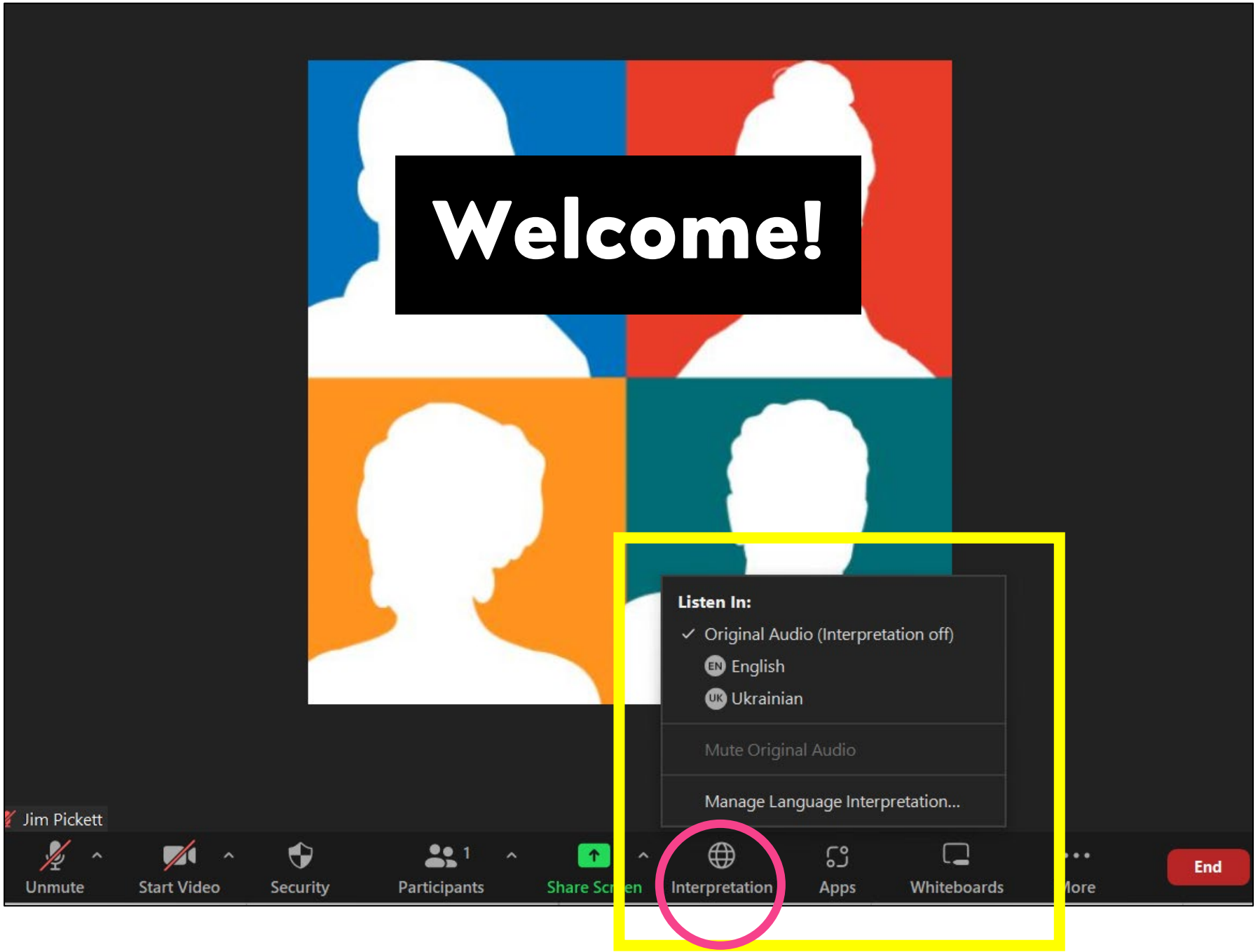

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THE CHOICE AGENDA

Faster, Smarter and More Equitable

Accelerating Roll Out and Uptake of CAB for PrEP

- Rachel Baggaley, WHO
- Mitchell Warren, AVAC
- Monica Gandhi, UCSF
- Caroline Carnevale, NY Presbyterian
- RJ Mitchell, Apretude consumer

Monday, August 8, 2022

AVAC
Global Advocacy for HIV Prevention

THE CHOICE AGENDA

- A very special welcome to our colleagues joining us from Ukraine today -

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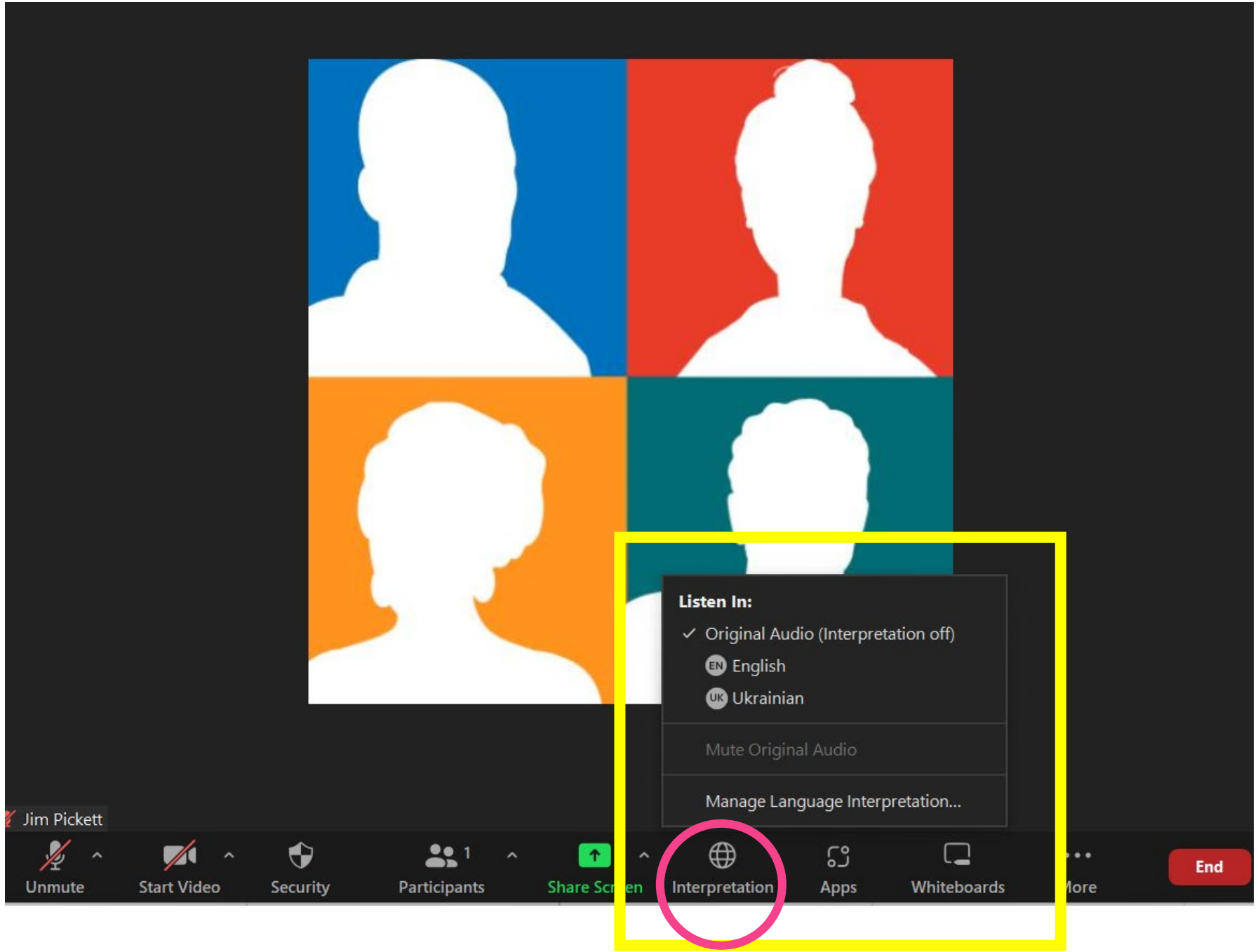

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More logistics

- This call is being recorded
  Your presence = consent
  - Please stay on mute, unless you are speaking
  - Qs after each presentation
- We will share links to recording and slides in follow-up email
- Access webinar resources here:
  - www.avac.org/choice-agenda

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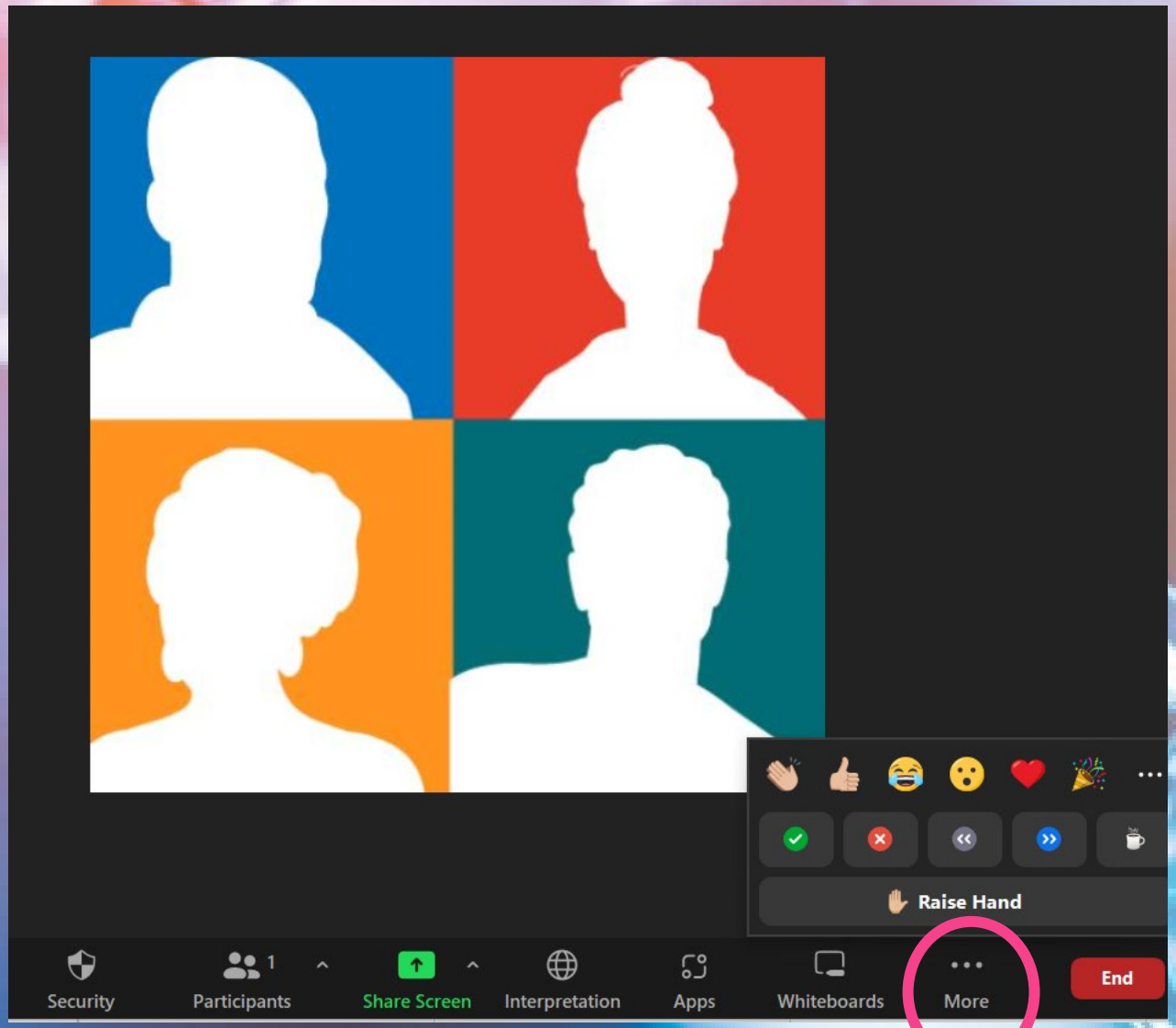

- **We will share today's slides and the recording**
- **Please comment, ask questions, share info/resources in the chat**
- **If you have answers to questions in the chat, please share in the chat. There is a lot of expertise here today!**
- **Raise hand to speak on camera**

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NEXT from TCA

WEBINAR

September 2022 (3rd week, stay tuned)

RINGing the Bell for Choice

Actions and Solutions on Dapivirine Ring Access

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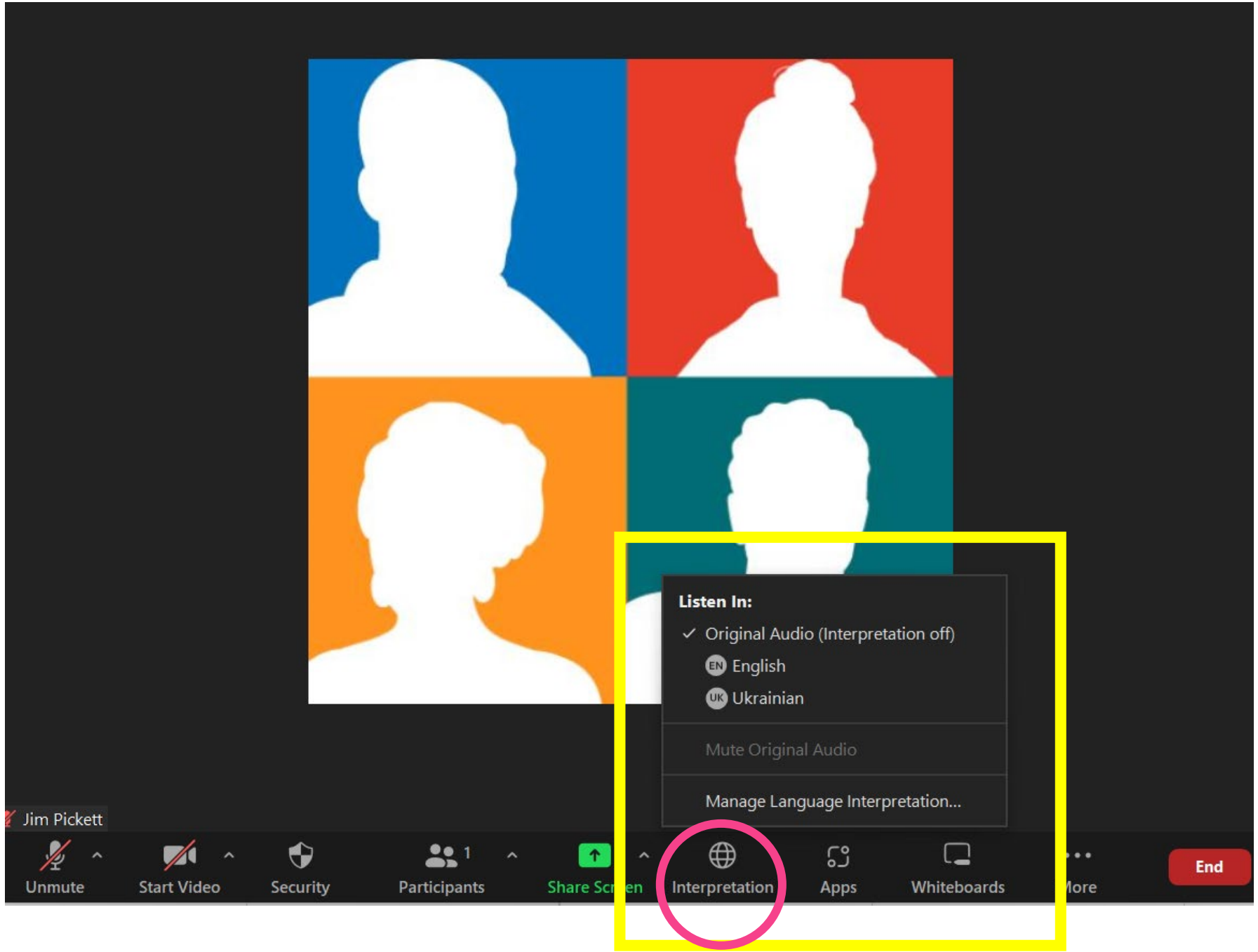

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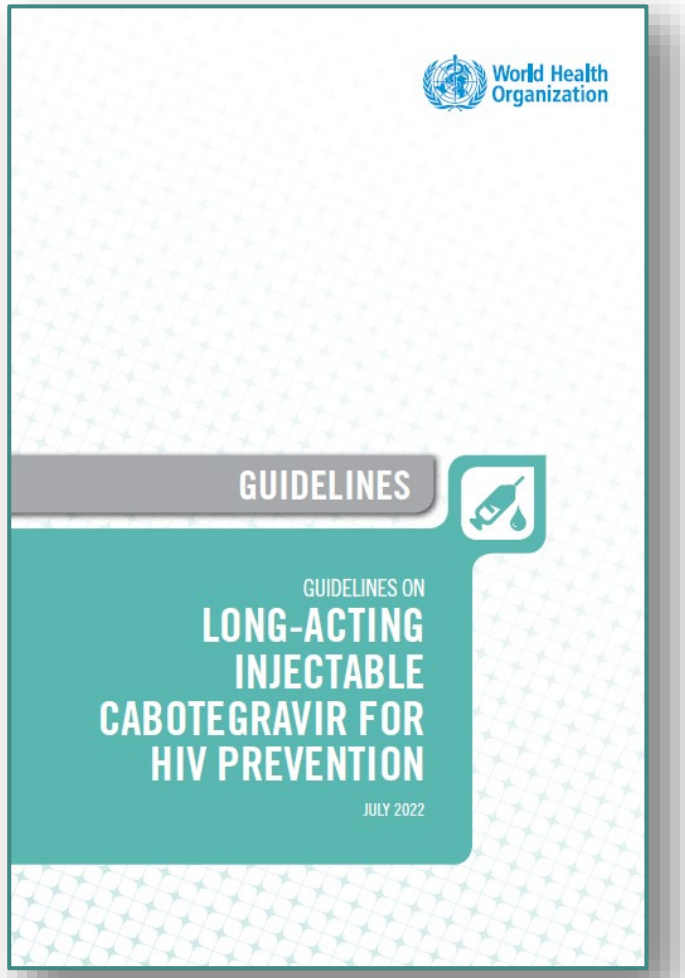

Long-acting injectable cabotegravir for HIV prevention

New WHO Guidelines

Dr Rachel Baggaley

WHO, Geneva

World Health Organization

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HIV prevention research - a new forum for advocacy on the latest

8th August 2022

Time: 9:00am ET / 1:00pm GMT / 15:00 SAST

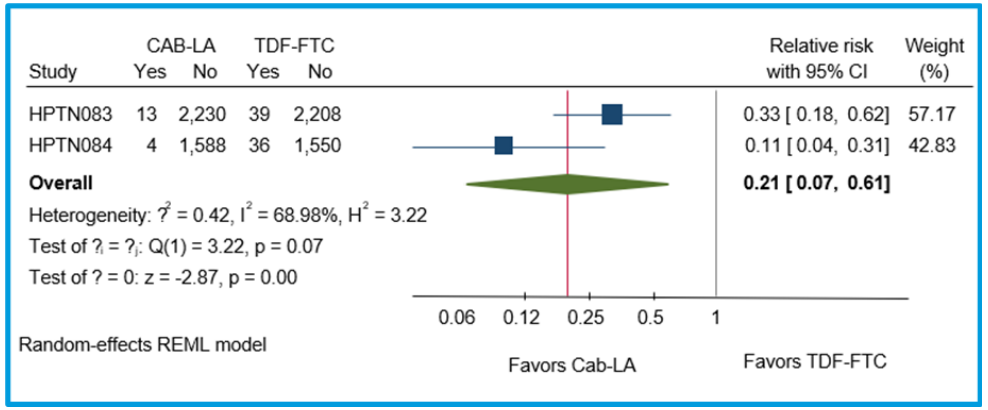
Long-acting injectable cabotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches

(conditional recommendation; moderate certainty of evidence)

CAB-LA is highly effective

Data from 2 large, multi-site RCTs across diverse populations suggest CAB-LA is a highly effective and safe biomedical HIV prevention tool

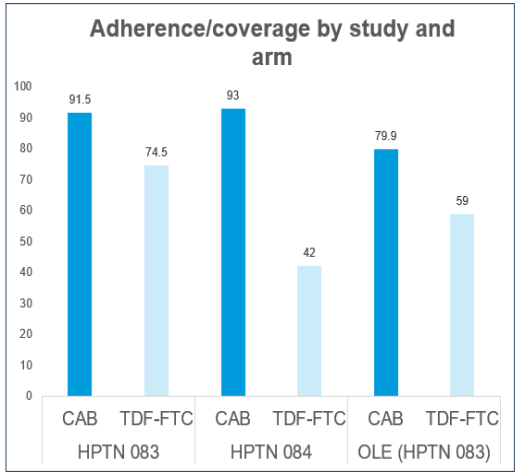
- CAB-LA reduces HIV incidence (RR: 0.21, 95% CI: 0. 07-0.61) - corresponding to a 79% relative risk reduction
- Note: Relative HIV risk reduction ranged from 66% in HPTN 083 to 88% in HPTN 084



Combined effect size across HPTN 083 and HPTN 084

High adherence to CAB-LA

- High adherence to CAB-LA across efficacy studies
  - Lower adherence to TDF-FTC
- Initial results from HPTN 083 OLE found decreased adherence to both CAB-LA and TDF-FTC in the first year following unblinding



Systematic review: Virginia Fonner

World Health Organization

CAB-LA is highly effective, but evidence gaps identified in WHO review

Gaps identified in review

- Data mainly from highly controlled trial settings; **"real world" data are lacking**
- **Data lacking for certain populations**
- Sparse (or non-existent) data on certain outcomes:
  - Sparse data on **drug resistance** (due to few cases)
  - Sparse data on **adverse events in pregnancy and breastfeeding** (being addressed in HPTN 084 OLE)
- **Lack of clarity regarding cost-effectiveness**

Additional areas with insufficient evidence

- Optimal HIV **testing approach**
- **Variability of CAB-LA pharmacokinetic properties** among disparate populations and individuals
- Extent and implications of **potential INSTI resistance** due to CAB-LA (and potential relevance to delays in detection)
- Supportive interventions to help **maintain adherence and overcome access barriers**
- Procedures for **switching to/from** CAB-LA from/to other PrEP modalities and for **stopping** CAB-LA

World Health Organization

New data following WHO review

Initial findings suggest there is no impact of gender affirming hormonal therapy (GAHT) on CAB concentrations

Transgender women (TGW) in HPTN 083: an evaluation of safety, efficacy, and gender affirming hormonal therapy (GAHT) interactions with long-acting cabotegravir (CAB-LA)

PRESENTER

Beatriz Grinsztejn

CAB drug concentrations measured in a subset of TGW who received on-time CAB injections (23 not taking GAHT, 30 taking GAHT).

CAB drug concentrations were comparable between the two groups, suggesting the lack of a GAHT effect on CAB PK

CAB-LA is a safe and effective HIV prevention strategy for TGW

HIV incidence reduction sustained in unblinded phase

- **CAB continues to be superior to TDF/FTC in preventing HIV infection cis-gender women**

Long acting cabotegravir: updated efficacy and safety results from HPTN 084

PRESENTER

Sinead Delany-Moretlwe

- 23 incident infections (3 CAB, 20 TDF/FTC) detected in the 12-month unblinded period.
  - 2 (1 CAB, 1 TDF/FTC) occurred during the blinded phase
  - 1 of CAB cases (blinded phase case) had ever received an injection.
  - ***Cumulatively***, 62 incident HIV infections (6 CAB, 56 TDF/FTC) observed over 6626 person-years of follow up (HIV incidence 0.94%, 95% CI 0.72, 1.20).
  - Superiority of CAB appears sustained (HR 0.11, 95% CI 0.05, 0.24)
- No new safety concerns were identified.
- 83 confirmed pregnancies (43 CAB, 40 TDF/FTC) occurred in the unblinded period
  - **No congenital anomalies reported**

CAB-LA is acceptable, but awareness limited

PrEP provider survey

(Mary Henderson, Robin Schaefer)

1353 responses (63% fully completed)

- 48% had heard about CAB-LA
- 71% would consider providing it if/when it gets regulatory approval; 6.6% would not provide it

Systematic review of values and preferences

(Lara Lorenzetti)

- Variability of preferences for injectable PrEP across regions and populations
- Injectable PrEP may best suit those with challenges taking daily oral PrEP, those valuing discretion, and those who have experience with other types of injectables

Values and preferences

(GATE, MPact, NSWP, INPUD)

- Interest and awareness varied across regions and population
- Choice is critical

"I think the injection, would be easier, because, once we inject, then we will inject it [again] the next month. Sometimes people forget to take the pill. Because if you're taking a pill, you must take it constantly at the specific time….but if it's an injection, then it's in your blood already….for me, that's good." Sex worker (46-50), Africa

NSWP Values and Preferences: Expanded Findings on PrEP

World Health Organization

Mixed results of CAB-LA cost-effectiveness

Included in the review

- 7 studies identified in systematic review
  - 6 involved modeling in South African context; 1 in U.S. context
- 4 unpublished preliminary results from:
  - model comparison of 2 HIC models (Atlanta and Montreal) and 2 South Africa models, plus 1 model for sub-Saharan Africa

Results

- Injectable PrEP cost-effective/cost-saving in some scenarios e.g., when targeting women in South Africa and when leveraged with complementary services or as MPT
- Injectable PrEP not cost-effective in other scenarios e.g., when targeting heterosexual men in South Africa

Wide variation in assumptions, including product cost.
Range: USD 6 per injection in South Africa to USD 25,850 per year in U.S.

World Health Organization

HIV testing for CAB-LA, a critical issue

HIV testing and drug resistance - limited experience outside trial settings

- Programmes should select a testing strategy & algorithm that promotes access to CAB-LA among those who would benefit most
- Programmes **can use current national HIV testing strategy**/algorithm (combination of RDTs &/or EIAs) as per WHO HIV testing recommendations
- **Some countries may include NAT**, in addition to the national algorithm, particularly at initiation.
    - Where NAT is used, important to have necessary assays, resources, regulatory approvals, and a clear testing strategy for resolving discrepant results and establishing HIV infection before initiating life-long ART

Ongoing monitoring of implementation is needed to further optimize HIV testing approaches for CAB-LA

While NAT might prevent a small number of cases of drug resistance, countries need to consider the feasibility of NAT. There are also uncertainties as to what impact these mutations will have on subsequent ART.

World Health Organization

Delivery issues I

Oral lead in

- FDA & company
  - Oral lead-in optional
- In OLE some clients choose oral lead-in; many don't

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APRETUDE safely and effectively. See full prescribing information for APRETUDE.

APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use
Initial U.S. Approval: 2021

2.4 Optional Oral Lead-in Dosing to Assess Tolerability of APRETUDE

The healthcare provider and individual may decide to use an oral lead-in with oral cabotegravir prior to the initiation of APRETUDE to assess the tolerability of cabotegravir or the healthcare provider and individual may proceed directly to injection of APRETUDE without the use of an oral lead-in *[see Dosage and Administration (2.5)]*.

Stopping CAB-LA and covering the tails

- In the RCTs, no cases of acquired INSTI drug resistance have been reported, to date, during the tail
- When stopping, discuss using other prevention options (condoms, PEP, other PrEP products), if client remains at risk of HIV acquisition

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215499s000lbl.pdf

Delivery issues II

World Health Organization

Pregnancy & breastfeeding

- Pregnancy & postpartum – periods of increased risk of acquiring HIV & increased risk of transmission to infants
- In HPTN 084 & HPTN 077 women required to take LARCs → therefore limited safety data
- CAB-LA use not contraindicated for PBFW – **but more implementation science/data needed**

Young people <18 years

- <18-year-olds were not included in ECLAIR, HPTN 077, HPTN 083, HPTN 084
- Additional studies including adolescent and young people are ongoing to assess safety and acceptability
- Young people frequently face additional barriers to accessing & effectively using other oral PrEP, and may require additional support for CAB-LA
- **Operational research with AGYW young KP a priority to understand preferences for products & acceptable effective delivery approaches**

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APRETUDE safely and effectively. See full prescribing information for APRETUDE.

APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use
Initial U.S. Approval: 2021

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to APRETUDE during pregnancy. Healthcare providers are encouraged to register individuals by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Cabotegravir use in pregnant women has not been evaluated. APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Because of detectable cabotegravir concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant.

The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of APRETUDE for

Delivery issues III

Providing CAB-LA for key populations

- HPTN 083 and HPTN 084 provided PrEP to MSM, transgender women & cisgender women
- Studies did not included people who use drugs or sex workers
- As SW & PWID could benefit from CAB, urgent implementation science needed

Choice and switching

- People who could benefit from PrEP have diverse HIV prevention needs and preferences, these may change over time
- A range of PrEP options should be available
- People interested in PrEP should be provided information on available options, relative efficacy and safety and counselled to make an informed decision regarding the best option for them
- Involving communities at all stages is critical – awareness, demand creation & delivery

Cost & cost-effectiveness

- Huge uncertainly - will depend on cost of product, service delivery costs and context/epidemiology/NNP (number needed to prevent)

CAB-LA, what is next for WHO?

WHO has added **CAB-LA to the WHO Expression of Interest (EOI)**, allowing the manufacturer to apply for inclusion on the WHO list of prequalified (PQ) medicinal products

Following this recommendation

- ❑ Global Fund etc. can include CAB-LA in its products for procurement
- ❑ Countries can consider how they would like to include CAB-LA in their prevention programmes

WHO is supporting and pushing for rapid implementation science

To answer important safety and implementation issues:

- ❑ Where to deliver
- ❑ Understand how people will choose and switch safely between PrEP options
- ❑ Provide further data on safety in pregnancy and breastfeeding – need for more prevention choices in ESA
- ❑ Monitor drug resistance and review testing approaches
- ❑ For geographies and populations (including sex workers and people who inject drugs) not included in the RCTs

WHO is collaborating on **global efforts for product availability and access**

WHO **updating PrEP implementation guidance** **to include CAB-LA (alongside oral PrEP and DVR)**

WHO **updating PEP guidance inc PEP🡐🡒PrEP**

World Health Organization

Thank you

Thanks to the **WHO HHS Testing, Prevention, and Populations** team for contributions to this presentation.

Contact the PrEP team for questions or comments:

- **Rachel Baggaley:** baggaleyr@who.int
- **Michelle Rodolph:** rodolphm@who.int
- **Robin Schaefer:** schaeferr@who.int
- **Heather-Marie Schmidt:** schmidth@unaids.org

WHO
Thanks to colleagues who supported the guidelines process:
Cheryl Johnson, Michael Jordan, Cadi Irvine, Anita Sands, Lara Vojnov, Belen Dinku and Valerie Amiel Fourtas

- **Amrit Ahluwalia** (Tufts University, Boston, USA)
- **Dobromir Dimitrov** (Fred Hutchinson Cancer Research Center, USA)
- **Virginia Fonner** (FHI360, USA)
- **Mary Henderson** (independent consultant)
- **Lara Lorenzetti** (FHI360, USA)
- **Andrew Philips** (University College London, UK)
- **GATE, Mpact, NSWP, and INPUD**

GDG group and peer reviewers

PEPFAR, USAID, Unitaid and BMGF who provide grants to WHO for work on PrEP

World Health Organization

Find the new WHO CAB-LA Guidelines here:

https://www.who.int/publications/i/item/9789240054097

Find the new Technical Brief here:

https://www.who.int/publications/i/item/9789240053694

WHO's global work on PrEP:

https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/pre-exposure-prophylaxis

WHO Global PrEP Network webinars:

https://www.who.int/groups/global-prep-network

Collaborative, Innovative Approaches to New Product Introduction

What Will It Take to Ensure Equity, Scale and Impact

Mitchell Warren

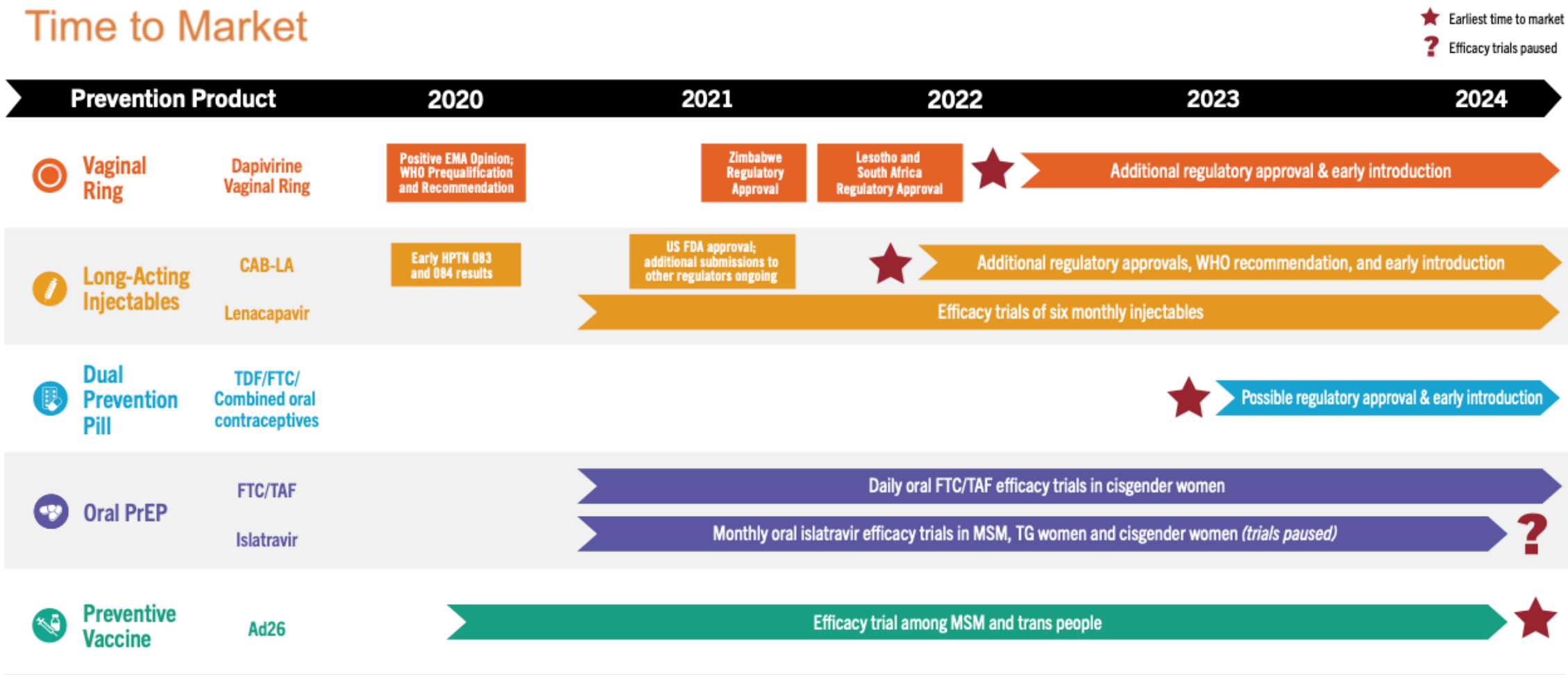
Executive Director, AVAC

The Choice Agenda: Faster, Smarter and More Equitable – Accelerating Roll Out and Uptake of CAB for PrEP

8 August 2022

AVAC
25 Years and Counting

Years Ahead in HIV Prevention Research



June 2022

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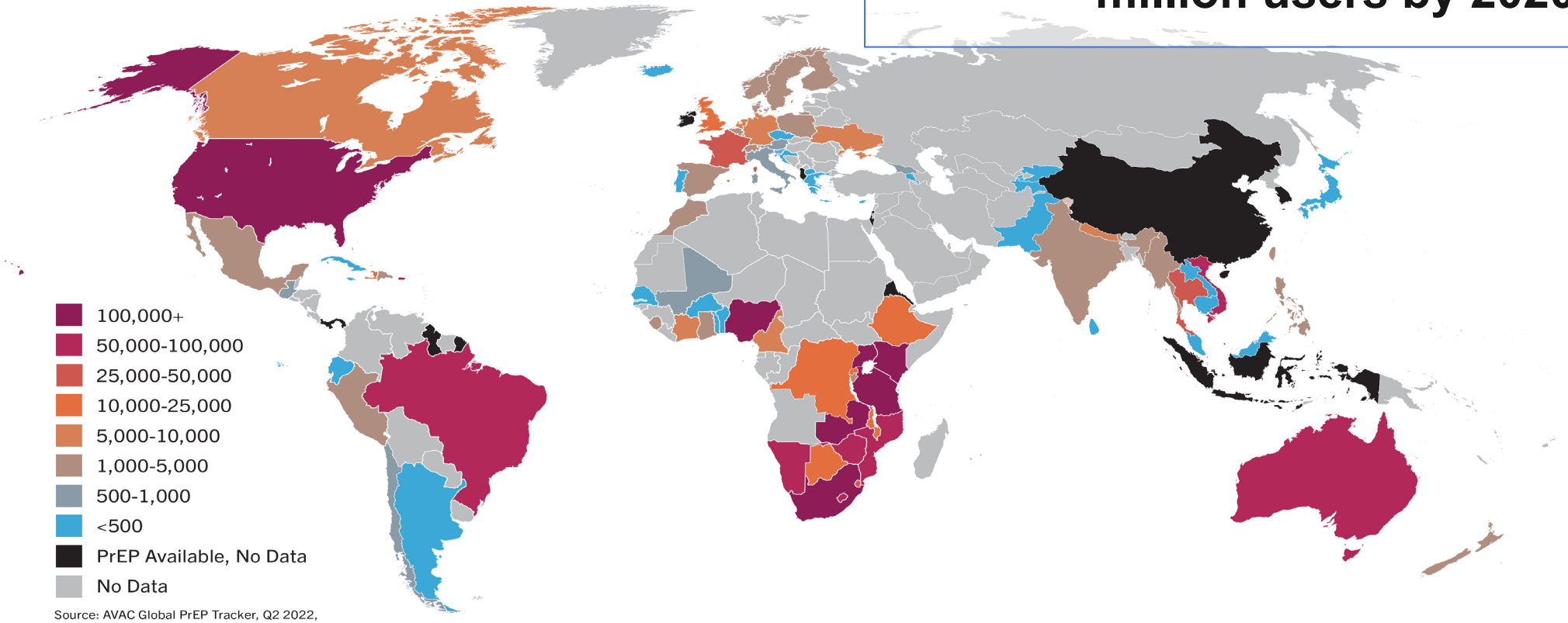
Global PrEP Uptake – 10 years in

Approx. total PrEP initiations: 2,797,304 with strong increases in 2021-2 – BUT significantly missed UN target of 3 million users by 2020



Source: AVAC Global PrEP Tracker, Q2 2022, https://www.prepwatch.org/country-updates/

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Learning from and Building on Oral PrEP

Oral PrEP Implementation Studies

Post-approval studies and projects

131 Distinct post-approval oral PrEP implementation projects and studies; most were small-scale

Countries

68 Different countries conducted projects including multiple in the same country (e.g. 25 in one country)

Stakeholders

54 Different organizations involved in oral PrEP implementation research

Key Takeaways from early Oral PrEP rollout

Post-approval studies were not all designed to address decision-maker questions

Data from research was not well timed to inform decision making at global or country level

Complex, fragmented stakeholder landscape

Lessons Lessons From Oral PrEP Programs & Implications for Next Generation Prevention

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The Way Forward

Requirements of Collaboratively Planning for Successful Introduction:

- **Mapping decision-maker questions against studies**
- **Planning in parallel with clinical trials**
- **Shared strategy developed by diverse stakeholders**

Ideal Scenario for Future Px Products:

Post-approval studies are **well designed** to address decision-maker questions

Data from research is **well timed** to inform decision-making at global and country level

Coordinated stakeholder landscape with roles agreed upon in advance

[BioPIC CAB-LA initial Introduction Strategy]

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Guiding Principles

- Lead with Equity
- Center the Community and User
- Accelerate Scale and Speed
- Deliver Impact
- Work With What We Know, While Continually Adding To The Evidence-Base

Pathway to Access & Impact

Full Report *Translating Scientific Advance into Public Health Impact:*
A Plan for Accelerating Access and Introduction of Injectable CAB for PrEP
—available at **www.avac.org/blog/accelerating-access-and-introduction-injectable-cab-prep**.

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Pathway to Access & Impact

Pathway	Immediate Priorities
Product	▶ **ViiV** to license injectable CAB to the Medicines Patent Pool (MPP). ▶ **The MPP and ViiV** to work with generic manufacturers and donors, including Africa-based manufacturers, to expedite technology transfer and ensure sustainable supplies of the product. ▶ **Generic manufactures, with MPP**, to identify capital expenditure needs and timeframe to be able to develop capacity. ▶ **Innovative donor(s)** to fund capital investments needed for generic manufacturing to reach scale. ▶ **ViiV** to confirm publicly, maximum quantity and minimum price for 2022-2025. ▶ **Donors** to negotiate this price/volume guarantee to ensure sustainable supply for initial introduction period, given the timeline for generic licensing agreements and manufacturing upgrades (likely 4-5 years).
Regulatory Approval & Normative Guidance	▶ **Eight regulators** currently reviewing injectable CAB for PrEP to ensure priority review. ▶ **ViiV** to pursue widespread registration of CAB in high-burden countries. ▶ **ViiV** to register with WHO Pre-Qualification (PQ) to allow expedited registration in countries participating in WHO's Collaborative Procedure for Accelerated Registration process.
Planning & Budgeting	▶ **Governments and donors** to set targets for supply and programs at scale – what is needed and possible in 2022-2023 in implementation science projects, and what is needed from 2024 to begin programs at scale.

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Pathway to Access & Impact

Delivery / Supply Chain	▶ **Large, resourced and coordinated implementation studies** to begin immediately to answer critical questions about how CAB performs outside the clinic setting and across populations. ▶ **Provider training** materials and tools updated to incorporate CAB administration and implementation studies that assess the feasibility of task-shifting to expand the cadres of providers that are authorized and trained to administer injections and that offer choice (explaining efficacy, clinic visits, side effects, etc. of all methods available) and assist in shared decision-making.
Individual Uptake & Continued Use	▶ **Innovative demand creation** strategies (for injectable PrEP and for "choice" among options) developed with process to test and iterate, and share across projects.
Delivery / Supply Chain	▶ **Testing requirements** should not become a barrier to CAB introduction. Testing strategies should be both robust and feasible and work with locally available tests and assays to, maximize the benefits of access to CAB while minimizing the risk of undetected cases.
Research	▶ **Data to be collected on the benefit of injectable CAB as PrEP for populations that were not part of efficacy trial**s, especially adolescents, pregnant and breast-feeding people, and transmasculine and gender non-conforming individuals. ▶ **Study alternate injection sites and frequency of injections**, recognizing that the impact of injectable CAB holds the potential to expand, if the injection schedule could align with injectable contraception.
Stakeholder Engagement	▶ **Integrate and engage civil society** in all decision-making relevant to planning and preparation for access to CAB, including designing, conducting and monitoring implementation studies and delivery programs.

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Coalition to Accelerate Access

- Convened by Unitaid, WHO, UNAIDS, Global Fund and PEPFAR, with AVAC as the Secretariat
- Coordinate key stakeholder activities on PrEP access, including:
  - Building on lessons learned from oral PrEP
  - Coordinate key stakeholder activities on PrEP access
  - Jointly develop strategies to identify and overcome access challenges for new PrEP options in the near to medium term (as relates to ViiV's injectable CAB, including generics, and dapivirine vaginal ring) and the medium to longer term (as relates to future PrEP products)
  - Ensure new, longer-acting PrEP options reaching the market will be available and equitably accessible to all who need them more quickly than ever before

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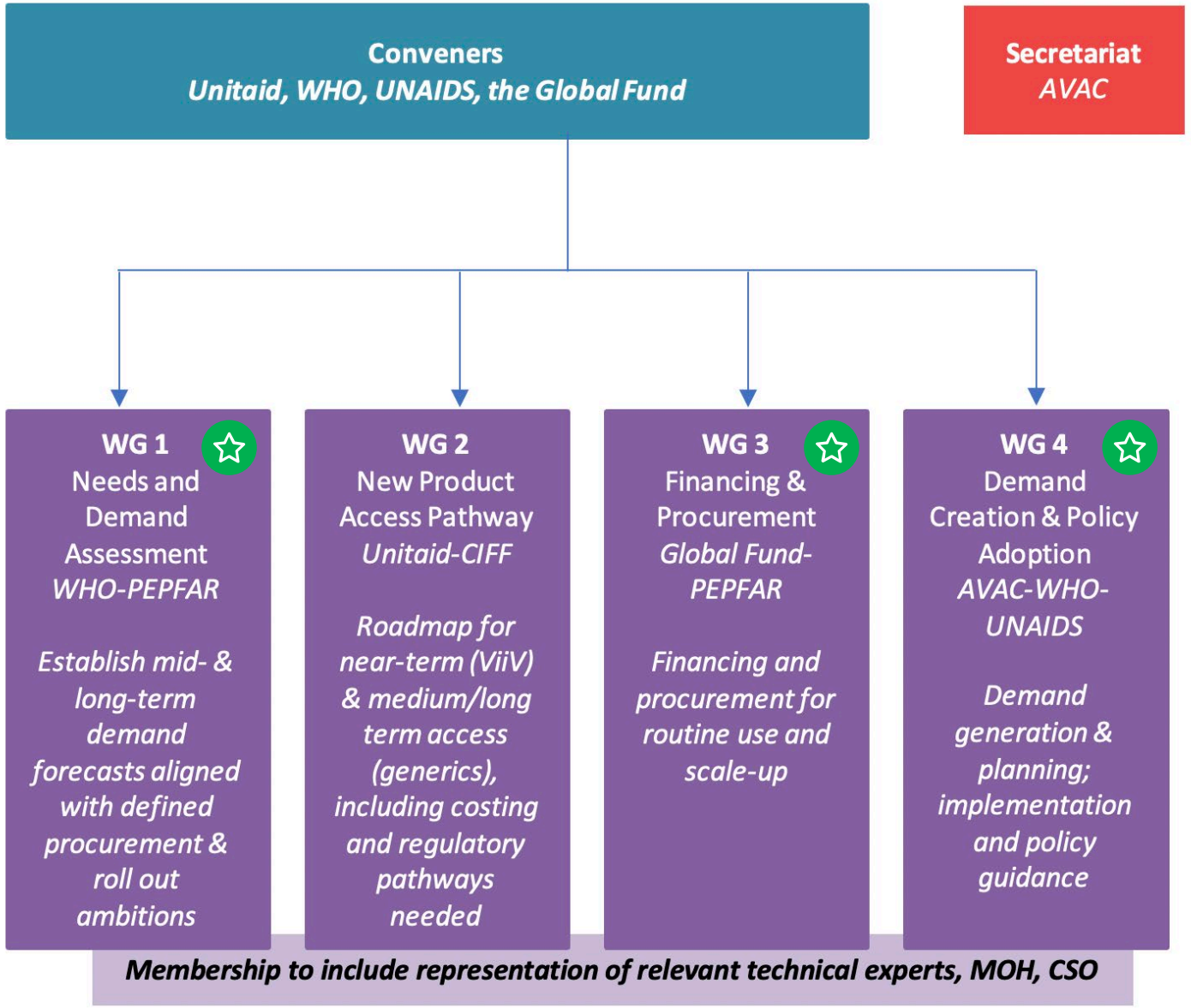
Coalition to Accelerate Access



IP/Voluntary License
MPP-ViiV

Implementation Science
WHO-AVAC-BioPIC

CSO Engagement
Various

Focused on Full Px Pipeline

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Product Considerations

For each product, understand and balance:

Clinical	Policy & Programs	Personal
▪ Biologic efficacy ▪ Dosing/duration ▪ Reversibility ▪ Side effect profile ▪ Systemic/Topical	▪ Delivery channel(s) ▪ Health system burden ▪ Product cost ▪ Program cost ▪ Provider training ▪ Demand creation	▪ User effectiveness ▪ User preference ▪ User burden ▪ Discretion of use ▪ Contribution to stigma

It's never just "the product" – it's the program;
new options can't solve for everything

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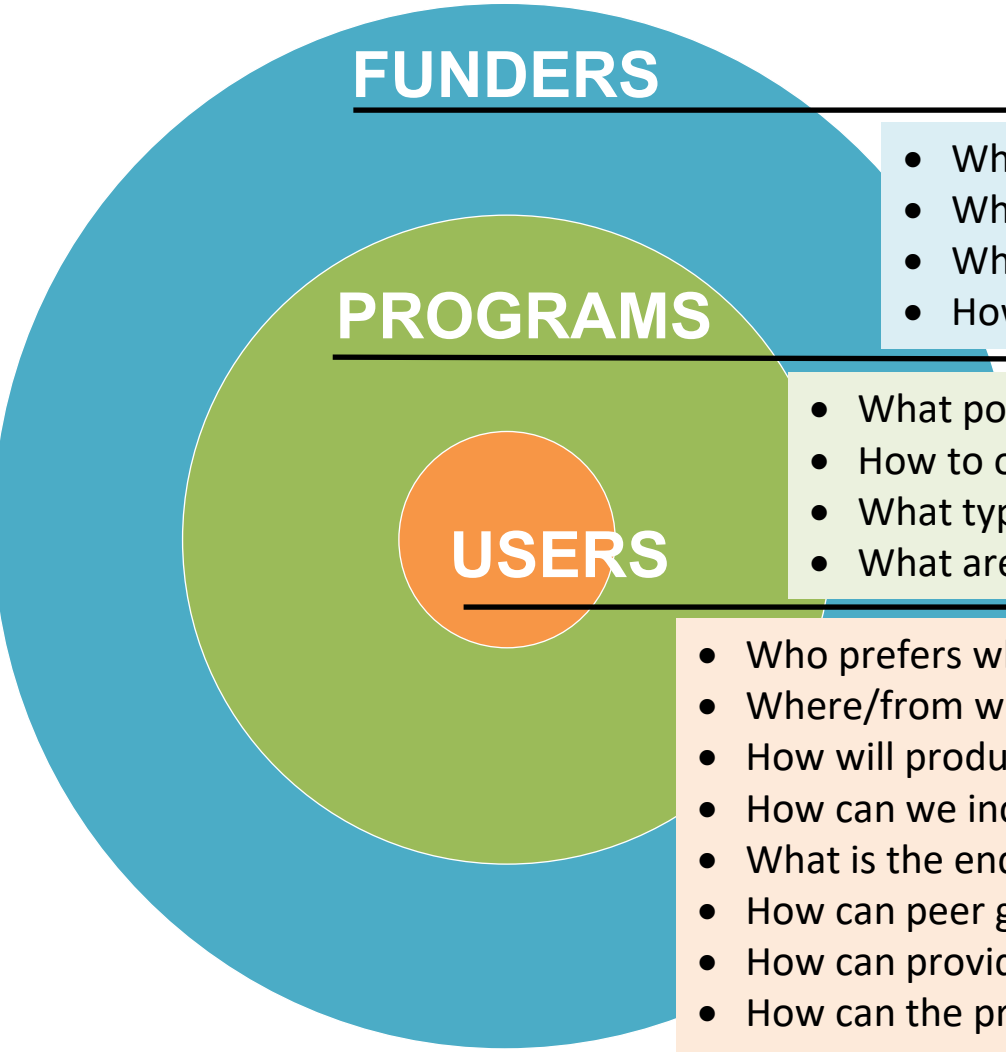
Accelerating Introduction of New Px Options

Those who Use; Those who Choose; Those who Pay the Dues



What we need to know – and fast

FUNDERS

- What is the cost for procurement AND for programming?
- What is the cost-effectiveness?
- What is the market size, generally and relative to other PrEP products?
- How will introduction affect the current market share and size of other PrEP?

PROGRAMS

- What policies need to change to to plan for & introduce new option?
- How to overcome siloes in procurement & service delivery?
- What type of training & support do providers need?
- What are optimal service delivery platforms and communication channels?

USERS

- Who prefers which option, and what are their motivators and barriers?
- Where/from whom do potential users desire to hear about and access product?
- How will product use/preference change over time?
- How can we increase & support adherence?
- What is the end user's path to initiation and continued, effective use?
- How can peer groups/influencers be leveraged to support uptake & adherence?
- How can providers be supported to have more knowledge and empathy?
- How can the product be packaged to better support uptake/ adherence?

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Now What?

- Translate biomedical options into viable choices for users, providers and health systems
  - Intro new options as part of marketing and programming for choice
  - Identify (and differentiate) service delivery models that work for users
  - Ask and answer critical implementation science questions for each product, while building prevention platforms for the future
- Understand testing and initiation needs for PrEP
- Ensure robust civil society engagement in intro/implementation research and planning
- Procurement/commodity funding – for launch and ongoing
- Provider training – both clinical guidelines AND appropriate counseling, support, empathy
- Realistic targets for interventions, especially intro – and not just coverage targets
- Identify what products can "solve for" – and what they can't
- Ensure we do better, more equitable intro with ring and injectable than with oral PrEP and COVID-19 vaccines

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25 Years and Counting

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- Kristine Torjesen
- Jacque Wambui

HIV Prevention Market Manager
Accelerating Product Introduction
Informing Product Development
Reducing Time to Impact
AVAC
Clinton Health Access Initiative
Supported by the Bill & Melinda Gates Foundation

BioPIC Biomedical Prevention Implementation Collaborative

Coalition to Accelerate and Support Prevention Research (CASPR)

Cooperative Agreement No. AID-OAA-A-16-00031
HIV Vaccine and Biomedical Prevention Research Project—Objective 3

PROMISE-CHOICE Partners

MOSAIC
Maximizing Options to Advance Informed Choice for HIV Prevention

CIFF Children's Investment Fund Foundation
Bill & Melinda Gates foundation
COMPASS

Faster, Smarter and More Equitable – Accelerating Roll Out and Uptake of CAB for PrEP

Monica Gandhi MD, MPH
Director, UCSF Center for AIDS Research and
Medical Director, Ward 86 HIV Clinic
Professor of Medicine, UCSF
AVAC: Global Advocacy for HIV Prevention
August 2, 2022

Daily PrEP trials with TDF/FTC–Adherence everything

Trial	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
iPrEX[1] (N = 2499)	MSM, 11 sites in U.S., S. America, Africa, Thailand	▪ Daily oral TDF/FTC	44% (95% CI 15-63, p 0.005)
Partners PrEP[2] (N = 4747)	Serodiscordant couples in Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC	▪ Women: 71%; men: 63% ▪ Women: 66%; men: 84%
TDF2[3] (N = 1219)	Heterosexual males and females in Botswana	▪ Daily oral TDF/FTC	62%* (underpowered for sex differences)
Bangkok TFV Study[6] (N= 2413)	IDU (use in last year) in Bangkok	▪ Daily oral TDF	49% (95% CI 9.6-72.2, p 0.01)
FEM-PrEP[4] (N = 2120)	High-risk women, Africa	▪ Daily oral TDF/FTC	▪ Study stopped early due to futility (adherence)
VOICE[5] (N = 5029)	High-risk women, Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC ▪ 1% TFV gel	▪ 1% TDF gel & daily oral TDF arm both stopped early, futile ▪ Daily TDF/FTC arm – no efficacy (adherence)
PROUD (N=523)[7]	High-risk men, U.K.	▪ Daily oral TDF/FTC, immediate vs deferred	86% (90% CI 58-96%, p=0.0002)

1. Grant RM. N Engl J Med. 2010. 2. Baeten JM. N Engl J Med. 2012 3. Thigpen MC. N Engl J Med. 2012; 4. Van Damme. N Engl J Med. 2012 5. Marrazzo J, N. Engl J. Med. 2015; 6. Choopanya Lancet June 2013; 7. McCormack. CROI 2015

Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis

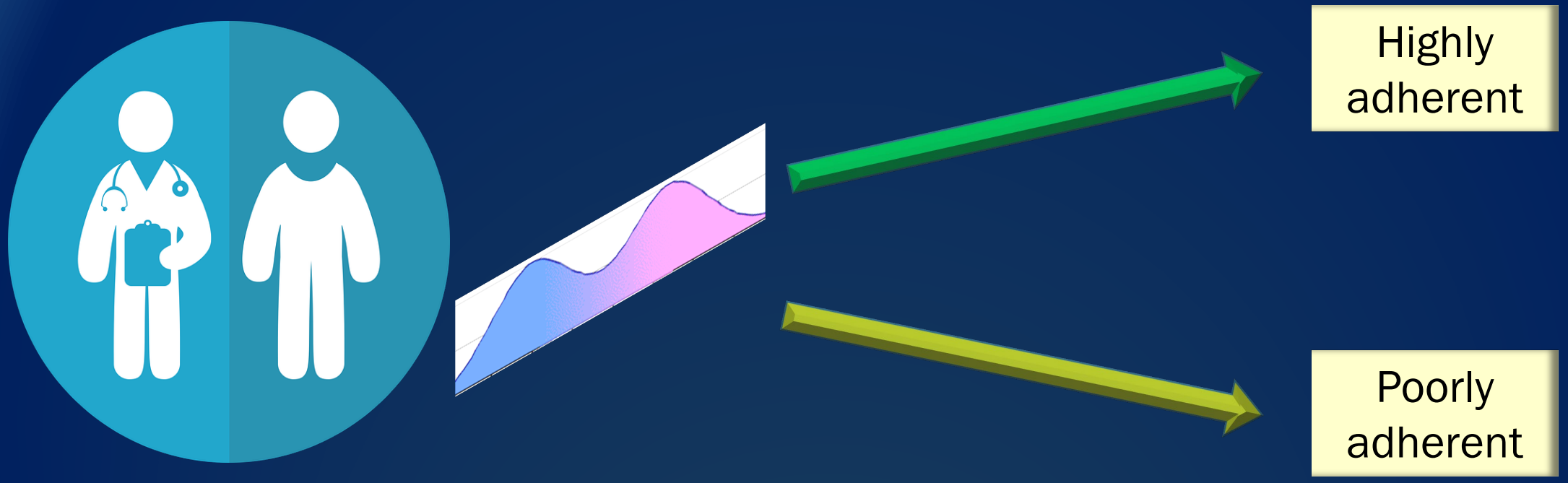
THE LANCET HIV

ARTICLES | VOLUME 9, ISSUE 4, E254-E268, APRIL 01, 2022

Jing Zhang*, Chunyan Li*, Junjie Xu*, Zhili Hu, Sarah E Rutstein, Joseph D Tucker, Jason J Ong, Yongjun Ji

- Systematic review, 41·0% of those on PrEP discontinued within 6 months; suboptimal adherence for those who stayed 37·7%
- Discontinuation rate higher in sub-Saharan Africa 47·5% than other regions
- Discontinuation rates lower in studies with adherence interventions than in those without (24·7% *vs* 36·7%, p=0·015). \
- Men who have sex with men and transgender women offered daily or non-daily dosing options had lower discontinuation rates than those offered daily dosing alone (21·6% *vs* 31·5%; p<0·001).
- **Though oral PrEP important, we need other options**

Bimodal population: Patient with challenges to PrEP/ART adherence would benefit from long-acting PrEP/ART



Would then KNOW date of “medication consumption” (not adherence, but coming in), pharmacies or mobile vans administering the shots, home health

THE LANCET
HIV

Equity in access to long-acting injectables in the USA

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, recently received regulatory approval in the Canada, the EU, and the USA as a monthly intramuscular long-acting injectable (LAI) antiretroviral therapy regimen in adults with HIV-1 who are virologically

Published Online
February 4, 2022
https://doi.org/10.1016/
S2352-3018(22)00031-5

*J Carlo Hojilla, Monica Gandhi, Derek D Satre, Mallory O Johnson, Parya Saberi

- Critically important population for Ending the HIV epidemic
- Equitable access across the US and across the world important
- WHO strongly endorsed Cabotegravir LA PrEP at International AIDS Conference, Montreal, July 28, 2022

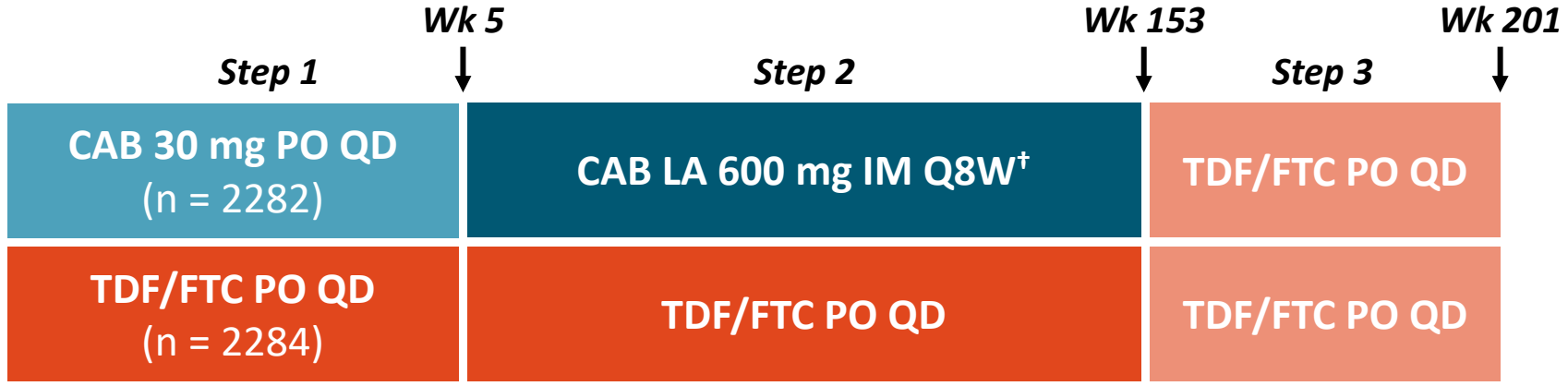
ViiV HEALTHCARE AND THE MEDICINES PATENT POOL SIGN NEW VOLUNTARY LICENSING AGREEMENT TO EXPAND ACCESS TO INNOVATIVE LONG-ACTING HIV PREVENTION MEDICINE

London, 28 July 2022 - ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer and Shionogi as shareholders, and the Medicines Patent Pool (MPP) today announced the signing of a new voluntary licensing agreement for patents relating to cabotegravir long-acting (LA) for HIV pre-exposure prophylaxis (PrEP) to help enable access in least developed, low-income, lower middle-income and Sub-Saharan African countries[1,2].

HPTN 083: Efficacy and Safety of LA Injectable CAB vs Daily Oral TDF/FTC for PrEP in MSM and TGW

- International, randomized, double-blind phase IIb/III study

HIV-uninfected MSM and TGW ≥ 18 yrs of age at high risk of HIV infection*; no HBV/HCV infection, (N = 4566)



*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 mos; or SexPro Score ≤ 16 (US only).
†First 2 doses given 4 wks apart then every 8 wks thereafter.

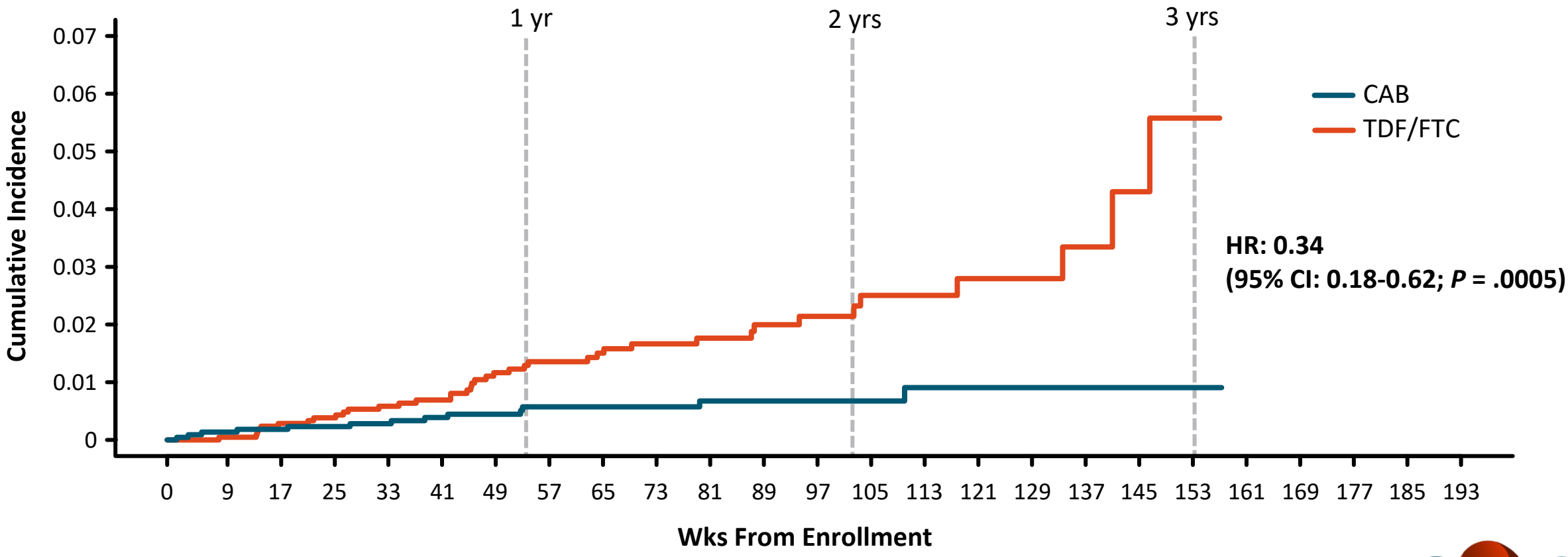
- Primary endpoints: incident HIV infections, grade ≥ 2 AEs

Landovitz. NEJM 2021.

HPTN 083
an HIV prevention clinical trial

HPTN 083: HIV Incidence (ITT) With LA Injectable CAB vs Daily Oral TDF/FTC PrEP

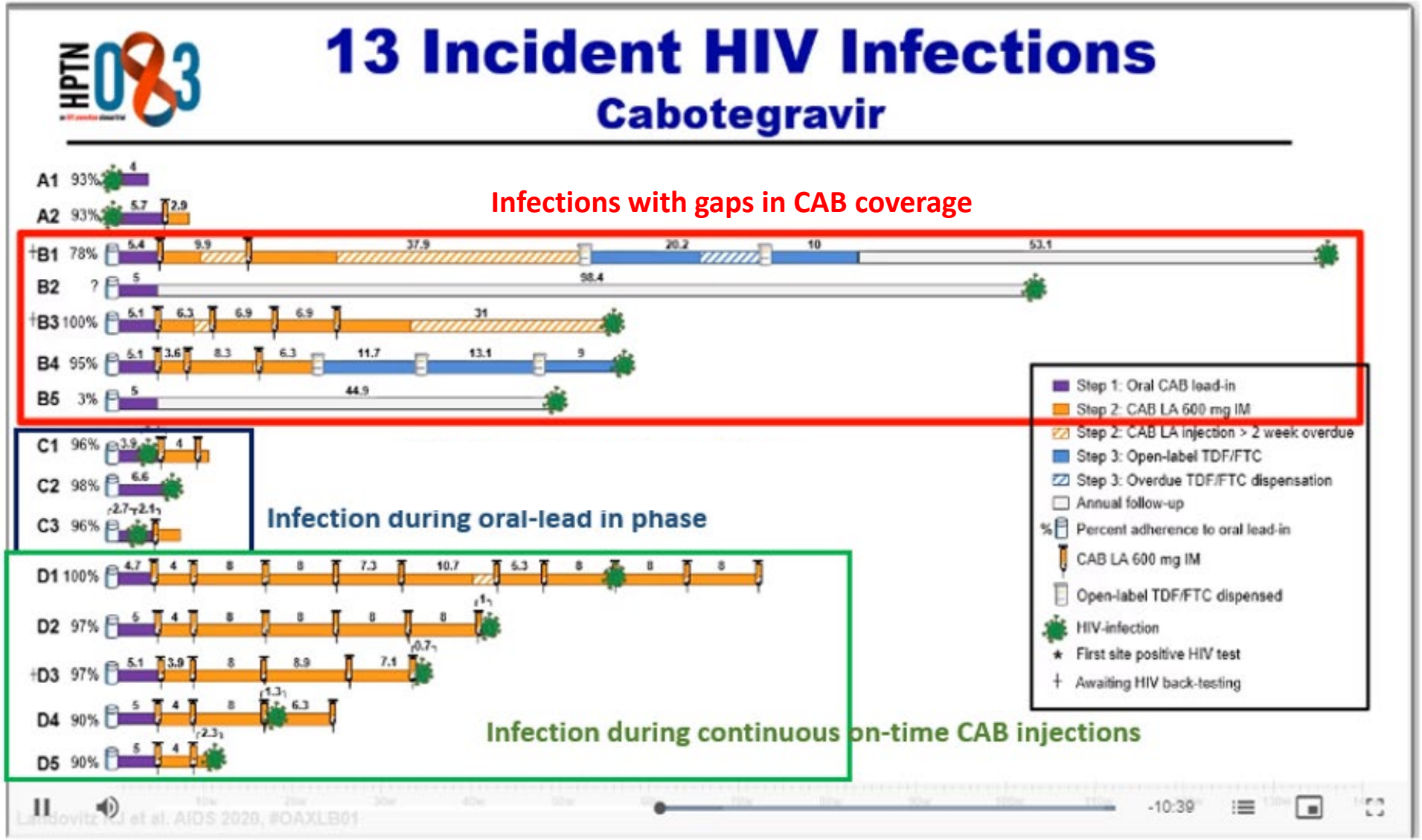
66% reduction over daily TDF/FTC



Landovitz. NEJM 2021.

HPTN 083
an HIV prevention clinical trial

5 out of 13 infections in CAB arm occurred despite on-time injections

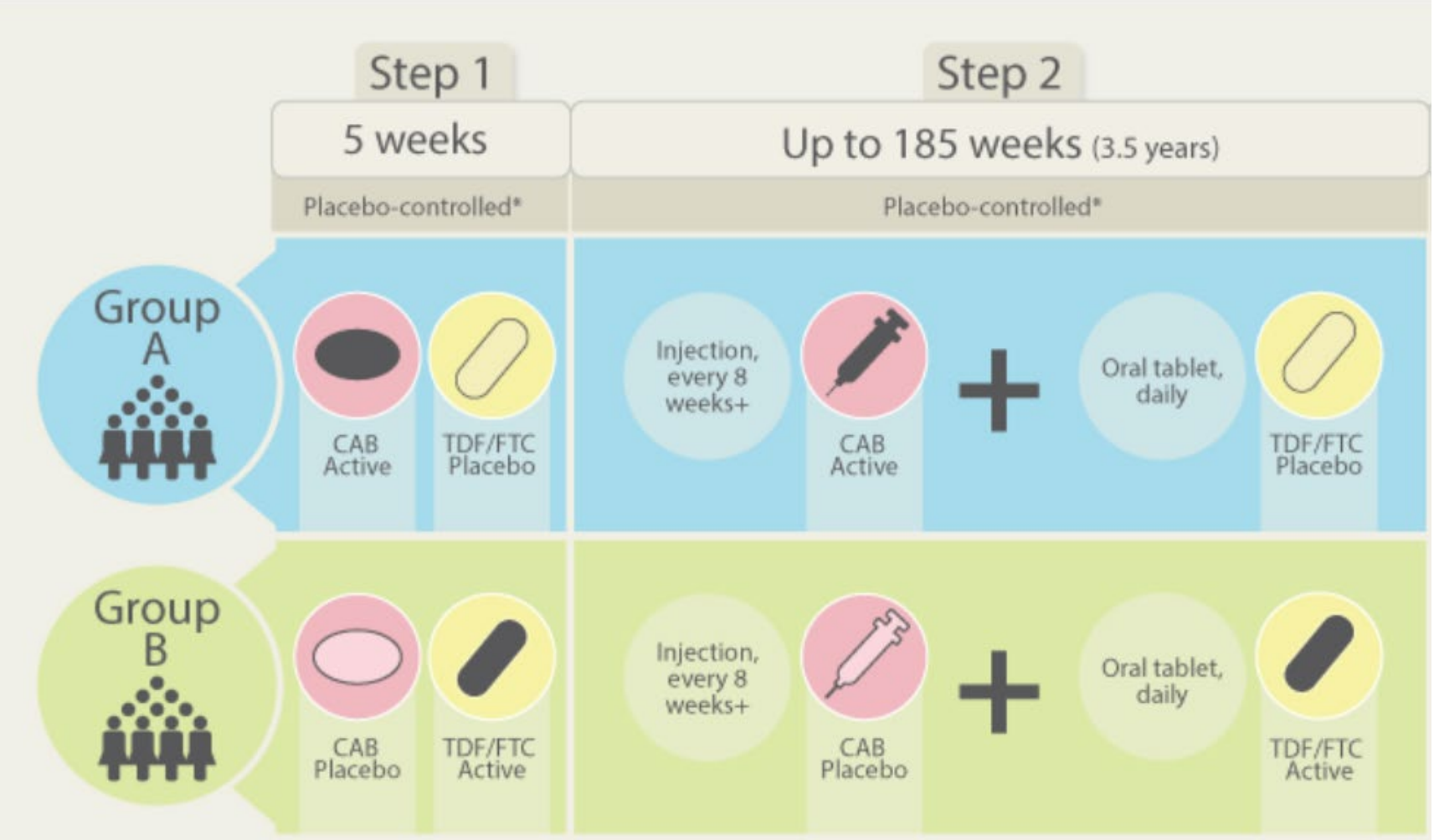


Landovitz. NEJM 2021; Markowitz JID 2022

Resistance 6 out of 12


HPTN
084
Long-acting Injectable For the Epidemic

Study design of HPTN 084



- Enrolled 3,223 women aged 18-45 years old at risk in 20 sites across 7 countries (Botswana, Kenya, Malawi, South Africa, eSwatini, Uganda and Zimbabwe)

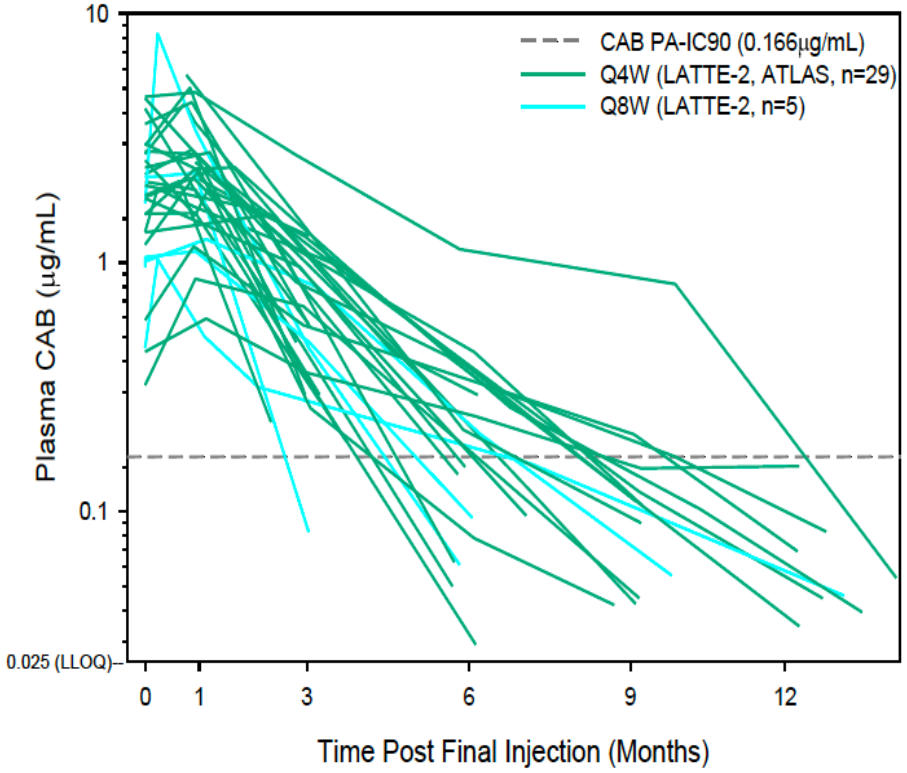
DSMB stopped study early and press release Nov 9, 2020

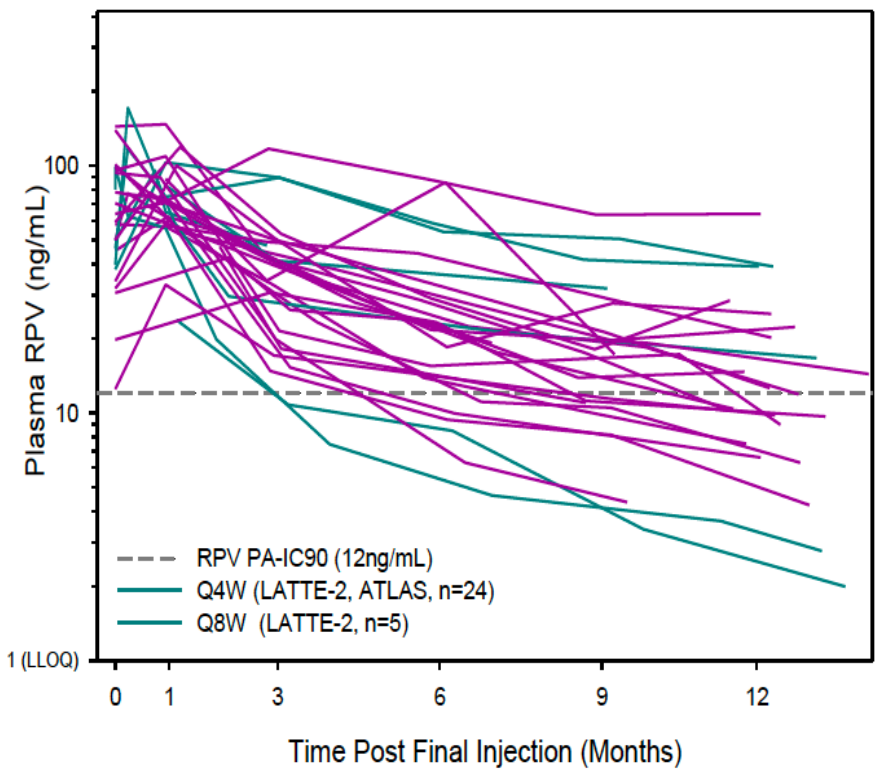
- Cabotegravir q8 weeks superior to daily TDF/FTC
- 38 women in trial acquired HIV
  - 4 randomized to the long-acting cabotegravir arm
  - 34 randomized to the daily, oral FTC/TDF arm.
  - Long-acting cabotegravir was 89% (95% CI 68-96%) more effective than FTC/TDF (compared to 66% more effective in HPTN 083) in intention to treat analysis
- All women >= 18 and, when DTG associated with neural tube defects, protocol amendment that trial participants needed to be on effective contraceptive so no knowledge of pregnancy

No resistance in all 4 breakthroughs (Eshleman JID 2022) and no additional breakthroughs in 1 year unblinded phase (IAS 2022)

Remember to counsel patients and start oral ART when they stop CAB on the PK tail

- Following LA treatment d/c, CAB and RPV LA may be detectable in plasma for ≥ 1 year
- PK sampling 1, 3, 6, 9, and 12 mos after final LA CAB + RPV IM injection

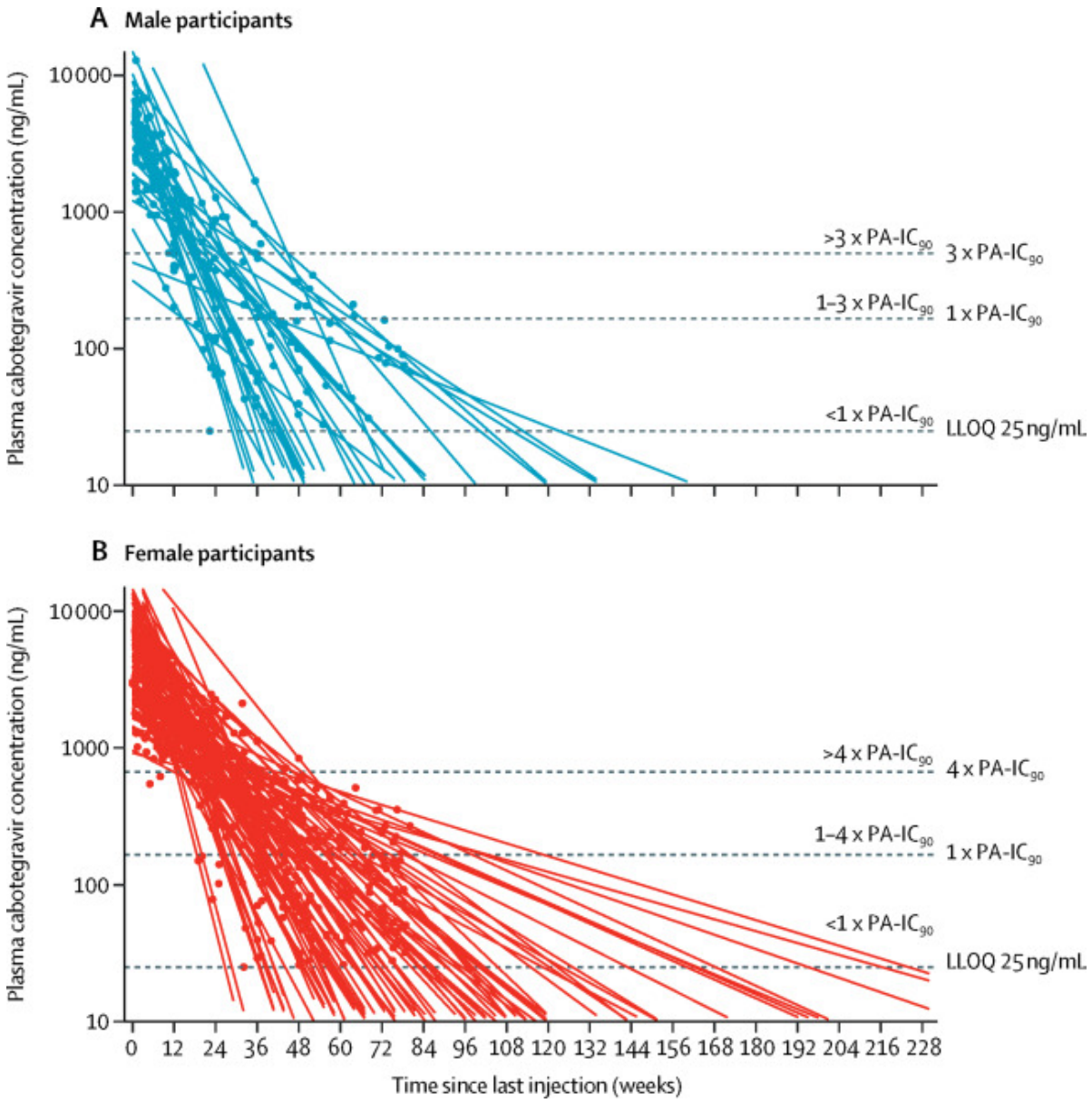




- Start ART after stopping
- Alternative ART selection after stopping LA CAB + RPV shouldn't have DDIs even with CYP3A and/or UGT1A1 inducers or inhibitors

Ford SL. CROI 2020; Abstract 466

CAB LA tail is longer in women than men



- Median time to undetectable cabotegravir is longer in women at 66.3 weeks (range 17.7 to 182) when compared to 42.7 weeks (range 20.4 to 134) in men

HPTN
HIV Prevention Trials Network

HPTN 077

Landovitz R. Lancet HIV. June 2020

Screening criteria in our clinic for starting IM cabotegravir

- HIV testing:
  - Negative serum HIV Ag/Ab test result within 3 days before initially prescribing PrEP
    – or–
  - Serum HIV Ag/Ab test pending *and* a negative POC STAT PAK HIV Ab test day of injection
- HIV RNA sent/pending
- No signs or symptoms of acute HIV infection
- Patient expresses willingness to receive CAB LA PrEP injections (injection in gluteal muscle)
- Patients who are on the following medications are not eligible (due to concern of decreased drug levels of CAB):
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Antimycobacterials: rifabutin, rifampin, rifapentine
  - Herbal: St. John's Wort

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

Dosage	• 600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle
	  ○ Initial dose
	  ○ Second dose 4 weeks after first dose (month 1 follow-up visit)
	  ○ Every 8 weeks thereafter (month 3,5,7, follow-up visits etc)

Follow-up care	**At follow-up visit 1 month after first injection** • HIV Ag/Ab test and HIV-1 RNA assay **At follow-up visits every 2 months (beginning with the third injection – month 3) provide the following:** • HIV Ag/Ab test and HIV-1 RNA assay • Access to clean needles/syringes and drug treatment services for PWID **At follow-up visits every 4 months (beginning with the third injection- month 3) provide the following:** • Bacterial STI screening[2] for MSM and transgender women who have sex with men[2] – oral, rectal, urine, blood **At follow-up visits every 6 months (beginning with the fifth injection – month 7) provide the following:** • Bacterial STI screening[1] for all heterosexually-active women and men – [vaginal, rectal, urine - as indicated], blood **At follow-up visits at least every 12 months (after the first injection) provide the following:** • Assess desire to continue injections for PrEP • Chlamydia screening for heterosexually active women and men – vaginal, urine **At follow-up visits when discontinuing cabotegravir injections provide the following:**

Conclusions

- Long-acting CAB PrEP is here
- Need global access and as fast as possible
- Question regarding frequent HIV RNA monitoring in resource-limited settings (CDC recommends every injection) important one

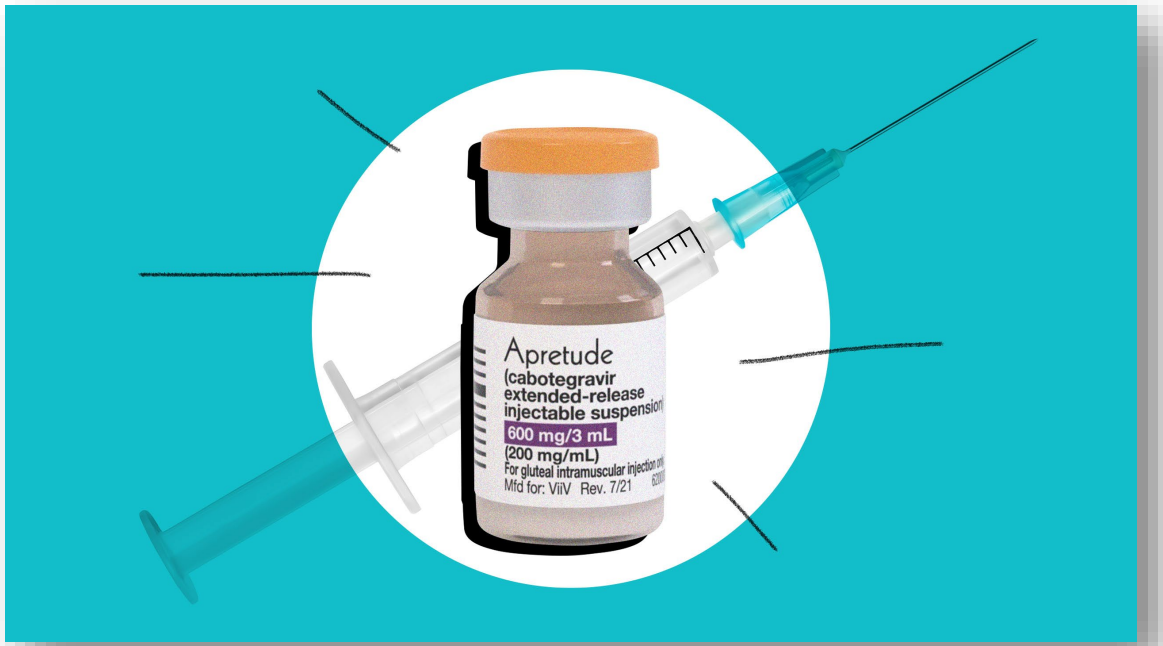
Long Acting Cabotegravir at NewYork-Presbyterian Hospital Columbia Irving Medical Center

Caroline Carnevale DNP MPH

Cabotegravir-LA at NYP/Columbia

- Cabotegravir-Long Acting Approved by the FDA in December 2021
  - NYP/Columbia had the medication approved by the NYP pharmacy review board in February 2022
  - First three patients expressed interest in CAB-LA injections at the NYP Sexual Health clinic March 2022
  - Since that time 12 total patients have presented with interest
    - 5 decided on TDF/FTC, 2 pending insurance approval, 5 started
    - 11 identified as MSM, 1 cis-woman

Cabotegravir-LA at NYP/Columbia



- 27 year old Black male who has an HIV positive male partner presented for routine quarterly PrEP visit requesting Cab-LA
  - Adherent to TDF/FTC but does not want the burden of taking pills everyday
  - PMH of depression, mood disorder
  - Fully insured with commercial insurance

Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"

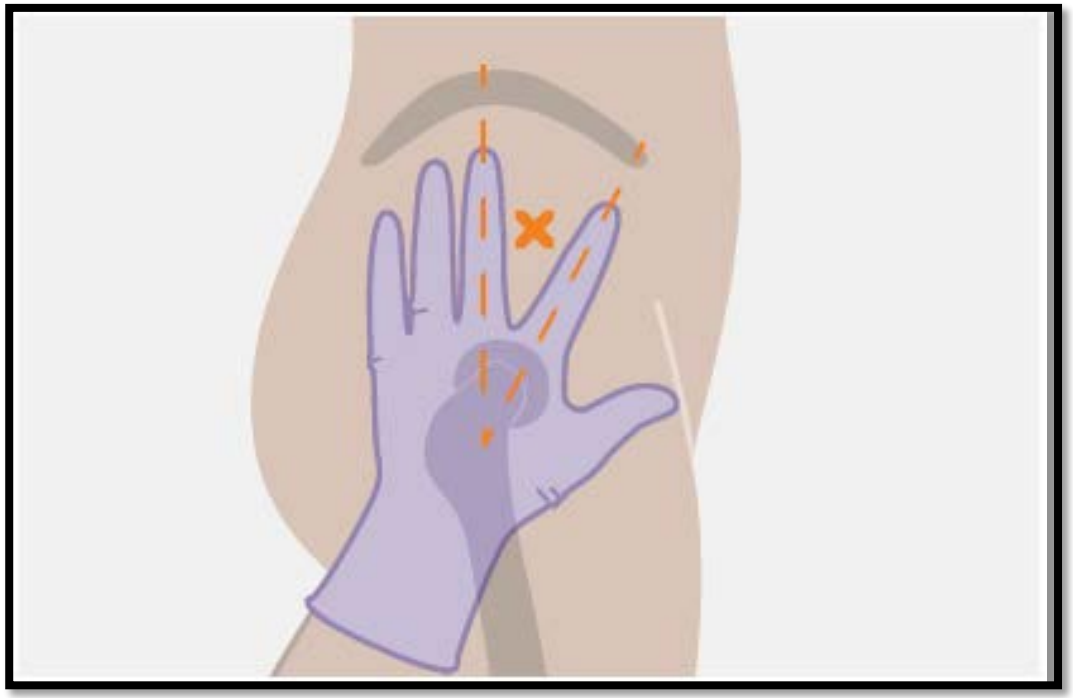
Table 2. Recommended Dosing Schedule (Direct to Injection) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
APRETUDE[a] 600 mg (3 mL)	APRETUDE[a] 600 mg (3 mL)

[a] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

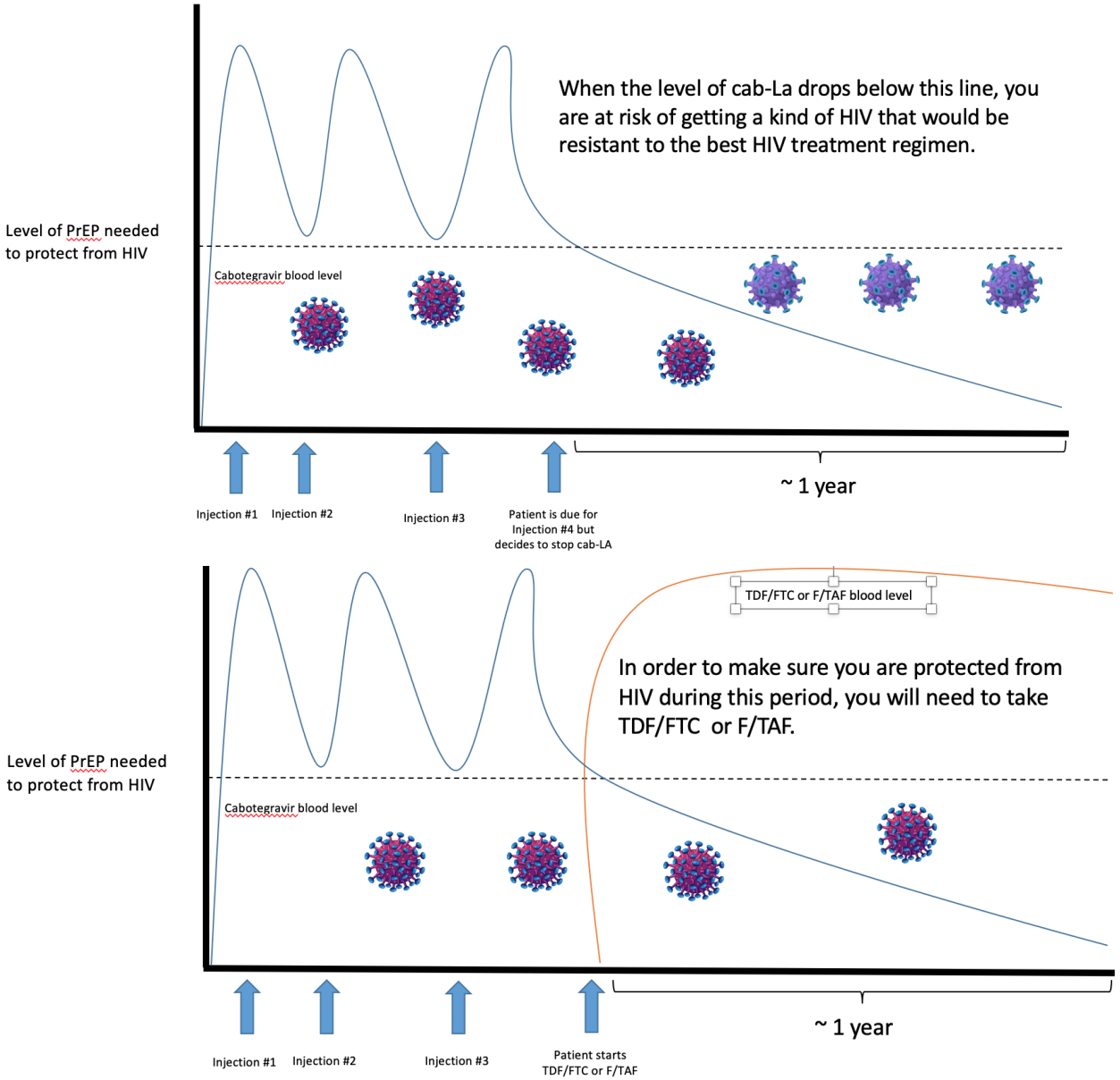
Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal

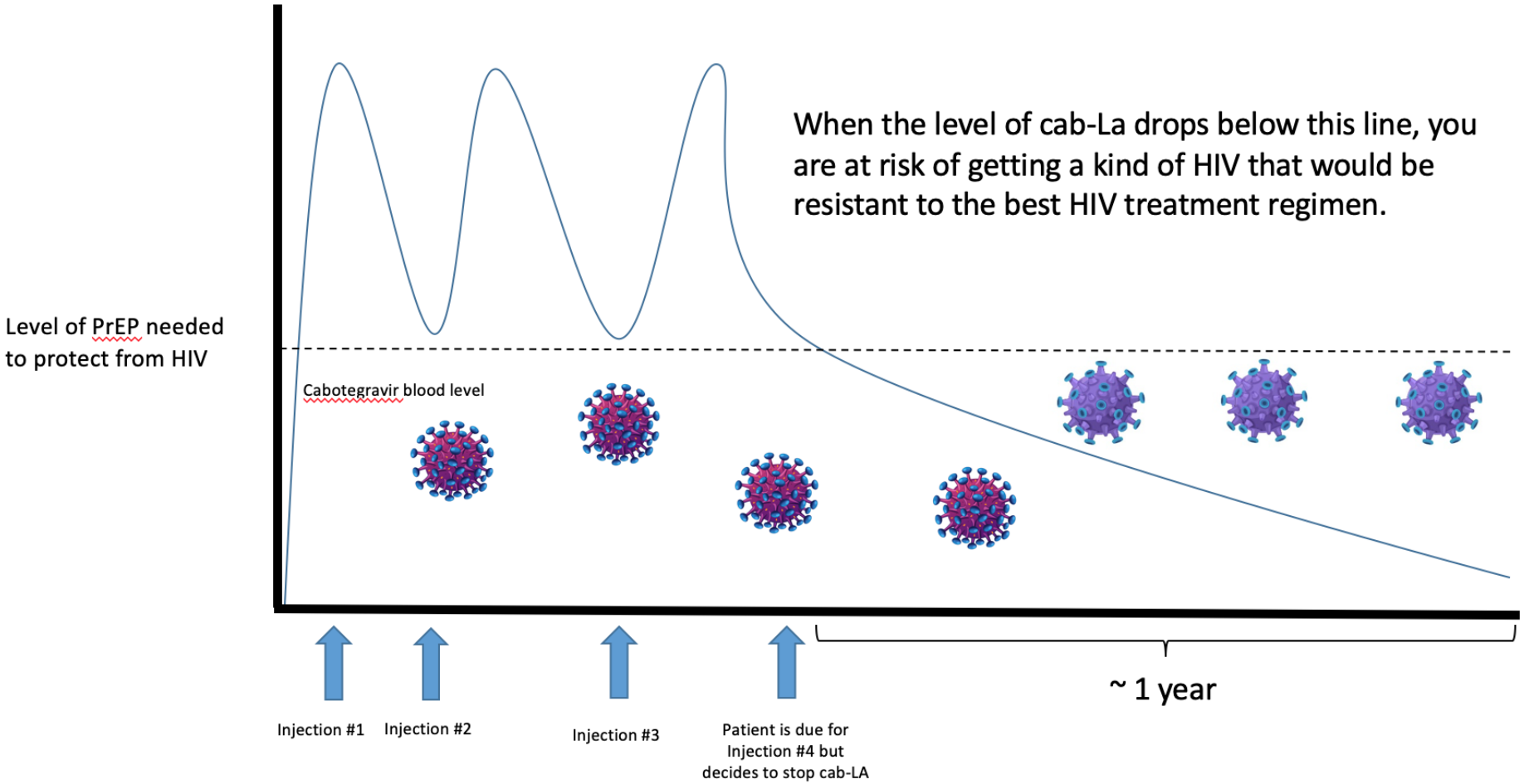


Cabotegravir Counseling

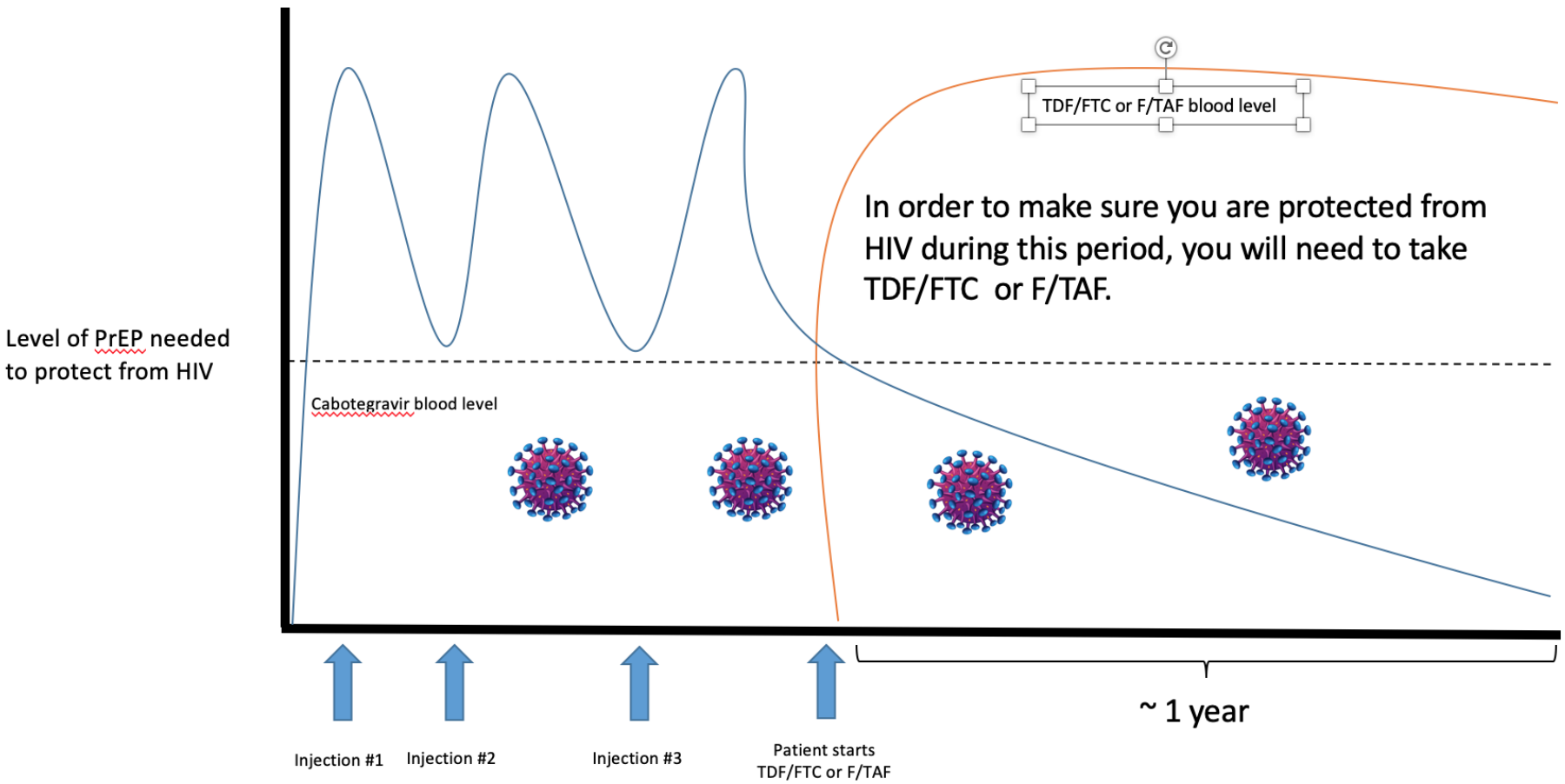
- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal
  - ❑ "Medication Tail"



Medication Tail Infographics



Medication Tail Infographics



Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal
  - ❑ "Medication Tail"
  - ❑ Medication side effects
    - ❑ Plan for depressive symptoms

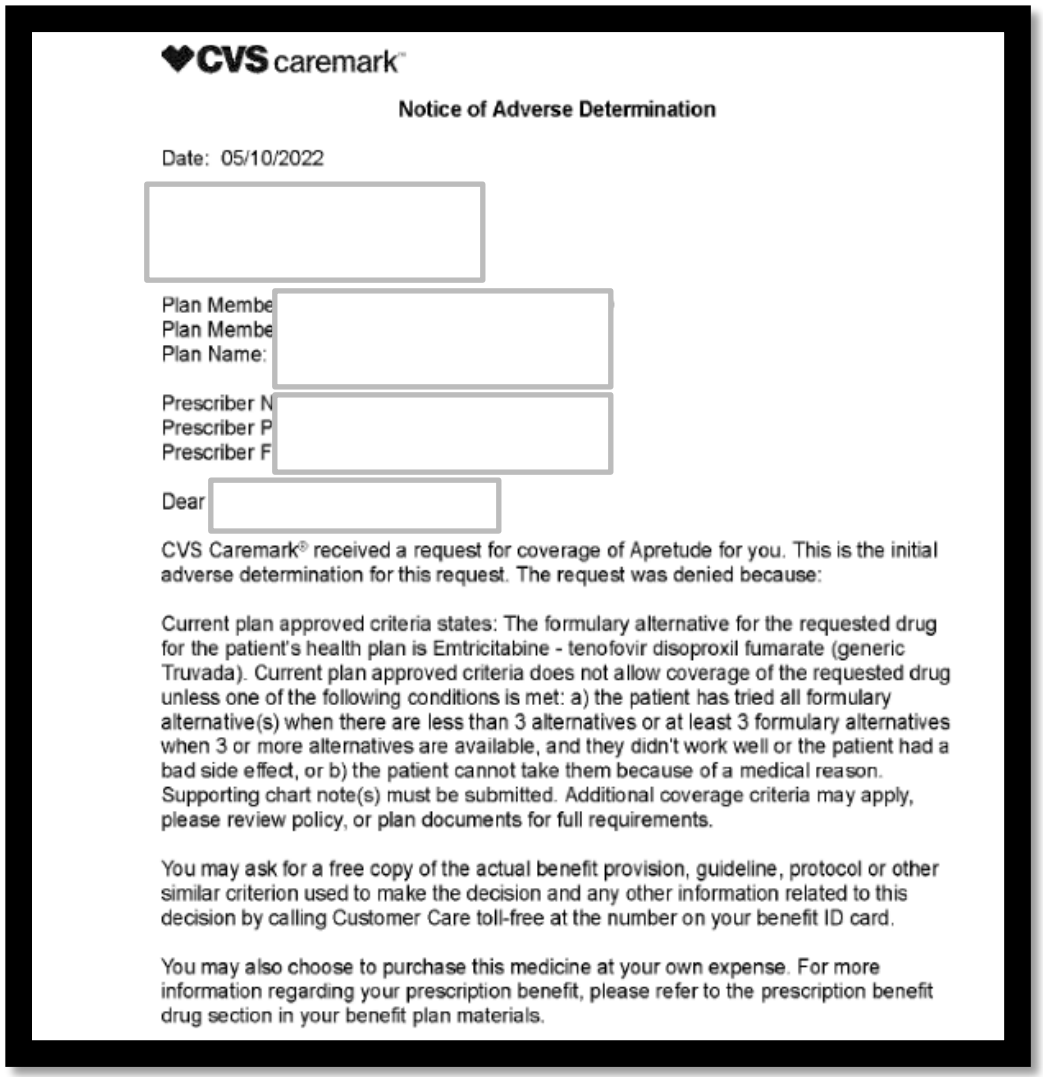
5.6 Depressive Disorders

Depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicide ideation or attempt) have been reported with APRETUDE *[see Adverse Reactions (6.1)]*. Promptly evaluate individuals with depressive symptoms to assess whether the symptoms are related to APRETUDE and to determine whether the risks of continued therapy outweigh the benefits.

Cabotegravir Cost and Financing

- Timing Challenges
  - Insurance authorization can take up to 2 weeks
    - No same-day starts
    - Provides time for labs and counseling
    - HIV testing and CAB-LA start may be separated by time

Cabotegravir Cost and Financing



CVS caremark

Notice of Adverse Determination

Date: 05/10/2022

Plan Membe
Plan Membe
Plan Name:

Prescriber N
Prescriber P
Prescriber F

Dear

CVS Caremark® received a request for coverage of Apretude for you. This is the initial adverse determination for this request. The request was denied because:

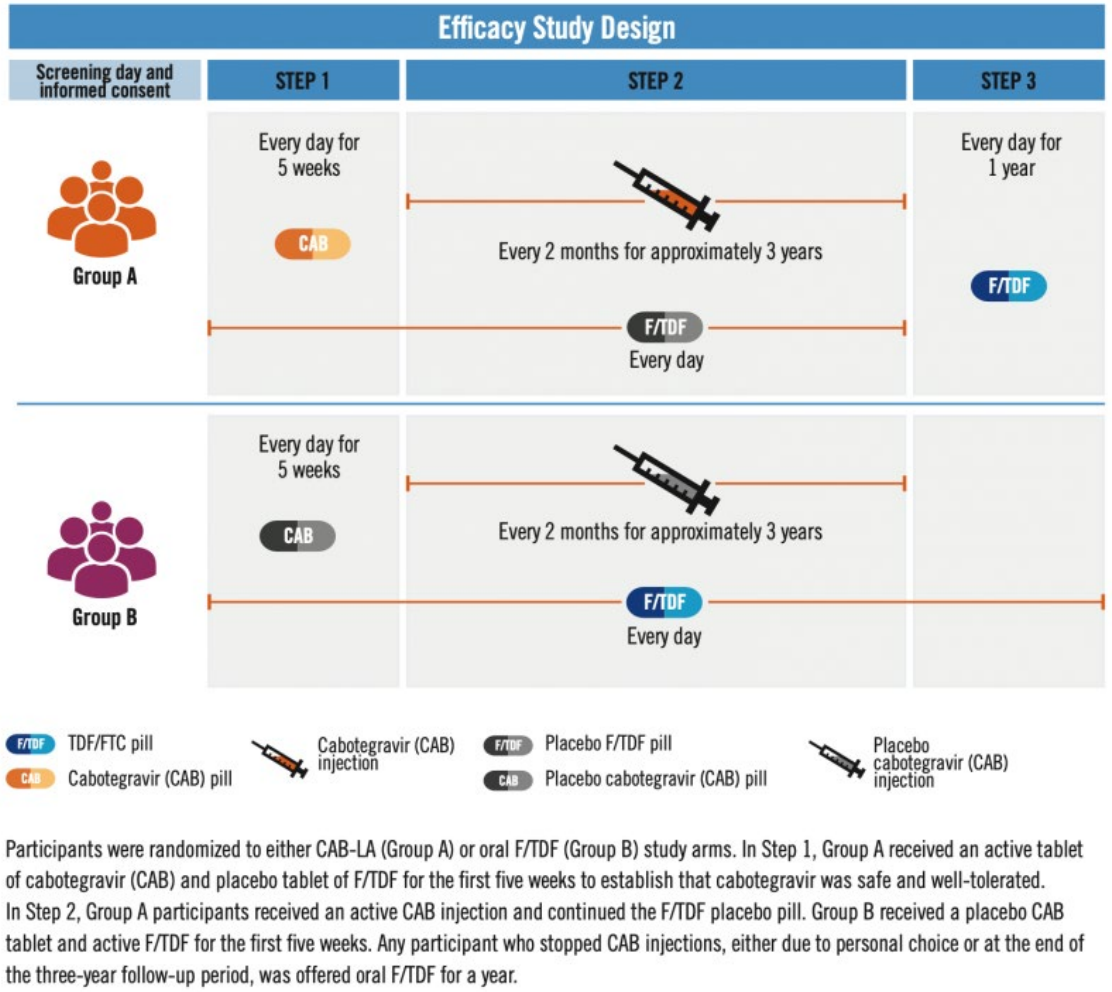
Current plan approved criteria states: The formulary alternative for the requested drug for the patient's health plan is Emtricitabine - tenofovir disoproxil fumarate (generic Truvada). Current plan approved criteria does not allow coverage of the requested drug unless one of the following conditions is met: a) the patient has tried all formulary alternative(s) when there are less than 3 alternatives or at least 3 formulary alternatives when 3 or more alternatives are available, and they didn't work well or the patient had a bad side effect, or b) the patient cannot take them because of a medical reason. Supporting chart note(s) must be submitted. Additional coverage criteria may apply, please review policy, or plan documents for full requirements.

You may ask for a free copy of the actual benefit provision, guideline, protocol or other similar criterion used to make the decision and any other information related to this decision by calling Customer Care toll-free at the number on your benefit ID card.

You may also choose to purchase this medicine at your own expense. For more information regarding your prescription benefit, please refer to the prescription benefit drug section in your benefit plan materials.

- Medical Benefits vs. Pharmacy/Drug Benefits
- Documentation of “failure” of an oral PrEP regimen before Cab-LA is a challenge in cases of:
  - Pill intolerance
  - Oral regimen to bridge injections
  - Oral regimen after discontinuation during the tail

Important Outstanding Questions

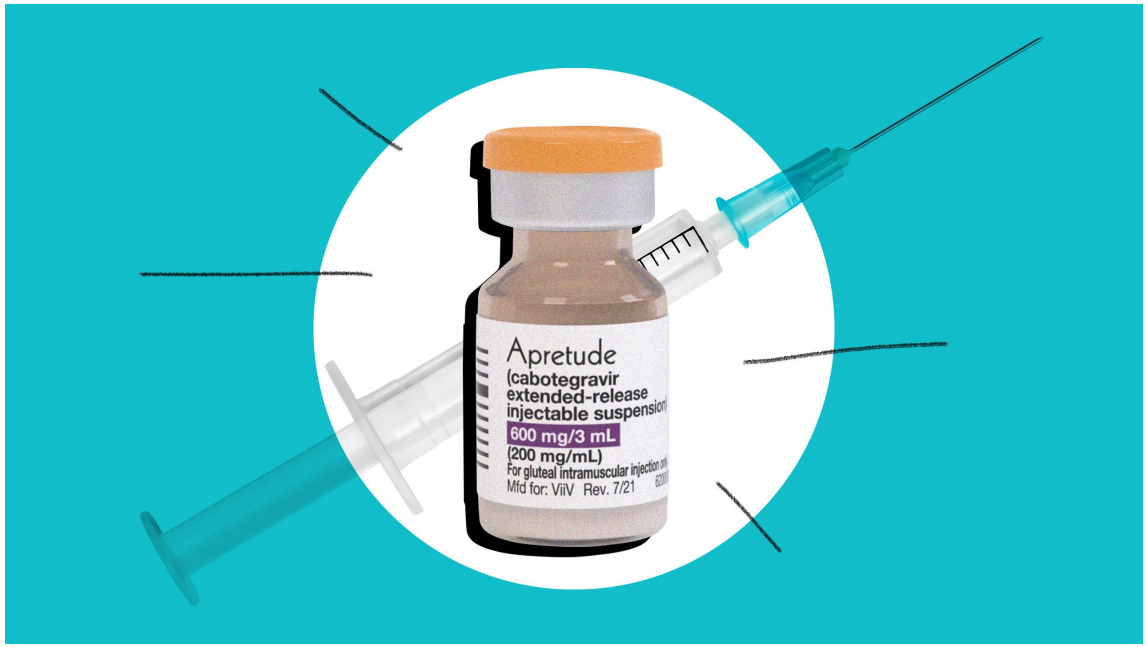


Participants were randomized to either CAB-LA (Group A) or oral F/TDF (Group B) study arms. In Step 1, Group A received an active tablet of cabotegravir (CAB) and placebo tablet of F/TDF for the first five weeks to establish that cabotegravir was safe and well-tolerated. In Step 2, Group A participants received an active CAB injection and continued the F/TDF placebo pill. Group B received a placebo CAB tablet and active F/TDF for the first five weeks. Any participant who stopped CAB injections, either due to personal choice or at the end of the three-year follow-up period, was offered oral F/TDF for a year.

- Limited information about when Cabotegravir is protective against HIV
  - Oral Lead-In?
  - How long after a single injection?
  - When a patient is bridging injections?

- **Do we need TAF/FTC or TDF/FTC during these times?**

Cabotegravir-LA at NYP/Columbia



- Our 27 year old MSM is receiving his forth injection of Cab-LA next week and reports to be feeling well and has no complaints with medication thus far

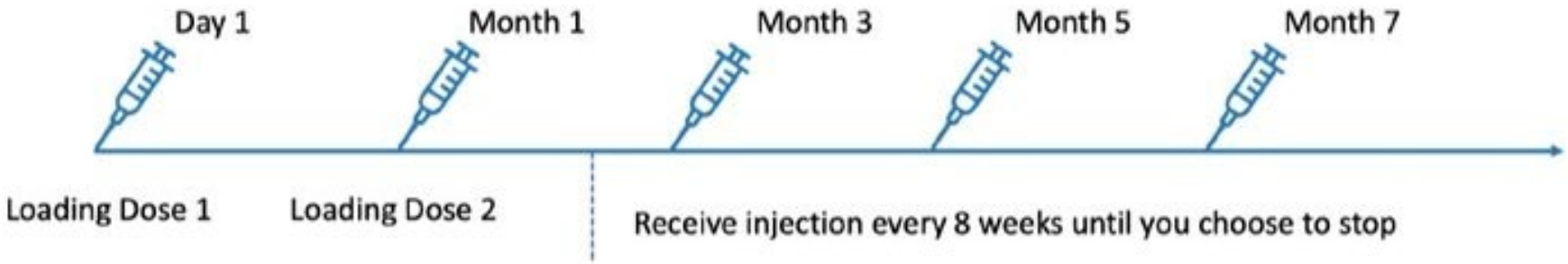
Cabotegravir Current Experience

- First an Informational Visit (via telehealth or in-person)
- Labs at each injection visit

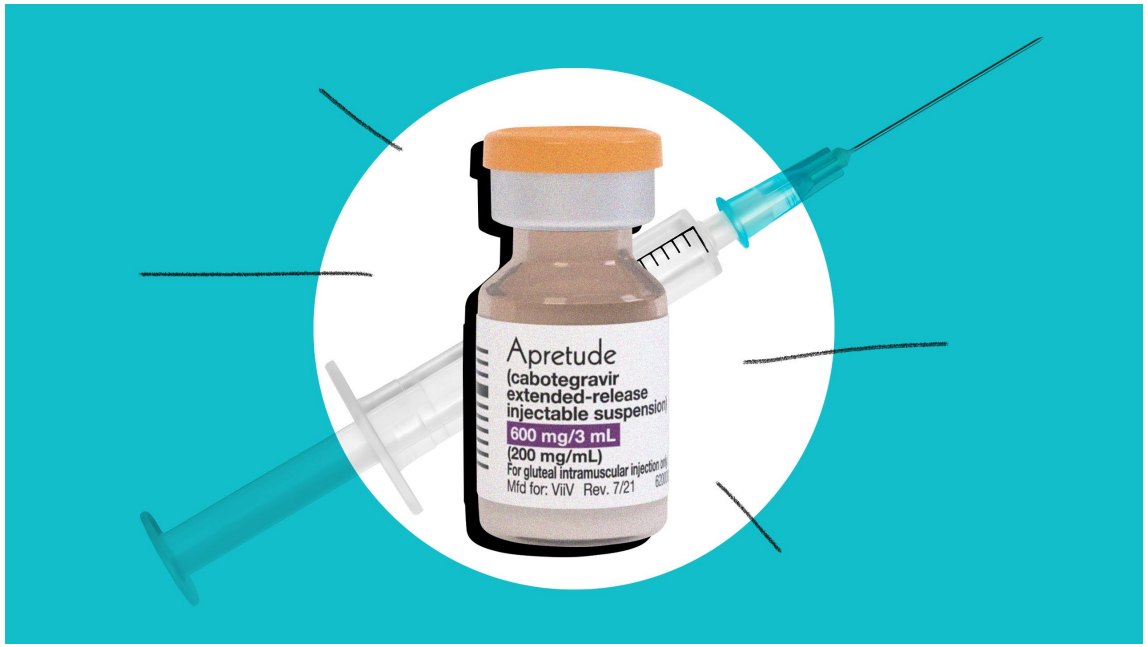
How do you take cab-LA?

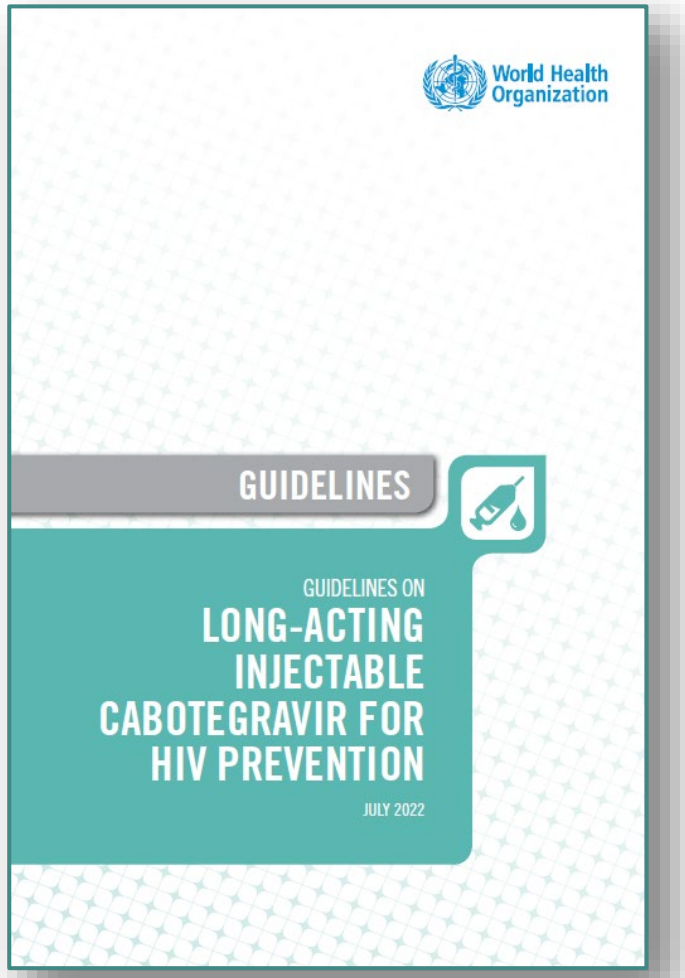
⇒ cab-LA is a shot injected by your health care provider in your gluteal muscle (butt). To start cab-LA, you will get 2 shots 4 weeks apart (loading dose 1 and 2) and then you will start a regular injection schedule every 8 weeks.

⇒ Your doctor may discuss whether you would like to take cabotegravir pills for 4 weeks before your first shot. This is a way to make sure you don't have any allergic reactions to the medication before you are injected with your first dose.



Questions? Comments?





Long-acting injectable cabotegravir for HIV prevention

New WHO Guidelines

Dr Rachel Baggaley

WHO, Geneva

World Health Organization

THE CHOICE AGENDA

HIV prevention research - a new forum for advocacy on the latest

8th August 2022

Time: 9:00am ET / 1:00pm GMT / 15:00 SAST

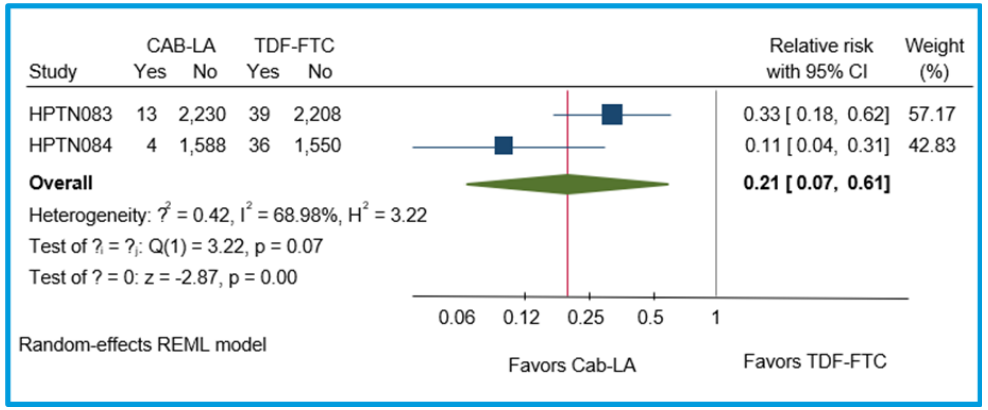
Long-acting injectable cabotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches

(conditional recommendation; moderate certainty of evidence)

CAB-LA is highly effective

Data from 2 large, multi-site RCTs across diverse populations suggest CAB-LA is a highly effective and safe biomedical HIV prevention tool

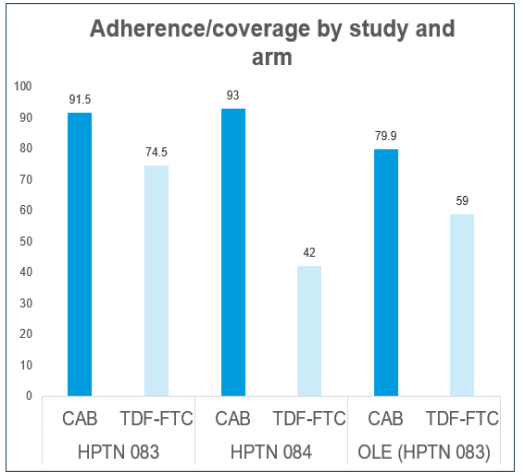
- CAB-LA reduces HIV incidence (RR: 0.21, 95% CI: 0. 07-0.61) - corresponding to a 79% relative risk reduction
- Note: Relative HIV risk reduction ranged from 66% in HPTN 083 to 88% in HPTN 084



Combined effect size across HPTN 083 and HPTN 084

High adherence to CAB-LA

- High adherence to CAB-LA across efficacy studies
  - Lower adherence to TDF-FTC
- Initial results from HPTN 083 OLE found decreased adherence to both CAB-LA and TDF-FTC in the first year following unblinding



Systematic review: Virginia Fonner

World Health Organization

CAB-LA is highly effective, but evidence gaps identified in WHO review

Gaps identified in review

- Data mainly from highly controlled trial settings; **"real world" data are lacking**
- **Data lacking for certain populations**
- Sparse (or non-existent) data on certain outcomes:
  - Sparse data on **drug resistance** (due to few cases)
  - Sparse data on **adverse events in pregnancy and breastfeeding** (being addressed in HPTN 084 OLE)
- **Lack of clarity regarding cost-effectiveness**

Additional areas with insufficient evidence

- Optimal HIV **testing approach**
- **Variability of CAB-LA pharmacokinetic properties** among disparate populations and individuals
- Extent and implications of **potential INSTI resistance** due to CAB-LA (and potential relevance to delays in detection)
- Supportive interventions to help **maintain adherence and overcome access barriers**
- Procedures for **switching to/from** CAB-LA from/to other PrEP modalities and for **stopping** CAB-LA

World Health Organization

New data following WHO review

Initial findings suggest there is no impact of gender affirming hormonal therapy (GAHT) on CAB concentrations

Transgender women (TGW) in HPTN 083: an evaluation of safety, efficacy, and gender affirming hormonal therapy (GAHT) interactions with long-acting cabotegravir (CAB-LA)

PRESENTER

Beatriz Grinsztejn

CAB drug concentrations measured in a subset of TGW who received on-time CAB injections (23 not taking GAHT, 30 taking GAHT).

CAB drug concentrations were comparable between the two groups, suggesting the lack of a GAHT effect on CAB PK

CAB-LA is a safe and effective HIV prevention strategy for TGW

HIV incidence reduction sustained in unblinded phase

- **CAB continues to be superior to TDF/FTC in preventing HIV infection cis-gender women**

Long acting cabotegravir: updated efficacy and safety results from HPTN 084

PRESENTER

Sinead Delany-Moretlwe

- 23 incident infections (3 CAB, 20 TDF/FTC) detected in the 12-month unblinded period.
  - 2 (1 CAB, 1 TDF/FTC) occurred during the blinded phase
  - 1 of CAB cases (blinded phase case) had ever received an injection.
  - ***Cumulatively***, 62 incident HIV infections (6 CAB, 56 TDF/FTC) observed over 6626 person-years of follow up (HIV incidence 0.94%, 95% CI 0.72, 1.20).
  - Superiority of CAB appears sustained (HR 0.11, 95% CI 0.05, 0.24)
- No new safety concerns were identified.
- 83 confirmed pregnancies (43 CAB, 40 TDF/FTC) occurred in the unblinded period
  - **No congenital anomalies reported**

CAB-LA is acceptable, but awareness limited

PrEP provider survey

(Mary Henderson, Robin Schaefer)

1353 responses (63% fully completed)

- 48% had heard about CAB-LA
- 71% would consider providing it if/when it gets regulatory approval; 6.6% would not provide it

Systematic review of values and preferences

(Lara Lorenzetti)

- Variability of preferences for injectable PrEP across regions and populations
- Injectable PrEP may best suit those with challenges taking daily oral PrEP, those valuing discretion, and those who have experience with other types of injectables

Values and preferences

(GATE, MPact, NSWP, INPUD)

- Interest and awareness varied across regions and population
- Choice is critical

"I think the injection, would be easier, because, once we inject, then we will inject it [again] the next month. Sometimes people forget to take the pill. Because if you're taking a pill, you must take it constantly at the specific time….but if it's an injection, then it's in your blood already….for me, that's good." Sex worker (46-50), Africa

NSWP Values and Preferences: Expanded Findings on PrEP

World Health Organization

Mixed results of CAB-LA cost-effectiveness

Included in the review

- 7 studies identified in systematic review
  - 6 involved modeling in South African context; 1 in U.S. context
- 4 unpublished preliminary results from:
  - model comparison of 2 HIC models (Atlanta and Montreal) and 2 South Africa models, plus 1 model for sub-Saharan Africa

Results

- Injectable PrEP cost-effective/cost-saving in some scenarios e.g., when targeting women in South Africa and when leveraged with complementary services or as MPT
- Injectable PrEP not cost-effective in other scenarios e.g., when targeting heterosexual men in South Africa

Wide variation in assumptions, including product cost.
Range: USD 6 per injection in South Africa to USD 25,850 per year in U.S.

World Health Organization

HIV testing for CAB-LA, a critical issue

HIV testing and drug resistance - limited experience outside trial settings

- Programmes should select a testing strategy & algorithm that promotes access to CAB-LA among those who would benefit most
- Programmes **can use current national HIV testing strategy**/algorithm (combination of RDTs &/or EIAs) as per WHO HIV testing recommendations
- **Some countries may include NAT**, in addition to the national algorithm, particularly at initiation.
    - Where NAT is used, important to have necessary assays, resources, regulatory approvals, and a clear testing strategy for resolving discrepant results and establishing HIV infection before initiating life-long ART

Ongoing monitoring of implementation is needed to further optimize HIV testing approaches for CAB-LA

While NAT might prevent a small number of cases of drug resistance, countries need to consider the feasibility of NAT. There are also uncertainties as to what impact these mutations will have on subsequent ART.

World Health Organization

Delivery issues I

Oral lead in

- FDA & company
  - Oral lead-in optional
- In OLE some clients choose oral lead-in; many don't

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APRETUDE safely and effectively. See full prescribing information for APRETUDE.

APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use
Initial U.S. Approval: 2021

2.4 Optional Oral Lead-in Dosing to Assess Tolerability of APRETUDE

The healthcare provider and individual may decide to use an oral lead-in with oral cabotegravir prior to the initiation of APRETUDE to assess the tolerability of cabotegravir or the healthcare provider and individual may proceed directly to injection of APRETUDE without the use of an oral lead-in *[see Dosage and Administration (2.5)]*.

Stopping CAB-LA and covering the tails

- In the RCTs, no cases of acquired INSTI drug resistance have been reported, to date, during the tail
- When stopping, discuss using other prevention options (condoms, PEP, other PrEP products), if client remains at risk of HIV acquisition

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215499s000lbl.pdf

Delivery issues II

World Health Organization

Pregnancy & breastfeeding

- Pregnancy & postpartum – periods of increased risk of acquiring HIV & increased risk of transmission to infants
- In HPTN 084 & HPTN 077 women required to take LARCs → therefore limited safety data
- CAB-LA use not contraindicated for PBFW – **but more implementation science/data needed**

Young people <18 years

- <18-year-olds were not included in ECLAIR, HPTN 077, HPTN 083, HPTN 084
- Additional studies including adolescent and young people are ongoing to assess safety and acceptability
- Young people frequently face additional barriers to accessing & effectively using other oral PrEP, and may require additional support for CAB-LA
- **Operational research with AGYW young KP a priority to understand preferences for products & acceptable effective delivery approaches**

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APRETUDE safely and effectively. See full prescribing information for APRETUDE.

APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use
Initial U.S. Approval: 2021

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to APRETUDE during pregnancy. Healthcare providers are encouraged to register individuals by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Cabotegravir use in pregnant women has not been evaluated. APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Because of detectable cabotegravir concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant.

The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of APRETUDE for

Delivery issues III

Providing CAB-LA for key populations

- HPTN 083 and HPTN 084 provided PrEP to MSM, transgender women & cisgender women
- Studies did not included people who use drugs or sex workers
- As SW & PWID could benefit from CAB, urgent implementation science needed

Choice and switching

- People who could benefit from PrEP have diverse HIV prevention needs and preferences, these may change over time
- A range of PrEP options should be available
- People interested in PrEP should be provided information on available options, relative efficacy and safety and counselled to make an informed decision regarding the best option for them
- Involving communities at all stages is critical – awareness, demand creation & delivery

Cost & cost-effectiveness

- Huge uncertainly - will depend on cost of product, service delivery costs and context/epidemiology/NNP (number needed to prevent)

CAB-LA, what is next for WHO?

WHO has added **CAB-LA to the WHO Expression of Interest (EOI)**, allowing the manufacturer to apply for inclusion on the WHO list of prequalified (PQ) medicinal products

Following this recommendation

- ❑ Global Fund etc. can include CAB-LA in its products for procurement
- ❑ Countries can consider how they would like to include CAB-LA in their prevention programmes

WHO is supporting and pushing for rapid implementation science

To answer important safety and implementation issues:

- ❑ Where to deliver
- ❑ Understand how people will choose and switch safely between PrEP options
- ❑ Provide further data on safety in pregnancy and breastfeeding – need for more prevention choices in ESA
- ❑ Monitor drug resistance and review testing approaches
- ❑ For geographies and populations (including sex workers and people who inject drugs) not included in the RCTs

WHO is collaborating on **global efforts for product availability and access**

WHO **updating PrEP implementation guidance** **to include CAB-LA (alongside oral PrEP and DVR)**

WHO **updating PEP guidance inc PEP🡐🡒PrEP**

World Health Organization

Thank you

Thanks to the **WHO HHS Testing, Prevention, and Populations** team for contributions to this presentation.

Contact the PrEP team for questions or comments:

- **Rachel Baggaley:** baggaleyr@who.int
- **Michelle Rodolph:** rodolphm@who.int
- **Robin Schaefer:** schaeferr@who.int
- **Heather-Marie Schmidt:** schmidth@unaids.org

WHO
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- **Dobromir Dimitrov** (Fred Hutchinson Cancer Research Center, USA)
- **Virginia Fonner** (FHI360, USA)
- **Mary Henderson** (independent consultant)
- **Lara Lorenzetti** (FHI360, USA)
- **Andrew Philips** (University College London, UK)
- **GATE, Mpact, NSWP, and INPUD**

GDG group and peer reviewers

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World Health Organization

Find the new WHO CAB-LA Guidelines here:

https://www.who.int/publications/i/item/9789240054097

Find the new Technical Brief here:

https://www.who.int/publications/i/item/9789240053694

WHO's global work on PrEP:

https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/pre-exposure-prophylaxis

WHO Global PrEP Network webinars:

https://www.who.int/groups/global-prep-network

Collaborative, Innovative Approaches to New Product Introduction

What Will It Take to Ensure Equity, Scale and Impact

Mitchell Warren

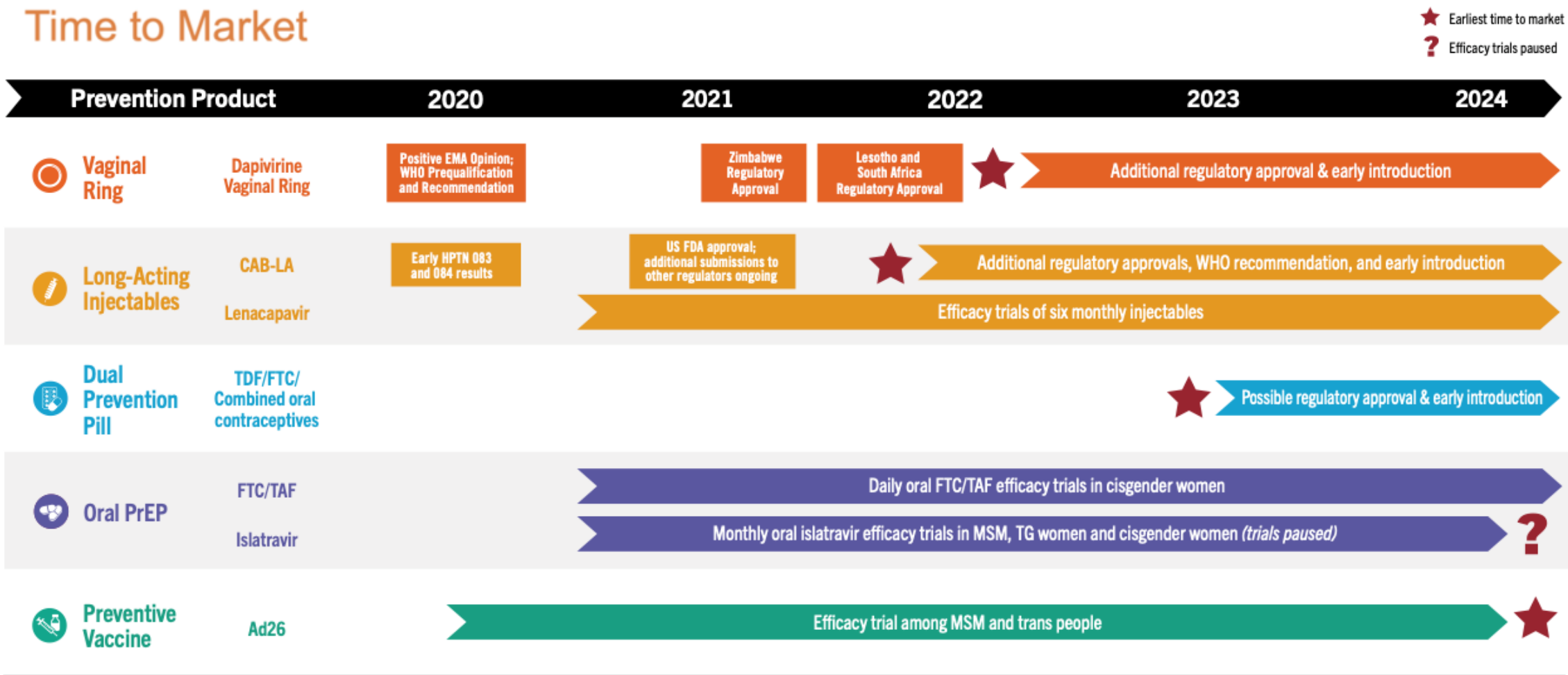
Executive Director, AVAC

The Choice Agenda: Faster, Smarter and More Equitable – Accelerating Roll Out and Uptake of CAB for PrEP

8 August 2022

AVAC
25 Years and Counting

Years Ahead in HIV Prevention Research



June 2022

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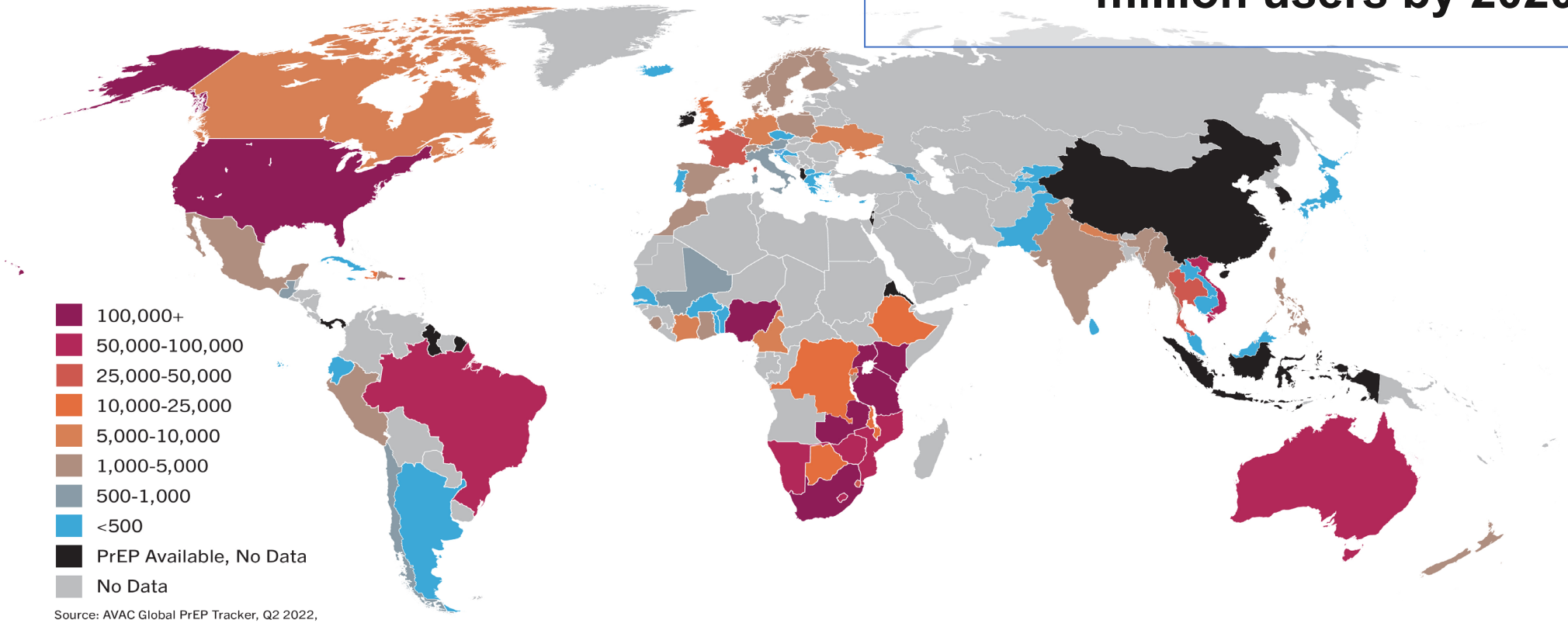
Global PrEP Uptake – 10 years in

Approx. total PrEP initiations: 2,797,304 with strong increases in 2021-2 – BUT significantly missed UN target of 3 million users by 2020



Source: AVAC Global PrEP Tracker, Q2 2022, https://www.prepwatch.org/country-updates/

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Learning from and Building on Oral PrEP

Oral PrEP Implementation Studies

Post-approval studies and projects

131 Distinct post-approval oral PrEP implementation projects and studies; most were small-scale

Countries

68 Different countries conducted projects including multiple in the same country (e.g. 25 in one country)

Stakeholders

54 Different organizations involved in oral PrEP implementation research

Key Takeaways from early Oral PrEP rollout

Post-approval studies were not all designed to address decision-maker questions

Data from research was not well timed to inform decision making at global or country level

Complex, fragmented stakeholder landscape

Lessons Lessons From Oral PrEP Programs & Implications for Next Generation Prevention

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The Way Forward

Requirements of Collaboratively Planning for Successful Introduction:

- **Mapping decision-maker questions against studies**
- **Planning in parallel with clinical trials**
- **Shared strategy developed by diverse stakeholders**

Ideal Scenario for Future Px Products:

Post-approval studies are **well designed** to address decision-maker questions

Data from research is **well timed** to inform decision-making at global and country level

Coordinated stakeholder landscape with roles agreed upon in advance

[BioPIC CAB-LA initial Introduction Strategy]

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Guiding Principles

- Lead with Equity
- Center the Community and User
- Accelerate Scale and Speed
- Deliver Impact
- Work With What We Know, While Continually Adding To The Evidence-Base

Pathway to Access & Impact

Full Report *Translating Scientific Advance into Public Health Impact:*
A Plan for Accelerating Access and Introduction of Injectable CAB for PrEP
—available at **www.avac.org/blog/accelerating-access-and-introduction-injectable-cab-prep**.

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Pathway to Access & Impact

Pathway	Immediate Priorities
Product	▶ **ViiV** to license injectable CAB to the Medicines Patent Pool (MPP). ▶ **The MPP and ViiV** to work with generic manufacturers and donors, including Africa-based manufacturers, to expedite technology transfer and ensure sustainable supplies of the product. ▶ **Generic manufactures, with MPP**, to identify capital expenditure needs and timeframe to be able to develop capacity. ▶ **Innovative donor(s)** to fund capital investments needed for generic manufacturing to reach scale. ▶ **ViiV** to confirm publicly, maximum quantity and minimum price for 2022-2025. ▶ **Donors** to negotiate this price/volume guarantee to ensure sustainable supply for initial introduction period, given the timeline for generic licensing agreements and manufacturing upgrades (likely 4-5 years).
Regulatory Approval & Normative Guidance	▶ **Eight regulators** currently reviewing injectable CAB for PrEP to ensure priority review. ▶ **ViiV** to pursue widespread registration of CAB in high-burden countries. ▶ **ViiV** to register with WHO Pre-Qualification (PQ) to allow expedited registration in countries participating in WHO's Collaborative Procedure for Accelerated Registration process.
Planning & Budgeting	▶ **Governments and donors** to set targets for supply and programs at scale – what is needed and possible in 2022-2023 in implementation science projects, and what is needed from 2024 to begin programs at scale.

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Pathway to Access & Impact

Delivery / Supply Chain	▶ **Large, resourced and coordinated implementation studies** to begin immediately to answer critical questions about how CAB performs outside the clinic setting and across populations. ▶ **Provider training** materials and tools updated to incorporate CAB administration and implementation studies that assess the feasibility of task-shifting to expand the cadres of providers that are authorized and trained to administer injections and that offer choice (explaining efficacy, clinic visits, side effects, etc. of all methods available) and assist in shared decision-making.
Individual Uptake & Continued Use	▶ **Innovative demand creation** strategies (for injectable PrEP and for "choice" among options) developed with process to test and iterate, and share across projects.
Delivery / Supply Chain	▶ **Testing requirements** should not become a barrier to CAB introduction. Testing strategies should be both robust and feasible and work with locally available tests and assays to, maximize the benefits of access to CAB while minimizing the risk of undetected cases.
Research	▶ **Data to be collected on the benefit of injectable CAB as PrEP for populations that were not part of efficacy trial**s, especially adolescents, pregnant and breast-feeding people, and transmasculine and gender non-conforming individuals. ▶ **Study alternate injection sites and frequency of injections**, recognizing that the impact of injectable CAB holds the potential to expand, if the injection schedule could align with injectable contraception.
Stakeholder Engagement	▶ **Integrate and engage civil society** in all decision-making relevant to planning and preparation for access to CAB, including designing, conducting and monitoring implementation studies and delivery programs.

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Coalition to Accelerate Access

- Convened by Unitaid, WHO, UNAIDS, Global Fund and PEPFAR, with AVAC as the Secretariat
- Coordinate key stakeholder activities on PrEP access, including:
  - Building on lessons learned from oral PrEP
  - Coordinate key stakeholder activities on PrEP access
  - Jointly develop strategies to identify and overcome access challenges for new PrEP options in the near to medium term (as relates to ViiV's injectable CAB, including generics, and dapivirine vaginal ring) and the medium to longer term (as relates to future PrEP products)
  - Ensure new, longer-acting PrEP options reaching the market will be available and equitably accessible to all who need them more quickly than ever before

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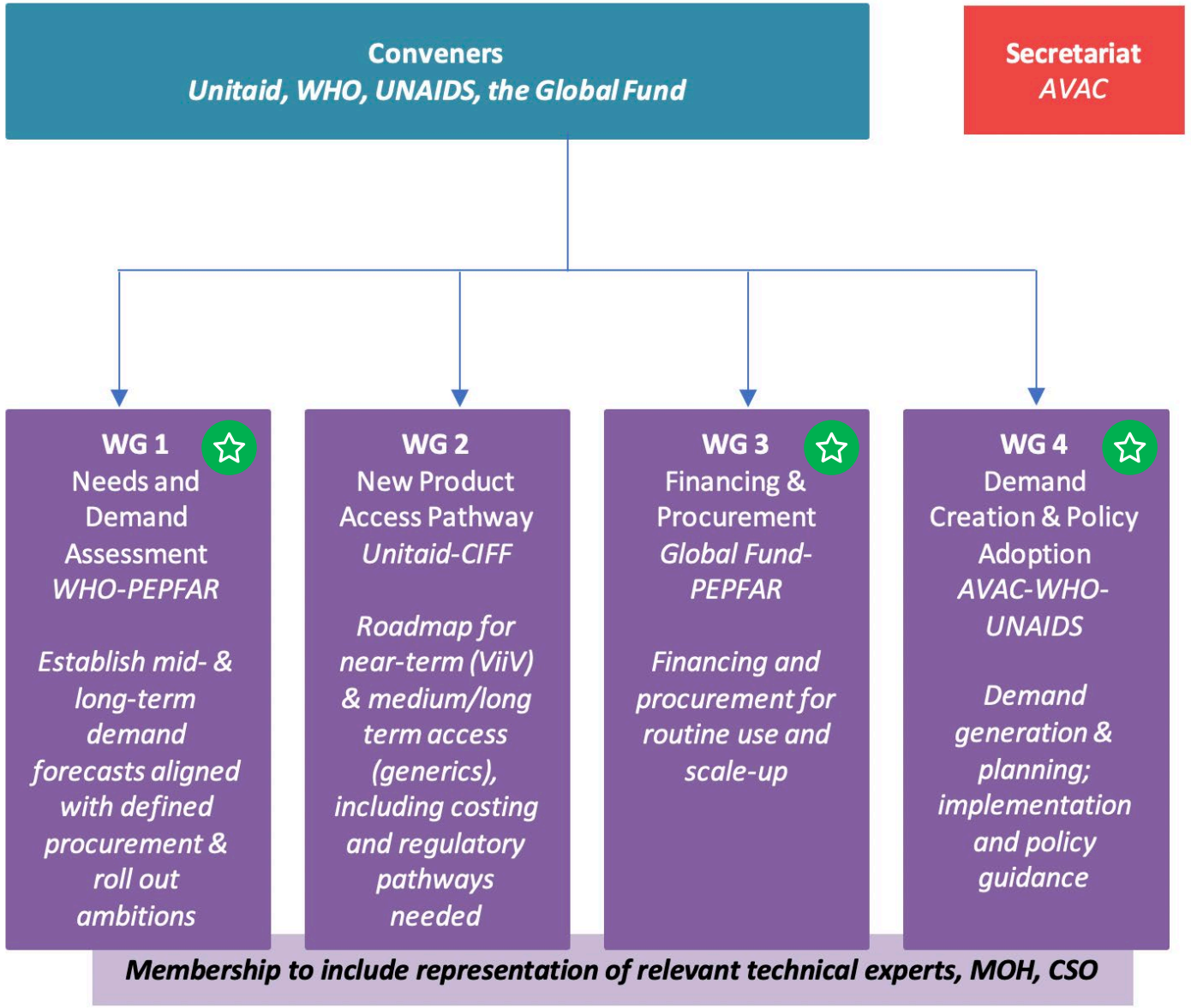
Coalition to Accelerate Access



IP/Voluntary License
MPP-ViiV

Implementation Science
WHO-AVAC-BioPIC

CSO Engagement
Various

Focused on Full Px Pipeline

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Product Considerations

For each product, understand and balance:

Clinical	Policy & Programs	Personal
▪ Biologic efficacy ▪ Dosing/duration ▪ Reversibility ▪ Side effect profile ▪ Systemic/Topical	▪ Delivery channel(s) ▪ Health system burden ▪ Product cost ▪ Program cost ▪ Provider training ▪ Demand creation	▪ User effectiveness ▪ User preference ▪ User burden ▪ Discretion of use ▪ Contribution to stigma

It's never just "the product" – it's the program;
new options can't solve for everything

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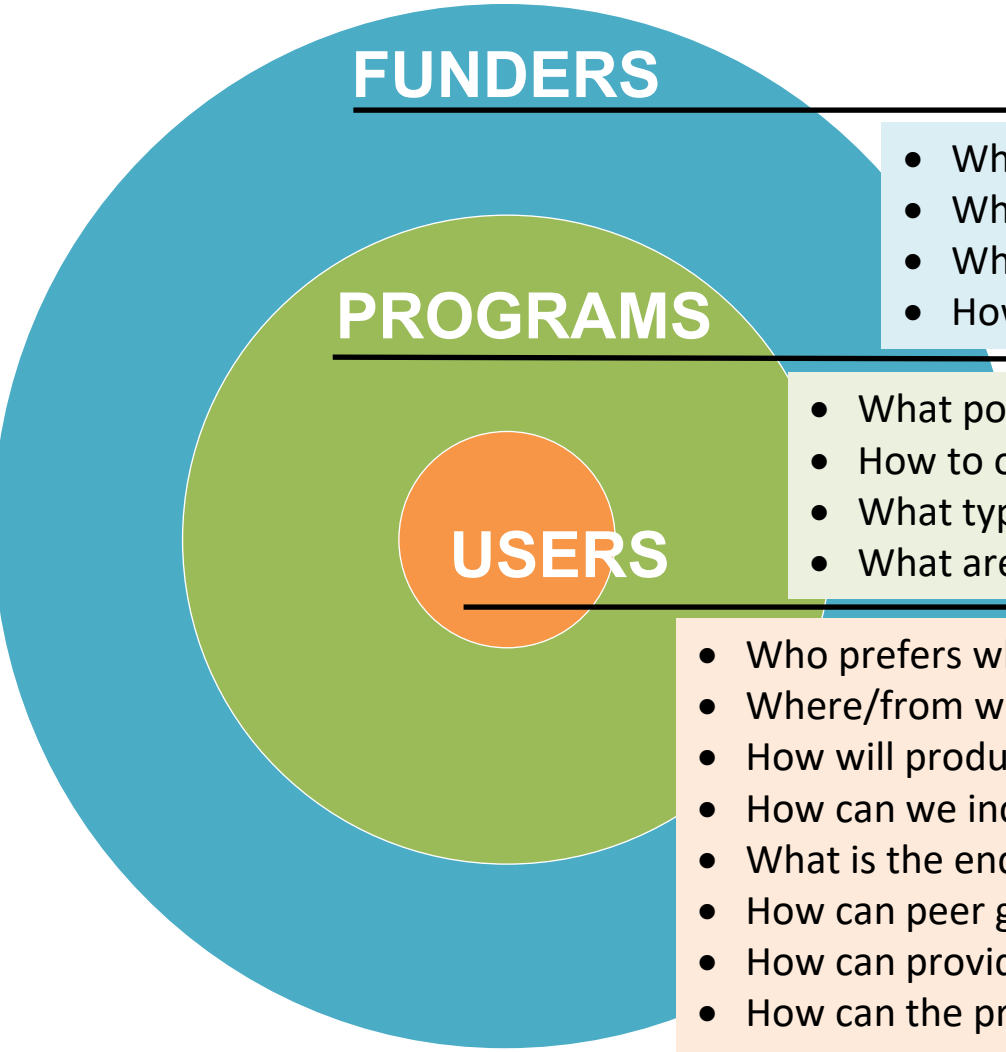
Accelerating Introduction of New Px Options

Those who Use; Those who Choose; Those who Pay the Dues



What we need to know – and fast

FUNDERS

- What is the cost for procurement AND for programming?
- What is the cost-effectiveness?
- What is the market size, generally and relative to other PrEP products?
- How will introduction affect the current market share and size of other PrEP?

PROGRAMS

- What policies need to change to to plan for & introduce new option?
- How to overcome siloes in procurement & service delivery?
- What type of training & support do providers need?
- What are optimal service delivery platforms and communication channels?

USERS

- Who prefers which option, and what are their motivators and barriers?
- Where/from whom do potential users desire to hear about and access product?
- How will product use/preference change over time?
- How can we increase & support adherence?
- What is the end user's path to initiation and continued, effective use?
- How can peer groups/influencers be leveraged to support uptake & adherence?
- How can providers be supported to have more knowledge and empathy?
- How can the product be packaged to better support uptake/ adherence?

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Now What?

- Translate biomedical options into viable choices for users, providers and health systems
  - Intro new options as part of marketing and programming for choice
  - Identify (and differentiate) service delivery models that work for users
  - Ask and answer critical implementation science questions for each product, while building prevention platforms for the future
- Understand testing and initiation needs for PrEP
- Ensure robust civil society engagement in intro/implementation research and planning
- Procurement/commodity funding – for launch and ongoing
- Provider training – both clinical guidelines AND appropriate counseling, support, empathy
- Realistic targets for interventions, especially intro – and not just coverage targets
- Identify what products can "solve for" – and what they can't
- Ensure we do better, more equitable intro with ring and injectable than with oral PrEP and COVID-19 vaccines

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25 Years and Counting

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- Jacque Wambui

HIV Prevention Market Manager
Accelerating Product Introduction
Informing Product Development
Reducing Time to Impact
AVAC
Clinton Health Access Initiative
Supported by the Bill & Melinda Gates Foundation

BioPIC Biomedical Prevention Implementation Collaborative

Coalition to Accelerate and Support Prevention Research (CASPR)

Cooperative Agreement No. AID-OAA-A-16-00031
HIV Vaccine and Biomedical Prevention Research Project—Objective 3

PROMISE-CHOICE Partners

MOSAIC
Maximizing Options to Advance Informed Choice for HIV Prevention

CIFF Children's Investment Fund Foundation
Bill & Melinda Gates foundation
COMPASS

Faster, Smarter and More Equitable – Accelerating Roll Out and Uptake of CAB for PrEP

Monica Gandhi MD, MPH
Director, UCSF Center for AIDS Research and
Medical Director, Ward 86 HIV Clinic
Professor of Medicine, UCSF
AVAC: Global Advocacy for HIV Prevention
August 2, 2022

Daily PrEP trials with TDF/FTC–Adherence everything

Trial	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
iPrEX[1] (N = 2499)	MSM, 11 sites in U.S., S. America, Africa, Thailand	▪ Daily oral TDF/FTC	44% (95% CI 15-63, p 0.005)
Partners PrEP[2] (N = 4747)	Serodiscordant couples in Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC	▪ Women: 71%; men: 63% ▪ Women: 66%; men: 84%
TDF2[3] (N = 1219)	Heterosexual males and females in Botswana	▪ Daily oral TDF/FTC	62%* (underpowered for sex differences)
Bangkok TFV Study[6] (N= 2413)	IDU (use in last year) in Bangkok	▪ Daily oral TDF	49% (95% CI 9.6-72.2, p 0.01)
FEM-PrEP[4] (N = 2120)	High-risk women, Africa	▪ Daily oral TDF/FTC	▪ Study stopped early due to futility (adherence)
VOICE[5] (N = 5029)	High-risk women, Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC ▪ 1% TFV gel	▪ 1% TDF gel & daily oral TDF arm both stopped early, futile ▪ Daily TDF/FTC arm – no efficacy (adherence)
PROUD (N=523)[7]	High-risk men, U.K.	▪ Daily oral TDF/FTC, immediate vs deferred	86% (90% CI 58-96%, p=0.0002)

1. Grant RM. N Engl J Med. 2010. 2. Baeten JM. N Engl J Med. 2012 3. Thigpen MC. N Engl J Med. 2012; 4. Van Damme. N Engl J Med. 2012 5. Marrazzo J, N. Engl J. Med. 2015; 6. Choopanya Lancet June 2013; 7. McCormack. CROI 2015

Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis

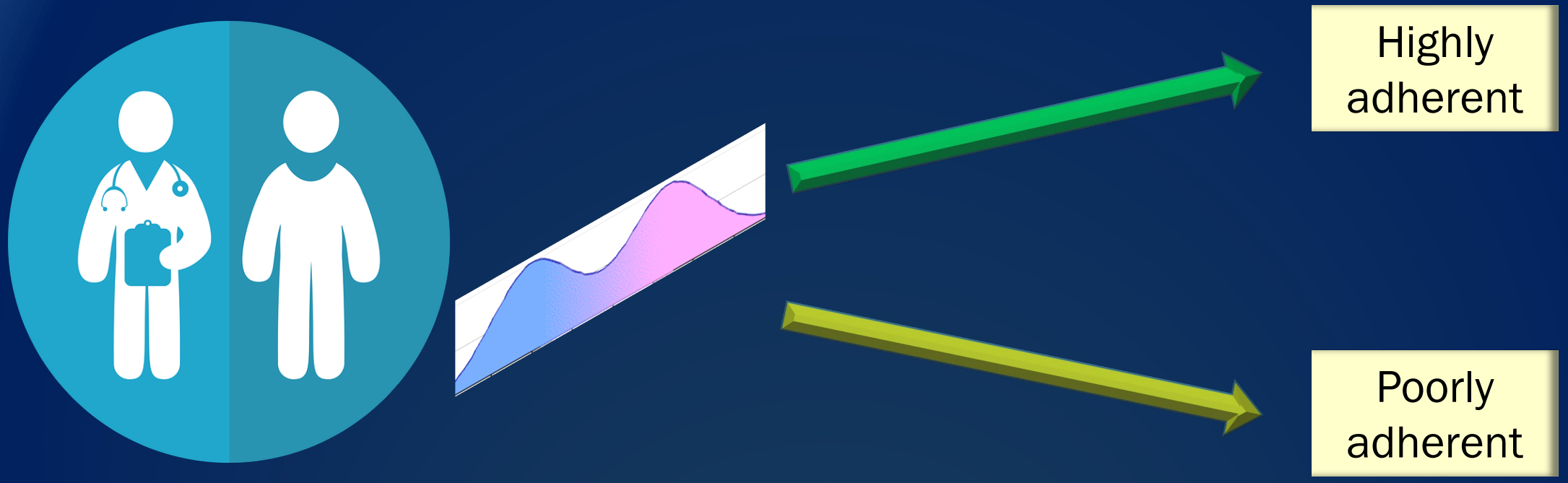
THE LANCET HIV

ARTICLES | VOLUME 9, ISSUE 4, E254-E268, APRIL 01, 2022

Jing Zhang*, Chunyan Li*, Junjie Xu*, Zhili Hu, Sarah E Rutstein, Joseph D Tucker, Jason J Ong, Yongjun Ji

- Systematic review, 41·0% of those on PrEP discontinued within 6 months; suboptimal adherence for those who stayed 37·7%
- Discontinuation rate higher in sub-Saharan Africa 47·5% than other regions
- Discontinuation rates lower in studies with adherence interventions than in those without (24·7% *vs* 36·7%, p=0·015). \
- Men who have sex with men and transgender women offered daily or non-daily dosing options had lower discontinuation rates than those offered daily dosing alone (21·6% *vs* 31·5%; p<0·001).
- **Though oral PrEP important, we need other options**

Bimodal population: Patient with challenges to PrEP/ART adherence would benefit from long-acting PrEP/ART



Would then KNOW date of “medication consumption” (not adherence, but coming in), pharmacies or mobile vans administering the shots, home health

THE LANCET
HIV

Equity in access to long-acting injectables in the USA

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, recently received regulatory approval in the Canada, the EU, and the USA as a monthly intramuscular long-acting injectable (LAI) antiretroviral therapy regimen in adults with HIV-1 who are virologically

Published Online
February 4, 2022
https://doi.org/10.1016/
S2352-3018(22)00031-5

*J Carlo Hojilla, Monica Gandhi, Derek D Satre, Mallory O Johnson, Parya Saberi

- Critically important population for Ending the HIV epidemic
- Equitable access across the US and across the world important
- WHO strongly endorsed Cabotegravir LA PrEP at International AIDS Conference, Montreal, July 28, 2022

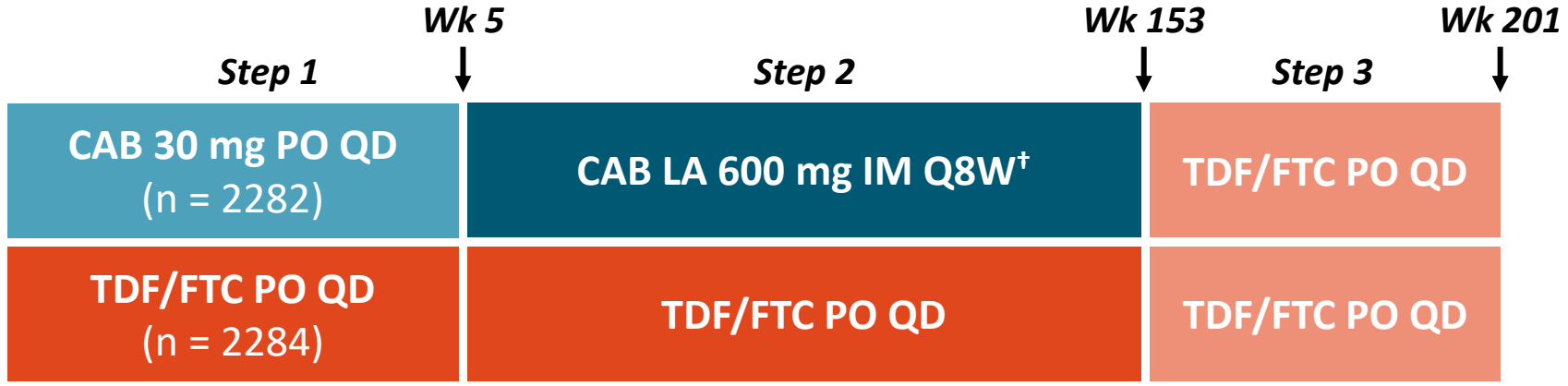
ViiV HEALTHCARE AND THE MEDICINES PATENT POOL SIGN NEW VOLUNTARY LICENSING AGREEMENT TO EXPAND ACCESS TO INNOVATIVE LONG-ACTING HIV PREVENTION MEDICINE

London, 28 July 2022 - ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer and Shionogi as shareholders, and the Medicines Patent Pool (MPP) today announced the signing of a new voluntary licensing agreement for patents relating to cabotegravir long-acting (LA) for HIV pre-exposure prophylaxis (PrEP) to help enable access in least developed, low-income, lower middle-income and Sub-Saharan African countries[1,2].

HPTN 083: Efficacy and Safety of LA Injectable CAB vs Daily Oral TDF/FTC for PrEP in MSM and TGW

- International, randomized, double-blind phase IIb/III study

HIV-uninfected MSM and TGW ≥ 18 yrs of age at high risk of HIV infection*; no HBV/HCV infection, (N = 4566)



*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 mos; or SexPro Score ≤ 16 (US only).
†First 2 doses given 4 wks apart then every 8 wks thereafter.

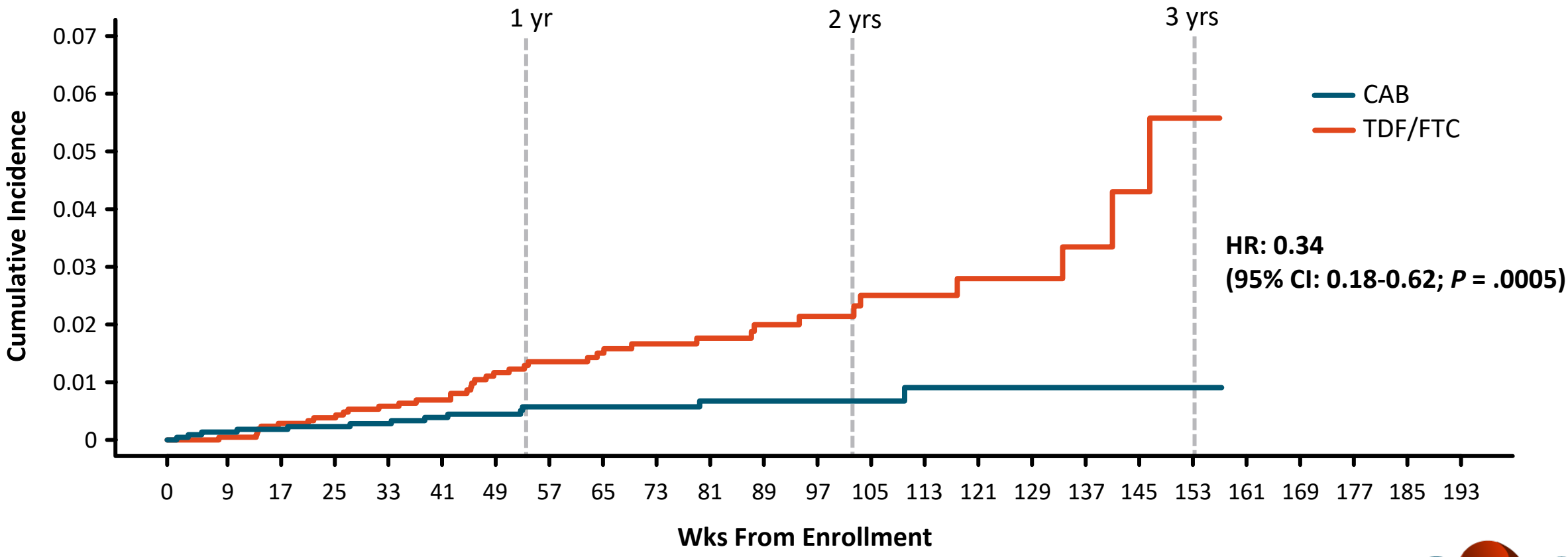
- Primary endpoints: incident HIV infections, grade ≥ 2 AEs

Landovitz. NEJM 2021.

HPTN 083
an HIV prevention clinical trial

HPTN 083: HIV Incidence (ITT) With LA Injectable CAB vs Daily Oral TDF/FTC PrEP

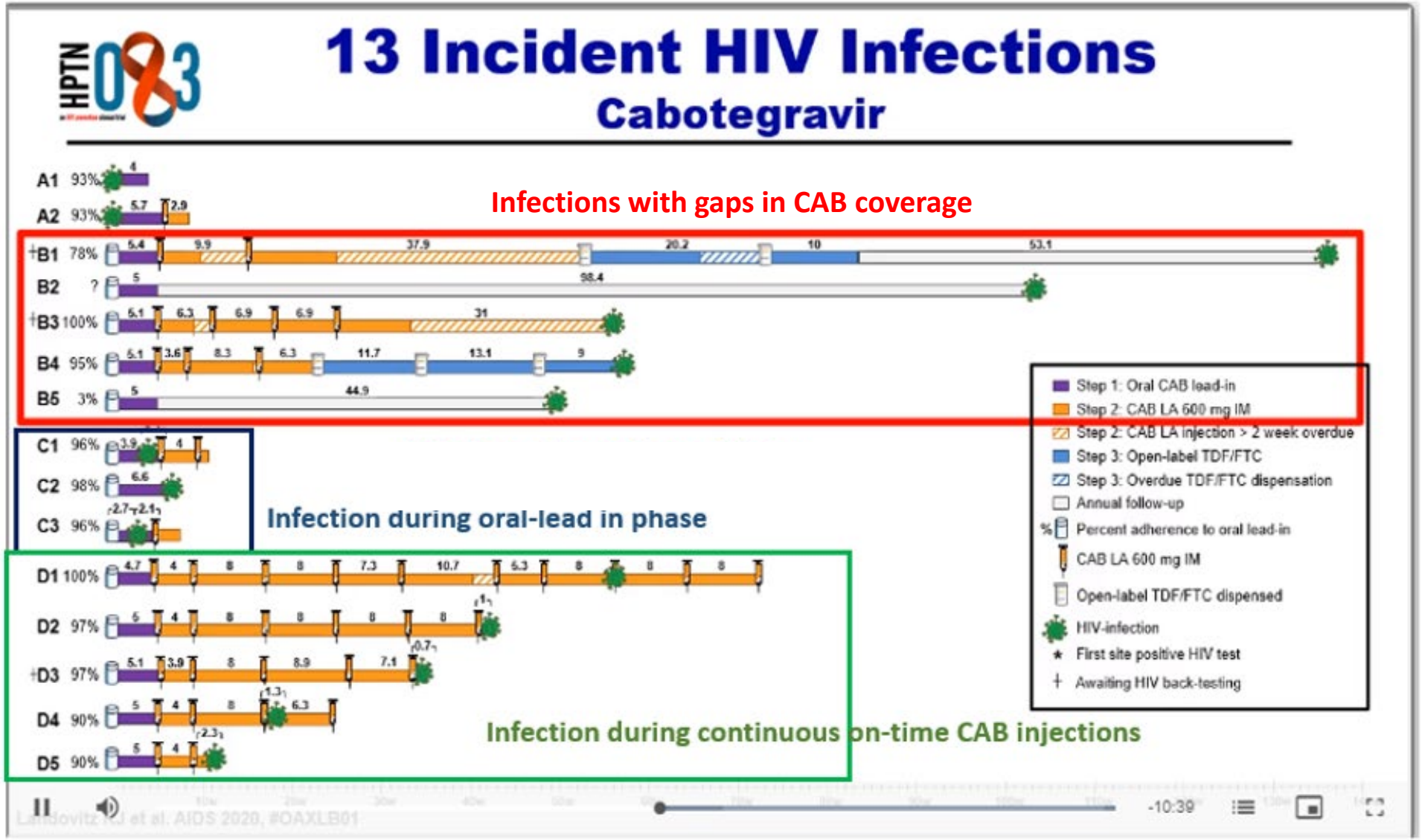
66% reduction over daily TDF/FTC



Landovitz. NEJM 2021.

HPTN 083
an HIV prevention clinical trial

5 out of 13 infections in CAB arm occurred despite on-time injections

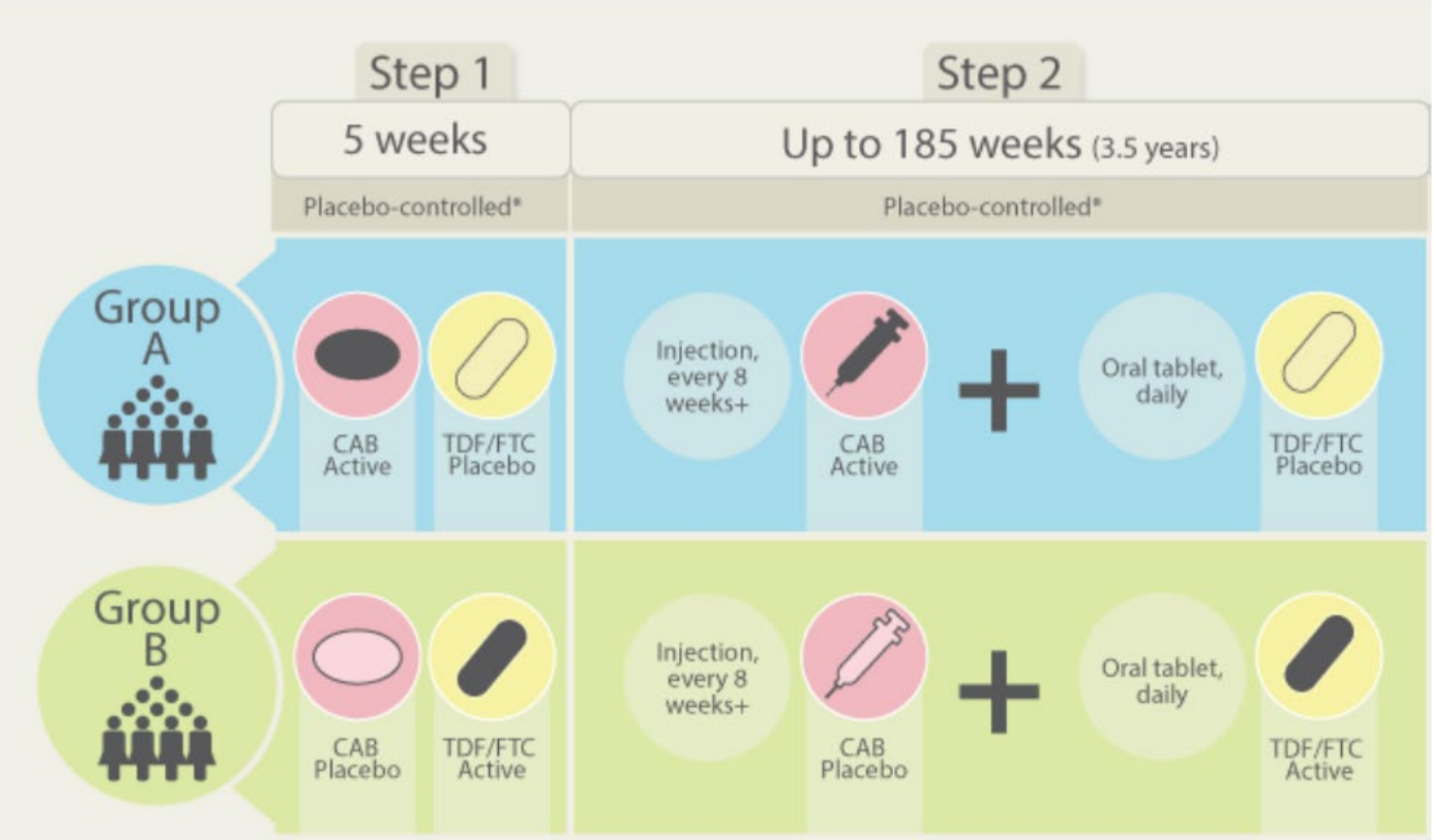


Landovitz. NEJM 2021; Markowitz JID 2022

Resistance 6 out of 12


HPTN
084
Long-acting Injectable For the Epidemic

Study design of HPTN 084



- Enrolled 3,223 women aged 18-45 years old at risk in 20 sites across 7 countries (Botswana, Kenya, Malawi, South Africa, eSwatini, Uganda and Zimbabwe)

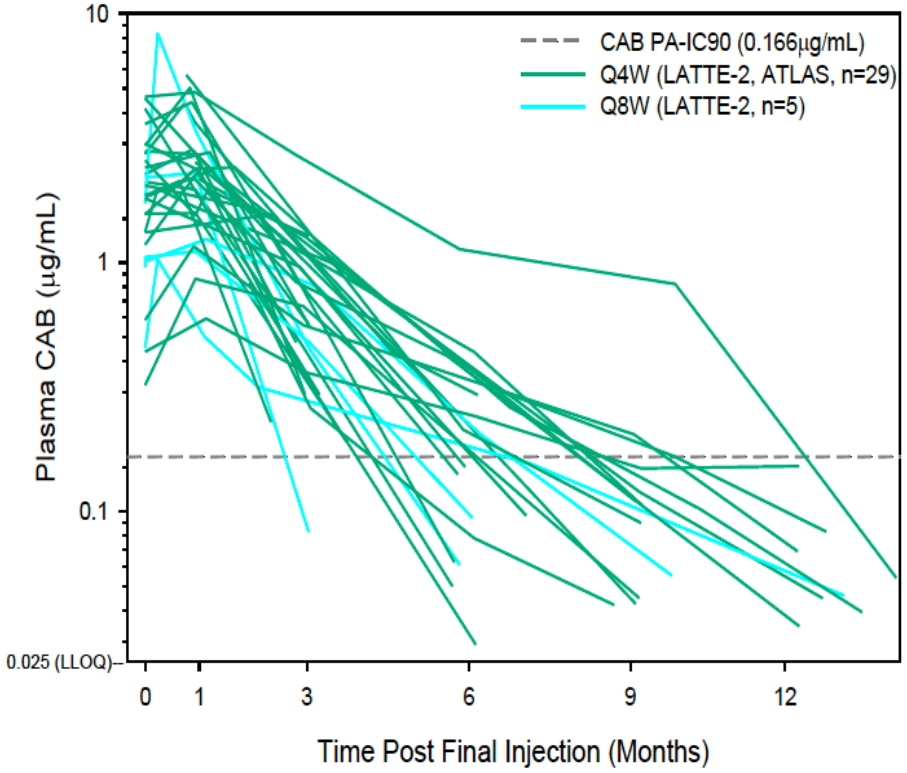
DSMB stopped study early and press release Nov 9, 2020

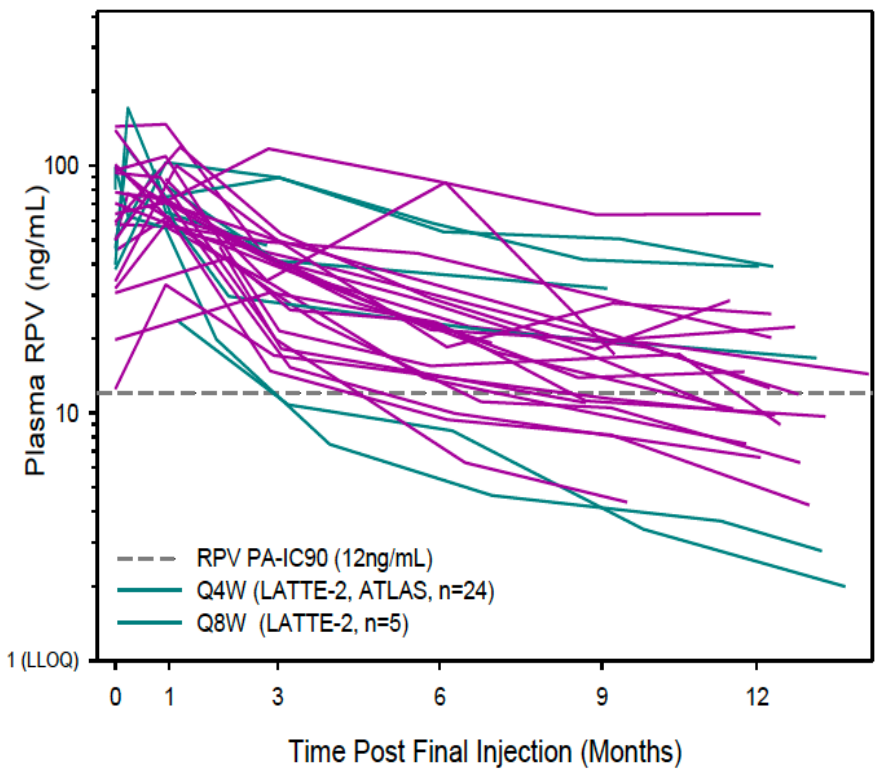
- Cabotegravir q8 weeks superior to daily TDF/FTC
- 38 women in trial acquired HIV
  - 4 randomized to the long-acting cabotegravir arm
  - 34 randomized to the daily, oral FTC/TDF arm.
  - Long-acting cabotegravir was 89% (95% CI 68-96%) more effective than FTC/TDF (compared to 66% more effective in HPTN 083) in intention to treat analysis
- All women >= 18 and, when DTG associated with neural tube defects, protocol amendment that trial participants needed to be on effective contraceptive so no knowledge of pregnancy

No resistance in all 4 breakthroughs (Eshleman JID 2022) and no additional breakthroughs in 1 year unblinded phase (IAS 2022)

Remember to counsel patients and start oral ART when they stop CAB on the PK tail

- Following LA treatment d/c, CAB and RPV LA may be detectable in plasma for ≥ 1 year
- PK sampling 1, 3, 6, 9, and 12 mos after final LA CAB + RPV IM injection

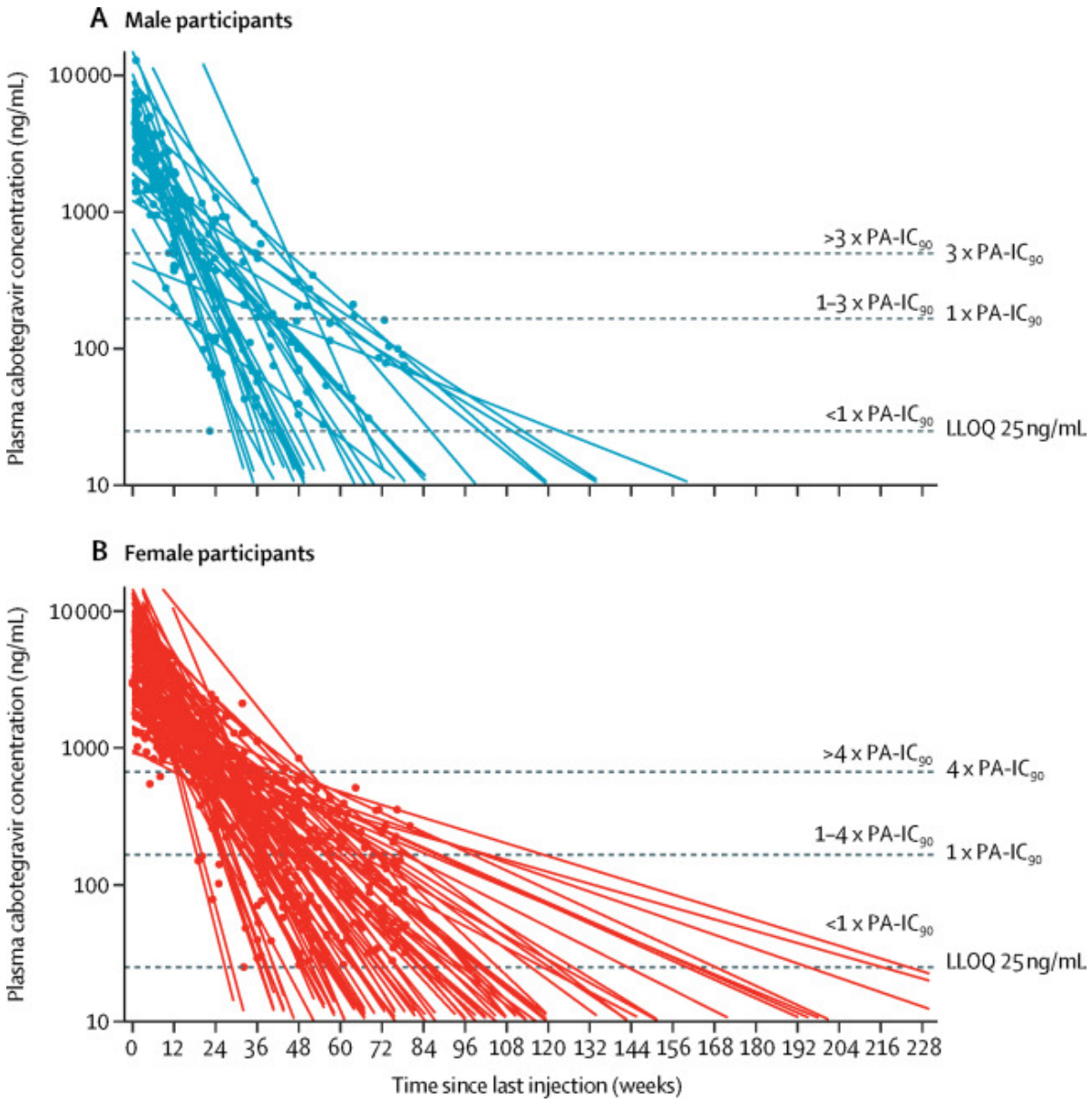




- Start ART after stopping
- Alternative ART selection after stopping LA CAB + RPV shouldn't have DDIs even with CYP3A and/or UGT1A1 inducers or inhibitors

Ford SL. CROI 2020; Abstract 466

CAB LA tail is longer in women than men



- Median time to undetectable cabotegravir is longer in women at 66.3 weeks (range 17.7 to 182) when compared to 42.7 weeks (range 20.4 to 134) in men

HPTN
HIV Prevention Trials Network

HPTN 077

Landovitz R. Lancet HIV. June 2020

Screening criteria in our clinic for starting IM cabotegravir

- HIV testing:
  - Negative serum HIV Ag/Ab test result within 3 days before initially prescribing PrEP
    – or–
  - Serum HIV Ag/Ab test pending *and* a negative POC STAT PAK HIV Ab test day of injection
- HIV RNA sent/pending
- No signs or symptoms of acute HIV infection
- Patient expresses willingness to receive CAB LA PrEP injections (injection in gluteal muscle)
- Patients who are on the following medications are not eligible (due to concern of decreased drug levels of CAB):
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Antimycobacterials: rifabutin, rifampin, rifapentine
  - Herbal: St. John's Wort

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

Dosage	• 600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle
	  ○ Initial dose
	  ○ Second dose 4 weeks after first dose (month 1 follow-up visit)
	  ○ Every 8 weeks thereafter (month 3,5,7, follow-up visits etc)

Follow-up care	**At follow-up visit 1 month after first injection** • HIV Ag/Ab test and HIV-1 RNA assay **At follow-up visits every 2 months (beginning with the third injection – month 3) provide the following:** • HIV Ag/Ab test and HIV-1 RNA assay • Access to clean needles/syringes and drug treatment services for PWID **At follow-up visits every 4 months (beginning with the third injection- month 3) provide the following:** • Bacterial STI screening[2] for MSM and transgender women who have sex with men[2] – oral, rectal, urine, blood **At follow-up visits every 6 months (beginning with the fifth injection – month 7) provide the following:** • Bacterial STI screening[1] for all heterosexually-active women and men – [vaginal, rectal, urine - as indicated], blood **At follow-up visits at least every 12 months (after the first injection) provide the following:** • Assess desire to continue injections for PrEP • Chlamydia screening for heterosexually active women and men – vaginal, urine **At follow-up visits when discontinuing cabotegravir injections provide the following:**

Conclusions

- Long-acting CAB PrEP is here
- Need global access and as fast as possible
- Question regarding frequent HIV RNA monitoring in resource-limited settings (CDC recommends every injection) important one

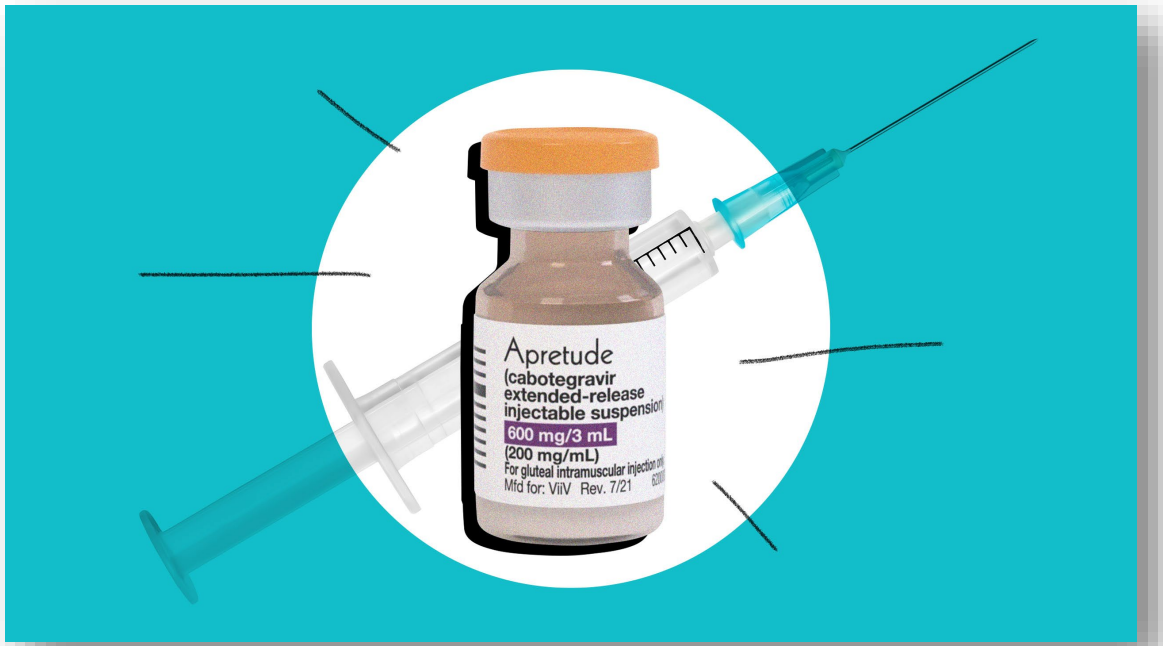
Long Acting Cabotegravir at NewYork-Presbyterian Hospital Columbia Irving Medical Center

Caroline Carnevale DNP MPH

Cabotegravir-LA at NYP/Columbia

- Cabotegravir-Long Acting Approved by the FDA in December 2021
  - NYP/Columbia had the medication approved by the NYP pharmacy review board in February 2022
  - First three patients expressed interest in CAB-LA injections at the NYP Sexual Health clinic March 2022
  - Since that time 12 total patients have presented with interest
    - 5 decided on TDF/FTC, 2 pending insurance approval, 5 started
    - 11 identified as MSM, 1 cis-woman

Cabotegravir-LA at NYP/Columbia



- 27 year old Black male who has an HIV positive male partner presented for routine quarterly PrEP visit requesting Cab-LA
  - Adherent to TDF/FTC but does not want the burden of taking pills everyday
  - PMH of depression, mood disorder
  - Fully insured with commercial insurance

Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"

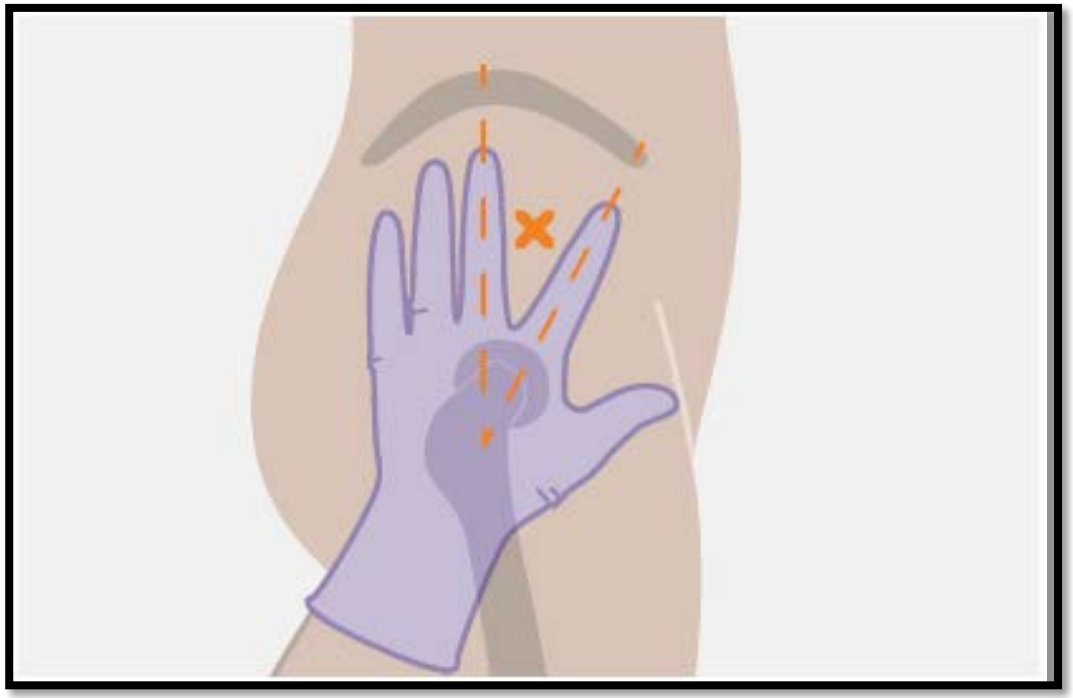
Table 2. Recommended Dosing Schedule (Direct to Injection) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
APRETUDE[a] 600 mg (3 mL)	APRETUDE[a] 600 mg (3 mL)

[a] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

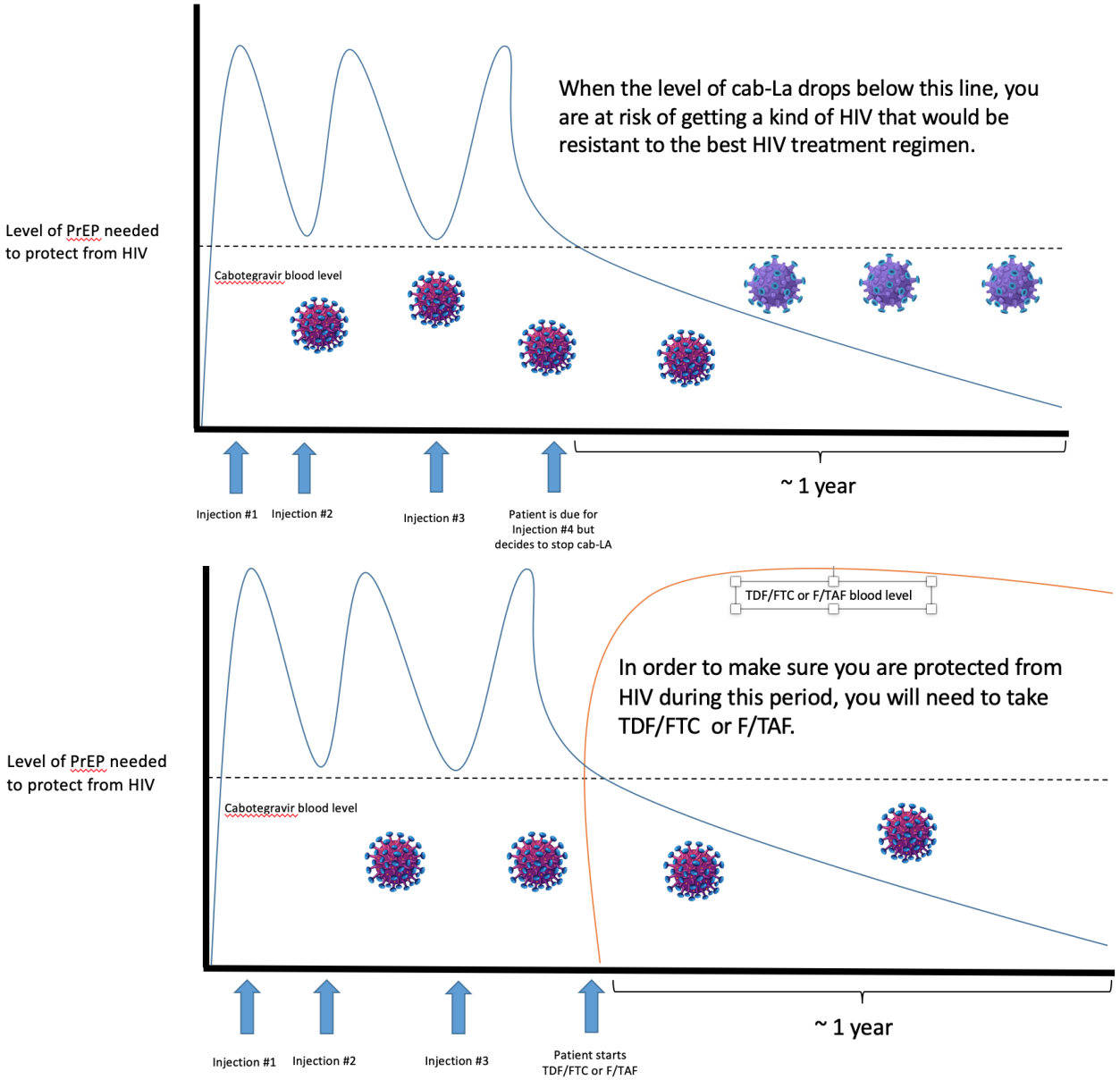
Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal

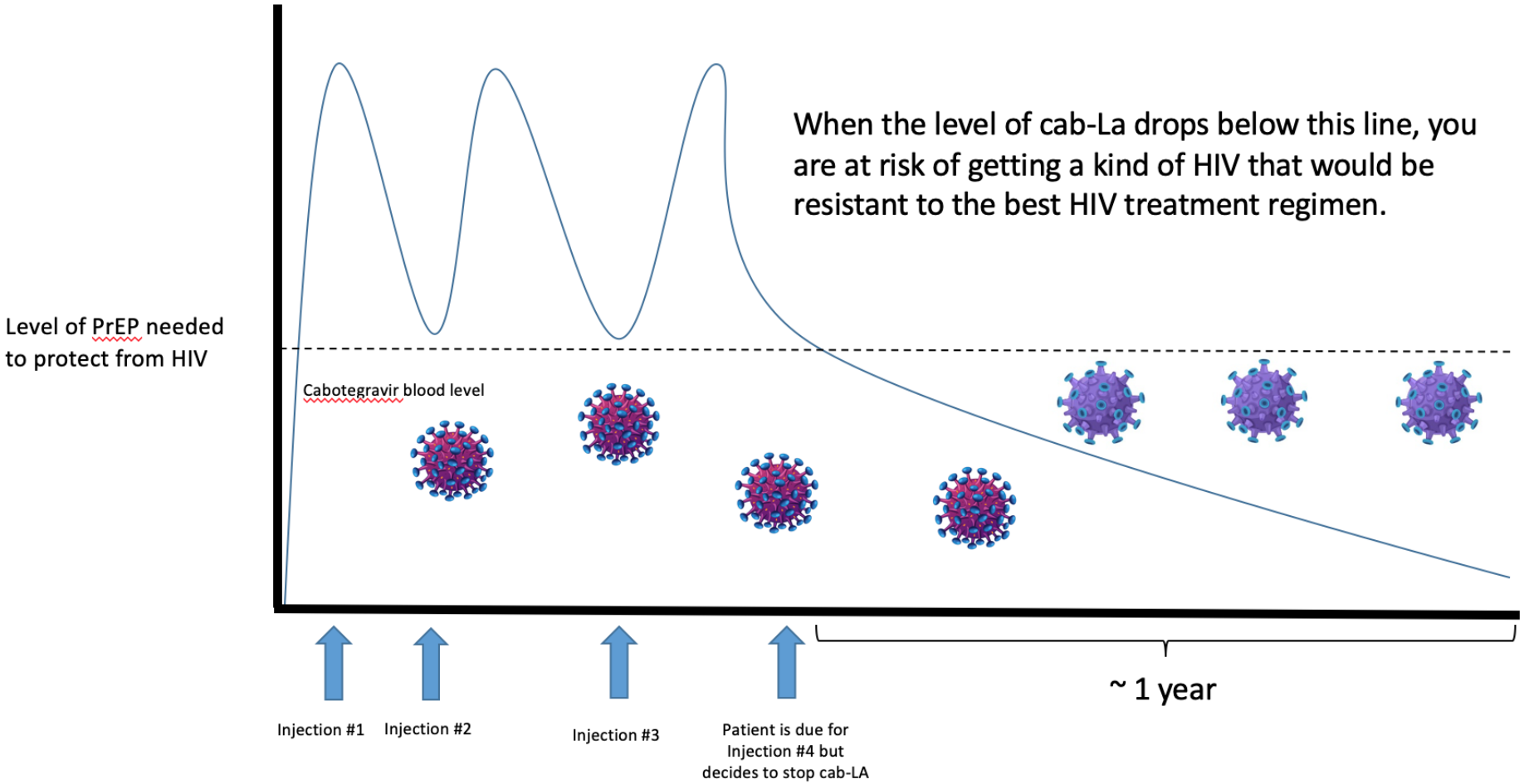


Cabotegravir Counseling

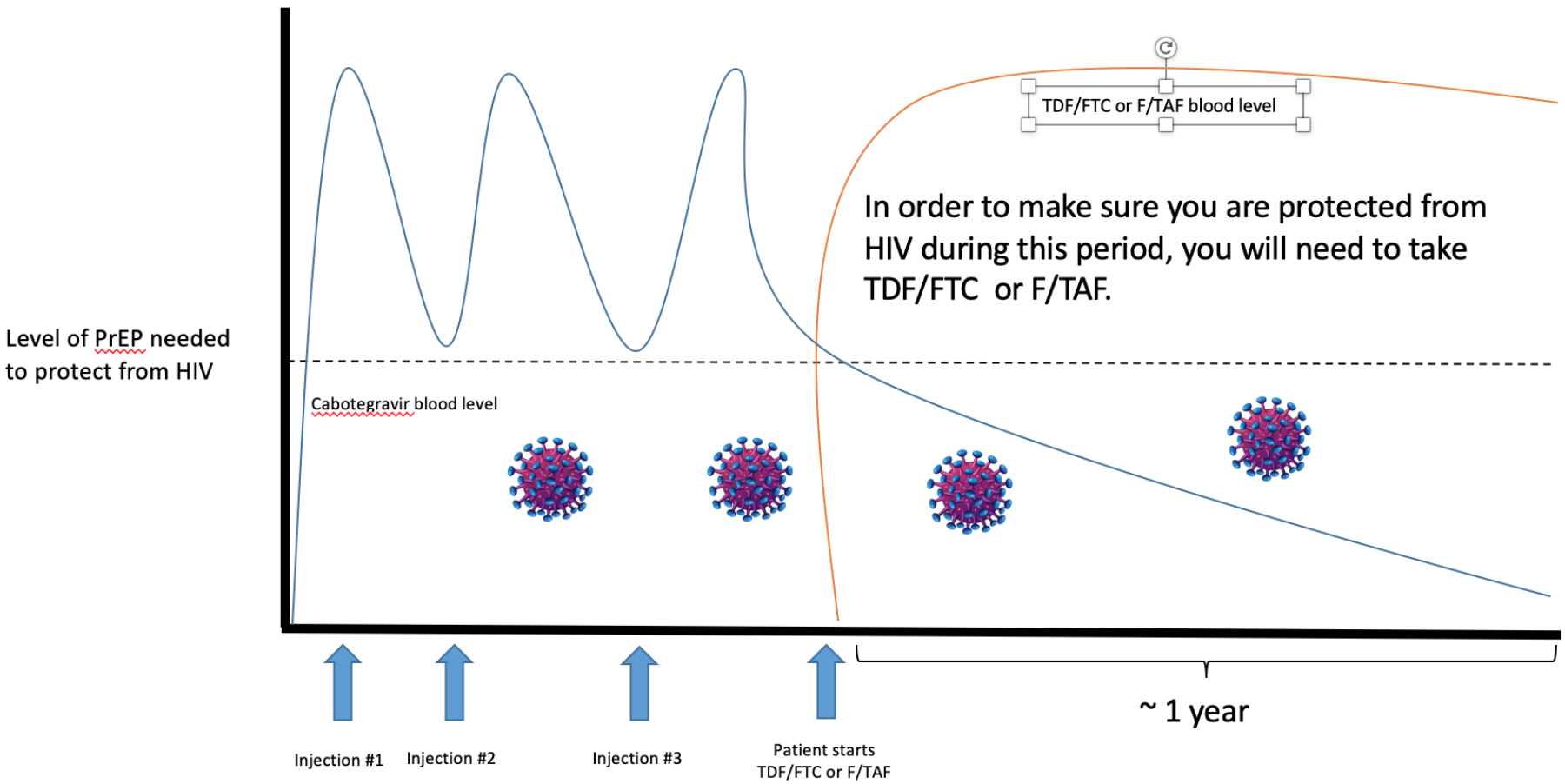
- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal
  - ❑ "Medication Tail"



Medication Tail Infographics



Medication Tail Infographics



Cabotegravir Counseling

- Educational points to be covered with patients ***prior to*** **"ordering" and administering the medication**
  - ❑ Dosing schedule and the importance of the dose "window period"
  - ❑ Site of injection is gluteal
  - ❑ "Medication Tail"
  - ❑ Medication side effects
    - ❑ Plan for depressive symptoms

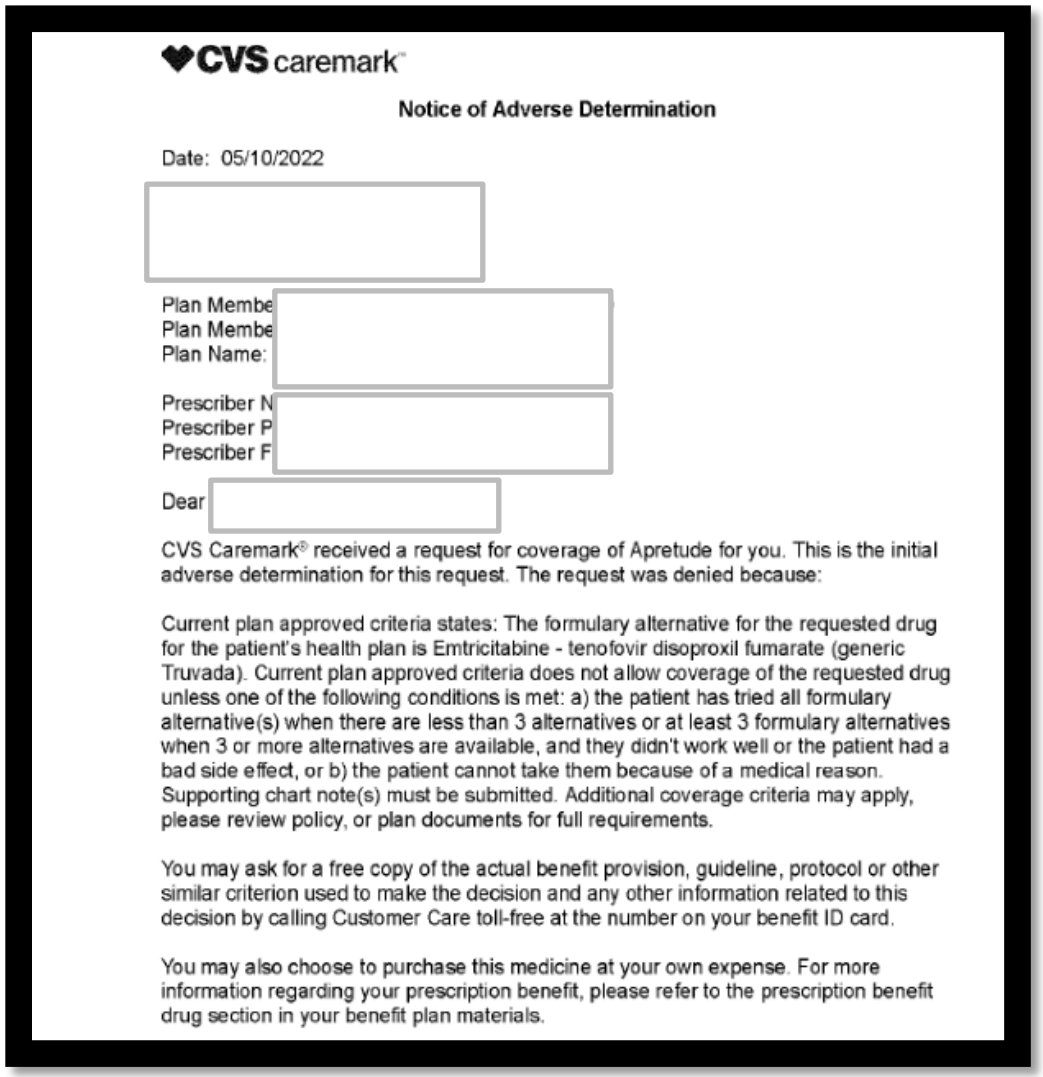
5.6 Depressive Disorders

Depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicide ideation or attempt) have been reported with APRETUDE *[see Adverse Reactions (6.1)]*. Promptly evaluate individuals with depressive symptoms to assess whether the symptoms are related to APRETUDE and to determine whether the risks of continued therapy outweigh the benefits.

Cabotegravir Cost and Financing

- Timing Challenges
  - Insurance authorization can take up to 2 weeks
    - No same-day starts
    - Provides time for labs and counseling
    - HIV testing and CAB-LA start may be separated by time

Cabotegravir Cost and Financing



CVS caremark

Notice of Adverse Determination

Date: 05/10/2022

Plan Membe
Plan Membe
Plan Name:

Prescriber N
Prescriber P
Prescriber F

Dear

CVS Caremark® received a request for coverage of Apretude for you. This is the initial adverse determination for this request. The request was denied because:

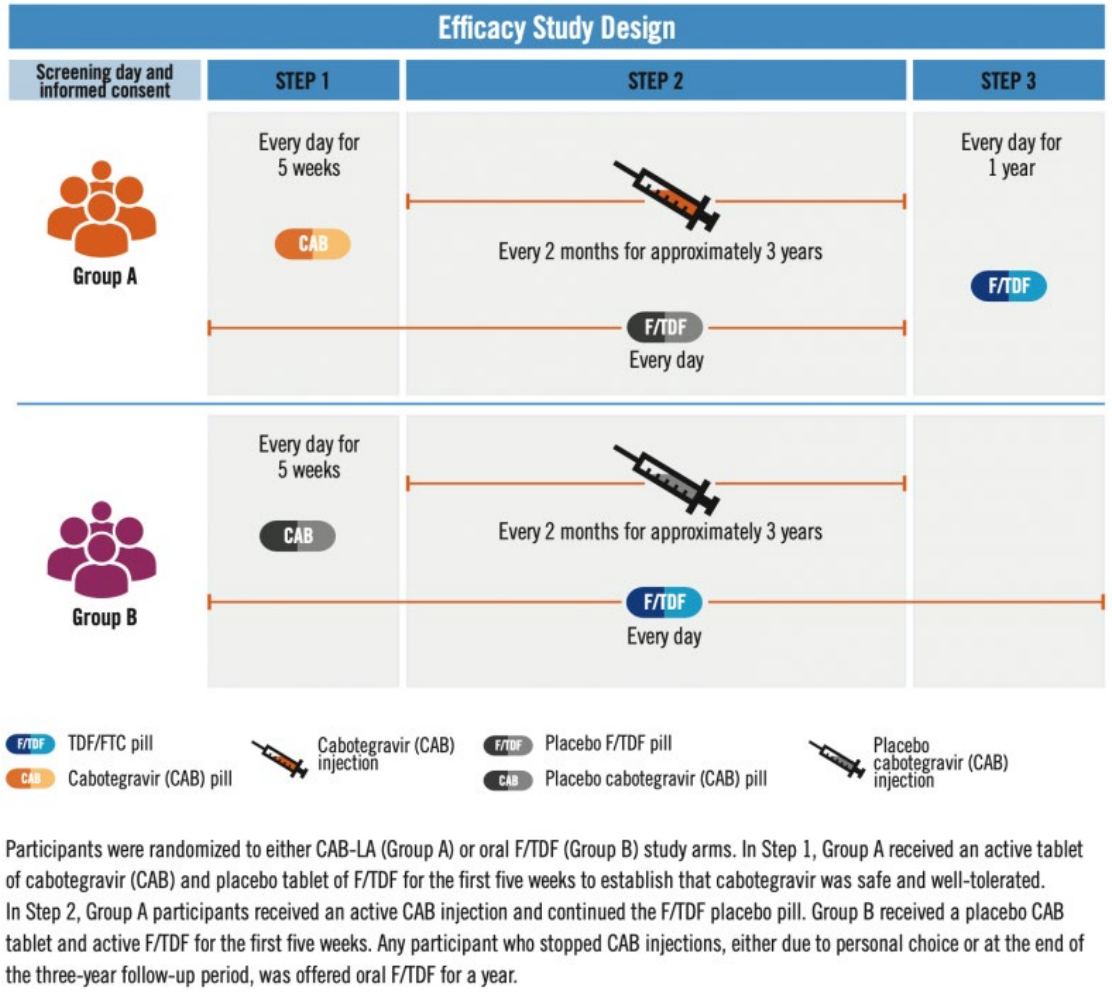
Current plan approved criteria states: The formulary alternative for the requested drug for the patient's health plan is Emtricitabine - tenofovir disoproxil fumarate (generic Truvada). Current plan approved criteria does not allow coverage of the requested drug unless one of the following conditions is met: a) the patient has tried all formulary alternative(s) when there are less than 3 alternatives or at least 3 formulary alternatives when 3 or more alternatives are available, and they didn't work well or the patient had a bad side effect, or b) the patient cannot take them because of a medical reason. Supporting chart note(s) must be submitted. Additional coverage criteria may apply, please review policy, or plan documents for full requirements.

You may ask for a free copy of the actual benefit provision, guideline, protocol or other similar criterion used to make the decision and any other information related to this decision by calling Customer Care toll-free at the number on your benefit ID card.

You may also choose to purchase this medicine at your own expense. For more information regarding your prescription benefit, please refer to the prescription benefit drug section in your benefit plan materials.

- Medical Benefits vs. Pharmacy/Drug Benefits
- Documentation of “failure” of an oral PrEP regimen before Cab-LA is a challenge in cases of:
  - Pill intolerance
  - Oral regimen to bridge injections
  - Oral regimen after discontinuation during the tail

Important Outstanding Questions

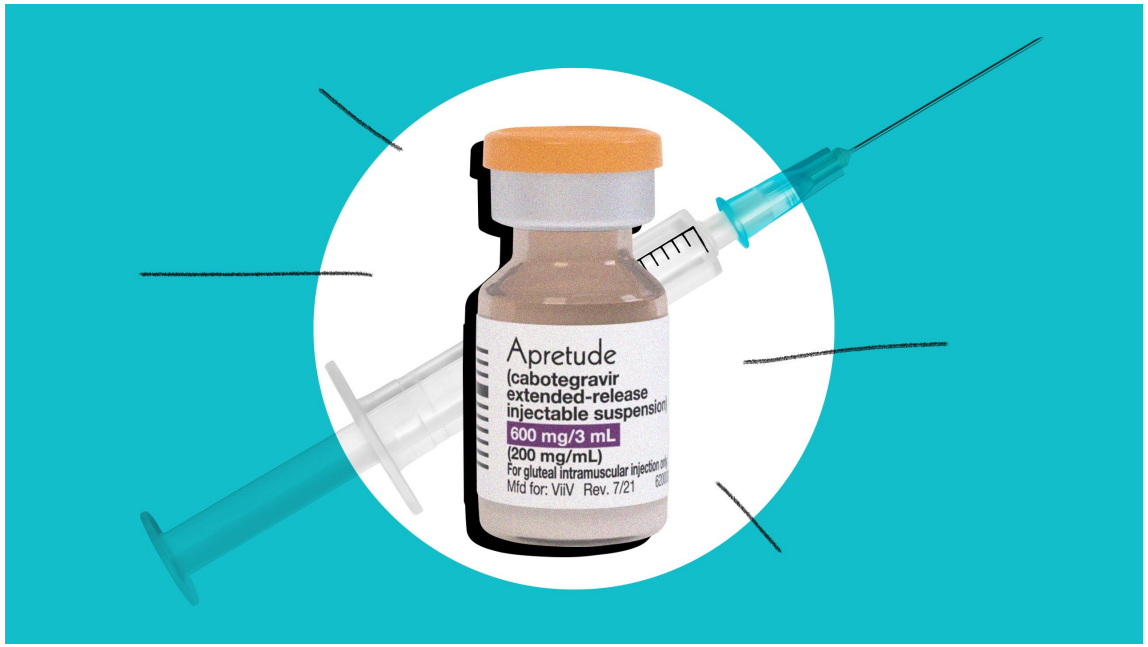


Participants were randomized to either CAB-LA (Group A) or oral F/TDF (Group B) study arms. In Step 1, Group A received an active tablet of cabotegravir (CAB) and placebo tablet of F/TDF for the first five weeks to establish that cabotegravir was safe and well-tolerated. In Step 2, Group A participants received an active CAB injection and continued the F/TDF placebo pill. Group B received a placebo CAB tablet and active F/TDF for the first five weeks. Any participant who stopped CAB injections, either due to personal choice or at the end of the three-year follow-up period, was offered oral F/TDF for a year.

- Limited information about when Cabotegravir is protective against HIV
  - Oral Lead-In?
  - How long after a single injection?
  - When a patient is bridging injections?

- **Do we need TAF/FTC or TDF/FTC during these times?**

Cabotegravir-LA at NYP/Columbia



- Our 27 year old MSM is receiving his forth injection of Cab-LA next week and reports to be feeling well and has no complaints with medication thus far

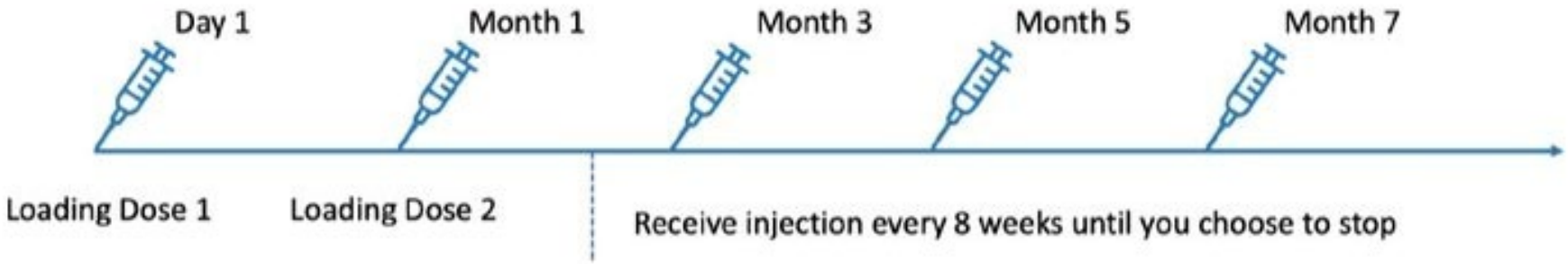
Cabotegravir Current Experience

- First an Informational Visit (via telehealth or in-person)
- Labs at each injection visit

How do you take cab-LA?

⇒ cab-LA is a shot injected by your health care provider in your gluteal muscle (butt). To start cab-LA, you will get 2 shots 4 weeks apart (loading dose 1 and 2) and then you will start a regular injection schedule every 8 weeks.

⇒ Your doctor may discuss whether you would like to take cabotegravir pills for 4 weeks before your first shot. This is a way to make sure you don't have any allergic reactions to the medication before you are injected with your first dose.



Questions? Comments?