AETC AIDS Education & Training Center Program Northeast/Caribbean

Emerging HIV Treatment Options

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Disclosures

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Disclosures

No financial disclosures

Learning Objectives

- Describe the role of cabotegravir/rilpivirine injectable for the treatment of HIV.
- Discuss injectable and other novel formulations in development for HIV treatment and prevention, including route of administration, dosing schedules, and approval timelines.
- Review shifting treatment paradigms, two vs three drugs for HIV treatment

James

- James is a 43 yo male, diagnosed HIV+ 2016
  - Initial CD4 320 cells/mm3, no significant mutations on initial genotype, currently on TAF/FTC/BIC
  - History of depression, on escitalopram 10 mg and sees a therapist. No other medical history or medication
  - He is generally good about coming to visits, but will sometimes go off medications or miss doses when feeling more depressed
  - States that taking medication reminds him he is HIV+, and that worsens his depression
  - His most recent CD4 is 540 cells/mm3 and his HIV RNA PCR is <20 copies/ml
  - He has heard there is a new injectable treatment and wants to know if he can take it

Is CAB/RPV LA (brand name Cabenuva) a good choice for him?

Are 2-drug regimens as good as 3 drugs?

Potential advantages of 2 drugs	Potential disadvantages of 2 drugs
➢ Cost ➢ Decrease adverse effects ➢ Decrease toxicity ➢ Less pills ➢ Smaller pills ➢ Less drug interactions	➢ Less potent/increased risk of failure? ➢ Less long-term data ➢ Low level viral replication in tissues/sanctuary sites ➢ Higher levels of immune activation?

Efficacy of 2-drug vs 3-drug regimens
What's the data?

Some 2-drug regimens have not done so well…..

2-drug vs 3-drug regimens for initial therapy

Study Name	2-drug	3-drug	Non-inferiority?	Comments	
Neat 001	DRVr/RAL	DRVr/TDF/FTC	Not in CD4<200 or HIV RNA> 100K	More resistance mutations in the 2-drug arm	
ACTG 5142	LPVr/EFV	EFV/3TC/NRTI LPVr/3TC/NRTI	Yes but 2-drug shorter time to VF than EFV regimen if baseline HIV RNA>100K	More resistance mutations in 2-drug More AE's in 2 drug	
Modern	DRVr/MVC	DRVr/FTC/TDF	No	More resistance mutations in the DT arm No difference in D/C for AE's	

DT, dual therapy; AE's, adverse events; DRVr, ritonavir boosted darunavir; RAL, raltegravir; LPVr, ritonavir booster lopinavir; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine;, FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitor; MVC, maraviroc

Raffi, et al. Lancet 2014; Riddler, et al. NEJM, 2008; Rossetti, et al. PLoS One, 2017

Success! Suppressed switch to 2-drug regimens

Non-inferiority for switching stably suppressed patients to:

GARDEL:	LPVr/3TC
OLE:	LPVr/3TC
SALT:	ATVr/3TC
ATLAS-M:	ATVr/3TC
DUAL-GESIDA:	DRVr/3TC
SWORD:	DTG/RPV
TANGO:	DTG/3TC
SALSA:	DTG/3TC

2018: DHHS Antiretroviral Guidelines or Adults and Adolescents.

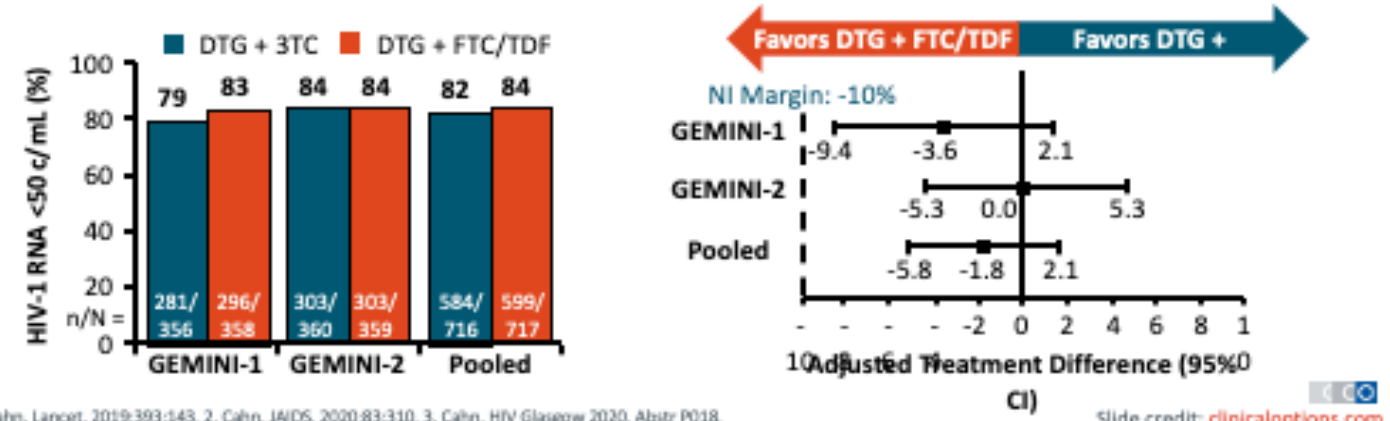
The Panel also notes that traditionally, the Guidelines have **recommended starting ART-naïve patients on a regimen consisting of at least 3 active drugs**. Several studies have now noted that persons with HIV **who have maintained viral suppression with no drug resistance may be maintained on regimens including only two active drugs**

What about 2 drugs for initial therapy?

GEMINI-1 and -2: Viral Suppression Through Wk 144 With DTG + 3TC vs DTG + FTC/TDF as Initial ART

- Parallel, international, randomized, double-blind phase III noninferiority studies comparing initial ART with DTG + 3TC (n = 716) vs DTG + FTC/TDF (n = 717)
  - DTG + 3TC noninferior at Wk 48 (primary analysis HIV-1 RNA <50 c/mL, ITT-E Snapshot)[1] and Wk 96[2]

Wk 144 Virologic Efficacy[3]



1. Cahn. Lancet. 2019;393:143. 2. Cahn. JAIDS. 2020;83:310. 3. Cahn. HIV Glasgow 2020. Abstr P018.

Slide credit: clinicalopinions.com

Recommended as first-line ART except baseline HIV-1 RNA >500 copies/ml,
If HBV infection, if resistance test results not yet available, ?CD4<200

Emerging evidence on viral replication/immune activation

- ATLAS-M: ”Simplification with atazanavir/ritonavir plus lamivudine does not affect plasma markers of systemic inflammation in virally suppressed patients” (IL-6, CRP, sCD14, D-dimer). Belmonti 2018

- TANGO: “Serum IL-6 levels and small changes from baseline at Week 96 were comparable between groups” (EACS 2021)

- TANGO: “Using the more stringent VL <40 c/ml and TND threshold, DTG/3TC 2DR shows no evidence of being less effective than TAF-based 3DR” (CROI 2022)

Belmonti, et al. J. of Antimicrob. Chemother. Vol 73 (7), 2018
Wang, et al. EACS 2021
Wang, et al. CROI 2022

Hot off the press- TRIDUAL study

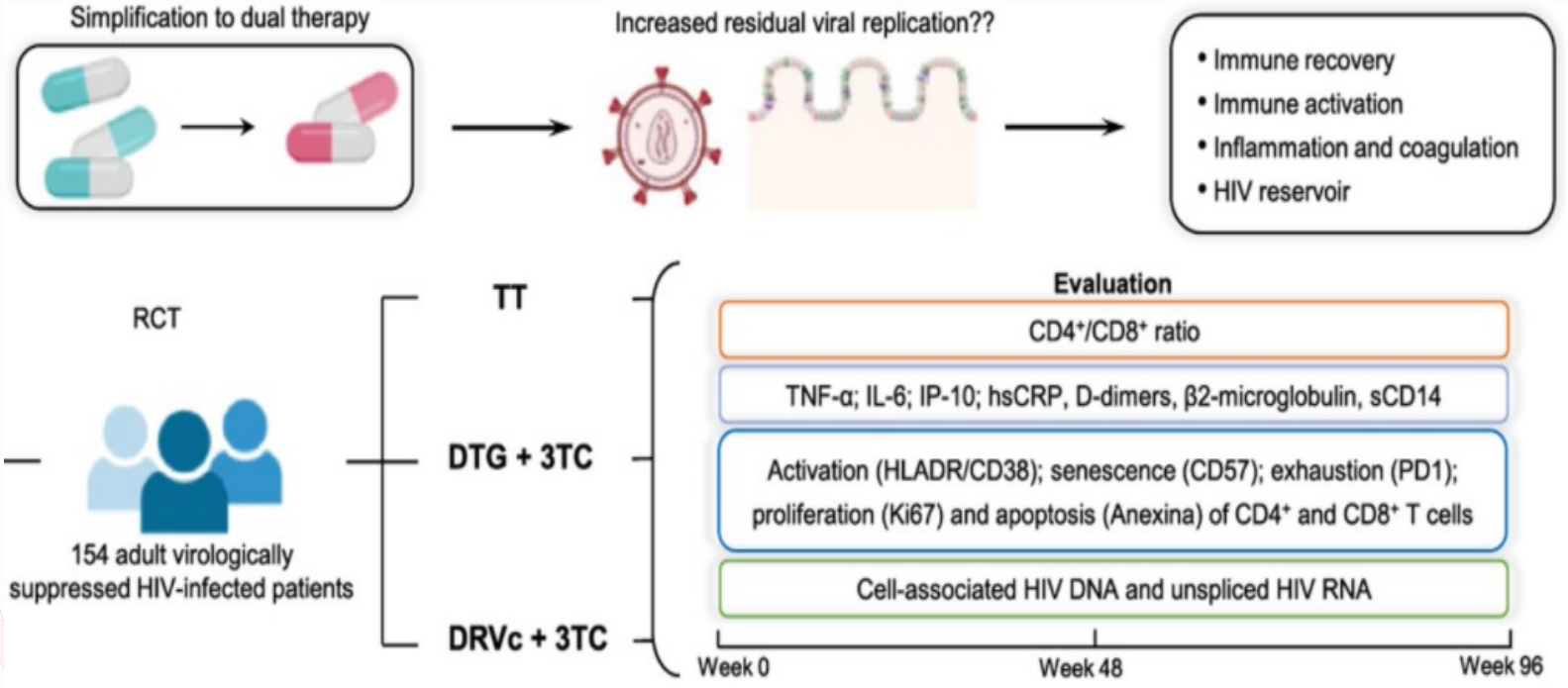


Fig open source, Science Direct

No differences detected in immune recovery, immune activation and inflammation, HIV reservoir, or transcriptional activity in virally suppressed patients regardless of triple therapy vs dual therapy

Trujillo-Rodriguez, et al. Clin Microbiol and Infect, online journal pre-proof, Mar 11, 2022

Are 2-drug regimens as good as 3 drugs?

Potential advantages of 2 drugs	Potential disadvantages of 2 drugs
➢ Cost ➢ Decrease adverse effects ➢ Decrease toxicity ➢ Less pills ➢ Smaller pills ➢ Less drug interactions	➢ Less potent/increased risk of failure? Effective with the right drugs ➢ Less long-term data- Continued efficacy over several years ➢ Low level viral replication in tissues/sanctuary sites? Accumulating data-not different ➢ Higher levels of immune activation? Accumulating data- no

Long-acting injectable for HIV treatment and prevention

James

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ART is Still a Challenge for Many

- Adherence/difficulty remembering
- Difficulty swallowing pills
- Hate to take pills
- Side effects
- Hard to get to the pharmacy on time for refills
- Mental health or substance use challenges
- Fear of discovery/disclosure
- Daily reminder of being HIV+

Long-acting treatments

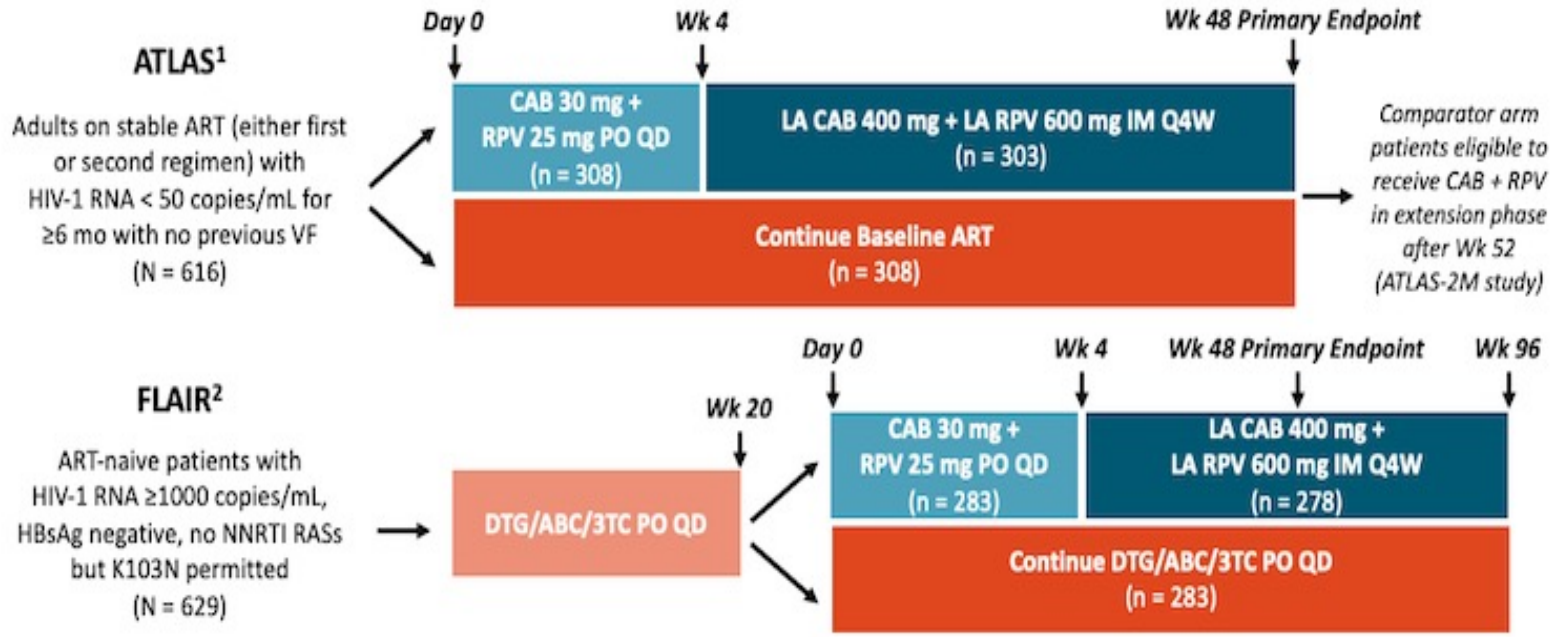
- Many (not all) people living with HIV desire long-acting treatments
- Studies in young MSM, transgender women, cis-gender women, injection drug users….

- Freedom from daily pill taking
- Freedom from daily reminder of HIV status
- Less risk of disclosure with no pill bottles at home

AIDS Patient Care STDS, 2021 Jan;35(1):23-30.doi: 10.1089/apc.2020.0164
AIDS Behav. 2020 May; 24(5): 1452–1462. doi: 10.1007/s10461-019-02703-5
PLoS One, 2014 Dec 11;9(12):e114700. doi: 10.1371/journal.pone.0114700. eCollection 2014
Int Assoc Provid AIDS Care. 2020 Jan-Dec; 19: 2325958220981265.

Data for CAB/RPV LA: ATLAS and FLAIR studies

- Multicenter, randomized, open-label phase III noninferiority trials



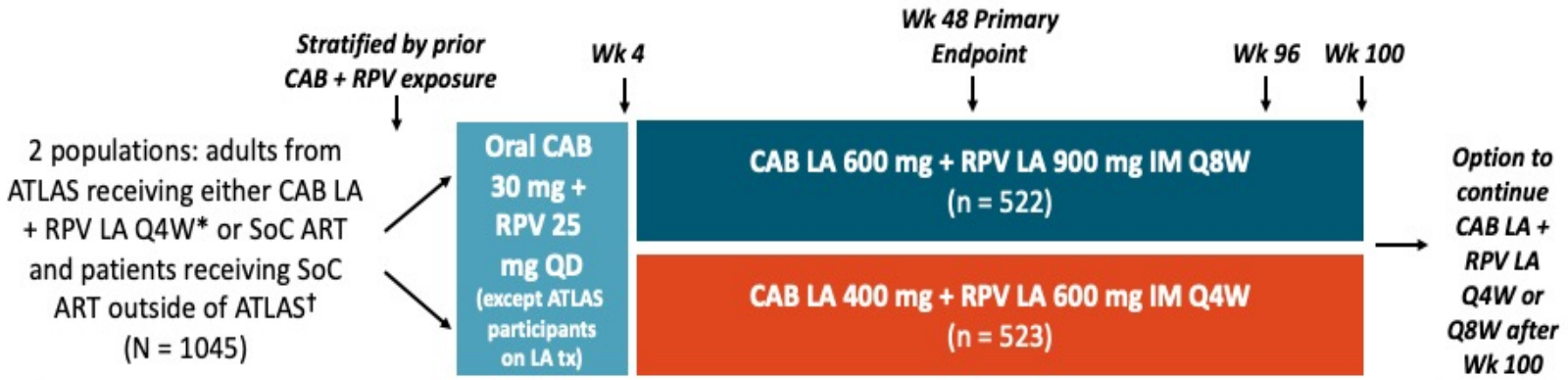
- Primary endpoint for both trials: HIV-1 RNA ≥50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

1. Swindells. NEJM. 2020;382:1112. 2. Orkin. NEJM. 2020;382:1124.

Slide credit: clinicaloptions.com

ATLAS-2M: Q4 week vs Q8 week LA CAB/RPV

- Multicenter, randomized, open-label phase III noninferiority trial



*Participants transitioning from ATLAS must have been on CAB LA + RPV LA Q4W or a current ART regimen through at least Wk 52 and had HIV-1 RNA < 50 c/mL at screening. †SoC participants not transitioning from ATLAS study on uninterrupted current regimen (initial or second combined ART) for ≥ 6 mos prior to screening and documented evidence of ≥ 2 plasma HIV-1 RNA < 50 c/mL in 12 mos prior to screening (one 6-12 mos and one within 6 mos prior to screening). Participants excluded if history of VF or if prior genotype results show any major INSTI or NNRTI mutations (except K103N).

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA snapshot in ITT-E
- Secondary endpoints: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA snapshot in ITT-E, safety and tolerability, VF, resistance, and treatment preference

Overton. CROI 2020. Abstr 34. NCT03299049.

Slide credit: clinicaloptions.com

Results

- All 3 studies showed non-inferiority to the comparator arm at 96 weeks (ATLAS), 124 weeks (FLAIR) and 152 weeks (ATLAS-2M) with low rates of confirmed virologic failures (CVF)
- Jan 2021 -LA CAB/RPV 400mg/600 mg approved as monthly dosing for HIV treatment
- Feb 2022 –LA CAB/RPV q 2-month dosing at 600mg/900 mg approved
- March 2022- Oral lead-in is now optional based on data from the week 100 extension phase of the FLAIR study

James

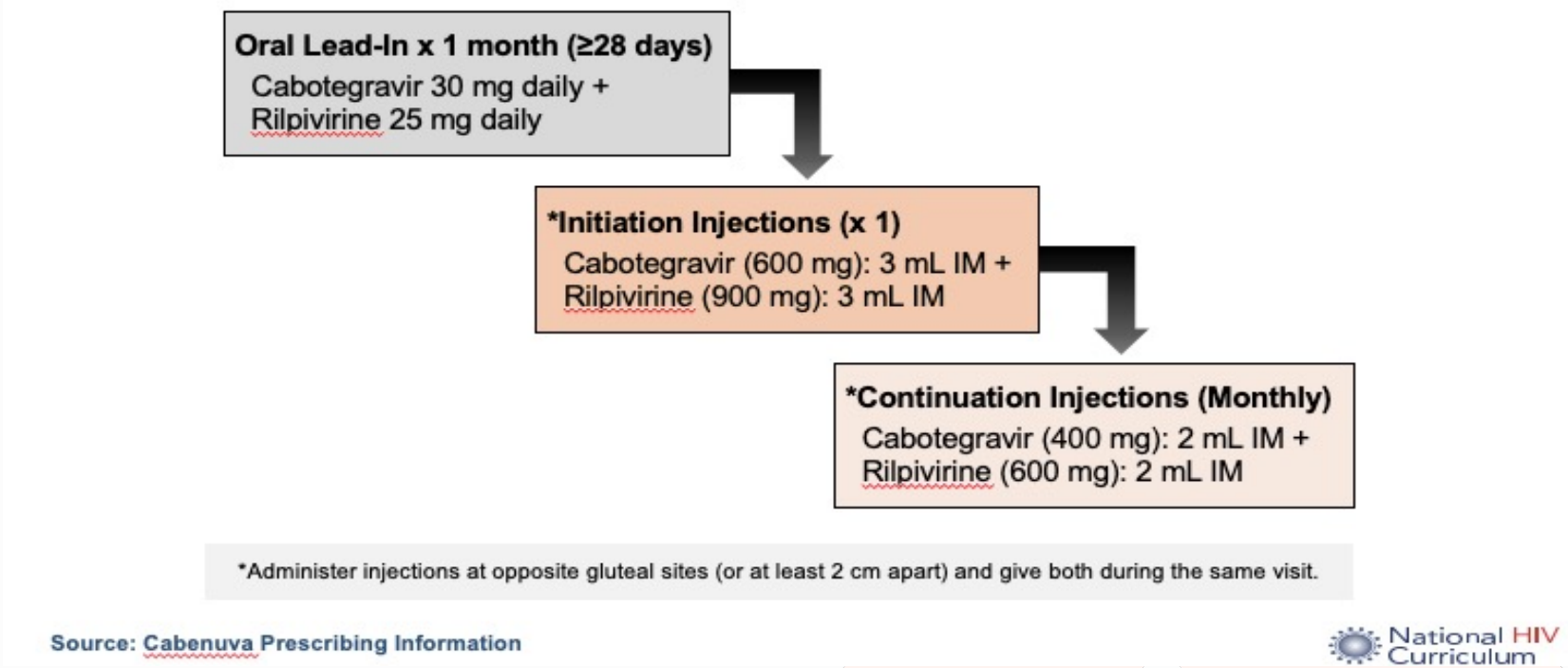
James has been on monthly CAB/RPV for the past 3 months. He has had some mild discomfort for 1-2 days post injection but reports it is not a problem and he loves the freedom of not taking pills. He is concerned because he found out his mother is having surgery and he needs to go and care for her for at least 2 weeks, and he will miss his next injection

What does the dosing schedule look like for LA CAB/RIL?

What is the window before and after a planned injection that is acceptable to receive an injection?

What do you do if a patient has to miss a planned injection?

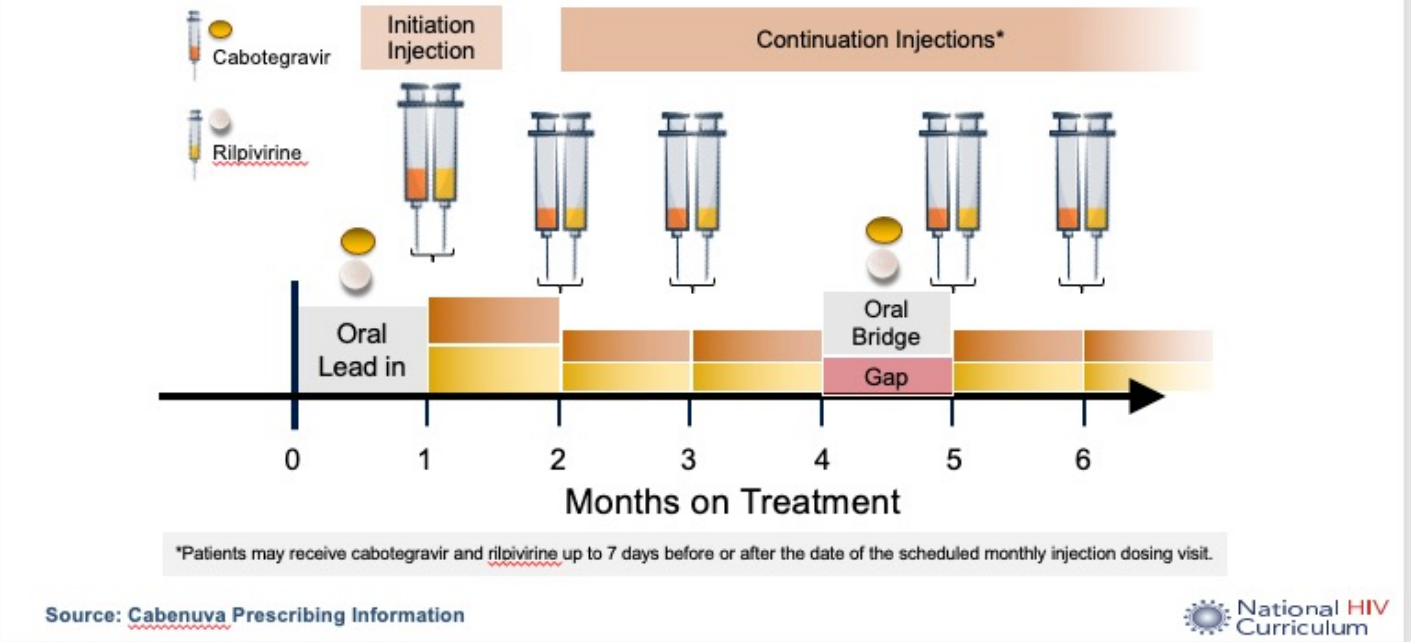
Dosing scheme- monthly (with oral lead-in)



There is a one-week window for scheduling injections, before or after the target date

Dosing for q 2 months: CAB 600/RPV 900 mg monthly x 2 doses then Q 2m after optional oral lead-in

Planned missed injection



Unplanned missed monthly injection > 7d

- ≤ 2 months: resume ASAP with 400/600 mg dose
- > 2 months: resume as soon as possible with 600/900 mg dose

Unplanned missed q 2month injection > 7d

- Resume ASAP within 2 months if the second initiation dose was missed, or within 3 months if a subsequent dose was missed
- Outside those windows a second dose should be administered one month following reinitation of injections

Downsides of LA CAB/RPV?

1. Injection site reactions
2. Some breakthrough infections despite on-time injections
3. Long pharmacokinetic tail
4. Lack of data on use during pregnancy or breastfeeding and in children and adolescents (16-week results of MOCHA study12-18 y.o. presented at CROI 2022)
5. Does not treat HBV coinfection.
6. Lack of data on use in patients with prior virologic failure
7. Frequent visits
8. Complex logistics for health centers to implement this treatment

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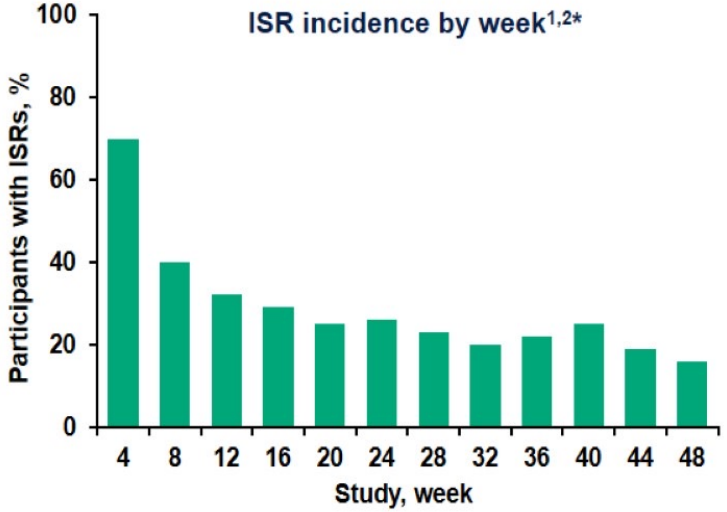
ISRs were common with CAB + RPV LA, though most were mild and incidence declined over time



Event	CAB + RPV LA[1,2] n=591
Participants receiving injections, n	**581**
Injections given, n (%)	**14,682**
ISR events	3,663 (24.9)
Pain	3,087 (21.0)
Nodule	140 (1.0)
Induration	136 (0.9)
Swelling	86 (0.6)
Grade 3 ISR pain	32 (0.2)
Median duration of ISR, days	**3**
Participants with ISR leading to withdrawal, n (%)	**6 (1)**

- The majority of participants (55%) reported ≤3 injection pain events over the 48-week treatment period[2]
- 85% of CAB + RPV LA participants rated pain as 'totally/very acceptable' at Week 48, as assessed by PIN[2]

~25% of injections were associated with ISRs, the majority (99%) being Grade 1 or 2, with a median duration of 3 days. Only 1% of participants discontinued due to ISRs[1]

*Bars represent incidence of onset ISRs relative to the most recent LA injection visit
PIN, Perception of Injection questionnaire

1. Overton ET, et al. IAS 2019. Poster MOPEB257
2. Teichner P, et al. IDWeek 2019. Oral 884

Despite ISRs, **98%** of participants in ATLAS and FLAIR stated a preference for injections over oral medication at week 48

Treatment failure

There were a small number of CVF despite on-time injections in each of the studies

- ATLAS and FLAIR -7 CVF week 48, 6 developed resistance-associated mutations (RAMs), majority 2-class resistance
- ATLAS-2M – 10 CVF week 48, 13 CVF week 152, 11/13 developed RAMs, majority 2-class resistance

Post-hoc multivariate analysis pooled data from 48-week data all 3 trials: 4 factors

-RPV RAMs at baseline (OR: 40.36; p<0001)
-historical genotype, baseline proviral DNA resistance test
-Log_2 post hoc wk 8 RPV trough concentration (OR: 5.0; p=.002)
-HIV subtype A6/A1 (OR 5.92;, p=.008)
-BMI ≥ 30 kg/m^2 at baseline (OR 1.13; p=.020)

2 or more of these factors were present in 9/13 virologic failures

Q8W dosing was *not* a factor

Cutrell, AIDS. 2021;35:1333

There is a LONG tail…

- It takes a *long* time for the medication to clear from the body
- With missed injections as levels decrease, there is not enough medication to suppress HIV, allowing the virus to reproduce and potentially mutate
- CAB was still detectable 32% of people at 12 months of d/c
- RPV was detectable in 100% of people at 12 months of d/c

Risk of developing resistance with stopping IF no other ART is taken!!!

Complex logistics

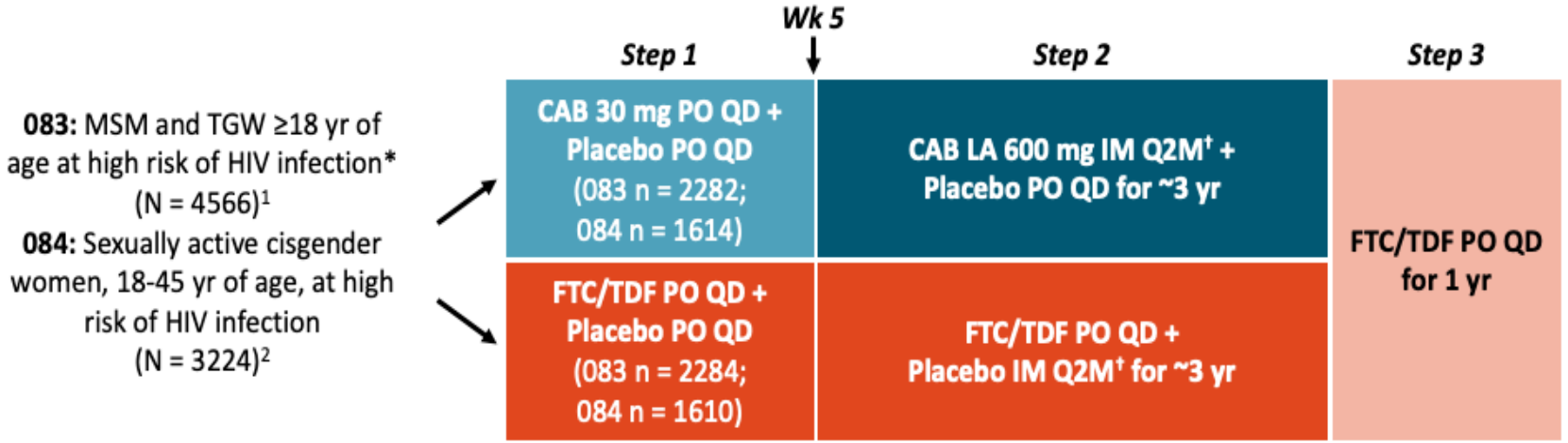
- Training and education of staff- providers, nurses, pharmacy, case managers, administrative staff
- Prior authorization process
- Obtaining and storing meds (requires refrigeration)
- Clinics potentially taking on risk of cost of medication
- Communication between different departments
- Establish billing protocols
- Tracking/reminder systems and patient communication
- Appointment availability, monthly visits!

Long-acting injectable for HIV prevention

- Long acting cabotegravir (CAB LA, brand name Apretude) is a long-acting integrase inhibitor
  - Approved Dec 2021 for the prevention of HIV via SEXUAL exposures (no data for injection use) for adults and adolescents weighing ≥ 35 kg
  - One 600 mg injection (deep intramuscular injection) every 2 months (after initial 2 injections 4 weeks apart), after an optional oral lead-in

HPTN 083 and 084: Efficacy and Safety of LA injectable CAB vs Daily Oral FTC/TDF for PrEP

- International, randomized, double-blind phase IIb/III (083) and phase III (084) trials



*Any noncondom receptive anal intercourse, >5 partners, stimulant drug use, incident rectal or urethral STI or incident syphilis in past 6 mo, or SexPro Score ≤16 (US only).
†First 2 doses given in Wk 5 and 9, then every 2 mo thereafter.

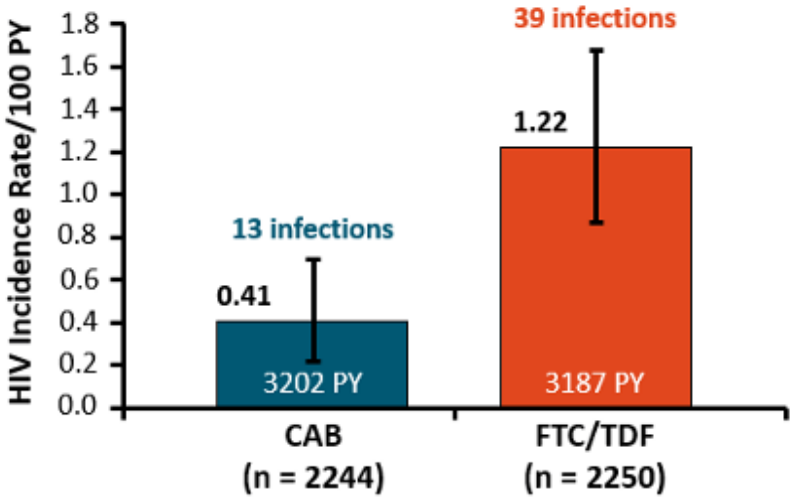
1. Landovitz. AIDS 2020. Abstr OAXLB0101. 2. Delany-Moretlwe. HIVR4P 2021. Abstr HY01.02.

Slide credit: clinicaloptions.com

3. Landovitz, et al. 385(7):595-8, NEJM 2021

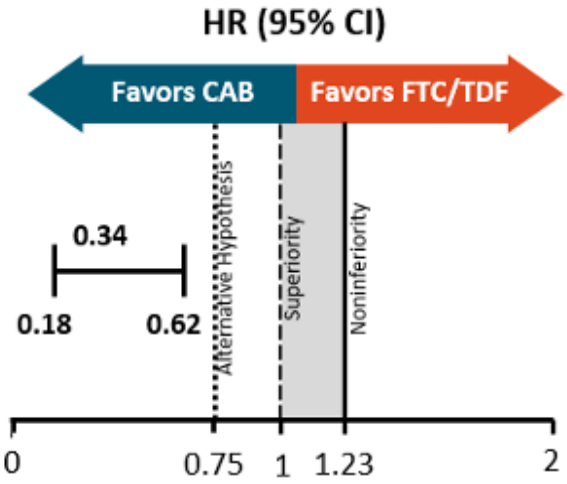
HPTN 083: HIV Incidence

- Pooled incidence: 0.81 per 100 PY (95% CI: 0.61-1.07)
  - 52 HIV infections in 6389 PYFU



Median follow-up per participant: 1.4 yrs (IQR: 0.8-1.9).

- LA CAB met alternative hypothesis (HR: 0.75) and demonstrated statistically significant superiority vs FTC/TDF



Landovitz. AIDS 2020. Abstr OAXLB0101. Reproduced with permission.

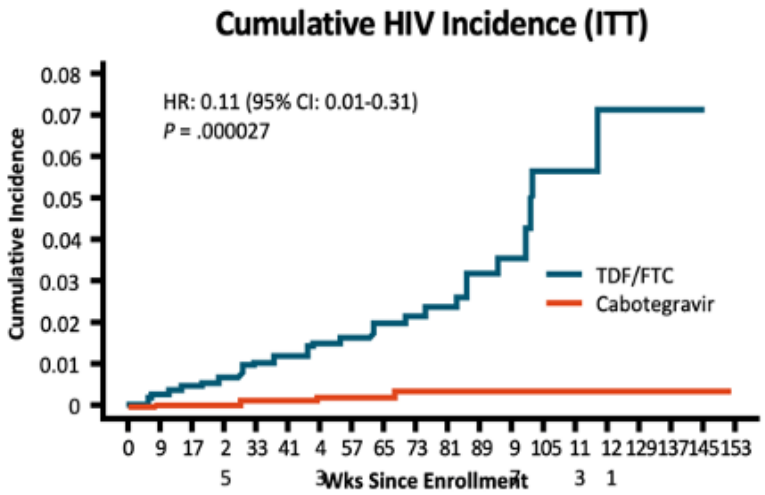
Slide credit: clinicaloptions.com

HPTN 084 Interim Analysis: HIV Incidence

- Pooled HIV incidence of 1.03 (95% CI: 0.73-1.40) per 100 PY suggests both agents highly effective in reducing HIV acquisition in study population
  - No differences in treatment effects between prespecified subgroups, including age, BMI, contraceptive use

Incidence	Cabotegravir (n = 1953 PY)	TDF/FTC (n = 1939 PY)
HIV infections, n	4	36
HIV incidence per 100 PY (95%)	0.2 (0.06-0.52)	1.86 (1.30-2.57)

- Women in cabotegravir arm had 89% lower risk of HIV infection vs TDF/FTC



Delany-Moretlwe. HIVR4P 2021. Abstr HY01.02.

Slide credit: clinicaloptions.com

Benefits of CAB LA as PrEP

- Indicated for all sexual exposures
- Every 2-month administration vs daily pill
- Directly observed therapy
- Beneficial for those who have can't or won't take a daily oral pill, have difficulty swallowing, have privacy/disclosure concerns, adherence challenges due to mental health, substance use, neurocognitive disorders, HIV/PrEP stigma
- Beneficial for those who don't tolerate the current oral options- GI, kidney, bone

Limitations of CAB LA as PrEP

- Deep intramuscular injection
- Injection site reactions
- Time to protection unknown
- Requires ≥ 6 in-person visits per year
- Potential for breakthrough HIV infections despite on time injections (7 to date!)
- Potential for integrase resistance if acquire HIV infection
- Long tail-phase once treatment is discontinued
- No protection against hepatitis B
- Not appropriate for individuals with injectable fillers or silicone in gluteal areas
- No data in pregnancy
- Can't do same-day start
- Cost
- Clinic logistics- acquisition, storage staffing, space, tracking, appointment availability, billing protocols, prior authorization

HPTN 083: Failure and resistance mutations

CAB: 16 infections, 12 incident

- 7/16 had resistance associated mutations
  - 5 had integrase RAMs (Q148R or Q148 with accessory mutations; or R263K);
    1 also had a NNRTI RAM
  - 1 had NNRTI RAMs only
  - 1 had NNRTI and NRTI RAMs

FTC/TDF: 42 infections, 39 incident

- 37/39 incident infections in nonadherent participants or those with suboptimal drug concentrations
- 13/42 had RAMs:
  - 7 to NNRTI RAMs only
  - 3 had NNRTI and NRTI RAMs
  - 3 had NRTI RAMs only

Of the 6 infections with nucleoside mutations present, 4 of the 6 were thought to have been infected with a resistant virus

2/6 acquired M184V/I mutations from TDF/FTC

Marzinke M, Grinsztejn B, Fogel JM, et al. Characterization of human immunodeficiency virus (HIV) infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. *J Infect Dis* 2021b;224(9):1581-1592. [PMID: 33740057] https://pubmed.ncbi.nlm.nih.gov/33740057

Delayed detection of HIV infection

- Detection of new infection was significantly delayed with the use of CAB-LA compared to TDF (98 days vs 31 days) with HIV Ag/Ab testing alone[1]
- If not detected quickly failure can lead to integrase resistance and a loss of a whole class of HIV treatment
- Use of a sensitive RNA test for screening would have detected infection before a major INSTI RAM was detected or before additional major INSTI RAMs accumulated in 5/7 seroconverters[2]
- Compare this to TDF/TAF/FTC, where resistance mutations upon failure is infrequent, and when it occurs it is typically the M184V/I mutation, which does not impact potential HIV treatment, including current first-line therapies. K65R (tenofovir) mutation is very rarely seen

Landovitz, et al. 385(7):595-8, NEJM 2021
Eshleman, et al. CROI 2022 Abtract 2434

Testing protocol for CAB LA

- Baseline
  - Same as TDF/FTC/TAF/FTC: HIV Ag/Ab (4th gen) test, HIV RNA PCR (viral load) test, STI screening, hepatitis testing, Comp metabolic

- Ongoing monitoring
  - HIV Ag/Ab testing at every injection visit
  - **HIV RNA PCR at every injection visit**
  - STI screening- every 2 months or every 4 months depending on level of risk

Managing PLANNED missed injections (with oral bridging)

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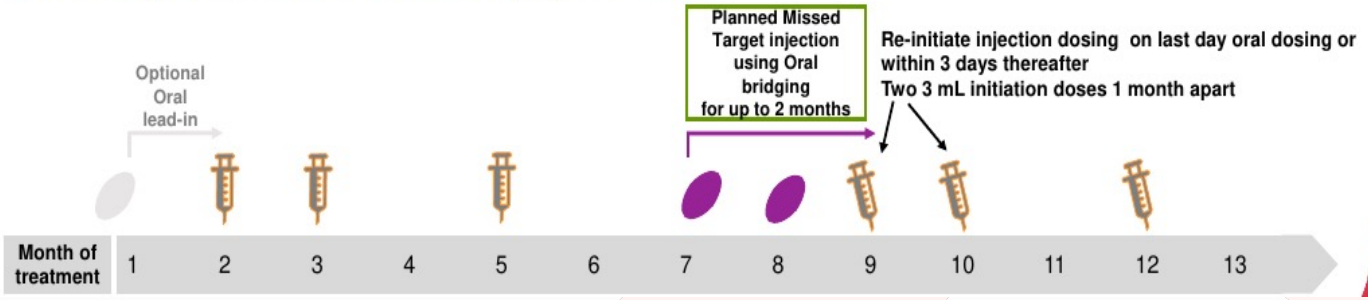
Resumption of injections after planned missed injection (with oral bridging)[1,2] *

Time since MISSED target injection date	Injection dosing recommendation
≤1 month	Continue with every 2 month (3 mL 600 mg CAB LA) IM injection dosing schedule as soon as possible
>1 month	Re-initiate injections with two (3mL, 600 mg CAB LA) injections,1 month apart, then every 2 months thereafter

- If the individual must miss an upcoming scheduled injection visit, oral cabotegravir (VOCABRIA®) can be used to replace the scheduled injection dose for up to 2 months[1]
  - Oral dosing should begin on the missed target injection date
- HIV negative status should be confirmed prior to resuming injections
- For example, the PWBP uses oral bridging for >1 month:



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* Note- schedule is the same for both planned and unplanned missed doses

40 Years of Progress

1987
AZT
monotherapy

1996
HAART

2006
First single
tablet
regimen

2012
First integrase
inhibitor

2012
PrEP

2020
Long-acting
Injectables
HIV treatment

2021
Long-acting
Injectable for
HIV prevention

Future
More long-acting
injectables, long-
acting oral
medications, implants
Vaginal rings, rectal
gels, and more
for treatment and
prevention

Compounds in development for treatment and prevention

Entry inhibitor	bNAb	NRTI NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	Topical
Albuvirtide	UB-421	Islatravir	Elsufavirine	S-365598	GS-1156	Lenacapavir	GSK254	Dapivirine
	Leronlimab	TAF implant	ACC007				GSK937	MIV 150 PC1005 gel
	VRC 01/LS VRC 07/LS							EVO-100 gel
	GS6423 GS2872							MB66 film
	N6LS							
	PG121 Elipovimab							

Islatravir

- First nucleoside reverse transcriptase translocation inhibitor
  - High potency, long ½ life, high genetic barrier to resistance

- In multiple studies as daily oral, weekly oral, long-acting oral and long-acting injectable (not yet started) for treatment, as well as once-monthly oral and once yearly implant as PrEP

But Islatravir's future is unclear!

- All studies on hold. Dose related concerns:
  - Treatment- mean drop in CD4 cells
  - PrEP- mean drop in total lymphocyte count
  - No safety findings of concern across trials at this time

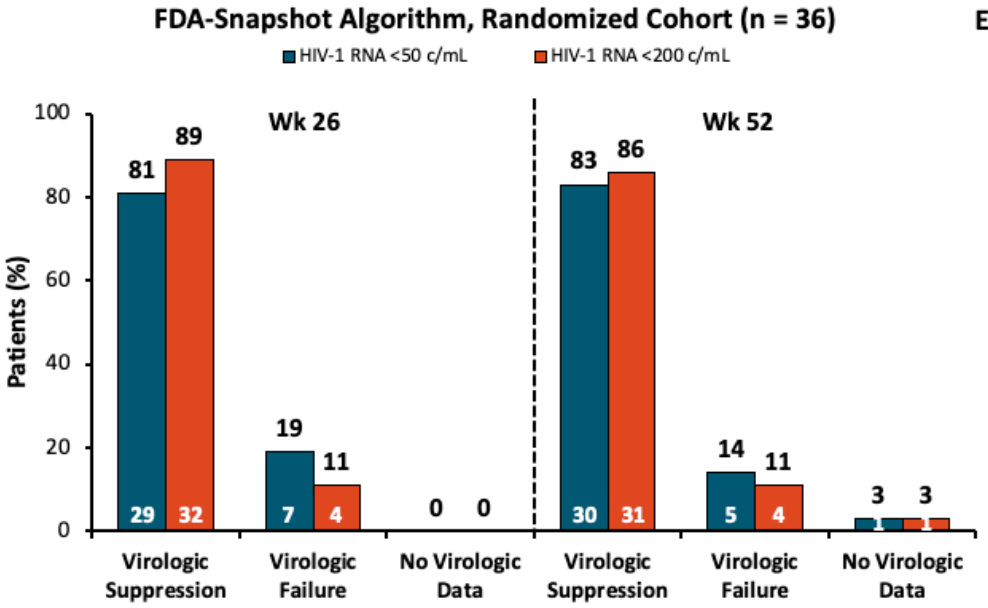
Lenacapavir

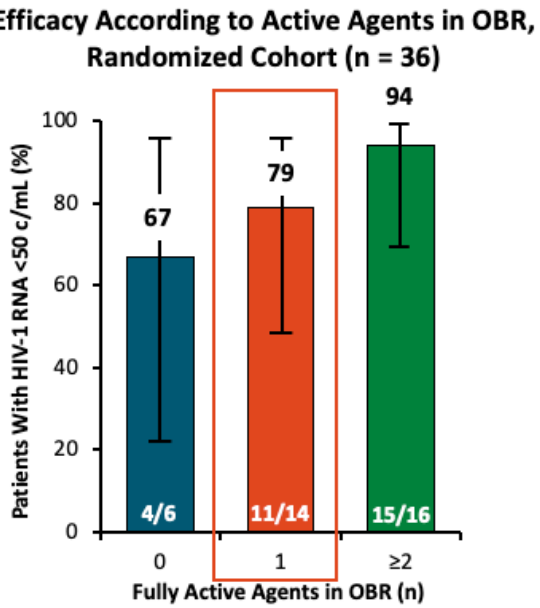
- First in class capsid inhibitor
  - No cross resistance with approved drugs
  - Oral or subcutaneous injection
  - 6 monthly dosing (!)
  - Trials for both initial therapy and treatment-experienced patients

Lenacapavir in heavily treatment experienced patients

* Resistance to ≥2 ARVs from ≥ 3 of 4 main ARV classes, ≤2 fully active ARV options remaining)

CAPELLA Secondary Endpoints: Lenacapavir Efficacy at Wk 52 in Randomized Cohort

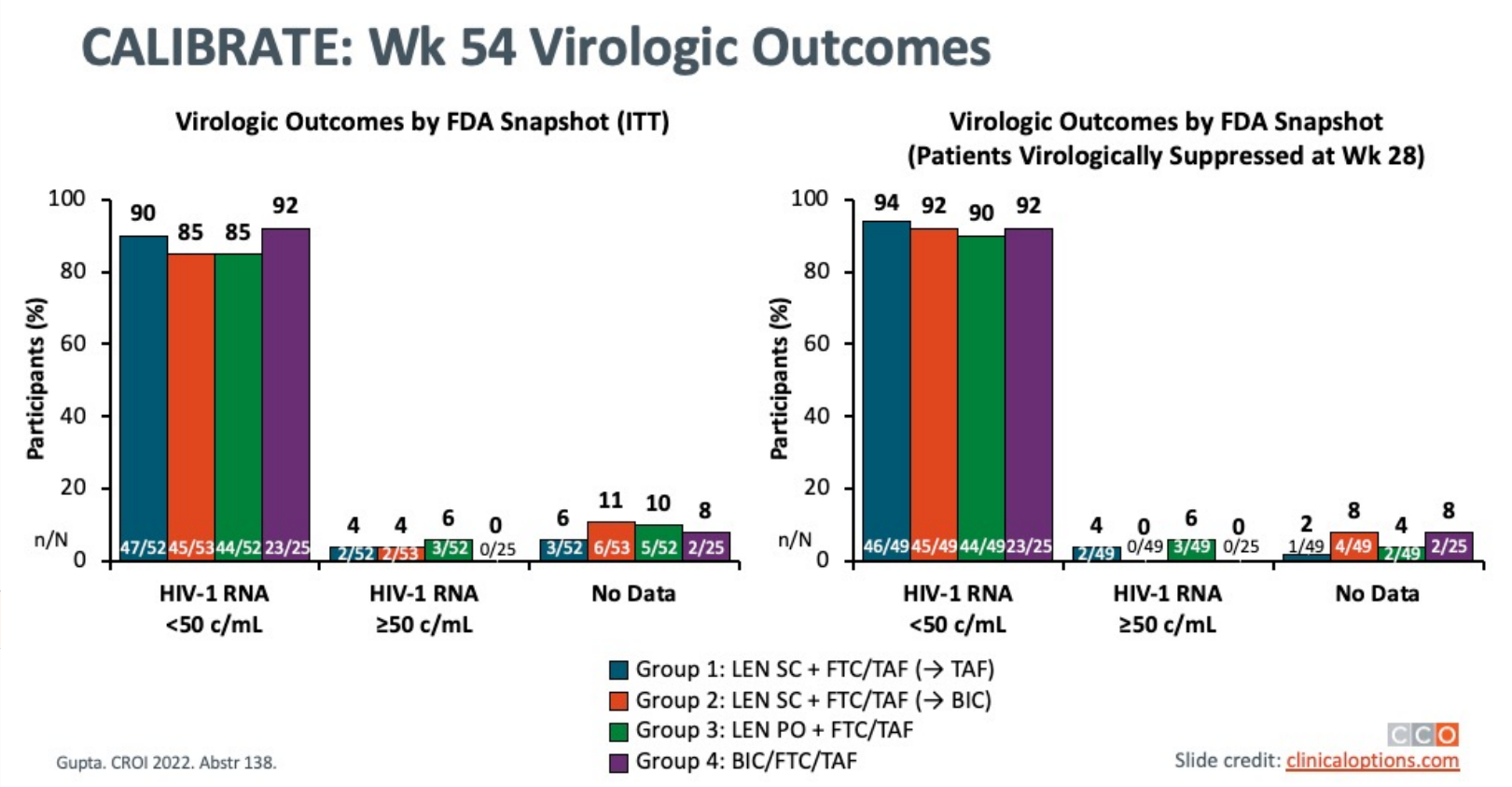




Ogbuagu. CROI 2022. Abstr 491.

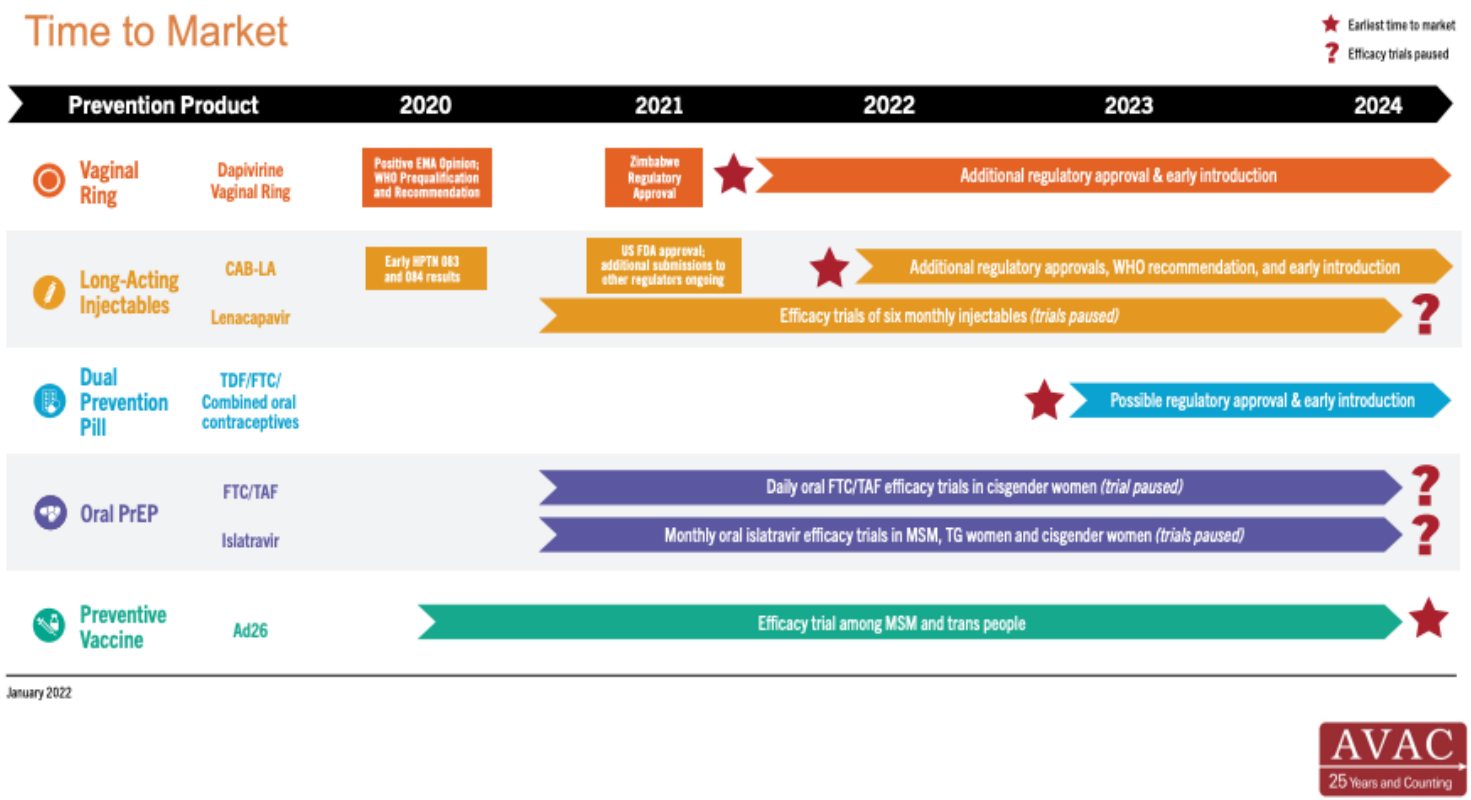
Slide credit: clinicaloptions.com

Lenacapavir for initial therapy



Approval delayed -FDA concern that borosilicate glass vial is not compatible with the medication
ALL studies for treatment and PrEP currently on hold until this is resolved

Years Ahead in HIV Prevention Research



Thank you

Questions?

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