CROI 2023 Report Back: Treatment Updates

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No conflicts of interest or relationships to disclose.

Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

Outline

- LAI CAB-RPV Updates
- D^2EFT Trial: ART for Drug-Resistant HIV
- Weight Gain Updates

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LAI CAB-RPV Updates

Background

- ATLAS, FLAIR, and ATLAS-2M studies have demonstrated efficacy[1,2]
  - Virologic failures in ATLAS-2M have occurred (2.3% q8w vs 0.4% q4w)[2]
- None of the studies included patients with viremia
- Ward 86 in SF published about their experience between June 2021-April 2022[3]
  - 51 PWH initiated LAI CAB-RPV q4w
  - 15 of 51 had detectable viremia
    - 12 of 15 achieved viral suppression (VS)

1-Orkin C et al, NEJM, 2020. 2-Overton ET et al, CID, 2023. 3-Christopoulos KA et al, CID, 2022.

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Ward 86 LAI CAB-RPV Update

- Between June 2021-November 2022, 133 PWH started LAI CAB-RPV[1]
  - Eligibility included willingness to receive q4w injections
  - Exclusion included history of RPV resistance and >1 CAB mutation

- Patients had drop-in access to clinic with rare injections in the community via street medicine

- 76 PWH with viral suppression and 57 PWH without VS were started on LAI CAB-RPV[2]

1-Christopoulos KA et al, CID, 2022. 2-Gandhi M et al, CROI 2023, #OA518.

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Ward 86 LAI CAB-RPV Results

Table 1: Demographics and clinical characteristics of cohort in Ward 86 LA ART program (n=133)

Characteristic	Distribution, n (%)
Age (median, range)	45 (38-45) years
Gender	
Cis Man	117 (88%)
Cis Woman	11 (8%)
Transgender Woman	5 (4%)
Race/ethnicity	
Black	21 (16%)
Latino/a	50 (38%)
White	43 (32%)
Multiracial	19 (14%)
Housing	
Unstable	77 (58%)
Stable	45 (34%)
Homeless	11 (8%)
Insurance	
Medicare or Medicaid or both	130 (98%)
ADAP	3 (2%)
Current stimulant use	44 (33%)
Major mental illness	51 (38%)
Virologically non-suppressed (>30 copies/ml)	57 (43%) with log10 viral load (mean, STD) 4.21 (1.30)
CD4 count (median with interquartile range)	Virologically suppressed 616 (395–818) Virologically non-suppressed 215 (75–402)

* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- 74% (66-81%) with on-time injections
- Among 76 with VS, 100% (95% CI 94-100%) remained suppressed
- Among 57 PWH without VS, 55/57 suppressed (at median of 33 days)
  - VF rate of 1.5%
  - 2 treatment failures occurred <24 weeks

Patient #1 with VF: Started with V179I mutation, baseline VL 214,540 → 39,293 copies/mL at first visit; developed Y181C, L100I

Patient #2 with VF: Started with T97A mutation, baseline VL 137,134 → 4371 copies/mL at first visit; developed E138K (NNRTI), R263K

Gandhi M et al, CROI 2023, #OA518.

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LAI CAB-RPV in PWH with Viremia: Conclusions

- PWH with viremia achieved high rates of VS on q4w LAI CAB-RPV
- Efforts at Ward 86 for those without VS are resource intensive (drop-in access, street medicine, incentives) but necessary to reach the last ~10% of the population
- Two individuals did not suppress and had VF < 24 weeks into therapy
  - Both had baseline RAMs (V179D and T97A, respectively) prompting an intensification of Ward 86 protocol to no longer allow any INSTI or NNRTI resistance, except K103N
- Eager to see longer term data and q8w data from this cohort
- Ward 86 LAI CAB-RPV protocol is available on www.gettingtozerosf.org

Other Key LAI CAB-RPV Abstracts

1. SOLAR Study: Switching from BIC/TAF/FTC to LAI CAB-RPV

2. Low concentrations of CAB-RPV in PWH

3. Predictors of Post-Switch Viremia

4. PK of CAB-RPV Administered in the Thigh

Other Key LAI CAB-RPV Abstracts

1. SOLAR Study: In a RCT of 670 stable PWH on BIC/TAF/FTC switched to LAI CAB-RPV q8w vs continued BIC/TAF/FTC, VS was non-inferior at 12 months[1]
   - 5 VFs in CAB-RPV – 3 with RAMs (one with INSTI-R at baseline on proviral DNA, injections on time)
   - 1 in BIC/TAF/FTC – none with RAMs
   - 90% in LA arm preferred CAB-RPV after switch from BIC/TAF/FTC

2. Low Concentrations of CAB-RPV: In a French prospective cohort of 58 virally suppressed switched to LAI CAB-RPV, CAB and RPV C_t were low at month (M) 1 and 3[2]
   - Only 1 person had VF (no baseline resistance)
     - 30 y/o MSM, BMI 29.4 kg/m^2, VS x 1.8y previously on ABC/3TC/DTG, no oral-lead in
     - HIV-1 RNA 2870 copies/mL at M1, no treatment emergent resistance
     - C_t CAB = 701 ng/mL, C_t RPV = 28 ng/mL at M1
   - No oral lead in and high BMI were associated with low C_t (median BMI in study = 24 kg/m^2, IQR 22-26)

1-Ramgopal MN et al, CROI 2023, #OA191. 2-Rubenstein E et al, CROI 2023, #OA195.

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Other Key LAI CAB-RPV Abstracts

3. Predictors of Post-Switch Viremia[1]
   - In a retrospective cohort of 144 PWH on LAI CAB-RPV, having at least one detectable VL in the year prior to switch was a risk factor for detectable viremia post switch

4. PK of CAB-RPV Administered in the Thigh[2]
   - In a substudy of 121 PWH in ATLAS-2M receiving ≥3 years of gluteal injections, with an interim switch to 16 weeks of thigh injections, difference in plasma concentrations between gluteal and thigh injections were not considered clinically relevant (in both the q4w and q8w arms)
     - High rates of VS and no confirmed VF
     - 30% preferred thigh injection
     - Median BMI 25.4 kg/m2 (range 17.88-52.69)
     - More data is needed on early and chronic thigh administration

1-Kenney S et al, CROI 2023, #OA516. 2-Felizarta F et al, CROI 2023, #519.

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D^2EFT: ART for Drug-Resistant HIV

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ART for Drug-Resistant HIV: Background

- DAWNING sub-analysis: DTG + 2 NRTIs, regardless of pre-existing RAMs to one of the NRTIs, maintained VS[1]
  - DTG can fail with INSTI-R but b/PI generally do not fail with PI-R
  - PI used was LPV/r

- NADIA Trial: Affirmed use of DTG with <2 active NRTIs in the setting of NRTI-R (and showed us some surprising results of TDF activity in the setting of a K65R)[2]
  - Reaffirmed that DTG can fail with INSTI-R but PIs generally do not
  - PI used was DRV/r

- VISEND Trial: Affirmed use of DTG or 2nd line PIs as 2nd line therapy[3]

1-Aboud M et al, Lancet Infect Dis, 2019. 2-Paton NI, CROI 2022, #OA137. 3-Mulenga LB, CROI 2022, #OA135.

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D²EFT Methods

Inclusion:
- PWH >18 years
- Failed first-line NNRTI + 2 NRTIs (at least 2 consecutive HIV RNA > 500 copies/mL at least 7 days apart after a minimum 24 weeks exposure)

Exclusion:
- Prior PI/INSTI exposure
- HBsAg positive
- Significant co-morbidity/active co-infection
- Pregnancy/breast feeding

Arm 1: Standard of Care (SOC)
DRV/r + 2NRTI

Arm 2: Intervention
DRV/r + DTG

Arm 3: Intervention*
DTG + XTC/TDF

~TLD

*Added in May 2018, so was excluded for stage 1 of study

D^2EFT Patient Characteristics

- 831 PWH in over 14 LMICs randomized to one of 3 arms
  - Stage 1: Arm 1 vs Arm 2 (n=109)
  - Stage 2: Arm 1 vs Arm 2 vs Arm 3 (n=722)
  - Only 7 withdrawals and 3 LTFU
- Pertinent baseline characteristics
  - Median CD4 (cells/mm3): 206 (IQR 93, 357)
  - Median HIV-1 RNA $log10_c$/mL: 4.2 (IQR 3.6, 4.8)
  - No genotyping required
- ART use
  - NNRTI at 1st line failure: 82.7% Efavirenz, 11.4% Nevirapine
  - NRTIs used in 2nd line with DRV/r: 76% AZT/3TC, 19% TDF/XTC

Matthews G et al, CROI 2023, #OA198.

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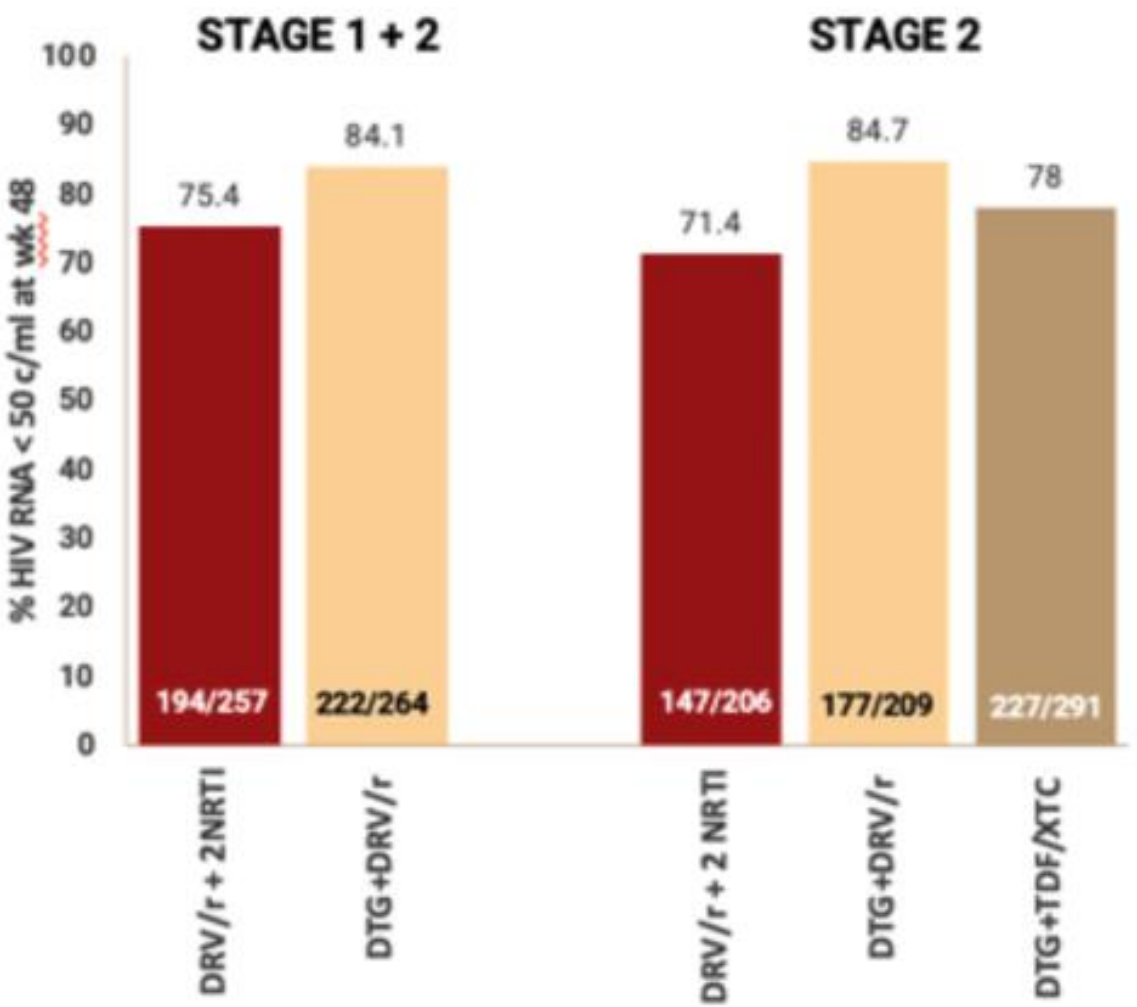
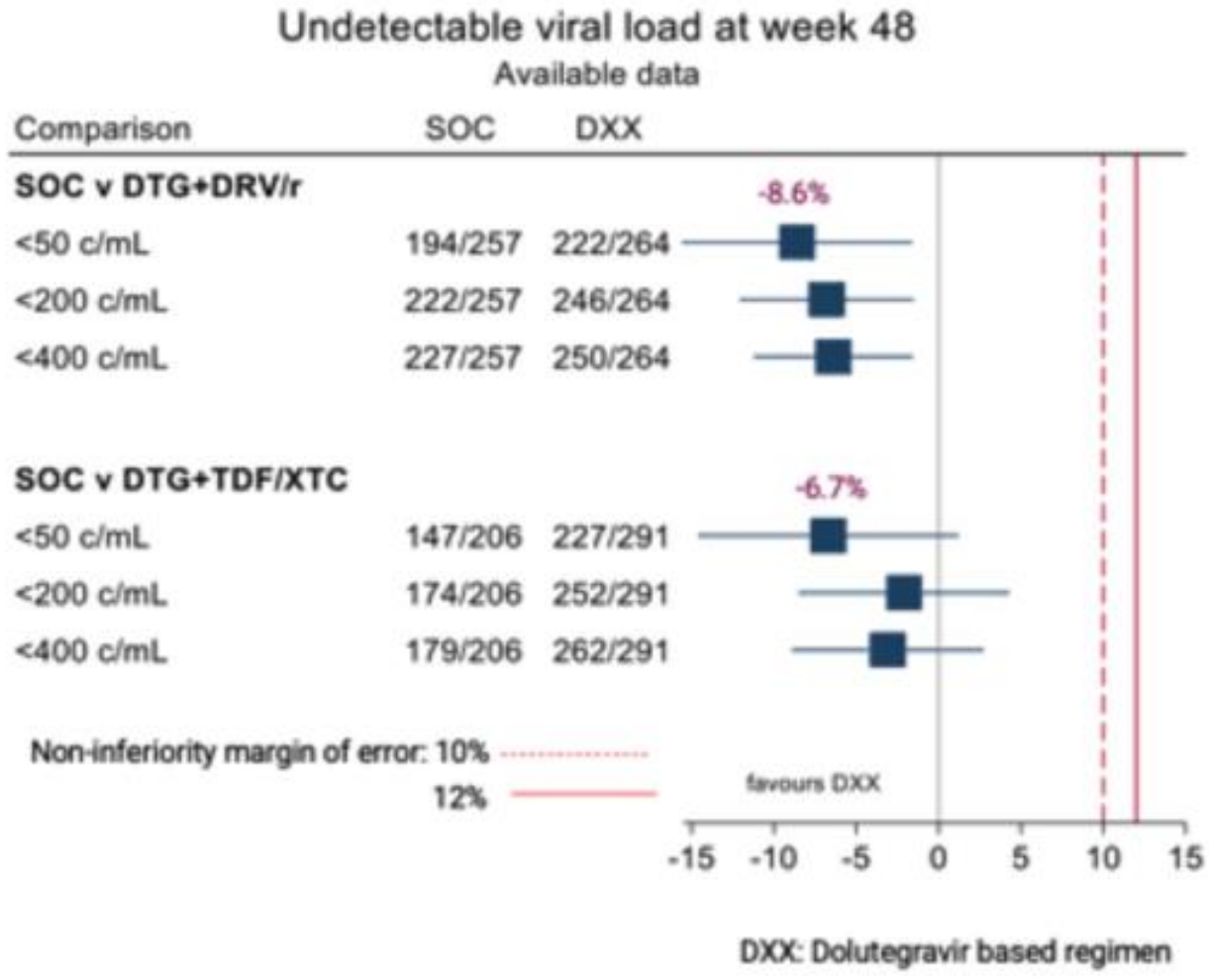
D²EFT Outcomes





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D^{2}EFT Conclusions

- After failure with NNRTI + 2 NRTIs,
  - DRV/r + DTG was superior to standard of care (DRV/r + 2 NRTIs)
  - DTG + XTC/TDF was non-inferior to standard of care (DRV/r + 2 NRTIs)
- Other outcomes
  - Mean CD4 gain at 48w greater in intervention arms as compared to SOC
  - Mean weight gain at 48w was greater in intervention arms as compared to SOC
- Caveats
  - Though the DRV/r + DTG arm demonstrated superiority to SOC, availability and low cost of TLD fixed dose combination (non-inferior) in LMICs is a key consideration when choosing ART
  - NRTI backbone used with DRV/r was 76% AZT/3TC, 19% TDF/XTC, so there was less representation from TDF-containing NRTI that we would more often use

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Weight Gain Updates

Weight Gain and ART: Background

- CROI 2019 – An association between INSTIs & weight gain is reported, perhaps more so with DTG[1-4]
- ADVANCE Study 2019 – RCT in Sub-Saharan Africa, combination of TAF/FTC + DTG led to the most weight gain[5]
- IAS 2020 – OPERA cohort demonstrated weight gain in PWH switching from TDF to a TAF-containing regimen, most pronounced in the 1st nine months after switch[6]
- ID Week 2020 – A cohort study finds switch from TDF to TAF associated with more weight gain than switch from ABC to TAF[7]
- IAS 2021 – TANGO 144w metabolic analysis showed weight gain with both TAF-based ART and DTG-3TC[8]

1-Lake, CROI 2019, OA#669. 2-Bourgi K et al, CROI 2019, #OA670. 3-McComsey GA et al, CROI 2019, #671. 4-Kerchberger, CROI 2019, OA #672. 5-Venter WDF et al. NEJM. 2019. 6-Mallon, AIDS 2020, #OAB0604. 7-McComsey GA, ID Week 2020. 8-van Wyk, IAS 2021 #PEB164

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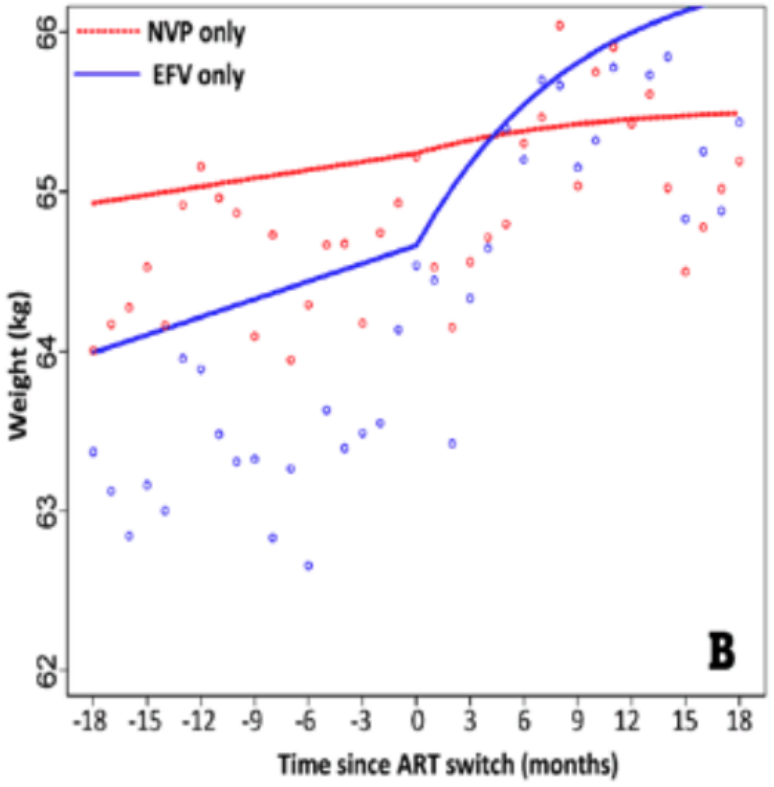
Weight Gain Updates

- SOLAR Study: In a RCT of 670 stable PWH on BIC/TAF/FTC switched to LAI CAB-RPV q8w vs continued BIC/TAF/FTC, switch to LAI CAB-RPV did not lead to weight loss[1]
- Weight Changes in Switch to DTG in Kenya: Of ~23K PWH, switch from EFV to DTG led to weight gain, but switch from NVP to DTG did not[2]



1-Tan DHS et al, CROI 2023, #196. 2-Bourgi K et al, CROI 2023, #OA674.

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- SOLAR Study: In a RCT of 670 stable PWH on BIC/TAF/FTC switched to LAI CAB-RPV q8w vs continued BIC/TAF/FTC, switch to LAI CAB-RPV did not lead to weight loss[1]

- Weight Changes in Switch to DTG in Kenya: Of ~23K PWH, switch from EFV to DTG led to weight gain, but switch from NVP to DTG did not[2]

- Weight Changes After Switch from TAF/FTC+DTG: After 4 years of weight gain on TAF/FTC + DTG, switch to TLD for 52w led to weight loss in women (median -1.6kg, $p<0.05$)[3]
  - Change in weight was not statistically significant for men

1-Tan DHS et al, CROI 2023, #196. 2-Bourgi K et al, CROI 2023, #OA674. 3-Bosch BE et al, CROI 2023, #OA671.

Conclusions

1. LAI CAB-RPV q4w is effective in a cohort of 57 PWH with viremia and is resource intensive, though this is likely what it will take to end the epidemic.
2. Some concerning data emerged re LAI CAB-RPV, including impact of baseline resistance, VF emerging even in the setting of on-time injections, modestly increased baseline BMIs, oral-lead in, and viremia in the year prior to switch.
3. LAI CAB-RPV administered in the thigh seems promising, but not ready for routine use.
4. After prior VF with NNRTI + 2NRTIs, D^2EFT Trial reaffirms that DTG + XTC/TDF is non-inferior to DRV/r + 2NRTIs and newly demonstrates that DTG + DRV/r is superior.
5. Regarding weight gain and ART, consider whether the effects seen are due to anorectic effects of TDF or EFV or due to obesogenic effects of TAF or DTG.

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