Long Acting Injectables in Australia

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The person depicted in this photo is a model, for illustrative purposes only.

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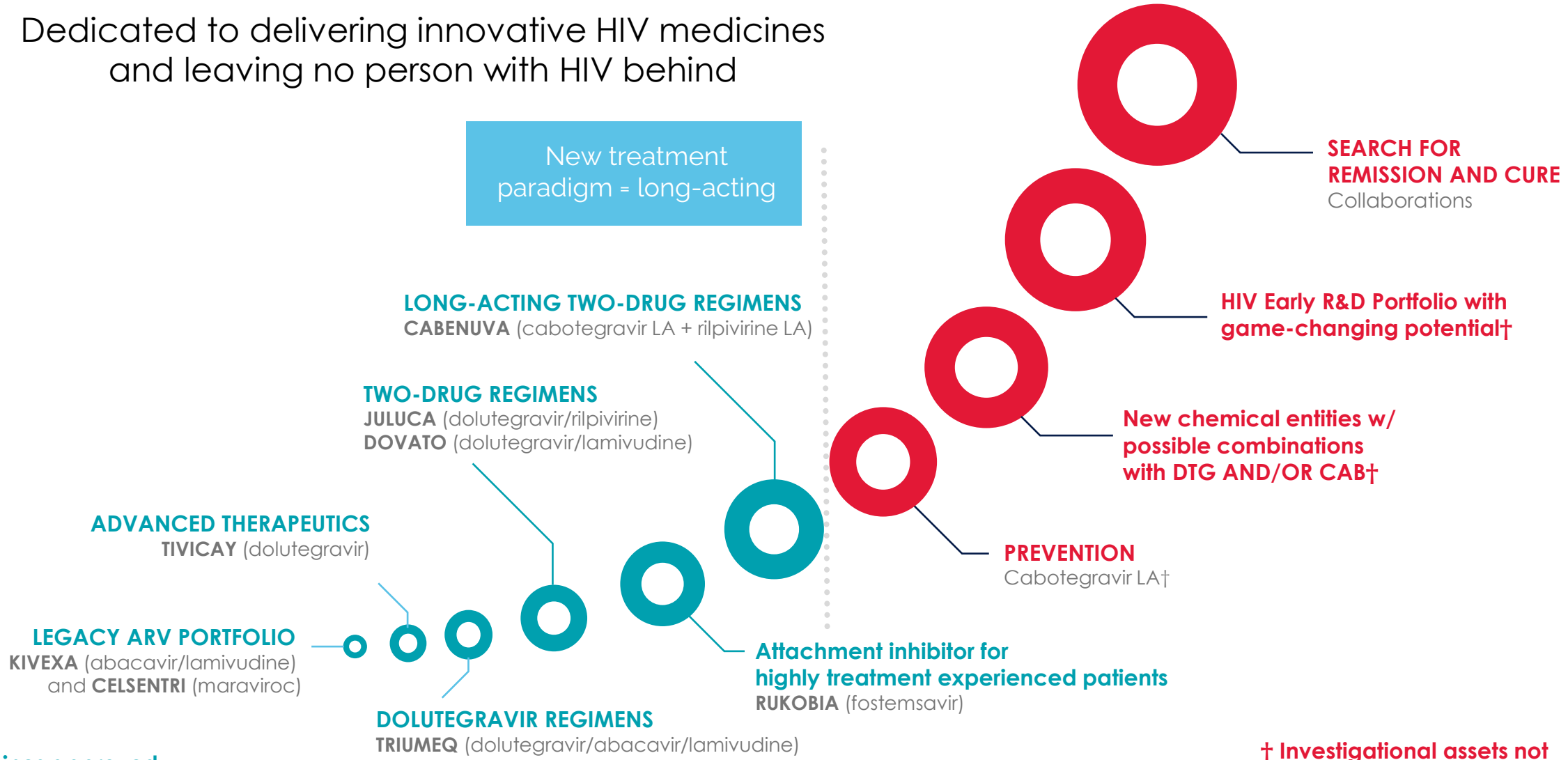
SUMMARY of presentation

1. ViiV HIV Treatment Pipeline
2. Unmet need
3. CAB + RPV LA
4. Patient reported outcomes
5. Frequently asked questions
6. Q&A

From evolution to revolution: entering the Long-acting ERA

Dedicated to delivering innovative HIV medicines and leaving no person with HIV behind

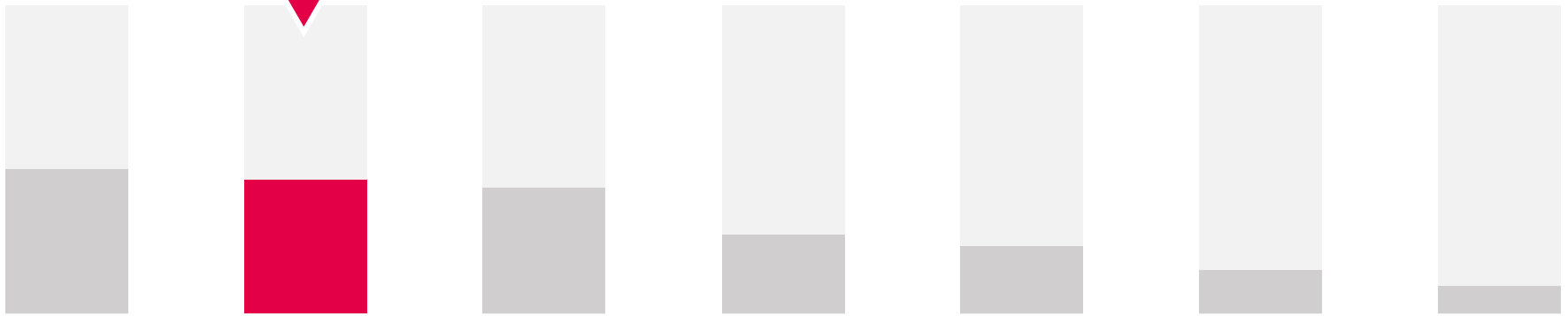


Medicines approved for prescription

† Investigational assets not currently approved for prescription

Patient surveys have identified long-lasting treatment, requiring less frequent dosing, as a priority for PLHIV

43.1% of respondents ranked **'longer-lasting medicine so I don't have to take it every day'** as their first or second priority* (N=2,389)



*The Positive Perspectives Study 2019 was conducted across 25 countries (N=2,389). Participants were enrolled from Europe (n=1,119), North America (n=520), South Africa (n=179), Australia (n=120), Japan (n=75), Mexico (n=63), Brazil (n=58), Taiwan (n=55), Argentina (n=50), Chile (n=50), China (n=50), and South Korea (n=50)

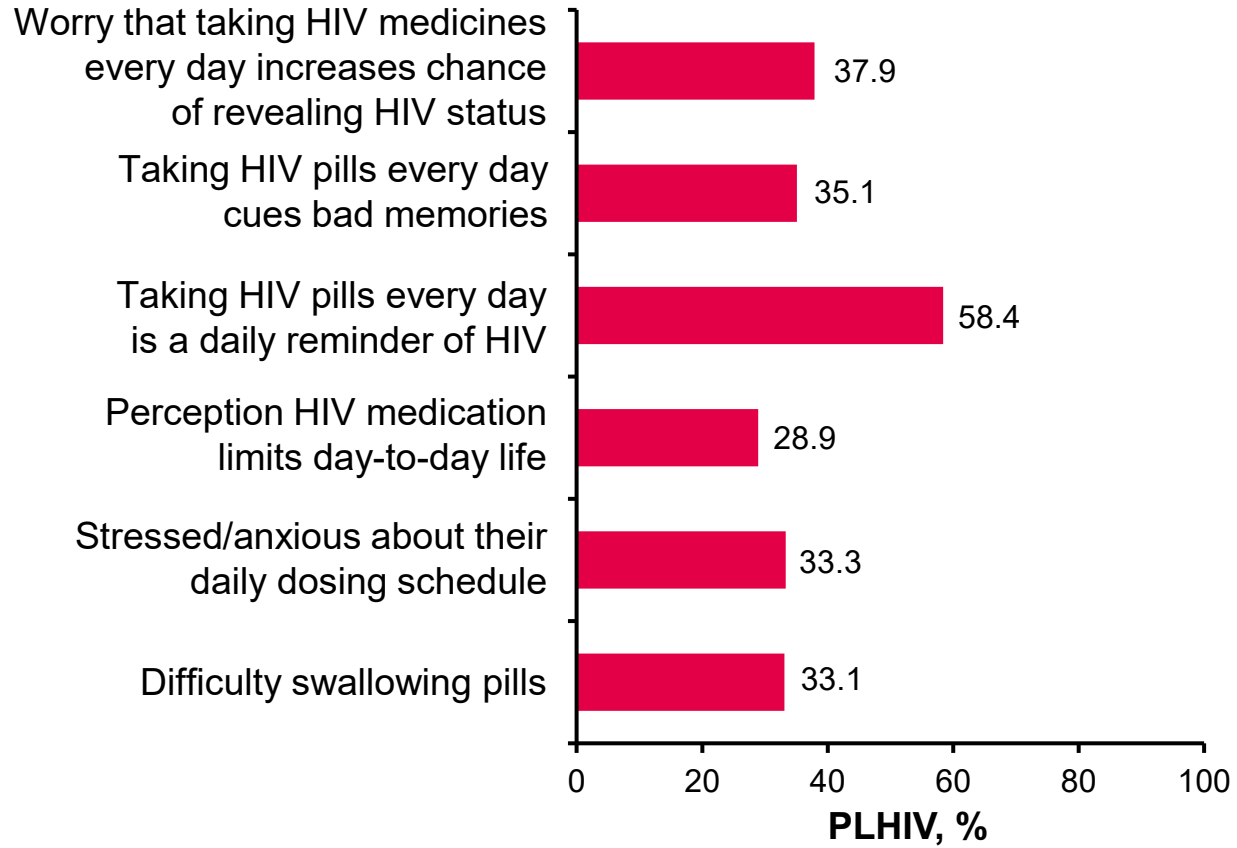
PLHIV, people living with HIV

de los Rios P, et al. Popul Med 2020;2:23

Increased flexibility of ART delivery is needed to meet the diverse needs of PLHIV

- PLHIV continue to face physical, emotional, and psychosocial challenges with daily oral ART[1]
- These challenges have been associated with poor health outcomes including low treatment satisfaction, self-reported virologic failure, suboptimal self-rated overall health, and poor adherence[1,2]

Percentage of PLHIV who reported challenges with their treatment*[1]



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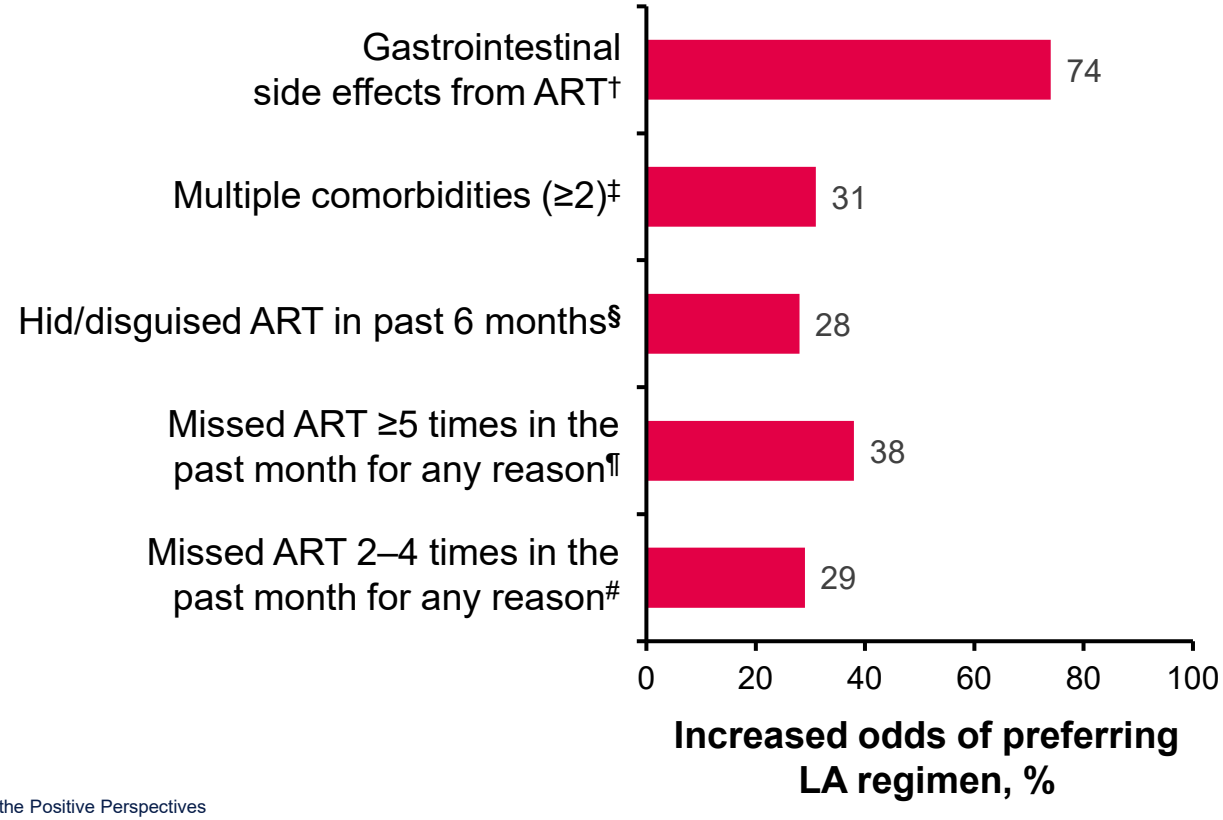
1. de los Rios P, et al. AIDS Behav 2020 [Epub ahead of print]
2. de los Rios P, et al. Prev Med 2020 [Epub ahead of print]

Surveys suggest that PLHIV believe LA injectable ART will address unmet needs in HIV treatment

Proportion of PLHIV indicating preference for a LA regimen (N=2,389)

Factors associated with increased preference for a LA injectable regimen (p<0.05)*



*Multivariable logistic regression analyses of factors associated with preference for a LA regimen among all participants in the Positive Perspectives Study, 2019 (N=2,389); †aOR=1.74 (95% CI: 1.41, 2.15; p<0.001) vs no side effects; ‡aOR=1.31 (95% CI: 1.05, 1.63; p=0.015) vs no comorbidities §aOR=1.28 (95% CI: 1.06, 1.55; p=0.011) vs never hid/disguised ART in the past 6 months; ¶aOR=1.38 (95% CI: 1.07, 1.78; p=0.015) vs never missed ART in the past month; #aOR=1.29 (95% CI: 1.01, 1.66; p=0.044) vs never missed ART in the past month

aOR, adjusted odds ratio; **LA,** long acting

de los Rios P, et al. Popul Med 2020;2:23

Cabotegravir + Rilpivirine Long Acting

CABENUVA

CABENUVA is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies per mL) and have no known or suspected resistance to either cabotegravir or rilpivirine

(Pregnancy Category B1)
There are no studies of cabotegravir injection or rilpivirine injection in pregnant women. The effect of CABENUVA on human pregnancy is unknown. CABENUVA should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus

CABENUVA PBS LISTING

CABENUVA (cabotegravir and rilpivirine prolonged-release injections) is PBS approved for virologically suppressed adult PWHIV

Authority required (STREAMLINED) 12636

Clinical criteria:

- Patient must have previously received PBS-subsidised therapy for this condition, AND
- The treatment must be the sole PBS-subsidised therapy for this condition.

Note: It is recommended that patients have previously received 4 weeks of PBS-subsidised initial oral lead-in treatment with cabotegravir and rilpivirine.

For full listing, please refer to pbs.gov.au

CAB + RPV LA combines two different LA injectable ARVs

- CAB LA and RPV LA are extended release suspensions that enable monthly and every 2-month dosing[1,2]
- CAB and RPV have a number of important attributes that support their use as a LA combination therapy:[1,2]
  - Different MoA and resistance profiles
  - Lack of DDI between CAB and RPV
  - Oral formulations of both drugs facilitate treatment initiation and oral bridging

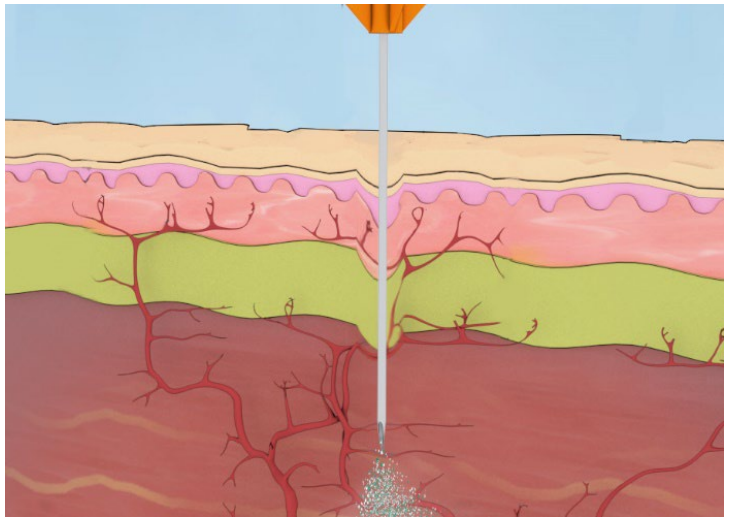
Attribute	CAB LA[1–3]	RPV LA[1,3–5]
ARV drug class	INI	NNRTI
Oral tablet size (t½)	30 mg (41 hours)	25 mg (~50 hours)
LA suspension (t½)	200 mg/mL (5.6–11.5 weeks)	300 mg/mL (13–28 weeks)
Dose – every 2 months	600 mg (3 mL)	900 mg (3 mL)

ARV, antiretroviral; **INI,** integrase inhibitor; **MoA,** mechanism of action
NNRTI, non-nucleoside reverse transcriptase inhibitor; **t½,** half-life

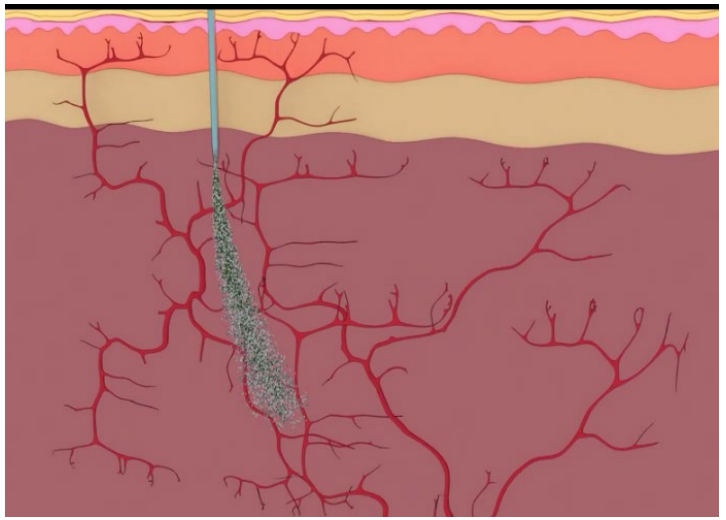
1. Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45
2. Ford SL, et al. Antimicrob Agents Chemother 2013;57:5472–7
3. Vocabria EU SmPC. Jan 2022; **4.** Rekambys EU SmPC. Jan 2022; **5.** Edurant US PI. Jan 2022

CAB + RPV LA formulation allows for monthly or every 2-month dosing

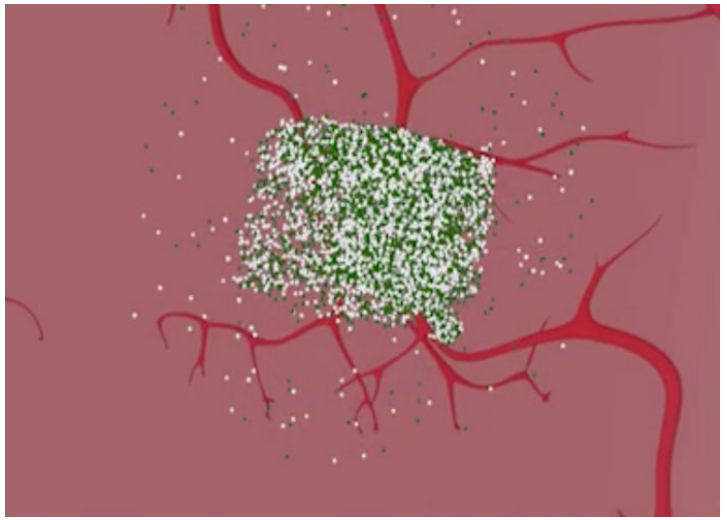
- CAB + RPV extended-release suspensions contain finely-milled drug particles suspended in an aqueous vehicle that supports LA dosing:



CAB + RPV LA is administered as separate IM gluteal injection



LA suspension forms a drug depot in the muscle



Medications are slowly absorbed from the depot site into the bloodstream

IM, intramuscular

Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45

Dosing Schedule

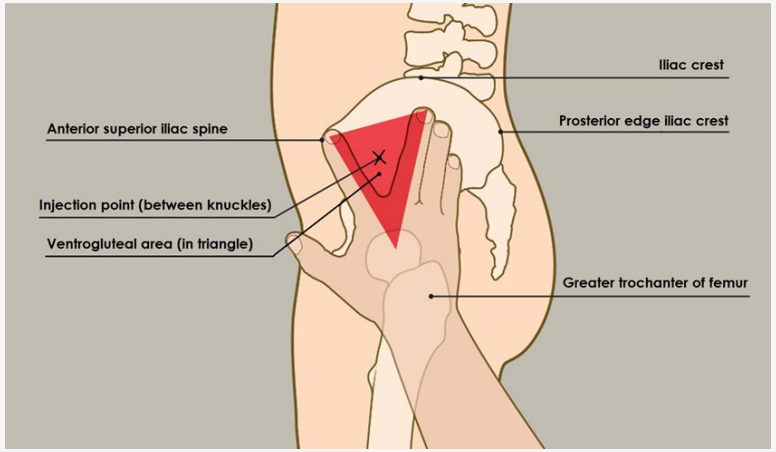
CAB + RPV LA: Two separate injections administered by an HCP

CAB + RPV LA every 2-month regimen[1,2]

(at least 28 prior the 1st injection)		**Oral lead-in***
Month 1		**1st injections†**
Month 2		**2nd injections‡**
Month 3		
Month 4		**Injections every 2 months‡**
Month 5		

Administering to the ventrogluteal site:[3,4]

- Find the greater trochanter and anterior iliac crest
- Place the palm of your hand over the trochanter
- Point the index finger toward the anterior iliac crest. Spread the second or middle finger towards the back, making a 'V'. The thumb should always point towards the front of the leg
- Give injection between the knuckles of index and middle fingers§



*Daily oral CAB (30 mg), and daily oral RPV (25 mg) taken with a meal for at least 28 days. OLI is optional in the EU; †First injection received on the last day of oral therapy if an OLI is used; ‡Injection dose: CAB LA (600 mg, 3 mL), RPV LA (900 mg, 3 mL); §Consider a routine of injecting one medicine into the right buttock and the other medicine into the left buttock, to support easy recall of which medicine has been administered at a given site

HCP, healthcare provider

1. Vocabria EU SmPC. Jan 2022
2. Rekambys EU SmPC. Jan 2022; **3.** INMO. Clinical Practice – IM injections: How's your technique? Available at: https://www.inmo.ie/MagazineArticle/PrintArticle/5676 (accessed Mar 2022)
4. Nicoll LH, Hesby A. Applied Nursing Res 2002;16:149–62

What efficacy data are available for the cabotegravir + rilpivirine long-acting regimen?

Efficacy of CAB + RPV LA has been demonstrated through a program of Phase III clinical trials

MONTHLY DOSING vs **DAILY ORAL ART**

FLAIR[1] (N=629)

Treatment-naïve adults with HIV-1 virologically suppressed* for 20 weeks on daily oral ARV therapy

ATLAS[2] (N=618)

Adults with HIV-1 virologically suppressed* for ≥6 months on daily oral ARV therapy

EVERY 2-MONTH DOSING vs **MONTHLY DOSING**

ATLAS-2M[3] (N=1,045)

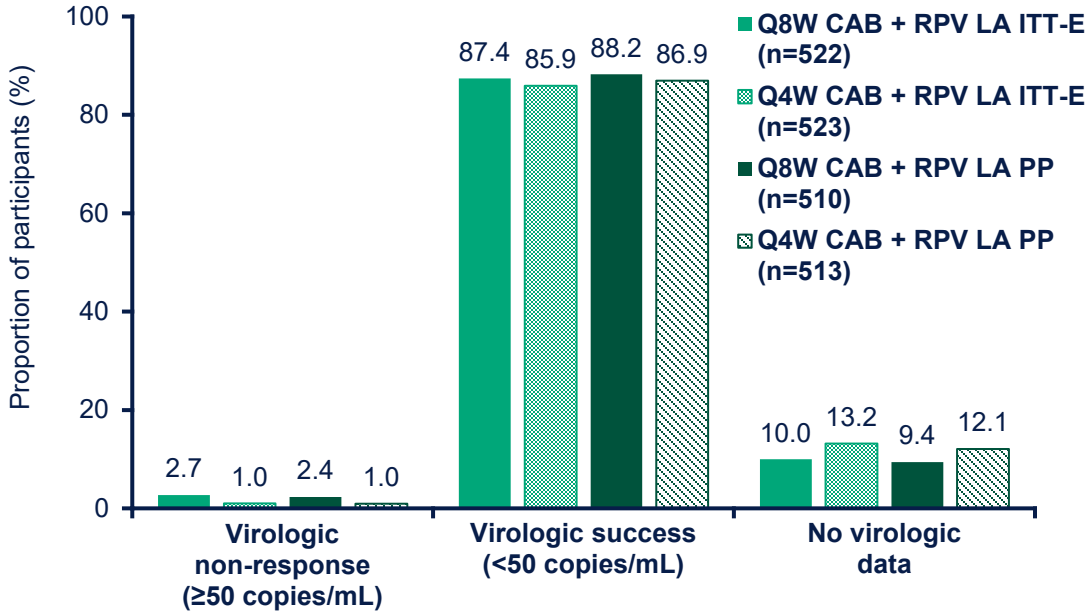
Adults with HIV-1 virologically suppressed* for ≥6 months on daily oral ARV therapy or monthly dosing

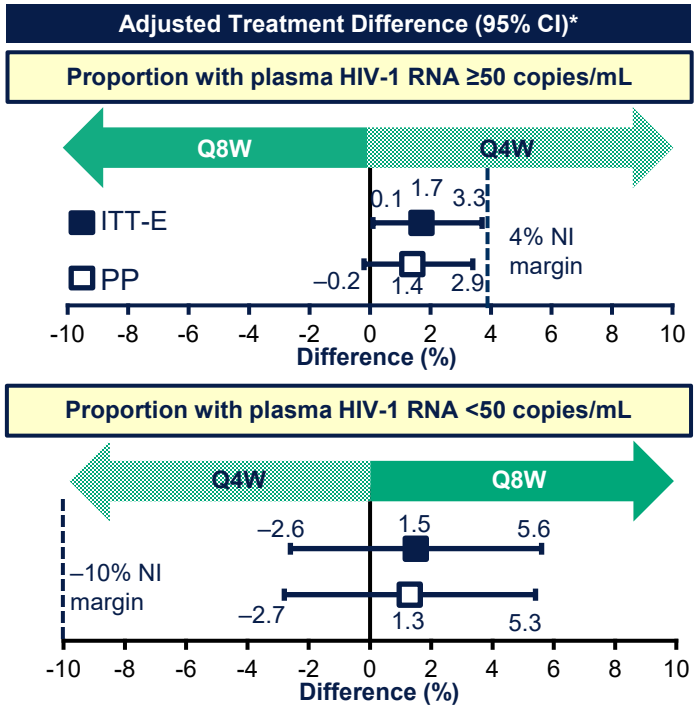
Established non-inferiority of long-acting therapy compared with daily oral regimens; every 2-month dosing non-inferior to monthly dosing[1–3]

*HIV-1 RNA <50 c/mL
ART, antiretroviral therapy; **ARV,** antiretroviral; **c/mL,** copies/mL

1. Orkin C, et al. N Engl J Med 2020;382:1124–35
2. Swindells S, et al. N Engl J Med 2020;382:1112–23
3. Overton ET, et al. Lancet 2021;396:1994–2005

Virologic Outcomes at Week 152





- Baseline characteristics were similar between arms; 27% (n=280) of participants were female at birth, median (range) age was 42 (19–83), 20% (n=211) had a BMI ≥30 kg/m^2, and 37% (n=391) had prior CAB + RPV exposure[1]
- Noninferiority between Q8W and Q4W was confirmed for pre-specified analyses of HIV-1 RNA ≥50 and <50 copies/mL
- Results for the pre-specified per-protocol population were consistent with those for the ITT-E population

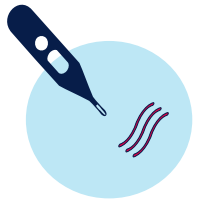
*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; PP, per protocol; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

1. Overton et al. *Lancet*. 2020;396:1994-2005.

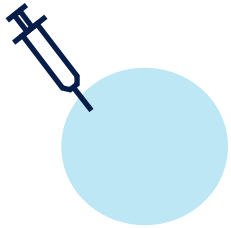
Safety

ATLAS, FLAIR, and ATLAS-2M: Frequently reported AEs* at Week 48

Headache[1,2]



Pyrexia[1,2]



Injection site reactions[1,2]

<2% (n=23/1,636†) of participants discontinued due to injection-related adverse events[3,4]

98% (n=9,196/9,322) of injection site reactions were mild-to-moderate and declined over time[3,4]

3 days median duration[3,4]

*Very common AEs (i.e. AEs reported at a frequency of ≥10%); please refer to the SmPCs for the full list of adverse reactions
†ATLAS n=308; FLAIR n=283; ATLAS-2M n=1,045
ISR, injection site reaction

1. Vocabria EU SmPC. Jan 2022
2. Rekambys EU SmPC. Jan 2022
3. Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506 (and suppl. appendix)
4. Overton ET, et al. Lancet 2021;396:1994–2005

Phase III/IIIb studies (pooled): No pattern of events leading to long-acting treatment discontinuation at Week 48

Pooled population of participants receiving CAB + RPV LA (Q8W + Q4W) through to Week 48*

n (%)	CAB + RPV LA n=1,223
Any adverse events	997 (82)
Grade 3–5 adverse events	64 (5)
Drug-related adverse events	278 (23)
Drug-related Grade 3–5 adverse events	10 (<1)
Any serious adverse events	41 (3)
Drug-related serious adverse events	2 (<1)†
Adverse events leading to withdrawal	23 (2)
Drug-related adverse events leading to withdrawal	11 (<1)‡

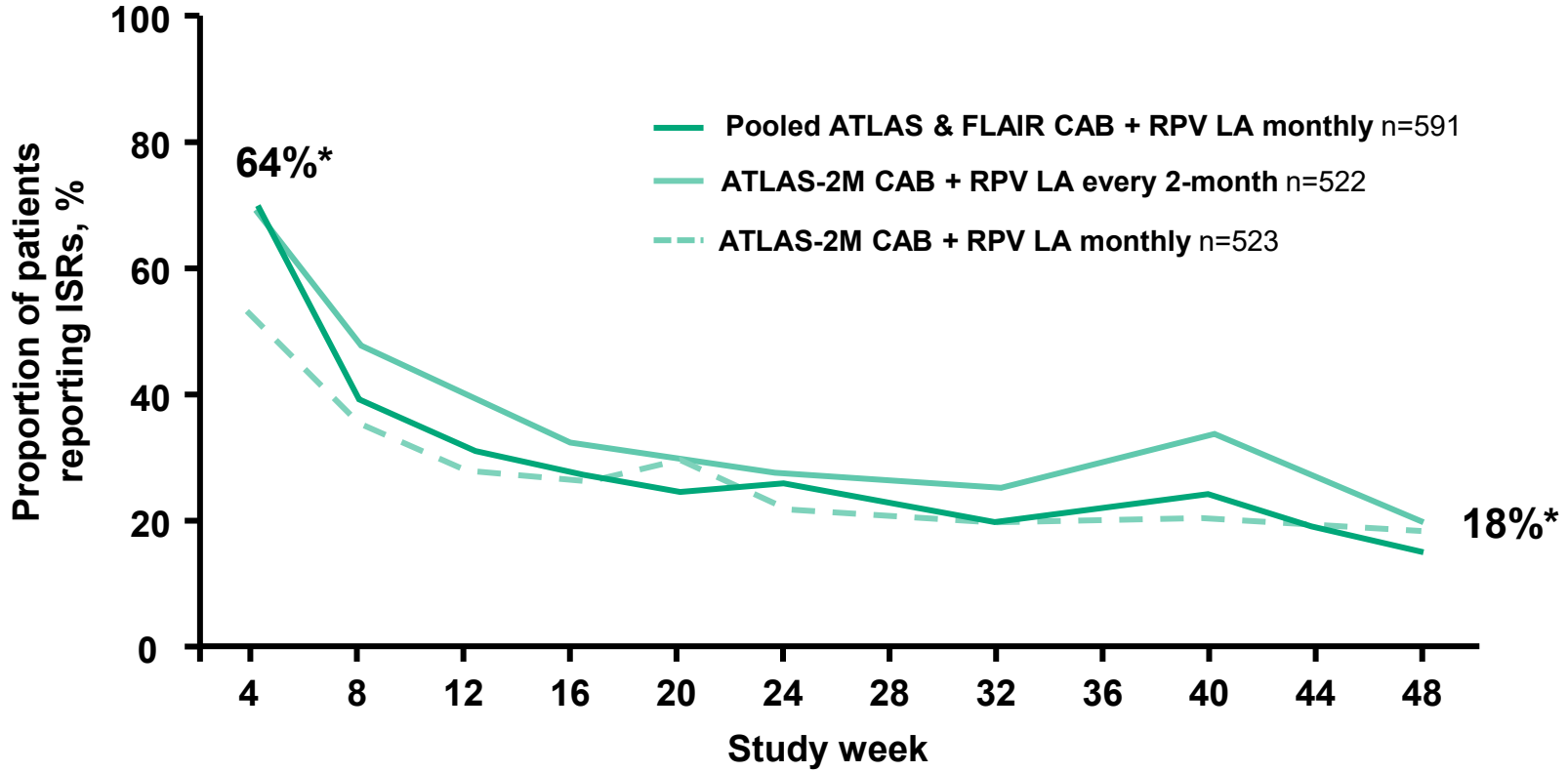
n (%)	CAB + RPV LA n=1,223
Adverse events occurring in ≥5% of participants	
Nasopharyngitis	183 (15)
Upper respiratory tract infection	139 (11)
Pyrexia	92 (8)
Headache	90 (7)
Diarrhea	75 (6)
Back pain	63 (5)
Drug-related adverse events occurring in ≥3% of participants	
Pyrexia	58 (5)

**Post hoc* analysis of participants pooled across ATLAS, FLAIR, and ATLAS-2M through to Week 48. Excludes the 4-week OLI period. Excludes ISRs; †Includes right knee monoarthritis (Grade 3, n=1), and RPV post-injection reaction reported as hypersensitivity (Grade 3, n=1); ‡Includes general discomfort (Grade 2, n=1), diarrhea (Grade 2, n=1; Grade 3, n=1), vomiting (Grade 2, n=1), headache (Grade 1, n=1; Grade 2, n=1; Grade 3, n=1), nausea (Grade 2, n=1; Grade 3, n-1), anxiety (Grade 2, n=1), fatigue (Grade 2, n=2), rash maculo-popular (flat and raised skin lesions; Grade 2, n=1), pyrexia (feeling warm; Grade 2, n=1; Grade 3, n=1), influenza (Grade 2, n=1), hyperhidrosis (abnormal excessive sweating; Grade 2, n=2), perisyncope (fainting sensation; Grade 2, n=1), dizziness (Grade 2, n=1), RPV post-injection reaction reported as hypersensitivity (Grade 3, n=1), abnormal dreams (Grade 1, n=1; Grade 2, n=1), chills (Grade 2, n=1), disturbance in attention (Grade 2, n=1), myalgia (muscle aches; Grade 2, n=1). More than one reason could be reported for withdrawal

ISR, injection site reaction; **OLI,** oral lead-in

Phase III/IIIb studies: Injection site reactions (ISRs) decreased over time

ISR incidence with CAB + RPV LA reported by study week[1–3]



Reported ISRs decreased over time across the three studies[1–3]

*Average (mean)
ISR, injection site reaction

1. Orkin C, et al. N Engl J Med 2020;382:1124–35 (and suppl. appendix)
2. Swindells S, et al. N Engl J Med 2020;382:1112–23 (and suppl. appendix)
3. Overton ET, et al. Lancet 2021;396:1994–2005 (and suppl. appendix)

Summary of safety data

CAB + RPV LA was well-tolerated across all Phase III clinical trials through to Week 152

Most adverse events were mild or moderate severity, and the safety profile was similar between every 2-month and monthly dosing

Injection site reactions were common, but were reported less frequently over time

Participants in Phase III clinical trials reported a high degree of acceptability for injection site reactions

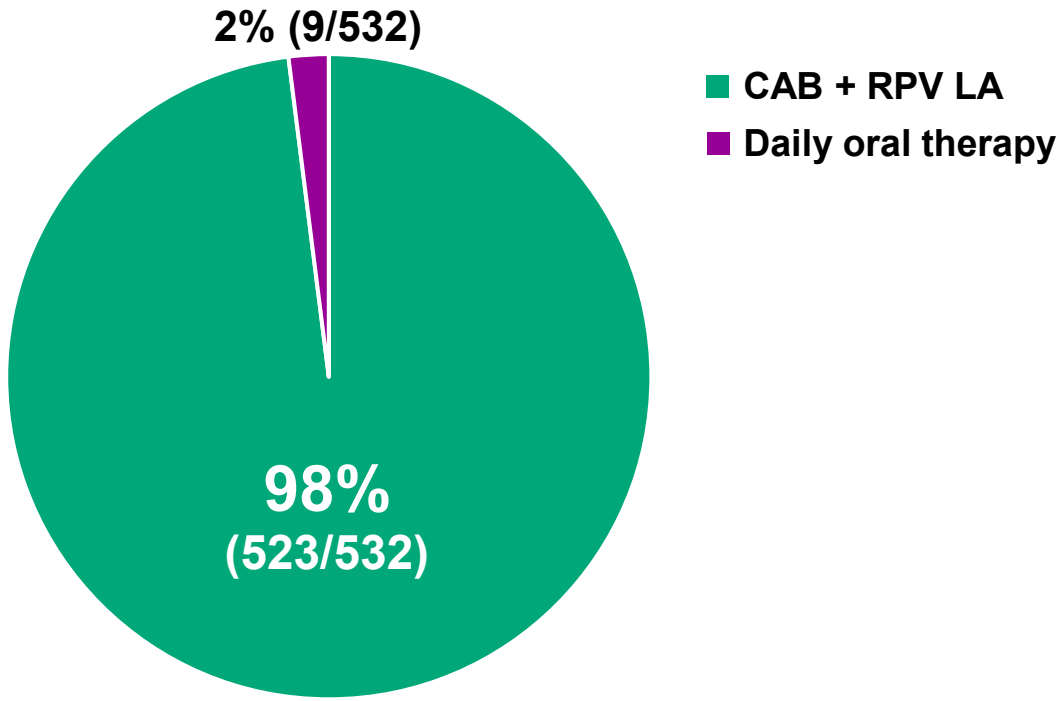
Patient-reported outcomes

ATLAS and FLAIR: Participants preferred cabotegravir + rilpivirine long-acting over daily oral therapy

"For the past 44 weeks you have received long-acting injectable HIV medication every month. Today we would like you to compare your experience on the long-acting injections with the oral medication you received prior to entering or during the induction phase of the study."

"Which therapy do you prefer?"

Preferences of responding participants

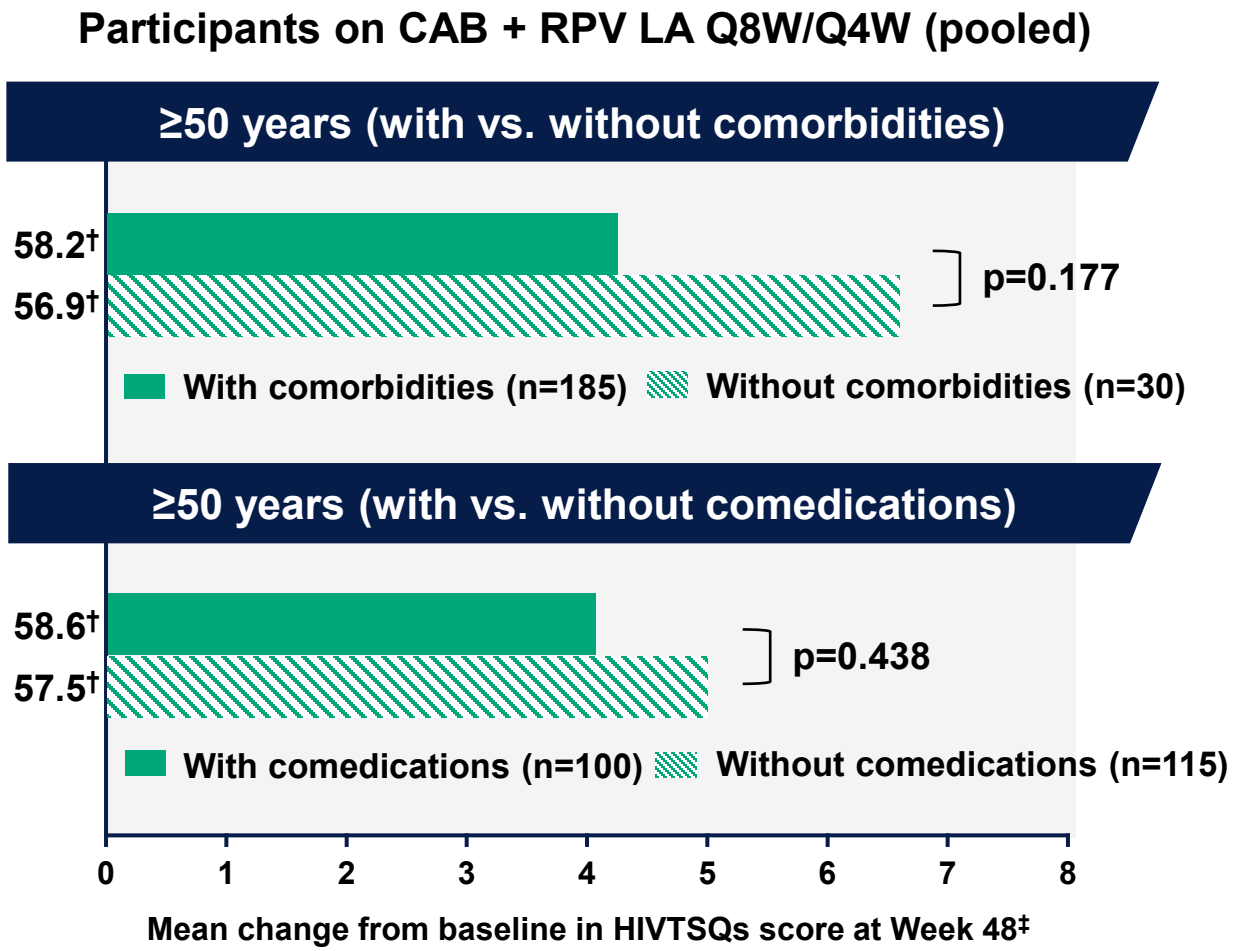


98% of responding participants from ATLAS + FLAIR preferred the long-acting regimen over daily oral therapy at Week 48

Murray M, et al. AIDS and Behav 2020;24:3533–44

High treatment satisfaction irrespective of age group, comorbidities or comedication at Week 48 (HIVTSQs)

- Significantly greater increase in HIVTSQs from baseline in participants receiving long-acting (Q8W/Q4W pooled) vs daily oral therapy regardless of age group
  - Participants <50 years old, p<0.001*
  - Participants ≥50 years old, p<0.001*
- No significant differences were observed in mean change from baseline in HIVTSQs when participants ≥50 years old were stratified by comorbidities or comedications



*p-values for difference of means; †Mean baseline HIVTSQs score
‡As HIVTSQs score was not collected at Week 48 in the ATLAS and FLAIR study, Week 44 values from ATLAS and FLAIR were pooled with Week 48 scores from ATLAS-2M

Benn PD, et al. CROI 2021. Oral 402

Qualitative interviews highlight the experience of Phase III study participants with long-acting therapy

Logistical and psychological freedom

"Less tied to a packet of pills"

"…So, I wanted to get rid of the minor inconvenience of it, like having to fill the prescription, having to make sure I picked up the prescription in time and all that. So, I have to - I just go to my next appointment. It's all taken care of, and it's a one-stop shop."

Male ATLAS/ATLAS-2M participant, U.S., age 29

Injection site reactions

"It got better over time"

"The first time I ever got the injection, the soreness lasted a couple days but I knew about it ahead of time so I wasn't scared. I just expected it. But after that… after the next month I didn't feel anything to the point that I called and asked them, 'I don't feel anything. Is that normal?' "

Female ATLAS participant, U.S., age 30

The importance of clinical efficacy of long-acting

"Are my numbers going down?"

"The only concern I have had… was how could it last a month… Since the pill was daily, I was certain that it was having an effect each day. But with the injection, I won't necessary receive it today, so what will happen tomorrow?"

Male FLAIR participant, Spain, age 22

Stigma associated with clinic attendance

Fear of potential discrimination

"The only thing is… the fact that you have to come here once a month… and the issue is not so much to receive the injection but to be seen out there waiting. If someone you know sees you, they might ask: "What are you doing here at the doctor?" and you may then need to invent an excuse."

Male FLAIR participant, Spain, age 38

Initial injection site pain

Limited mobility in the days following the injection

"I was actually on the verge of withdrawing from the study because it was limiting my activity. I mean, it was impacting walking, running, going to the gym and my sleep. Because you roll over and the pain wakes you up. And so then it seemed like it got better over time."

Male ATLAS participant, U.S., age 47

Dosing frequency

"The less I need to come to a hospital the better"

"…I mean, if it's the same thing and you just – you can cut your visits by half. So you don't have to do the visit, and also don't have six more times of walking around with a limp. Even if it's just for a day, that's six days out of the year less that you have that."

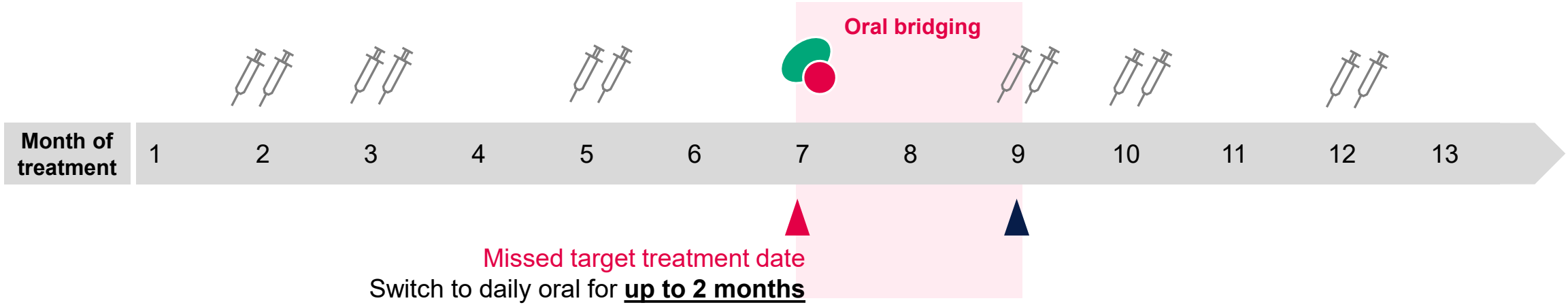
Male ATLAS/ATLAS-2M participant, U.S., age 49

Mantsios A, et al. AIDS Behav 2020;24:3473–81

What if you miss a dose?

Managing planned missed injections (<u>with</u> oral bridging): 2-month dosing

- CAB and RPV oral tablets QD can be used to replace CAB + RPV LA injections for up to 2 months[1,2]
  - For oral therapy durations greater than 2 months, an alternative oral regimen is recommended[1,2]
- The first dose of oral therapy should be taken on the target date for injection (±7 days)[1,2]
- It is recommended to resume injection dosing on the target treatment date. Oral dosing completes on the same day as injections restart[3]



QD, once daily

1. Vocabria EU SmPC. Jan 2022; **2.** Rekambys EU SmPC. Jan 2022
3. ViiV Healthcare. HCP consultation guide.
Available at: https://gskpro.com/content/dam/global/hcpportal/fi_FI/unprotected/pdf/hcp-patient-consultation-guide-finland-42021.pdf (accessed Feb 2022)

Does cabotegravir + rilpivirine (long-acting) interact with other medications (including herbal supplements, alcohol, or recreational drugs)?

CAB + RPV LA and drug–drug interactions

CAB + RPV LA injections bypass the gut…

…avoiding drug–drug interactions related to oral absorption…

…which means:[1]

- No food requirements
- No pH constraints
- No binding to polyvalent cations (e.g. aluminum, calcium, iron etc.)

People with HIV should not take CAB + RPV LA with:[2,3]

- Anticonvulsants used to treat epilepsy and prevent seizures (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin)
- Antibiotics to treat some bacterial infections such as tuberculosis (rifapentine, rifampicin, and rifabutin)
- Dexamethasone*, St John's wort[3]

Caution is recommended when taken with:

- Antibiotics such as clarithromycin and erythromycin (alternatives such as azithromycin should be considered)[3]

Clinical monitoring is recommended when taken with:

- Methadone (as levels may decrease)[3]

People with HIV are advised to speak with their healthcare professional for further information

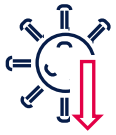
*More than a single dose

1. Letendre SL, et al. J Antimicrob Chemother 2020;75:648–55
2. Vocabria EU SmPC. Jan 2022; **3.** Rekambys EU SmPC. Jan 2022

What factors should people with HIV take into consideration before initiating the cabotegravir + rilpivirine long-acting regimen?

Matching people with HIV and therapy: Clinical considerations

Clinical

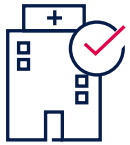


Virologically-suppressed* adults on a stable antiretroviral regimen[1,2]

No prior non-nucleoside reverse transcriptase or integrase inhibitor treatment failure or known resistance† to these classes[1,2]

No contraindications or potential drug-drug interactions[1,2]

Personal and clinical



Motivated and able to attend a clinic visit every 2 months[1,2]

*HIV-1 RNA <50 c/mL
†Past or present

1. Vocabria EU SmPC. Jan 2022
2. Rekambys EU SmPC. Jan 2022