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The Long-Acting Cabotegravir Tail as an Implementation Challenge: Planning for Safe Discontinuation

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Abstract

The long-acting feature of cabotegravir, an integrase-inhibitor highly effective in preventing acquisition of HIV in adolescents and adults, is both its greatest strength and a challenge to its implementation. Cab-LA is administered at 8-week intervals (after an initial loading dose) but has a long, variable drug “tail” that may leave users vulnerable to future drug resistance if they contract HIV during this critical period. The potential for cab-LA to meaningfully contribute to ending the HIV Epidemic is hindered by, among other factors, limited resources to guide patients and providers on how to safely discontinue injections. We suggest three key strategies to overcome this specific challenge: (1) Comprehensive patient education and counseling about the drug tail; (2) Training and coaching PrEP care teams, including clinical and non-clinical

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staff, on communication around the tail; (3) Adherence support strategies, including monitoring of cabotegravir drug levels after discontinuation, for a personalized medicine approach to safe discontinuation.

Keywords

PrEP; cabotegravir; implementation; drug level monitoring

Introduction

Oral pre-exposure prophylaxis (PrEP) is highly effective but underutilized, with only 25% of people deemed eligible for PrEP prescribed it in the United States (US).[1, 2] Novel forms of delivering PrEP, for example by injection, are appealing to some prescribers and may attract new people or support sustained use for existing users of biomedical HIV prevention methods. Recent FDA approval of cabotegravir-long-acting (cab-LA), an injectable integrase inhibitor and the first form of long-acting injectable PrEP, presents an opportunity to increase uptake and persistent use of PrEP. This may be particularly true among individuals for whom adherence to a daily oral medication or an event-driven schedule is challenging or undesired. Cab-LA also heralds a new era of HIV biomedical prevention choice for cisgender women in the US, who to date, have only been eligible for daily oral TDF/FTC. While many of the issues that we raise are critical globally, particularly in low- and middle-income countries, we restrict our focus in this commentary to the US settings in which we are working as social, behavioral, and clinical scientists. In addition, we recognize that other implementation challenges related to logistics of drug procurement, storage, and dispensation and navigation of coverage for insured, uninsured, and under-insured patients also hinder implementation and uptake of cab-LA. Our focus on the drug-tail is deliberately narrow and is focused at the level of the provider-patient interaction.

The long-acting feature of cab-LA is both its greatest strength and a challenge to its implementation. Cab-LA allows users to go eight weeks between injections but has a long, variable drug “tail” of waning drug levels, that may leave users vulnerable to future drug resistance if they contract HIV during this critical period. The tail is the period starting eight weeks after the last injection during which there are gradually declining drug concentrations over time, which could allow for the development of integrase-inhibitor resistance if a patient were to acquire HIV while sub-therapeutic levels of cabotegravir are present. To mitigate against this risk for patients discontinuing cab-LA, the CDC advises switching to an oral form of PrEP for as long as patients are at risk for HIV, but does not provide a time-frame for how long tail coverage is needed.[3] The manufacturer of cab-LA recommends that patients remain on oral PrEP “for up to 12 months or longer.”[4] However, data from the Phase 2a safety and pharmacokinetic (PK) study of cab-LA demonstrated significant inter-participant variation in the cabotegravir half-life; among these participants, 12-months of oral PrEP would result in too much coverage for some, but too little coverage for others (Fig. 1).[5] A limited number of empirical and modeling studies have examined potential predictors of inter-participant variability in cabotegravir half-life (e.g., sex, body mass index,

race/ethnicity, needle length),[6, 7] but have not reached consensus on what factors reliably predict difference in half-life, and specifically the length of the drug tail. Further, a key knowledge gap is what minimal concentration of cabotegravir is associated with risk of cabotegravir resistance – or put another way, what is a safe level of residual cabotegravir? Without more guidance and data on which to base counseling their patients, providers are "flying blind."

Why It Matters

Whether the cab-LA drug tail will lead to integrase-resistance and what impact this may have on HIV treatment remains unknown. However, because of the potential for such an outcome to have significant implications for individual and population health, this issue warrants consideration and attention. At the individual level, integrase inhibitors are a first-line treatment worldwide, thus resistance could severely undermine an individual's treatment options. At the population level, the spread of integrase-inhibitor resistant HIV could limit the ability to provide immediate ART and potentially rule out a whole class of highly effective drugs. Although HIV infection in the cab-LA arm of the two Phase 3 trials was rare with only 17 HIV infections out of 3896 randomized to cab-LA, of these, 5 out of 17 infections (29%) resulted in integrase resistance with 2 cases resulting in class-wide resistance.[8–10] None of these infections occurred during the "tail" phase, but the lack of documented seroconversions occurring during the period of waning drug levels may be attributable to the protocols in these two Phase 3 studies. Specifically, because the two studies met prespecified criteria for stopping early on the basis of efficacy, they were continued as open-label designs with trial participants switched to active cabotegravir injections rather than proceeding to Step 3 of the efficacy trials, during which participants would have discontinued cab-LA injections and switched to daily oral PrEP while under study observation. To our knowledge, there is no published data to date documenting outcomes for trial participants who discontinued injections, including those who were purposively transitioned to oral PrEP and those who simply discontinued on their own. Therefore, the absence of documented seroconversions during the drug tail is not evidence of the absence of a problem, but rather highlights a critical evidence gap that needs to be addressed by the scientific community to inform policy and patient care.

Further, while absolute numbers of integrase-resistant HIV infections in this Phase 3 study are very small, the preference for injectable PrEP documented in the literature [11–13] suggests thousands, if not tens of thousands, of individuals could initiate cab-LA in the next few years, leading to many more opportunities for integrase resistance to develop.[14] Compounding this, and as evidenced by the ~ 40% pooled estimate of 6-month discontinuation rate among > 22,000 oral PrEP users in observational real-world studies,[15] we expect that real-world discontinuation of cab-LA followed by continued need for HIV prevention will be higher than in patients enrolled in clinical trials.

Timely implementation of oral PrEP was initially hindered by low provider knowledge and lack of protocols for how to safely and effectively deliver it.[16–18] Similar delays in cab-LA implementation will result without more clear guidance on how to counsel patients about the drug tail and safely guide them through discontinuation. In addition, implicit

biases have been shown in several experimental studies to affect oral PrEP prescribing intentions among prescribers and medical students and similar patterns may emerge for cab-LA.[19, 20] Often mediated by providers' anticipation of patients' risk compensation and assessment of patients' potential to adhere, providers prioritized PrEP prescriptions for White over Black women,[21] men who have sex with men (MSM) and men who have sex with women (MSW) over men who inject drugs,[22] and heterosexuals over MSM.[23] The uncertainty of the cab-LA tail may leave providers more vulnerable to perpetuating existing inequities in PrEP access, basing prescription of injectable PrEP on default assumptions about who they believe will "reliably" return for injections or continue to engage in oral PrEP and PrEP services after discontinuing cab-LA.

In the context of an NIH grant to develop tools to support equitable implementation of newly approved PrEP formulations (R01MH123262), co-authors Meyers and Golub have recently interviewed staff at PrEP programs in diverse clinical settings around the US to elicit their perspectives on cab-LA implementation and its potential to either redress or exacerbate inequity (manuscript under development). Preliminary thematic analyses suggest that while PrEP providers are enthusiastic about the potential of cab-LA to provide a highly effective biomedical HIV prevention option specifically for people who have not been sufficiently engaged in PrEP until now – including adolescents and young adults, cisgender women, people who use substances, and people who are unstably housed – some providers are wary of introducing PrEP without more data and guidance on how to counsel patients about the tail. They also expressed concerns that the high cost of the injections and the provision of cab-LA in traditional medical settings that are not reaching those at highest risk of HIV with oral PrEP, will increase disparities in PrEP uptake along existing racial, ethnic, and socioeconomic lines.

On the patient side, the tail presents several challenges. First, if injectable and other new forms of PrEP are to have a population-level impact on curbing incident HIV infections, then new modalities will need to attract new users to biomedical HIV prevention. However, individuals who have chosen not to adopt oral PrEP to date, but would consider injectable formulations, may be unable or unwilling to adhere to an oral PrEP regimen to cover the tail. In our own investigation of interest in long-acting injectable versus oral PrEP among men who have sex with men in China, one third of study participants who said they would consider injectable PrEP would not use oral PrEP, [24] making it clear that PrEP prescribers who initiate patients on injectable PrEP will need strategies to support safe discontinuation among those who will not transition to oral PrEP. Second, the decision to stop PrEP is often driven by a decrease in perceived risk of HIV, despite program data that demonstrates high incidence of STIs and HIV after discontinuing.[25] Cab-LA users who discontinue injections may be hesitant to take oral PrEP if they no longer feel at risk for acquiring HIV, despite being vulnerable to acquiring drug resistant HIV. Across the two Phase 3 studies, 94% (73/78) of participants randomized to the oral TDF/FTC arm who acquired HIV infection during the study had drug concentrations indicating suboptimal adherence.[8–10] Adherence to daily oral TDF/FTC will likely be lower in a non-clinical trial setting without adherence support and close clinical monitoring. As every person who initiates cab-LA will at some point elect to stop injections, it is critical that cab-LA roll-out includes strategies

to prepare patients and their care teams for discontinuation, including approaches to address challenges to adherence to oral PrEP during the cab-LA tail.[26–29].

Potential Implementation Strategies to Address Challenges

Programs in the US that are planning to introduce cab-LA into their services must develop strategies to address the issue of the drug tail. Below we share three potential strategies that we are beginning to develop and implement in the Comprehensive HIV Program (CHP) at New York-Presbyterian/Columbia University Irving Medical Center that can be layered to provide maximum support to patients and providers as they safely discontinue cab-LA.

1. Ensure that information about the drug tail is part of every patient's decision-making calculus.

At minimum, every person who is considering initiating cab-LA should be provided with information about the tail and its implication for stopping or switching to a different PrEP regimen. The "teach back" method, which has been found to be effective at increasing patient comprehension across a wide range of settings and populations,[30] could be used so that the patient can demonstrate their understanding of the key issues and any misunderstandings can be clarified by their PrEP care team. If a patient decides to initiate cab-LA, they should articulate a game plan for discontinuation, including a commitment to communicate the decision to discontinue with the clinic and a plan on how to minimize their risk of acquiring HIV during the period of declining drug levels. Oral PrEP use is cyclical and seasonal, with patients starting and stopping frequently depending on sexual activity and perceived risk.[15, 31] However, most patients do not communicate their intention to discontinue using oral PrEP – patients simply do not return for visits. Therefore, it will be particularly important for patients and providers to engage in a plan-making process that emphasizes the need to remain engaged in care even after discontinuing. These strategies should be considered the minimum requirement for any program offering cab-LA.

2. To support patient decision-making, train and coach PrEP care teams, including clinical and non-clinical staff, on how to educate and counsel about the tail.

Explaining the need for oral PrEP coverage during the cab-LA drug tail is complex, requiring sufficient time to explain in plain language PK, acute HIV infection, and drug resistance. Rather than expecting individual clinics to craft their own counseling messages and training plans, we call for a centralized effort built on relevant psychological constructs to inform counseling approaches, designed with strong training pedagogy, and developed in partnership with community, including creation of materials in multiple languages. Such materials should include an algorithm with exemplar statements, consistent with evidence-based principles from motivational interviewing, to tailor health communication in ways that affirm and build patients' intrinsic motivation toward HIV prevention, including oral PrEP adherence. PrEP programs should consider whether the introduction of cab-LA provides an opportunity for task-shifting and the ways in which behavioral health specialists and non-clinical staff could contribute to this counseling work. To support scalability, video recordings modeling the use of these skills could be developed. Nascent efforts to develop materials by individual teams are underway (see for example https://hivbluprint.org/cabla)

and should be augmented by capacity building organizations with deep training experience and national reach, such as the HIV/STD Prevention Training Centers and AIDS Education and Training Centers.

3. Develop and expand adherence support strategies that provide feedback and future guidance to both patients and their PrEP care teams.

Adherence to oral anti-retrovirals for treatment and prevention are familiar problems, and adherence support strategies should be offered to patients specifically during the drug tail. Advancements in pharmacologic adherence measurement tools now make it possible to monitor both recent and cumulative adherence to several HIV and PrEP oral medications, including dried blood spots and point of care urine assays, both of which can be self-collected by the patient at home, to provide feedback that reinforces and informs their continued adherence.[32].

Once cab-LA assays are available commercially and covered by insurance, programs could take a personalized medicine approach to tailor oral PrEP adherence support during the cabotegravir tail to each patient's specific circumstance. Specifically, patients could provide monthly blood samples starting the month that they discontinue cab-LA to monitor the amount of residual cabotegravir and determine whether coverage of the tail with oral PrEP is still necessary for the following month. PrEP care teams would receive training and coaching in how to tailor their communication on adherence based on personalized drug level feedback, consistent with evidence-based approaches, like motivational interviewing. This would allow patients and their providers to track their "progress" in clearing the drug tail and would increase the salience of the recommendation for oral PrEP use, potentially leading to better adherence to the oral regimen. Such PK data collected over several months could also inform a personalized trajectory, allowing providers to project for patients when their drug tail may end.

If implemented at scale for all cab-LA users and collected anonymously and systematically through a centralized data collection system, widespread PK monitoring data could also address the critical knowledge gap about what factors may predict differences in drug tail durations across patient populations as well as operate as a reporting hub for incident HIV infections with evidence of drug-resistance and first-line treatment failure to quantify the extent to which the cab-LA drug tail is or is not contributing to rates of drug-resistance HIV infection and affecting HIV treatment strategies. Such real-world data will be invaluable for monitoring the public health impact of introducing cab-LA, particularly given the fact that neither Phase 3 study included the planned "tail" phase during which cab-LA discontinuation was to be studied for safety.

Concluding Thoughts

We propose that the potential for cab-LA to meaningfully contribute to ending the HIV Epidemic in the US is hindered by limited resources and information to guide patients and providers on how to safely discontinue injections – an outcome that will eventually be experienced by everyone who initiates cab-LA. Patients and providers need support on how to cover the highly variable drug tail when cab-LA concentration drops to sub-therapeutic

levels because without a plan (a) patients may be vulnerable to acquiring and transmitting integrase-resistant HIV during this period, and (b) providers may be unwilling to prescribe cab-LA to the patients who could benefit most from this new prevention tool. We propose three strategies to help patients safely discontinue cab-LA and hypothesize that they will lead to greater acceptability and uptake of cab-LA among patients and providers. Common across all these strategies is the critical role of clinical and non-clinical staff in the educating and communicating with patients. Training PrEP care teams in interpretation of drug level measurement, communication of the results, and counseling patients to motivate adherence will be critical to the success of these approaches.

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References

1. National Center for HIV VH, STD, and. Prevention TB,. PrEP for HIV Prevention in the U.S.: National Center for HIV, Viral Hepatitis, STD, and TB Prevention; 2021 [Available from: https://www.cdc.gov/nchhstp/newsroom/fact-sheets/hiv/PrEP-for-hiv-prevention-in-the-US-factsheet.html#Sect.2.
2. U.S. Department of Health and Human Services. Ending the HIV Epidemic in the U.S.: U.S. Department of Health and Human Services; 2021 [updated 07/2021. Available from: https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview.
3. Centers for Disease Control and Prevention. US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. Centers for Disease Control and Prevention; 2021.
4. ViiV Healthcare. Apretude Full Prescribing Information In: Healthcare V, editor. Research Triangle Park, NC 27709: GlaxoSmithKline; 2021.
5. Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. PLoS Med. 2018;15(11):e1002690. [PubMed: 30408115]
6. Lazarus G, Wangsaputra VK, Christianto, Louisa M, Soetikno V, Hamers RL. Safety and Pharmacokinetic Profiles of Long-Acting Injectable Antiretroviral Drugs for HIV-1 Pre-Exposure Prophylaxis: A Systematic Review and Meta-analysis of Randomized Trials. Frontiers in Pharmacology. 2021;12.
7. Han K, Baker M, Lovern M, Paul P, Xiong Y, Patel P, et al. Population pharmacokinetics of cabotegravir following administration of oral tablet and long-acting intramuscular injection in adult HIV-1-infected and uninfected subjects. Br J Clin Pharmacol. 2022.
8. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022.
9. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385(7):595–608. [PubMed: 34379922]
10. Marzinke MA, Grinsztejn B, Fogel JM, Piwowar-Manning E, Li M, Weng L, et al. 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. J Infect Dis. 2021;224(9):1581–92. [PubMed: 33740057]
11. Biello KB, Hosek S, Drucker MT, Belzer M, Mimiaga MJ, Marrow E, et al. Preferences for injectable PrEP among young US cisgender men and transgender women and men who have sex with men. Arch Sex Behav. 2018;47(7):2101–7. [PubMed: 28929260]

12. Chan C, Vaccher S, Fraser D, Grulich AE, Holt M, Zablotska-Manos I, et al. Preferences for current and future PrEP modalities among PrEP-experienced gay and bisexual men in Australia. AIDS Behav. 2022;26(1):88–95. [PubMed: 34142274]
13. Footer KH, Lim S, Rael CT, Greene GJ, Carballa-Diéguez A, Giguere R, et al. Exploring new and existing PrEP modalities among female sex workers and women who inject drugs in a US city. AIDS care. 2019.
14. Phillips AN, Bansi-Matharu L, Cambiano V, Ehrenkranz P, Serenata C, Venter F, et al. The potential role of long-acting injectable cabotegravir-rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis. Lancet Glob Health. 2021;9(5):e620–e7. [PubMed: 33770513]
15. Zhang J, Li C, Xu J, Hu Z, Rutstein SE, Tucker JD, et al. Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis. Lancet HIV. 2022;9(4):e254–e68. [PubMed: 35364026]
16. Petroll AE, Walsh JL, Owczarzak JL, McAuliffe TL, Bogart LM, Kelly JA. PrEP awareness, familiarity, comfort, and prescribing experience among US primary care providers and HIV specialists. AIDS Behav. 2017;21(5):1256–67. [PubMed: 27885552]
17. Pleuhs B, Quinn KG, Walsh JL, Petroll AE, John SA. Health care provider barriers to HIV pre-exposure prophylaxis in the United States: a systematic review. AIDS Patient Care STDs. 2020;34(3):111–23. [PubMed: 32109141]
18. Storholm ED, Ober AJ, Mizel ML, Matthews L, Sargent M, Todd I, et al. Primary Care Providers' Knowledge, Attitudes, and Beliefs About HIV Pre-Exposure Prophylaxis (PrEP): Informing Network-Based Interventions. AIDS Educ Prev. 2021;33(4):325–44. [PubMed: 34370571]
19. Meyers K, Price D, Golub S. Behavioral and social science research to support accelerated and equitable implementation of long-acting preexposure prophylaxis. Curr Opin HIV AIDS. 2020;15(1):66–72. [PubMed: 31644482]
20. Gold J, Zucker J, Theodore DA, Carnevale C, Olender S, Gordon P, et al. Attitudes in Assessing Patients for Pre-Exposure Prophylaxis among Pediatric and Internal Medicine Residents Training in New York City. Late Breaker Abstract. HIV Research for Prevention October 21–25. 2018 Madrid, Spain. 2018.
21. Hull SJ, Tessema H, Thuku J, Scott RK. Providers PrEP: Identifying Primary Health care Providers' Biases as Barriers to Provision of Equitable PrEP Services. J Acquir Immune Defic Syndr. 2021;88(2):165–72. [PubMed: 34506359]
22. Calabrese SK, Kalwicz DA, Modrakovic D, Earnshaw VA, Edelman EJ, Bunting SR, et al. An Experimental Study of the Effects of Patient Race, Sexual Orientation, and Injection Drug Use on Providers' PrEP-Related Clinical Judgments. AIDS Behav. 2022;26(5):1393–421. [PubMed: 34750695]
23. Calabrese SK, Earnshaw VA, Krakower DS, Underhill K, Vincent W, Magnus M, et al. A Closer Look at Racism and Heterosexism in Medical Students' Clinical Decision-Making Related to HIV Pre-Exposure Prophylaxis (PrEP): Implications for PrEP Education. AIDS Behav. 2018;22(4):1122–38. [PubMed: 29151200]
24. Meyers K, Wu Y, Qian H, Sandfort T, Huang X, Xu J, et al. Interest in Long-Acting Injectable PrEP in a Cohort of Men Who have Sex with Men in China. AIDS Behav. 2018;22(4):1217–27. [PubMed: 28707025]
25. Greenwald ZR, Maheu-Giroux M, Szabo J, Robin JAB, Boissonnault M, Nguyen V-K, et al. Cohort profile: l'Actuel Pre-Exposure Prophylaxis (PrEP) Cohort study in Montreal, Canada. BMJ open. 2019;9(6):e028768.
26. Krakower D, Maloney KM, Powell VE, Levine K, Grasso C, Melbourne K, et al. Patterns and clinical consequences of discontinuing HIV preexposure prophylaxis during primary care. J Int AIDS Soc. 2019;22(2):e25250. [PubMed: 30768762]
27. Morgan E, Ryan DT, Newcomb ME, Mustanski B. High rate of discontinuation may diminish PrEP coverage among young men who have sex with men. AIDS Behav. 2018;22(11):3645–8. [PubMed: 29728950]

28. Scott HM, Spinelli M, Vittinghoff E, Morehead-Gee A, Hirozawa A, James C, et al. Racial/ethnic and HIV risk category disparities in preexposure prophylaxis discontinuation among patients in publicly funded primary care clinics. Aids. 2019;33(14):2189–95. [PubMed: 31436610]

29. Whitfield TH, John SA, Rendina HJ, Grov C, Parsons JT. Why I quit pre-exposure prophylaxis (PrEP)? A mixed-method study exploring reasons for PrEP discontinuation and potential re-initiation among gay and bisexual men. AIDS Behav. 2018;22(11):3566–75. [PubMed: 29404756]

30. Talevski J, Wong Shee A, Rasmussen B, Kemp G, Beauchamp A. Teach-back: A systematic review of implementation and impacts. PLoS ONE. 2020;15(4):e0231350. [PubMed: 32287296]

31. Rowe K, Theodore DA, Zucker J, Cohensedgh O, LaSota E, Carnevale C, et al. Lost2PrEP: Understanding Reasons for Pre-Exposure Prophylaxis and Sexual Health Care Disengagement Among Men Who Have Sex with Men Attending a Sexual Health Clinic at a Large Urban Academic Medical Center in New York City. AIDS Patient Care STDS. 2022;36(4):153–8. [PubMed: 35438522]

32. Spinelli MA, Haberer JE, Chai PR, Castillo-Mancilla J, Anderson PL, Gandhi M. Approaches to Objectively Measure Antiretroviral Medication Adherence and Drive Adherence Interventions. Curr HIV/AIDS Rep. 2020;17(4):301–14. [PubMed: 32424549]

33. Landovitz RJ, Li S, Eron JJ Jr, Grinsztejn B, Dawood H, Liu AY, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV. 2020;7(7):e472–e81. [PubMed: 32497491]

34. Andrews CD, Spreen WR, Mohri H, Moss L, Ford S, Gettie A, et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science. 2014;343(6175):1151–4. [PubMed: 24594934]

35. DiFrancesco R, Tooley K, Rosenkranz SL, Siminski S, Taylor CR, Pande P, et al. Clinical pharmacology quality assurance for HIV and related infectious diseases research. Clin Pharmacol Ther. 2013;93(6):479–82. [PubMed: 23588323]

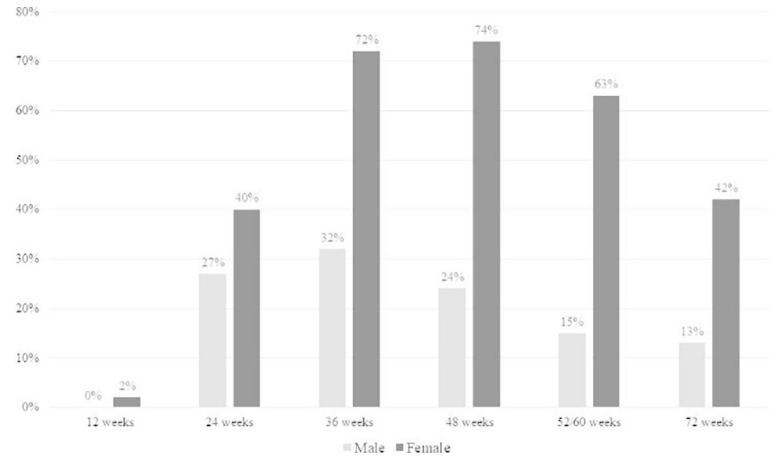

Fig. 1. Proportions of males and females with detectable but sub-therapeutic concentrations of cabotegravir aggregated by 12 weeks since last cabotegravir injection

Data derived from Phase 2a Safety and Pharmacokinetic study of cab-LA (HPTN-077).[33] Male cabotegravir concentrations > LLoQ-1xPA-IC_{90} are assumed sub-therapeutic based on simian-human immunodeficiency virus (SHIV) 162p3 rectal challenge model, in which plasma cabotegravir concentrations of less than one times PA-IC_{90} provided 45% protective efficacy, compared to control-untreated macaques.[34] Female cabotegravir concentrations > LLoQ - < 4x PA-IC_{90} are assumed sub-therapeutic based on in simian immunodeficiency virus (SIV) mac251 vaginal challenge model, in which plasma cabotegravir concentrations less than four times the PA-IC_{90} (166–664 ng/mL) were not protective compared to control-untreated macaques. [35] LLoQ = lower limit of quantification. PA-IC_{90} = protein-binding adjusted 90% inhibitory concentration.