Lessons Learned from the Roll-Out of LA CAB-RPV

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Disclosures

- No pharmaceutical or device company relationships.

- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel

CAB/RPV: Phase 3 Studies

Study (reference)	Study population	Design	Result (week 48); f/u reference
FLAIR Orkin NEJM 2020;382: 1124-1135	Rx-naïve adults (N=629)	ABC/3TC/DTG X 20 wks → CAB + RPV (oral X 4 wks, then IM monthly) or continue oral regimen (non-inferiority Δ6%)	VS >93%; CAB + RPV **non-inferior** to oral regimen IAS 2021: 144 wks
ATLAS Swindells NEJM 2020;382: 1112-1123	Adults with VS on 2 NRTI + PI, NNRTI, or INSTI (N=616)	continue ART or change to CAB + RPV (oral X 4 weeks, then IM monthly) (non-inferiority Δ6%)	VS >92%; CAB + RPV **non-inferior** to oral regimen AIDS 2022;36:185: 96 wks

IM CAB + IM RPV: U.S. FDA Approved (January 27, 2021)

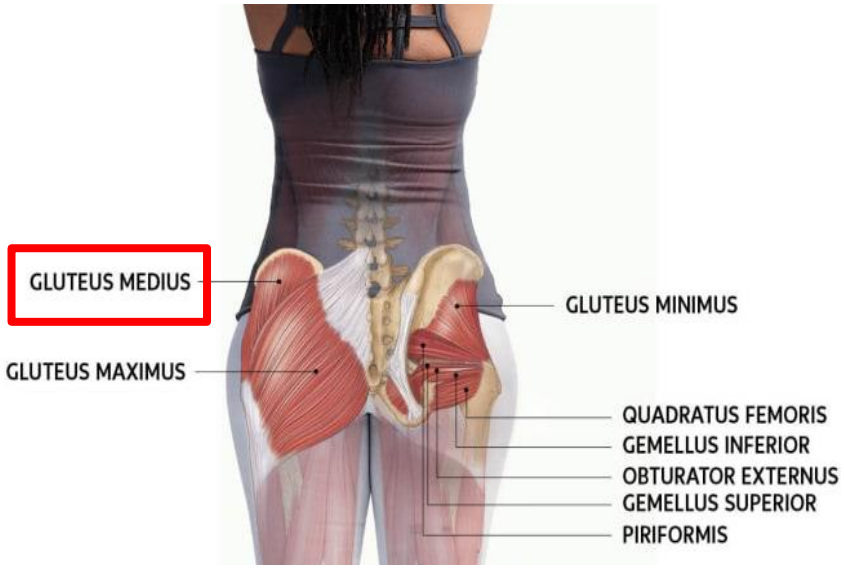
- Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ART regimen in those who are virologically suppressed (HIV-1 RNA <50 cpm) on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

CAB/RPV: Phase 3 Studies

Study (reference)	Study population
FLAIR Orkin NEJM 2020;382:1124-1135	Rx-naïve adults (N=629) All virologically suppressed 51% <35 years old 22% women
ATLAS Swindells NEJM 2020;382:1112-1123	Adults with VS on 2 NRTI + PI, NNRTI, or INSTI (N=616) All virologically suppressed 26% <35 years old 33% women

Injectable CAB/RPV: Considerations

- Loading dose: CAB LA 600 mg + RPV LA 900 mg (3 mL injections at 2 different sites)
- Monthly maintenance dose: CAB LA 400 mg + RPV LA 600 mg (2 mL injections at 2 different sites)
- RPV LA requires cold chain storage: 2-8° C.
- Injection into gluteus medius (upper outer quadrant) – Z-track method
  - Private place for injections
  - Obesity, buttock implants, tatoos



US FDA CAB/RPV Package Insert January 2021

Injectable CAB/RPV: Missed Doses

- Adherence to monthly injection dosing schedule is strongly recommended

- **PLANNED MISSED INJECTIONS** (>7 days)
  - daily oral CAB + RPV starting one month after last injection and continued until the day injections are restarted (bridging strategy)
- **UNPLANNED MISSED INJECTIONS**
  - Reassess patient to determine if resumption of injection dosing remains appropriate
  - ≤2 months: resume monthly injections with CAB 400 mg + RPV 600 mg as soon as possible
  - >2 months: re-initiate with CAB 600 mg + RPV 900 mg, then CAB 400 mg + RPV 600 mg monthly

US FDA CAB/RPV Package Insert January 2021

Injectable CAB/RPV: Challenges (1)

DRUG-LEVEL BARRIERS

- Oral lead-in
- High-volume gluteal injections
- Injection site reactions
- Drug-drug-interactions
- Drug resistance due to pharmacologic tail

Cooper, Rosenblatt, Gulick (submitted)

Injectable CAB/RPV: Challenges (2)

PATIENT-LEVEL BARRIERS

- Frequent clinic visits / Adherence requirements
- Gluteal injection site issues (e.g. obesity, implants)
- Access (transportation, insurance)
- Lack of efficacy/safety data in children <12 years old, pregnant/breastfeeding women, transgender
- Prior virologic failure or HBV co-infection

Cooper, Rosenblatt, Gulick (submitted)

Injectable CAB/RPV: Challenges (3)

SYSTEM-LEVEL BARRIERS

- Education and training requirements
- Increased clinic volume
- Need for cold-chain storage capacity
- Drug cost ($4K-$7K/month)
- Staffing and space constraints

Cooper, Rosenblatt, Gulick (submitted)

U.S. DHHS ART Guidelines (February 24, 2021)
www.clinicalinfo.hiv.gov

- Panel recommends monthly IM CAB + IM RPV as an optimization strategy for people with HIV currently on oral ART with documented viral suppression ≥3 months (AI), who—
  - have no baseline resistance to either medication
  - have no prior virologic failures
  - do not have active HBV infection (unless also receiving an oral HBV active regimen)
  - are not pregnant and are not planning on becoming pregnant
  - are not receiving medications with significant drug interactions with CAB and RPV

- Before initiation of the IM injection, patients should receive oral CAB and oral RPV for 28 days as an oral lead-in to assess tolerance.

CAB/RPV: Phase 3 Study

Study (reference)	Study population	Design	Result (week 48); f/u reference
ATLAS-2M Overton Lancet 2021;396: 1994-2005	Adults on SOC ART or CAB + RPV LA with VL <50 (N=1045)	CAB 400 + RPV 600 LA IM q4 wks or CAB 600 + RPV 600 LA IM q8 wks (non-inferiority Δ4%)	VS >93%; CAB + RPV q8 wks **non-inferior** to q4 wks CROI 2022: 152 wks

2/1/22: FDA approves IM CAB/RPV <u>every other month</u>

Injectable CAB/RPV: Direct-To-Inject

FLAIR STUDY subanalysis: Week 100

- Original oral ART arm (n=232)
- Option for CAB/RPV: direct-to-injection (n=111) or 4-week oral lead-in (n=121)
- Week 124 HIV RNA <50 copies/ml
  - 99% (direct-to-inject) and 93% (oral lead-in)
- Adverse event type, severity, frequency were similar

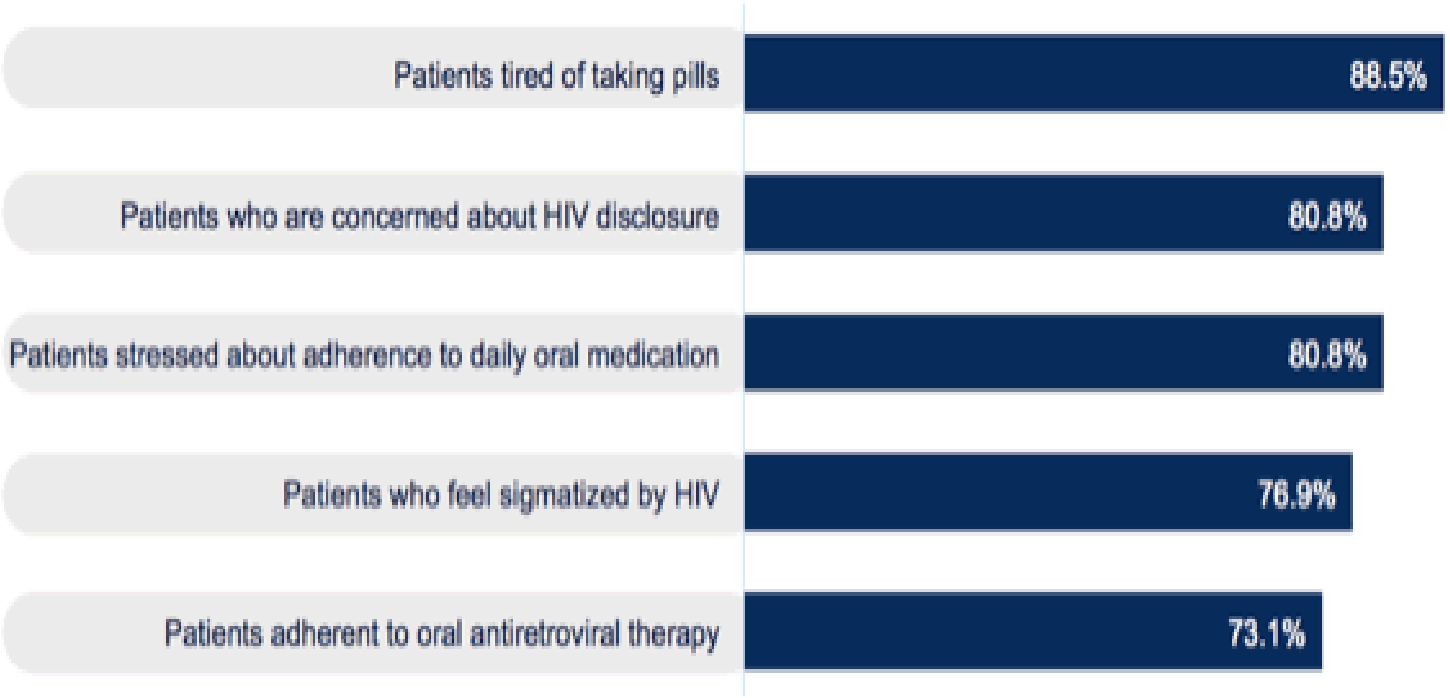
Orkin Lancet HIV 2021;8:e668-e678

3/24/22: FDA label update: lead-in dosing optional

CAB/RPV Study Staff Survey (1): CUSTOMIZE Appropriate Candidates

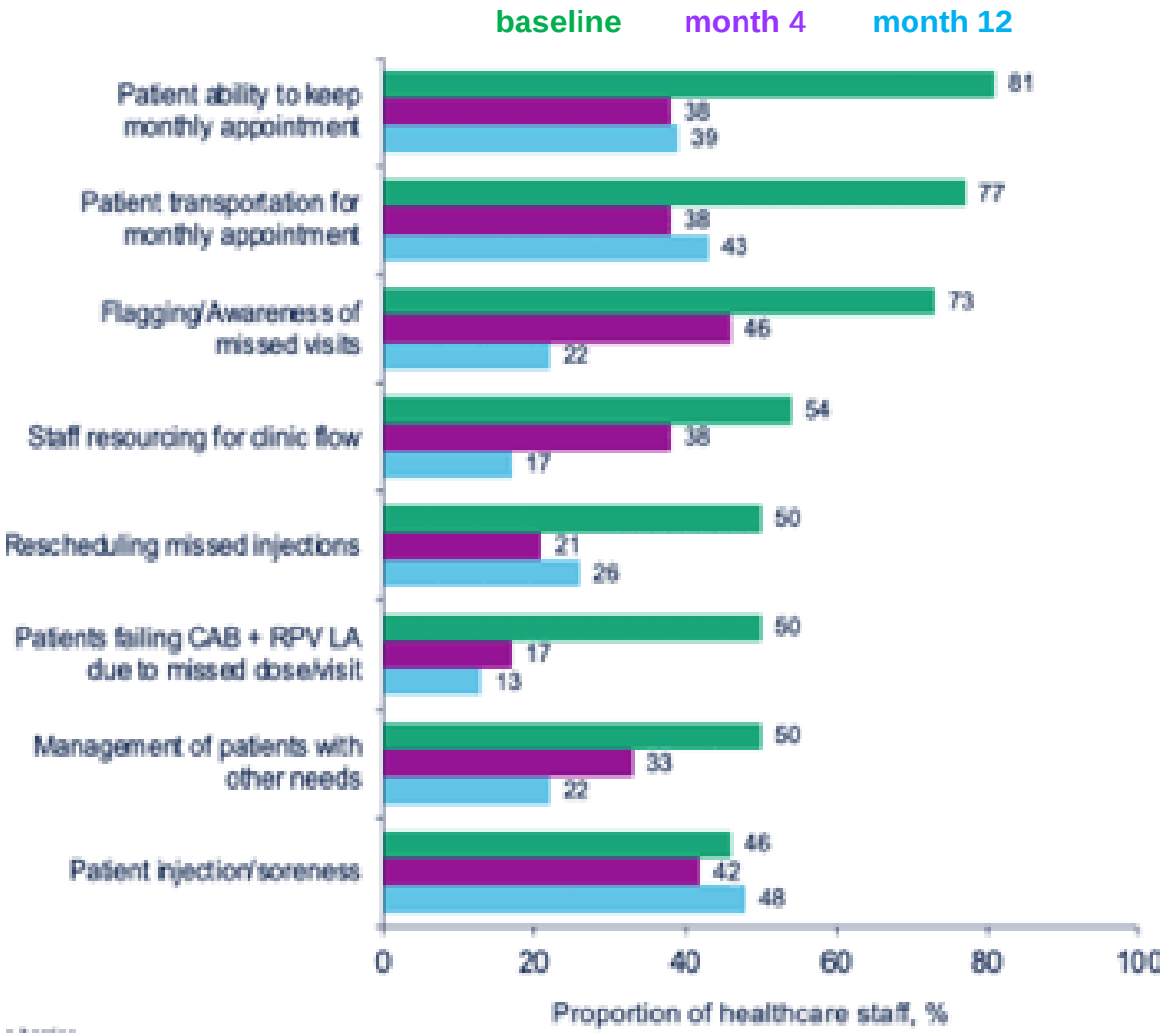
- Quantitative survey of MDs, RNs, office staff at U.S. clinics
- 26 staff (MDs, injectors, administrators) from 5 clinic types (FQHC, academic, private, foundation, HMO) in 8 U.S. cities

Figure 5. Top 5 Characteristics of Appropriate Candidates for Long-Acting Cabotegravir + Rilpivirine



CUSTOMIZE: Implementation of LA Injectable CAB + RPV

- Phase 3b, hybrid III implementation-effectiveness survey (7/19-10/20)
  - 109 pts switched to long-acting injectable CAB + RPV
  - Staff found acceptable (96%), appropriate (100%), feasible (95%)
    - 78% felt optimal implementation was achieved in 1-3 months
  - Staff perceived barriers ↓ from baseline to month 12
    - Mitigated with minor process adjustments that varied by clinic type
- Median duration of visit length:
  - Month 1: 57 min→ Month 11: 34 min



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CUSTOMIZE Study:
Implementation of LA Injectable CAB + RPV – U.S.
Impact of COVID-19 (N=102)

- 93% of pts maintained monthly CAB LA + RPV LA dosing schedule despite COVID-19 disruptions
- 7% used temporary oral therapy (CAB + RPV or alternative ART) or rescheduled LA injections (<1%)
- 19% of pts (19/102) had a COVID-19–impacted visit (missed/rescheduled visit, quarantine, COVID-19 diagnosis, clinic closure)

Patient Perspectives of LA CAB + RPV LA (Mo 12)	Impacted by COVID-19 (n = 19)	Not Impacted by COVID-19 (n = 83)	Total (N = 102)
Acceptability	97%	98%	98%
Treatment preference			
▪ LA CAB + RPV	95%	92%	92%
▪ Daily oral tablet regimen	5%	2%	3%
▪ No preference	0%	6%	5%

Czarnogorski IAS 2021 #OAD0705

CAB/RPV: What's Next? (1)

- **Injections / Formulations**
  - IM injections in vastus lateralis muscle (**thigh**) NCT04371380
  - Injections administered IM (buttock, **thigh**) or **SC (abdominal)** NCT04484337
  - More concentrated formulation that would ↓ injection volume
  - Hyaluronidase preparation

- **Special populations**
  - ACTG 5359/LATITUDE: pts with a history of **suboptimal adherence**
  - IMPAACT 2040/CREAT: **pregnancy** and **postpartum**
  - IMPAACT 2036/CRAYON: **children 2 to <12** years old

CAB/RPV: What's Next? (2)

- Implementation of CAB/RPV
  - **Strategies** for successful implementation NCT04001803
  - Continuous **quality improvement** for implementation NCT 04399551
  - Administration in **infusion centers** NCT04982445
  - Administration in **community partner spaces** NCT04973254
  - Self-infection / provider injection at **drop-in clinics** for **transgender** women NCT03856580
  - Use of **alerts** in the CHORUS App NCT04863261

Conclusions: CAB/RPV -- Lessons Learned

- Injectable CAB/RPV **maintains virologic suppression** in virologically suppressed people

- There are challenges to implementation
  - **Drug**-level, **Patient**-level, **System**-level

- Some of these challenges have already been addressed
  - monthly dosing → every other month dosing
  - requirement for lead-in dosing → optional direct-to-inject

- Research studies in progress to address additional challenges
  - Injections / formulations, expanded patient populations, implementation

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