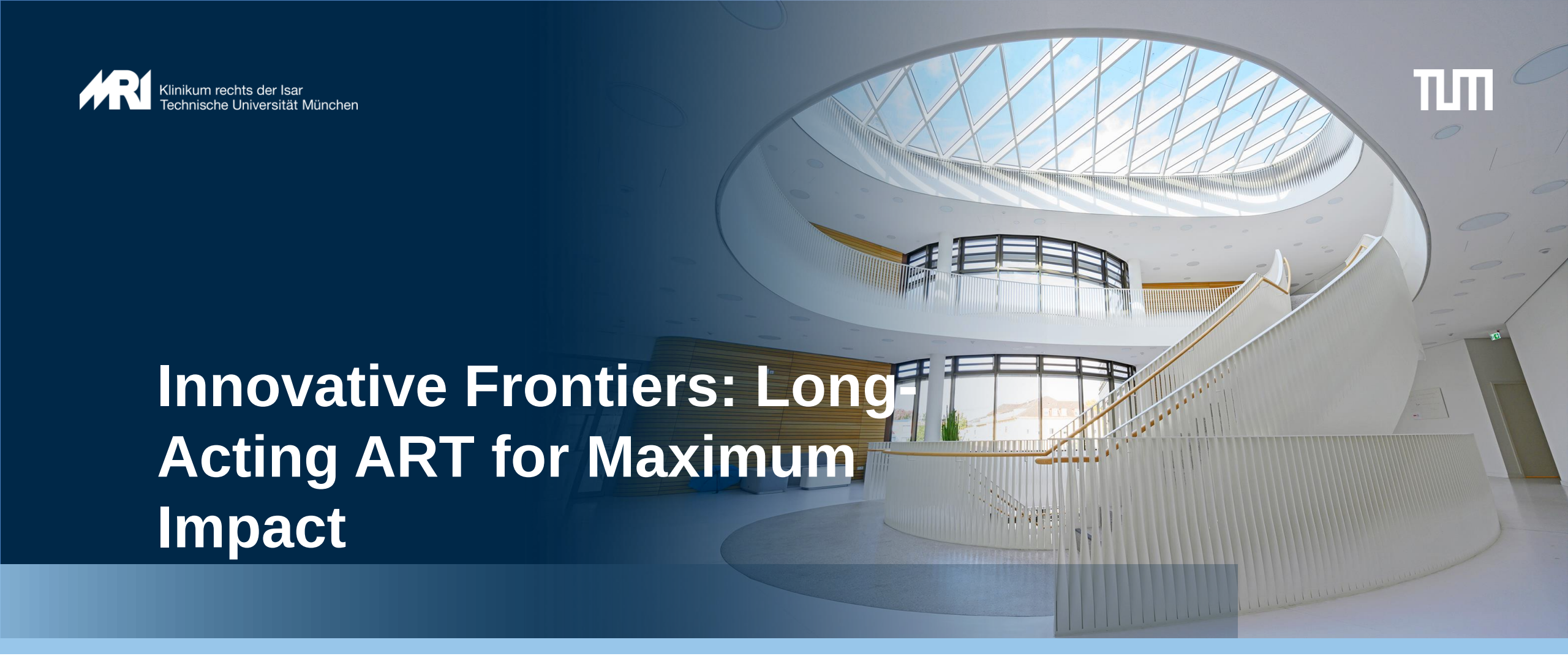
Klinikum rechts der Isar
Technische Universität München



Innovative Frontiers: Long-Acting ART for Maximum Impact

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Potential COI Statement

Christoph D. Spinner

CDS reports grants and personal fees from AbbVie, grants, fees and non-financial support from Gilead Sciences, grants and personal fees from Janssen-Cilag, grants and personal fees from MSD, grants from Cepheid, personal fees from GSK, grants and personal fees from ViiV Healthcare, during the conduct of the study; fees from AstraZeneca, other from Apeiron, grants, personal fees and non-financial support from BBraun Melsungen, grants, personal fees from BioNtech, personal fees from Eli Lilly, personal fees from Formycon, personal fees from Moderna, personal fees from Molecular partners, personal fees from Novartis, grants and personal fees from Eli Lilly, personal fees from Roche, personal fees from SOB, personal fees from Pfizer.

HIV Therapy: Where do we come from and where do we stand in 2024?

ART has become highly effective, tolerable and convenient

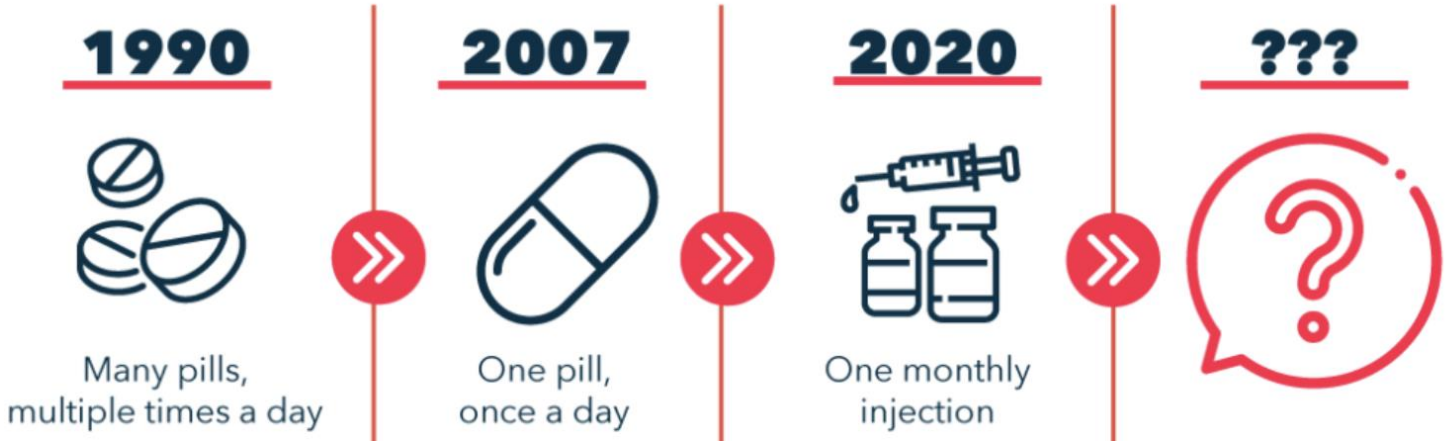
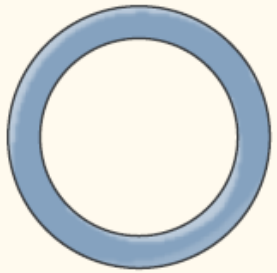


Image: https://paninbc.ca/2023/03/20/join-the-fight-for-access-to-hiv-treatment-that-eliminates-the-need-for-daily-oral-medication/

Available options of antiviral LA application

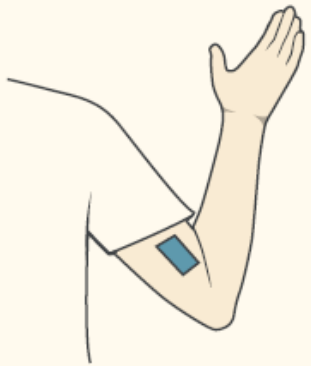
INTRAVAGINAL RING (IVR)



Polymer ring inserted into the vagina releases antiretroviral drug over time.

PrEP

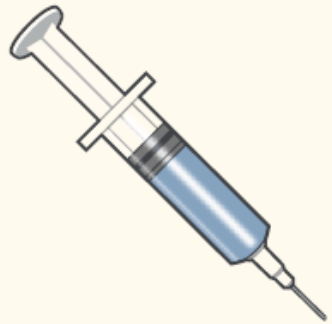
IMPLANT



Device implanted in the body releases antiretroviral drug over time.

PrEP

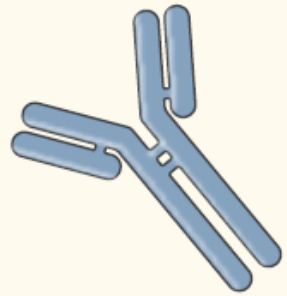
INJECTABLE



Long-acting antiretroviral drug is injected into the body.

PrEP & ART

ANTIBODY



Antibody is infused or injected into the body.

ART

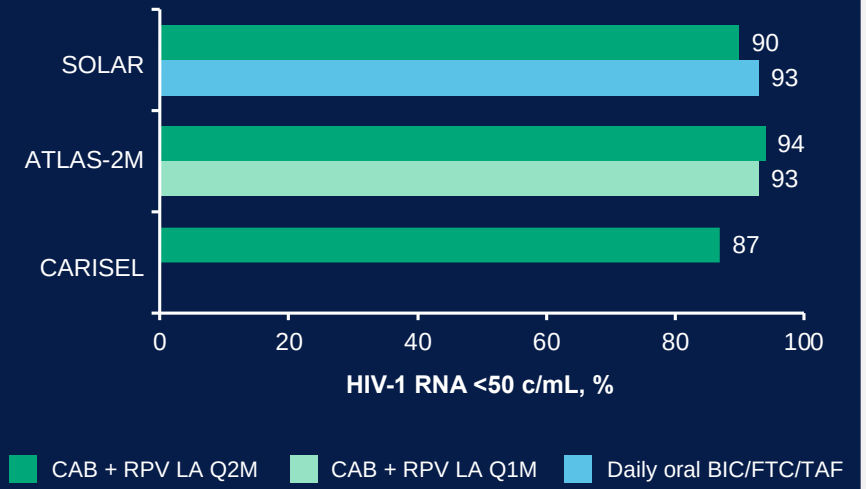
Source: National Institute of Allergy and Infectious Diseases

National Institute of Allergy and Infectious Diseases

Studies demonstrated LA ART high efficacy of Q2M CAB/RPV

Efficacy

Virological Snapshot outcomes after 1 year of treatment*[1–3]



*Outcomes reported at Month 12 in SOLAR and CARISEL. Outcomes reported at Week 48 in ATLAS-2M
BIC, bictegravir; **c/mL,** copies/mL; **FTC,** emtricitabine; **TAF,** tenofovir alafenamide; **Q1M,** every 1 month; **Q2M,** every 2 months

Safety and tolerability

CAB + RPV LA was well tolerated
with few serious adverse events and a comparable safety profile to daily oral BIC/FTC/TAF[1–3]

Injection-site reactions were common, but typically mild or moderate **and rarely led to withdrawal**[1–3]

1. Ramgopal MN, et al. Lancet HIV 2023;10:e566–77
2. Overton ET, et al. Lancet 2021;396:1994–2005
3. Jonsson-Oldenbüttel C, et al. AIDS 2022. Poster EPLBB05

Risk factors of viral failure w or w/o emergence of resistance

- Factors associated with increased odds of confirmed virologic failure:
  - **RPV RAMs at baseline** (OR: 40.36; *P* <.001)
  - Log_2 of post hoc Wk 8 RPV trough concentration (OR: 5.00; *P* = .002)
  - **Baseline HIV-1 subtype A6/A1** (OR: 5.92; *P* = .008)
  - **BMI ≥30 kg/m² at baseline** (OR: 1.13; *P* = .020)
- Q8W dosing was not a significant factor

Baseline Factors	Patients, % (n)*	CVF, % (n)	HIV-1 RNA <50 c/mL, % (n)
None	70.5 (732)	0.41 (3)	94.8 (694)
1	26.2 (272)	0.37 (1)	96.0 (261)
≥2	**3.37 (35)**	**25.71 (9)**	**71.4 (25)**

*For CVF analysis, N = 1039

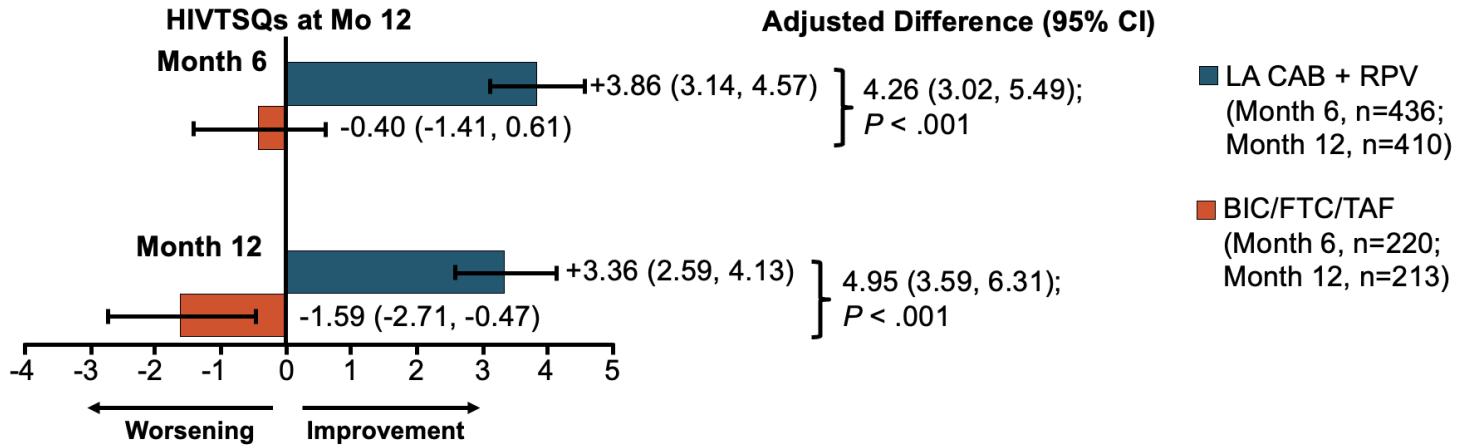
Cutrell. AIDS. 2021;35:1333.

Slide credit: clinicaloptions.com

PRO: Patients' perspective on CAB/RPV

SOLAR study demonstrates high overall treatment satisfaction

- Mean HIVTSQ score at baseline: 58



- Of 425 participants in the CAB + RPV arm, 90% preferred LA CAB + RPV vs 5% preferred BIC/FTC/TAF

Ramgopal. CROI 2023. Abstr 191. Reproduced with permissions.

Slide credit: clinicaloptions.com

Guideline recommendations focus to specific switch issues, such as simplification, reduced pill burden, stigma or convenience

EACS V12

Switch Strategies for Virologically Suppre

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen, see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions,** page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between Viral Hepatitis Drugs and ARVs
4. **Planned pregnancy or women wishing to conceive,** see Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

https://www.eacsociety.org/media/guidelines-12.0.pdf

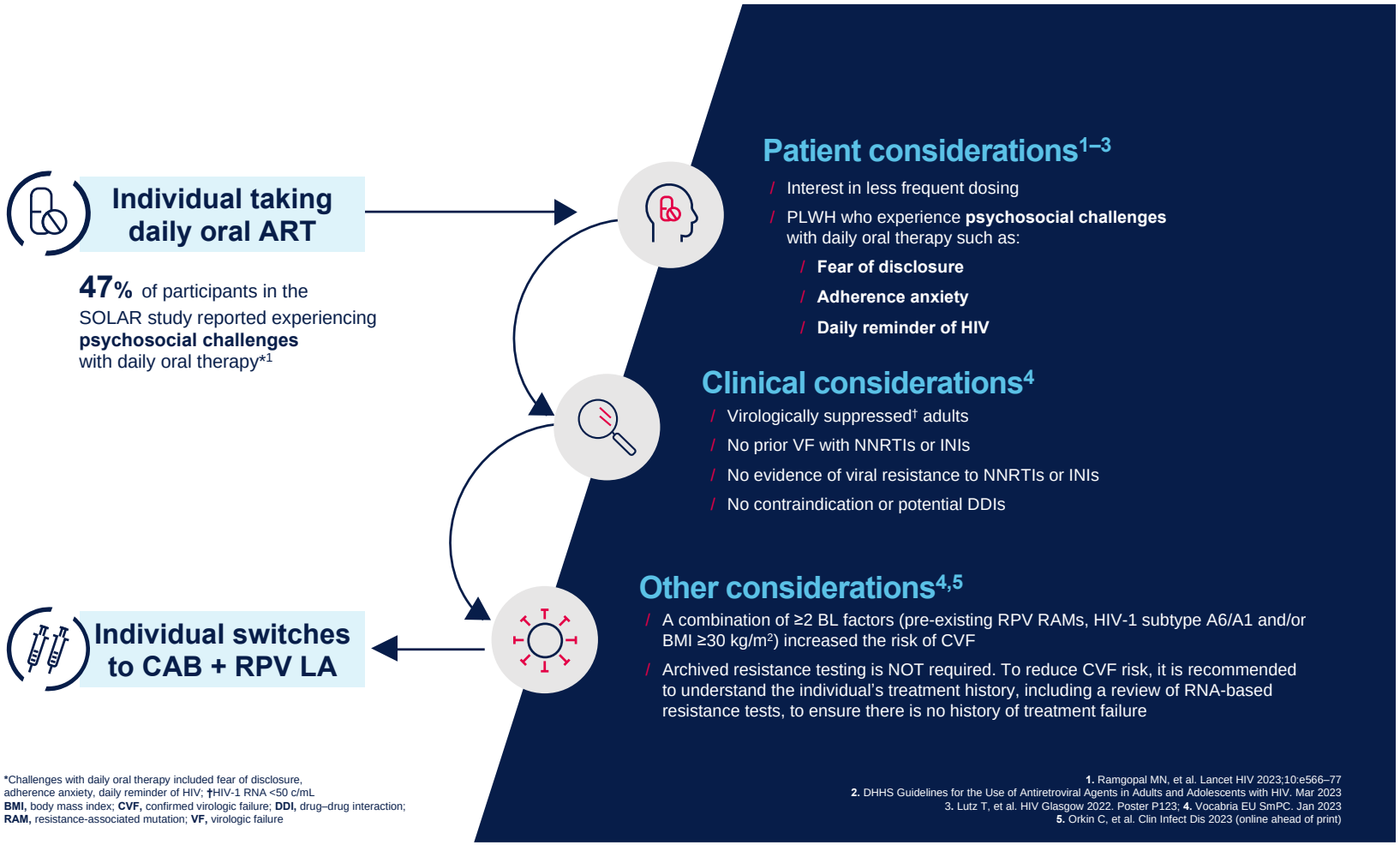
IAS-USA 2022

Switches to Long-acting Cabotegravir and Rilpivirine

In persons with no history of treatment failure and no known or suspected resistance to either drug, injectable cabotegravir and rilpivirine, given either every 1 or 2 months, was noninferior to continued oral ART.[48,49] Those interested in non-oral options for ART because of privacy, stigma, or convenience reasons will usually have greater satisfaction with cabotegravir and rilpivirine than continued oral ART.[50] One recent report described use of this regimen in 15 people with viremia not receiving oral ART.[19] Despite the short-term success of this approach in this study, cabotegravir plus rilpivirine is not recommended in the setting of viremia outside of a research setting and should be started only after viral suppression has been achieved with oral ART.

https://jamanetwork.com/journals/jama/fullarticle/2799240

Patient selection and considerations for CAB/RPV-switch



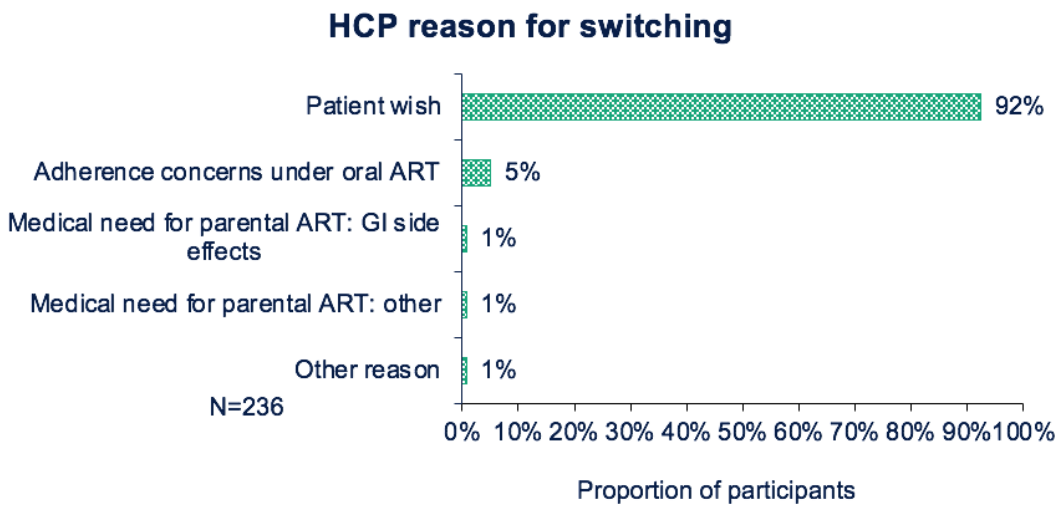
*Challenges with daily oral therapy included fear of disclosure, adherence anxiety, daily reminder of HIV; †HIV-1 RNA <50 c/mL
BMI, body mass index; **CVF,** confirmed virologic failure; **DDI,** drug–drug interaction; **RAM,** resistance-associated mutation; **VF,** virologic failure

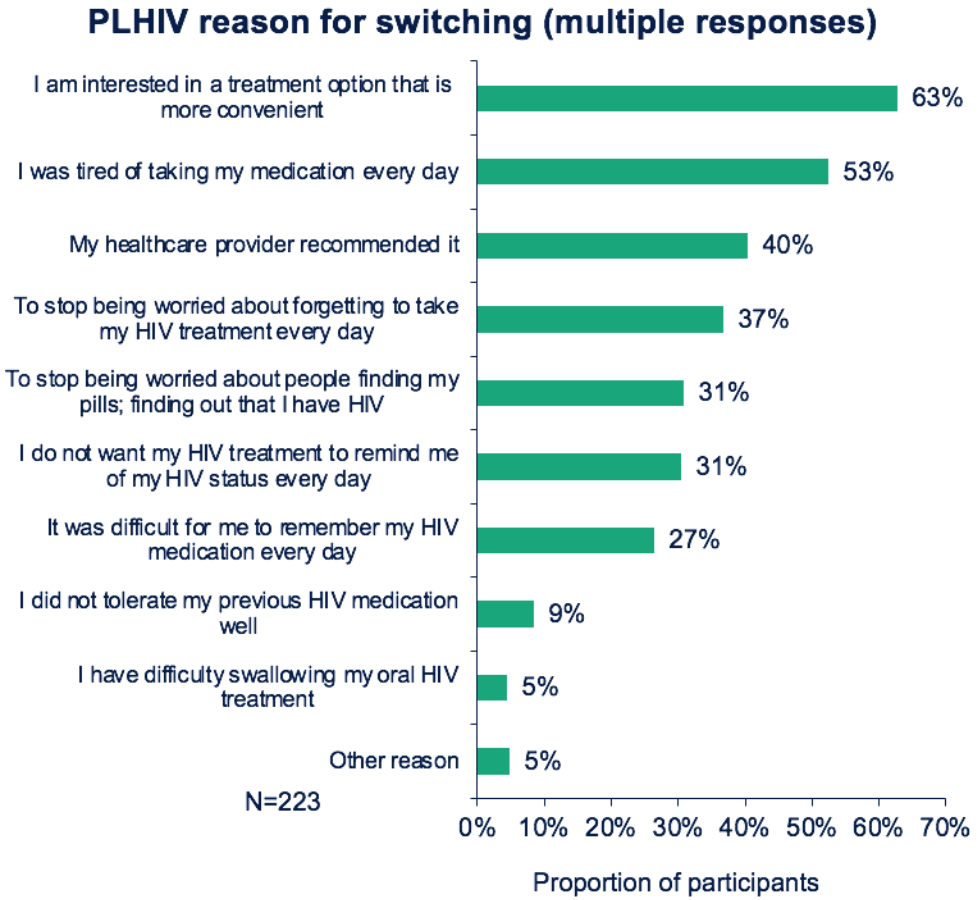
1. Ramgopal MN, et al. Lancet HIV 2023;10:e566–77
2. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Mar 2023
3. Lutz T, et al. HIV Glasgow 2022. Poster P123; **4.** Vocabria EU SmPC. Jan 2023
5. Orkin C, et al. Clin Infect Dis 2023 (online ahead of print)

CARLOS: The German experience on switching to CAB/RPV

Patient wish is the main reason for switch

- **Design:**
  - Non-interventional, multicenter cohort study
  - Study centers: 19, n=236





Scherzer J et al AIDS 2022 #EPB179

PRO and CON of CAB/RPV in clinical routine (selection)

PRO

- Patient demand, simplification and improvement of therapy outcomes in dedicated populations
- Increased adherence and stigma reduction
- Reduced anxiety and fear
- Option for adherence improvement

CON

- Availability and costs
- Increased patient contacts for injections
- Need for HCP i.m. injection and re-call management
- Risk of failure with resistance

CAB/RPV in „difficult“ populations?

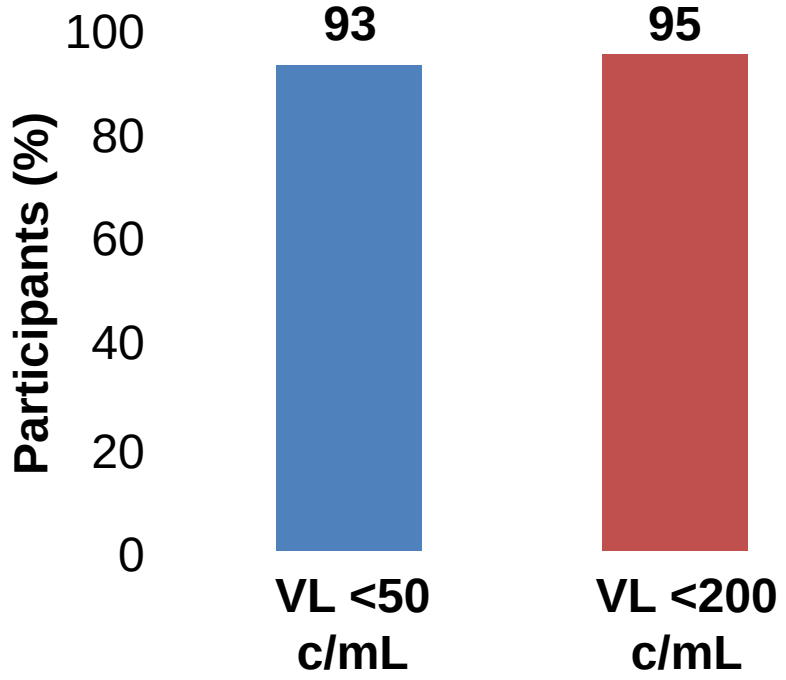
Is CAB/RPV another option?

Setting:
- Ward 86 HIV clinic, San Francisco
- n = 286 (approx. 90% male)

Cohort disposition of non-suppressed PLWH
- N = 59/286 not suppressed at BL
- 61% amphetamine use, 10% opioids
- Frequent co-morbidities

▸ LA–CAB/RPV 400/600mg Q4 i.m.

Viral Suppression on LA CAB + RPV + Alternative ART at Wk 48 **(n =** 59**)**



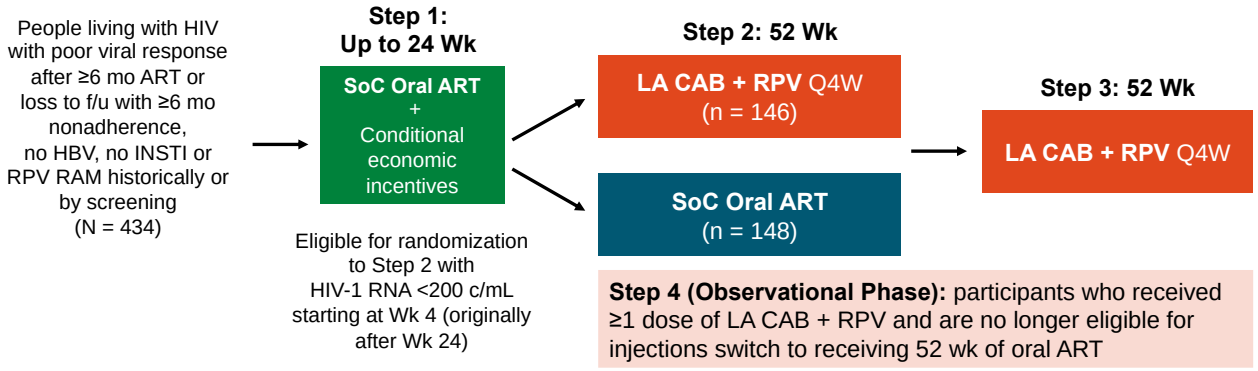
81% (48/59) remained on LA CAB + RPV with **VL <50 c/mL** at Wk 48

Hickey. CROI 2024. Abstr 628.

LA CAB+RPV in PLWH with oral adherence challenge (LATITUDE, ACTG A5359) is superior to oral ART

Design

- Prospective, randomized, open-label phase III trial



- **Primary endpoint:** treatment regimen failure defined as earliest confirmed virologic failure or discontinuation during step 2
- **Key secondary endpoints:** virologic failure, treatment-related failure, permanent treatment discontinuation

Main findings and meaning:

- LA CAB+RPB is superior to SoC oral ART, even though basline HIV RNA was higher in LA group
  - 93% injections were on time, only 3% were not
  - Tolerability was good, mainly mild-to-moderate ISR
- DSMB stopped trial early
- LA CAB+RPV is a safe option in PLWH with adherence challenges

Rana. CROI 2024. Abstr 212.

Updates IAS-USA recommendation on LA

LA-CAB+RPV, March 2024

- When supported by **intensive follow-up** and case management services, injectable LA CAB + RPV may be considered for people with viremia who meet the criteria below when **no other treatment options are effective** due to a patient's persistent inability to take oral ART:
  - **Unable to take oral ART consistently** despite extensive efforts and clinical support
  - **High risk of HIV disease progression** (CD4 cell count <200/µL or history of AIDS-defining complications)
  - **Virus susceptible to both CAB and RPV**
- If applicable, patients *should also be referred for treatment of substance use disorder* and/or mental illness.

LEN: LA for MDR populations (CAPELLA)

Treatment intensification with LEN is a safe and effective option!

N=72

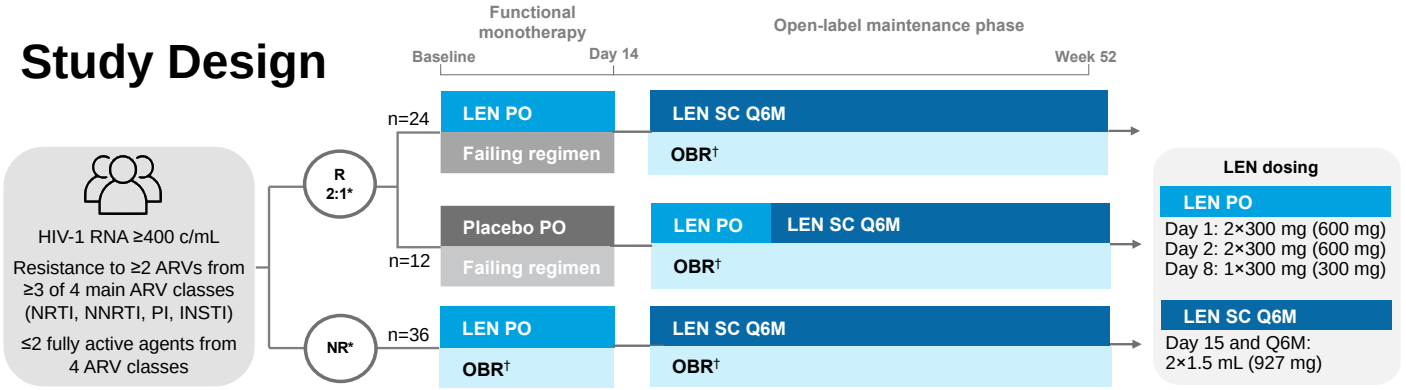
HTE PLWH with MDR, aged ≥12 years and weighing ≥35 kg

Outcomes

Primary: ≥0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from BL at Day 15
Secondary: HIV-1 RNA <50 c/mL and <200 c/mL at W26 and W52 (FDA Snapshot)
Exploratory: PROs at W26 and W52[3]

2019–present (ongoing)

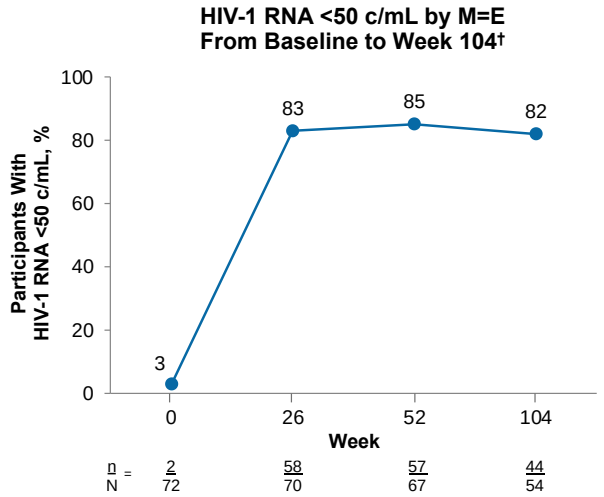
Study Design



LEN dosing

LEN PO
Day 1: 2×300 mg (600 mg)
Day 2: 2×300 mg (600 mg)
Day 8: 1×300 mg (300 mg)

LEN SC Q6M
Day 15 and Q6M:
2×1.5 mL (927 mg)



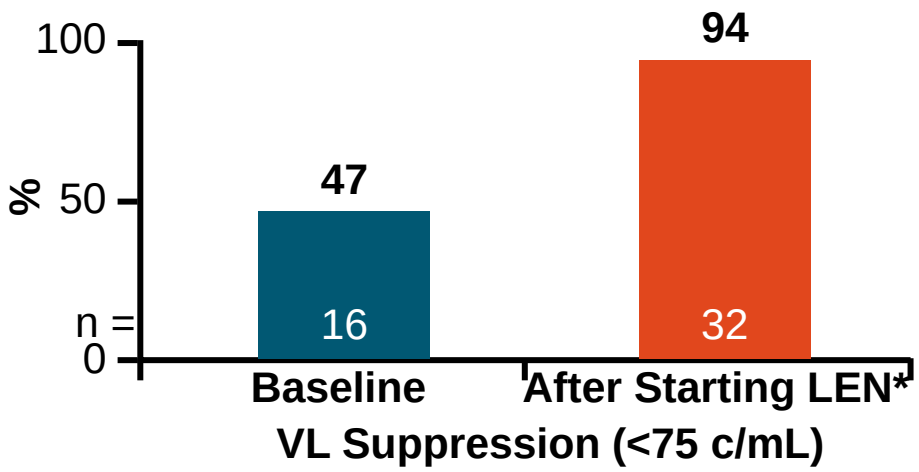
Results: Participants continued to maintain high rates of VS (82% by M=E analysis at Week 104)

1. Ogbuagu O, et al. IDWeek 2022, Oral 1585; 2. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-1803; 3. Ramgopal M, et al. IAS 2023, Poster EPB0216, Ogbuagu O, et al. IDWeek 2023, Poster 1596

Off-Label Use of LA CAB (± RPV) + LEN: Case Series

- LA CAB + RPV is the only recommended complete LA ART regimen but is not approved by WHO in low- and middle-income countries
  - Many LMICs have >10% resistance to NNRTIs
  - Disparities in availability of LA ART
- Case series of 4 US clinics where use of LA CAB (± RPV) + LEN off-label is occurring for selected patients due to adherence challenges with oral ART (N = 34)
  - Most common reason for off-label combination use was NNRTI mutations
- Call for trial to study LA CAB + LEN in those with NNRTI resistance worldwide

Patient Characteristics/Results	All Patients (N = 34)
Male or cis/trans female, %	76/24
Black/Latino/a, %	41/38
CAB Q4W/CAB Q8W, %	29/71
Reason(s) for using LA CAB (± RPV) + LEN, n (%) ▪ Documented/suspected NNRTI mutations ▪ Integrase mutations ▪ High VL ▪ Cont. viremia on LA CAB + RPV alone	 21 (59) 5 (15) 6 (18) 4 (12)



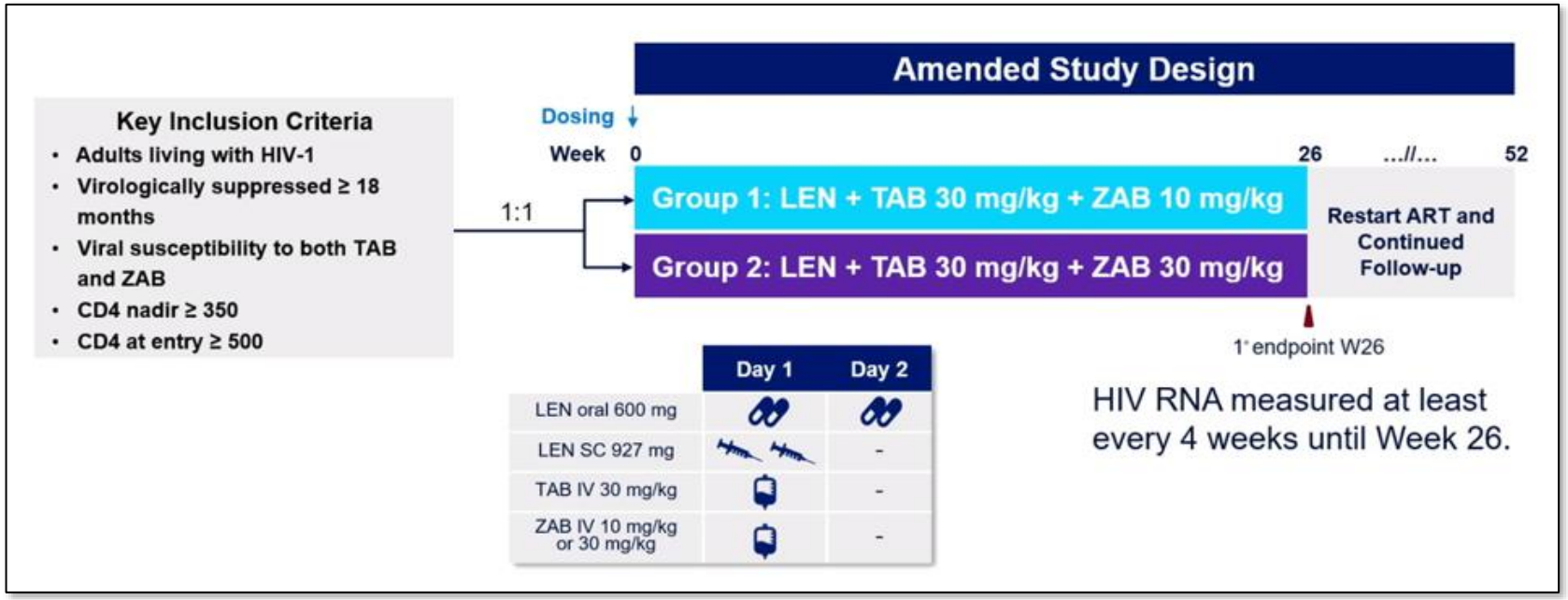
*Suppression occurred a median of 8 (4-16) wk after starting LEN.

Slide credit: clinicaloptions.com

Gandhi. CROI 2024. Abstr 629. who.int/publications/i/item/97892400863

LA: What comes next?

LEN With bNAbs Teropavimab and Zinlirvimab in PLWH (GS-US-536-5816) maintainend viral suppression in 90% in phase I study



Design:

- Blinded phase 1b study, n=21
- 85% male, median ART 2,6 years

Results:

- CD4+ counts remained stable to Wk 26
- 1 patient with viral rebound at Wk 16
  - TAB and ZAB phenotypic susceptibility and no LEN RAMs at baseline
  - Resuppressed on baseline ART

Eron. CROI 2023. Abstr 193.

Behind ART: Injectables for PrEP

World Health Organization

Health Topics | Countries | Newsroom | Emergencies

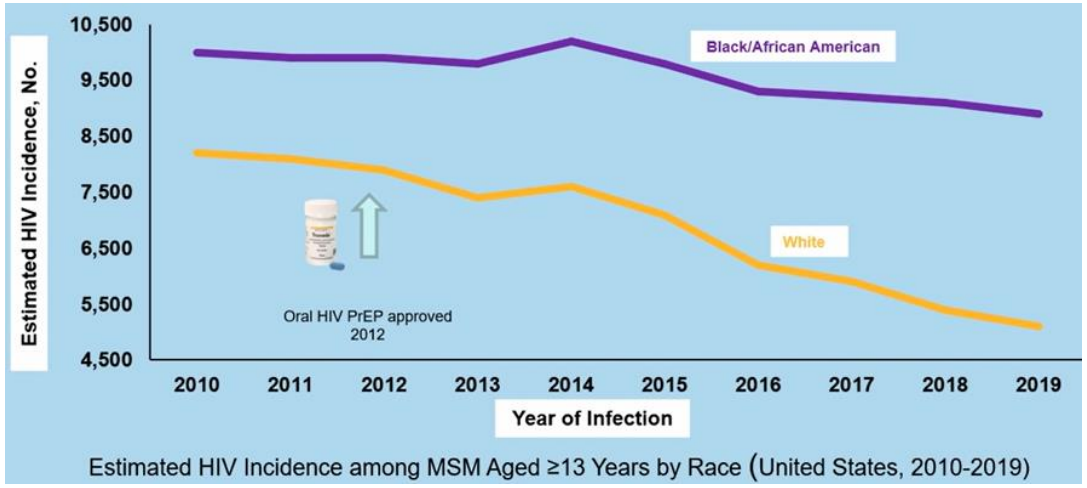
Home / News / WHO recommends long-acting cabotegravir for HIV prevention

WHO recommends long-acting cabotegravir for HIV prevention

New WHO guidelines advise countries to deliver long-acting cabotegravir as part of comprehensive approach to HIV prevention

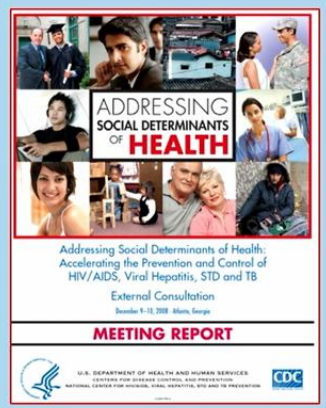
Advantages of CAB for PrEP

Injectable PrEP might reach populations other than „Caucasian MSM“



Estimated HIV Incidence among MSM Aged ≥13 Years by Race (United States, 2010-2019)

- Growing recognition that social determinants of health impact HIV and other sexually transmissible infections
- **Unstable Housing**
  - Poor HIV outcomes
  - Poor respiratory health
- **Unemployment**
  - Decline in immune function
  - Higher hospitalization risk for PLWHA
- **Incarceration History**
  - HIV infection
  - Self-reported HIV risk (condom use)
  - Re-integration related substance abuse



- FTC/TDF PrEP is only in Caucasian MSM highly efficient, African and female persons do not benefit sufficient, while being at increased risk -> Novel strategies needed

- CAB-LA PrEP might overcome this – CAVE: Resistance might become a new challenge!

Nelson LE et al. CROI 2023 #024; Solomon SS et al. CROI 2023 #025

Long-acting early viral inhibition syndrome (LEVI) and CAB-LA PrEP

- In HPTN 083 evaluating LA IM CAB every 2 mo as HIV PrEP in MSM and TGW, **6 cases** of incident HIV infection occurred despite on-time injections
- **LEVI** with LA CAB led to delays in HIV diagnoses for case infections
- INSTI resistance emergence:
  - **10/18 cases** when CAB administered **within 6 mo** of first HIV+ visit
  - **None** when first HIV+ visit was **>6 mo** after CAB administered
- **Retrospective HIV-1 RNA testing detected most infections before emergence of INSTI resistance**
- Current FDA prescribing information and CDC guidelines recommend HIV-1 RNA screening during LA CAB PrEP
  - WHO guidelines do not include this recommendation
  - HPTN 083 and 084 open-label studies evaluating this strategy

Eshleman. CROI 2023. Abstr 160.

Slide credit: clinicaloptions.com

Conclusion

Injectables do add competitive advantage to ART and PrEP

- Injectables offer competitive advantage to dedicated populations for ART and reduce pill burden, make treatment simpler, reduce stigma and increase adherence.
- Evidence suggests improved Tx outcomes in patients with adherence challenges
- CAB/RPV Q8W is effective and safe, LEN Q6M is an option in people with MDR
- Failure in LA is currently low, resistance evolution is rare in ART, but might be an additional challenge in PrEP-LA populations
- More research is needed to improve the current ART strategies

AIDS 2024

AIDS 2024, the 25th International AIDS Conference

25th AIDS 2024 in Munich

22 – 26th July 2024