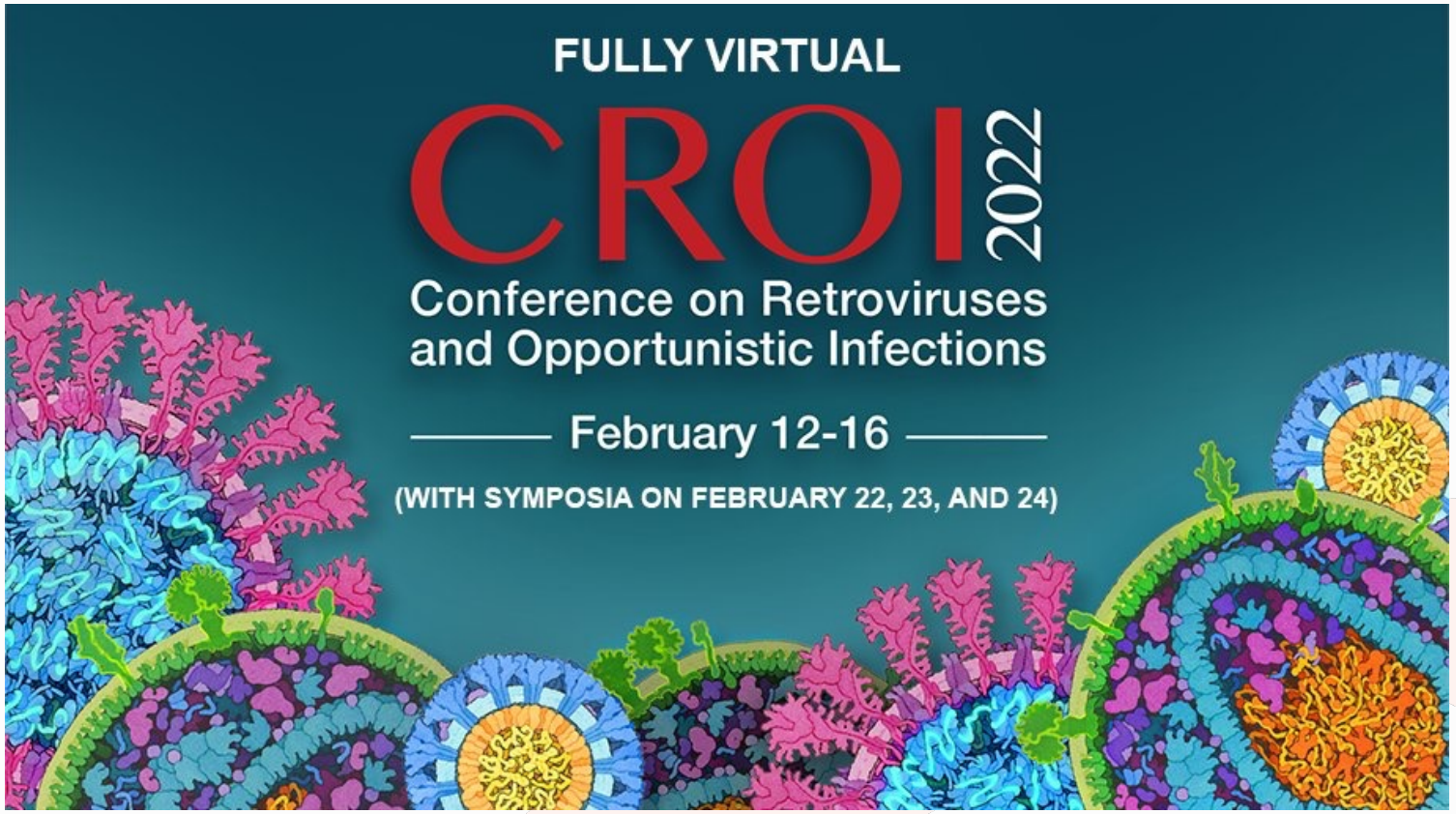
AETC AIDS Education & Training Center Program Northeast/Caribbean



John Faragon, PharmD

ALBANY MED

Disclosures

“This program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,845,677 with zero percentage financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.”

Disclosures

- Past 24 months
- J Faragon has disclosed:
  - Gilead speaker/advisory
  - ViiV advisor
  - Thera advisor
  - Merck speaker
  - Janssen speaker/advisory

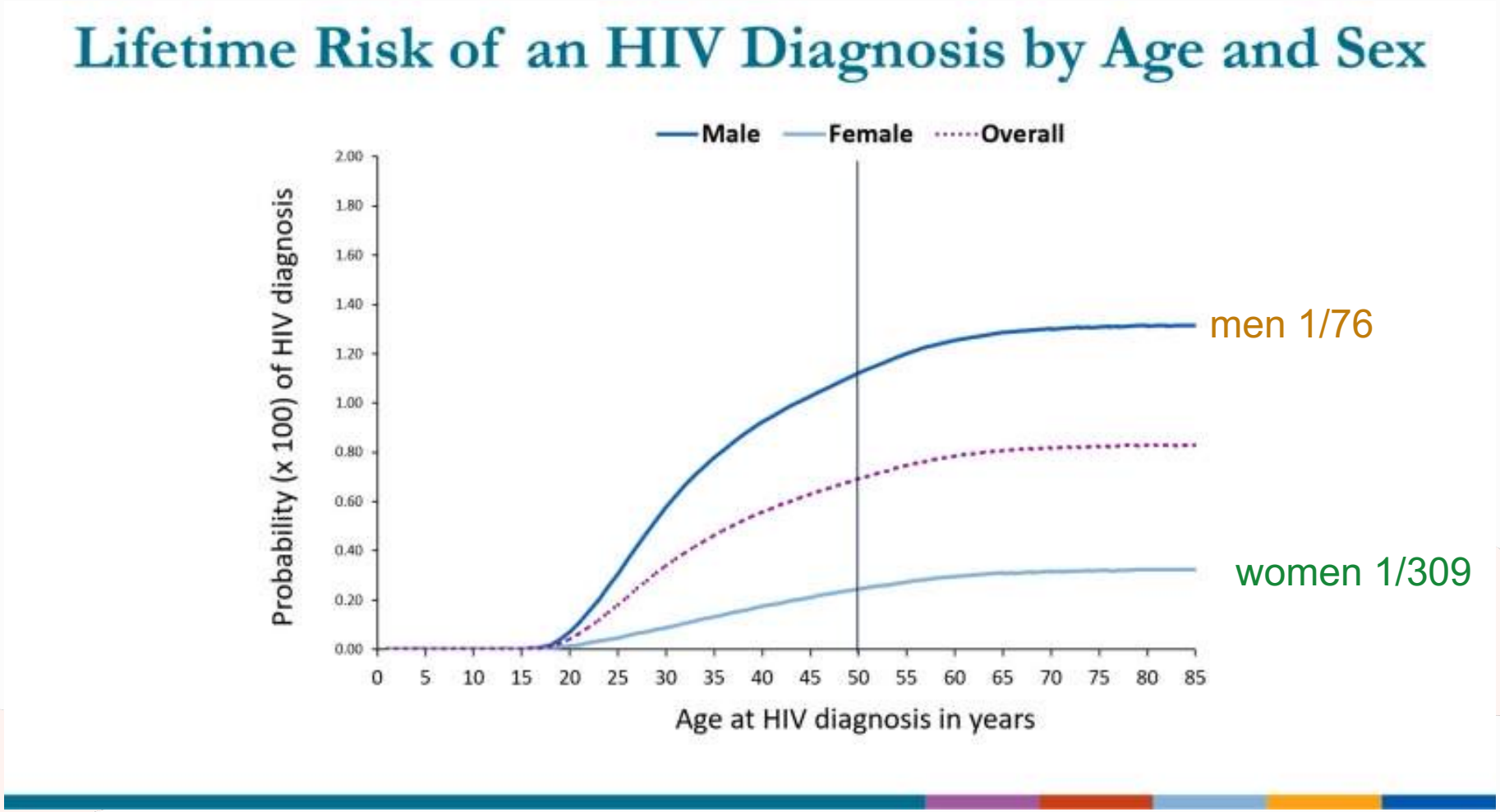
Overview

- Update on epidemiology of HIV in the U.S.
- Antiretrovirals—treatment and PrEP
- HIV “cure” case
- Miscellaneous, PK, etc
- COVID-19 prevention/treatment

EPIDEMIOLOGY/STATS

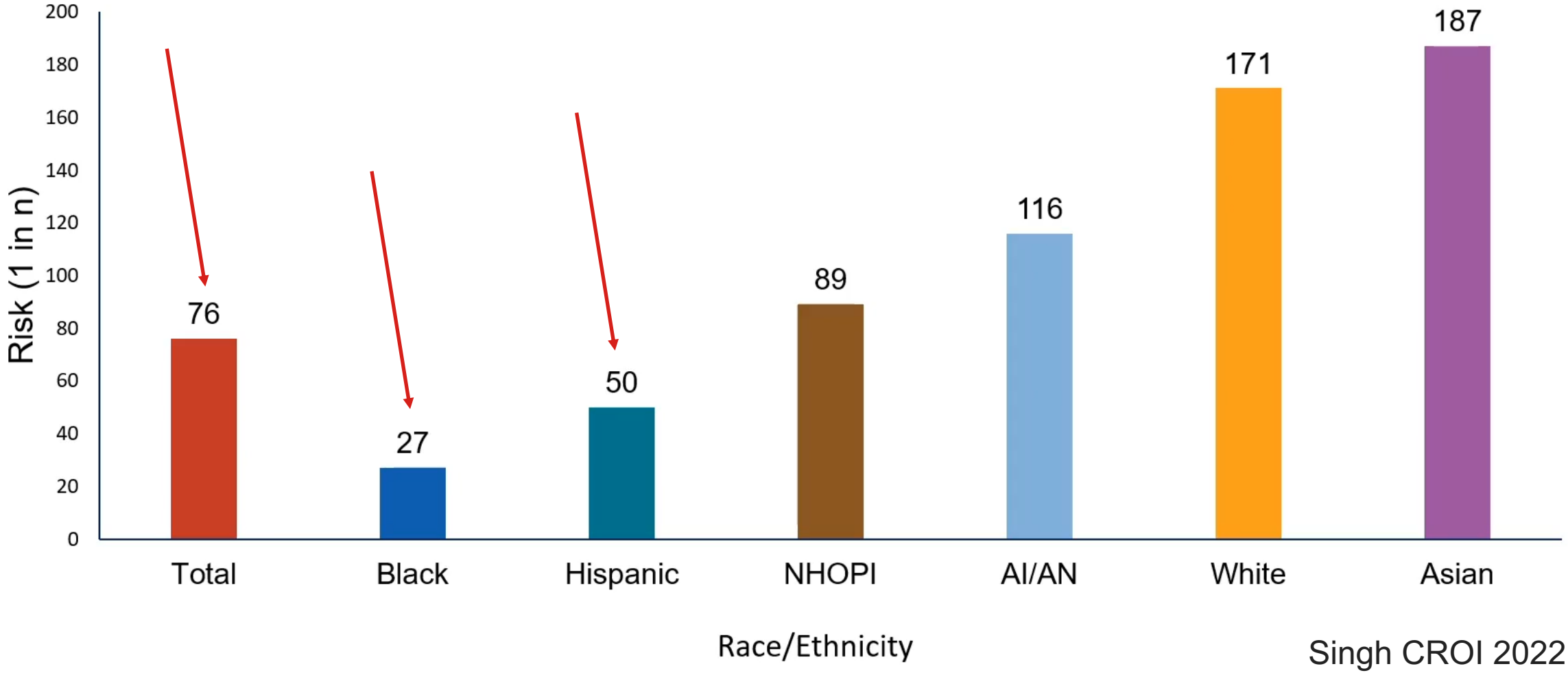
CDC: Lifetime Risk of HIV in U.S.

- National HIV Surveillance System (NHSS)
  - Previous estimate: 2010-2014
  - Updated to: 2017-2019
- Lifetime risk for U.S. resident **1/120** (previously 1/106: **11%↓**)



Lifetime Risk of an HIV Diagnosis Among Males

Assuming 2017-2019 Diagnosis Rates Continue

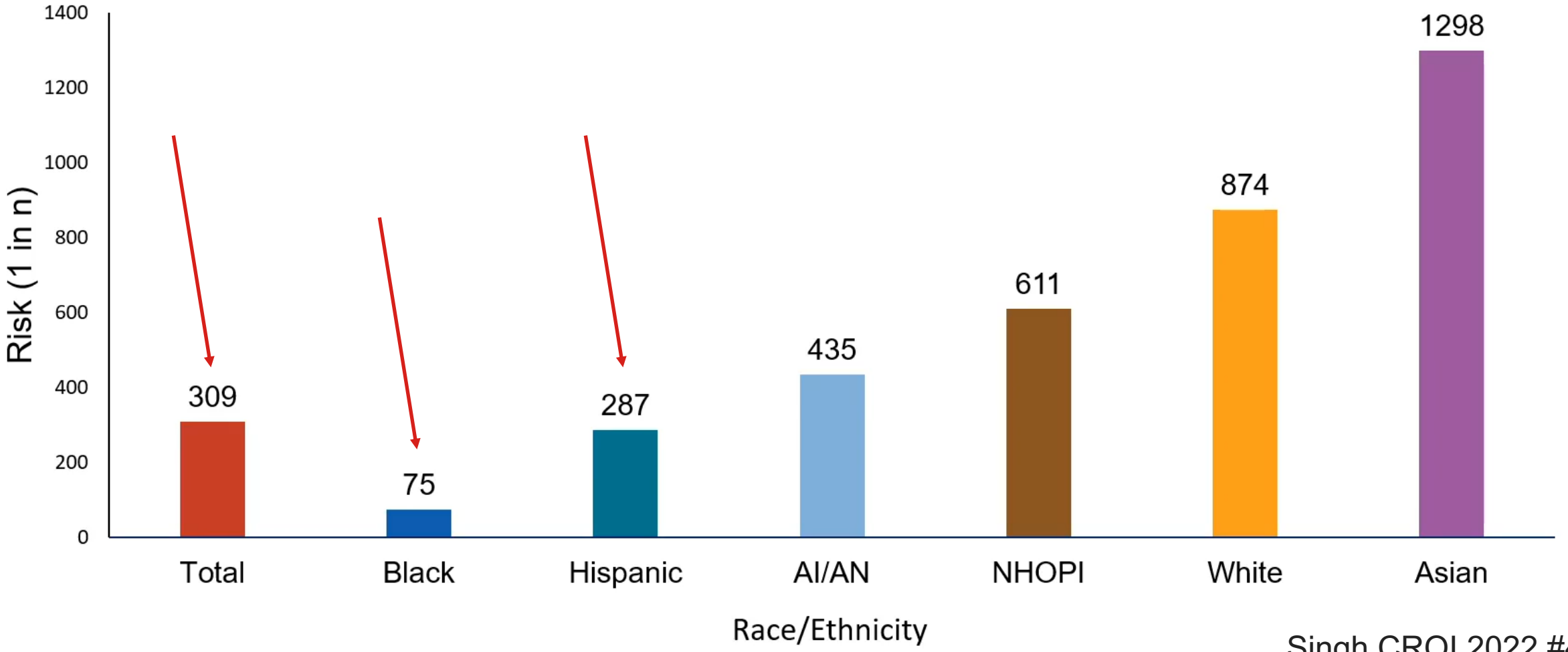


Singh CROI 2022 #43

AI/AN = American Indian/Alaskan Native; NHOPI = Native Hawaiian/Other Pacific Islander

Lifetime Risk of an HIV Diagnosis Among Females

Assuming 2017-2019 Diagnosis Rates Continue



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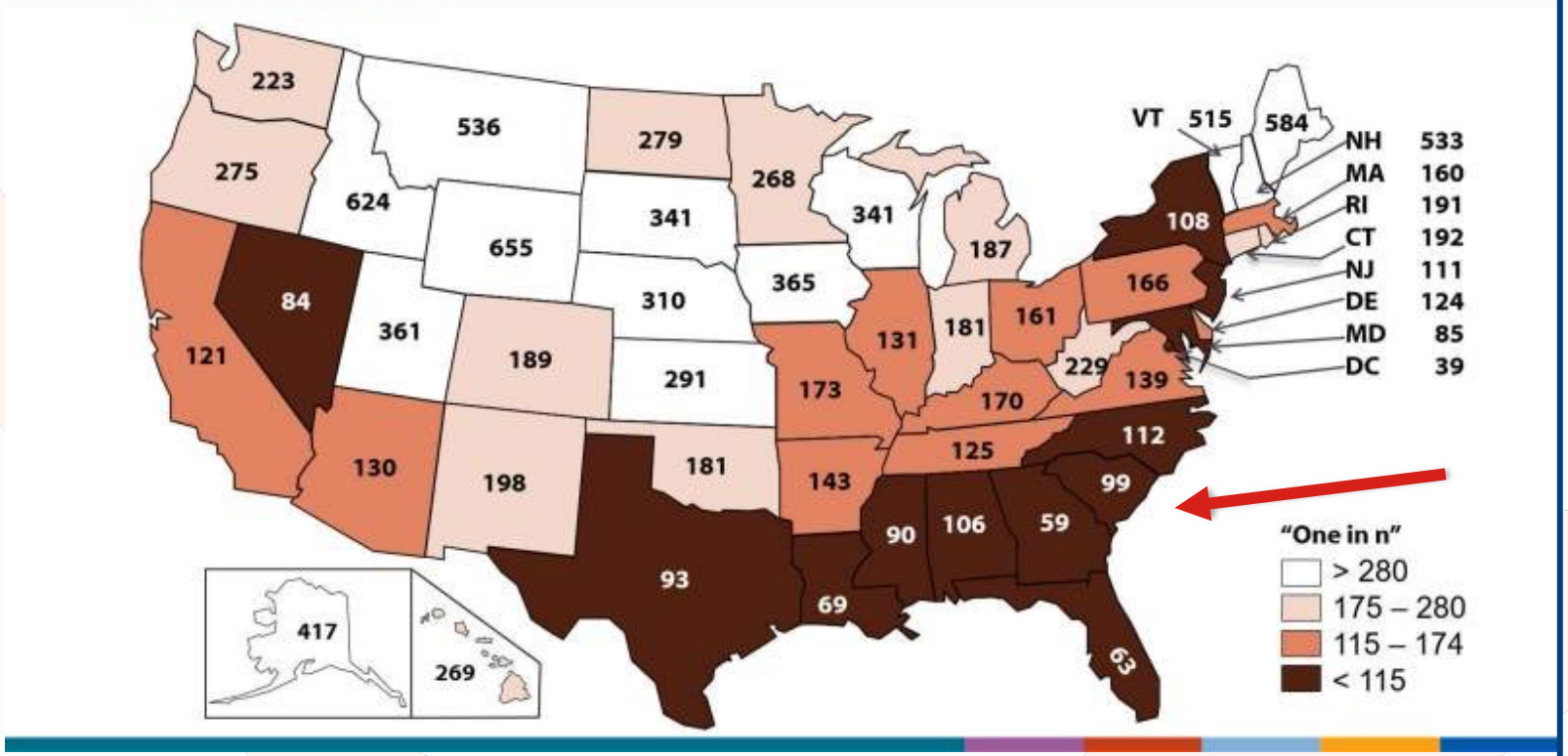
AI/AN = American Indian/Alaskan Native; NHOPI = Native Hawaiian/Other Pacific Islander

CDC: Lifetime Risk of HIV in U.S.



- **<u>9 of 10 areas</u> of residence with highest risk are in <u>South</u>**
- Lifetime risk has decreased vs 2010-14 analysis
- Disparities persist by sex and race/ethnicity
- May be a useful tool to communicate burden of HIV overall and in specific communities

HIV TREATMENT

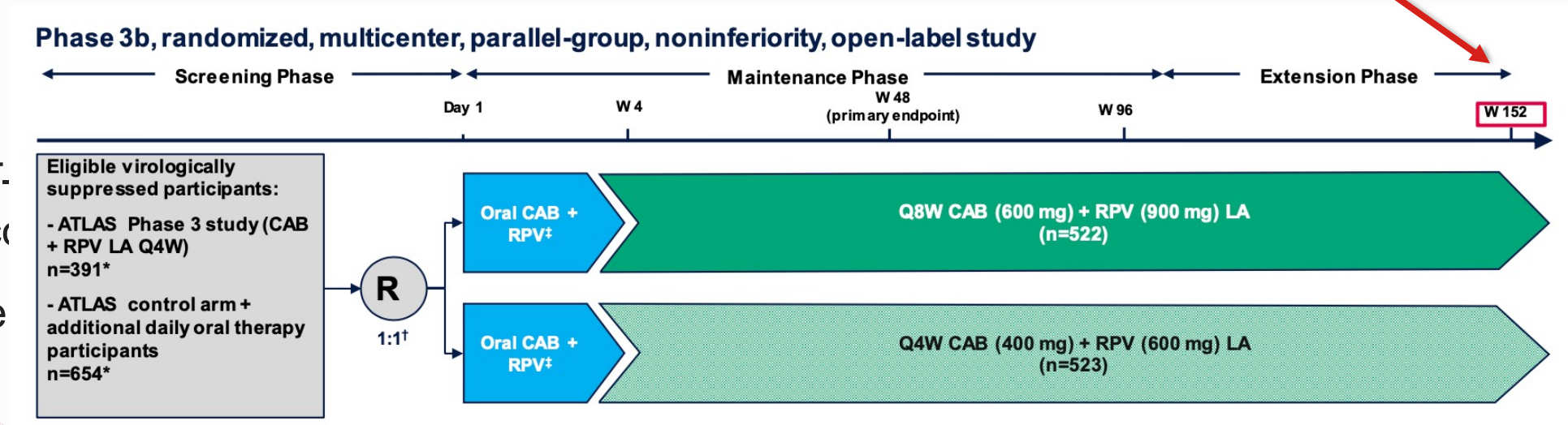
ATLAS 2M

- Long-acting cabotegravir + rilpivirine administered monthly or every 2 months now FDA approved
- Reduced dosing frequency compared with daily oral antiretroviral therapy
- Noninferior efficacy of CAB + RPV was demonstrated between monthly dosing and oral comparator ART, as well as between every 2 months and monthly dosing
- 3 year efficacy, safety of CAB + RPV LA monthly and every 2 months dosing from the Phase 3b ATLAS-2M study presented

Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M Design

- Primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (FDA Snapshot)



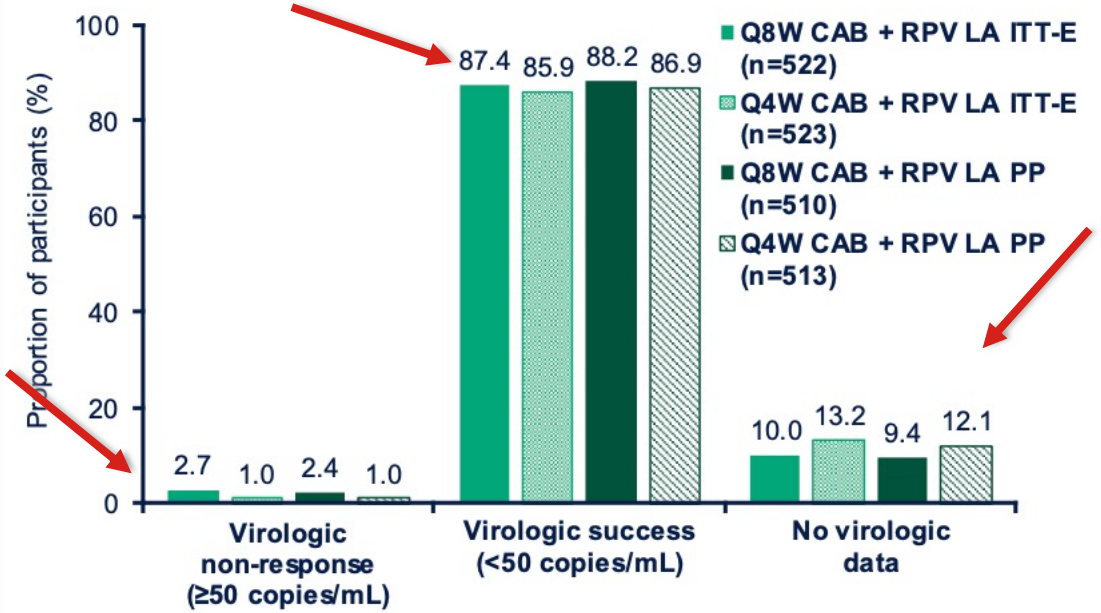
- ITT-
- Seco 50 or <50
  - Pe eek 96, and

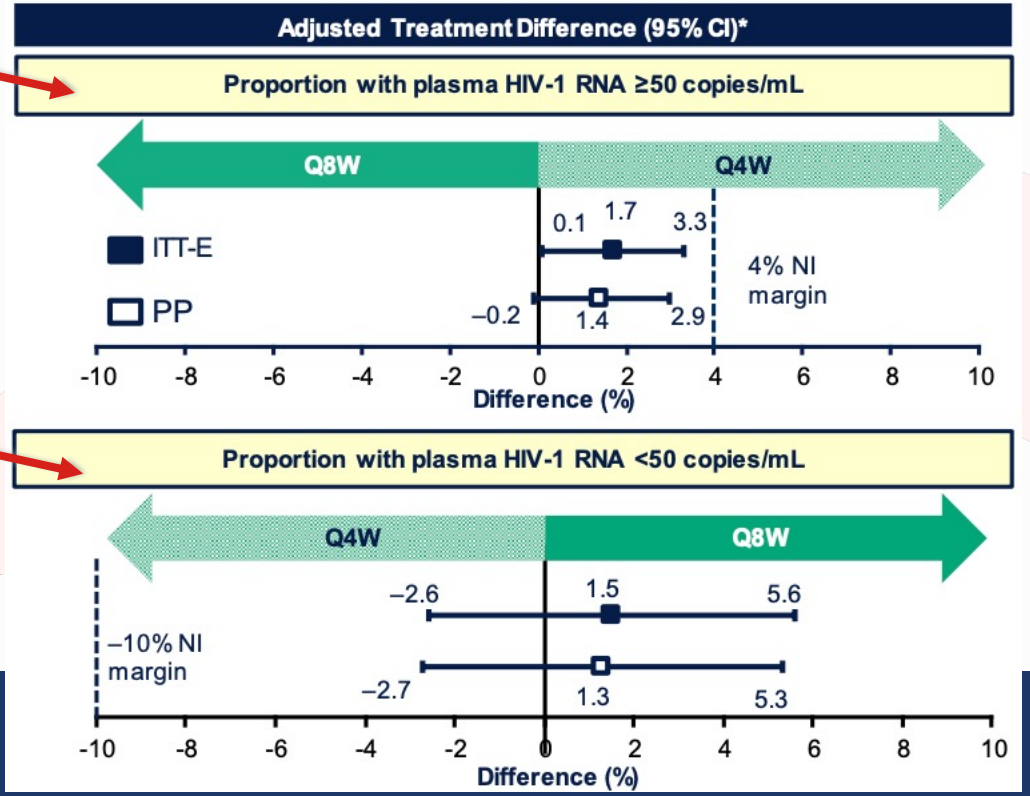
- Other endpoints assessed at Week 152 included the incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA levels ≥200 copies/mL), incidence of viral resistance in participants with CVF, safety and tolerability, and treatment satisfaction

Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M

- Noninferiority between Q8W and Q4W was confirmed for pre-specified analyses of HIV-1 RNA ≥50 and <50 copies/mL
- Results for the pre-specified per-protocol population were consistent with those for the ITT-E population





Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 copies/mL	456 (87)	449 (86)
HIV-1 RNA ≥50 copies/mL	14 (3)	5 (1)
Data in window not below threshold	1 (<1)	0 (0)
Discontinued for lack of efficacy	12 (2)	4 (1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)
No virologic data	52 (10)	69 (13)
Discontinued study due to AE or death*	23 (4)	24 (5)
Discontinued study for other reason†	28 (5)	44 (8)†
On study but missing data in window	1 (<1)‡	1 (<1)

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
Discontinued study for other reason	28 (5)	44 (8)
Withdrawal by participant	16 (2)*	33 (6)
Physician decision†	5 (1)	3 (<1)
Protocol deviation	2 (<1)	4 (<1)
Protocol-specified withdrawal criterion met‡	2 (<1)	3 (<1)
Lost to follow-up	2 (<1)	1 (1)
Lack of efficacy	1 (<1)	0 (0)

- Withdrawal by participant more common in the Q4W arm
- The most common reasons for withdrawal by participant included frequency of visits (Q8W, n=4; Q4W, n=10), participant relocated (Q8W, n=1; Q4W, n=6), and intolerability of injections (Q8W, n=1; Q4W, n=8)

Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M

- 2 participants (Q8W arm) met the CVF criterion between Week 96 and 152 (Week 112 and Week 120)
  - Neither had RAMs at baseline
  - Participant with subtype A6 had L74I polymorphism at baseline
  - Treatment-emergent RAMs to CAB (Q148R) and RPV (E138A+Y181Y/C; E138A+M230M/L)

Participants With CVF Since Week 96					
#, arm	Sex at birth, BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at failure (copies/mL)	RPV RAMs observed at failure	INI RAMs observed at failure
1, Q8W	Male, <30, Germany	B	24,221	E138A+M230M/L	Q148R
2, Q8W	Male, <30, Russia	A6*	59,467	E138A+Y181Y/C	Q148R

Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M – Confirmed Virologic Failures through 152 weeks

- 13 participants had CVF
  - Q8W, n=11 (2%); Q4W, n=2 (<1%)
- Most CVFs occurred by Week 48 (77%,n=10/13)
  - 6/10(60%) having ≥ 2 baseline factors
  - Proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m2), associated with failure
- No participants with CVF through Week 152 had injection visits >7days later than the scheduled visit date
- 12/13 CVFs resuppressed on alternative regimens

Overton, et al. CROI 2022; Virtual Poster 479.

ATLAS 2M – Safety/ADRs

- Safety profiles consistent with the previous analyses, with no new significant safety information observed
- Since Week 96, excluding ISRs, there were two participants with drug-related AEs leading to withdrawal (both Q4W, lipoatrophy and pyrexia); no drug-related serious AEs
- ISRs most common AEs; most were mild to moderate in severity (99%, n=9555/9662), short-lived (median duration 3 days), with few participants discontinuing due to injection-related reasons
- 3 participants withdrew due to injection-related reasons between Week 96 and Week 152 (Q8W, n=1; Q4W, n=2)

Overton, et al. CROI 2022; Virtual Poster 479.

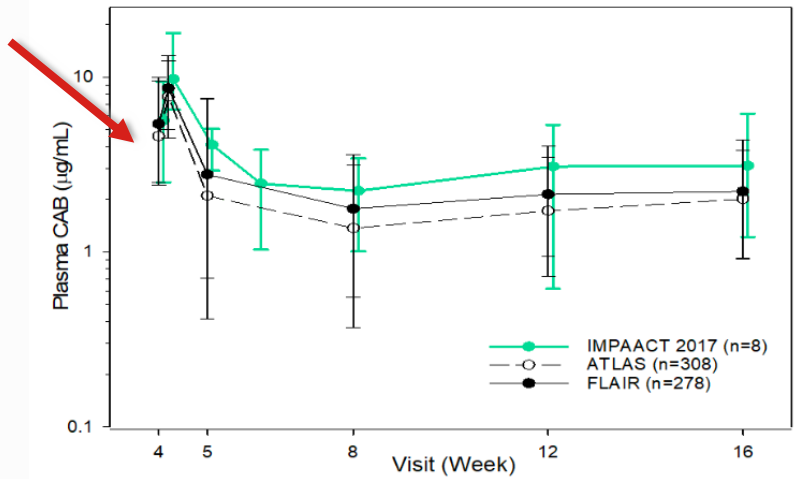
ATLAS 2M – 152 Week Summary

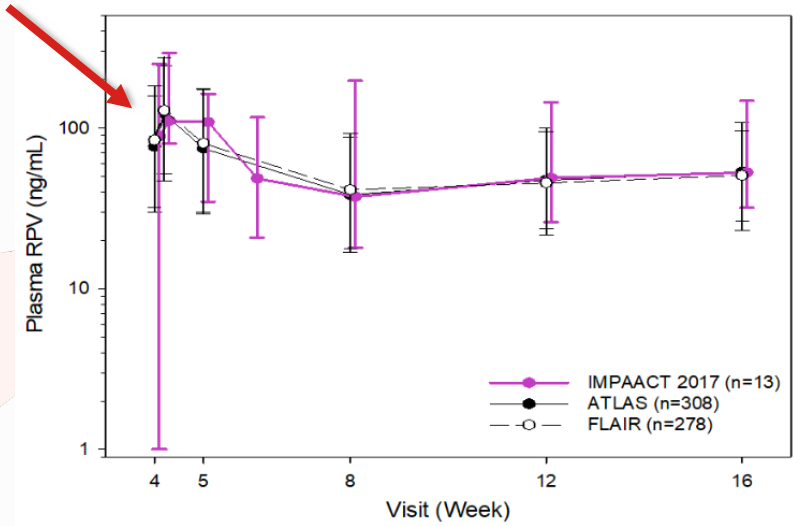
- CAB + RPV LA Q8W continued to be noninferior to Q4W at Week 152
  - Both regimens maintaining high levels of virologic suppression (86–87%)
- Through Week 152, the overall rate of CVF was low (1%, n=13/1045)
  - 2 additional participants (Q8W arm) meeting the criterion after Week 96.
- 11/13 participants developed resistance to CAB and/or RPV; 12/13 resuppressed on an alternative treatment regimen (one participant was non-adherent to PI-based ART)
- CAB + RPV LA was well tolerated, with a comparable safety profile between arms
- No new safety signals were identified since the Week 48 analysis
- ISRs were mostly Grade 1–2 (99%), short-lived (median 3 days), with few discontinuations (2%) due to injection-related reasons

Overton, et al. CROI 2022; Virtual Poster 479.

Adolescent Data: CAB/RPV

- IMPAACT 2017 (MOCHA)
  - Phase I/II non-comparative, open-label study
  - Adolescents, ≥12 to <18 years, virologically suppressed
- 4 weeks of oral lead-in with CAB 30mg once daily or RPV 25mg once daily, then CAB-LA (600mg/3mL at Week 4, 400mg/2mL at 8/12 weeks) or RPV-LA (900mg/3mL at Week 4, 600mg/2mL at 8/12 weeks
- IM administration of CAB-LA or RPV-LA in adolescents achieved target exposure concentrations comparable adults receiving monthly intra-muscular dose

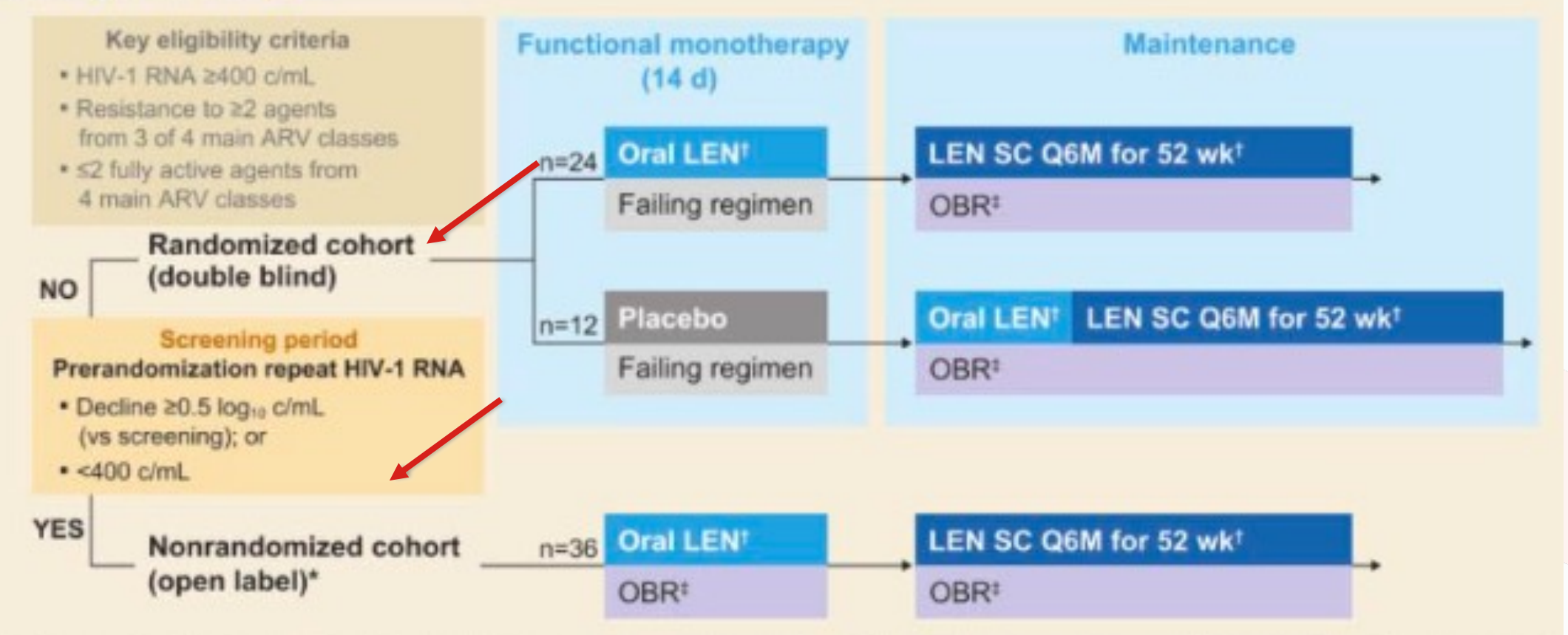




- This Week!
- FDA approved in virologically suppressed adolescents 12 years of age or older, at least 35 kg, stable regimen
- No history of treatment failure, no known/suspected resistance to cabotegravir or rilpivirine

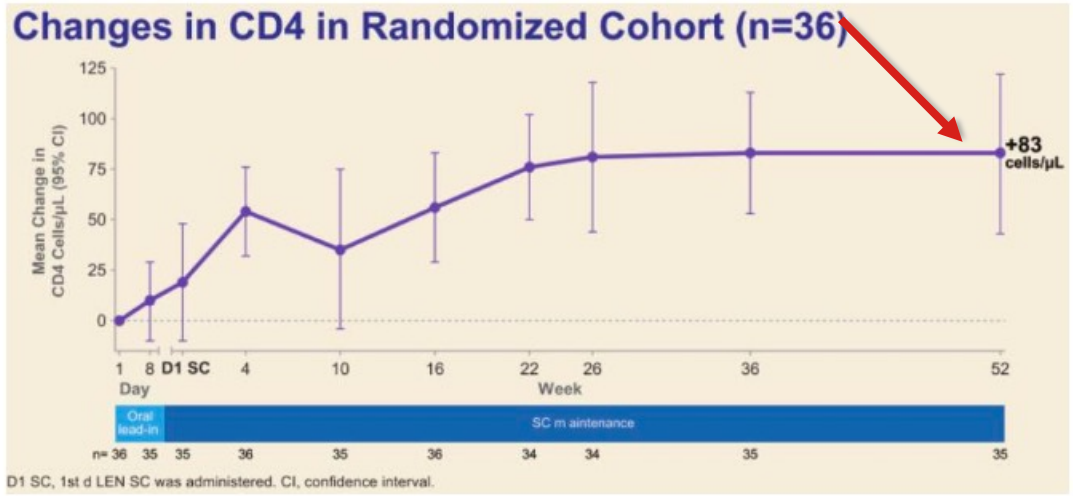
Moore, et al. CROI 2022; Virtual Poster 738., FDA March 2022

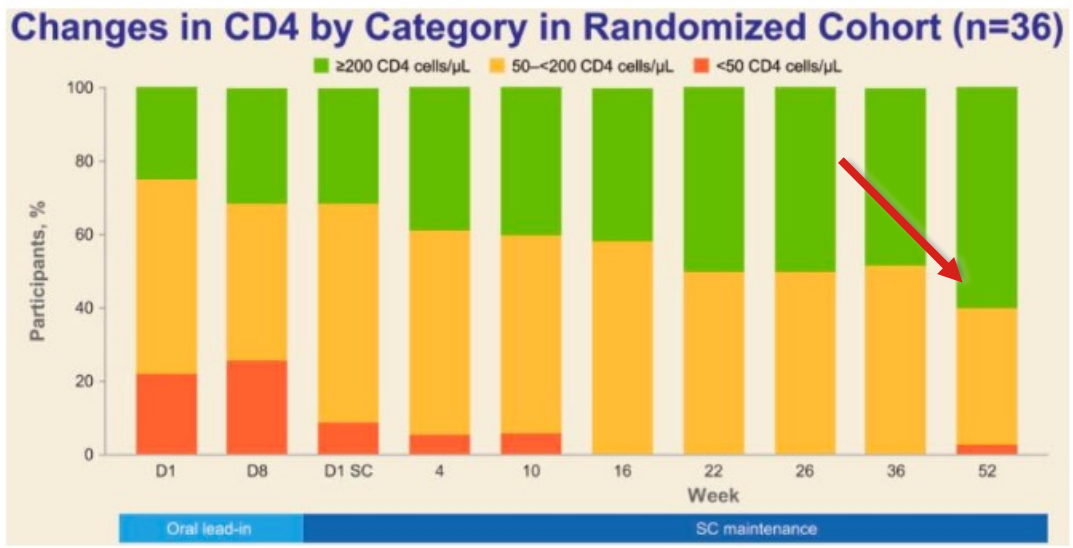
Lenacapavir, 52 week data, CAPELLA

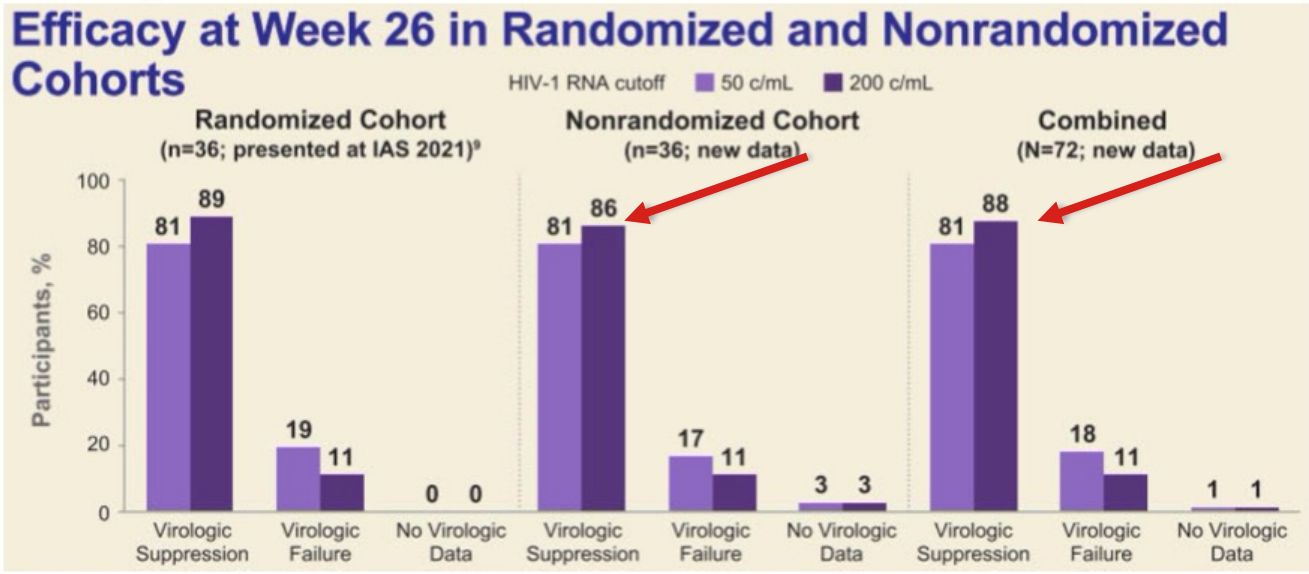


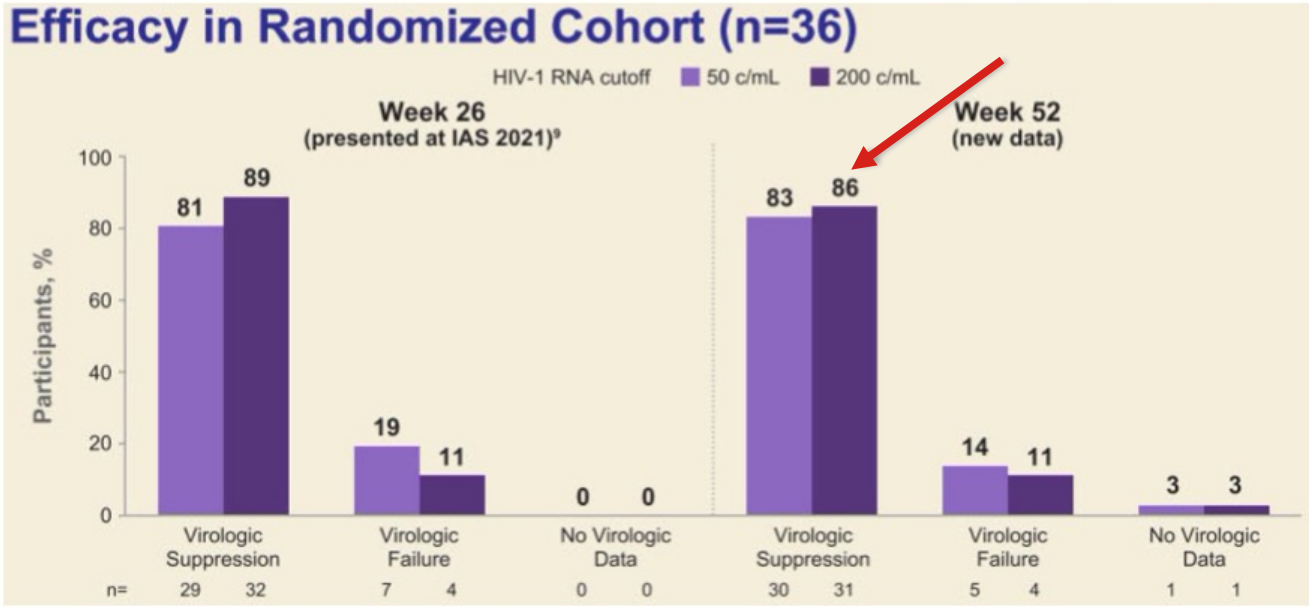
Ogbuagu et al. CROI 2022; Virtual Poster 491.

Lenacapavir, 26/52 week data CAPELLA









Ogbuagu et al. CROI 2022; Virtual Poster 491.

Lenacapavir, 52 Week, CAPELLA

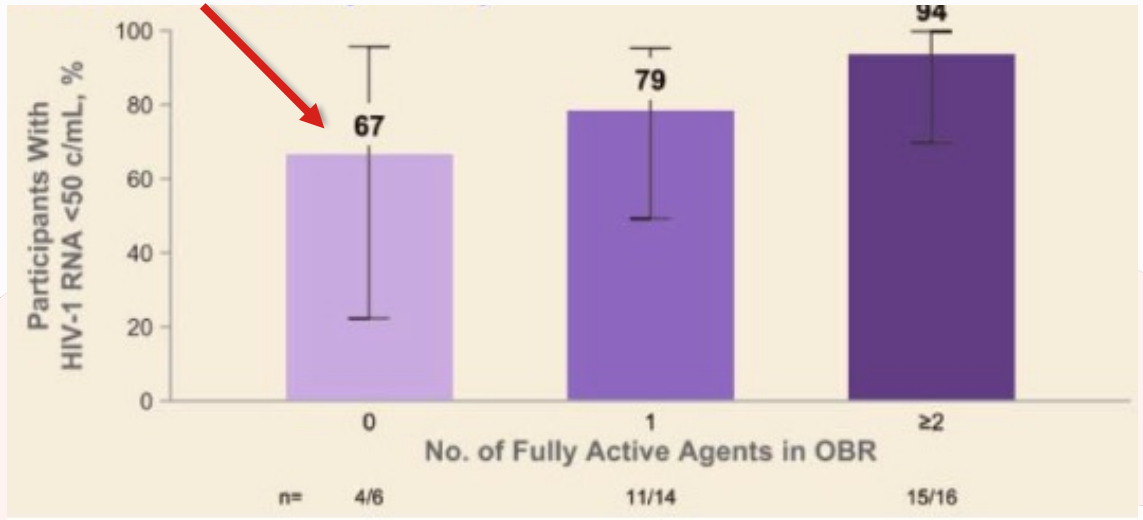
Safety

- Median (IQR) duration of follow-up: 376 (306, 501) days
- No serious AEs related to study drug; 1 participant with serious AE of malignant neoplasm with a fatal outcome that was not related to study drug
- No grade 4 ISRs; 2 participants with grade 3 ISRs: 1 participant with swelling and erythema that resolved in 4 and 8 days, respectively; 1 participant with pain that resolved in 1 day
- 1 participant had 2 AEs of grade 2 nodules, each after 2nd and 3rd injections (both resolved after 3 days)
- 1 participant discontinued study drug at Week 52 due to ISR (nodule; grade 1)
- No grade 3 or 4 laboratory abnormalities were clinically relevant

Incidence of ISRs Related to SC LEN*

ISR Types, %	After 1st SC Dose at Week 1 N=72	After 2nd SC Dose at Week 26 n=70	Median Duration, d
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

*Only includes AEs related to LEN and excludes those not related to it.



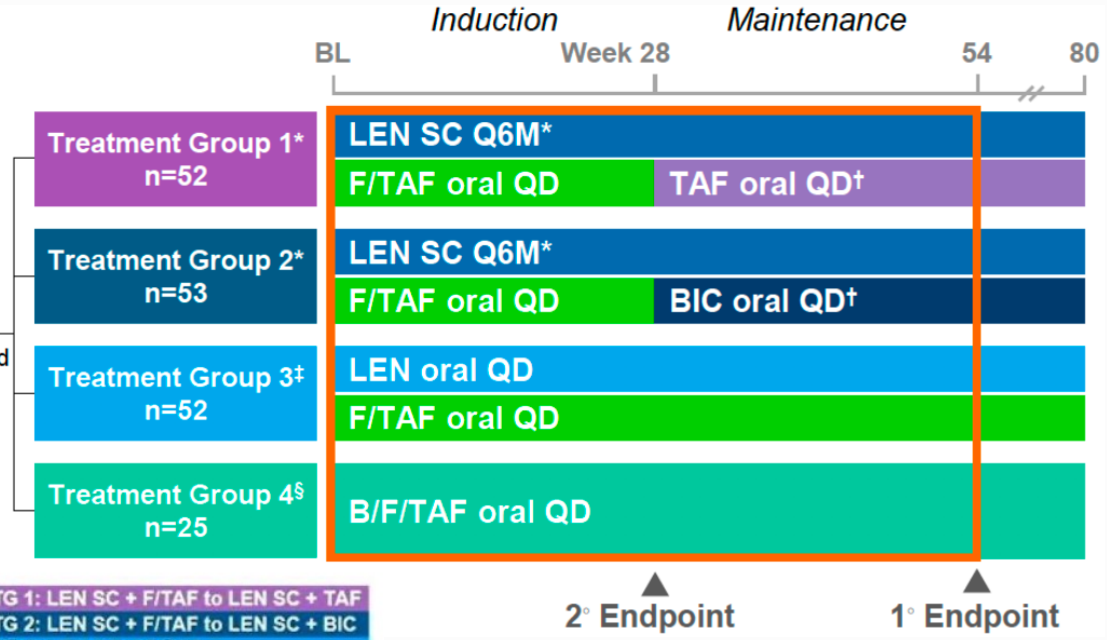
Ogbuagu et al. CROI 2022; Virtual Poster 491.

Lenacapavir, Naives CALIBRATE

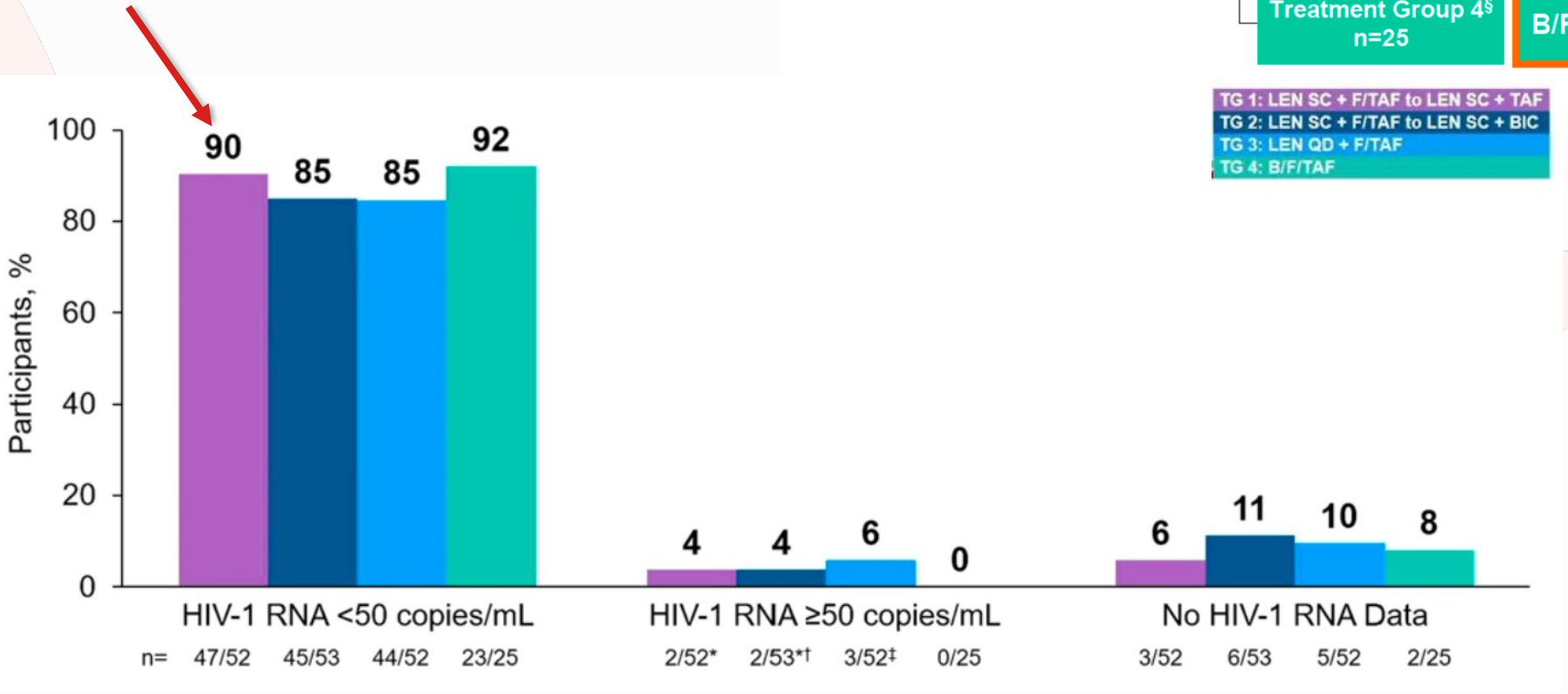
Treatment naïve
N=182

Key eligibility criteria:
- ARV naïve
- HIV-1 RNA ≥200 copies/mL
- CD4+ cell count ≥200 cells/μL

Open label
Randomized



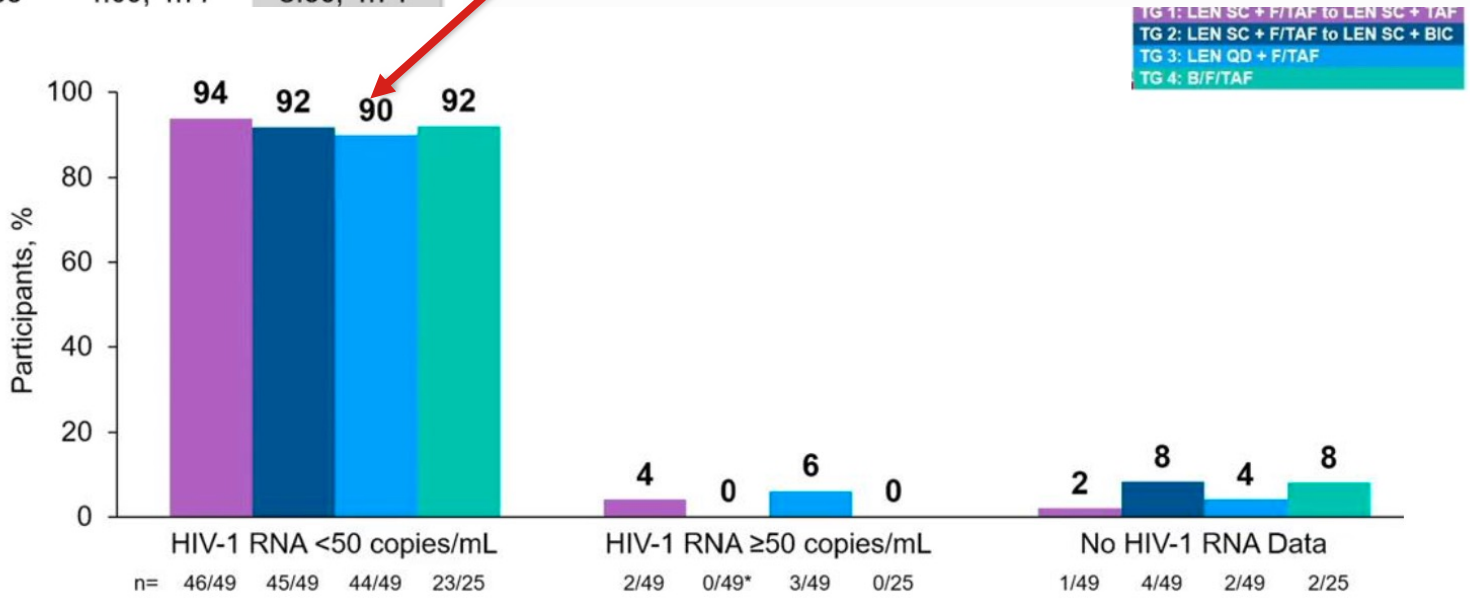
TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF



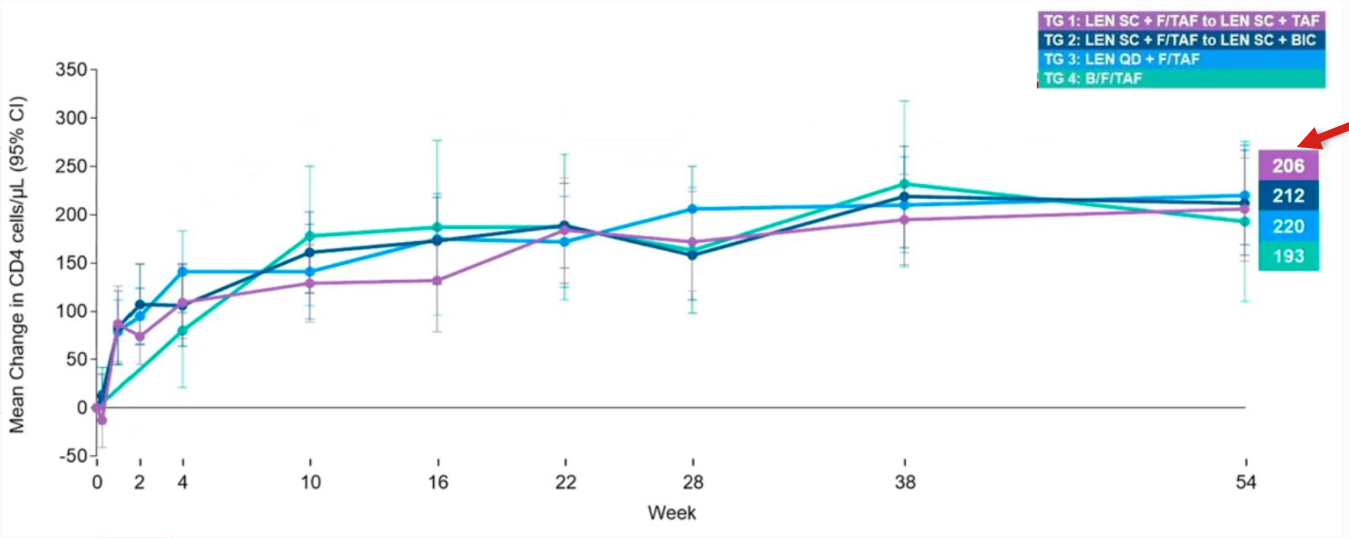
Lenacapavir CALIBRATE, Naives

	LEN Total			B/F/TAF	
	TG 1 n=52	TG 2 n=53	TG 3 n=52	TG 4 n=25	Overall N=182
Age, median (range), years	31 (19, 61)	28 (19, 56)	28 (19, 72)	29 (21, 61)	29 (19, 72)
Sex, % female at birth	10	2	12	0	7
Race, % Black	46	45	60	64	52
Ethnicity, % Hispanic/Latinx	48	40	46	48	45
HIV-1 RNA, median log_{10} copies/mL	4.27	4.32	4.53	4.37	4.37
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.86, 4.74
>100,000 copies/mL, %	10	17			
CD4 count, median cells/μL	404	450			
Q1, Q3	320, 599	332, 599			
<200 cells/μL, %	0	2			

- Among participants virologically suppressed at Week 28



Lenacapavir CALIBRATE, Resistance, ISRs



ISR Types*	After 1st SC Dose at Week 1 n=103†	After 2nd SC dose at Week 26 n=95†	Median duration (days)
Swelling	14%	12%	11
Erythema	14%	18%	5
Pain	15%	9%	4
Nodule	11%	8%	195
Induration	9%	6%	202

- Emergent LEN resistance in 2/157(1.5%) participants
- One participant in TG2 developed Q67H+K70R (LEN fold change=20) Week10, preceded by M184M/I
  - Pattern of mutation emergence suggests incomplete adherence to F/TAF
- One participant in TG3 developed Q67H (LEN fold change=7) at Week 54
  - Nonadherence to F/TAF as assessed by pill count and drug levels
- Both participants later re-suppressed on a regimen of INSTI + 2 NRTI

LEN Summary

- In treatment-naïve PWH, SC LEN, initially in combination with F/TAF and later with oral TAF or BIC, achieved and maintained high rates of virologic suppression through 1 year (90% and 85%, respectively)
- Oral LEN in combination with F/TAF had similar efficacy (85%)
- LEN was well tolerated; discontinuations due to adverse events were infrequent
- These Phase 2 data support the ongoing evaluation of LEN for treatment and prevention of HIV-1 infection
  - In heavily treatment-experienced PWH in the ongoing CAPELLA study
  - In treatment-naïve and -experienced PWH in combination with other agent(s)
  - In people who could benefit from pre-exposure prophylaxis (PrEP)

SALSA – Archived Resistance and Response to DTG/3TC

- Adults with VL <50 c/mL for ≥6 months without evidence of virologic failure were randomized to DTG/3TC FDC or continued CAR.
- The primary population assessed here was the PRAP (proviral resistance analysis population)
- PRAP is defined as all participants in the intention-to-treat–exposed (ITT-E) population having
  - **BL proviral genotype data**
  - **at least one post-BL on-treatment VL result**
  - **and not meeting protocol deviation criteria**

Underwood, et al. CROI 2022; Virtual Poster 481.

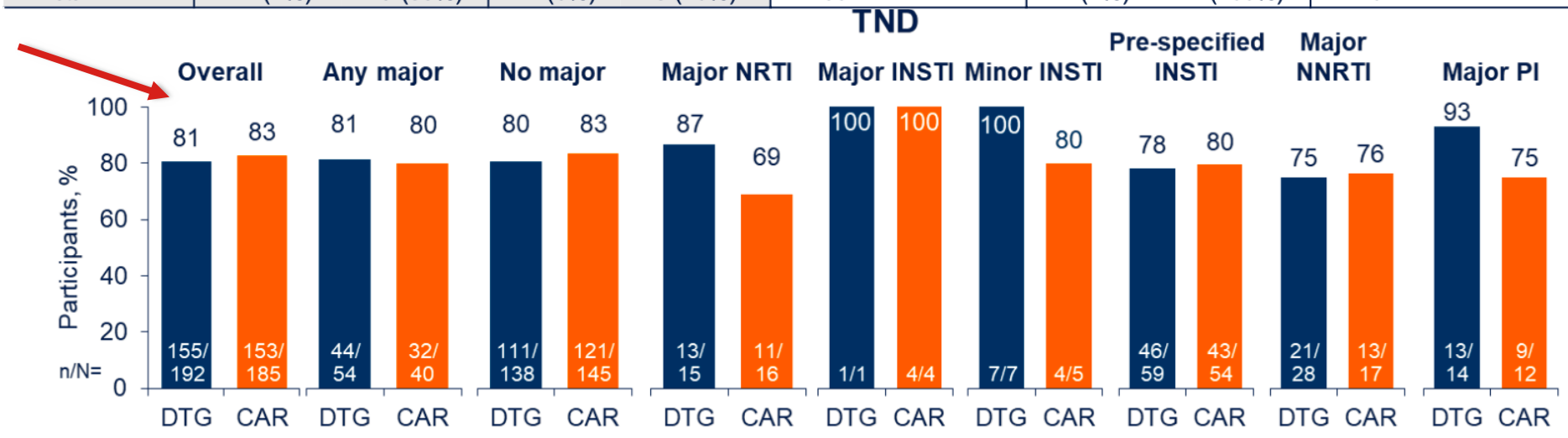
SALSA – Archived Resistance and Response to DTG/3TC

- Of 246 and 247 participants randomized to the DTG/3TC and CAR arms, respectively
  - BL proviral DNA genotypes were generated for 196/224 and 189/216 available samples
    - Of these with BL genotypes, 192/196 and 185/189 fit PRAP criteria
- Frequency of any overall major class resistance was similar across treatment arms with 54/192 (28%) receiving DTG/3TC vs 40/185 (22%) receiving CAR
- M184V/I – 3% frequency across both DTG/3TC and CAR arms
  - M184V/I with ≥1 major resistance mutation for DTG/3TC in 2 pts and for CAR in 3 pts
- For M184V/I in the DTG/3TC and CAR arms, respectively, 4/5 vs 3/5 had VL <40 c/mL and TND
- In the respective DTG/3TC and CAR arms, VL <40 c/mL and TND was observed for 1/1 and 4/4 in those with major INSTI mutations, and for 8/8 and 4/5 in those with minor INSTI mutations

Underwood, et al. CROI 2022; Virtual Poster 481.

SALSA – Archived Resistance and Response to DTG/3TC

Mutation[a]	DTG/3TC (N=192)		CAR (N=185)		Mutation	DTG/3TC (N=192)		CAR (N=185)	
Category	n (%)[b]	TND (%)[c]	n (%)	TND (%)	Category	n (%)	TND (%)	n (%)	TND (%)
NRTI Total[d]	15 (8%)	13 (87%)	16 (9%)	11 (69%)	INSTI Major Total[d]	1 (<1%)	1 (100%)	4 (2%)	4 (100%)
Any TAM[e]	7 (4%)	6 (86%)	5 (3%)	4 (80%)	Y143H	1 (<1%)	1 (100%)	2 (1%)	2 (100%)
A62V	5 (3%)	4 (80%)	4 (2%)	3 (75%)	Q148R	0	NA	1 (<1%)	1 (100%)
M184V	5 (3%)	4 (80%)	4 (2%)	2 (50%)	Y143C	0	NA	1 (<1%)	1 (100%)
M184I	0	NA	1 (<1%)	1 (100%)	INSTI Minor Total[d]	8 (4%)	8 (100%)	5 (3%)	4 (80%)
NNRTI Total[f]	28 (15%)	21 (75%)	17 (9%)	13 (77%)	T97A	3 (2%)	3 (100%)	5 (3%)	4 (80%)
PI Total[f]	14 (7%)	13 (93%)	12 (6%)	9 (75%)	E138K	2 (1%)	2 (100%)	0	NA



Underwood, et al. CROI 2022; Virtual Poster 481.

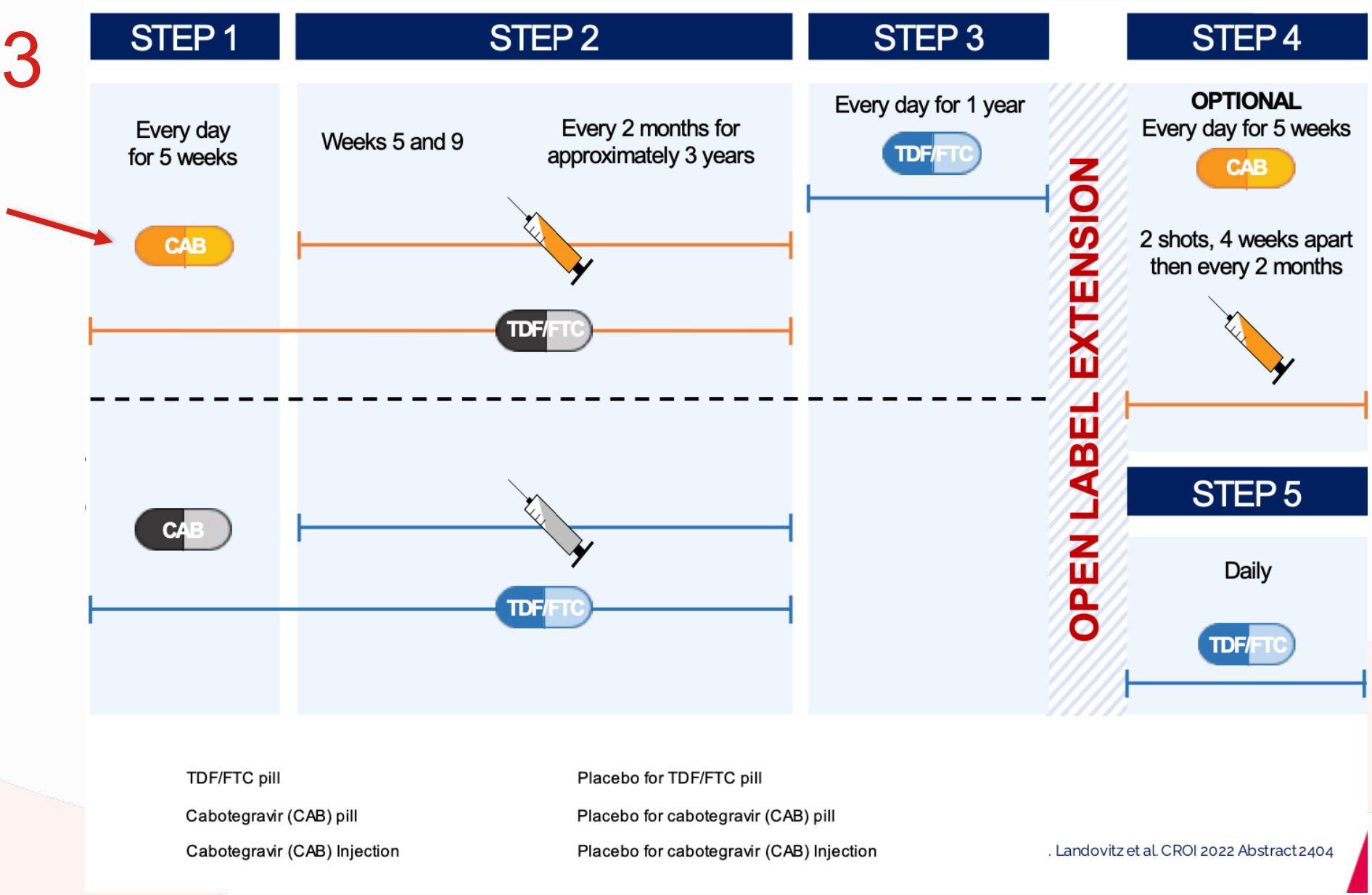
HIV PREVENTION

HPTN-083 Update

- Phase 2b/3 randomized controlled trial of increased-risk, HIV-uninfected MSM + TGW at 43 sites in 7 countries
- HPTN 083 and 084 demonstrated that long-acting injectable cabotegravir (CAB-LA) is superior to daily oral TDF/FTC for HIV PrEP across populations and regions
- 4566 participants were enrolled, 37.2% from the US, 43% from Latin America, 16.5% from Asia, and 3.3% from Africa
  - 12.5% transgender women
  - 49.8% of US enrollment, Black
  - 67.4% <30 years of age

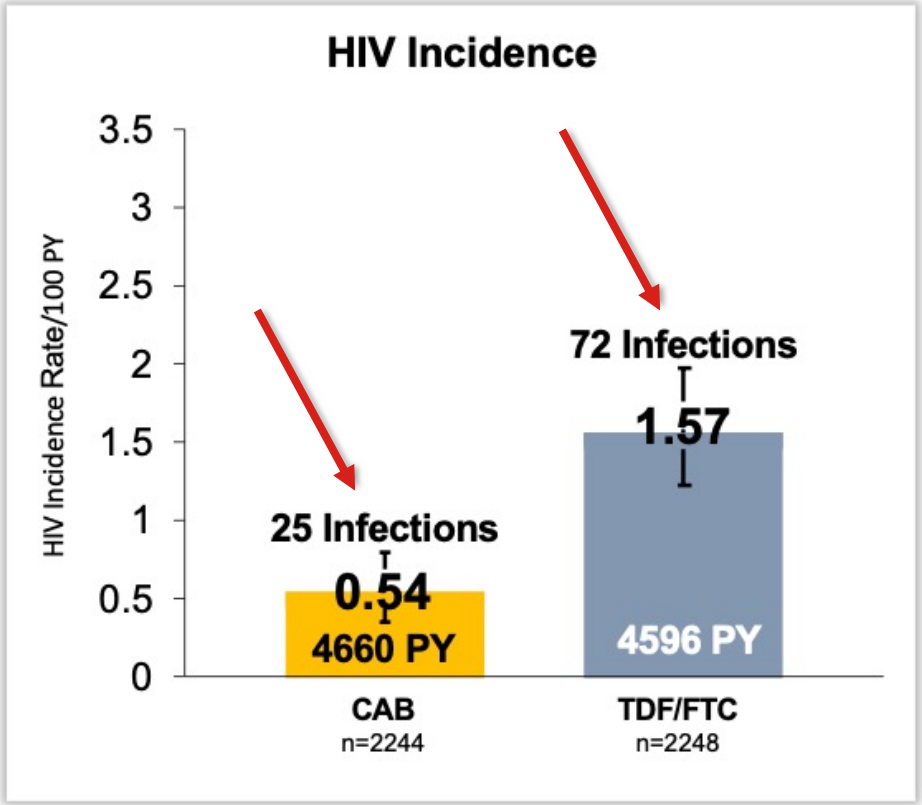
Landovitz et al. CROI 2022 Abstract 2404

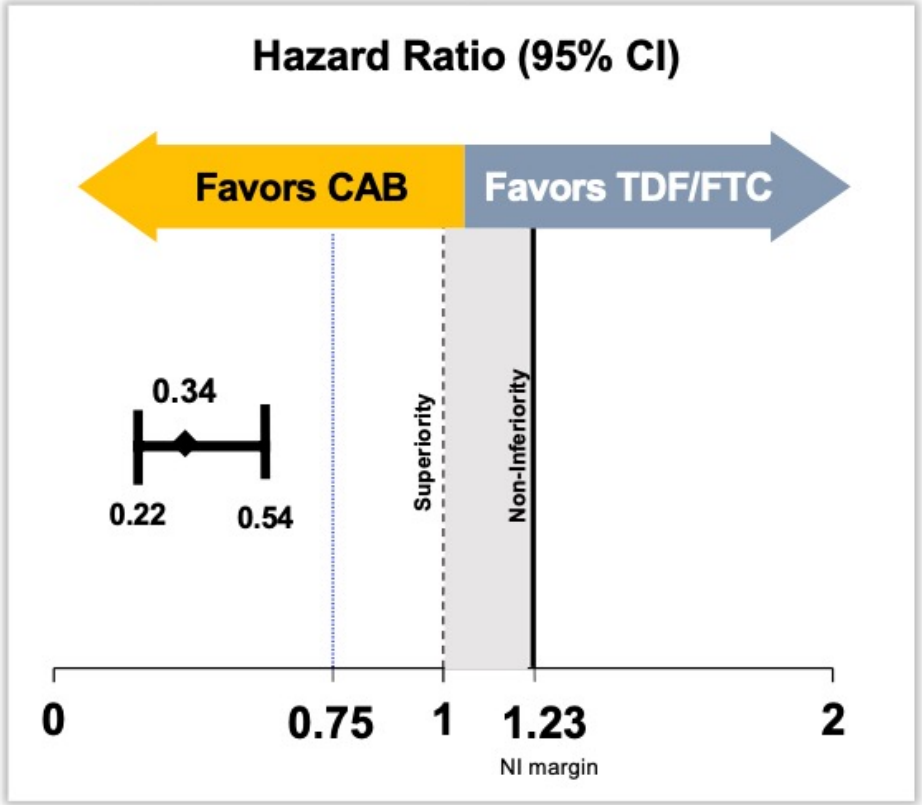
HPTN-083 Update



HPTN-083
Upda

Combined Efficacy Analysis

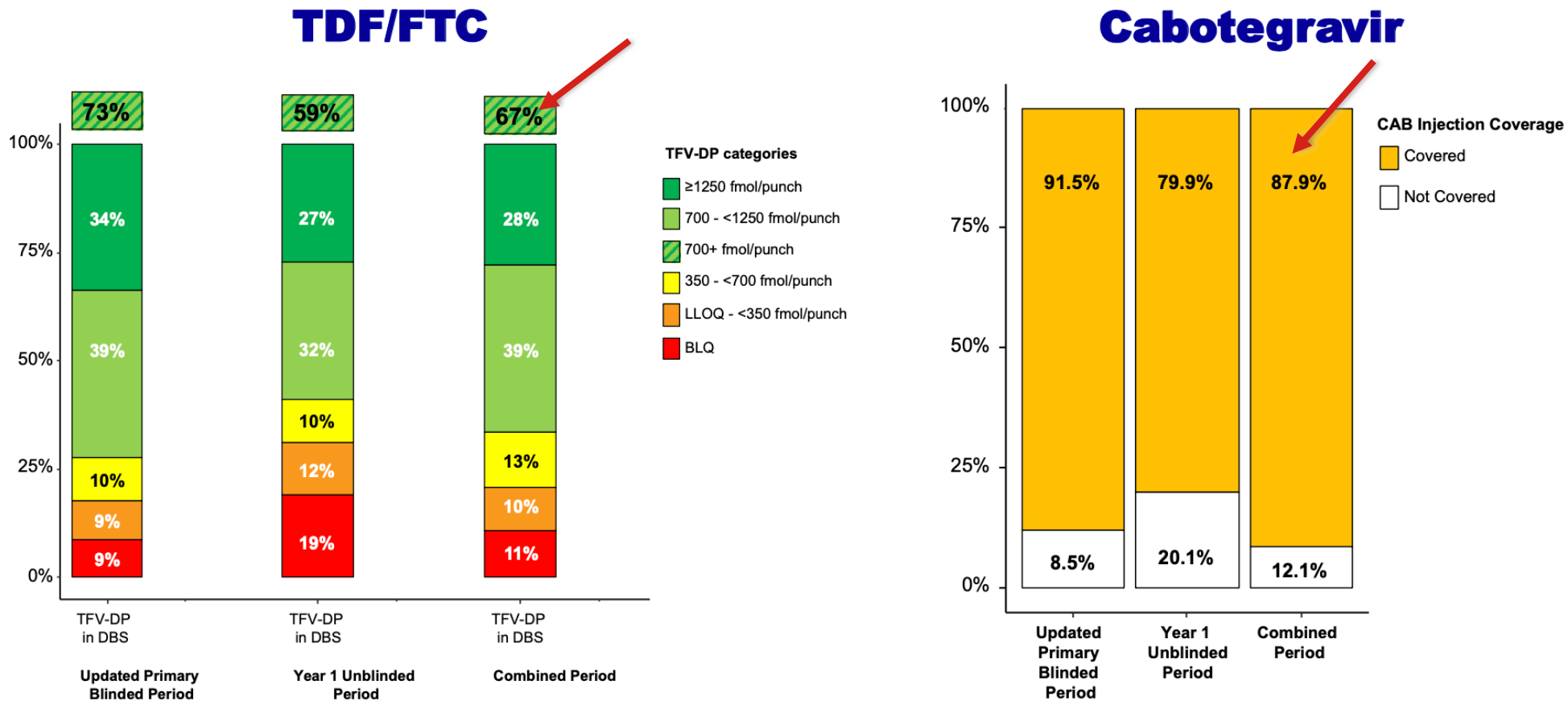




CI, confidence interval

Landovitz et al. CROI 2022 Abstract 2404

HPTN-083 Update Adherence

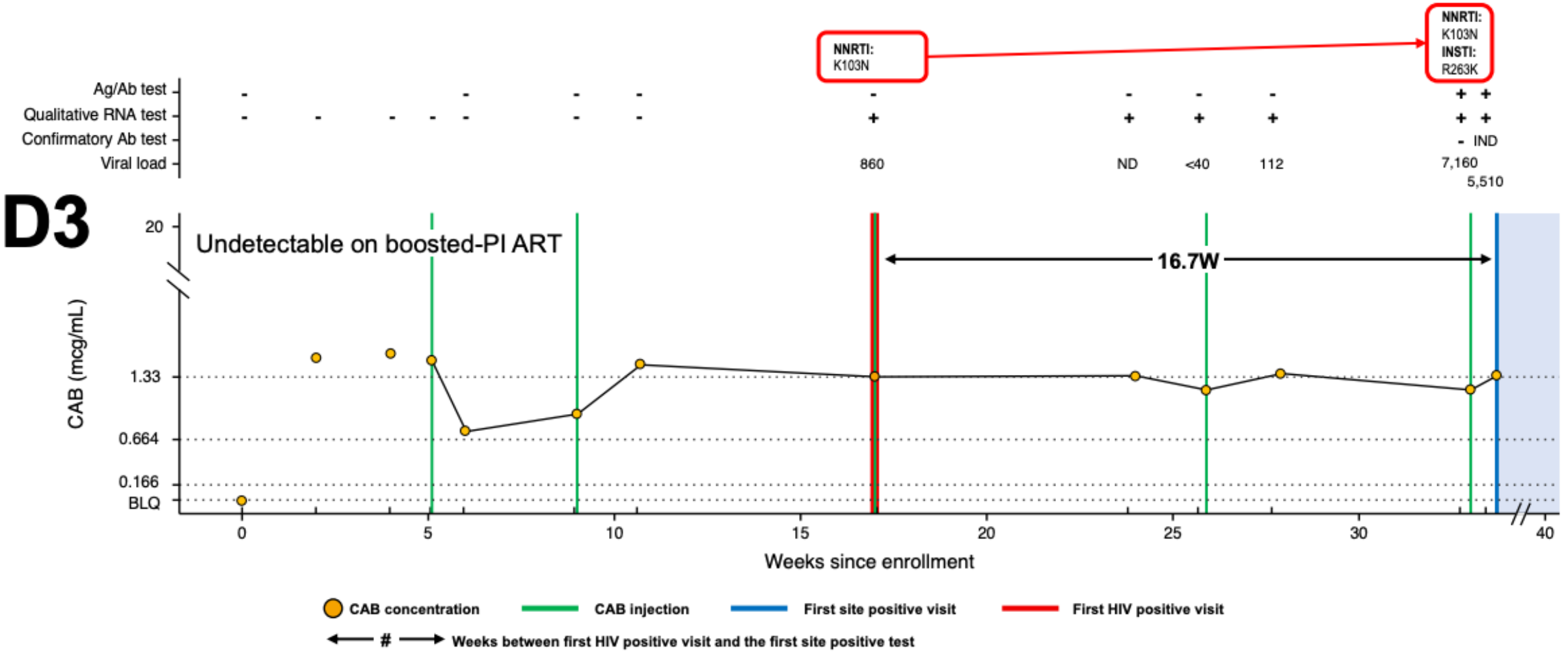


Conclusions

- The advantage of CAB-LA for HIV PrEP in MSM/TGW persists in magnitude (~66% reduction in HIV incidence) with 1 additional year of follow-up, unblinded
  - Despite increases in HIV incidence in both arms, like attributable to both attenuation of adherence/persistence and increased contribution from high incidence regions
  - No new safety concerns were identified
- CAB-LA PrEP breakthrough infections very rare, but unexplained
- HPTN 083 now reports a total of **7 cases of breakthrough** despite on-time injections in 4660 person years of CAB-LA participant follow-up (0.15 per 100 PY)

Infected during on Time CAB Injections

Prevent

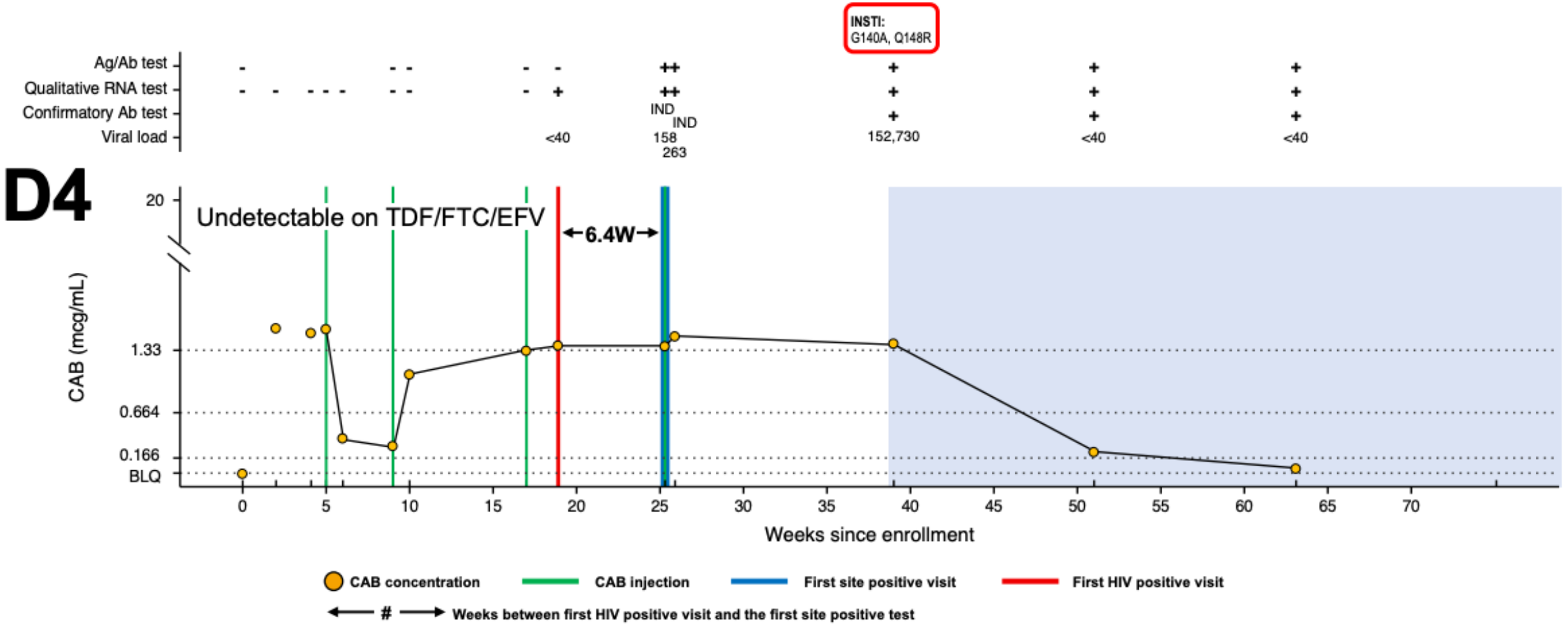


The shaded area represents time on ART.

Landovitz R, et al. CROI 2021, March 6-10, 2021. Abstract 153

Infected during on Time CAB Injections

Prevent



The shaded area represents time on ART.

Early detection of HIV infection may reduce INSTI resistance risk with CAB for PrEP

- CAB suppresses viral replication and delays antibody production
- Rapid tests and Ag/Ab assays often fail to detect infection
- Supplemental Ab tests may be negative/indeterminate for many months
- HIV RNA levels often remain low or undetectable for long periods
  - Delayed ART initiation
  - Emergence of INSTI resistance
  - Potential to impact personal health or on-going HIV transmission

Eshelman, S. et al. CROI 2022 Oral LB

INSTI Genotyping

- **Prior testing – HPTN 083 CAB arm**
  - CAB arm: 16 HIV infections among 2,282 enrolled (4 baseline, 12 incident)
  - VL >500 c/mL - GenoSure PRIme assay (Monogram Biosciences)
  - 5/16 cases had INSTI resistance (includes 1 baseline case)
  - 2 cases had no results (VL <500 at all visits)
- In 5/7 cases, major INSTI RAMs were first detected in samples with low VLs - not just in high VL "breakthrough" samples
  - Use of an RNA assay for HIV screening would have detected infection before a **major** INSTI RAM was detected (4 cases) or before **additional major** INSTI RAMs accumulated (2 cases)

PrEP Guidelines 2021, Lab Testing

Prevent

- Patients starting or restarting PrEP after a long stop, test using an HIV antigen/antibody test (lab-based preferred)
- Patients taking or recently taken PrEP (including patients who have taken oral PrEP in the last 3 months or patients who had a CAB injection in the last 12 months), **test using an HIV antibody/antigen assay AND a qualitative or quantitative HIV-1 RNA assay**
  - If positive antigen/antibody test and a detectable HIV-1 RNA test confirming the patient has HIV, link to HIV care.
  - If negative antigen/antibody test and undetectable HIV-1 RNA test, continue prescribing PrEP

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

PrEP Guidelines 2021, Ongoing Assessments

Prevent

- **Oral PrEP**
  - CrCl once every 12 months for patients under 50 years old or patients with baseline CrCl greater than 90 mL/min
    - Everyone else CrCl every 6 months
  - If taking F/TAF, annual triglyceride, cholesterol, weight
  - Review medications for interactions
- **Injectable PrEP**
  - Kidney, triglyceride, cholesterol assessments are not needed
  - Recommended assessments is different for CAB users:
    - HIV testing every 2 months (at each injection visits)
    - STI testing every 4 months (at every other injection visit)

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

MISCELLANEOUS

CROI 2022

HIV-1 REMISSION WITH CCR5Δ32Δ32 HAPLO-CORD TRANSPLANT IN A U.S. WOMAN: IMPAACT P1107

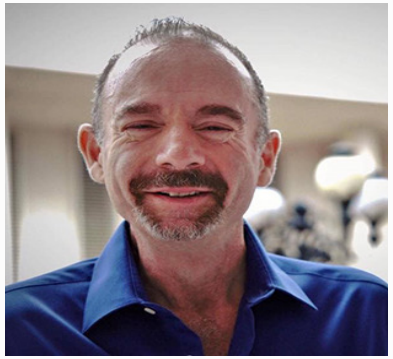
Yvonne Bryson, MD

David Geffen School of Medicine at UCLA and Mattel Children's Hospital, Los Angeles, California, USA

Disclosure: None

Cases of HIV-1 Cure

Berlin Patient (2009)



Timothy Ray Brown
(1966-2020)
Caucasian male
Provided proof-of-concept for cure with transplantation of CCR5Δ32/Δ32 cells

Strategy that led to cure

- Chemotherapy for relapsed AML
- Stem cell transplant x 2 (Chemo & TBI conditioning)
- Graft: **Adult donor CCR5Δ32/Δ32 bone marrow cells** (10/10 HLA match)
- Graft versus host disease
- ART stopped immediately after transplant
- HIV-1 remission **20 months; >12 years** (deemed cured)

Hutter G. et al. NEJM 2009 .
Hutter G. et al. AIDS 2011
Yukl SA et al. PLoS Pathog 2013

London Patient (2019)

Adam Castillejo
(40 years old)
Latino male

Strategy that led to cure

- Chemotherapy for Hodgkin's lymphoma
- Stem cell transplant (chemo conditioning)
- Graft: **Adult donor CCR5Δ32/Δ32 homozygous peripheral blood stem cells (9/10 HLA match**)
- Graft versus host disease
- ART stopped 16 months after transplant
- HIV-1 remission **18 months; 30 months (deemed cured)**

Gupta R.K. et al. Nature 2019
Gupta R.K. et al. Lancet HIV 2020; 7: e340–47

Why Only Two Cases of HIV-1 Cure Following Transplantation?

MAJOR ROLE of CCR5Δ32/Δ32 cells

- Mutation is rare (<1%)
- Most common in Northern Europe, **No routine screening of BM or donors**
- **Cord blood banks** as a potential solution

Adult unrelated donor grafts vs. cord blood donors

Advantage: High cell dose and rapid engraftment

Disadvantage: Stringent HLA match needed because of risk for GVHD

Umbilical cord blood grafts

Advantages: Banked and therefore readily available for screening, less stringent HLA match needed because of lower risk for GVHD

Disadvantages: Lower cell dose, delay in engraftment

Potential solution: Combined haploidentical cord grafts

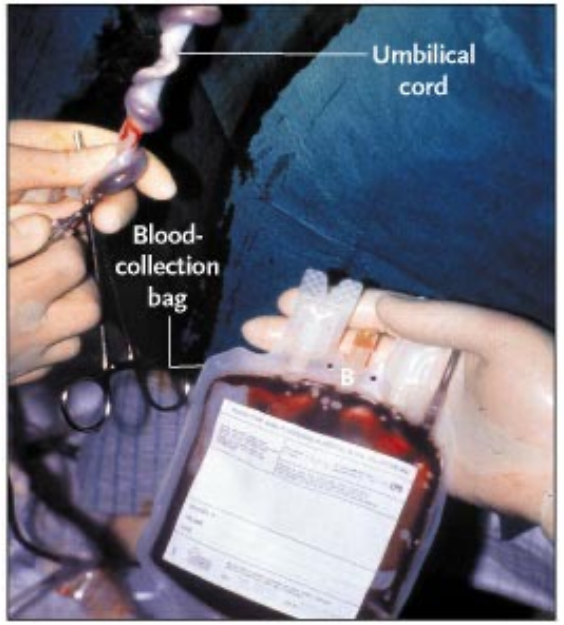
Adult graft assures accelerated engraftment until cord graft takes over

Van Besien K and Childs R, Semin Hematol, 2016

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT P1107

- Observational study
- Cord blood transplantation with CCR5Δ32 donor cells
- Children (>12 months of age) and adults living with HIV-1 requiring transplantation for other underlying diseases (cancer or hematopoietic diseases)
- Designed to use **previously screened cord blood units for transplantation (StemCyte Inc.)**; maintain =>300 CBU prescreened for **CCR5Δ32Δ32**
- Collaboration between IMPAACT and the Center for International Blood and Marrow Transplant Research (CIBMTR); co-endorsed by ACTG



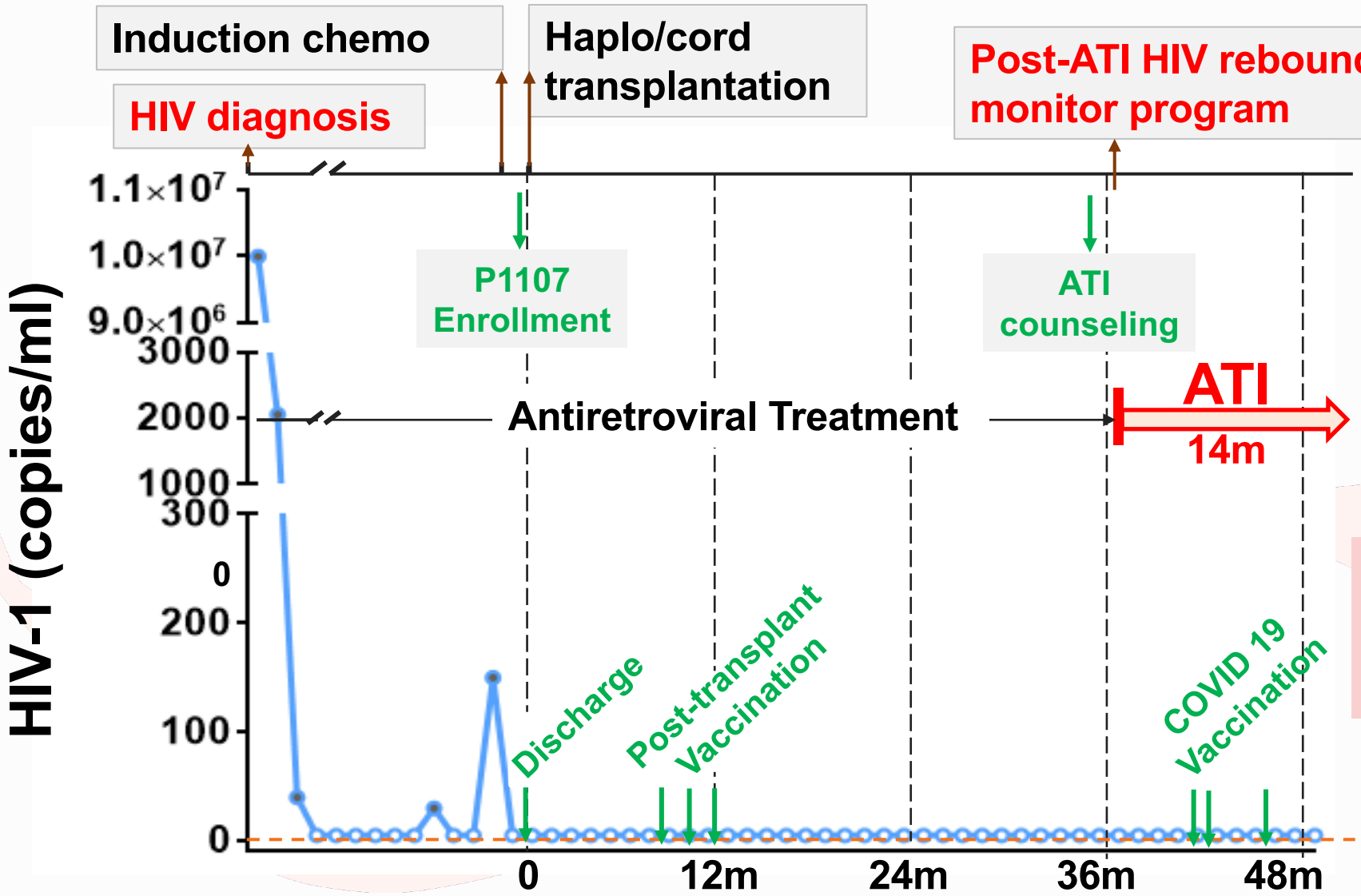
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

CASE REPORT

- Female; mixed race
- DX acute HIV-1 (2013)
- High-risk AML monosomy 7 (2017)
- 3-partially matched CCR5 delta 32/32 cord units (StemCyte)
- Haplo-cord transplant:5/8 match CBU & relative's PBMC (2017)

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

HIV-1 and AML Treatment Course



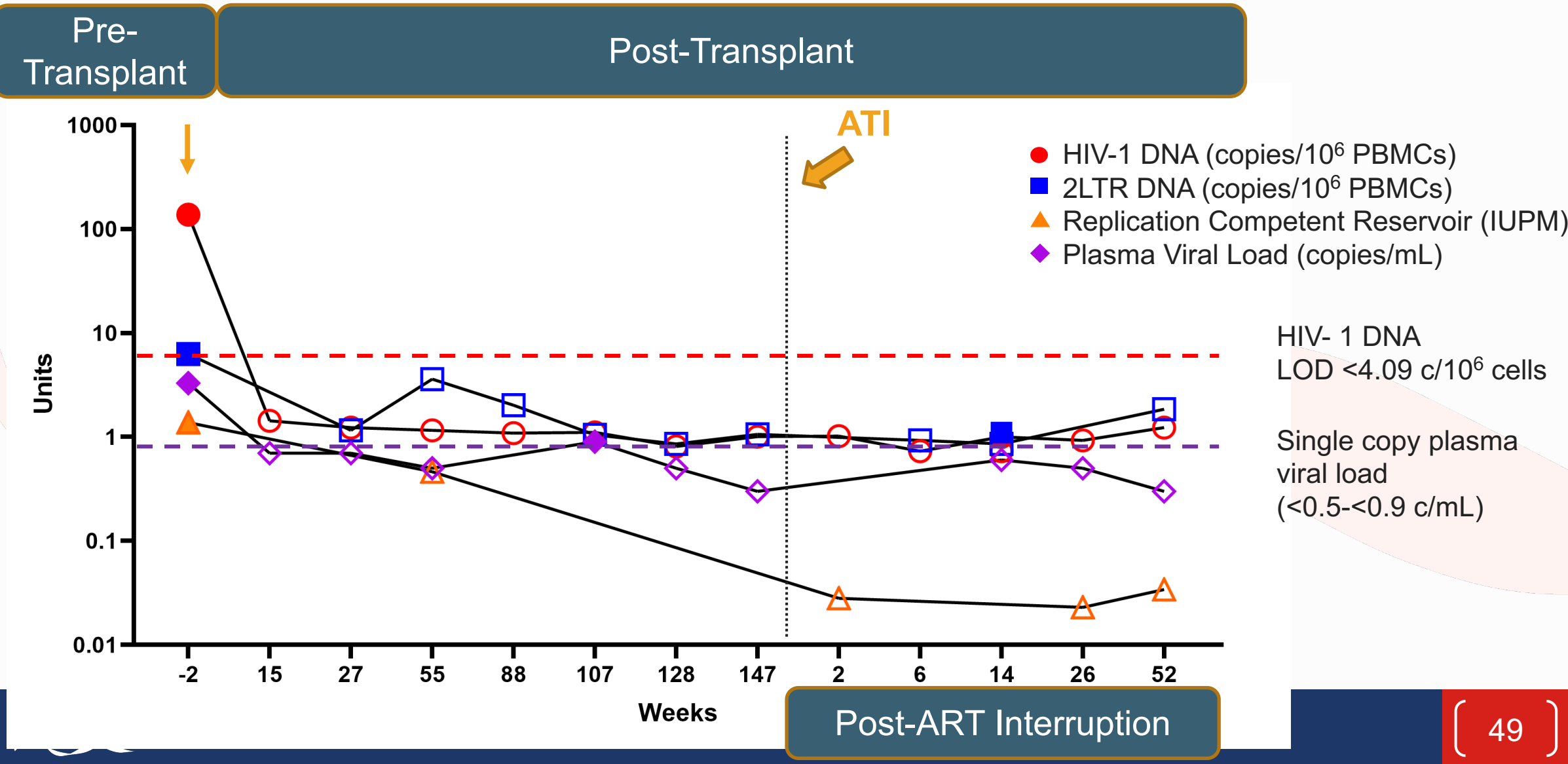
Fludarabine/melphalan/ TBI_{400}/ATG

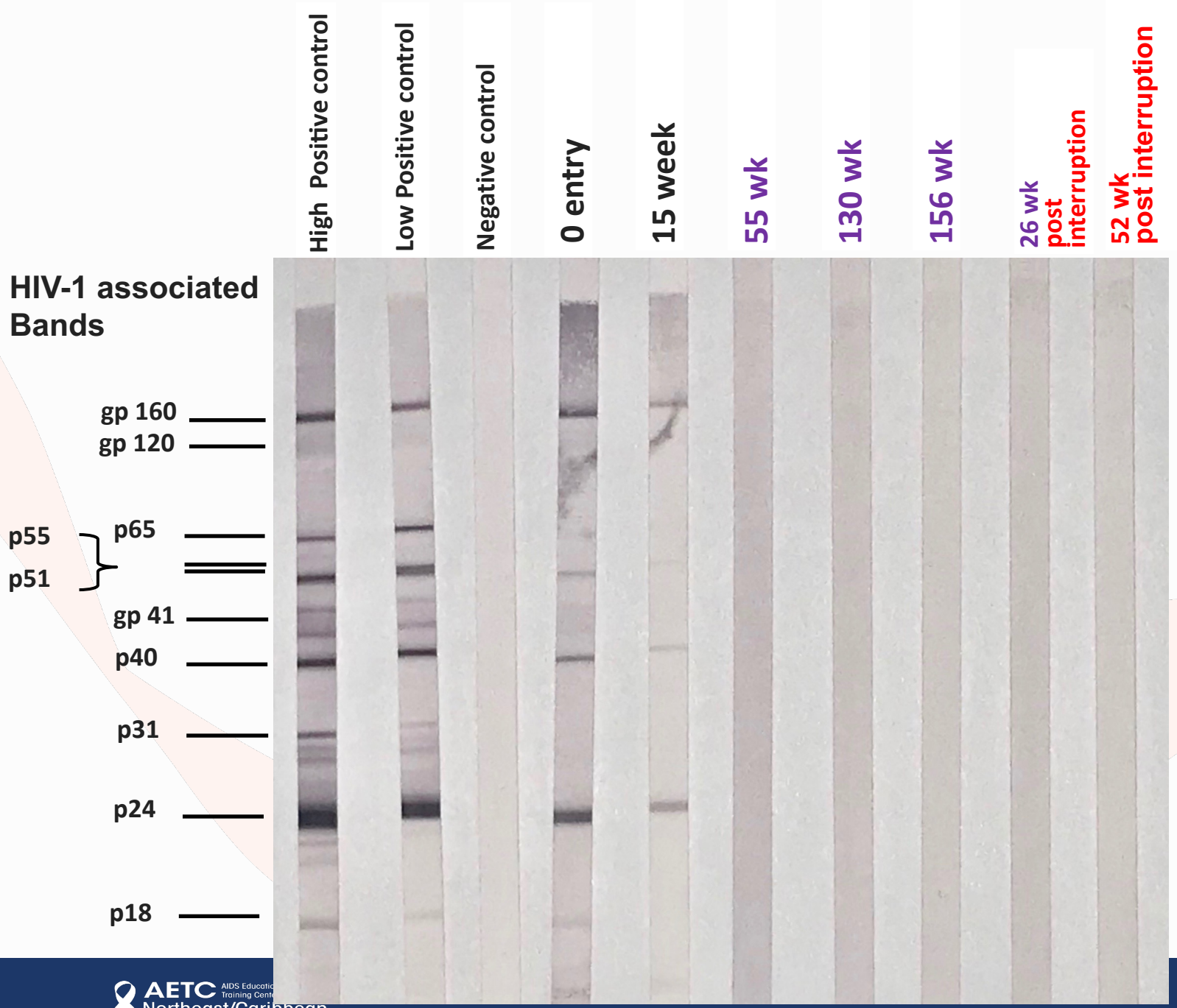
ART stopped 37 months post T

ATI: antiretroviral treatment interruption

LOD: limit of detection

Cell-Associated HIV-1 DNA Levels, Latent Reservoir Size and Low-level Viremia Pre-and Post-Transplantation and Following ART Interruption





Loss of HIV-1-specific antibody responses by Week 55 post-transplant through 52 weeks post-ATI

IMPAACT P1107: Conclusions

- **First US woman of mixed race** living with HIV-1 successfully transplanted with CCR5Δ32/Δ32 haplo-cord SCT with 100% sustained engraftment of cord blood and in HIV-1 remission
- Durable remission of AML 4 years 6 months post SCT
- **14 months off ART; no viral rebound (no ARV's in plasma)**
- **No detectable replication-competent latent reservoir** (74.5 million CD4+ T cells analyzed)
- **Undetectable HIV-1-specific cellular immune** responses and **HIV antibody negative; *in-vitro* resistance to lab & autologous virus**
- Negative-(transient trace) HIV-1 DNA by ddPCR
- Remains clinically well with **NO GVHD**

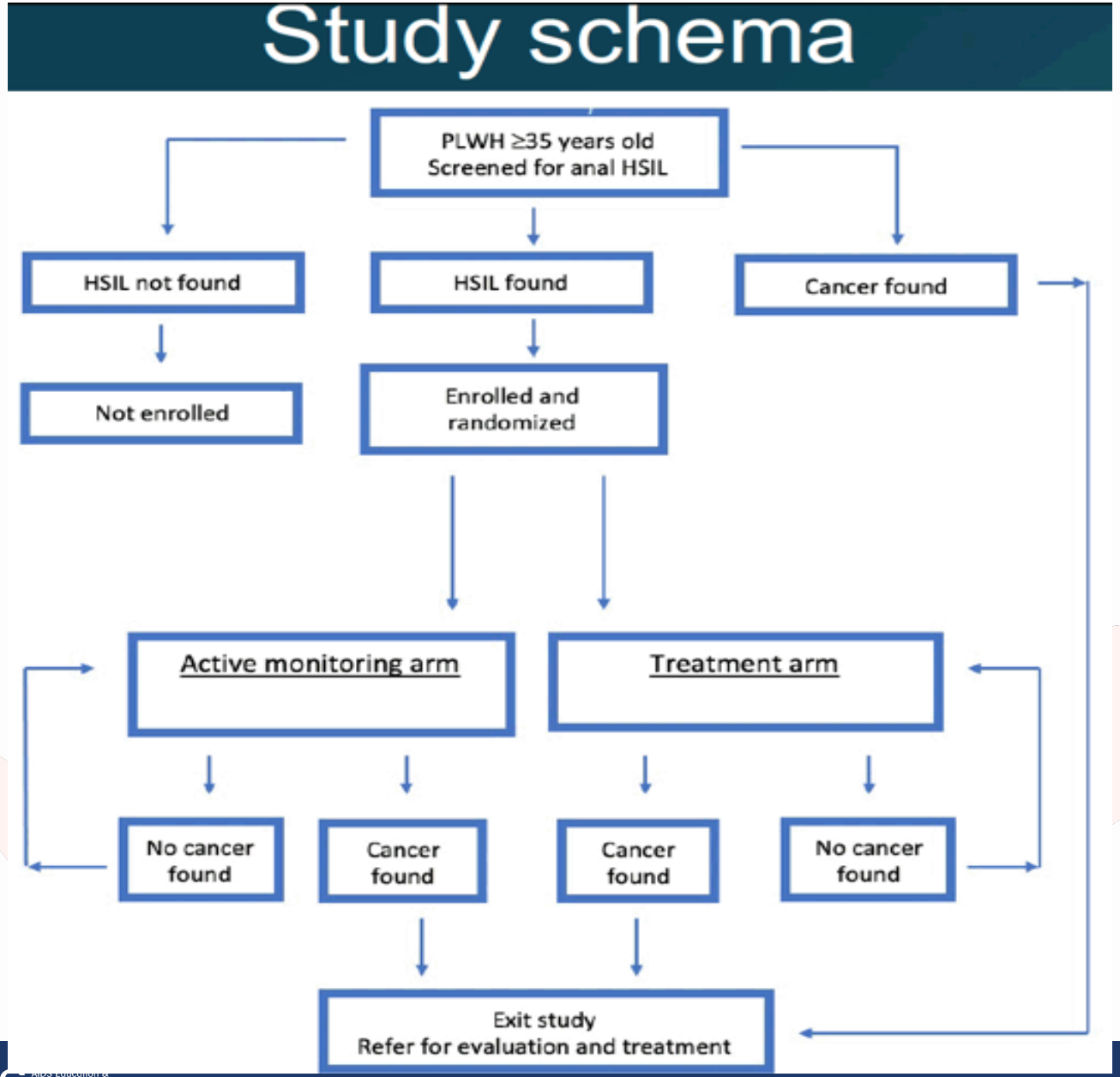
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT P1107: Conclusions

- **PROVIDES HOPE** for use of cord blood cells or halpo-cord to achieve HIV-1 remission for individuals requiring transplantation for other diseases

- Additional proof that HIV-1 reservoirs can be cleared sufficiently to afford remission/cure in the setting of resistant target cells

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network



Study population:
PLWH ≥35 yo

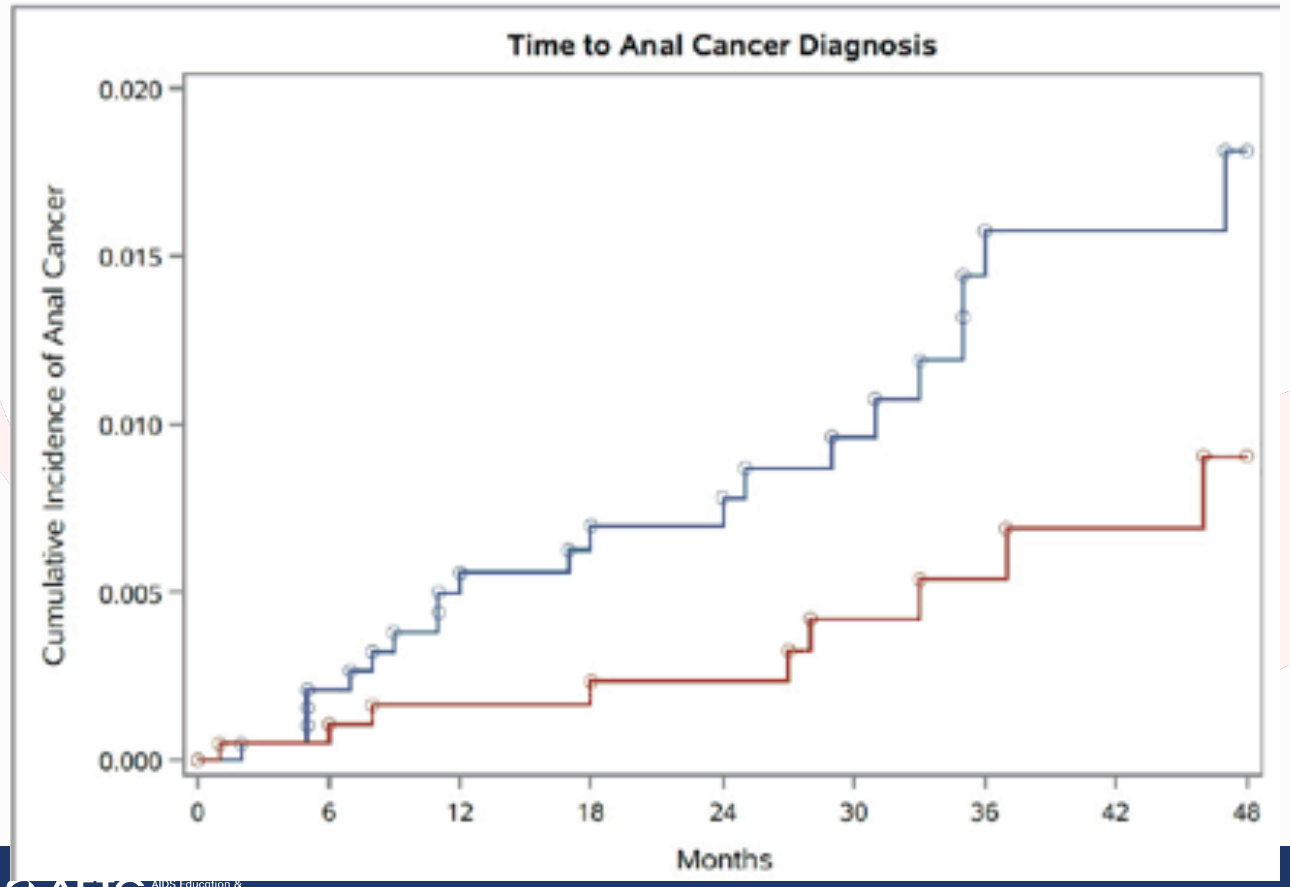
Study treatment:
Active monitoring or Immediate treatment (electrocautery ablation, IRC, 5-FU, imiquimod)

Followed every 3-6 months

Palefsky CROI 2022 abstract #106

- Results:
  - 10,723 screened between 9/14-8/21
    - 52% had biopsy-proven HSIL (hi-grade squamous intraepithelial lesion): 53% men, 42% women, 62% transgender
    - 17 (0.2%) had biopsy-proven anal cancer
  - 4446 participants randomized
    - 80% men, 16% women, 3% transgender
    - 32% White, 42% AA, 16% Latino, 1% Asian, 8% other/unknown
    - 78% homosexual, 23% heterosexual, 7% IDU
    - 83% with HIV RNA <50 cps/ml
    - median CD4 ~600; 50% had nadir CD4 <200
  - On study, 93% had electrocautery ablation and 6% IRC

- **Outcome:** Over a median 26 months, 30 cancers diagnosed:
  - 9 (treatment) vs. 21 (observation) ; median f/u 26 m
    - 173 vs 402 cases per 100,000 P-Y
    - 57% reduction (95% CI, 6%, 80%; p=0.029)



active monitoring

treatment

- DSMB recommended stopping the study for efficacy
- Recommendation made to treat all individuals in the monitoring arm
- We will continue to follow all individuals who wish to be treated and/or followed

Anticholinergic Meds and Fall/Fraility

- 669 HIV-infected persons >50 years of age
- 28% reported using ACMs, 9% on 2 or more
  - Codeine (12%)
  - Citalopram (12%)
  - Loperamide (9%)
  - Amitriptyline (7%)
  - Diazepam (6%)
- Falls reported more commonly in ACM users, 17% versus 6% ($p<0.001$)
- Frailty 32% versus 17% ($p<0.001$)
- Avoid ACMs if possible – use Beers Criteria

PK – Miscellaneous

- TDF/FTC levels in Transgender Men and Women
  - Sex hormones also measured
    - TGW on stable estrogen doses
      - No difference in estradiol levels after start of TDF/FTC
    - TGM on stable testosterone
      - No difference in testosterone levels after start of TDF/FTC
    - No change in TFV-DP
- Rifapentine/INH – Decreased DRV/c levels up to 71-96% - avoid
- BID DTG with rifapentine/INH –use caution, DTG levels reduced\
- TFV-vaginal ring designed for 90 days, dropped below target at 56 days, still a potential
- SC Doravirine that then “forms” an implant that’s removable
- Islatravir – vast majority of studies on hold – decreases in total lymphocyte and CD4 cells

CROI 2022. Abstract 84, 431, 78, 82, 446,

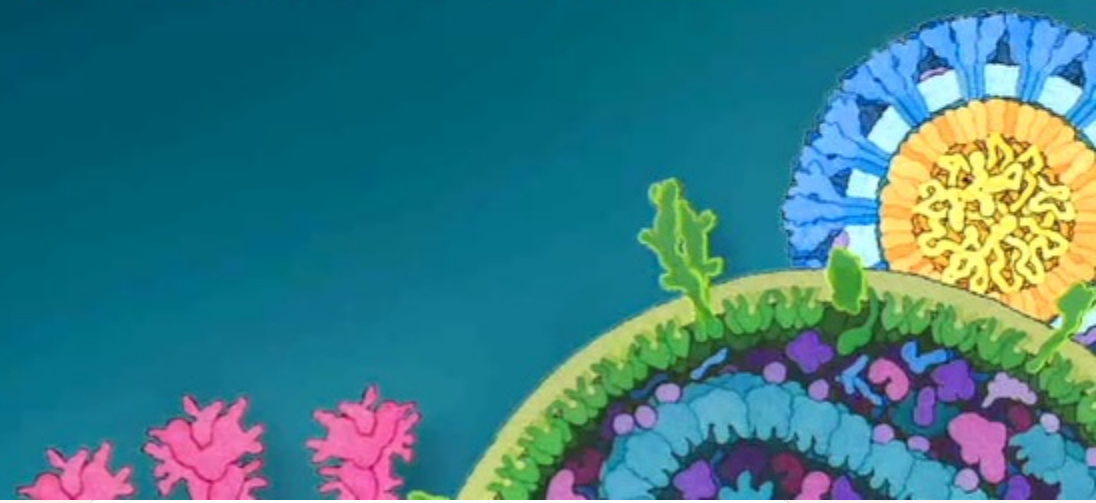
COVID-19

COVID-19 BOOSTER VACCINE EFFECTIVENESS IN PEOPLE WITH AND WITHOUT IMMUNE DYSFUNCTION

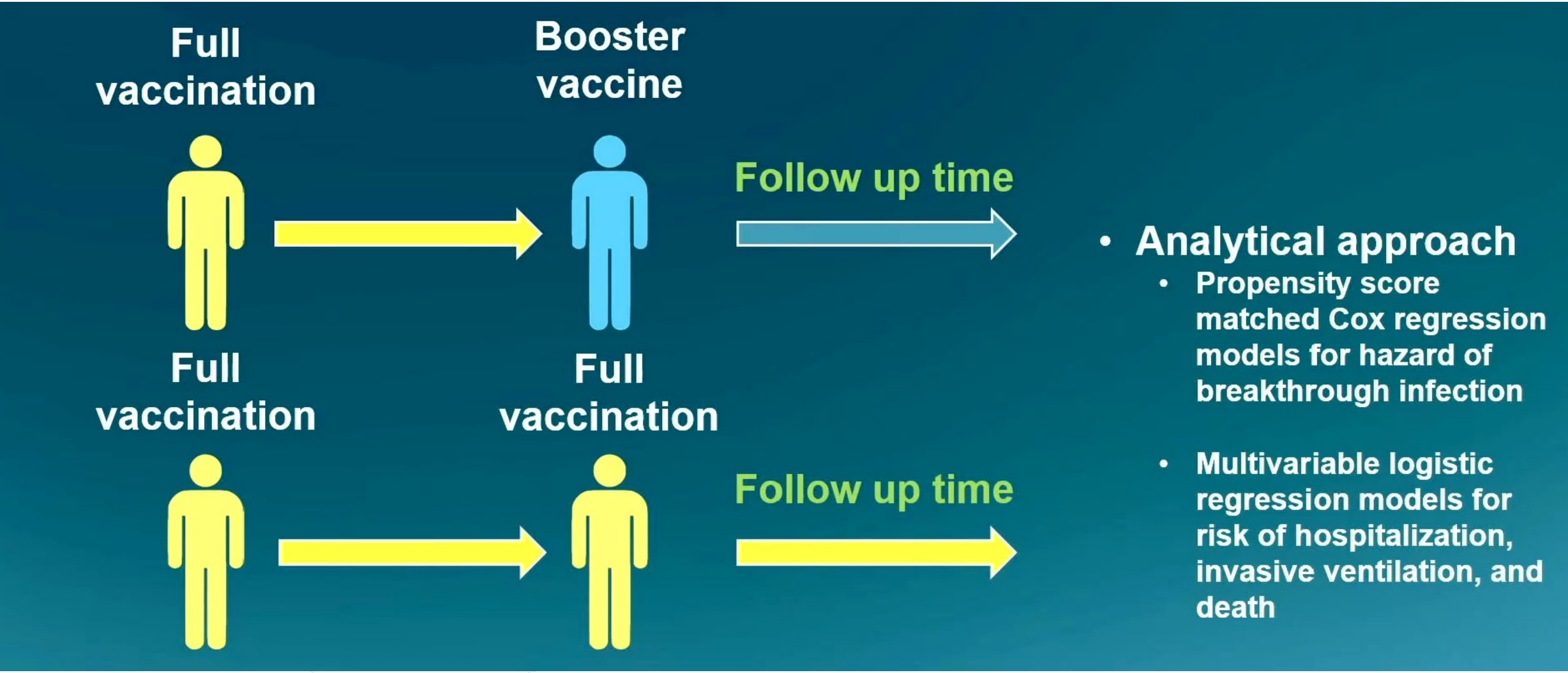
Jing Sun, MD, PhD

Johns Hopkins Bloomberg School of Public Health,

Baltimore, MD, USA



Immune dysfunction = HIV, solid or bone marrow tx, autoimmune disease, cancer



- **Analytical approach**
  - **Propensity score matched Cox regression models for hazard of breakthrough infection**
  - **Multivariable logistic regression models for risk of hospitalization, invasive ventilation, and death**

PATIENT CHARACTERSTICS

Variables	Overall cohort (N = 784,555)	Full vaccination (N=614,750)	Full vaccination with booster (N=174,042)
Age, median (IQR)	50 (33, 65)	49 (31, 64)	57 (41, 69)
Female sex, N (%)	450,202 (57%)	350,219 (57%)	99,983 (57%)
Race and ethnicity, N (%)			
Non-Hispanic White	433,374 (55%)	323,156 (53%)	110,218 (63%)
Non-Hispanic Black	85,710 (11%)	71,896 (12%)	13,814 (7.9%)
Hispanic	138,124 (18%)	113,986 (19%)	24,138 (14%)
AAPI	37,918 (4.8%)	27,861 (4.6%)	10,057 (5.8%)
Others	67,834 (8.6%)	55,535 (9.1%)	12,299 (7.1%)
Number of comorbidities, N (%)			
0	413,616 (53%)	334,127 (55%)	79,489 (46%)
1	182,638 (23%)	139,303 (23%)	43,335 (25%)
2	87,827 (11%)	64510 (11%)	23,317 (13%)
≥3	100,474 (13%)	72,573 (12%)	27,901 (16%)

	Patients without immune dysfunction		Patients with immune dysfunction	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Hospitalization	0.13 (0.12, 0.15)	<0.001	0.21 (0.19, 0.23)	<0.001
Invasive ventilation	0.09 (0.05, 0.19)	<0.001	0.25 (0.18, 0.34)	<0.001
Death	0.13 (0.06, 0.30)	<0.001	0.17 (0.11, 0.27)	<0.001

TENOFOVIR DISOPROXIL FUMARATE AND SEVERITY OF COVID-19 IN PEOPLE WITH HIV INFECTION 00867

Julia Del Amo[1], Rosa Polo[1], Santiago Moreno[2], Esteban Martinez[3], Alfonso Cabello Úbeda[4], José A. Iribarren[5], Adrià Curran[6], Juan Macias[7], Marta Montero[8], Carlos Dueñas[9], Ana Mariño[10], Asun Diaz[11], Jose R. Arribas[12], Inmaculada Jarrín[11], Miguel Hernán[13] and the CoVIHd Collaboration (*)
1 Ministry of Health, MADRID, Spain, 2 University Hospital Ramón y Cajal Madrid, Spain, 3 Hospital Clinic of Barcelona, Barcelona, Spain, 4 Fundacion Jimenez Diaz, Madrid, Spain, 5 Hospital Donostia, San Sebastián, Spain, 6 Hospital Universitario de la Vall d'Hebron,Barcelona, Spain, 7 Hospital Universitario de Valme, Seville, Spain, 8 Hospital Universitario La Fe,Valencia, Spain, 9 University Clinical Hospital of Valladolid, Valladolid, Spain, 10 Ferrol University Hospital, Ferrol, Spain, 11 Institute of Health Carlos III, Madrid, Spain, 12 La Paz University Hospital,Madrid, Spain, 13 Harvard TH Chan School of Public Health, Boston, MA, United States

RESULTS

Of 51,558 eligible individuals, 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC,21.8% on other regimes (Table 1). There were 2,402 documented SARS-CoV-2 infections (425 hospitalizations, 45 ICU admissions, 37 deaths). Compared with TAF/FTC, the estimated risk ratios(RR) (95% CI) of hospitalization were 0.66 (0.43, 0.91) for TDF/FTC and 1.29 (1.02, 1.58) for ABC/3TC, the RRs of ICU admission were 0.28 (0.11, 0.90) for TDF/FTC and 1.39 (0.70, 2.80) for ABC/3TC, and the RRs of death were 0.37 (0.23, 1.90) for TDF/FTC and 2.02 (0.88-6.12) for ABC/3TC. The corresponding RRs of hospitalization for TDF/FTC were 0.49 (0.24, 0.81) in individuals ≥50 years and 1.15 (0.59, 1.93) in younger individuals (Table 2).

- N = 51,558
  - 40% on TAF/FTC, 12% on TDF/FTC, 27% on ABC/3TC, 22% other regimens
  - 2,402 documented SARS-CoV-2 infections (425 hospitalized, 45 ICU, 37 deaths)
- Adjusted RR compared to TAF/FTC:

	Hospitalization	ICU Admission	Death
TDF/FTC	0.66 [0.43, 0.91]	0.28 [0.11, 0.90]	0.37 [0.23, 1.90]
ABC/3TC	1.29 [1.02, 1.58]	1.39 [0.70, 2.80]	2.02 [0.88, 6.12]

NIH COVID GL Update

- **Preferred Therapies**
- For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, the Panel recommends using 1 of the following therapies (listed in order of preference):
- **Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.
- ~~**Sotrovimab 500 mg** as a single intravenous (IV) infusion, administered as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(AIIa)**.~~
- **Remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV once daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg **(BIIa)**.
- **Alternatives**
- **Bebtelovimab 175 mg** as a single IV infusion, administered as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg, **ONLY** if none of the preferred therapies are available, feasible to deliver, or clinically appropriate **(CIII)**.
  - The data that support the use of this anti-SARS-CoV-2 mAb largely come from in vitro studies that demonstrated its potent activity across a broad spectrum of VOCs (including both the BA.1 and BA.2 subvariants of Omicron) and a Phase 2 randomized trial that showed no unexpected safety events and more rapid viral decay in patients at low risk for progression to severe disease.[1-3]
  - Although there are insufficient data on hospitalization and mortality outcomes in patients at high risk of disease progression who have received bebtelovimab, the agent has a mechanism of action similar to other anti-SARS-CoV-2 mAbs that have demonstrated a reduction in hospitalization or death in high-risk patients in Phase 3 trials.
  - Thus, the laboratory and Phase 2 clinical data for bebtelovimab, coupled with the aggregate evidence for this class of agents, support the use of bebtelovimab in high-risk patients when other options are not available, feasible to deliver, or clinically appropriate.

Overview

- Update on epidemiology of HIV in the U.S.
- Antiretrovirals—treatment and PrEP
- HIV “cure” case
- Miscellaneous, PK, etc
- COVID-19 prevention/treatment

Slide Acknowledgments

- Marshall Glesby, MD, MPH
- Trip Gulick, MD, MPH