Bridging from the HPTN 083 and 084 Open Label Extensions to Implementation

BioPIC Implementation Science Think Tank

Catherine Verde Hashim

14 March 2023

AVAC
Global Advocacy for HIV Prevention

Agenda

Time	Agenda Item	Facilitators
15 mins	Introduction and WHO Priorities	Catherine Verde Hashim, AVAC Robin Schaefer, WHO
30 mins	Insights from HPTN 083 OLE	Raphael Landovitz, UCLA Beatriz Grinsztejn, Fiocruz
30 mins	Insights from HPTN 084 OLE	Sinead Delany-Moretlwe, Wits RHI Mina Hosseinipour, UNC
40 mins	Facilitated Discussion	Catherine Verde Hashim, AVAC Robin Schaefer, WHO
10 mins	Key Takeaways and Closing Remarks	Mitchell Warren, AVAC Robin Schaefer, WHO

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Why discuss the HPTN 083 and 084 OLEs?

- **HPTN 083** compared CAB for PrEP to daily oral PrEP use by **cisgender gay and bisexual men and transgender women who have sex with men**, and found risk of HIV **reduced by 66 percent** in the group taking CAB
- **HPTN 084** study compared CAB for PrEP to daily oral PrEP use by **cisgender women**, and found risk of HIV **reduced by 92 percent** in the group taking CAB
- Both studies have transitioned to OLE to collect information on method preference, use patterns, user perspectives, additional safety information
- There is an opportunity to garner insights from the OLE phase of the HPTN 083 and 084 trials, to provide valuable lessons on how to create an effective bridge from CAB for PrEP trials to implementation

HPTN 083
an HIV prevention clinical trial

HPTN 084
Long-acting Injectable For the Epidemic

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Think Tank Objectives and Outcomes

Objectives

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

Intended Outcomes

1. Brief report summarising discussion, key lessons from HPTN 083 and 084 OLE, and how these may be applied to CAB for PrEP implementation studies.
2. Maintain implementation study tracker for dissemination.

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Long-acting injectable cabotegravir (CAB-LA) for HIV prevention

Key questions and outstanding issues

Robin Schaefer

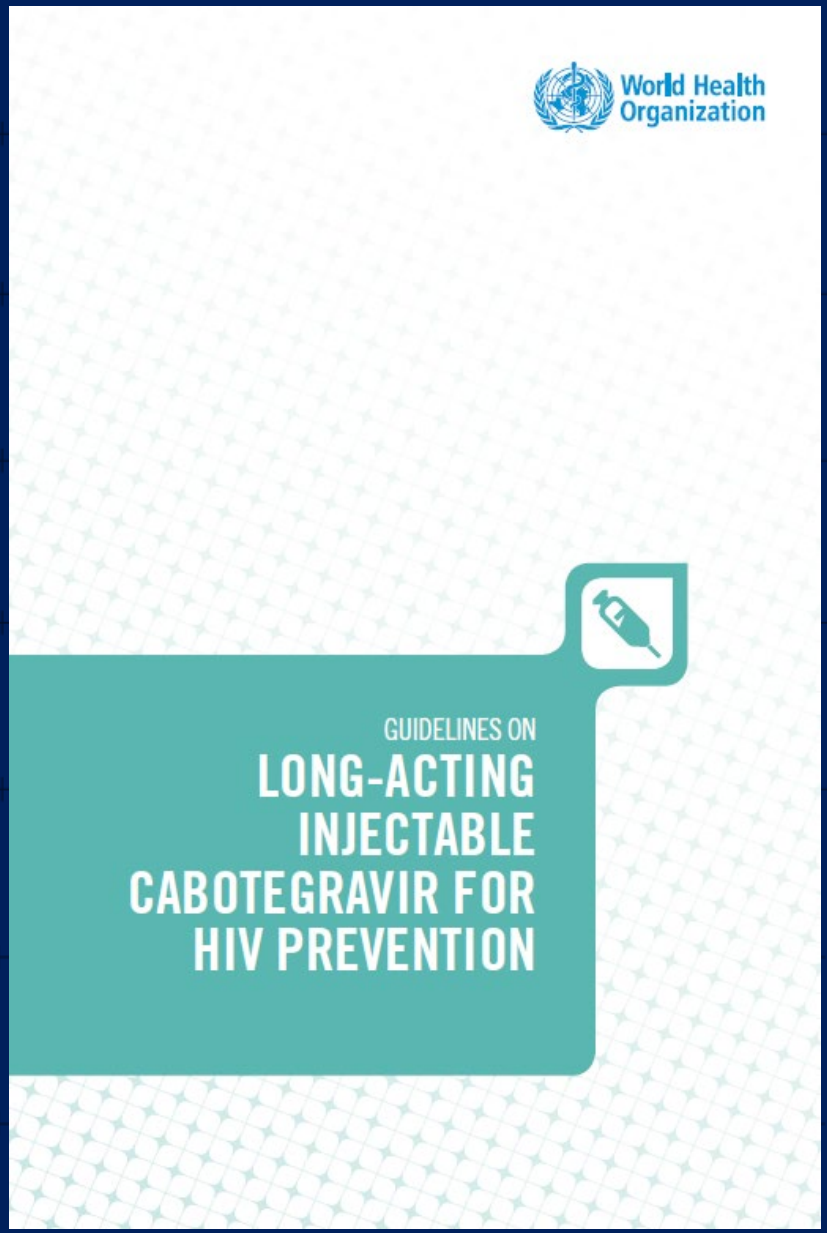
Global HIV, Hepatitis and STIs Programmes

World Health Organization

Presenting on behalf of the WHO HHS PrEP team:

Heather-Marie Schmidt, Michelle Rodolph, Rachel Baggaley

World Health Organization



Critical gaps and outstanding issues with CAB-LA

GUIDELINES ON

LONG-ACTING INJECTABLE CABOTEGRAVIR FOR HIV PREVENTION

5. RESEARCH GAPS AND NEEDS

Operational research is needed to inform decisions on the implementation and scale-up of CAB-LA. It is important to partner with communities of populations affected by HIV to identify priorities and to inform the design and implementation of research and the monitoring of outcomes.

VIEWPOINT

Long-acting injectable cabotegravir: implementation science needed to advance this additional HIV prevention choice

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Heather-Marie Ann Schmidt[1,2], Michelle Rodolph[1,§], Robin Schaefer[1], Rachel Baggaley[1] and Meg Doherty[1]

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- **"Real world" data lacking**
- **Data lacking for certain populations**
- **Safety during pregnancy and breastfeeding**
- **Product switching and stopping CAB-LA**
- **Impact, costs, and cost-effectiveness**
- **HIV testing and drug resistance**
- **Service delivery models**

HIV drug resistance and HIV testing

- Concerns about **HIV drug resistance** that may **compromise HIV treatment efficacy** (DTG = recommended first-line)
  - **Initiation despite infection**
  - **Infections despite on-time injections:** Observed among men
  - **Pharmacokinetic 'tail'** after discontinuation: Less of a concern?

Early data suggest that these cases are rare. Modelling suggested that population-level benefits outweigh risks.


THE LANCET HIV

ARTICLES | ONLINE FIRST

Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study

Jennifer Smith, PhD † • Loveleen Bansi-Matharu, PhD † • Valentina Cambiano, PhD † • Dobromir Dimitrov, PhD • Anna Bershteyn, PhD • David van de Vijver, PhD • et al. Show all authors • Show footnotes

Open Access • Published: January 12, 2023 • DOI: https://doi.org/10.1016/S2352-3018(22)00365-4 •


AIDS

Characterization of dolutegravir drug resistance in persons diagnosed with HIV after exposure to long-acting injectable cabotegravir for preexposure prophylaxis

Ahluwalia, Amrit Kaur[a]; Inzaule, Seth[b]; Baggaley, Rachel Clare[b]; Vitoria, Marco[b]; Schaefer, Robin[b]; Schmidt, Heather-Marie Ann[b,c]; Rodolph, Michelle[b]; Giron, Amalia[b]; Jordan, Michael R.[a]

Author Information

AIDS 36(13):p 1897-1898, November 1, 2022. | *DOI:* 10.1097/QAD.0000000000003322

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HIV drug resistance and HIV testing

- Concerns about **HIV drug resistance** that may **compromise HIV treatment efficacy** (DTG = recommended first-line)
  - **Initiation despite infection**
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  - **Pharmacokinetic 'tail'** after discontinuation: Less of a concern?

Early data suggest that these cases are rare. Modelling suggested that population-level benefits outweigh risks.

- **WHO guidelines:** Programmes **can use current national HIV testing strategy/algorithm** (combination of RDTs &/or EIAs) as per WHO HIV testing recommendations. Consider approaches that **promotes access to CAB-LA.**
- **Some countries may include NAT testing**, 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
- 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**.

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Further data needed to determine risks of drug resistance (including predictors of risks), cross-resistance between CAB and DTG, and optimal HIV testing approaches.

Population gaps

Pregnancy & breastfeeding

- Pregnancy and postpartum: Periods of increased risk of HIV acquisition + risk of transmission to child
- **Limited safety data** due to requirements for long-acting reversible contraceptives in trials
- **Country regulations:** Emphasise balance of benefits and harms

More data on safety needed and implementation research on how to deliver CAB for these populations

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Population gaps

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Missing populations

- **Young people <18 years**: Additional studies ongoing; often additional barriers/**require additional support for CAB-LA**
- **Key populations**
  - HPTN 083 and HPTN 084 provided PrEP to MSM, transgender women & cisgender women
  - Need further research on **trans and gender diverse populations**, including specific needs
    - Interaction with **gender-affirming hormones** – recent data suggest not an issue
    - **Alternative injection sites**
  - Urgent need for research on key populations not included: **People who use drugs, sex workers**

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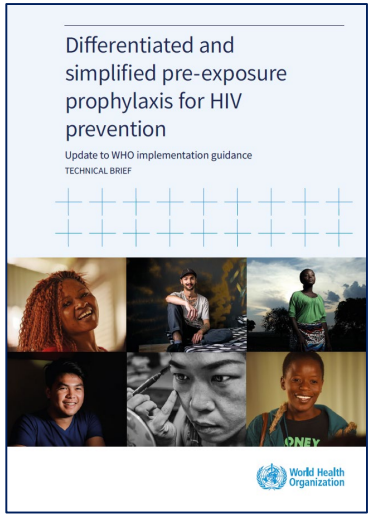
Need implementation science involving a range of populations across diverse geographies

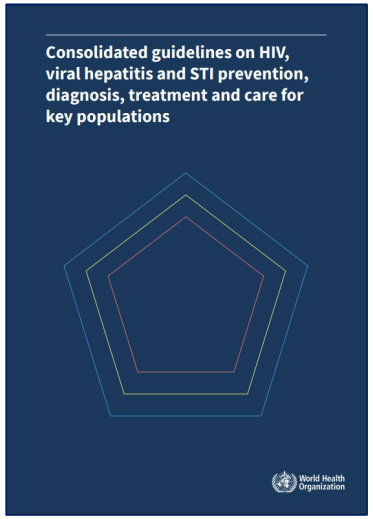
Where and how to deliver choice and acceptable services

People who would benefit from PrEP have **diverse preferences and needs**

- **A range of options** should be available – how to ensure i**nformed choice?**
  - What are **needs of providers** (e.g., training)?
- **Uptake of and switching between products:** Limited data on enacted preferences and use patterns
- **Differentiated service delivery:** Services adapted to needs and preferences of clients
  - Need implementation science on how CAB-LA fits into this
- **Structural barriers persist** (e.g., criminalization, stigmatization, and discrimination)

Involving communities at all stages is critical – awareness, demand creation & delivery





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Where and how to deliver choice and acceptable services

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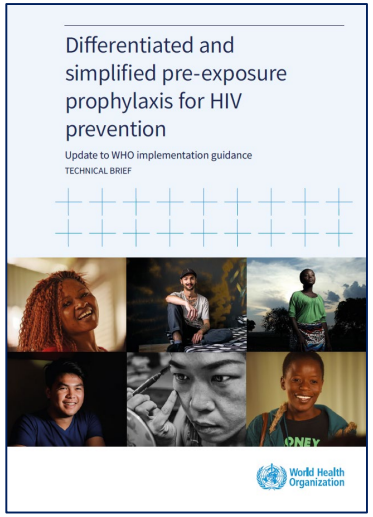
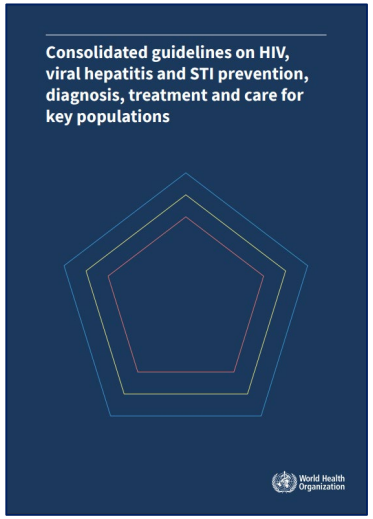
Involving communities at all stages is critical – awareness, demand creation & delivery

Uncertainty around programme impact, costs and cost-effectiveness

- Modelling studies suggest **price of CAB-LA cannot be much higher than oral PrEP for cost-effectiveness** (influenced by costs of product, service delivery, and context/epidemiology)





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Cost-effectiveness should not be the only consideration for programme implementation

Conclusions

There will be limited supply of CAB-LA in the near future

- Need to use supply wisely
- Answer critical questions
- Reach populations in highest need
- Coordinate and harmonise as much as possible
- Share learnings and insights in a timely way

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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'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

World Health Organization

WHO GLOBAL PrEP NETWORK WEBINAR SERIES

26 October 2022 10:00 – 11:30 CET

Long-acting injectable cabotegravir (CAB LA) for HIV prevention: WHO guidelines, implementation considerations, and project examples

29 November 2022 10:00 – 11:30 CET

Long-acting injectable cabotegravir (CAB LA) for HIV prevention: Community perspectives

WHO resources

WHO guidelines on CAB-LA:
https://www.who.int/publications/i/item/9789240054097

WHO technical brief on PrEP implementation guidance:
https://www.who.int/publications/i/item/9789240053694

WHO consolidated key population guidelines:
https://www.who.int/publications/i/item/9789240052390

WHO consolidated HIV guidelines:
https://www.who.int/publications/i/item/9789240031593

WHO PrEP Implementation Tool: https://www.who.int/tools/prep-implementation-tool

STI module of WHO PrEP Implementation Tool:
https://www.who.int/publications/i/item/9789240057425

Further updates to WHO PrEP Implementation Tool expected in 2023

Coordinating Implementation Science for CAB for PrEP:

Bridging from the HPTN 083 Open Label Extension to Implementation

Raphael J. Landovitz, MD MSc

Beatriz Grinsztejn, MD PhD

The Biomedical Prevention Implementation Collaborative (BioPIC)

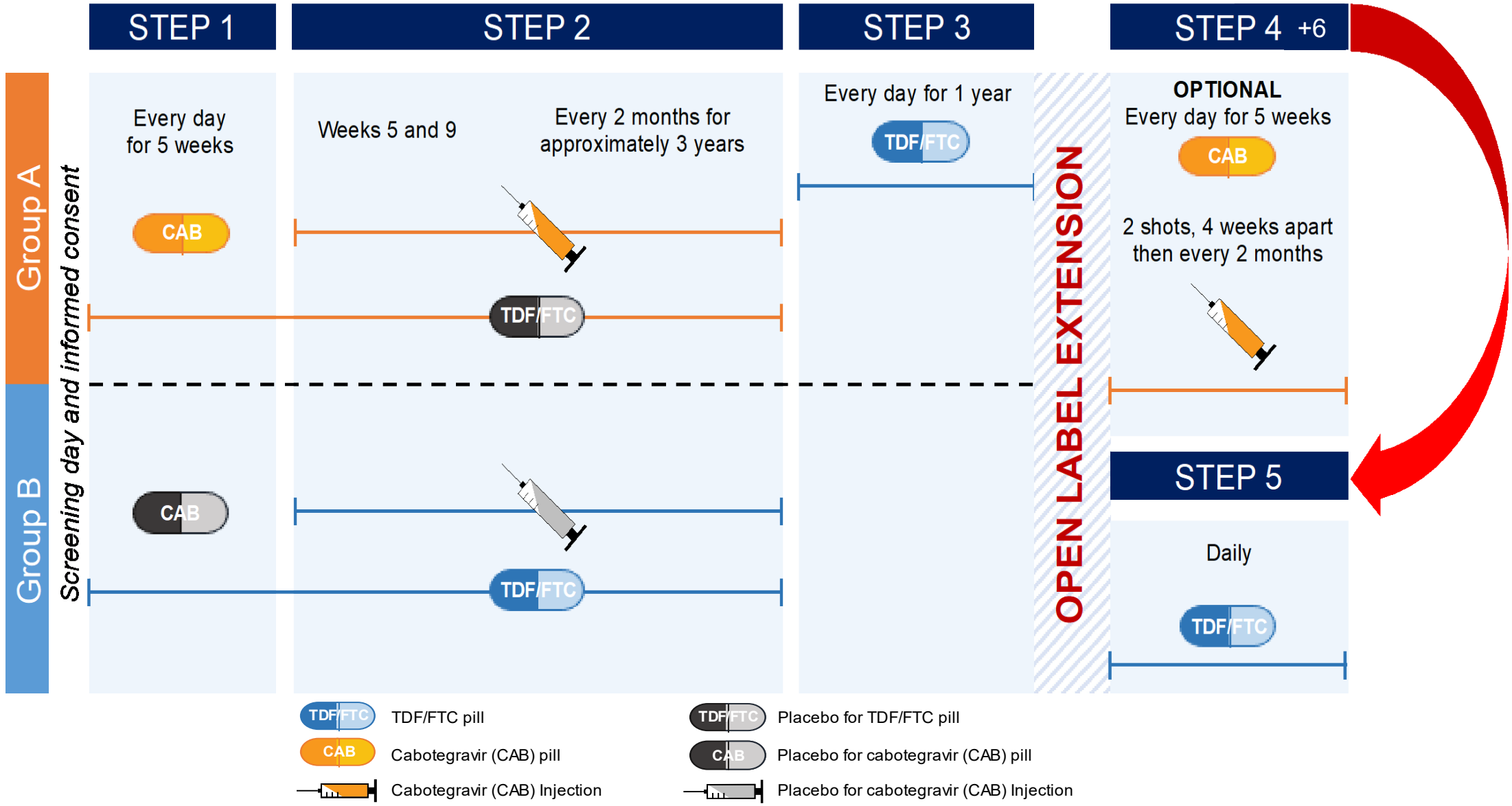
March 14, 2023

Disclosure

Raphael J. Landovitz has served on Scientific Advisory Boards for Merck.

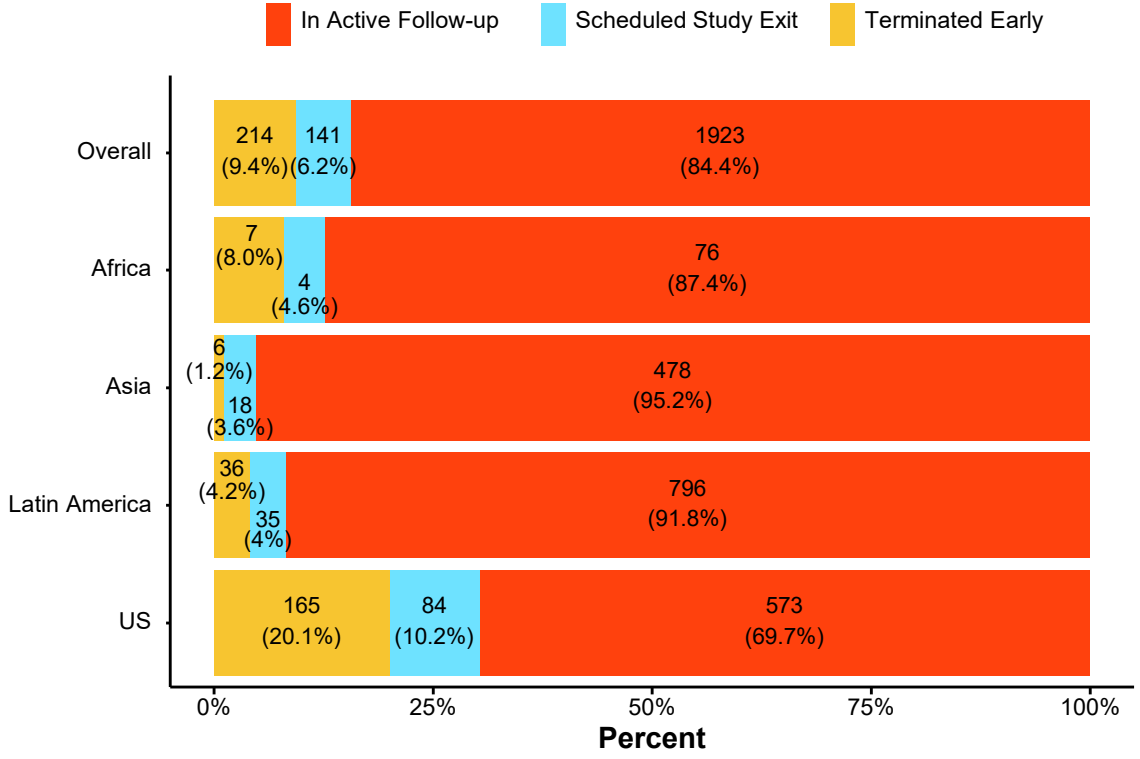
Beatriz Grinsztejn has served on Scientific Advisory Boards for GSK, Merck and Gilead Sciences.

HPTN 083 Study Design

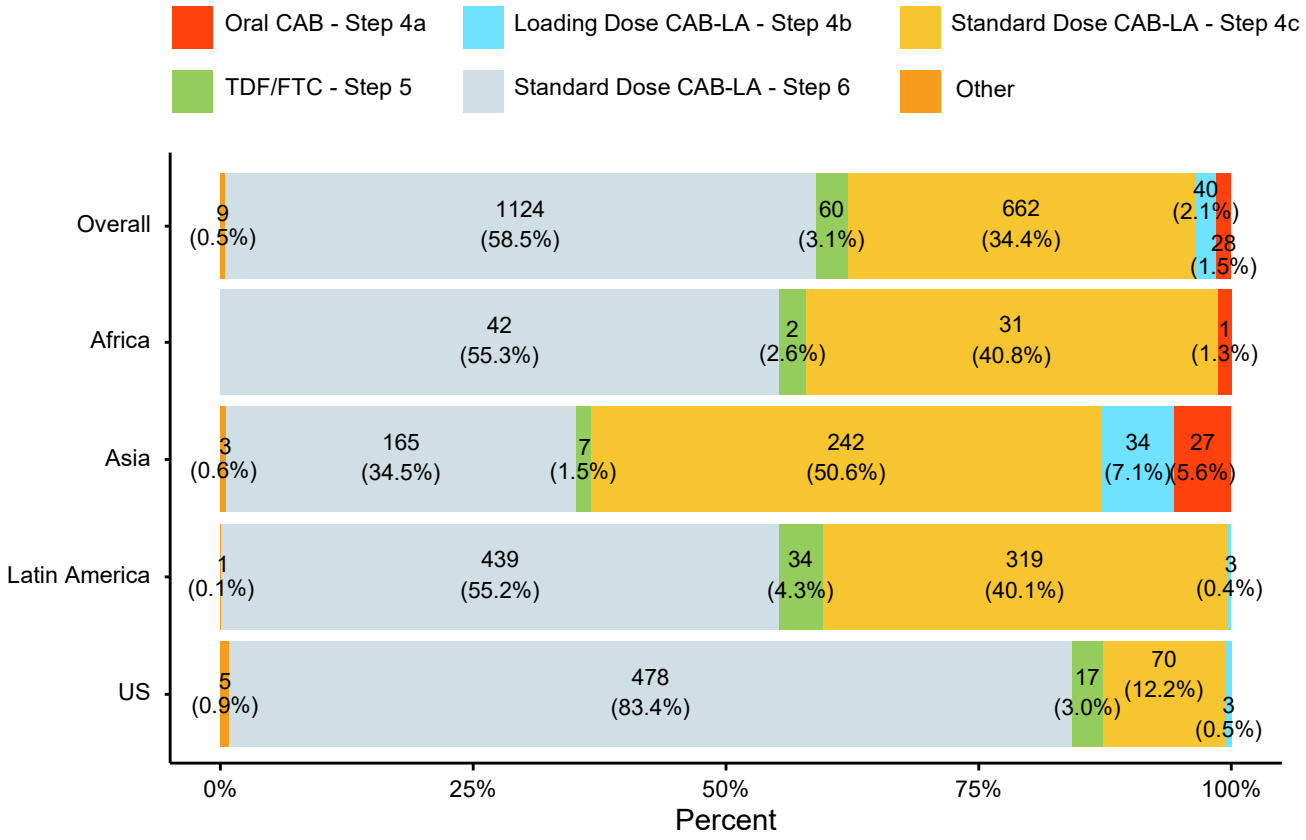


HPTN 083 OLE Participant Disposition by Region

Total Persons in OLE by Region

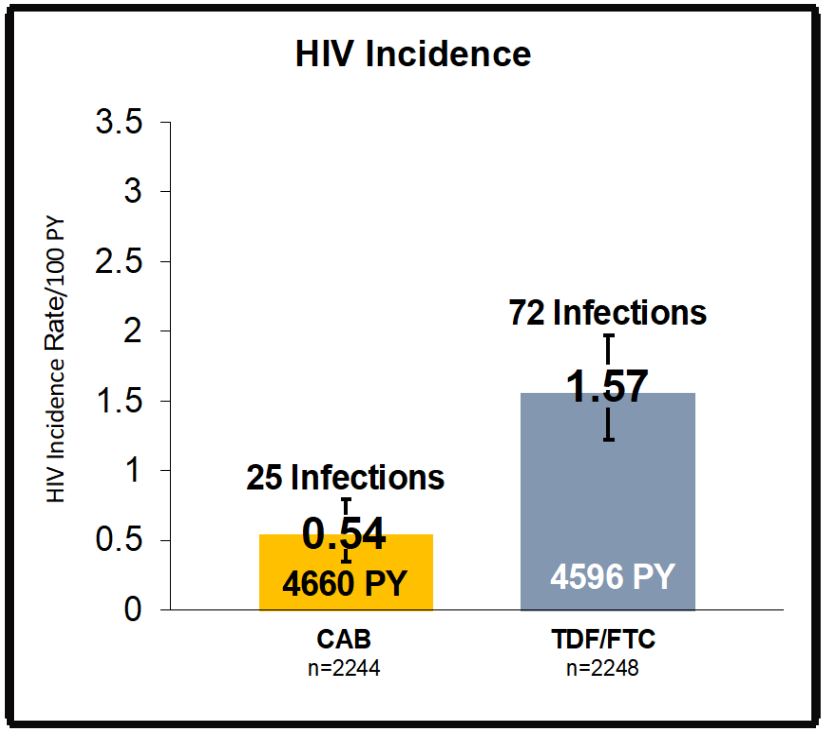


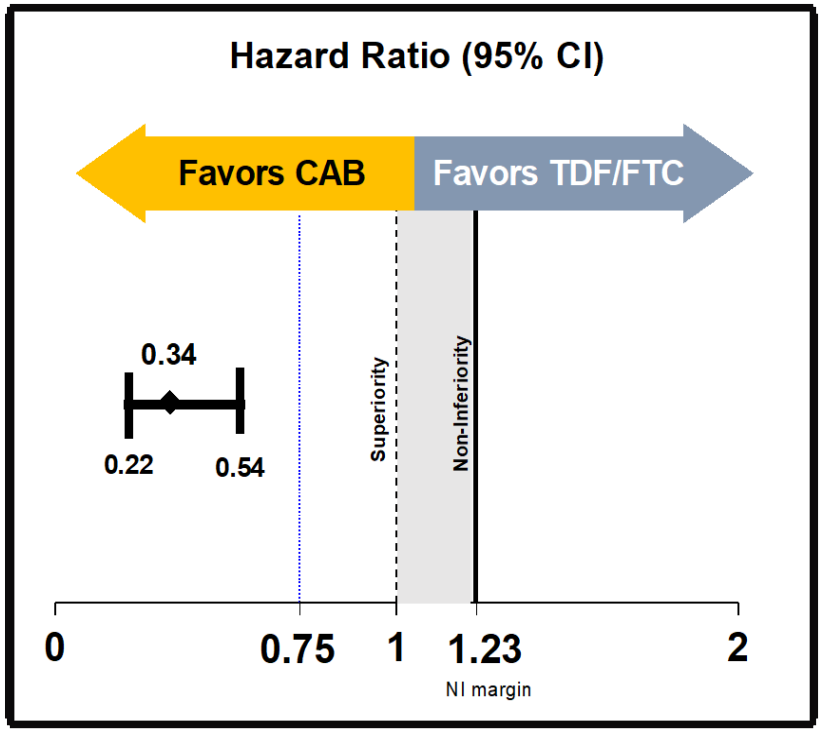
Total Persons in OLE Active Follow-up by Region



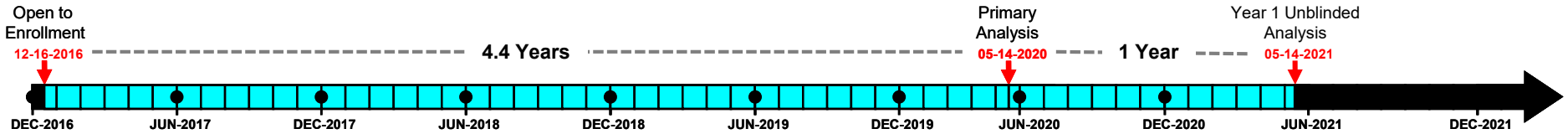
HIV Incidence: CAB vs. TDF/FTC

Combined Efficacy Analysis



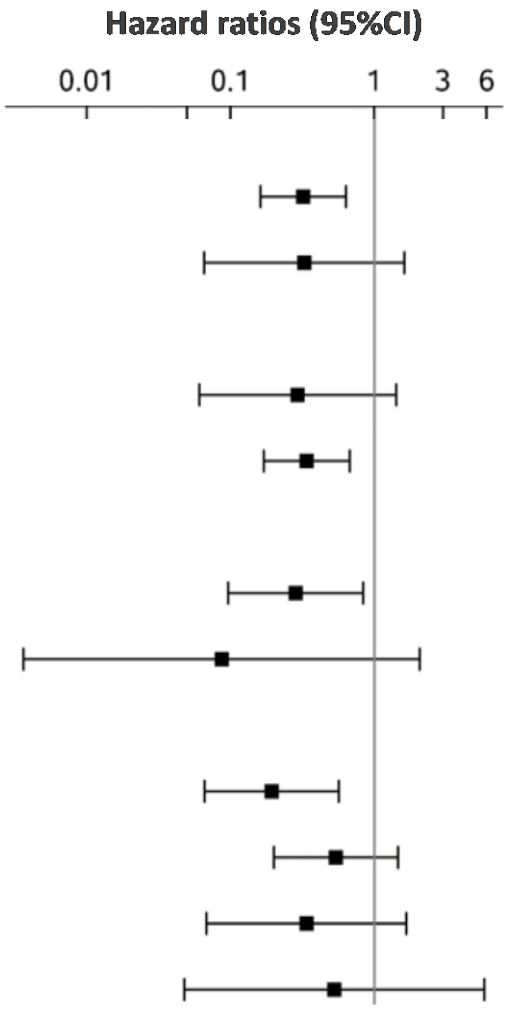


CI, confidence interval



HPTN 083 HIV Incidence by Subgroup CAB vs. TDF/FTC

Subgroup	CAB Events/PY (IR%)	TDF/FTC Events/PY (IR%)	HR (95%CI)
Age			
≤30	11/2185 (0.50)	33/2114 (1.56)	0.32 (0.16, 0.63)
>30	2/1016 (0.20)	6/1071 (0.56)	0.33(0.07, 1.61)
Cohort			
TGW	2/368 (0.54)	7/383 (1.83)	0.29 (0.06, 1.41)
MSM	11/2829 (0.39)	32/2800 (1.14)	0.34 (0.17, 0.67)
Race			
Black/African-American	4/686 (0.58)	15/711 (2.11)	0.28 (0.10, 0.83)
Non-Black/African-American	0/837 (0.00)	5/790 (0.63)	0.09 (0.00, 2.06)
Region			
US	4/1523 (0.26)	20/1501 (1.33)	0.19 (0.07, 0.56)
Latin America	6/1016 (0.59)	11/1007 (1.09)	0.54 (0.20, 1.46)
Asia	2/569 (0.35)	6/580 (1.03)	0.34 (0.07, 1.66)
Africa	1/92 (1.08)	2/96 (2.08)	0.52 (0.05, 5.77)



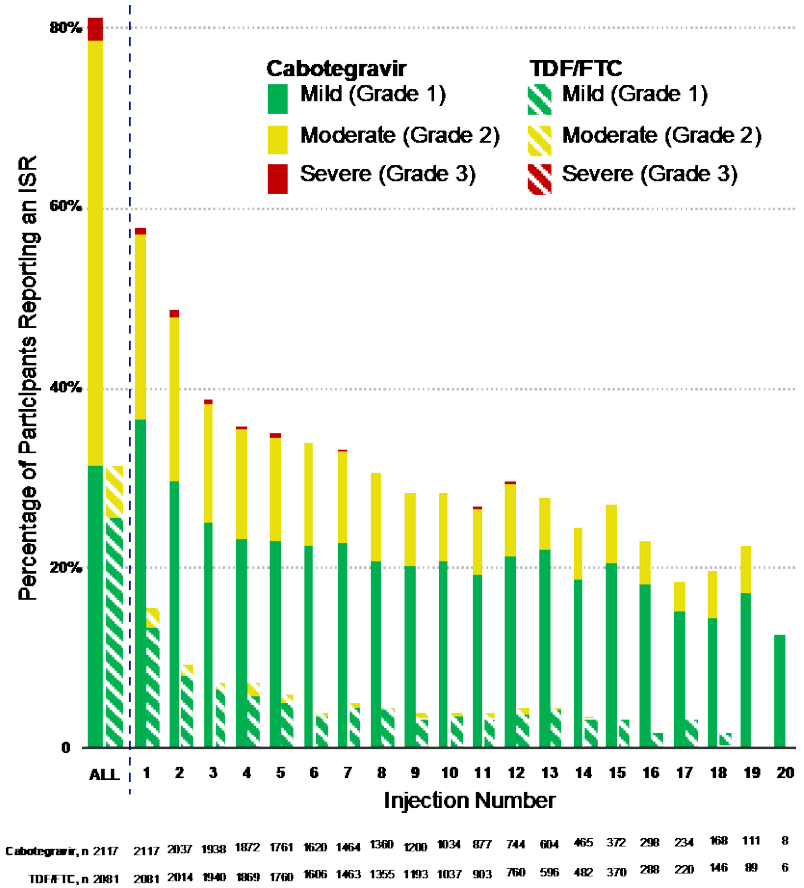
Grinsztejn, B. AIDS 2022. #12707

The Bottom Line: Efficacy

- **Long-acting cabotegravir is very effective at preventing HIV in MSM, TGW, and cisgender women**
  - 66% reduction in HIV infection when compared to MSM and TGW who were offered TDF/FTC
  - 89% reduction in HIV infection when compared to cisgender women who were offered TDF/FTC
- **Long-acting cabotegravir is also very effective at preventing HIV in:**
  - Young individuals
  - Black individuals
  - Transgender women
  - Individuals from various regions of the world

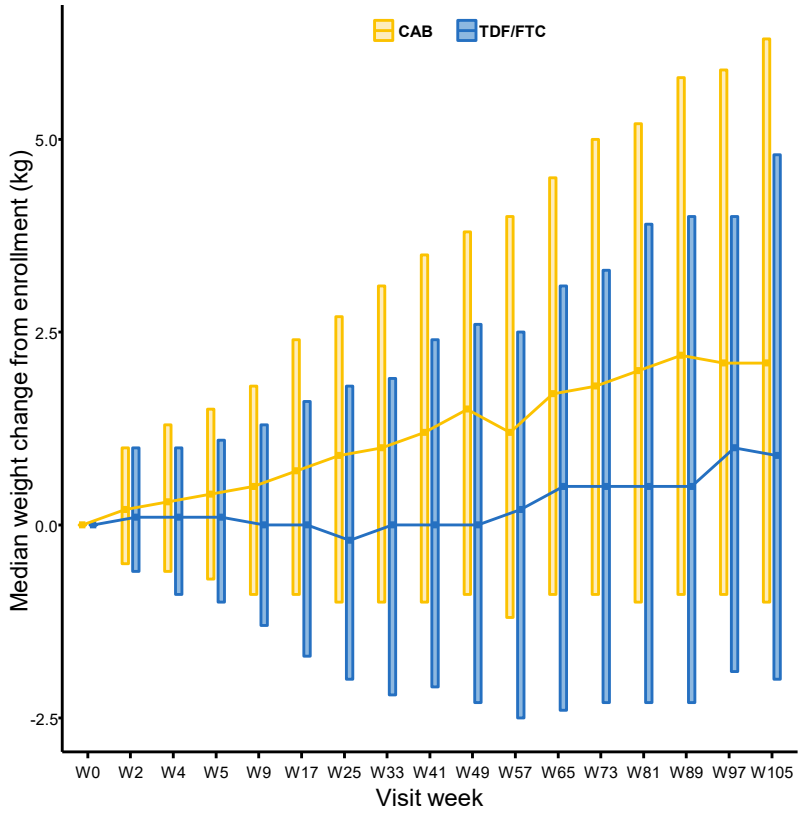
HPTN 083: Safety

Injection Site Reactions



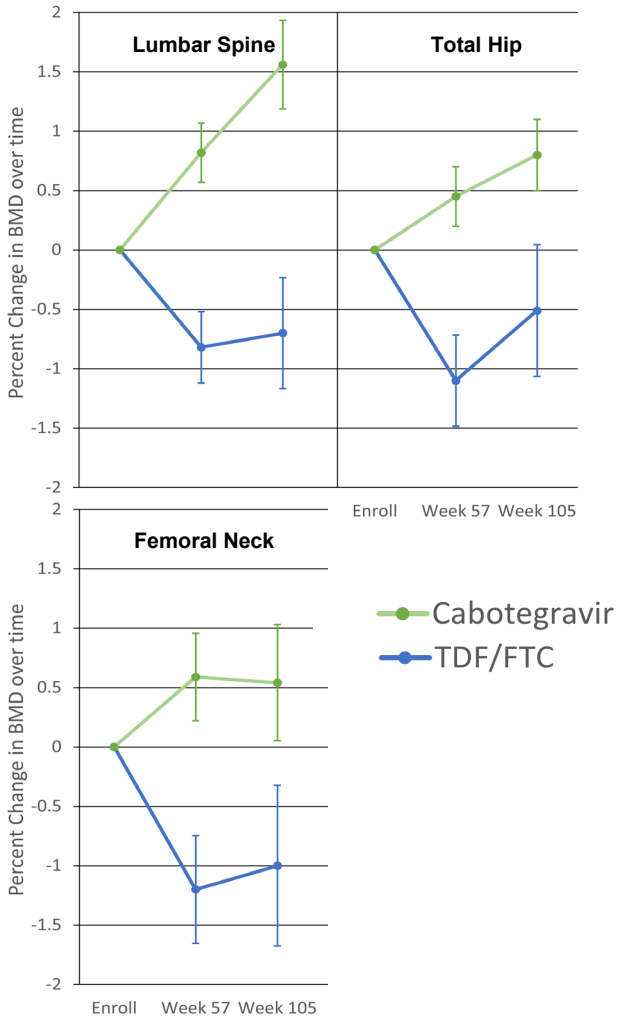
Landovitz RJ et al. NEJM 2021

Median Change in Weight (kg)



Landovitz RJ et al. NEJM 2021

DXA BMD change over time



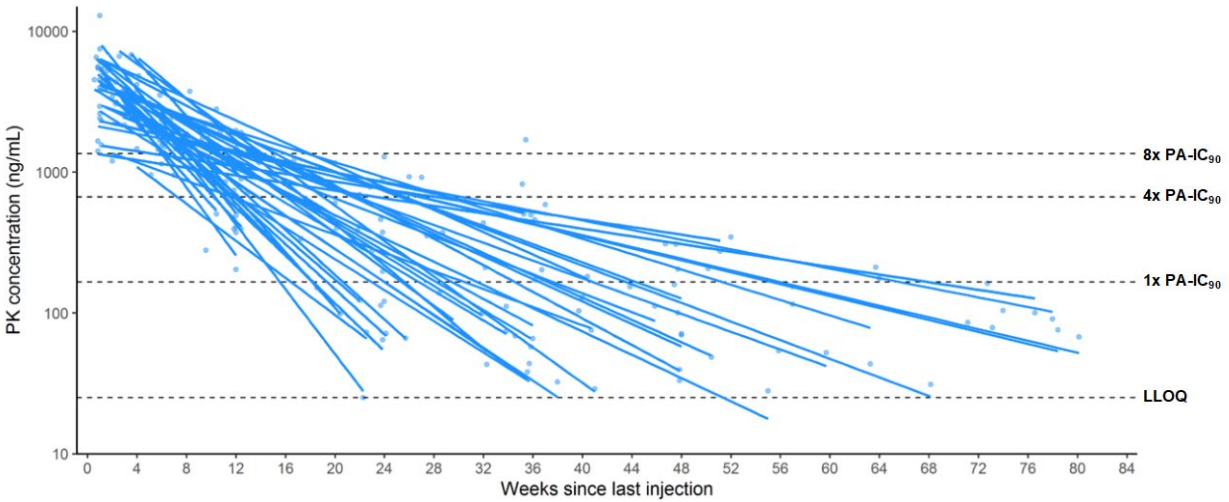
Brown T et al. CROI 2023. Poster #987.

The Bottom Line: Safety

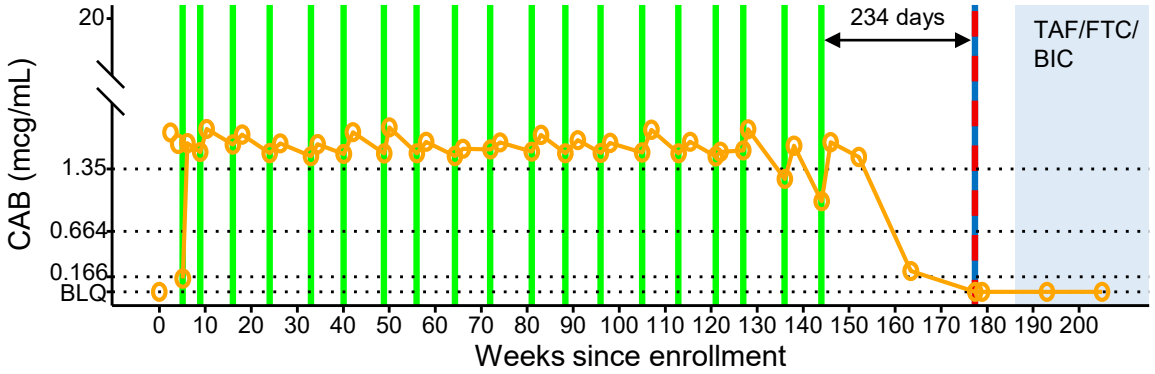
- **Long-acting cabotegravir was safe and well tolerated**
- **The most common side effect was injection site reaction (ISR)**
  - The majority were mild to moderate in severity
  - Reports of ISRs decreased over time
  - Very few ISRs led to the discontinuation of cabotegravir
- **We're all gaining weight, people on CAB-LA and TDF/FTC at about the same rate EXCEPT for the first year, where TDF/FTC people LOST weight (but then gained thereafter)**
- **By DXA measurement, CAB-LA had better outcomes than TDF-FTC over two years; no clinical differences**

Pharmacokinetics

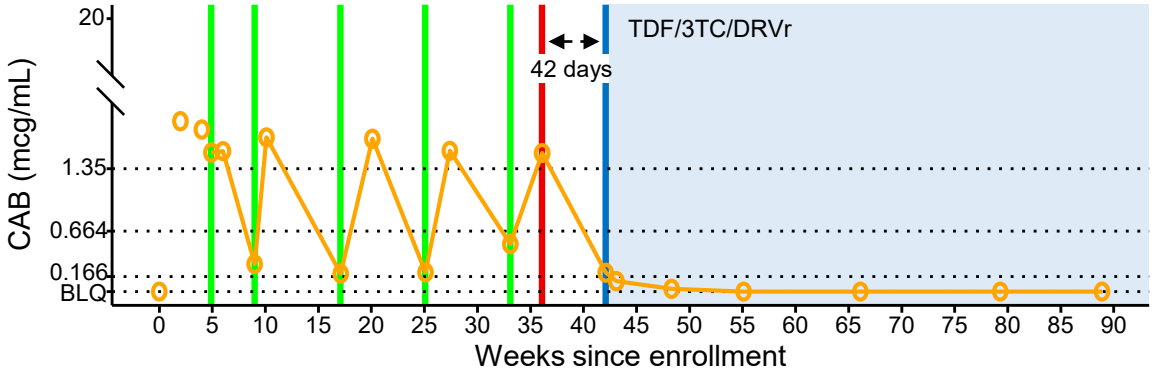
CAB Subsequent to Final Injection (Log Scale) Males



Expected Pattern of CAB Concentrations



Fast Elimination – One case so far



CAB concentration
CAB injection
First HIV positive visit
First site positive visit
First HIV positive visit and first site positive visit

Landovitz, R et al. Lancet HIV. 2020.

The Bottom Line:
Pharmacokinetics in Men

- **People born male**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 10.1 Months
- Higher BMI associated with more prolonged period of exposure
- Rapid concentration decay in rare participants remains to be fully explained but likely is not a genetic “fast metabolizer” abnormality

Landovitz, R. Lancet HIV. 2020.

Infections in CAB-exposed ppts

- **Group A (4 cases):** HIV acquired at enrollment
- **Group B (16 cases):** HIV acquired w/o recent CAB exposure
- **Group BR (2 cases):** HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
- **Group C (3 cases):** HIV acquired during oral lead-in
- **Group D (6 cases):** HIV acquired in the setting of on-time CAB injections
- **Group DX (3 cases):** HIV acquired while on CAB with at least one 10-week delayed injection

CAB arm, Group A

What we learned:

- **If we do not diagnose HIV before PrEP agents start (acute or eclipse phase infection = very early infection), CAB can make it challenging to diagnose later**
- **Failure to diagnose HIV infection can lead to continued CAB administration, and even continued CAB injections**
  - **Exposure to prolonged CAB without recognition of HIV infection may lead to INSTI resistance**

CAB arm, Group B & BR

What we learned:

- **If you don't take CAB, it doesn't prevent HIV infection**
- **In multiple participants, exposure and HIV acquisition during the "tail" did not result in CAB resistance**
  - **This is reassuring, but DOES NOT RULE OUT THAT IT CAN HAPPEN WE NEED MORE DATA**
  - **When CAB is restarted after prolonged hiatus, failure to diagnose interim newly acquired HIV can lead to INSTI resistance, much as "A" cases can**
- **When people were provided open-label TDF/FTC to "cover they tail" they did not take it – this likely contributed to HIV acquisition**

CAB arm, Group C

What we learned:

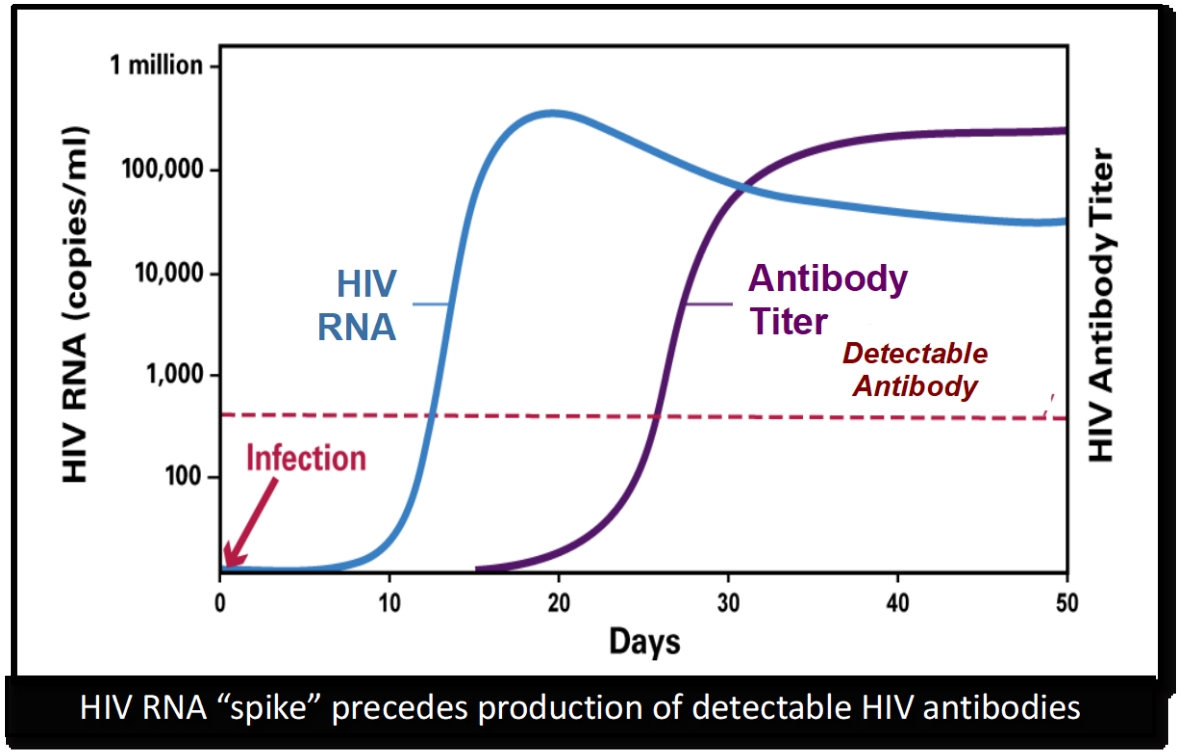
- If you don't take CAB, it doesn't prevent HIV infection
  - We don't know how "forgiving" it is to missed doses
- There is likely a "time to onset" of protection with oral CAB
  - We don't know how long
- If CAB delays new (incident) HIV detection by delaying testing, CAB injections can inadvertently be given
- As with the "A" Cases, viral "escape" at HIGH CAB levels can lead to INSTI resistance

CAB arm, Group D & DX

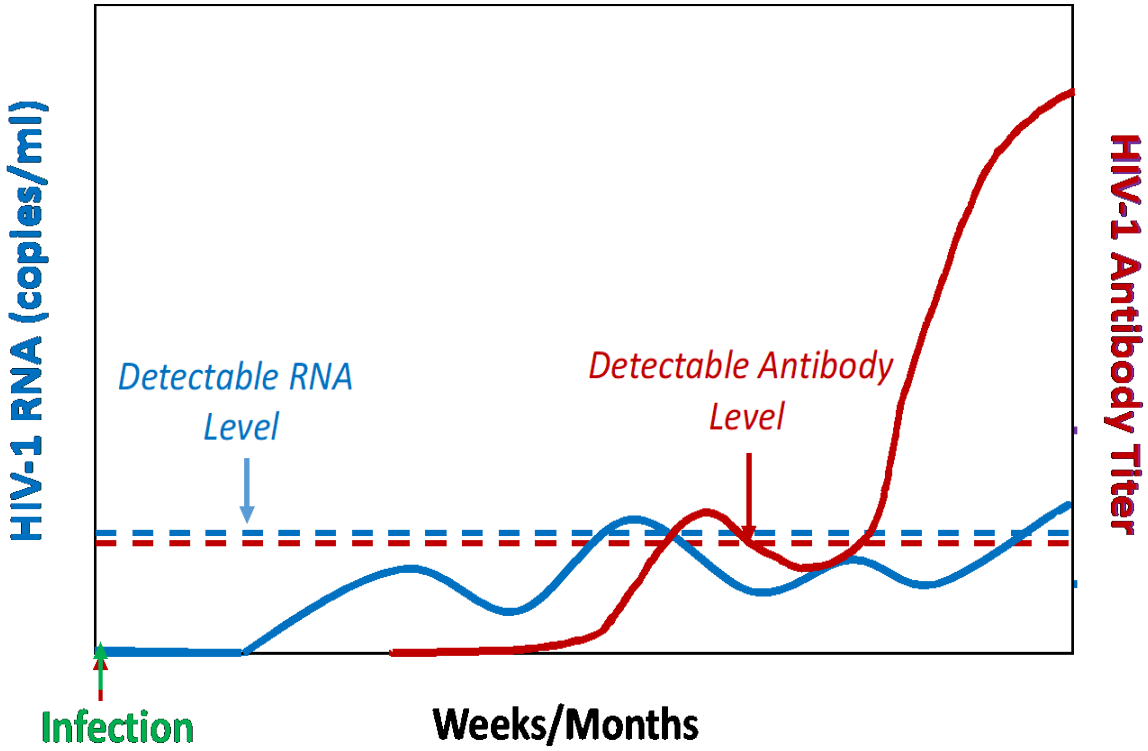
What we learned:

- Delays in HIV tests detecting “new” HIV infections
- CAB levels in the blood were as expected
  - It wasn’t “unexpectedly” low concentrations of CAB that explain the PrEP failure
- If HIV “smolders” after a PrEP failure, it can lead to CAB (and other integrase) resistance
  - That resistance can be often avoided by earlier detection
  - When delays occur, CAB levels can drop, losing protection – but not leading to INSTI resistance to-date

Testing Delays



HIV RNA "spike" precedes production of detectable HIV antibodies



The Bottom Line:
Testing Delays

- RNA testing finds infections earlier, but is costly, may not be feasible in many settings, and may confuse patients and providers

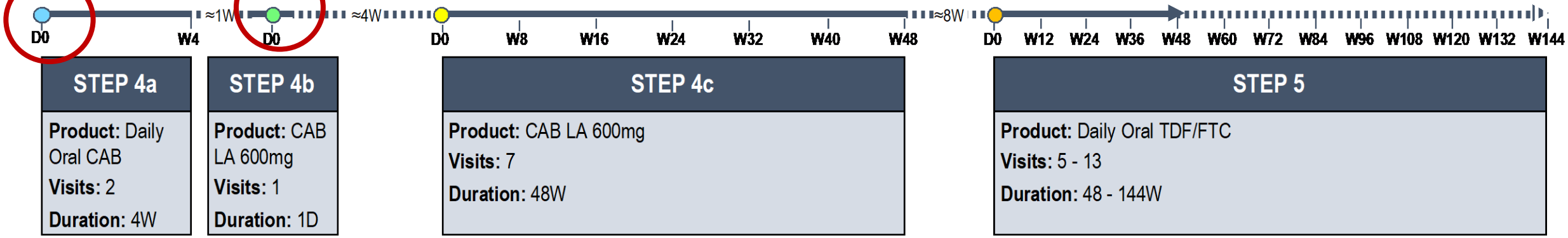
- No delays seen in MSM/TGW when infection is acquired > 6 months after last injection
  - Likely a longer timeline for ciswomen/TGM

What the HPTN 083/084 OLEs Will Inform

Optional Oral Lead-in

Participants who chose the oral lead-in start the HPTN 083 OLE here (**Step 4a**)

Participants who chose the direct-to-injection start the HPTN 083 OLE here (**Step 4b**)



STEP 4a	STEP 4b	STEP 4c	STEP 5
Product: Daily Oral CAB **Visits:** 2 **Duration:** 4W	**Product:** CAB LA 600mg **Visits:** 1 **Duration:** 1D	**Product:** CAB LA 600mg **Visits:** 7 **Duration:** 48W	**Product:** Daily Oral TDF/FTC **Visits:** 5 - 13 **Duration:** 48 - 144W

- **Direct-to-injection CAB-LA/RPV-LA has shown similar safety and efficacy profiles to CAB-LA/RPV-LA preceded by an oral lead-in for PLWH[1]**
  - Is this the same for people using CAB-LA as PrEP?
  - Hypersensitivity? Liver toxicity?
- **Is direct-to-injection CAB-LA without an oral lead-in preferable for individuals starting PrEP?**
  - Will this remove barriers to access and increase uptake of LA PrEP agents?
- **Are the pharmacokinetics different for those who choose and oral lead-in when compared to those who choose direct-to-injection?**

1.Orkin, C. Lancet HIV. 2021.

Optional Oral Lead-in

- **In the CAB/RPV TREATMENT context, no oral lead-in and high BMI associated with lower cabotegravir trough concentrations**

- **Mechanism?**
- **Generalizable?**

Drug trough concentrations		At 1 month (n=58)	At 3 months (n=56)
CAB	**Trough < 1120 ng/mL**, n (%)	**35 (60)**	**43 (77)**
	Median trough, ng/mL (IQR)	**976 (706 – 1434)**	**701 (440 – 1087)**
	No lead-in (n=42)	*951 (681 – 1196)*	*625 (397 – 880)*
	Lead-in (n=16)	*1213 (908 – 1479)*	*1103 (689 – 1246)*
RPV	**Trough < 32 ng/mL**, n (%)	**16 (28)**	**15 (27)**
	Median trough, ng/mL (IQR)	**48 (29 – 66)**	**43 (32 – 55)**
	No oral rilpivirine before switch (n=25)	*47 (35 – 68)*	*44 (30 – 58)*
	Oral rilpivirine before switch (n=33)	*49 (29 – 62)*	*43 (32 – 53)*

Characteristics	M1 cabotegravir trough level				M3 cabotegravir trough level		
	< 1120 ng/mL (n=35)	≥ 1120 ng/mL (n=23)	p	p*	< 1120 ng/mL (n=43)	≥ 1120 ng/mL (n=13)	p
Median age, years (IQR)	29 (26 – 34)	31 (28 – 34)	0.7		29 (26 – 34)	31 (30 – 36)	0.1
Male, n (%)	29 (83)	22 (96)	0.2		38 (88)	11 (85)	0.7
European origin, n (%)	25 (71)	15 (65)	0.8		32 (74)	8 (62)	0.5
Median BMI, kg/m² (IQR)	24 (22 – 27)	22 (20 – 25)	**0.01**	**0.009**	24 (22 – 26)	24 (22 – 27)	0.5
No lead-in, n (%)	29 (83)	13 (57)	**0.04**	**0.02**	35 (81)	6 (46)	**0.03**

* Multivariate analysis

Rubenstein, E. CROI 2023. Abstract #195.

HPTN 083 Follow-up Visit Testing Algorithm

Initial Blinded/Unblinded Period

- US FDA-cleared HIV rapid test
- Laboratory-based HIV Immunoassay capable of detecting antigen and antibody

Unblinded OLE Period

- US FDA-cleared HIV rapid test
- Laboratory-based HIV Immunoassay capable of detecting antigen and antibody
- HIV viral load

The Bottom Line:
New Testing Algorithm in the OLE Period

- Using a sensitive RNA assay at screening finds infections earlier
- Earlier detection would allow the start of ART sooner, reducing the risk of integrase inhibitor resistance
- This approach may be too costly
- This approach may not be feasible in some settings
- Modelling by A. Phillips and team suggest population-level survival benefit w/o VL testing
  - Accompanied by increases in circulating INSTI resistance
  - Surveillance needed

ISRs and Other Adverse Events

What rate of ISR and other Aes will those who switch from oral TDF/FTC to CAB-LA experience?

HPTN 083 OLE Choices

- **Total US enrollment was 1698 participants, of whom 803 had regimen choice data available.**
- **770 (95.9%) chose CAB-LA and 33 (4.1%) chose TDF/FTC.**
  - Among those initially randomized to CAB-LA (n=415), 13 (3.1%) chose TDF/FTC and 402 (96.9%) chose CAB-LA
  - Among those initially randomized to TDF/FTC (n=388), 20 (5.2%) chose TDF/FTC and 368 (94.8%) chose CAB-LA
- **Nearly all US participants chose CAB-LA over oral TDF/FTC**
- **No specific subgroup drove this choice disparity**
  - **Data from the non-US participants in HPTN 083 will provide important insights into regional/cultural differences in product preference**

Clement, ME et al. CROI 2023. Abstract #: 994

HPTN 083 OLE Choices

Reason for choosing CAB-LA (n=770)	N (%)
Prefer injection and/or don't like pills	541 (70.3)
CAB-LA shown to be superior to TDF/FTC for HIV prevention	112 (14.5)
CAB more convenient, discreet, or easier to adhere to	37 (4.8)
Want to avoid side effects of TDF/FTC	32 (4.2)
Contribute to research or research-dependent Issue	16 (2.1)
Curious to try something new	12 (1.6)
More than one response	5 (0.6)
Other	15 (2.1)
Reason for choosing TDF/FTC (n=33)	
Don't like injections and/or prefer pills	17 (51.5)
The potential side effects of TDF/FTC are better understood or preferable to those of CAB-LA	4 (12.1)
Concerned about resistance if injectable PrEP fails	4 (12.1)
Scheduling constraints/difficulties with visits	4 (12.1)
Undecided or not yet ready for CAB	2 (6.1)
Prior injection site reactions	1 (3.0)
Does not like long-term commitment of injections	1 (3.0)

Clement, ME et al. CROI 2023. Abstract #: 994

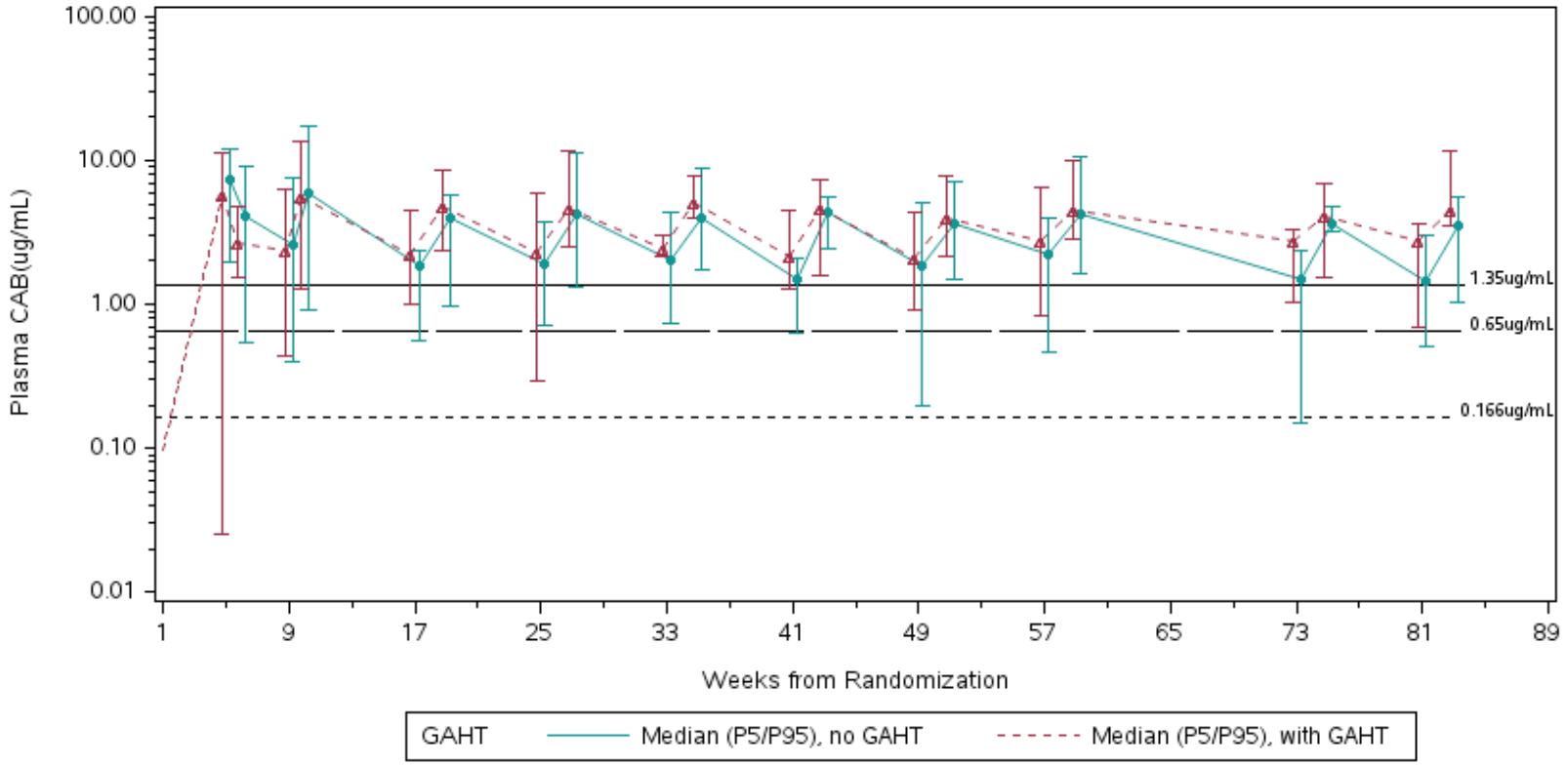
Optimal Response to Treatment

- **7 of the 16 infections in HPTN 083 after CAB exposure developed INSTI resistance**
- **Can treatment with DTG or BIC be used to treat individuals with INSTI resistance?**
  - The NADIA and ADVANCE studies portend effectiveness in using dolutegravir with NRTIs to treat individuals with NRTI resistance (even K65R + M184V)
  - Use of TLD to salvage CAB PrEP breakthroughs globally need to be catalogued, tracked, and reported on

Paton NI et al. NEJM. 2021.
Marzinke M et al. JID. 2021.
Eshleman S et al. JID. 2022.

Gender Affirming Hormone Therapy on CAB-LA

- Initial findings suggest that Gender Affirming Hormone Therapy does not impact CAB concentrations.
- Bidirectional data needed
- Transmasculine data needed



Grinsztejn, B. et al. AIDS 2022. Abstract #: 12707

Other Considerations

- Cardiovascular outcomes
- Neurocognitive outcomes
- Weight gain
- Bone Mineral Density outcomes

Thank you!

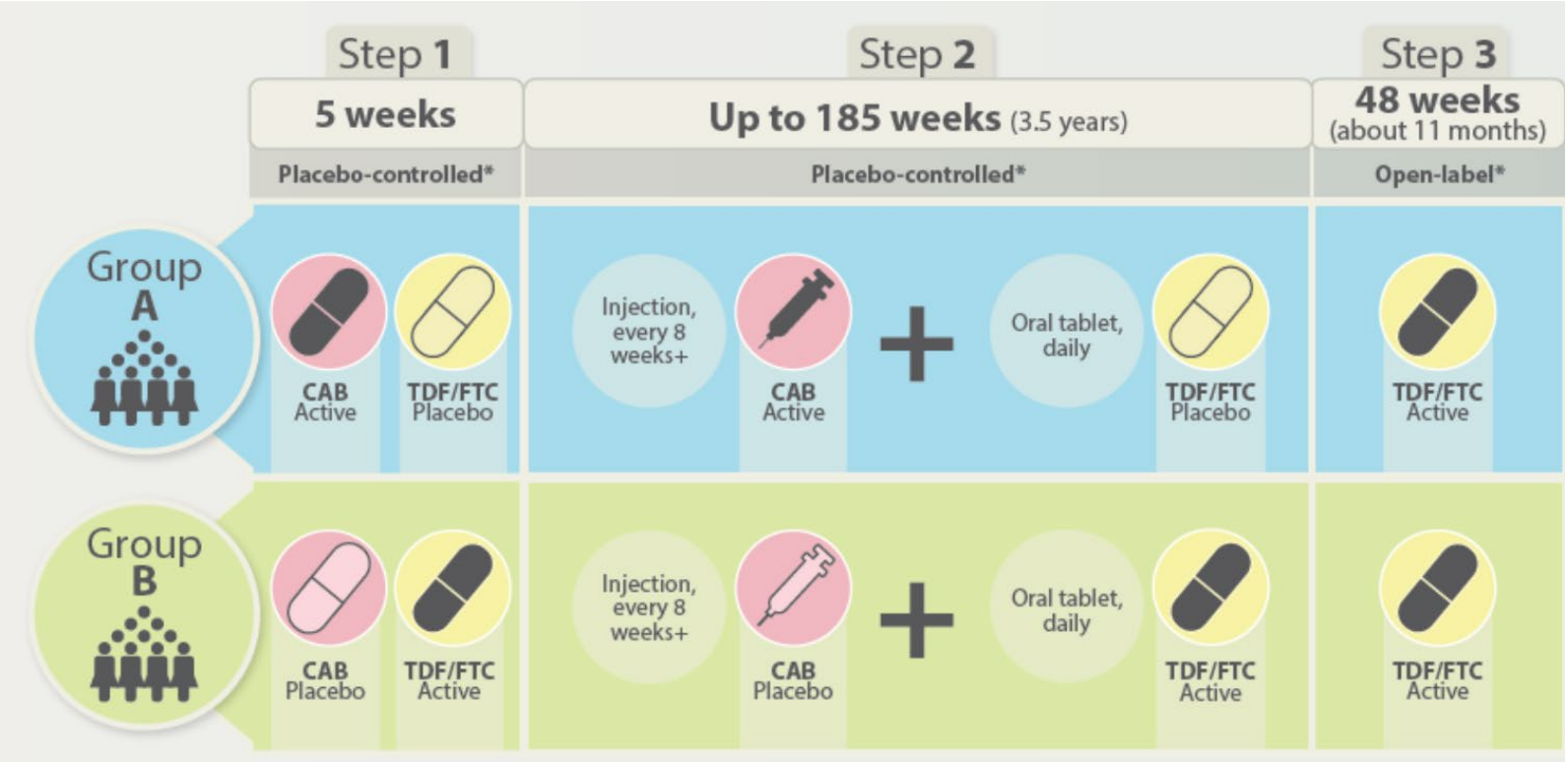
Questions?

rlandovitz@mednet.ucla.edu

Bridging from HPTN 084 open-label extensions to implementation

S Delany-Moretlwe, MBBCh PhD DTM&H
M Hosseinipour, MD MPH
March 2023

Study design: blinded period



HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

Objectives: HPTN 084 open-label extension

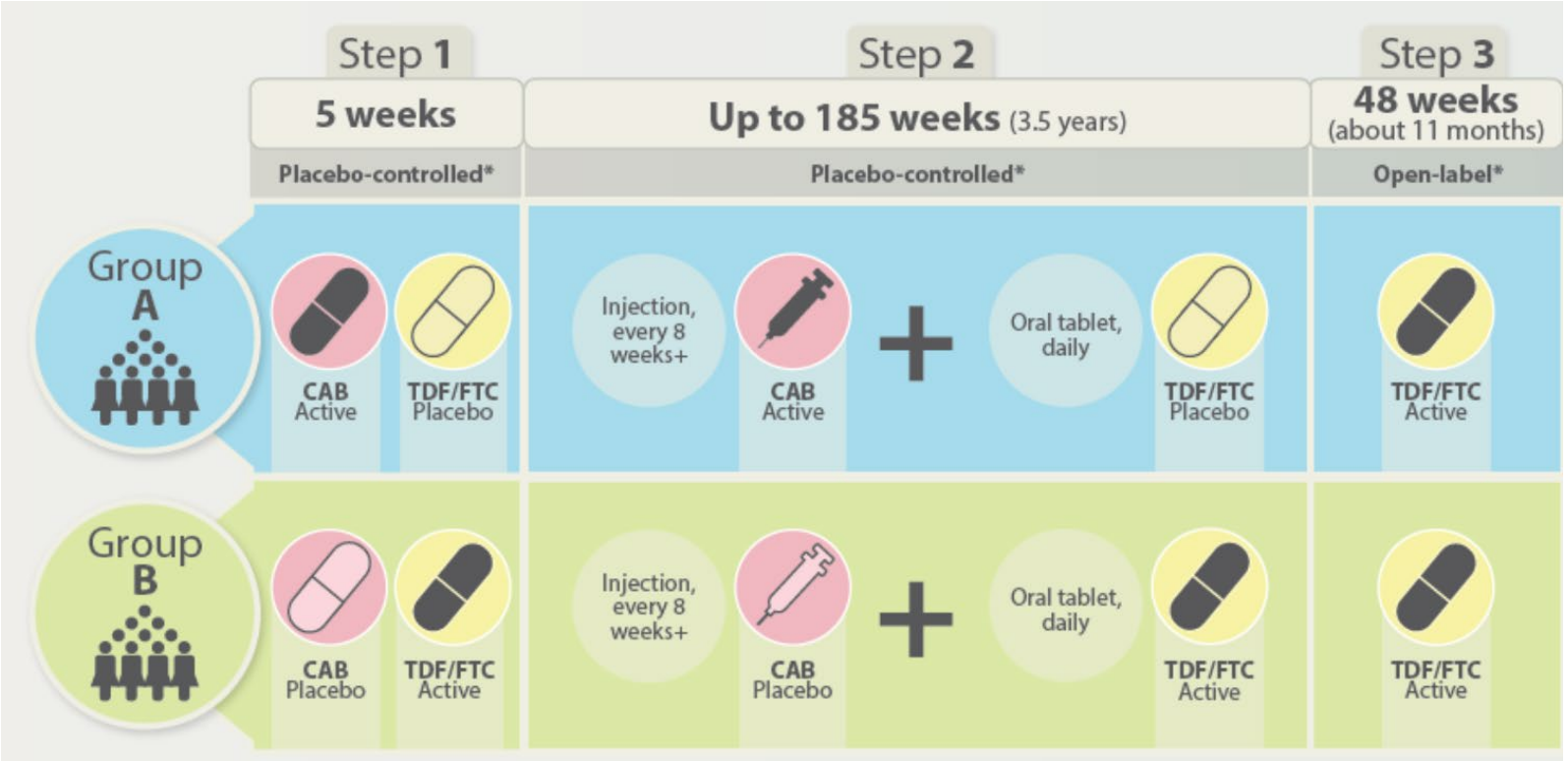
- To estimate the **incidence of HIV** among participants who use CAB LA, combining blinded, unblinded and OL periods
- To evaluate the **safety of open-label CAB LA with and without an oral lead-in** over 48 weeks
- To evaluate the **acceptability** (uptake, continuation, discontinuation) of OL CAB LA over 48 weeks
- To describe the diagnostic test profile, PK, HIV drug resistance, and response to antiretroviral treatment in **those who become infected after CAB LA exposure**, combining blinded, unblinded and OL periods
- To characterize **pharmacokinetics** and duration of detectable drug among those who discontinue CAB LA injections, combining blinded, unblinded and OL periods

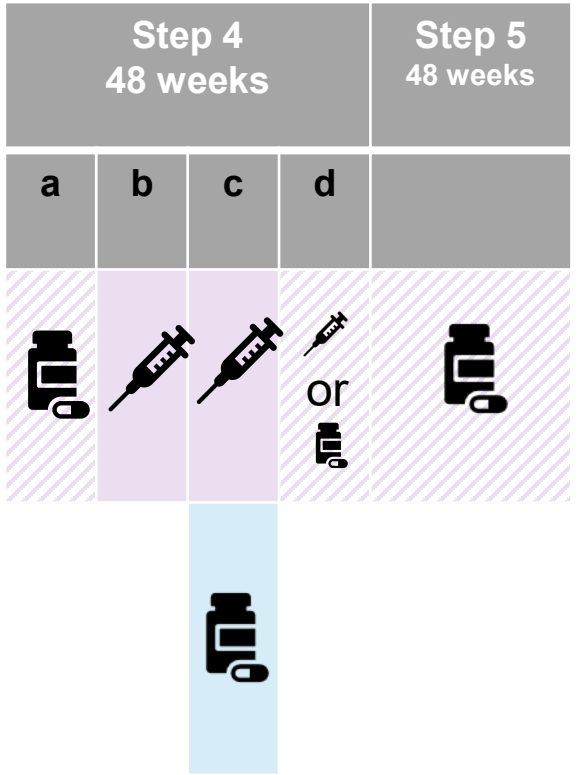
Objectives: HPTN 084 open-label extension

Pregnant and post-partum participants **with prior or current exposure to CAB** during pregnancy:

- To estimate the **incidence of pregnancy** among participants during the OL period
- To evaluate **safety and infant outcomes** among pregnant participants
- To evaluate the **PK of CAB LA** among pregnant participants, combining blinded, unblinded and OL periods
- To evaluate **concentration in breastmilk and infants** among women who receive CAB LA injections during pregnancy and/or the early post-partum period.

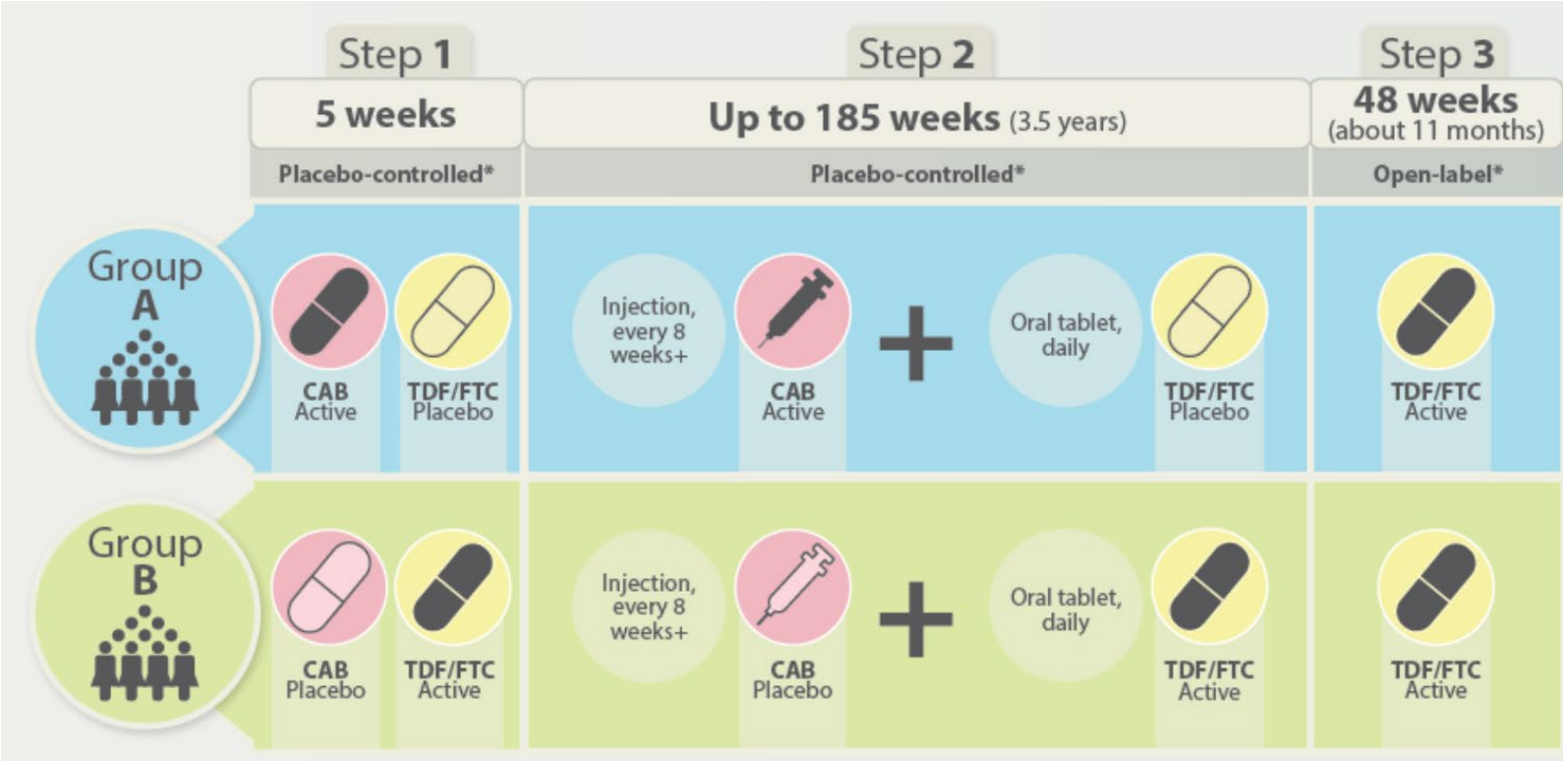
Study design: open-label extension

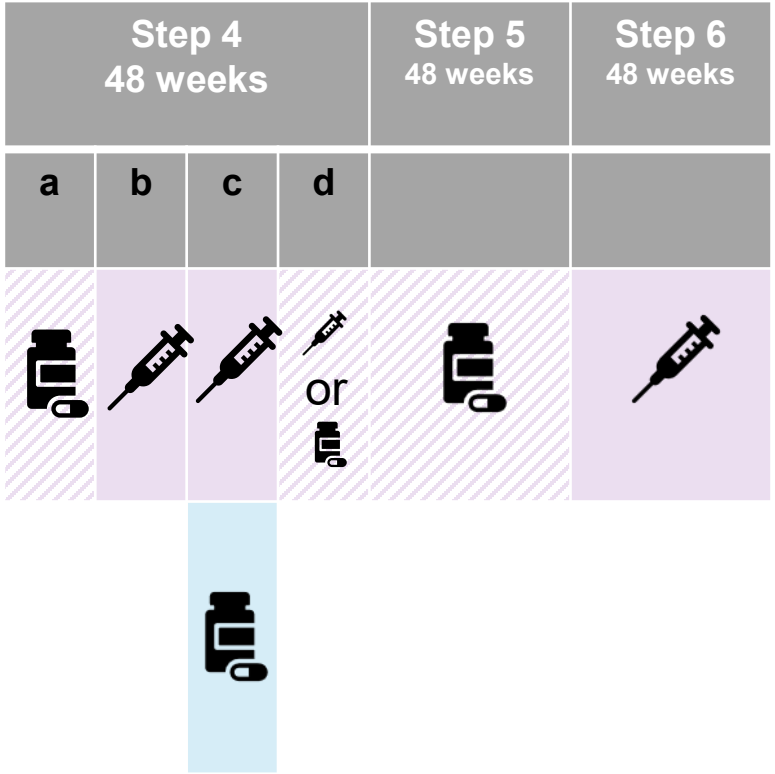




HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

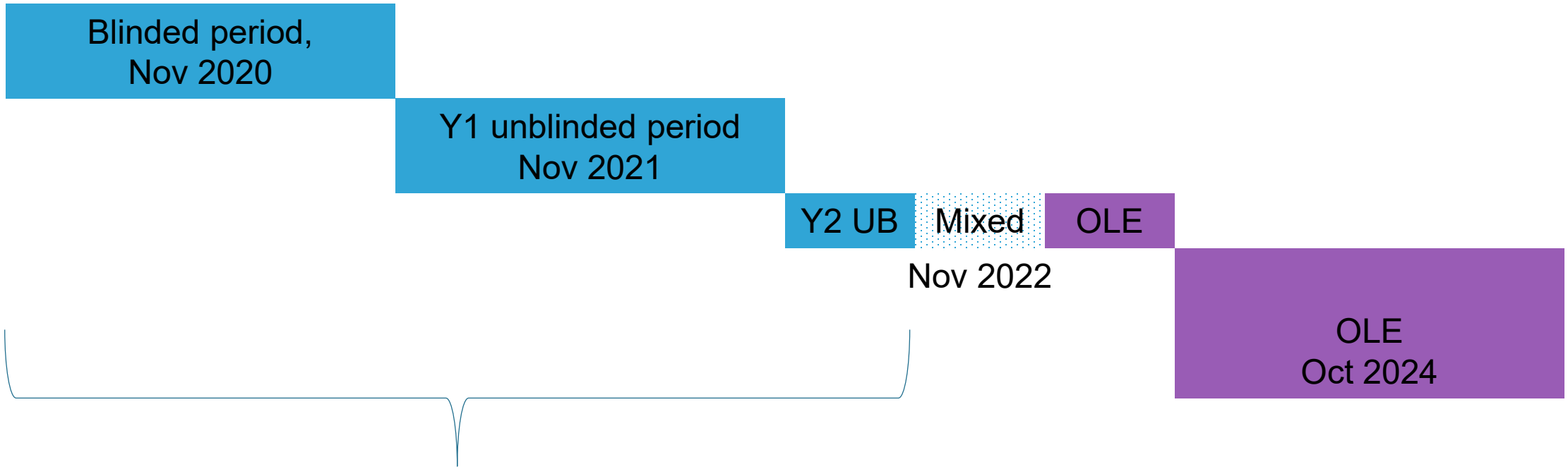
Study design: open-label extension





HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

Timelines



Data available from each of these periods
Focus has been on sharing data from blinded and unblinded periods that is relevant to programmes

Lessons learned

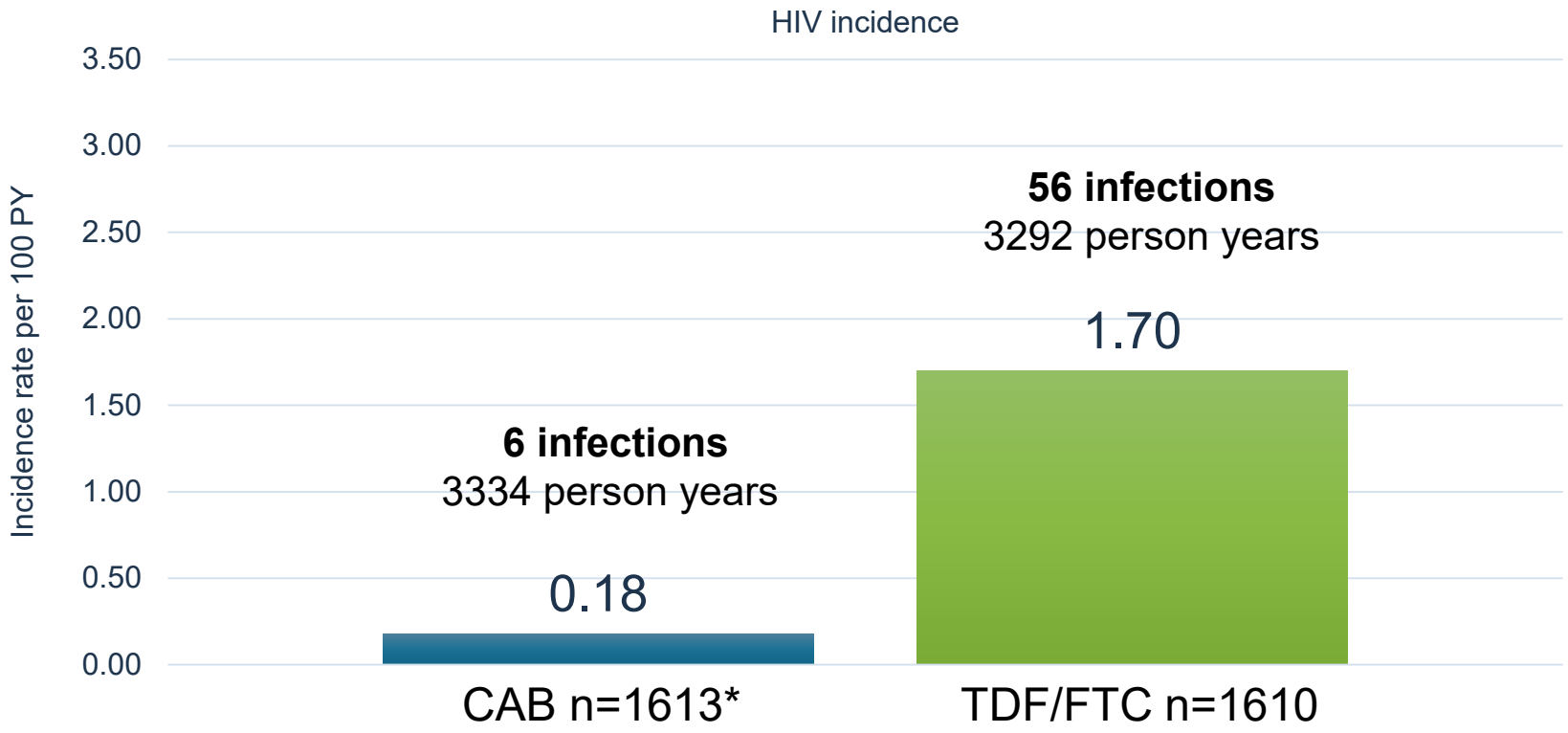
1. HIV efficacy and diagnosis
2. Safety
3. Pregnancy
4. Acceptability and Product choice

HIV incidence: CAB vs TDF/FTC

HPTN HIV Prevention Trials Network

Combined blinded and unblinded period, through Dec 2021

HR 0.11; 95% CI 0.05 - 0.24



*Excludes 1 baseline infection from the blinded period

No differences in efficacy by sub-group

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Trials Network

Table 2. Cabotegravir effectiveness, overall and by sub-group

	Cabotegravir events/PY (IR%)	TDF/FTC events/PY (IR%)	Hazard ratio (95% CI)[a]	p-value for interaction
Overall	4/1956 (0.20%)	36/1942 (1.85%)	0.12 (0.05, 0.31)[b]	<0.0001
Age				0.53
<25	3/866 (0.35%)	20/851 (2.34%)	0.17 (0.05, 0.54)	
≥25	1/1090 (0.09%)	16/1091 (1.47%)	0.09 (0.02, 0.49)	
Contraceptive method				0.87
DMPA	3/1009 (0.30%)	21/1000 (2.10%)	0.16 (0.05, 0.53)	
NET-EN	1/175 (0.57%)	6/182 (3.30%)	0.22 (0.03, 1.48)	
Implant	0/606 (0.00%)	8/607 (1.32%)	0.06 (0.00, 1.16)	
Other	0/165 (0.00%)	1/152 (0.66%)	0.32 (0.01, 9.89)	
Body mass index (kg/m^2)				
≤30	4/1389 (0.29%)	27/1447 (1.87%)	0.16 (0.06, 0.45)	0.47
>30	0/567 (0.00%)	9/495 (1.82%)	0.05 (0.00, 0.96)	

CI: confidence interval; IR: incidence rate; PY: person-years; DMPA: depot medroxyprogesterone acetate; NET-EN: norethisterone enanthate

[a] Firth's method was used to estimate the hazard ratio and confidence interval when subgroup had zero infections; used for sub-group analysis only, stratified by site.
[b] Median unbiased estimate (MUE) hazard ratio (95% CI) for CAB vs. TDF/FTC overall displayed.

HPTN 084 LENACAPAVIR

Cabotegravir infections: cumulative

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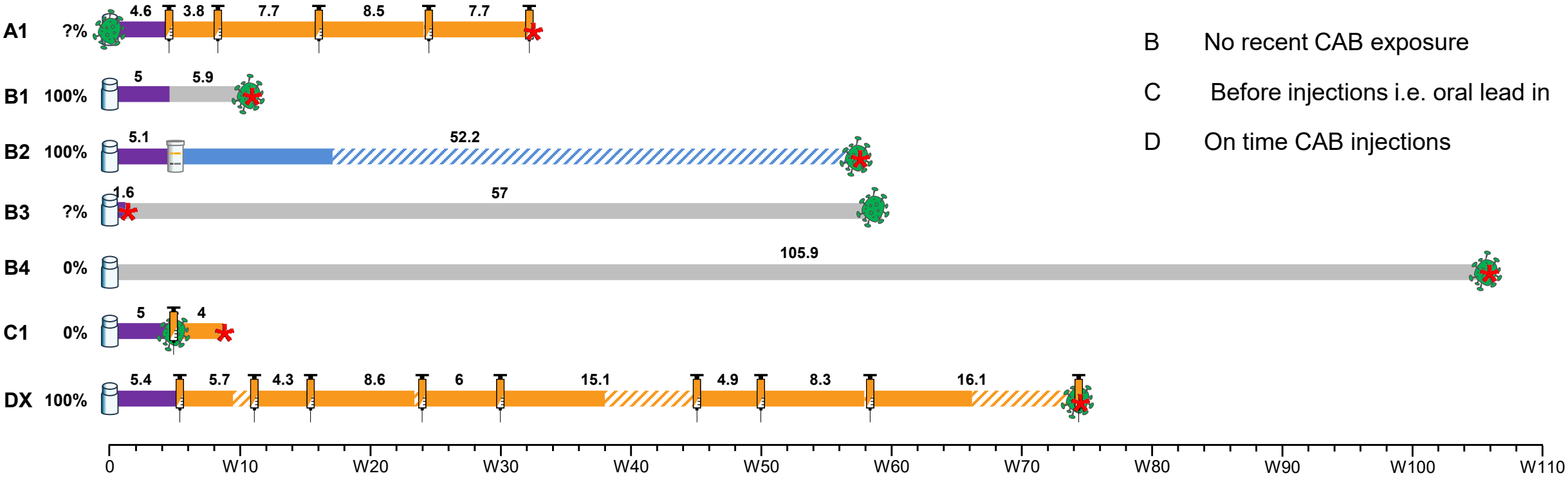


A Before enrollment i.e. baseline

B No recent CAB exposure

C Before injections i.e. oral lead in

D On time CAB injections

HPTN 084 LENACAPAVIR

HIV infections: lessons learned

- HIV infections rare in both groups

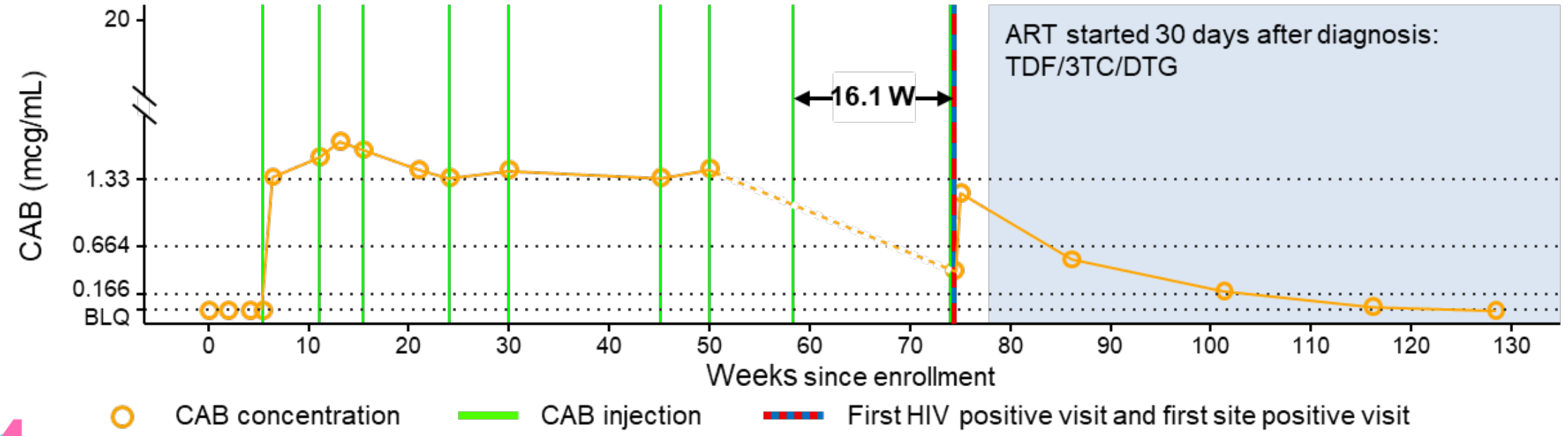
- CAB-LA delayed detection of HIV with conventional diagnostics e.g. A case
  - CAB-LA suppresses viral replication and delays antibody production
  - *Prolonged monotherapy may lead to INSTI resistance in rare cases (not yet observed in 084)*
  - Use of a sensitive HIV RNA assay may detect early infection and prevent INSTI resistance
    - OLE will assess utility of HIV RNA

- Majority of infections have occurred in absence of detectable drug e.g. B, C
  - Concerns about tail-phase infections not supported by data to date
  - Oral-lead in may have limitations in a population that desires injectable
    - OLE will assess direct-to-inject strategy

- No breakthrough infections in on-time injections observed yet in HPTN084
  - Compound delayed injections associated with HIV infection

HIV Infections in Participant with Delayed Injections

- During blinded phase of HPTN 084, one participant acquired HIV in the background of late injections
  - 3/9 injections occurred late (8.5, 15.1, 16.1 weeks)
  - CAB concentration at first HIV positive visit: 0.416 mcg/mL (<4x PA-IC_{90})



Delany-Moretlwe et al. Lancet. 2022; 399
Eshleman et al. J Infect Dis. 2022; 225(10)

Delayed injections: Conclusions

- HPTN 084 participants on a CAB-LA 600 mg Q2M regimen who received late injections maintained CAB concentrations >4x PA-IC_{90} and >8x PA-IC_{90} 98% and 87% of the time, respectively, following a 6 week delay (12-14 weeks between injections)

- Data from HPTN 084 suggest that there may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed CAB injections.

Delayed injections: Future Considerations

- While data suggest injection forgiveness in persons assigned female at birth, adoption of quarterly dosing (CAB-LA 600 mg Q3M) has not been evaluated for prevention
  - Q3M dosing should not be pursued in persons assigned male at birth
  - Empiric evidence to ensure target concentrations are achieved with alternative dosing regimens is needed

HIV infections: lessons learned

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- False reactive tests
  - At least one reactive test
  - Subsequent testing excludes HIV infection

- False reactive tests are possible
  - Frequency of testing
  - Other factors including co-infections, pregnancy, steroid use
  - Positive predictive value influenced by prior probability of outcome
  - **COMING SOON: PPV of rapid tests, Ag/Ab ELISA and characteristics associated with false reactive results in HPTN 084 blinded/unblinded period**

- Programmatic implications
  - Start treatment/hold PrEP?
    - Define approach for clinicians to confirm decision to start ART or re-start PrEP

HPTN 084 LEGACY

Safety: CAB vs. TDF/FTC, Y1 unblinded

HPTN HIV Prevention Trials Network

Participants with ≥ Grade 2 events	Total (n=2865)		CAB (n=1440)		TDF/FTC (n=1425)	
	n	%	n	%	n	%
Any Grade 2+ events	2391	83%	1194	83%	1197	84%
Creatinine clearance decreased	1146	40%	562	39%	584	41%
Chlamydia infection	453	16%	225	16%	228	16%
Gastrointestinal disorders	385	13%	211	15%	174	12%
Creatinine increased	338	12%	168	12%	170	12%
Urinary tract infection	258	9%	140	10%	118	8%
Gonorrhoea	213	7%	115	8%	98	7%
Upper respiratory tract infection	184	6%	89	6%	95	7%
Trichomoniasis	165	6%	94	7%	71	5%
Headache	164	6%	91	6%	73	5%
Vulvovaginal candidiasis	157	5%	78	5%	79	6%
Back pain	154	5%	75	5%	79	6%
Blood glucose decreased	140	5%	71	5%	69	5%
Abnormal uterine bleeding	123	4%	59	4%	64	4%
Any SAE/EAE	48	2%	26	2%	22	2%
Deaths	2	0,1%	2	0,1%	0	0%
ISR - Grade 2+ (n=1318)			32	2%		

Median f/u time 2.2 years

*80% of Grade 2+ adverse events considered **unrelated** to study products, both arms*

Grade 2+ events reported at frequency ≥ 5% in unblinded period

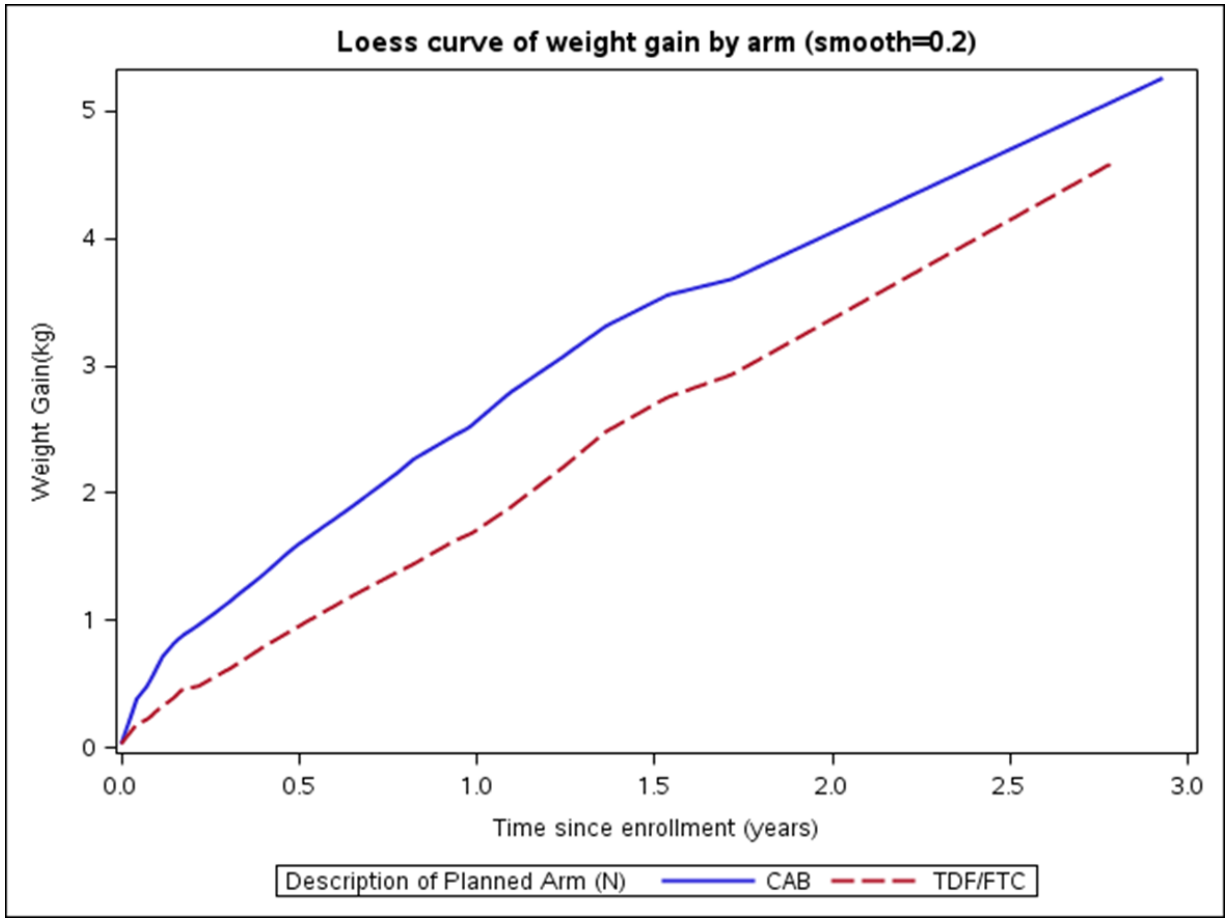
HPTN 084 LENACAPAVIR

Safety: injection site reactions

- ISRs – blinded period
  - 38% CAB vs 11% TDF/FTC
  - 13% CAB vs 2% TDF/FTC Grade 2+ events
  - Mostly associated with pain 4% CAB vs 1% TDF/FTC group injections
  - Most ISR at first injection (29%), diminished with time (2% unblinded period)
  - No discontinuations due to ISR

- Lessons learned
  - Training on injection technique
  - Counselling on pain mitigation approaches e.g. cold packs, analgesia (avoid aspirin), pain diminishes with time

Safety: weight gain



- Blinded period
- 28% participants BMI≥30 kg/m2
- Weight gain in both groups
- Initial weight gain in CAB group mean 0.4 kg
- CAB 2.4 kg/year vs TDF/FTC 2.14 kg/year

- Coming soon: Planned analyses to assess prevalence and incidence of risk factors for cardio-vascular disease, by study arm

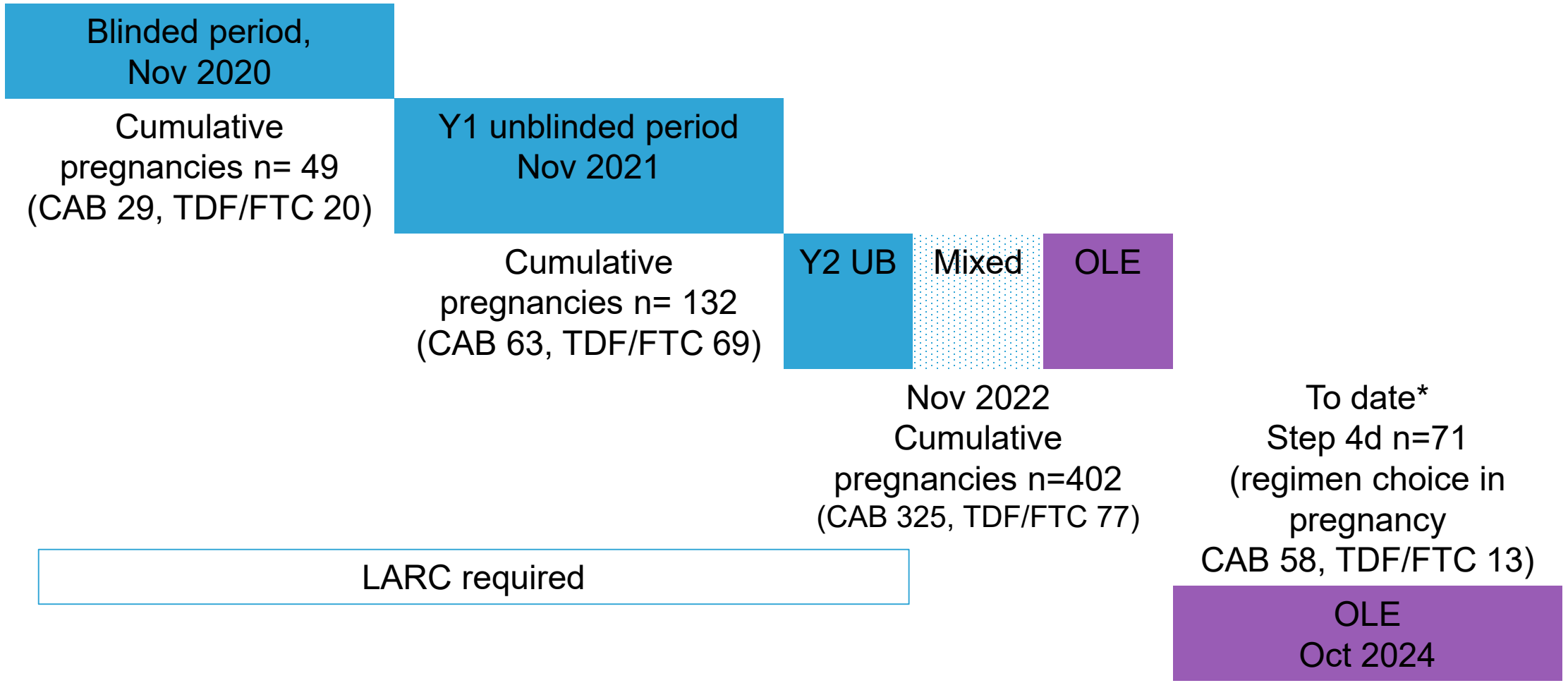
Safety: other AESI

- No differences by arm in blinded period in
  - STI incidence CT 19.6%, GC 8%
  - Seizures <1%
  - Discontinuations due to hepatic-related AEs <1%
  - Suicidality <1%

- Additional analyses to explore these topics in more detail pending

- Lessons for programs
  - Need comprehensive, integrated care approach
  - People at risk for HIV also likely to be at risk for other sexually transmitted infections, poor mental health and/or substance use
  - Need adequate training to assess and balance risks of HIV vs other outcomes and decisions to hold PrEP

Pregnancies

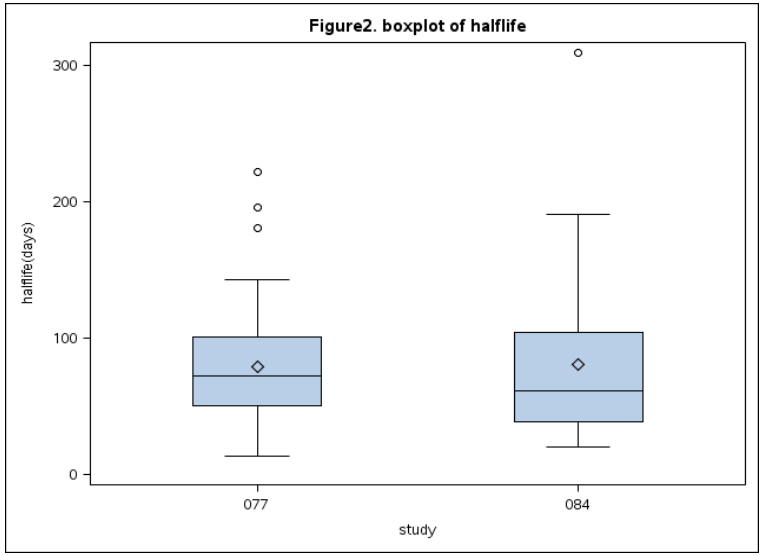


*in-stream data and numbers subject to change

Pregnancy: lessons learned blinded period

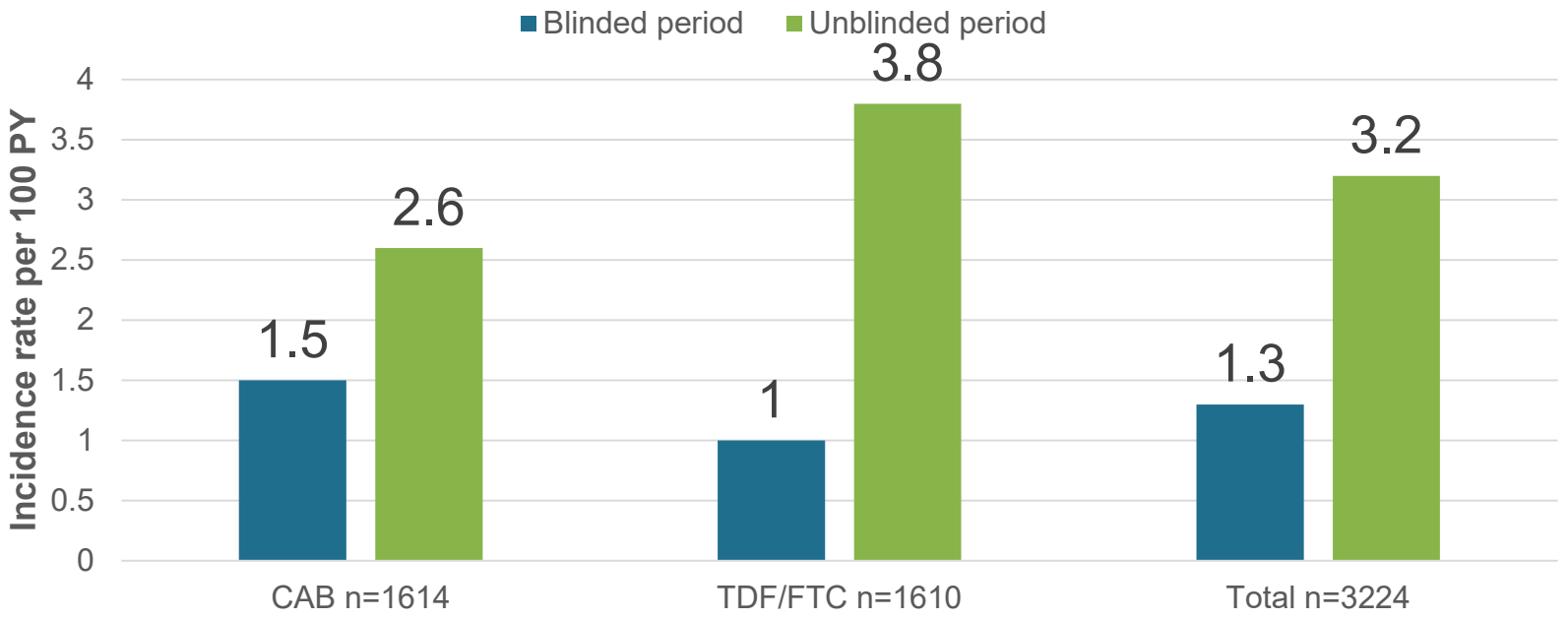
- In pregnant women who received CAB-LA up until pregnancy diagnosis
  - No congenital anomalies
  - Residual CAB exposures throughout pregnancy (range 36-228 weeks)
  - Residual CAB-LA generally well tolerated during pregnancy
  - Drug concentrations comparable in pregnant vs non-pregnant women

	CAB		TDF/FTC		
	Events/per person-year (n=39 py)	Incidence (95% CI)	Events/per person-year (n=29 py)	Incidence (95% CI) (per 100 py)	P-value
Any Grade 2+ AE	44	113	49	166	0.06



Delany-Moretlwe, CROI 2022;

Pregnancy: lessons learned



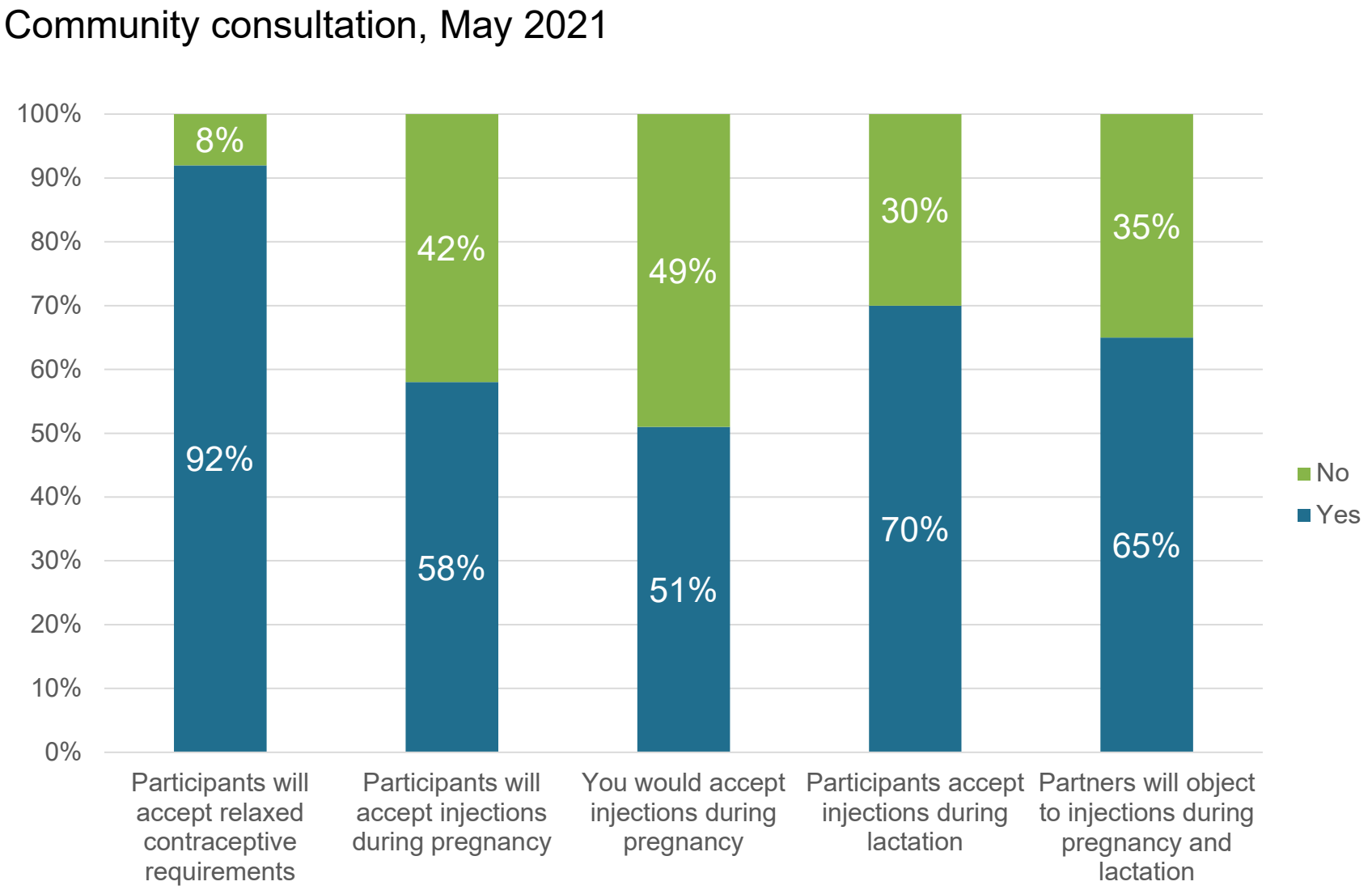
	CAB n=1614	TDF/FTC n=1610	Total n=3224
Cumulative confirmed pregnancies	63	69	132
Cumulative person-years	3239.1	3238.3	6477.3

2-3 fold increase in pregnancy incidence

Women wish to conceive safely without fear of HIV infection

Confirms importance of ongoing evaluation of CAB safety and pharmacology in pregnancy during the HPTN 084 open-label extension

Need to be able to communicate risks, benefits, knowns and unknowns

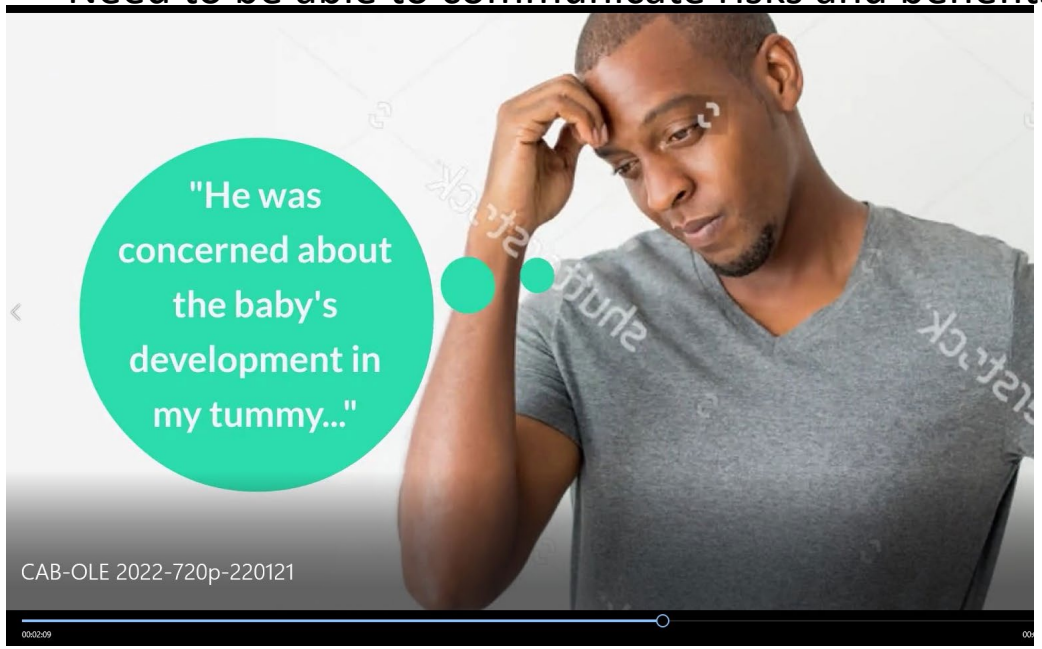


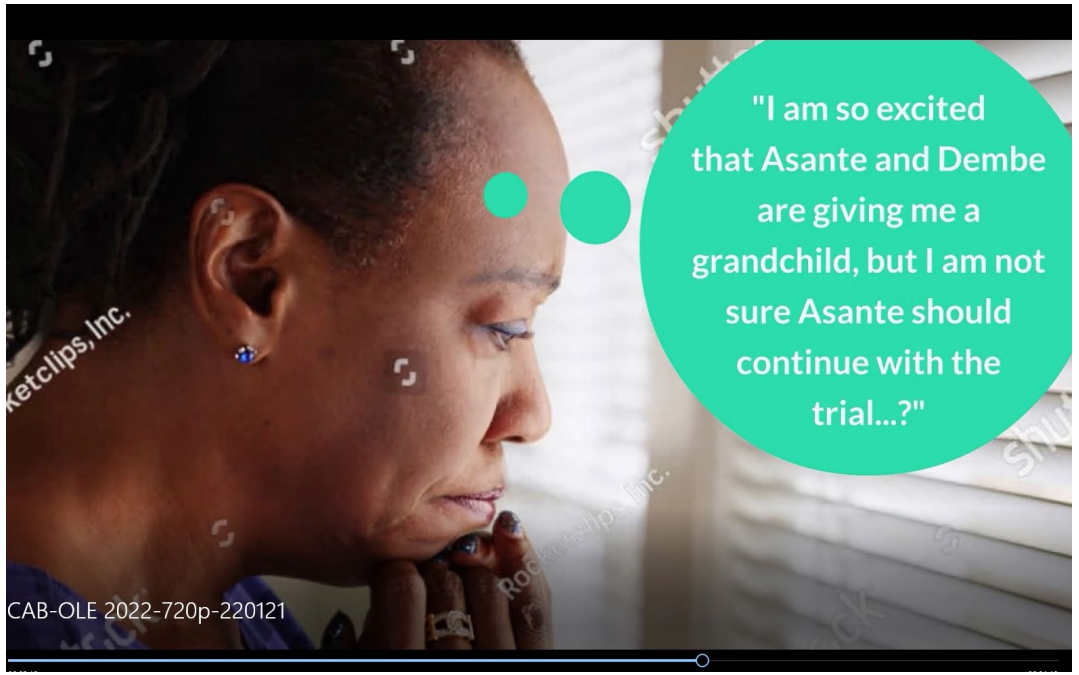
N=101 participants, mainly community stakeholders

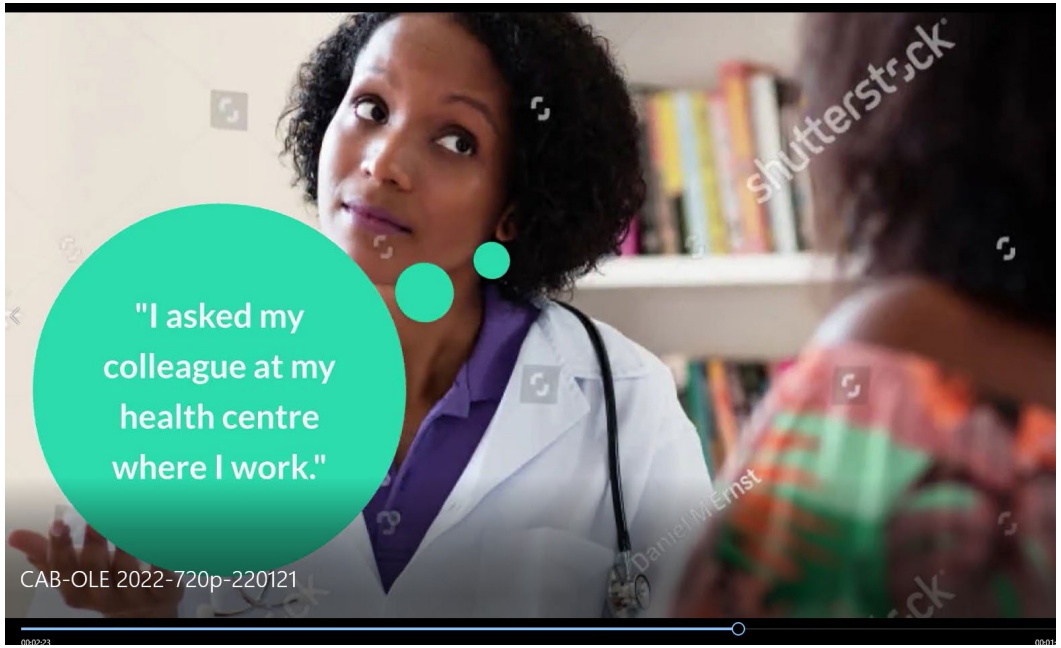
Emphasized safety concerns and need for information +++

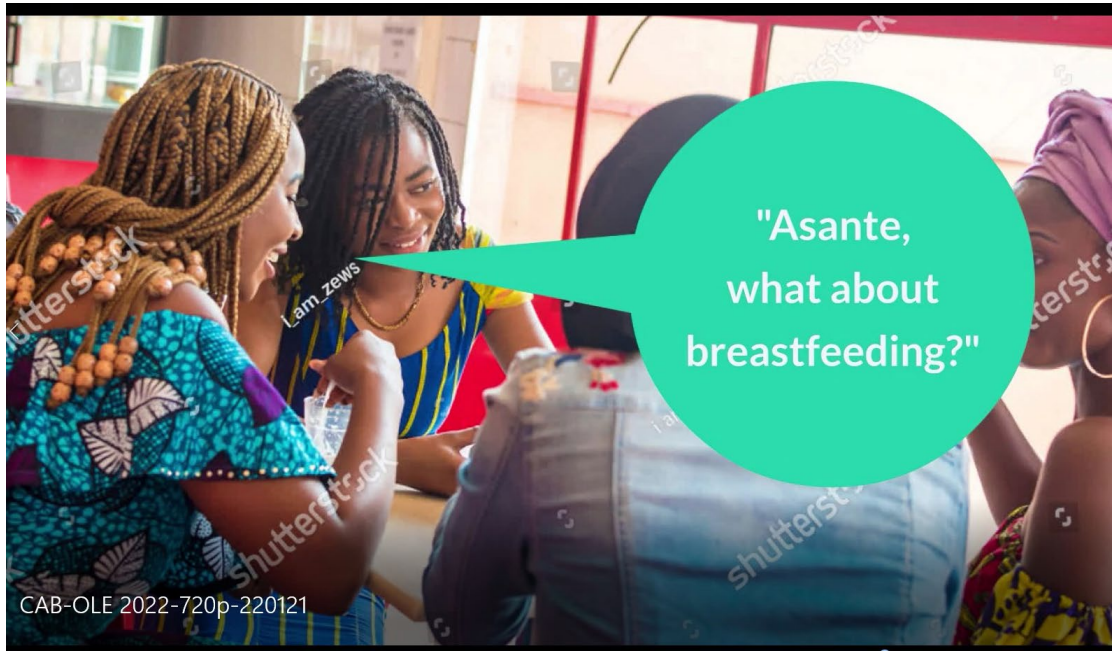
Pregnant women part of social network with many stakeholders in a safe pregnancy outcome

Need to be able to communicate risks and benefits









Pregnancy

- HPTN 084 will answer questions on
  - PK in pregnancy and breastfeeding and need for dose adjustment
  - Short-term safety and pregnancy outcomes
- Cannot address questions regarding rare outcomes e.g. NTD
  - Will require careful consideration of approaches to surveillance in programmes
- Lessons learned
  - Participants need time to consider 1) pregnancy 2) whether or not to use CAB
  - Staff need to be able to talk about knowns and unknowns, risks and benefits
  - Decision support aids help

Contraception

- Limited evidence
  - No effect of oral CAB on LNG/EE oral contraceptives (Trezza, 2017)
  - HPTN 077 COC use associated with lower peak CAB concentrations but no other differences (Blair, 2020)
  - HPTN 077 no other differences in PK parameters for other contraceptives
  - HPTN 084 blinded period pregnancy incidence 1% with LARC

- Planned analyses to assess
  - PK CAB and DMPA, NET-EN and etonogestrel (implant)
    - Testing in progress, results by end 2023
  - Fertility intentions, contraceptive choice and experience with co-administration – planned

Acceptability and product choice

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Acceptability of injectable cabotegravir versus daily oral TDF/FTC for PrEP: Lesson from HPTN 084

Authors: Juliane Etima[1*], Elizabeth Tolley[2], Agatha Bula[3], Miria Chitukuta[4], Nomhle Khoza[5], Emily Namey[2], Doreen Kemigisha[1], Lerato Makhale[5], Mercy Tsidya[3], Leah Schrumpf[2], Mina Hosseinipour[3], Sinead Delany-Moretlwe[5] on behalf of the HPTN 084 study team.

[1]Makarere-Johns Hopkin University Clinical Research Site, Kampala, Uganda
[2]FHI 360, Durham, North Carolina, USA
[3]UNC-Project Malawi, Malawi Clinical Research Site, Lilongwe, Malawi
[4]University of Zimbabwe-Spilhaus Clinical Research Site, Harare, Zimbabwe
[5]Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa

Take home message:
Women's desire for privacy and ease of use outweighed other injectable concerns, resulting in a strong preference for Injectable PrEP. Concerns about cost and accessibility will need to be addressed by implementation programs.

…So, there was a certain month when I was reckless because I went
away for a long time, and I stopped taking my pills…. I had more confidence in the injection and although I missed the oral pills, I had
the feeling that the injection would protect me because it is long acting."

- 63 participants from four HPTN 084 sites
- Majority single (44%), 20% self-identified sex workers
- Confirmed that participants liked a discreet convenient PrEP method, especially if they had busy lives and could not adhere to daily pills

HPTN 084
Long-acting Injectable For the Epidemic

HPTN 084

Acceptability and product choice

- 2472/3024 (82%) eligible participants accepted OLE
  - Relocation, loss to follow up or change in HIV risk reasons for non-enrollment

- 78% of all participants have accepted CAB LA for PrEP
  - Choice influenced by fear of injection site pain vs preferences for a discreet, convenient method, pregnancy concerns and preferences
    - Limited discussion about reversibility
  - Partners, family and others influential in decisions

- Decision support tools helpful for discussing risks/benefits

HPTN 084-01: acceptability and product choice

- CAB-LA was found to be safe and tolerable, with no discontinuations of product due to adverse events
- Adherence to the injection visits was exceptional (100%)
- Interest in a long-acting HIV prevention product was high among cisgender AGYW under the age of 18
- Participants found CAB-LA to be acceptable and expressed interest in future use
- Most participants (94%) chose to continue CAB-LA over TDF/FTC when given a choice and joined OLE
- It is feasible to enroll sexually-active adolescents into biomedical HIV prevention trials, with and without parental/guardian consent

Summary

- Multiple lessons learned
  - HIV diagnosis, resistance and response to treatment
  - PK and delayed dosing
  - Safety
  - Pregnancy
  - Product choice and acceptability

- Additional relevant analyses forthcoming
  - Performance of conventional HIV diagnostics
  - Sexually transmitted infections, hepatitis
  - Cardiovascular risk
  - Contraceptive DDI, dual administration
  - Pregnancy PK and safety during active dosing
  - Factors associated with product choice

Acknowledgments

Sponsor
- U.S. National Institute of Allergy and Infectious Diseases (NIAID), all components of the U.S. National Institutes of Health (NIH)

Additional funding support
- ViiV Healthcare
- Bill & Melinda Gates Foundation
- National Institutes of Mental Health

Pharmaceutical support
- Gilead Sciences
- ViiV Healthcare

HIV Prevention Trials Network
- Leadership and Operations Centre, FHI360
- Laboratory Centre (Johns Hopkins)
- Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
- HPTN Leadership

HPTN 084 Study team
- 20 sites in 7 countries in sub-Saharan Africa
- Community advisory boards and partners

… and our study participants!

UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).