

Long-acting HIV Pre-Exposure Prophylaxis

Cabotegravir and Beyond: Implications for Testing Algorithms and Implementation

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Professor of Medicine

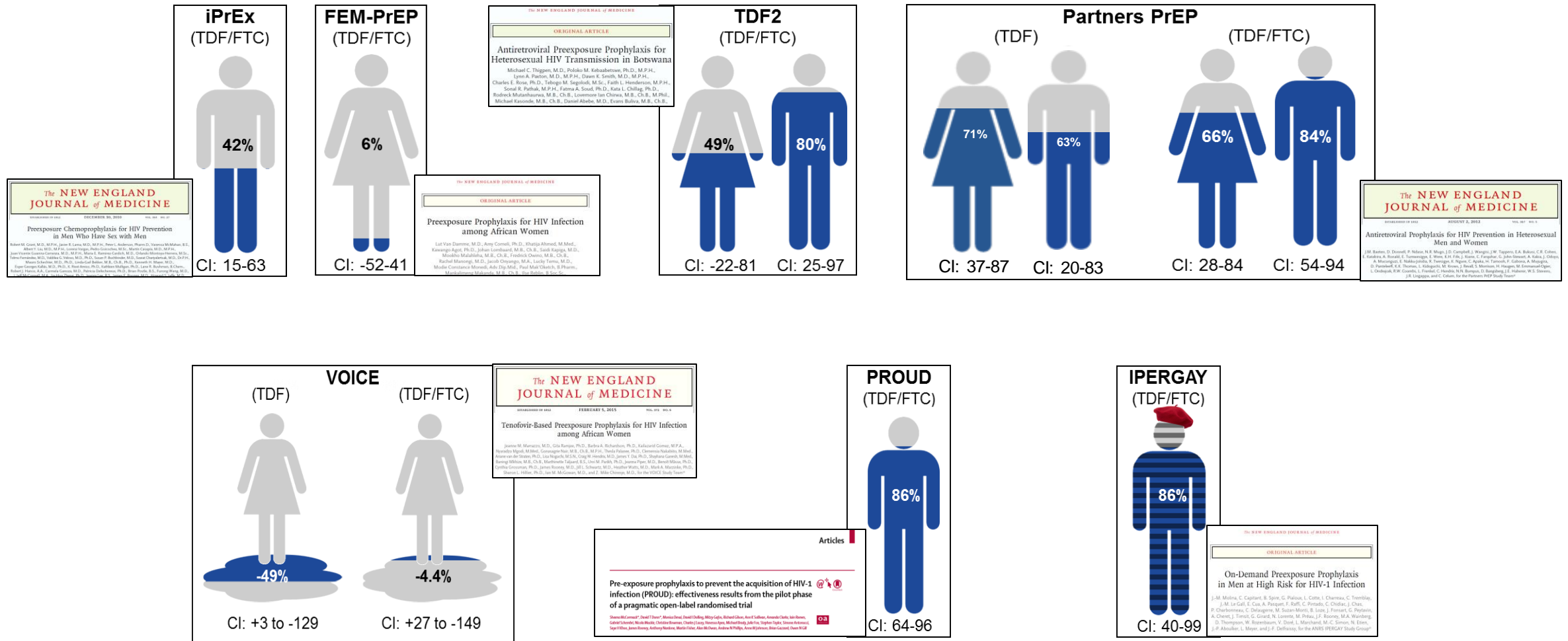
UCLA Center for Clinical AIDS Research & Education

Last Updated: January 18, 2022

Disclosures

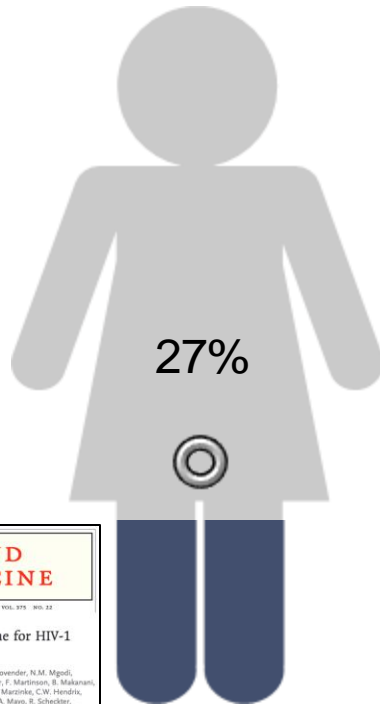
Raphael J. Landovitz has served on scientific advisory boards for Gilead Sciences and Merck Inc., and has received honoraria from Janssen and Cepheid.

Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



“PrEP 2.0”: Trials of Novel PrEP Agents

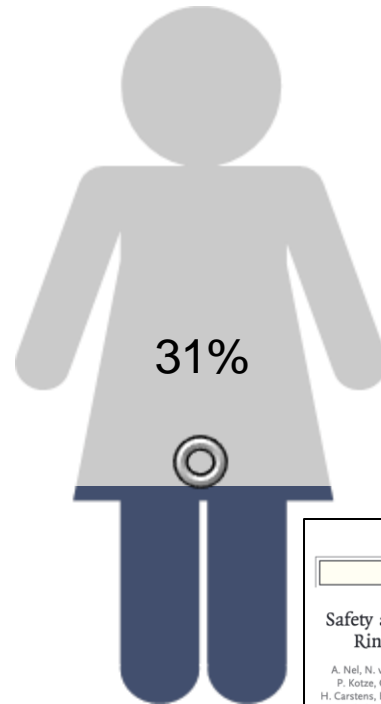
ASPIRE (Dapivirine)



CI: 1 – 46

The NEW ENGLAND
JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2016 VOL. 375 NO. 22
Use of a Vaginal Ring Containing Dapivirine for HIV-1
Prevention in Women
J.M. Baeten, T. Palanee-Phillips, E.R. Brown, K. Schwartz, L.E. Soto-Torres, V. Govender, N.M. Mgedi,
F. Maitso Kweema, G. Nair, F. Mhlango, S. Siva, L.-G. Bekker, N. Jeenaarain, Z. Gaffoor, F. Martinson, B. Makasa,
A. Pather, J. Naidoo, M. Hranik, B.A. Richardson, L.M. Purdie, J.W. Mellors, M.A. Marston, C.W. Hendrix,
A. van der Straten, G. Ramjee, Z.M. Chirenje, C. Nakhalilo, T.E. Taha, J. Jones, A. Mayo, R. Schoeter,
J. Benhassan, E. Luani, C. Jacobson, P. Misasi, R. White, K. Patterson, D. Gormiga, B. Cabalka, K. Rugege,
D. Singh, D.W. Steyn, E.T. Montgomery, B.S. Mensch, K. Torgesen, C.I. Grossman, N. Chabikwa, A. Nel,
Z. Rosenberg, I. McGowan, and S. Hillier, for the MTN-025-ASPIRE Study Team*

Ring (Dapivirine)



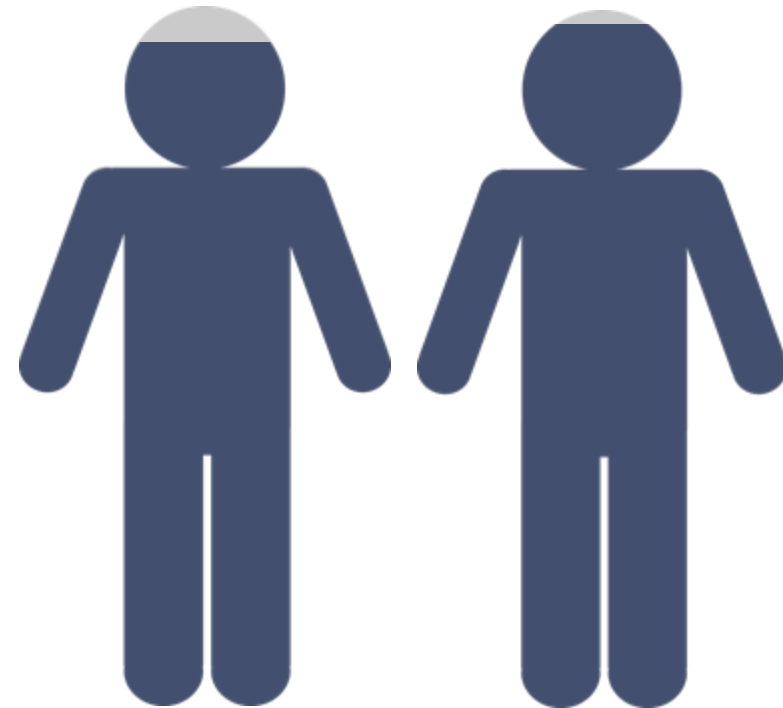
CI: 1 – 51

THE NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Safety and Efficacy of a Dapivirine Vaginal
Ring for HIV Prevention in Women
A. Nel, N. van Niekerk, S. Kapiga, L.-G. Bekker, C. Gama, K. Gill, A. Kamali,
P. Kotze, C. Louw, Z. Mabude, N. Miti, S. Kusemererwa, H. Tempelman,
H. Carstens, B. Devlin, M. Isaacs, M. Malherbe, W. Mans, J. Nuttall, M. Russell,
S. Ntshole, M. Smit, L. Solai, P. Spence, J. Steytler, K. Windle, M. Borremans,
S. Ressler, J. Van Rooy, W. Parys, T. Vangeneugden, B. Van Baelen,
and Z. Rosenberg, for the Ring Study Team*

DISCOVER

(TDF/FTC)

(TAF/FTC)

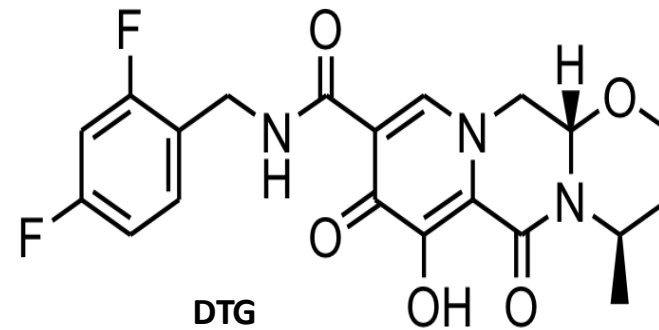
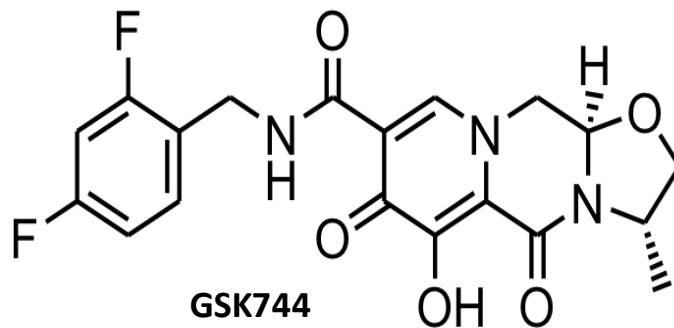


Incidence rate
0.30%

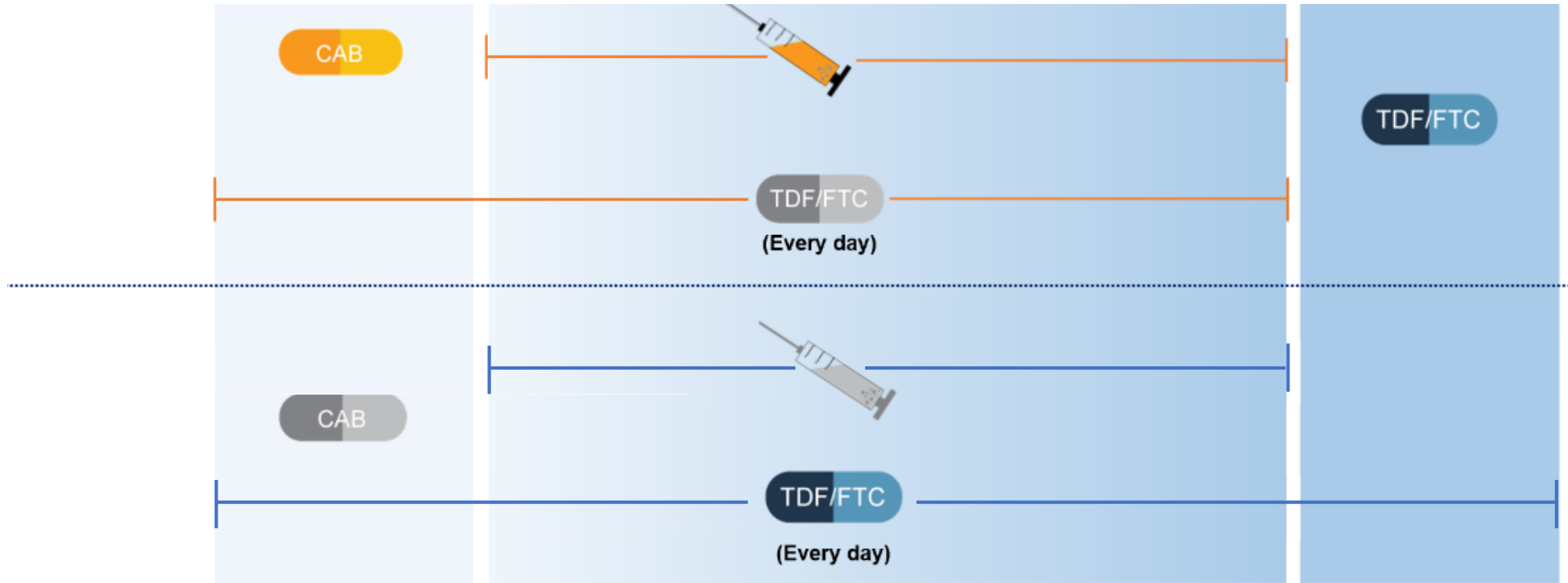
Incidence rate
0.16%

Cabotegravir (GSK1265744)

- **Analogue of Dolutegravir (DTG)**
- **CAB and DTG have similar preclinical profiles; CAB is well-suited to long-acting nanosuspension**
- **Development for HIV treatment and PrEP**
 - PrEP: mono- or combo-ARV approach; possible MPT use
 - HIV treatment: CAB + RPV (US, Canada, Europe regulatory approvals)

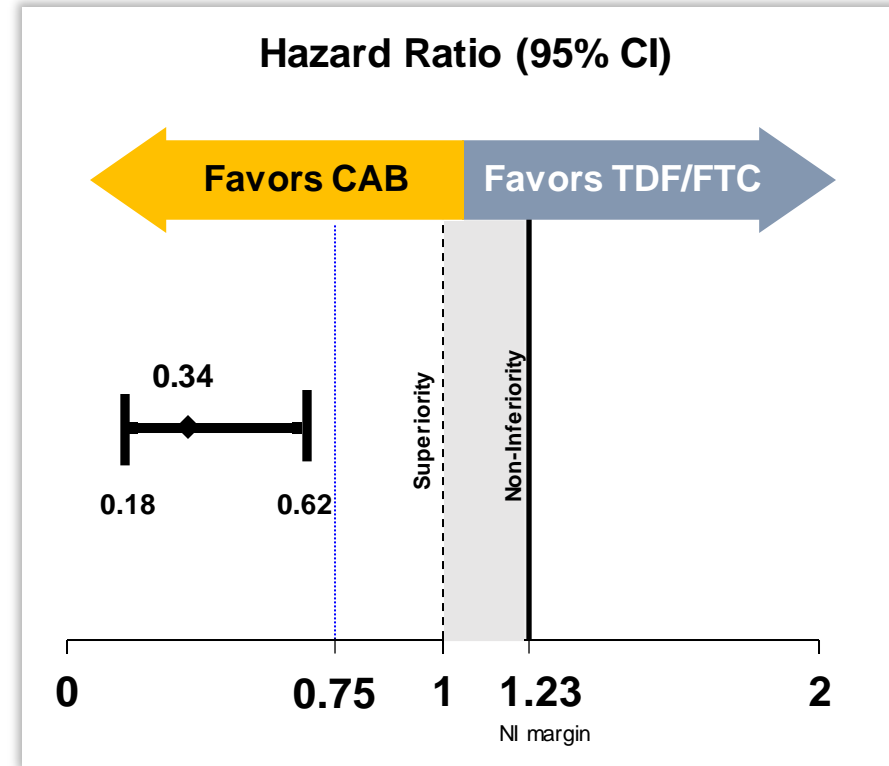
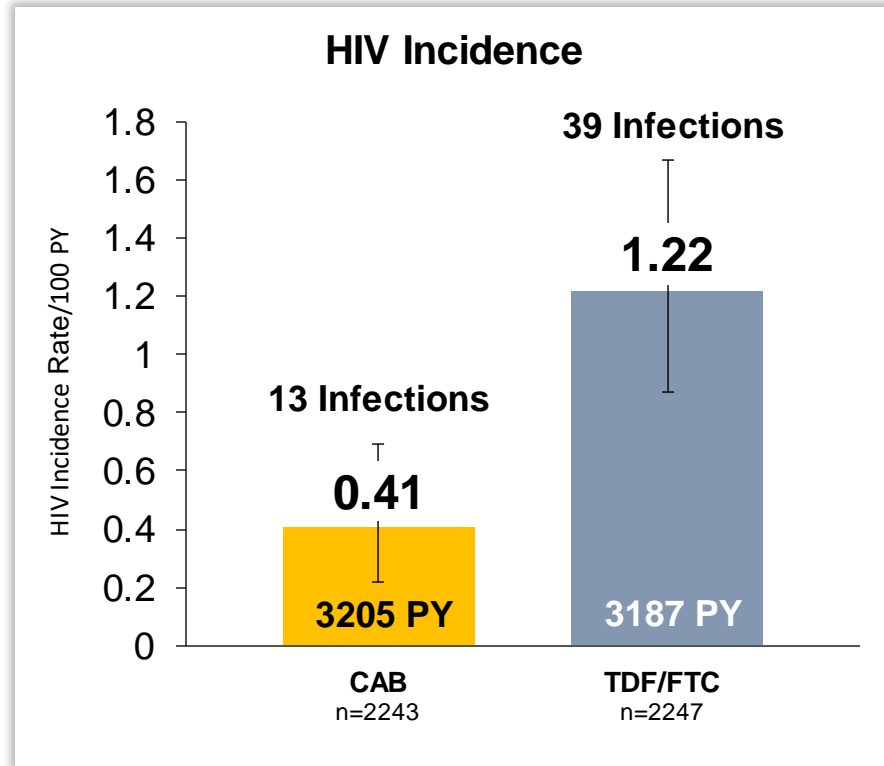


HPTN 083 Study Design



- TDF/FTC pill
 Cabotegravir (CAB) injection
 Placebo for TDF/FTC pill
 Placebo for cabotegravir (CAB) injection
- Cabotegravir (CAB) pill
 Placebo for cabotegravir (CAB) pill

HIV Incidence: CAB vs. TDF/FTC



CI, confidence interval

Pre-specified HIV Testing

Real-time site testing

Rapid (Point-of-Care)
Antibody Test

4th or 5th gen (Ag/Ab)
HIV test (lab)

HPTN LC testing (retrospective)

4th gen (Ag/Ab) HIV test

Confirmatory Test

APTIMA Qualitative RNA Test

“Backtesting” until negative x 1

Extended HPTN LC Testing

HPTN LC testing (retrospective)

4th gen (Ag/Ab) HIV test

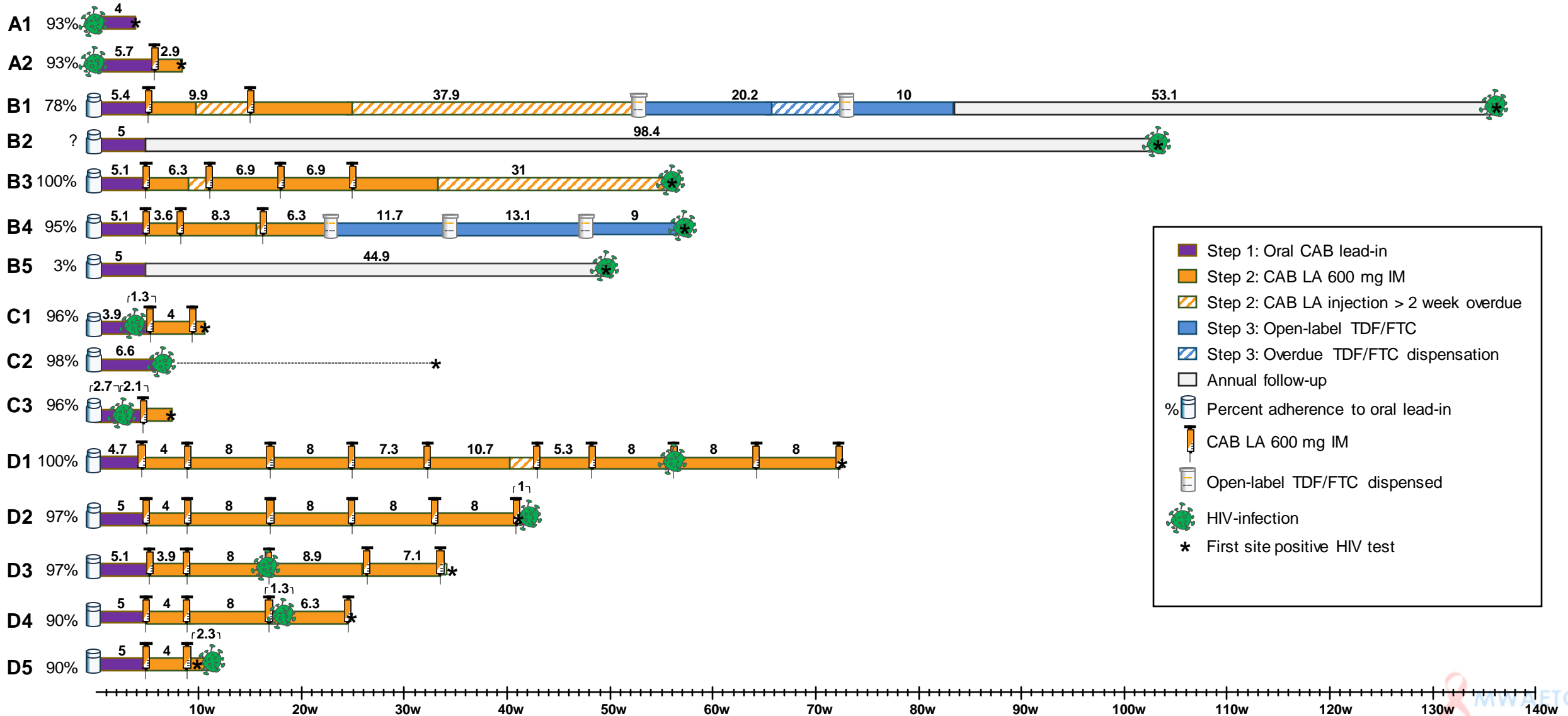
Confirmatory Test

APTIMA Qualitative RNA Test

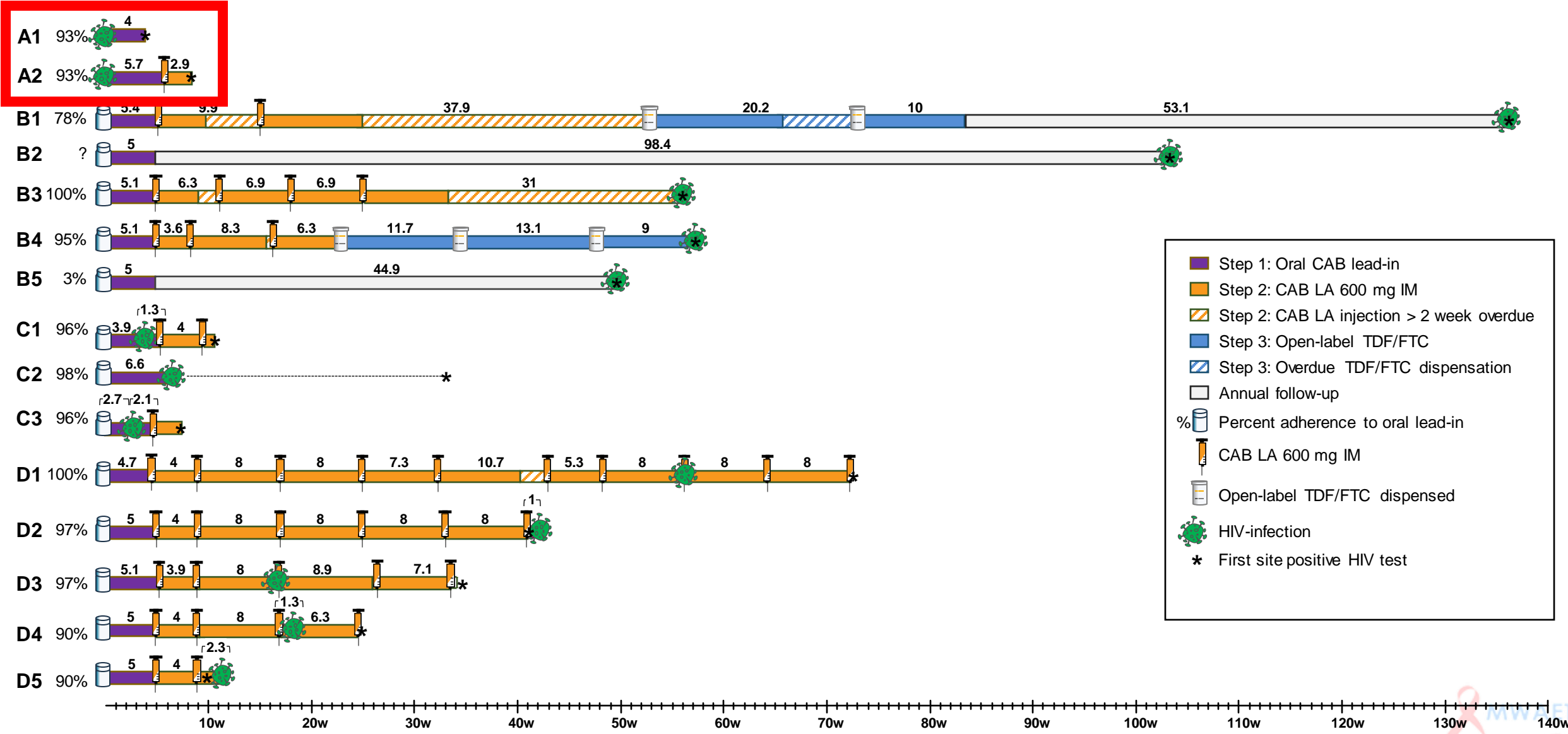
Quantitative (“number”) RNA (Viral Load Test)

“Backtesting” all the way back to enrollment*

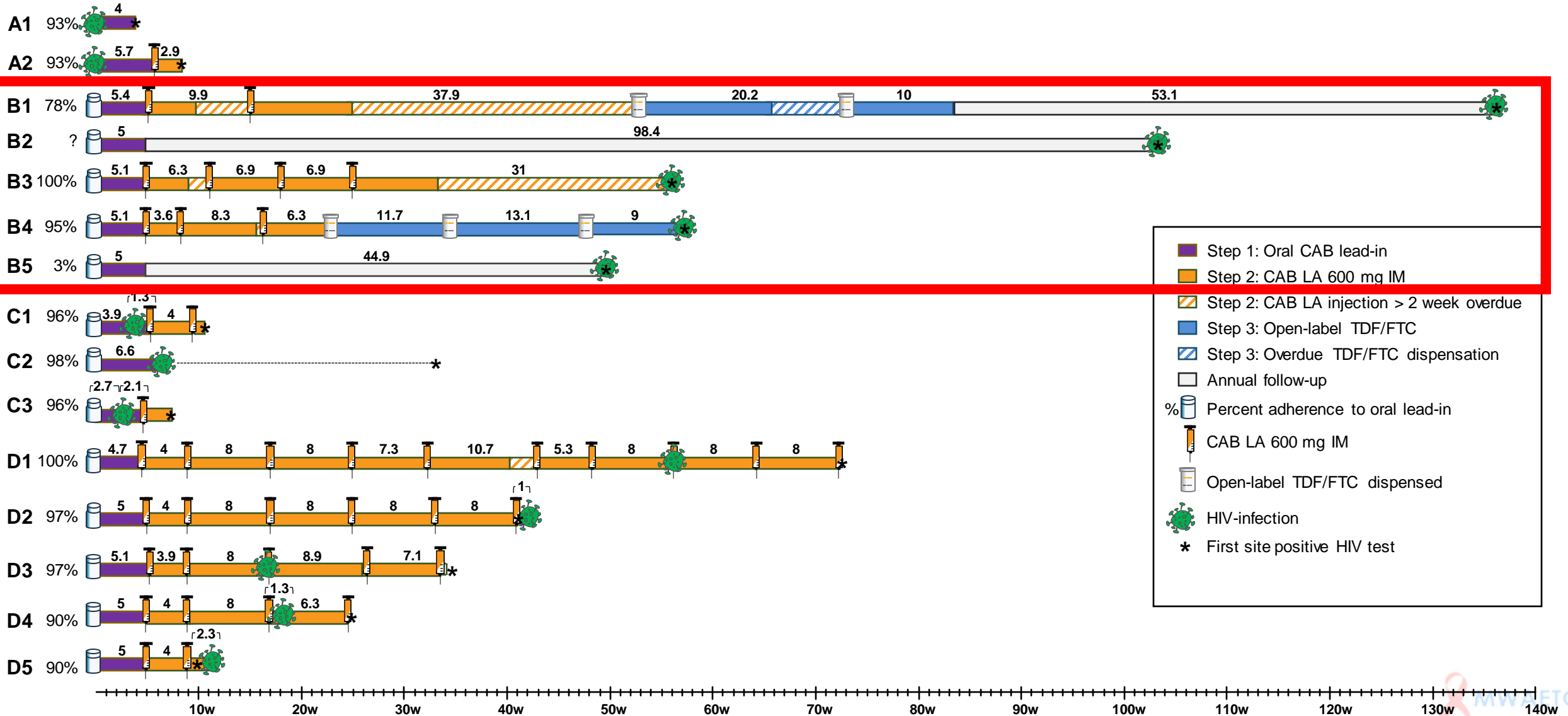
13 Incident, 2 baseline Infections: Cabotegravir



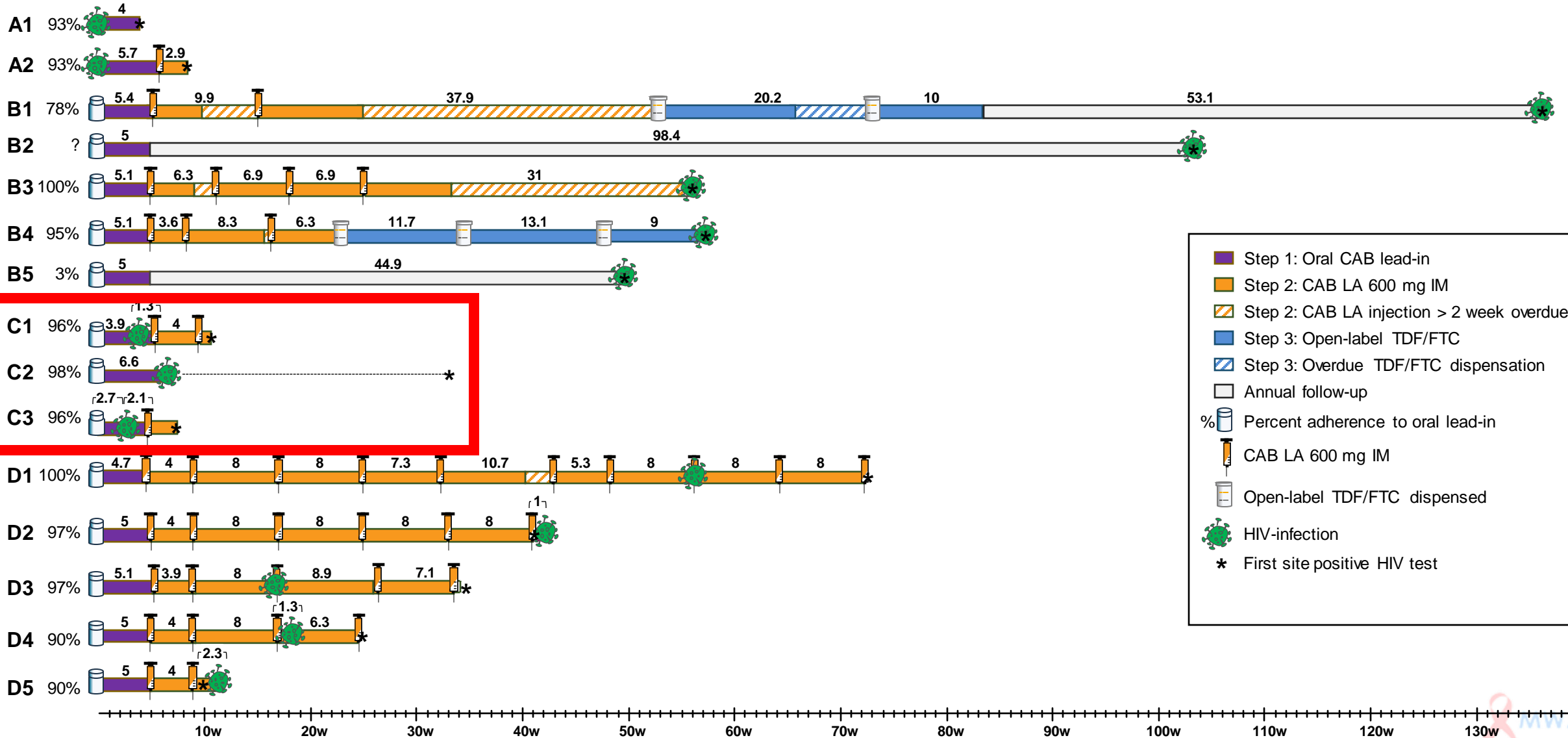
13 Incident, 2 baseline Infections: Cabotegravir



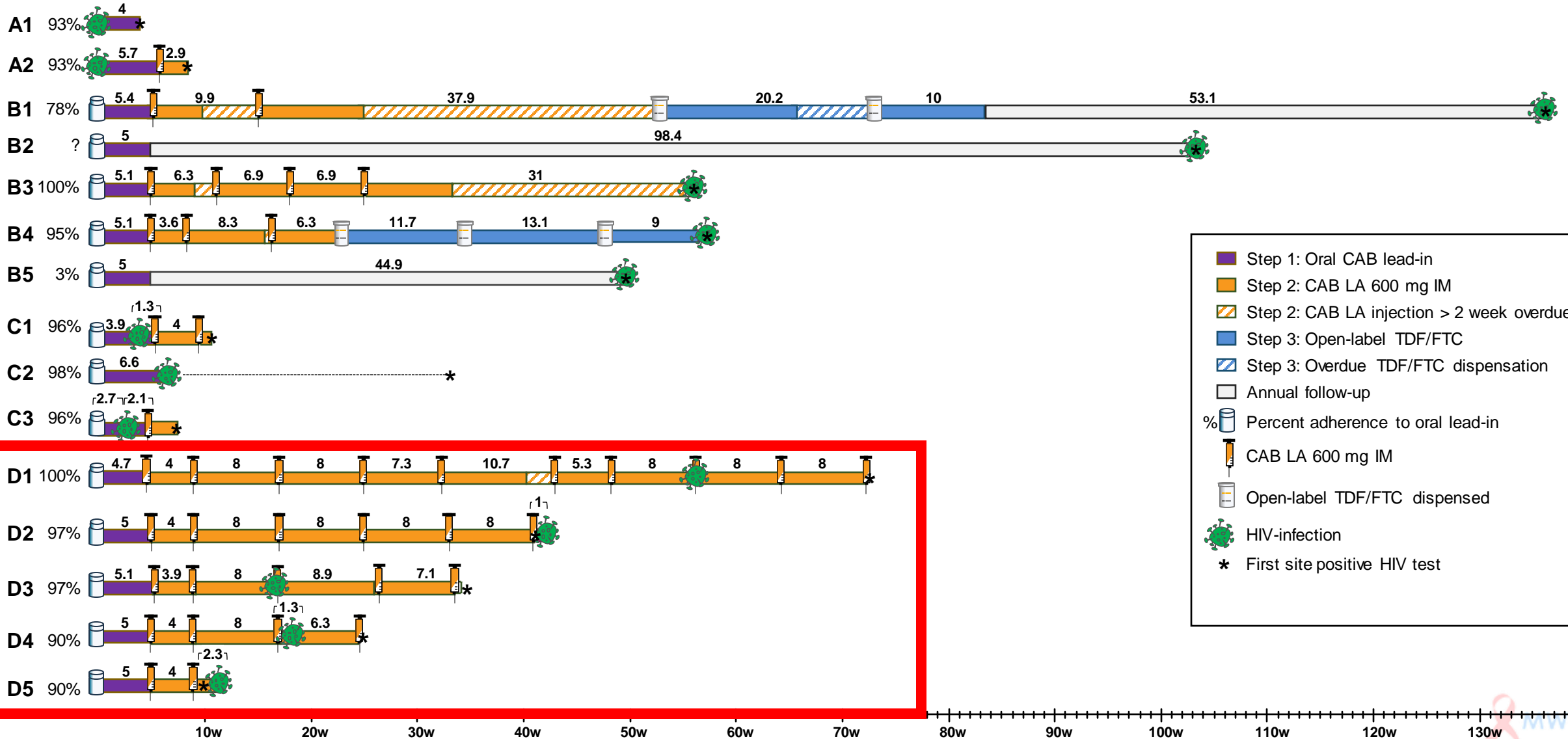
13 Incident, 2 baseline Infections: Cabotegravir



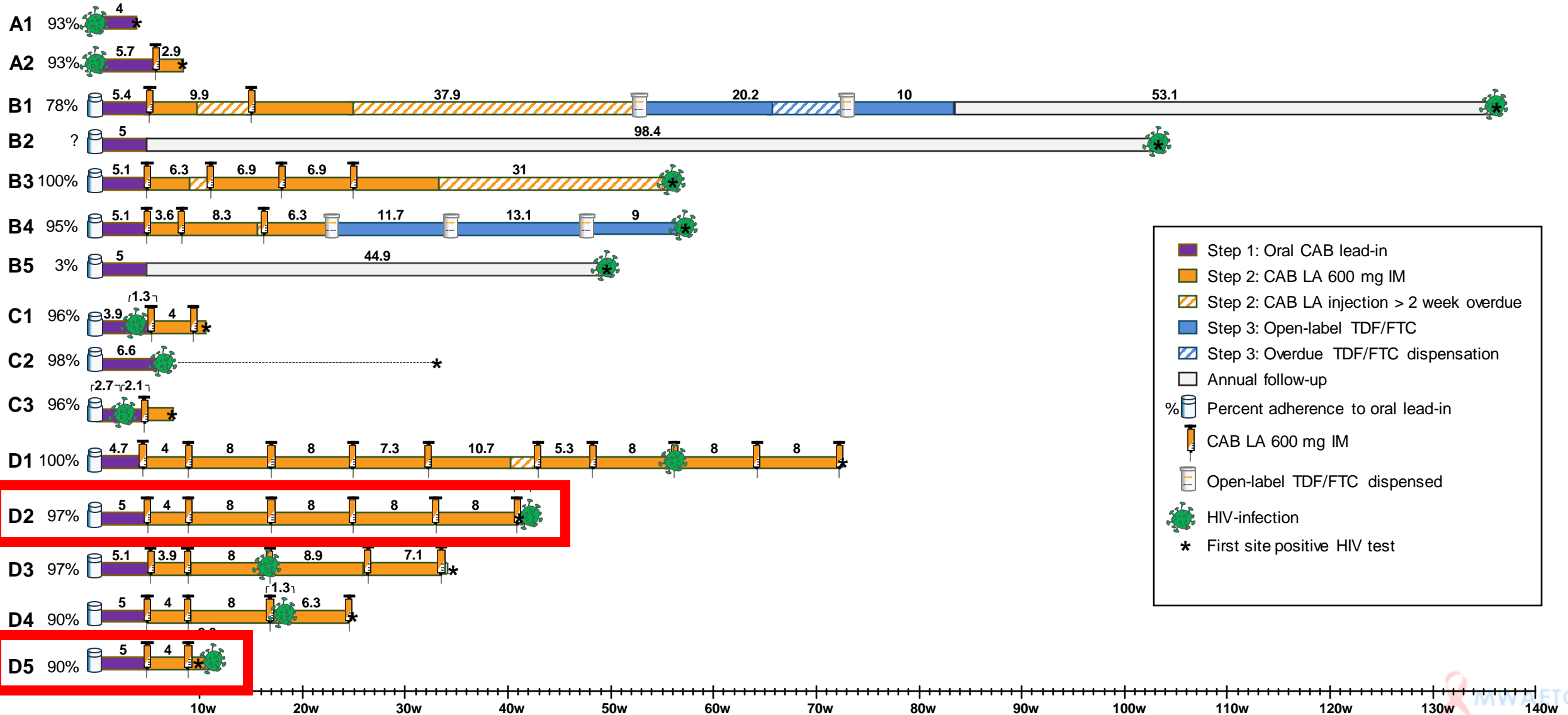
13 Incident, 2 baseline Infections: Cabotegravir



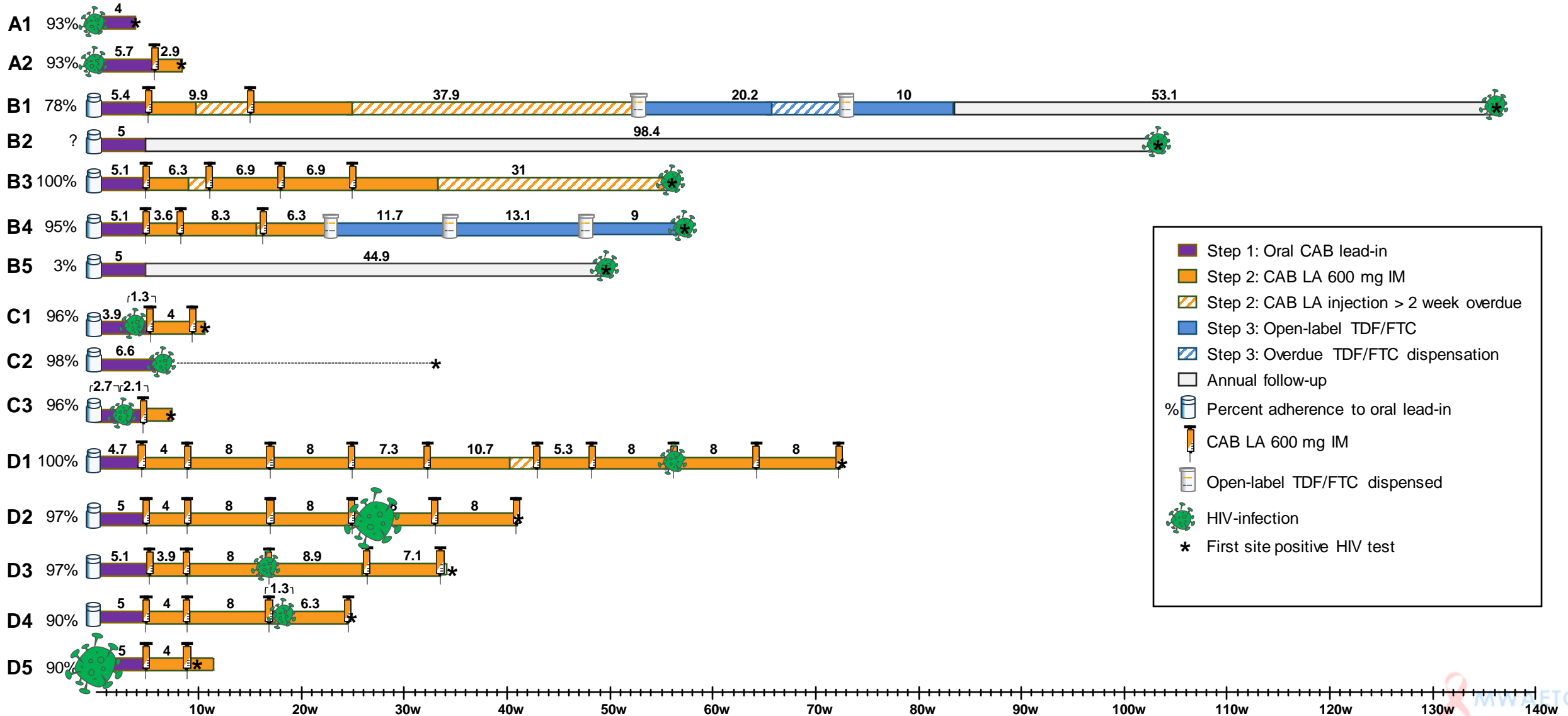
13 Incident, 2 baseline Infections: Cabotegravir



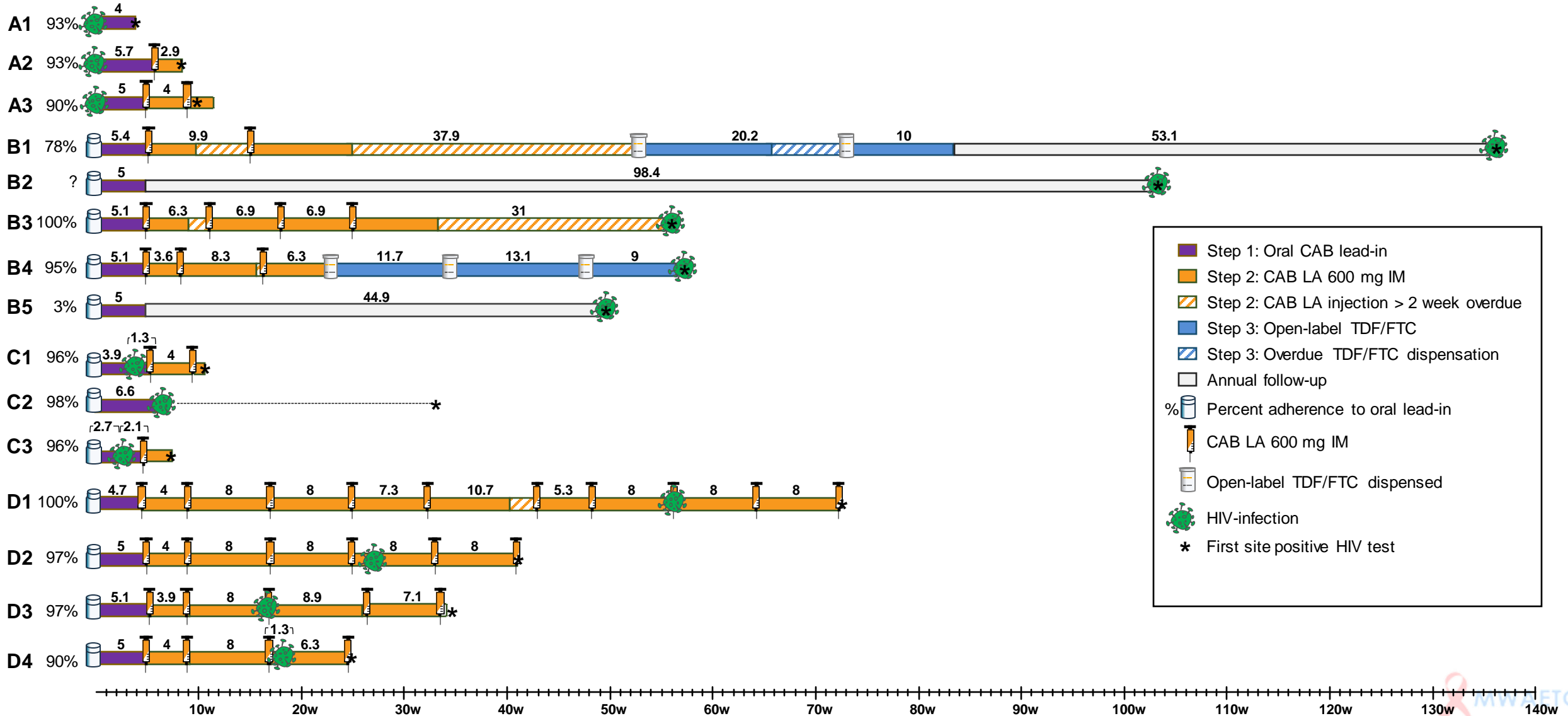
13 Incident, 2 baseline Infections: Cabotegravir



13 Incident, 2 baseline Infections: Cabotegravir

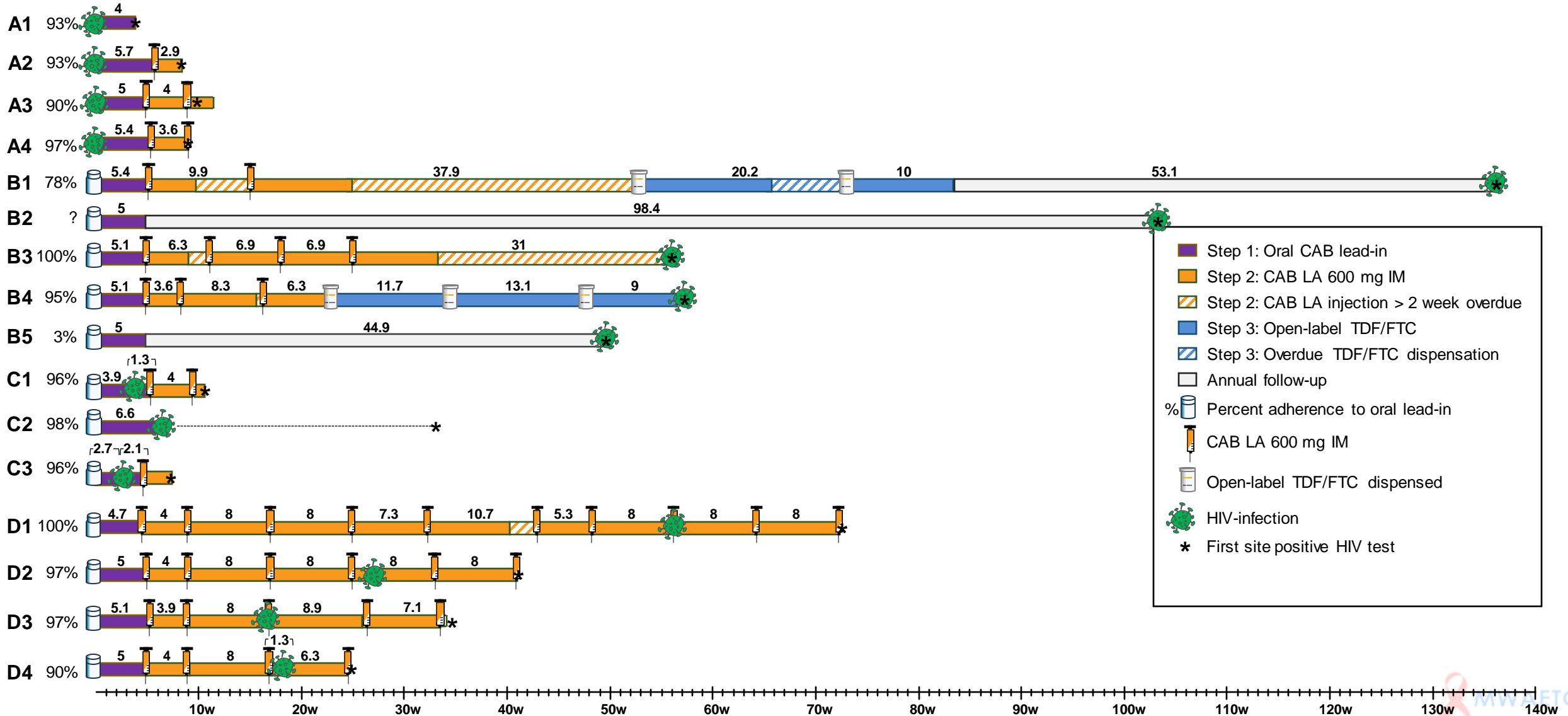


12 Incident, 3 baseline Infections: Cabotegravir

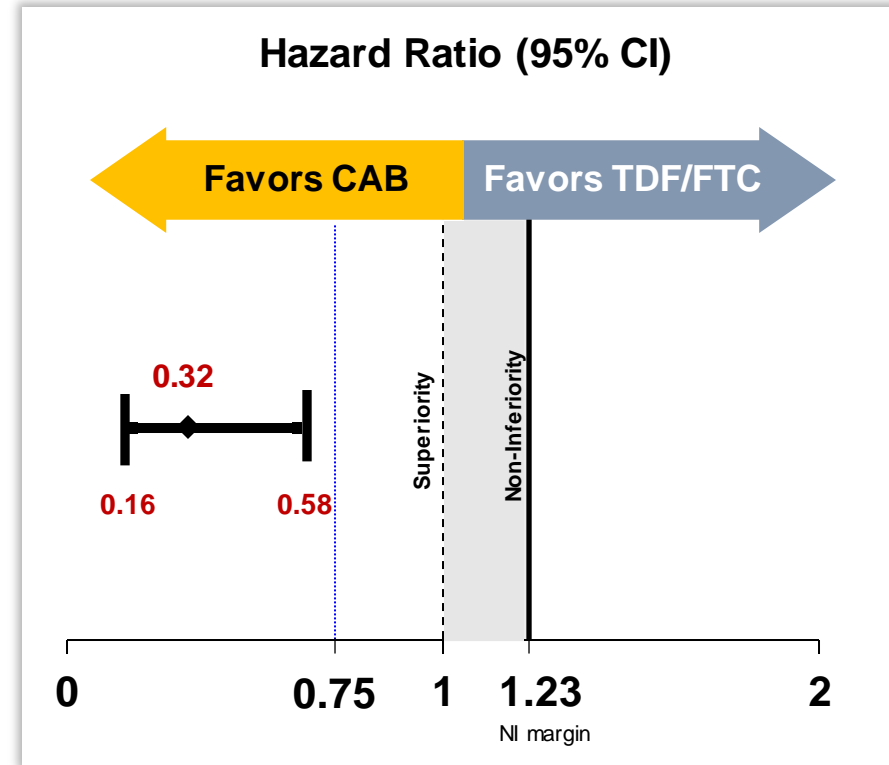
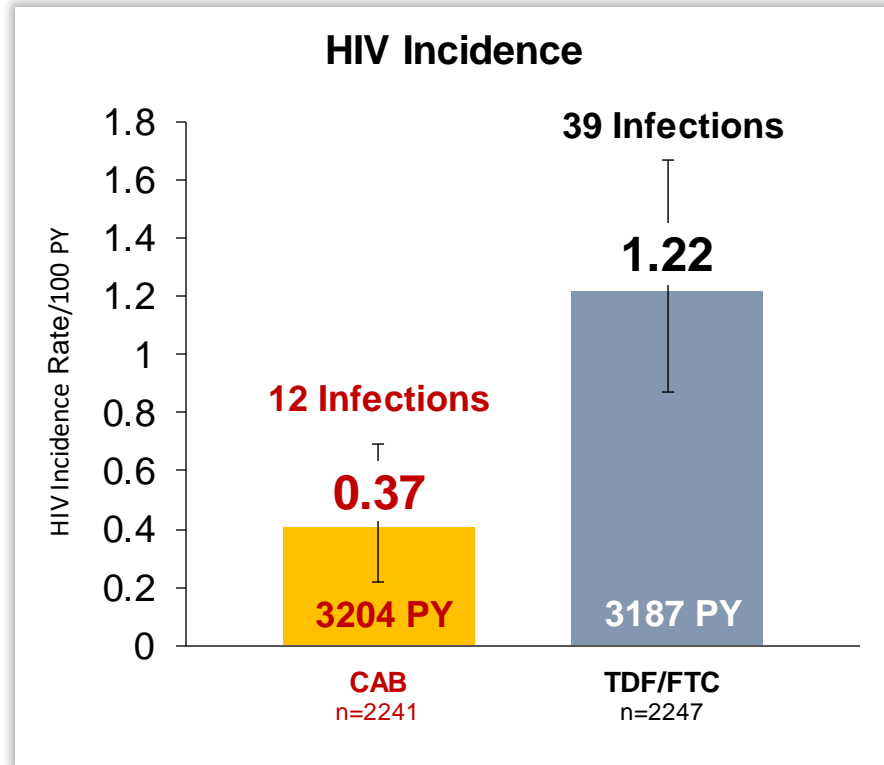


- Step 1: Oral CAB lead-in
- Step 2: CAB LA 600 mg IM
- Step 2: CAB LA injection > 2 week overdue
- Step 3: Open-label TDF/FTC
- Step 3: Overdue TDF/FTC dispensation
- Annual follow-up
- % Percent adherence to oral lead-in
- CAB LA 600 mg IM
- Open-label TDF/FTC dispensed
- HIV-infection
- * First site positive HIV test

12 Incident, 4 baseline Infections: Cabotegravir



HIV Incidence: CAB vs. TDF/FTC



CI, confidence interval

CAB arm, Group A
HIV positive at study enrollment

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**
 - **Viral load is lower and may even be undetectable**
 - **Aptima/RNA testing was test to detect infection the earliest**
 - **Point-of-care (rapid) and 4th/5th generation lab tests were delayed in turning reactive and would “flicker”**
- **Failure to diagnose HIV infection can lead to continued CAB administration, and even continued CAB injections**
 - **With levels that are HIGH, if the virus “escapes” CAB, it can be CAB resistant (we had 1 case)**
 - **BUT, when the virus “escapes” CAB during the tail, it DID NOT have CAB resistance (we had 1 case)**

CAB arm, Group B
No recent CAB exposure

CAB arm, Group B

What we learned:

- **If you don't take CAB, it doesn't prevent HIV infection**
- **In 3 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**
- **In at least 2 cases, where 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
Infected during CAB oral lead-in period

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 CAB (and other integrase) resistance**

CAB arm, Group D
Infected in the setting of on-time CAB
injections

CAB arm, Group D

What we learned:

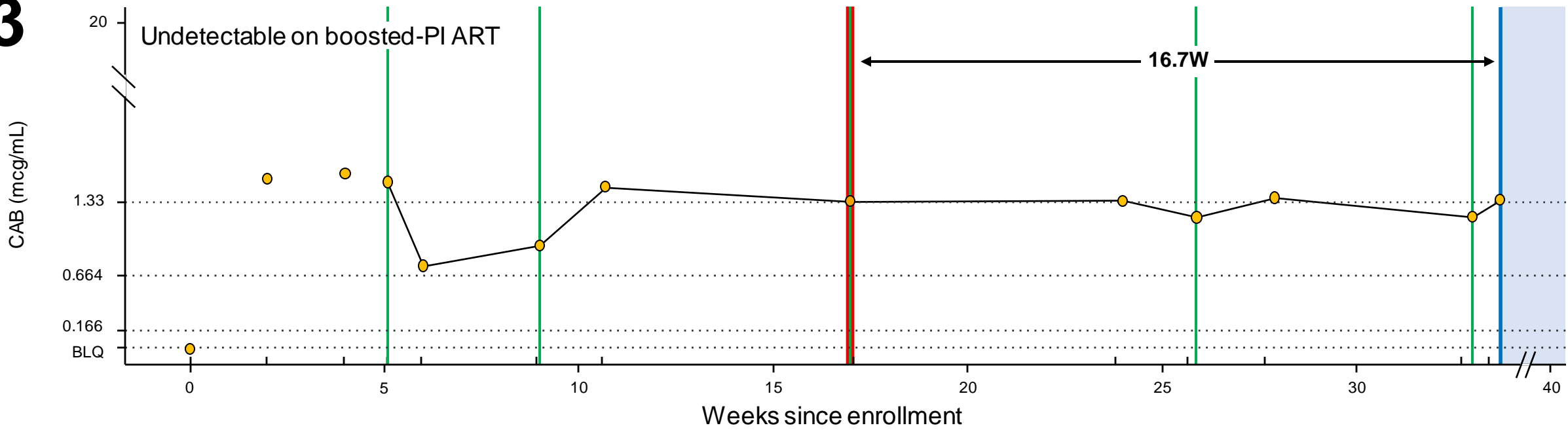
- **Delays in HIV tests detecting “new” HIV infections**
- **CAB levels in the blood were as expected**
 - **It wasn’t “unexpectedly” low concentrations of CAB that explain the PrEP failure**
- **If HIV “smolders” after a PrEP failure, it can lead to CAB (and other integrase) resistance**
 - **We do not yet know if that resistance can be avoided by earlier detection**

Ag/Ab test	-	-	-	-	-	-	-	-	-	+	+				
Qualitative RNA test	-	-	-	-	-	-	-	-	-	+	+				
Confirmatory Ab test	-	-	-	-	-	-	-	-	-	-	IND				
Viral load										860	ND	<40	112	7,160	5,510

NNRTI:
K103N

NNRTI:
K103N
INSTI:
R263K

D3



● CAB concentration
 — CAB injection
 — First site positive visit
 — First HIV positive visit
 ← # → Weeks between first HIV positive visit and the first site positive test

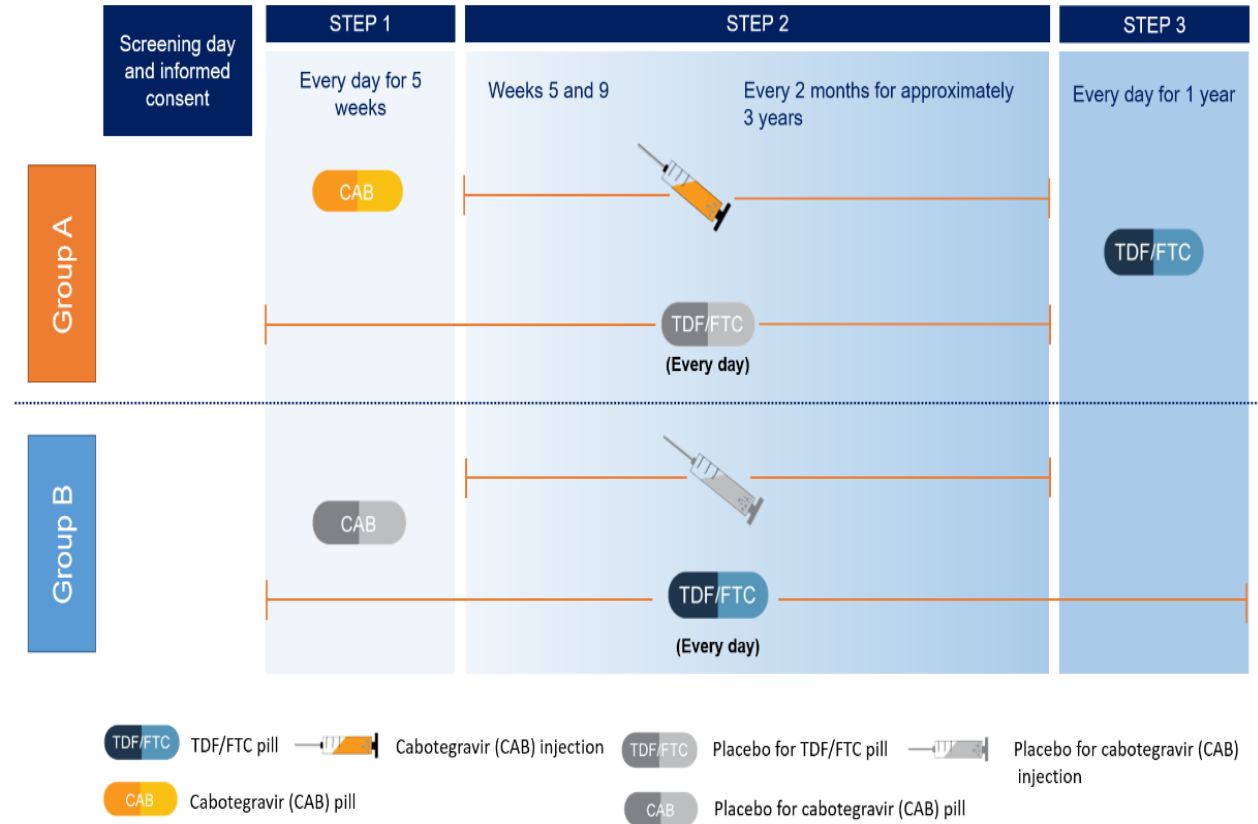
The shaded area represents time on ART.

CAB-LA vs. daily oral TDF/FTC for Women in Sub-Saharan Africa

Sinead Delaney-Moretlwe and Mina Hosseinipour, *Protocol Chairs*

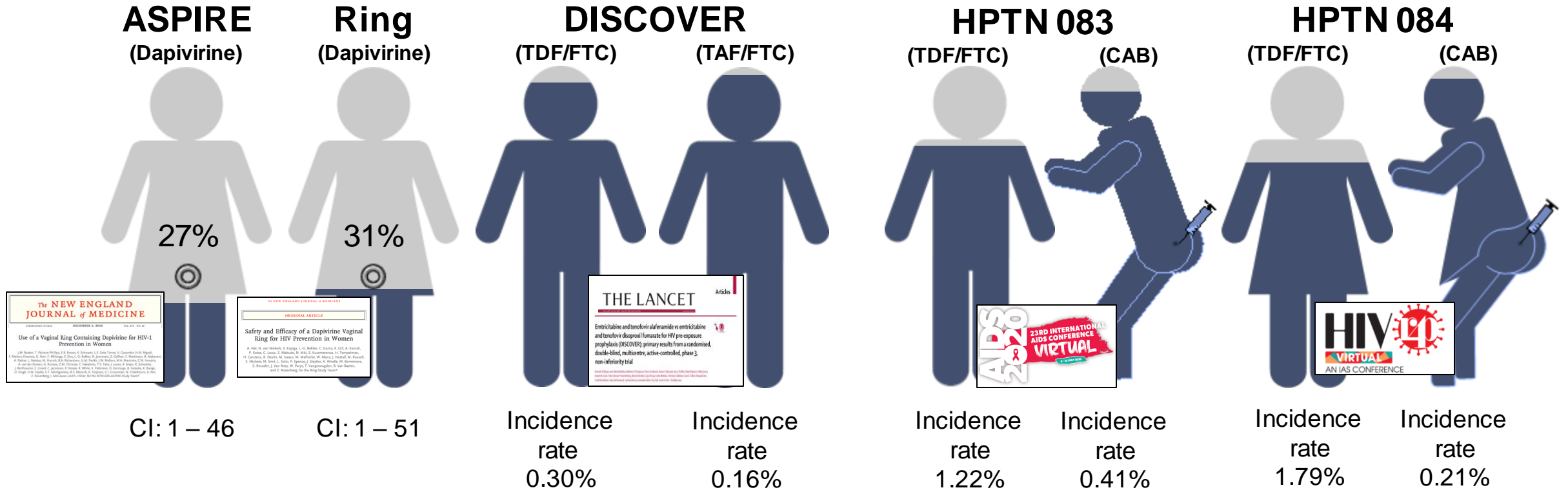


- **Primary Objective: Reduce HIV Incidence** (superiority, double blind, double dummy design)
- Endpoint-driven trial (HIV infection) – monitored by NIAID DSMB every 6 months
- Est. study duration: enrollment 24 months; follow-up up to 4.5 years
- N=3200 at 20 sites in Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe



Start Nov 2017
Blinded Study halted by DSMB November 2020

“PrEP 3.0”: Trials of Novel PrEP Agents



In advanced phase clinical trials:
Islatravir (NRTTI, monthly oral, Phase III; implant SC Phase II)
Lenacapavir (Capsid Inh, q6mos SC, Phase III)
BNABs (Antibody, ? Q6mos IV/SC, Phase I-III)

Injectable PrEP Guidance: CABOTEGRAVIR

- Optional daily oral Cabotegravir 30 mg for 1 month
- Cabotegravir 600 mg (3 mL injection, gluteal only)
- 2nd injection 4 weeks later
- 3rd and subsequent injections at 8-week intervals (the goal is to administer +/- 7 days of injection target date)
- If >7 days late, can bridge up to two months with daily oral CAB 30 mg (for longer hiatuses, alternative daily oral PrEP is recommended)
- If any injection is 4 or more weeks late, “reload” with initial 4-week interval between first 2 injections and then return to 8-week intervals

Do not use with rifampin, rifapentine, carbamazepine, oxcarbamazepine, phenytoin, or phenobarbital. Halve dosing intervals for use with rifabutin (2-week interval between first 2 injections, 4-week injections for maintenance).



BEFORE STARTING

HIV Ag/Ab test (lab-based)
HIV RNA¹
CMP²
HAV
HBsAb/HBsAg/HBcAb
HCV Ab
Rectal, Urinary, Pharyngeal GC/CT
RPR



BEFORE EACH INJECTION

HIV Ag/Ab test (lab-based) + HIV RNA

EVERY 4 MONTHS (2 INJECTIONS)

Rectal, Urinary, Pharyngeal GC/CT
RPR

PREP BREAKTHROUGH INFECTIONS ARE VERY CHALLENGING TO DETECT ON CAB PREP AND REQUIRE A VERY HIGH INDEX OF SUSPICION. CONSEQUENCES OF MISSED BREAKTHROUGH INCLUDE INSTI CLASS RESISTANCE THAT CAN COMPROMISE THE ACTIVITY OF BICTEGRAVIR AND DOLUTEGRAVIR. RECOMMEND EXPERT CONSULTATION FOR ANY REACTIVE/POSITIVE HIV TESTING RESULTS ON CABOTEGRAVIR.

When stopping injectable Cabotegravir, it is important to remember that the long-acting injectable product remains in the body at declining levels for approximately 1 year (for males) and 1.5 years (for females). If HIV risk persists, immediate transition to another potent form of HIV prevention upon discontinuation is appropriate (for example, daily oral TDF/FTC).

1. The most sensitive viral load test available at your institution

2. Not part of FDA/CDC guidelines, but clinically makes sense to have baseline values before starting a new, recently approved medication

Key Thoughts

- **In these trials, CAB-LA and TDF/FTC were both highly effective for HIV prevention**
- **CAB-LA was superior to daily oral TDF/FTC for HIV PrEP in HPTN 083 and HPTN 084**
- **This seems to be due to better “coverage” of sex acts with the injectable product**
 - **Adolescent bridging studies ongoing**
 - **Oral lead-in will be optional in OLEs**
 - **Use of VL testing as a primary screen for HIV infection will be assessed in OLEs**
 - **In the setting of CAB-LA, prompt diagnosis and ART initiation are needed to avoid resistance**
 - **If we can create COVID19 vaccines in a year, can we challenge the global community to make better diagnostics by the time CAB is available?**

Acknowledgments

Sponsor

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HIV Prevention Trials Network (HPTN)

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- Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutchinson Cancer Research Center
- Leadership and Operations Center, FHI 360
- HPTN Leadership

Pharmaceutical Support

- ViiV Healthcare
- Gilead Sciences, Inc.

HPTN 083 Study Team

Community Program Managers Community Educators & Recruiters, CAB Members

Our 43 Sites in 7 countries

...our Study Participants



Questions? Email rlandovitz@mednet.ucla.edu or

[@doc_in_a_box](https://twitter.com/doc_in_a_box)



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