

In Case You Missed It: Updates From CROI 2022 and Beyond

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Gandhi has no relevant financial relationships with ineligible companies to declare. (Updated 03/22/22)

Slide 2

Outline

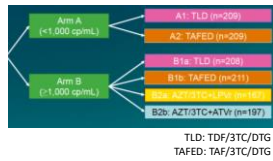
- Current ART
- HIV and Pregnancy
- New ART
- Comorbidities and Coinfections
- HIV Cure
- Pre-exposure prophylaxis
- COVID-19 Advances



Current ART

VISEND: Switching Therapy in Suppressed and Non-Suppressed PWH

- Randomized trial in Zambia
- Patients switching from NNRTI-based treatment (n=1201)
- Arm A: VL <1000
 - About 20% VL 50-999
 - Randomized to TLD or TAFED
- Arm B: VL ≥1000
 - Randomized to TLD, TAFED, AZT/3TC/LPV/r or AZT/3TC/ATV/r



Mulenga L, CROI 2022, Abstract 135

Current ART

VISEND: HIV-1 RNA Suppression at Week 48

HIV-1 RNA at Wk 48, %	VL <1000		VL ≥1000			
	DTG + TDF/3TC (n = 209)	DTG + TAF /3TC (n = 209)	DTG + TDF/3TC (n = 208)	DTG + TAF /3TC (n = 211)	ATV/r + 3TC/ZDV (n = 197)	LPV/r + 3TC/ZDV (n = 167)
ITT (FDA Snapshot) • <50 c/mL	81	76	72	82	71	56
Per protocol (FDA Snapshot) • <50 c/mL	90	86	82	89	78	68

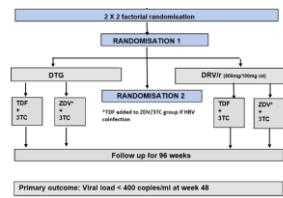
- In PWH on NNRTI-based regimen with virologic non-suppression (VL≥1000), switching to DTG + tenofovir/3TC results in high rates of viral suppression

Current ART

Mulenga L, CROI 2022, Abstract 135

NADIA: 2nd-Line ART after NNRTI Failure

- Participants in Sub-Saharan Africa with virologic failure on TDF/3TC/NNRTI (n=464)
- 2x2 factorial randomization
- Study participants:
 - CD4 <200: 51%
 - VL ≥100,000: 28%
 - Resistance:
 - K65R/N: 50%
 - M184V: 86%
 - Int/high resistance: TDF: 59%. AZT resistance: 18%; 3TC: 92%

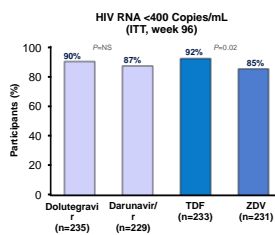


Current ART

Paton N et al, NEJM, 2021.

NADIA: 2nd-Line ART after NNRTI Failure

- DTG + 2 NRTIs non-inferior to DRV/r + 2 NRTIs
 - High rate of suppression even when no NRTIs predicted to be active!
- Continuing TDF/3TC superior to switching to AZT/3TC
- Confirmed viral rebound ≥1000 with ≥1 resistance mutation to DTG or DRV:
 - N=7 (all DTG)
 - TDF/3TC (n=2 – intermediate level DTG resistance)
 - AZT/3TC (n=5 – high level DTG resistance)



Current ART

Paton N, et al. CROI 2022. Abstract LB-137.

Lessons from Trials of Switching ART: VISEND, NADIA

- DTG + tenofovir + 3TC or FTC suppresses HIV RNA in majority of PWH even when NRTIs not anticipated to be active
- In patients virologically suppressed on complicated regimens, switching to tenofovir/FTC + drug with high barrier to resistance (DTG, BIC, PI) likely to maintain suppression, even when there is pre-existing NRTI resistance

Current ART

ART: Short Takes

- In PWH on ART who have cognitive impairment, adding DTG or DTG + MVC (ART intensification) does not improve neuropsychological performance or depressive symptoms (ACTG A5342, InMIND)
- In transgender individuals, hormone (estrogen or testosterone) therapy does not affect tenofovir-diphosphate concentrations; serum estradiol levels not affected by TDF/FTC
- In patients with multi-drug resistant HIV who had not failed an INSTI and who had no evidence of DRV resistance, switching to once daily DTG + DRV/c maintained virologic suppression

Current ART

Letendre, S, CROI 2022, Abstract 133; Blumenthal, J, CROI 2022, Abstract 84; Santos, J, CROI 2022, Abstract 510

ART in Pregnancy

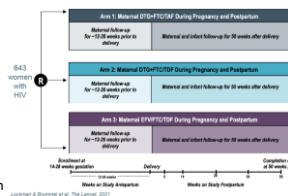


IMPAACT 2010 (VESTED) Trial

- Women initiating ART during pregnancy randomized at 14-28 weeks to DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF

- Adverse pregnancy outcomes less frequent with DTG + FTC/TAF vs DTG + FTC/TDF and EFV/FTC/TDF

- Adverse outcomes linked to lower maternal weight gain – more common in women who received EFV



Pregnancy

Chinua, CROI 2021, Abstract 177; Hoffman RM et al, CROI 2021, Abstract 13; Stranik-Chibanda, L, CROI 2022, Abstract 30

Growth of Infants with Perinatal Exposure to Maternal DTG-based ART vs Efavirenz/FTC/TDF

- Compared growth through 1 yr in infants (n=617)
- Monitored Z-scores: length-for-age (LAZ), weight-for-age (WAZ), weight-for-length (WHZ)
- With maternal EFV/FTC/TDF exposure versus DTG-based ART
 - Infants significantly smaller (LAZ and WAZ Z-scores)
 - Rate of stunting highest among EFV/FTC/TDF group (20%) vs DTG-based ART (14%)

Post Delivery	Dolutegravir + F/TAF	Dolutegravir + F/TDF	Efavirenz/F/TDF
Week 26 (n=193/193/188)	15%	15%	20%
Week 50 (n=479/479/470)	13%	14%	21%

Strain-Chibanda, L. CROI 2022, Abstract 30

DHHS Guidelines Dec 30, 2021: What to Start in Pregnancy

Two NRTIs
 Abacavir/3TC or TAF/FTC, TAF/3TC or TDF/FTC, TDF/3TC

Plus

Bictegravir (limited data)
 Elvitegravir/cobi (PK concerns)
 DRV/cobi (PK concerns)
 ATV/cobi (PK concerns)
 DOR (no data)
 Fostemsavir (limited data)
 Oral or IM CAB/RPV (insufficient data)

Integrase inhibitor:
 Raltegravir (twice daily) or Dolutegravir

or

Protease inhibitor:
 Darunavir/ritonavir (twice daily) or Atazanavir/ritonavir

<https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines>

New ART

- Entry inhibitors:**
 - Attachment inhibitor: Fostemsavir, UB-421
 - CCRS Antagonist: Leronevimab
 - Fusion inh.: Albuviridine
 - Multisite: Combivir
 - Broadly neutralizing Abs
- Reverse Transcriptase Inh. (RTI)**
 - Nucleoside RTI (NRTIs)
 - Nonnucleoside RTI (NNRTIs)
 - Long-acting rilpivirine (RPV) MK-8507
 - Nucleoside RT translocation inhibitor: Islatravir**
- Integrase strand transfer inhibitors (INSTI)**
 - Long-acting cabotegravir (CAB)
- Capsid inhibitor: Lenacapavir**
- Maturation inhibitor: GSK3640254 (non-boosted)**

Gandhi M, Gandhi RT. NEJM 2016;373:246-258

NRTTI

Islatravir (ISL)

Translocase Inhibition

- Nucleoside RT translocase inhibitor (NRTTI)
- Being evaluated for treatment: daily dosing (ISL/doravirine) or weekly dosing (ISL + lenacapavir)
- Being evaluated for pre-exposure prophylaxis trial: monthly dosing; ISL implant
- Studies on hold: dose dependent lymphopenia, decline in CD4 cell count
 - In some participants who received higher dose, CD4 cell decline of >50%

Phase 1b, single-dose, monotherapy study
Study population: ART naive (N=30)

New ART

<https://www.aidsmap.com/news/2021/06/21/phase-1b-single-dose-monotherapy-study-islatravir-na-art-naive-n-30>

Capsid inh.

CALIBRATE: LEN in Treatment Naïve PWH

- Oral formulation: half-life 11-13 d; subcutaneous injection; every 6 months

Treatment naïve N=152

Key eligibility criteria:

- ARV naïve
- HIV-1 RNA <200 copies/mL
- CD4+ cell count >500 cells/μL

Randomized

- About 50 participants per arm
- Maintenance phase: SC LEN q 6 m + TAF or BIC daily; PO LEN+TAF/FTC daily; or BIC/TAF/FTC

New ART

Gupta, S, CROI 2022, Abstract 138

Capsid inh.

CALIBRATE: LEN in Treatment Naïve PWH

Efficacy at Week 54 (FDA Snapshot)

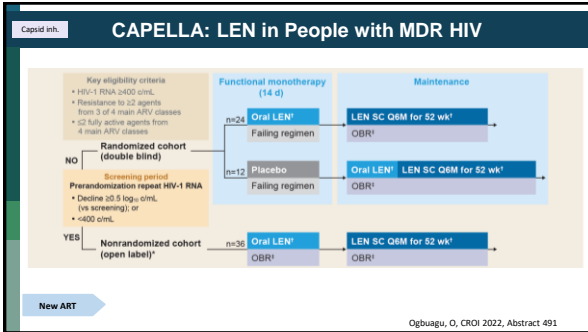
2 of 157 (1.5%) developed LEN resistance: Q67N +/- 70R

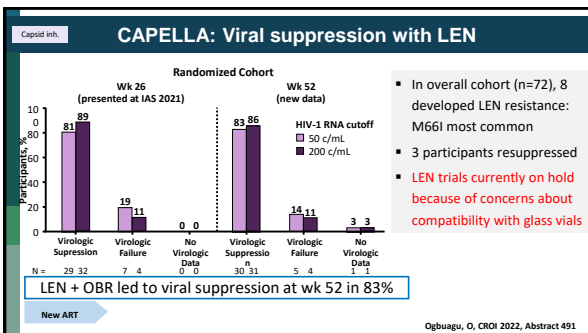
- Possibly related to non-adherence
- Both resuppressed on 2 NRTI + INSTI
- 3 d/c due to ISR

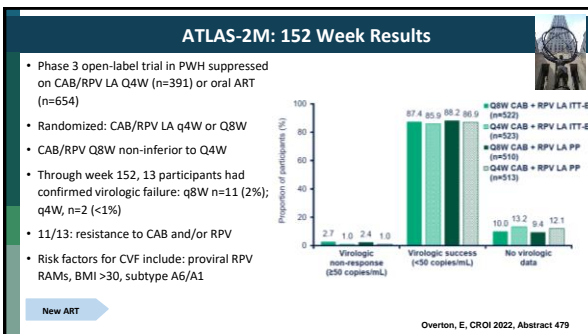
In LEN SC cohort (Groups 1, 2; LEN initially with F/TAF then with TAF or BIC): 88% achieved and maintained virologic suppression at Wk 54

New ART

Gupta, S, CROI 2022, Abstract 138







Coinfections

ANCHOR: Treatment of Anal High-Grade Squamous Intraepithelial Lesions (HSIL) to Prevent Anal Cancer

- Randomized trial to evaluate anal cancer incidence with treatment of anal HSIL vs active monitoring (AM)
- PWH > age 35 w/o prior tx of HSIL or hx of cancer screened for anal HSIL using high-resolution anoscopy (HRA)
- Patients with anal HSIL randomized to AM or immediate HSIL treatment
- Screened 10,723 PWH from 2014-2021
- 52% had HSIL: 53% of men, 46% of women, 63% of transgender people
- Active monitoring: cytology, HRA Q6 months; Biopsied Q12 months or if concern for cancer
- Treatment arm: electrocautery (92.9%); topical 5-FU or imiquimod (8.2%)

Anal dysplasia

Palefsky J, et al. CROI 2022. Abstract 106.

ANCHOR: Study Participants

- 80% men, median age 51 yr
- Median time since HIV dx: 17 years
- ~90% with VL <200
- CD4 nadir ≤200: 51%
- 78% self-identified as homosexual
- ~1/3 smokers

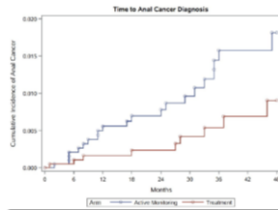
Race/Ethnicity	Monitor (n=2219)	Treatment (n=2227)
Non-Hispanic Whites	31%	33%
African American	42%	42%
Hispanic, non-African American	17%	15%
Asian/Pacific Islander	1%	1%
Other/Unknown	8.5%	7.9%

Anal dysplasia

Palefsky J, et al. CROI 2022. Abstract 106.

Treatment of HSIL reduces risk of anal cancer by 57%

- 30 anal cancers diagnosed in median f/u of 25.8 months
 - 9 in Treatment arm (173/100,000 PY)
 - 21 in Active Monitoring arm (402/100,000 PY)
- 8 study-related serious AEs:
 - 7 in treatment arm (3 pain, 3 abscess, 1 skin ulceration)
 - 1 in AM arm (infection)



Anal dysplasia

Palefsky J, et al. CROI 2022. Abstract 106.

Implications and Remaining Questions

- Screening PWH for HSIL and treating it if found is warranted
- Study authors suggested focusing on highest risk patients: older PWH, those with lower nadir CD4 counts
- Remaining questions:
 - Who should be screened for HSIL (PWH, MSM, older PWH)?
 - How should they be screened (digital rectal exam, HRA, cytology)?
 - How often should screening take place?
 - Is screening cost effective?

Anal dysplasia

Palefsky J, et al. CROI 2022. Abstract 106.

HIV Cure Research

Slide 28 of 44 From RT Gandhi, MD at New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE, IAS-USA.

IMPAACT P1107: HIV-1 Remission With CCR5 Delta 32 Haplo-Cord Transplant in a Woman

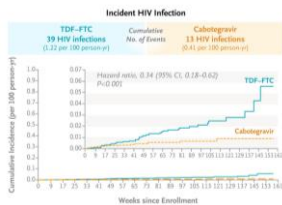
- Middle-aged woman
- 2013: diagnosed with acute HIV
- 2017: diagnosed with acute myeloid leukemia
- 2017: CCR5Δ32/Δ32 cord blood transplant (5/8 match) + peripheral blood mononuclear cells (to aid engraftment) from relative
 - Induction chemotherapy = fludarabine/melphalan/ATG + TBI with 400 cGy
- Day 100: 100% cord chimerism and full remission of acute myeloid leukemia
- ART stopped 37 months post-transplant
- 14 months off ART with no viral rebound (no ARVs in plasma)
- Loss of HIV specific antibody responses; undetectable HIV DNA, no detectable replication competent latent reservoir

Brinson V, et al. CROI 2022. Abstract 65.

Pre-Exposure Prophylaxis

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

Landovitz RJ et al. DOI: 10.1093/NEJM/2022.01.01



- 1 year of follow-up after unblinding:
 - 25 incident HIV infections in CAB arm
 - 7 in participants with on-time injections, adequate CAB concentrations (0.15 per 100 PY); several had INSTI RAMs
 - HIV RNA testing identified infection earlier than Ag/Ab testing
 - RNA testing would have potentially prevented giving CAB to people with incident HIV

Landovitz. CROI 2022. Abstr 96.

FDA-Approved and CDC-Recommended PrEP Regimens

FTC/TDF oral daily dosing[†]	<ul style="list-style-type: none"> ▪ Men and women at risk through sex or IDU ▪ Creatinine clearance ≥ 60
FTC/TAF oral daily dosing[†]	<ul style="list-style-type: none"> ▪ Men and TG women who have sex with men at risk through sex ▪ Not for persons at risk for HIV from receptive vaginal sex ▪ Creatinine clearance ≥ 30
CAB IM injection every 2 months	<ul style="list-style-type: none"> ▪ Men and women at risk through sex

[†]CDC guidelines include option of on-demand or event driven (2-1-1) FTC/TDF dosing in MSM (off label per FDA).
[‡]Screen for HBV if status unknown. If appropriate, administer vaccination. If HBV infection, discuss danger of stopping PrEP without monitoring for potential hepatitis flares. PrEP initiation should not be withheld while waiting for HBV test results.

PrEP
CDC PrEP Guidelines, December 2021, FTC/TDF Pr, FTC/TAF Pr

CDC 2021 Guidelines: PrEP Monitoring

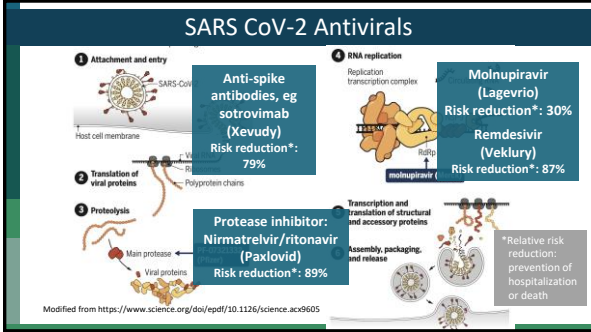
Renal function monitoring with daily TDF/FTC or TAF/FTC:
 Every 12 mo: <50 years old and eCrCL ≥ 90 at PrEP initiation
 Every 6 mo: ≥ 50 years old or eCrCL <90 at PrEP initiation
 No renal monitoring required with CAB

HIV testing while on PrEP:
 Daily oral PrEP: HIV Ag/Ab + HIV RNA at least every 3 months
 CAB: HIV Ag/Ab + HIV RNA at month 1, then every 2 months

STI testing: every 3-4 months for MSM/transgender women

CDC PrEP Guidelines, December 2021

COVID-19 Advances



What About Omicron Lineage BA.2?

- BA.2 has replaced BA.1 in many parts of the world; about 23% of US isolates, 39% in Northeast
- Sotrovimab: decreased activity in lab studies
- Bebtelovimab: active against BA.1, BA.2
 - Authorized when alternative treatments not available or clinically appropriate
- Nirmatrelvir/ritonavir, remdesivir, molnupiravir still expected to be active

Iketani S et al, Nature 2022
<https://covid.cdc.gov/covid-data-tracker/#variant-proportions>

Summary

- In patients with NRTI resistance, treatment with DTG or DRV/r + Tenofovir/FTC results in high virologic suppression rate
- DTG + TAF/FTC is now a preferred regimen during pregnancy
- Novel ART: islatravir (NRTTI) on hold because of lymphopenia; lenacapavir (capsid inh.) advancing but recent issues related to glass vials
- Screening for and treating anal HSIL prevents cancer
- New PrEP guidelines include injectable cabotegravir
- HIV Cure: another case; woman who received cord blood transplant
- COVID-19 treatment: multiple options; keep your eye on BA.2

Question-and-Answer Session