Update on Antiretroviral Therapy: Navigating the Era of Excellence

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Update on ART:
Navigating the Era of Excellence

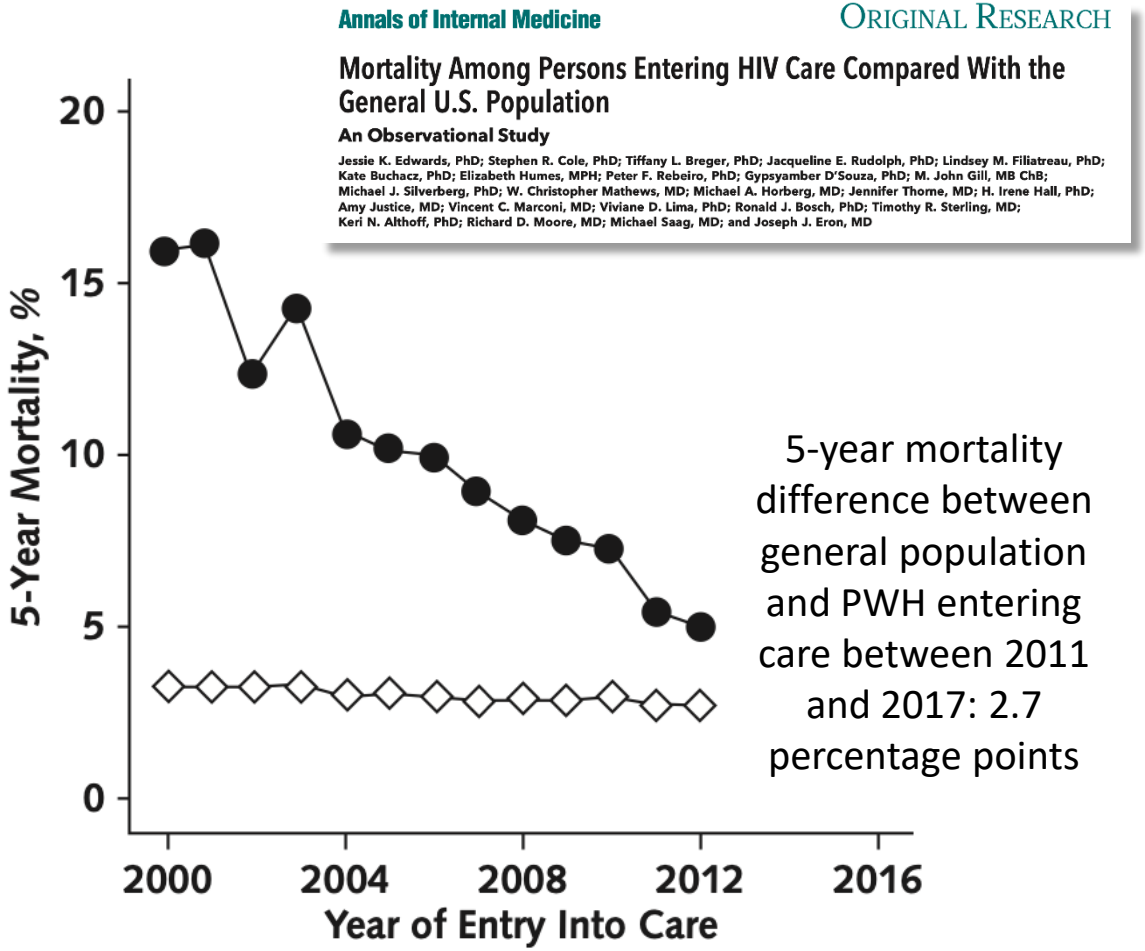
ART: Current Options and What's on the Horizon

Improving Outcomes by Preventing Comorbidities

What Do We Need to Do to Make Excellent Care Better?

Dramatic Decline in Mortality Among People Entering HIV Care

- Adults entering HIV care in the US between 1999 and 2017 (n=82,766)
- Difference in 5 year mortality between people with HIV (PWH) and general population decreased over time
- Likely because of earlier initiation of therapy, improved treatment



5-year mortality difference between general population and PWH entering care between 2011 and 2017: 2.7 percentage points

Edwards JK et al, Ann Int Med, 2021

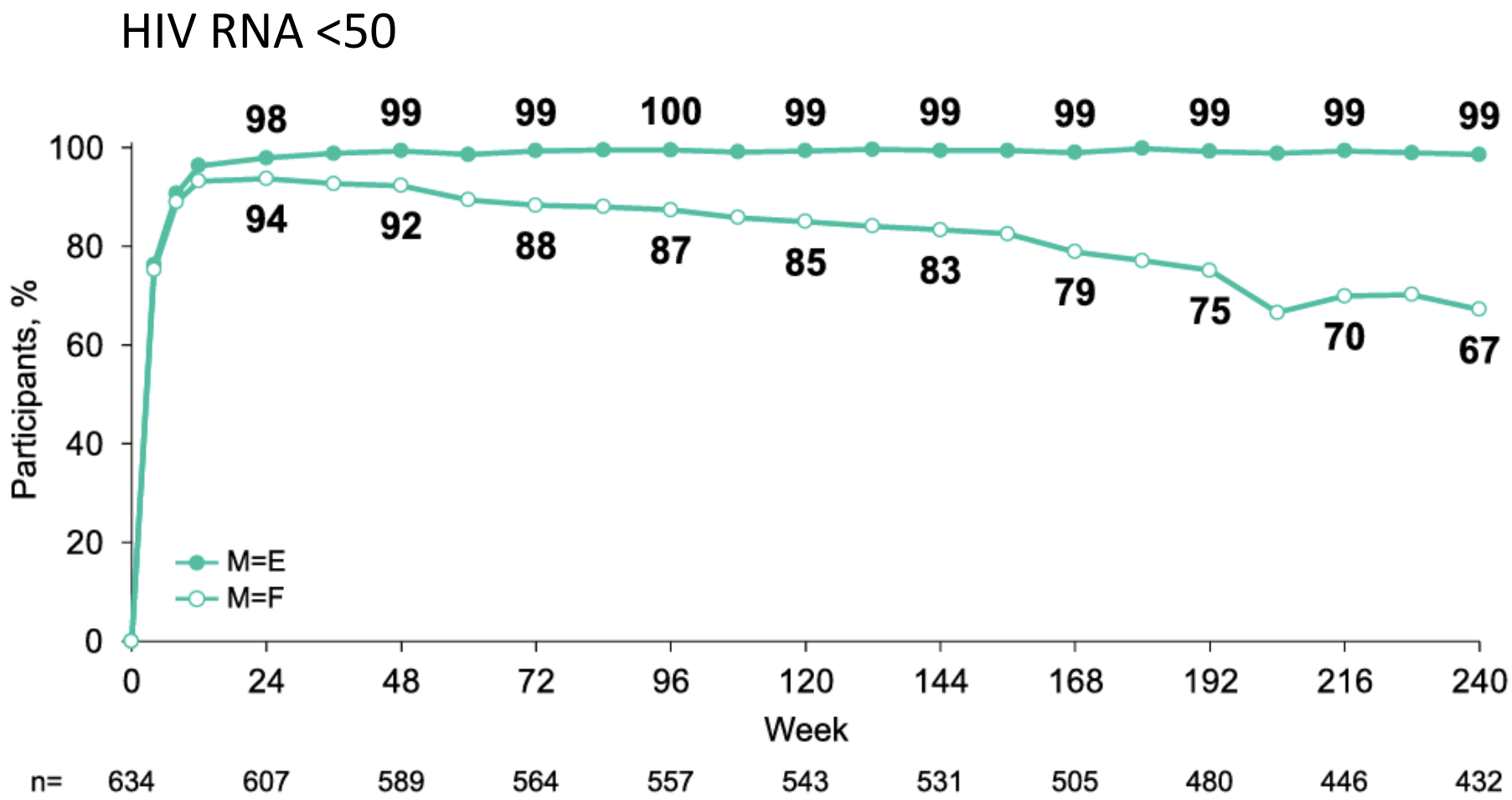
Initial Therapy for Adult People with HIV (PWH): What do the guidelines say? Integrase Inhibitor-based Therapy

WHO	IAS-USA	US DHHS	EACS
▪ DTG+XTC+TDF	▪ BIC/FTC/TAF ▪ DTG+XTC+(TAF or TDF) ▪ DTG/3TC**	▪ BIC/FTC/TAF ▪ DTG/3TC/ABC* ▪ DTG+ XTC +(TAF or TDF) ▪ DTG/3TC**	▪ BIC/FTC/TAF ▪ DTG + 3TC/ABC* ▪ DTG + TAF/FTC or TDF/XTC ▪ RAL + TAF/FTC or TDF/XTC ▪ DTG/3TC or DTG + XTC** ▪ DOR/3TC/TDF or DOR + FTC/TAF or XTC/TDF

XTC: 3TC or FTC. DTG: dolutegravir; BIC: bictegravir; RAL: raltegravir; DOR: doravirine. TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ABC: abacavir. *If HLA-B*5701 and HBsAg negative. **Except for individuals with baseline HIV RNA >500,000, HBV, or for whom results of HIV resistance testing or HBV testing not yet available. Limited data in people with CD4 count <200

WHO Consolidated Guidelines, 2021; Gandhi RT et al JAMA. 2022; US DHHS Guidelines. 2023; EACS Guidelines, 2023

Bictegravir/FTC/TAF: High Rates of Long-term Viral Suppression



Sax P et al, Lancet HIV, 2023

What are the Options for 2-drug therapy in PWH Who are Already Virologically Suppressed?

Treatment	Studies
Boosted PI + 3TC	Multiple studies[1-3]
Dolutegravir/rilpivirine	SWORD trials[4]
Dolutegravir + darunavir/r	DUALIS[5]
DTG/3TC	TANGO[6]; SALSA[7]
DTG + FTC	SIMPL'HIV[8]
Cabotegravir/rilpivirine LA injection	ATLAS[9]; FLAIR[10]; ATLAS-2M[11]

Remember not to use two drug regimens alone in people with HIV/HBV; need to continue tenofovir

[1]Arribas JR, Lancet ID 2015; [2]Perez-Molina JA, Lancet ID, 2015; [3]Pulido F, CID, 2017; [4]Aboud M, Lancet, 2019; [4]Libre J, Lancet, 2018; [5]Spinner C, OFID, 2020; [6]van Wyk J, CID, 2020; [7]Llibre J, CID, 2022; [8]Marinosci A, AIDS 2022, Abstract OAB0302; [9]Swindells S, NEJM, 2020; [10]Orkin C, NEJM, 2020; [11]Overton J, Lancet, 2020

Injectable Cabotegravir/Rilpivirine (CAB/RPV)

- Approved for PWH who are virologically suppressed on antiretroviral therapy and who do not have a history of treatment failure or resistance to either medication.

- Among ≈1600 participants in ATLAS, ATLAS-2M, and FLAIR trials, 1.4% developed virologic failure (VF)
- Among the 4% of participants with ≥2 risk factors, VF occurred in 19%
- Among participants who had 0 or 1 risk factor, VF occurred rarely (0.4% and 2%, respectively).

Risk Factors for virologic failure
Rilpivirine resistance mutations*
HIV subtype A6/A1**
Body mass index ≥30 kg/m^2

* Detected post hoc on proviral genotyping

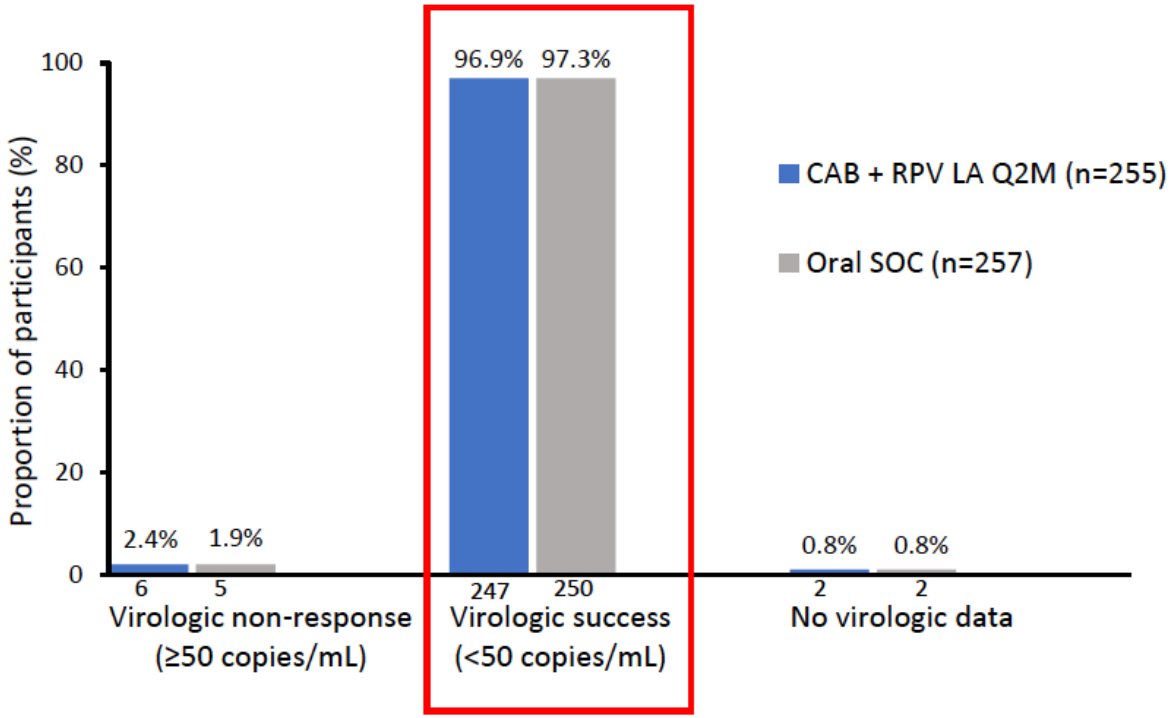
** More common in Eastern Europe, Russia, parts of Africa than in U.S.

Orkin C et al, Clin Infect Dis, 2023

CARES: CAB/RPV in Sub-Saharan Africa

- Adults on oral ART, VL <50, no history of treatment failure or HBV (n=512)
- Randomized: continue oral ART (standard of care) or switch to CAB/RPV q 2 months
- HIV RNA checked every 24 weeks
- Female: 58%. BMI ≥30: 21%; A1 subtype: 53%
- Archived proviral DNA: RPV resistance mutations, 14%; CAB resistance, 16% (but some mutations have minimal impact on antiviral activity)

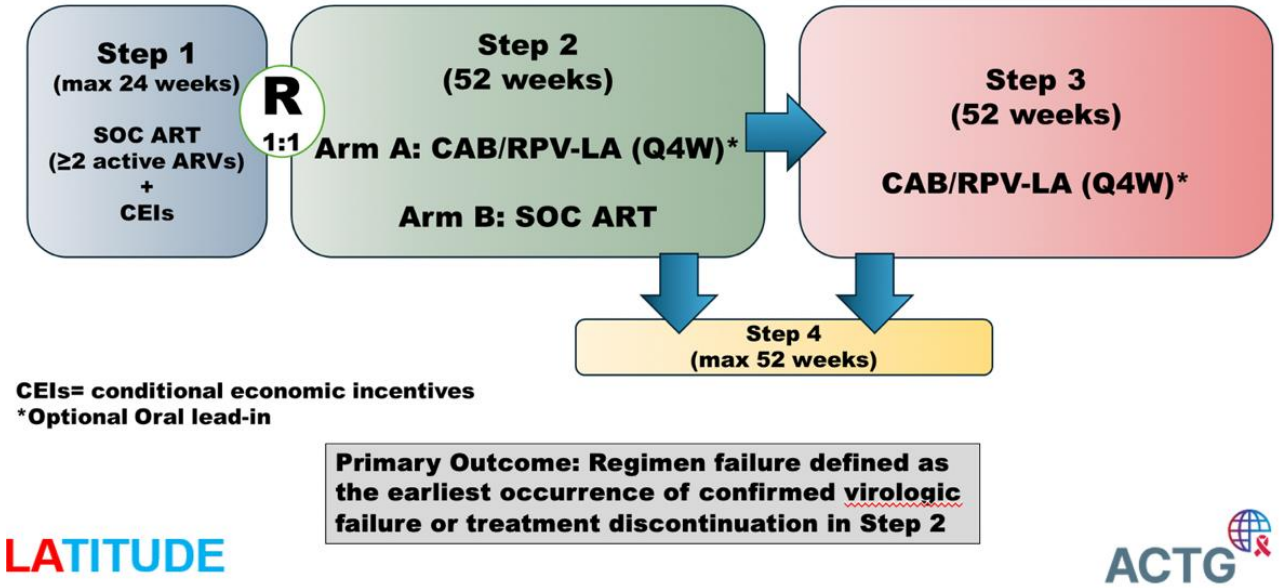
Switching to CAB/RPV non-inferior to continuing oral ART: 97% remained virologically suppressed



Kityo C, Lancet 2024

Does CAB/RPV Have a Role in People with Adherence Challenges? LATITUDE (AIDS Clinical Trials Group A5359)

- Phase 3 randomized trial
- PWH with difficulties adhering to oral ART
- Participants received oral standard of care (SOC) ART with conditional economic incentives until they achieved virologic suppression
- Then randomized to monthly CAB/RPV vs. oral SOC ART



Who was in LATITUDE?

- 434 PWH enrolled
- Age <=30: 20%. Black/AA: 64%. Hispanic: 17%
- Injection drug use (previous or current): 14%
- Randomized to CAB/RPV or SOC oral ART (n=294)

Rana A et al, CROI 2024, Abstract 212

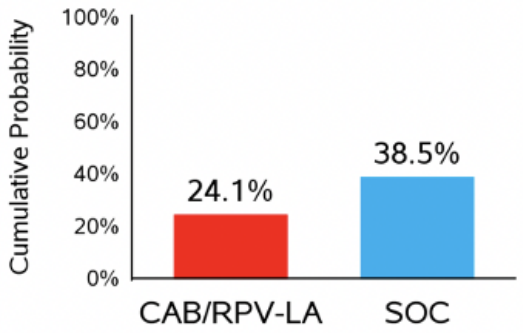
LATITUDE: Results

Rana A et al, CROI 2024, Abstract 212

Primary Outcome

Regimen Failure

Difference	Nominal 98.75% CI
-14.5%	(-29.8%, 0.8%)



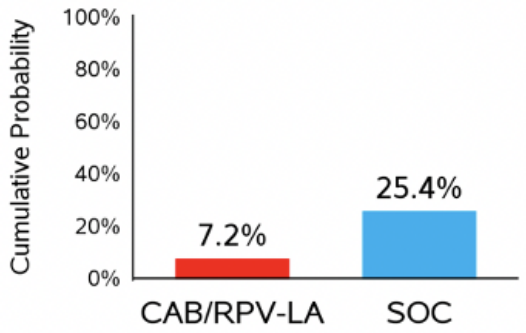
Number of participants

	CAB/RPV-LA	SOC
Regimen Failure	28	47
VF	5	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

Difference	Nominal 98.75% CI
-18.2%	**(-31.1%, -5.4%)**

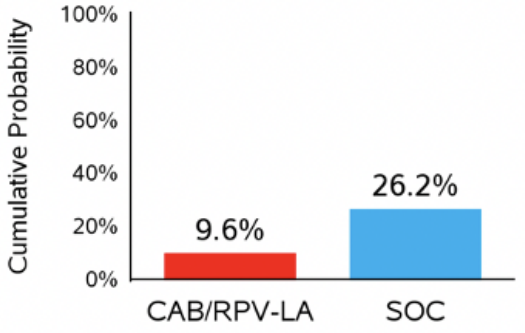


Number of participants

	CAB/RPV-LA	SOC
Virologic Failure	6	28

Treatment-related Failure

Difference	Nominal 98.75% CI
-16.6%	**(-29.9%, -3.3%)**

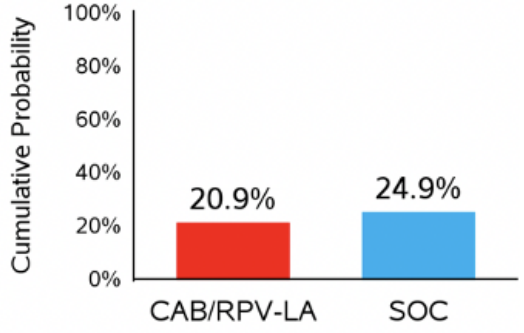


Number of participants

	CAB/RPV-LA	SOC
Treatment-related Failure	9	29
VF	6	28
TRT-DISC (AE)	3	1

Permanent Treatment Discontinuation

Difference	Nominal 98.75% CI
-4.1%	(-18.0%, 9.8%)



Number of participants

	CAB/RPV-LA	SOC
Permanent TRT-DISC	25	30

Considering all endpoints together, CAB/RPV superior to daily oral ART in people with adherence challenges

Does CAB/RPV Have a Role in People with Adherence Challenges? CAB/RPV in People with HIV Viremia

Setting/Reference	Participants	Results	Follow-up
Compassionate use (UK, US, other countries) D'Amico R, HIV Medicine 2023	• N=28 • Median VL 60,300	VS: 57% New resistance: NNRTI: 6/28 (21%) INSTI: 3/28 (11%)	10 mo. (1-47)
San Francisco, Ward 86 Gandhi M, Ann Int Med, 2023	• N=57 • Mean VL 15,850	VS: 95% New resistance: NNRTI (1), INSTI (1)	Median injections 7 (2-18)
OPERA Database (US) Hsu R, IDWeek, 2023	• N=93, VL>200 • Median VL 15,850	VL <200: 90% Resistance not specified	7.4 mo (IQR 3.9, 10.9)
Mississippi Brock J, CID, 2023	• N=12 • Mean VL 153,000	VS: 100%	1-17 mo.

VS: viral suppression

Who Should Receive Injectable Cabotegravir/Rilpivirine? My Take

- For PWH who are virologically suppressed and do not have resistance to INSTI or NNRTI, offer injectable CAB/RPV if it is preferred by the patient over daily oral ART. Counsel patients on small risk of viral failure (≃1-2%) and resistance.
- For patients with history of NNRTI mutations, I usually choose different regimen if patient able to take oral ART (difficult to exclude low-frequency RPV mutations; reports of virologic failure with CAB/RPV).
- For people who are viremic and have CD4 count <200 (high risk for HIV complications) and not able to take oral ART, consider on case-by-case basis; address barriers to engagement in care; provide concurrent intensive support

Beyond Initial Therapy: Navigating HIV Drug Resistance

Navigating Resistance Scenario 1: HIV Suppressed on ART; NRTI resistance; INSTI, PI active

Resistance challenge

Scenario	Options	Studies
HIV suppressed on ART; NRTI resistance	• Boosted darunavir + tenofovir/XTC • DTG or BIC + tenofovir/XTC	2SD, GHESKIO

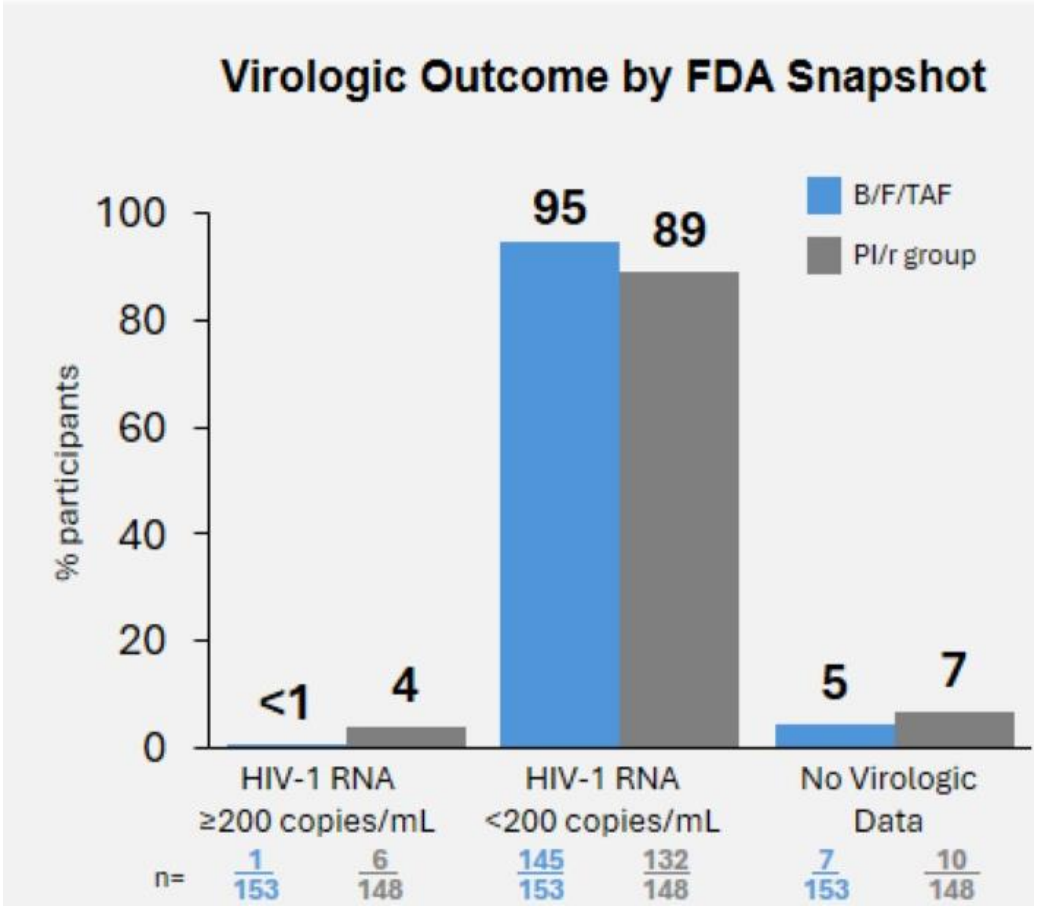
2SD, GHESKIO: People with HIV suppression on boosted PI + 2 NRTI maintain viral suppression when switched to DTG or BIC with tenofovir/FTC despite expected high rate of NRTI resistance

NRTI; nucleoside RT inhibitor; INSTI; integrase strand transfer inhibitor; PI: protease inhibitor; DTG: dolutegravir; BIC: bictegravir; XTC: FTC or 3TC.

Sax PE, et al. *AIDS*. 2022; Mulenga L, CROI 2022, Abstract 135; Ombajo L et al, NEJM 2023; Paton N, et al. Lancet HIV 2022; Matthews G et al. CROI 2023. Abstract LB-198

Switching from 2nd-line RTV-boosted PI Regimen to BIC/FTC/TAF

- Study done in Haiti by GHESKIO
- 301 PWH with history of 1st-line ART failure and subsequent virologic suppression on boosted PI + 2NRTI
- At week 48, switching to BIC/FTC/TAF non-inferior to staying on PI + 2NRTI



Pierre S, et al. AIDS 2024. Abstract OAB3805.

Navigating Resistance Scenario 2: Virologic failure (viremic) on NNRTI; NRTI resistance; INSTI, PI susceptibility

Resistance challenge

Scenario	Options	Studies
HIV suppressed; NRTI resistance	• DTG or BIC + tenofovir/XTC • Boosted darunavir + tenofovir/XTC	2SD GHESKIO
Virologic failure on an NNRTI (viremic); NRTI resistance. ✓ genotype	• Boosted darunavir + DTG • Boosted darunavir + tenofovir/XTC • DTG or BIC + tenofovir/XTC	D2EFT NADIA VISEND

NADIA, D2EFT, VISEND: high rates of HIV suppression with DRV/r + tenofovir/3TC; DRV/r + DTG; DTG + tenofovir/3TC despite extensive NRTI resistance.
Rate of INSTI resistance with DTG + tenofovir/XTC: NADIA, 4%, D2EFT, 1%; VISEND 0%

NRTI; nucleoside RT inhibitor; INSTI; integrase strand transfer inhibitor; PI: protease inhibitor; DTG: dolutegravir; BIC: bictegravir; XTC: FTC or 3TC.

Sax PE, et al. *AIDS*. 2022; Mulenga L, CROI 2022, Abstract 135; Ombajo L et al, NEJM 2023; Paton N, et al. Lancet HIV 2022; Kumarasamy N, et al. AIDS 2024. Abstract OAB3804; Sivile S, et al. AIDS 2024. Abstract OAB3806LB.

Navigating Resistance Scenario 3: Virologic failure (viremic); NRTI, PI and INSTI resistance

Segal-Maurer S et al, NEJM, 2022; Kozal M et al, NEJM, 2020; Emu B et al, NEJM, 2018

- Step 1: If INSTI resistance, might twice daily DTG have some activity?
- Step 2: If NNRTI resistance, does doravirine retain activity?
- Step 3: R5 tropic virus? If so, consider maraviroc
- Step 4: If needed, consider additional options:
  - Fostemsavir (oral)
  - Lenacapavir (subcutaneous)
  - Ibalizumab (iv)
- Treat with two or more active drugs

Where to Next? New ART

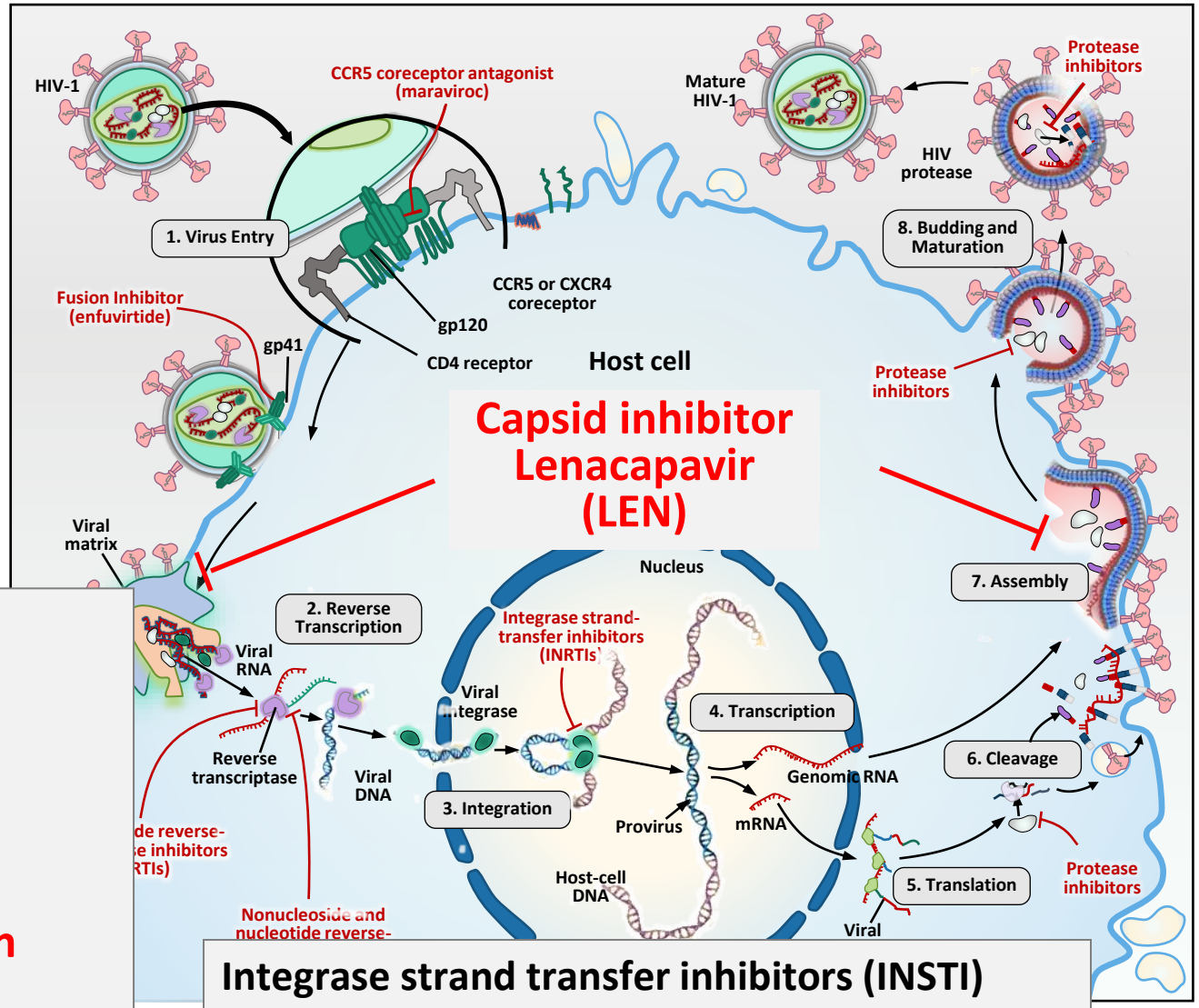
Entry inhibitors:

- Attachment inhibitor:
  - Fostemsavir
  - UB-421
- CCR5 Antagonist:
  - Leronlimab
- Fusion Inh.: Albuvirtide
- Multisite: Combinectin
- Broadly neutralizing Abs

Reverse Transcriptase Inh. (RTI)

- Nucleoside RTI (NRTIs)
- Nonnucleoside RTI (NNRTIs)
  - Long-acting rilpivirine (RPV)
  - MK-8507

Nucleoside RT translocation inhibitor: Islatravir (ISL)



Integrase strand transfer inhibitors (INSTI)

- Long-acting cabotegravir (CAB)

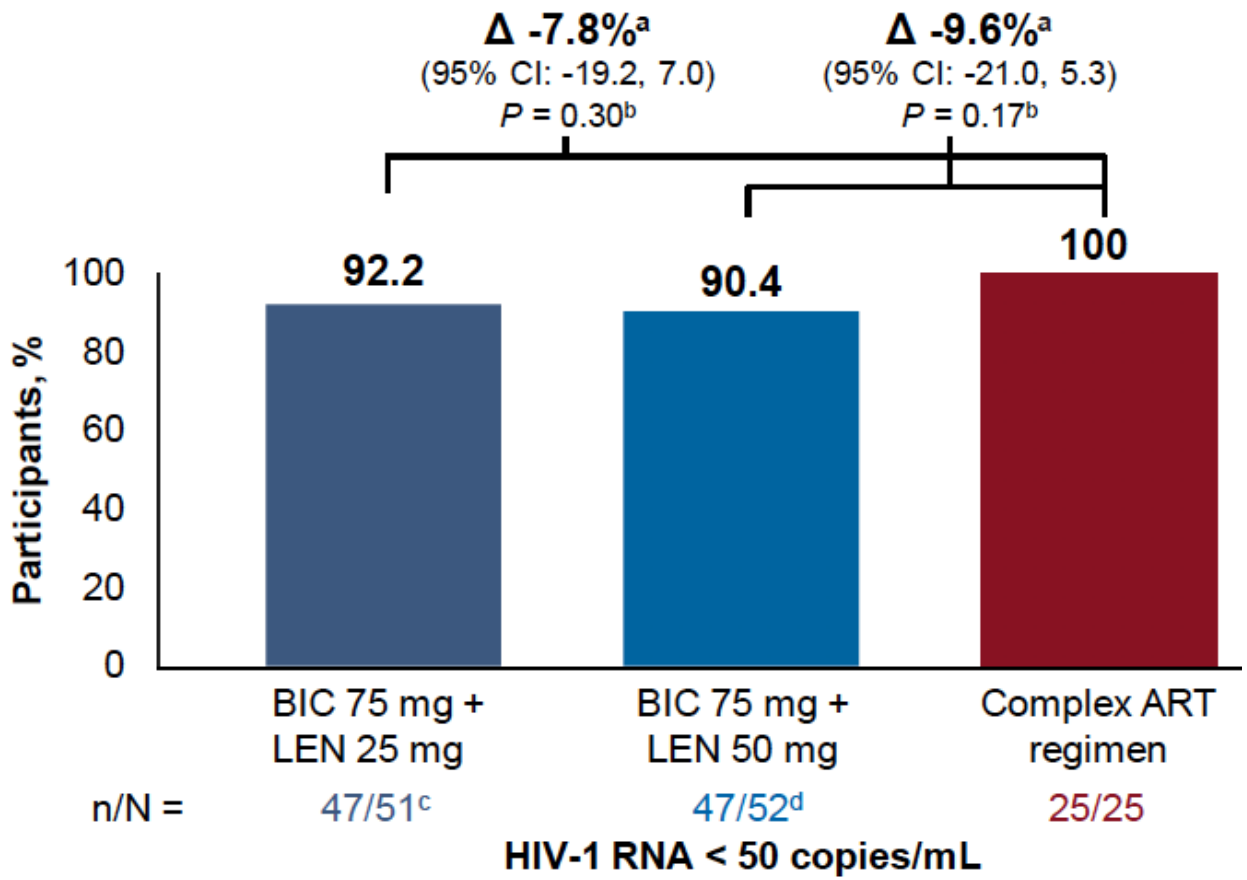
Maturation inhibitor

- GSK3640254 (non-boosted)

Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

ARTISTRY-1: Switching to Oral Bictegravir + Lenacapavir

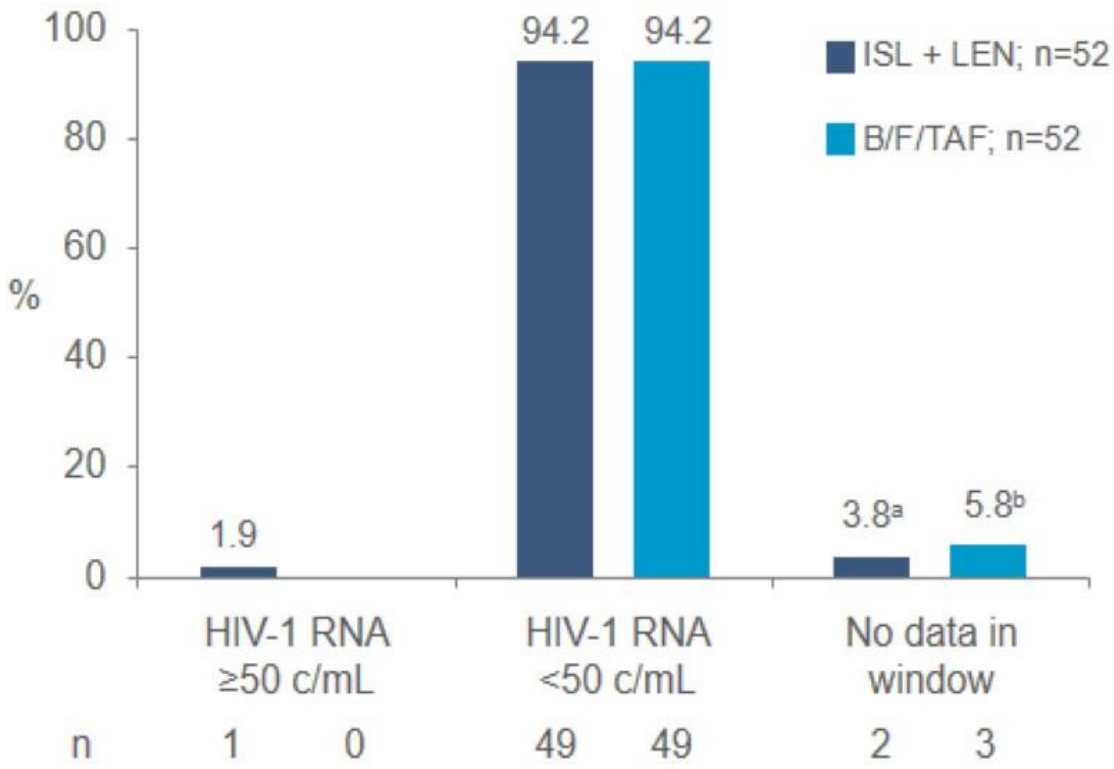
- Randomized study of switching complex ART regimens (multi-class or multi-pill) to oral Bictegravir plus Lenacapavir (HIV capsid inhibitor) in virologically suppressed PWH (n=128)
- Historical resistance: INSTI: 0%; NNRTI: 52%; NRTI: 64%; PI: 36%
- High rates of sustained virologic suppression with oral BIC plus LEN
- BIC 75 mg/LEN 50 mg single tablet regimen to be assessed in phase 3 study



Mounzer K, et al. AIDS 2024. Abstract OAB2602.

Switching to Oral Weekly Islatravir (ISL) + Lenacapavir (LEN) in Virologically Suppressed PWH

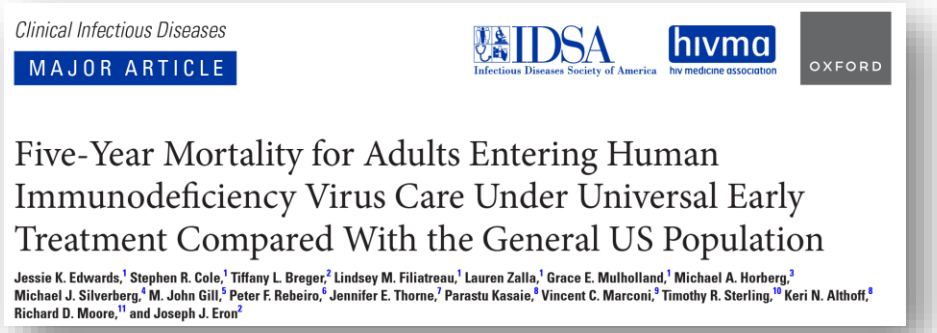
- ISL: nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Dose chosen (2 mg weekly) not anticipated to cause lymphopenia
- Pharmacokinetics of ISL and LEN support once weekly dosing
- Phase 2 study of switching virologically suppressed PWH to daily BIC/FTC/TAF or weekly oral ISL plus oral LEN
- No differences in lymphocyte and CD4 counts between groups
- Phase 3 studies planned

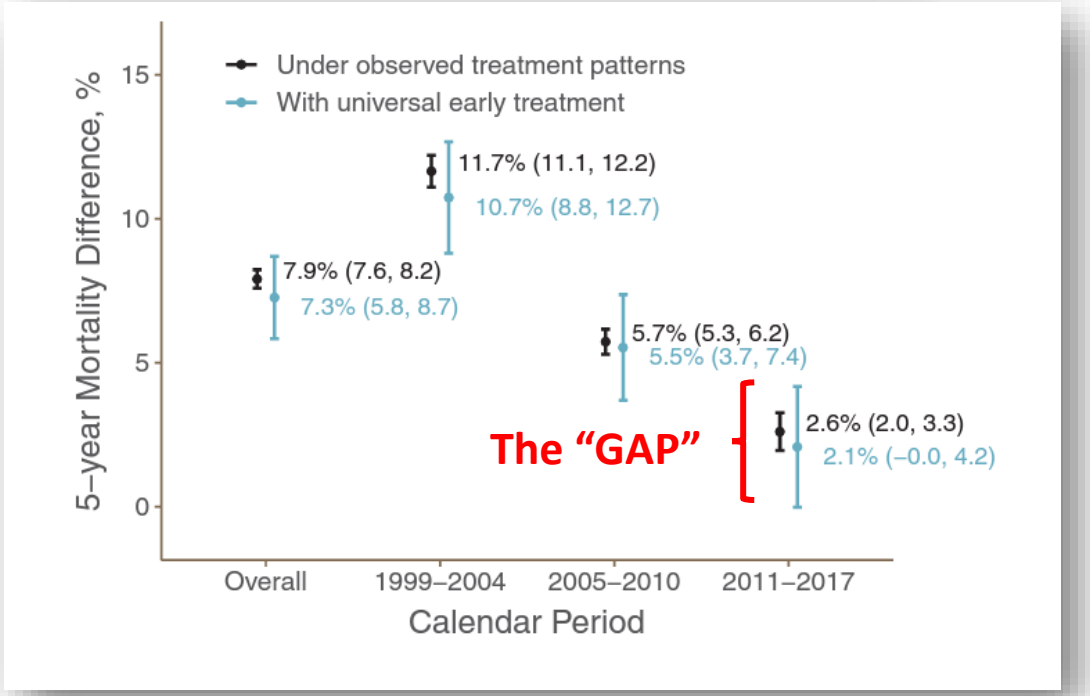


Colson A, et al. CROI 2024. Abstract 208LB.

Improving Outcomes by Preventing Comorbidities

Despite Our Current Era of Excellence, a mortality gap remains





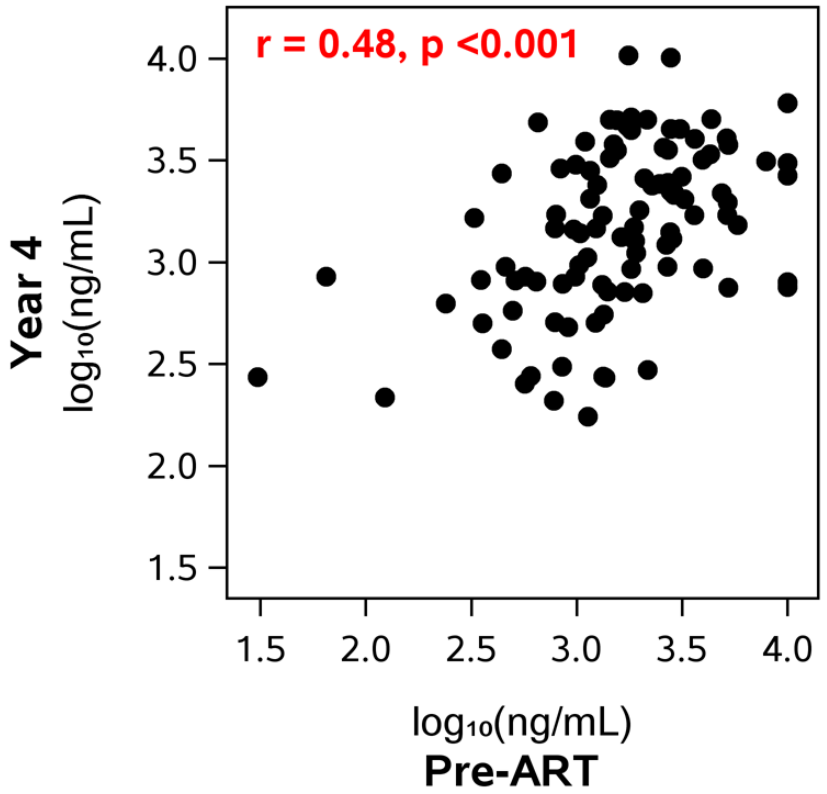
- Study of 83,000 adults entering HIV care in North America
- Mortality gap between people with HIV and similar individuals without HIV is decreasing but has not fully closed

Edwards JK et al, Clinical infectious Diseases. 2022

Potential Reasons for Mortality Gap

- Social determinants of health, including poverty, inequitable access to care, substance use disorder, smoking
- Persistent inflammation
  - High levels of inflammation before ART correlate with high levels while on ART ("immune dysregulation legacy effect")
  - Excess inflammation linked to comorbidities, including cardiovascular disease (CVD)
  - Will anti-inflammatories, like statins, prevent comorbidities?

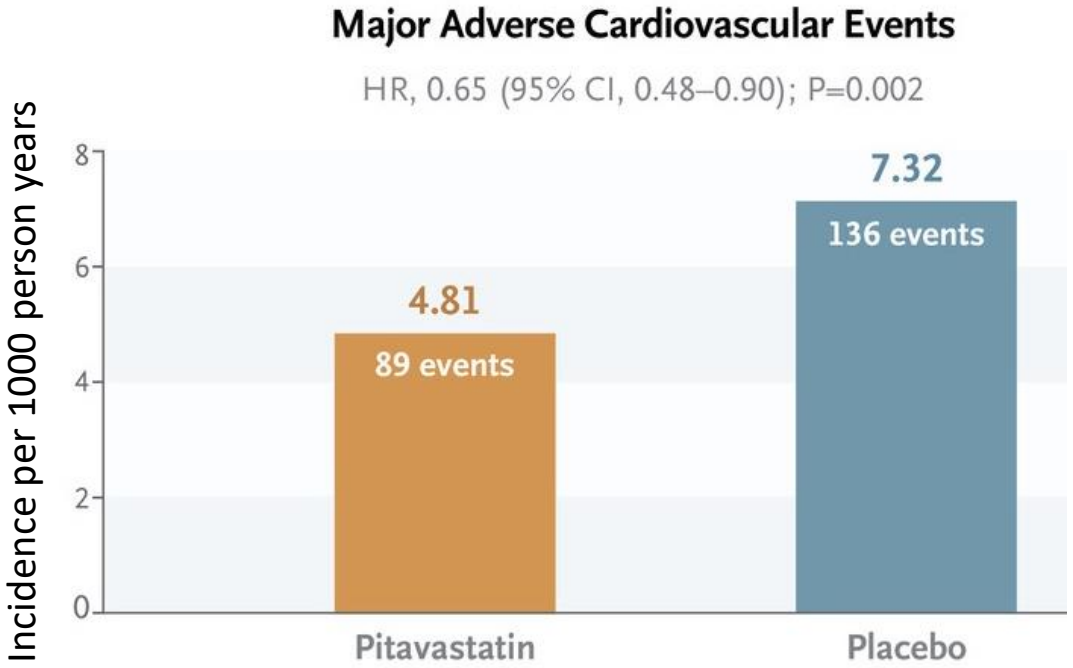
High pre-ART CRP levels correlated with high on-ART levels



Insight START Study Group, NEJM Evidence, 2023; Gandhi RT et al, PLoS Pathogens, 2017

Do Statins Reduce Cardiovascular Events in PWH? REPRIEVE

- Statins lower cholesterol but also have anti-inflammatory effects
- 7700 PWH aged 40–75 yr receiving ART and with low-to-moderate CVD risk (median ASCVD risk score, 4.5%)
- Randomized to pitavastatin or placebo
- Statin group had 35% lower rate of major cardiovascular events (e.g., myocardial infarction, stroke) than placebo group



Grinspoon SK et al, NEJM 2023

Which PWH Should Receive Statins?

HIV Clinical Guidelines: Adult and Adolescent ARV

CLINICAL INFO HIV.gov

Updated: February 27, 2024

- In PWH 40-75 years old with ASCVD >5%, recommend starting pitavastatin, atorvastatin, or rosuvastatin
- In PWH 40-75 years old who have ASCVD <5%, discuss starting statin, particularly if HIV-related risk factors:
  - Long period of HIV viremia
  - Low current or nadir CD4 (<350)
  - Exposure to older ARVs associated with cardiometabolic complications
  - HCV coinfection

	Number need to treat to prevent one CVD event
Overall	106
ASCVD 0 - 2.5	199
ASCVD 2.5 - <5	149
ASCVD 5-10	53
ASCVD >10	35
Rx HTN	80-160

Grinspoon SK et al, NEJM 2023

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new

What Do We Need to Do to Make Excellent Care Better?

1. Diagnose and treat HIV earlier

- Too many people have late diagnosis of HIV
  - Almost 20% have CD4 count <200
- Delayed ART initiation and low nadir CD4 counts associated with lower rate of HIV suppression, higher rates of low-level viremia, higher rates of virologic failure; increased rates of subsequent complications (RESPOND cohort)

Edwards JK et al, Ann Int Med, 2021; Lee JS et al, CID, 2020; IeDEA and COHERE Cohort Collaborations, CID, 2018; Alvarez H/Llibre J, CID 2023

2. Address disparities in HIV prevalence and care delivery within countries and globally

Marked inequities in HIV prevalence in the US and globally

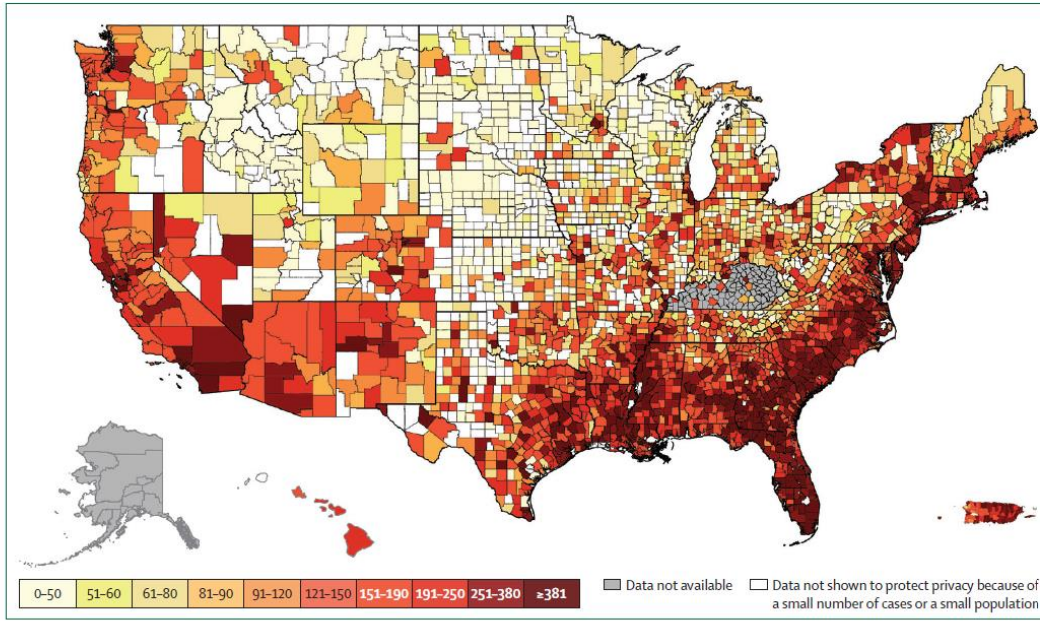
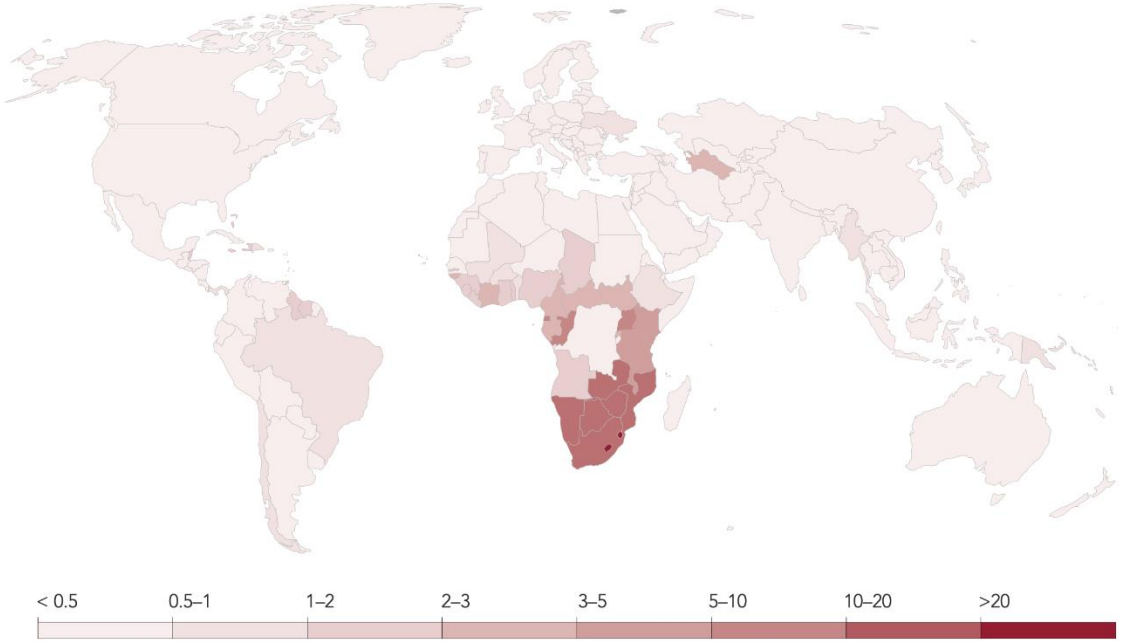


Figure 2: Diagnosed HIV prevalence by US county, 2018

FIGURE 0.1 | **HIV PREVALENCE AMONG ADULTS (AGED 15–49 YEARS), GLOBAL, 2020**



Source: UNAIDS special analysis, 2021.
Note: Data includes 244 countries and territories.

Sullivan P et al, Lancet HIV, 2021; https://reliefweb.int/report/world/2021-unaids-global-aids-update-confronting-inequalities-lessons-pandemic-responses-40

3. Continue investments to improve ART, address comorbidities, achieve cure

<u>World AIDS Day, 2013:</u>

. . . [We] should be at the forefront of new discoveries into how to put HIV into long-term remission without requiring lifelong therapies -- or, better yet, to eliminate it completely.

Patient: One day I'd love to say, "I used to have HIV."

Summary: Navigating our Era of Excellence in ART and What Comes Next

- Several excellent regimens for initial ART, including 2-drug regimens
- For patients who are virologically suppressed, injectable CAB/RPV is an option
- In patients who have difficulty adhering to daily oral ART, injectable CAB/RPV may improve outcomes but must be conjoined with intensive support
- New understanding of how to manage drug resistant HIV in patients with varying resistance levels; novel antiretroviral regimens are coming
- Advances in preventing comorbidities, including statins
- Despite current era of excellence in ART, we need to diagnose and treat HIV earlier; address disparities and inequities; invest in improving care and promoting research