available evidence and highlights where further inquiry is needed.

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
HIV testing and drug resistance	What is the risk of integrase strand transfer inhibitor (INSTI) resistance?	In multiple participants, HIV acquisition during the pharmacokinetic tail did not result in INSTI resistance	Additional data on HIV acquisition, including during the pharmacokinetic tail, as initial number who acquired HIV was small
		Viral escape at high CAB levels can lead to INSTI resistance	The impact of INSTI resistance following CAB exposure on dolutegravir (DTG) as a first-line treatment[1]
		If HIV is not detected quickly after a CAB for PrEP failure, INSTI resistance can develop	Whether RNA testing can be useful clinically for detecting CAB for PrEP failure before INSTI resistance develops (being evaluated in the OLE), and if so whether and how it can be feasible to implement
	What are optimal HIV testing strategies?	If an early HIV infection is not diagnosed before CAB for PrEP is started, CAB can make it challenging to diagnose later on	How to resolve discrepant results and diagnose HIV, particularly where there is a discrepancy between RNA testing and rapid testing (being evaluated in the OLE)
		RNA testing may detect some infections earlier but there are a range of barriers, including costs, lengthy turnaround times, and lack of regulatory approvals, so it may not be feasible in many settings. Modelling by University College London suggests CAB still has a population-level benefit on HIV-related mortality despite increases in INSTI resistance, with limited impact of RNA testing[2]	How barriers can be minimised to catalysing the development, testing, and regulatory approvals for more sensitive HIV diagnostics that are cheap, have durable supply chains, and can be done at point of care in low and middle income settings Whether RNA testing can be useful clinically for detecting CAB for PrEP failure before INSTI resistance develops, and if so whether and how it can be feasible to implement

[1] This gap will be addressed in both the PICASSO study being run by Ezintsha and the Action R01 study run by University of California San Francisco and University of Pittsburgh

[2] See April 2022 BioPIC Think Tank- *Modelling Impact of Injectable Cabotegravir for PrEP on Drug Resistance* for further details

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
		Rapid tests can result in false positives due to frequency of testing and factors like co-infections, pregnancy, and steroid use	Optimal strategies for providers to manage false positives
		Viral load testing can also result in false positives; the HPTN 083 and 084 trials define positive as either any single RNA measurement at greater than 200 copies per millilitre (ml) or two RNA measurements at any level	Further follow-up with participants identified as false positives in HPTN 083 and 084 to confirm accuracy of positivity criteria used
Patterns of use	Is direct to injection CAB for PrEP without an oral lead-in safe, efficacious, and preferable to users?	In CAB/Rilpivirine (RPV) for treatment, direct to injection CAB has shown similar safety and efficacy profiles as that with an oral lead-in, though it is associated with lower CAB concentrations in users with high body mass index	Additional pharmacokinetics data on initiation of CAB for PrEP without an oral lead-in to understand generalisability of CAB/RPV for treatment findings (being evaluated in the OLE)
		In the countries that have begun the HPTN 083 OLE, 36% of participants have chosen the oral lead-in, while in HPTN 084 OLE, 15% have chosen the oral lead-in	Reasons for choosing the oral lead-in vs direct to injection
	Which users prefer CAB vs oral PrEP and why?	96% of participants in the HPTN 083 OLE in the USA chose CAB for PrEP- though this is not necessarily generalisable as participants had joined the trial because they were interested in CAB; there is no specific subgroup driving this choice disparity; 70% who chose CAB cited a preference for injections to pills generally, with only 15% citing efficacy as the reason for their choice	User preference outside the context of a CAB trial, and outside the USA

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
		78% of participants in the HPTN 084 OLE chose CAB for PrEP; those who chose oral PrEP noted fear of injection site pain, while those who chose CAB noted preference for a more discreet, convenient method; partners, family, and others were influential in decision making There were different patterns of choice of CAB vs oral PrEP at site level in HPTN 084, which could suggest multiple factors, including the influence of providers, users' social networks, and their community impacting choice; while this was not observed in HPTN 083, there were differences in choice of oral lead-in vs direct to injection at site level which may also have been provider or community influence	Reasons for method preference in real world contexts, including influence of providers and community in user choice
	Is CAB still safe and efficacious if given every three months?	Early data suggests some dose forgiveness in three month dosing in individuals assigned female at birth (AFAB), but not those assigned male at birth; however, some AFAB trial participants were found to have lower CAB concentrations at three months which may suggest lower efficacy[3] so three month dosing is not recommended	Data do not support three month dosing, and further research is not recommended with this formulation of CAB; more data is required on population and individual differences in the pharmacokinetics of CAB and its predictors, including why some individuals assigned male at birth got infected despite on-time injections

[3] See CROI 2023 presentation: Cabotegravir Pharmacology in the Background of Delayed Injections in HPTN 084

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
Safety, acceptability, and efficacy for diverse populations	Is CAB safe, acceptable, and efficacious for pregnant and lactating populations?	Participants in HPTN 084 who received CAB injections until a pregnancy diagnosis had residual CAB concentrations similar to non-pregnant populations, tolerated the residual CAB well, and experienced no congenital abnormalities	How well CAB is tolerated if it is continued throughout pregnancy, what dose adjustment may be needed during pregnancy, and association with adverse pregnancy outcomes, including more rare outcomes
	Is CAB safe, acceptable, and efficacious for people under 18 years old?	CAB has been found to be safe and efficacious in individuals over 35 kg, regardless of age The HPTN 083-01 sub study is evaluating whether CAB is safe and tolerable in cisgender men and trans women under 18, though data from this study has not yet been made available The HPTN 084-01 sub study found that CAB was safe and tolerable in cisgender women under 18, with 100% adherence to injection visits; 94% chose CAB in the OLE phase	Additional data on use of CAB in people of all genders under the age of 18
	Is CAB safe, acceptable, and efficacious for gender diverse populations?	HPTN 083 demonstrated that CAB is safe and effective for trans women	Data on use of CAB by trans men and non binary individuals
		Initial findings suggest feminising gender affirming hormone therapy (GAHT) does not impact CAB concentration	Data on impact of CAB on GAHT is needed Data on masculinising GAHT is needed
	Is CAB safe, acceptable, and efficacious for people who inject drugs?	HPTN 083 and 084 did not include individuals who reported injection drug use in the past 90 days, though on-study injection behaviour did not lead to discontinuation	Data on use of CAB by people who inject drugs

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
	Is CAB safe, acceptable, and efficacious for sex workers?	40% of participants in HPTN 084 reported transactional sex in the one month prior to enrolment; 20% of participants in the qualitative sub-study self identified as sex workers and noted they liked the discretion provided by CAB	Additional data on use of CAB by sex workers to answer questions on implementation and generate additional evidence on uptake and acceptability
Service delivery models	Where and how can providers deliver choice and acceptable services?	HPTN 083 and 084 were not designed to answer this question	Data on CAB delivery via a variety of service delivery models
	What are optimal strategies for liver function testing (LFT)?	Participants were screened for abnormal levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) at each visit, with 2.1% in HPTN 083 and less than 1% in HPTN 084 discontinuing due to concerns around liver function; these rates were the same in each arm of their respective studies and similar to what has been found in oral PrEP trials Participants who contracted Hepatitis C Virus (HCV) during the trials were not automatically discontinued though most had to discontinue due to LFT results	Additional data to confirm the liver safety of CAB for PrEP and whether there are any groups that may require monitoring, such as those with HCV or heavy alcohol use[4]

[4] ViiV reviews each study proposal/protocol and makes recommendations on ALT assessments based on the study proposal itself and the regulatory status within the country of study participants.

Category	Research Question	Evidence from HPTN 083/084 and Other Studies	Remaining Gaps to Be Addressed
	What are the optimal strategies for sexually transmitted infection (STI) screening?	Participants were screened for syphilis, chlamydia, and gonorrhoea (both studies) and trichomonas (084 only) at the start of the trials and OLEs and every 24 weeks thereafter; symptoms or an exposure could also trigger testing at any time The WHO issued guidance in September 2022 on optimal screening algorithms for PrEP programmes	Additional data to inform strategies to increase access to laboratory-based STI testing
		STI rates were not higher in the CAB arms of HPTN 083 and 084, though in general HPTN 084 found very high STI rates amongst AFAB participants	Optimal strategies to address high rates of STIs within PrEP programmes
Costing	How much does CAB for PrEP cost to deliver?	HPTN 083 and 084 were not designed to answer this question	Data on cost of CAB delivery via a variety of service delivery models
	At what price is CAB for PrEP cost effective?	Cost-effectiveness studies using evidence from HPTN 083 and 084 suggest that CAB for PrEP can be cost-effective, particularly if priced at one to two times the costs of oral PrEP	Data on cost effectiveness of CAB delivery via a variety of service delivery models

Key Takeaways and Recommendations

- Researchers carrying out implementation science studies on CAB for PrEP should take account of evidence from the HPTN 083 and 084 trials and OLEs as well as the remaining priority evidence gaps when designing and implementing projects.
- Coordination and harmonisation across implementation science is critical to ensure that outstanding research questions can be addressed in a timely manner.
- Initial data from the HPTN 083 and 084 OLEs suggest that the most important reason for choosing a PrEP product is unrelated to efficacy; users have complex reasons behind why they select their chosen method.
- To keep the Implementation Science Tracker up to date, all additions and changes should be shared with Catherine Verde Hashim.

Additional Resources:

- Summary of the HPTN 083 Study
- Summary of the HPTN 084 Study
- Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women, *NEJM*, August 2021
- Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women- Supplementary Appendix, *NEJM*, August 2021
- An Advocates' Primer on Injectable Cabotegravir for PrEP: Trials, Approvals, Rollout and More, AVAC, February 2022
- Cost-Effectiveness of Long-Acting Injectable HIV Preexposure Prophylaxis in the United States : A Cost-Effectiveness Analysis, *Annals of Internal Medicine*, February 2022
- Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial, *The Lancet*, April 2022
- Accelerating access and introduction of injectable CAB for PrEP, June 2022
- WHO Guidelines on Long-Acting Injectable Cabotegravir for HIV Prevention, July 2022
- Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis, *The Lancet HIV*, November 2022
- Cabotegravir Pharmacology in the Background of Delayed Injections in HPTN 084, CROI, February 2023
- CAB for PrEP Implementation Science Tracker, March 2023