# Long-Active Cabotegravir + Rilpivirine for HIV Maintenance: FLAIR Week 48 Results

Chloe Orkin,[1] Keikawus Arasteh,[2] Miguel Górgolas Hernández-Mora,[3] Vadim Pokrovsky,[4] Edgar T. Overton,[5] Pierre-Marie Girard,[6] Shinichi Oka,[7] Ronald D'Amico,[8] David Dorey,[9] Sandy Griffith,[8] David A. Margolis,[8] Peter Williams,[10] Wim Parys,[10] William R. Spreen[8]

*[1]Queen Mary University, London, UK; [2]EPIMED GmbH, Berlin, Germany; [3]Fundación Jiménez Díaz, Madrid, Spain; [4]Central Institute of Epidemiology, Moscow, Russia; [5]University of Alabama at Birmingham, Birmingham, AL, USA; [6]Hôpital Saint Antoine, Paris, France; [7]National Center for Global Health and Medicine, Tokyo, Japan; [8]ViiV Healthcare, Research Triangle Park, NC, USA; [9]GlaxoSmithKline, Mississauga, Ontario, Canada; [10]Janssen Research and Development, Beerse, Belgium*

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# Disclosures

- I have received grants to my institution from Gilead, Janssen, ViiV Healthcare, and Merck Sharpe & Dohme
- I have received travel scholarships, honoraria for advisory boards, and speaker fees from Gilead, Janssen, ViiV Healthcare, and Merck Sharpe & Dohme

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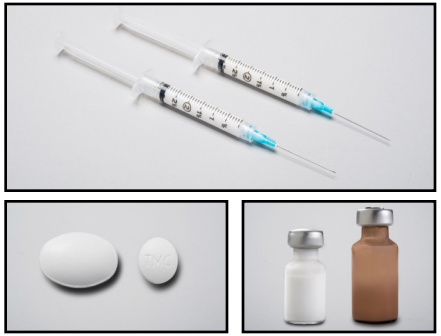
# FLAIR Background

- Approved therapies for HIV now include once-daily oral regimens containing 2 or 3 antiretrovirals
- Despite the success of daily oral therapy, considerable interest exists in LA treatment options
- Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor
  - Oral 30 mg tablet: $t_{½}$ ≈ 40 hours
  - Long-acting IM injection, 200 mg/mL: $t_{½}$ ≈ 40 days
- Rilpivirine (RPV) is an HIV-1 non-nucleoside reverse transcriptase inhibitor
  - Oral 25 mg tablet: $t_{½}$ ≈ 50 hours
  - Long-acting IM injection, 300 mg/mL: $t_{½}$ ≈ 90 days



- LATTE-2: CAB LA + RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years[1]
- Two pivotal phase 3 studies (ATLAS[2] and FLAIR) have reached their primary endpoints at 48 weeks

IM, intramuscular; LA, long-acting.

**1.** Margolis et al. HIV Glasgow 2018; Glasgow, UK. Poster 118. **2.** Swindells et al. CROI 2019; Seattle, WA. Abstract 1475.

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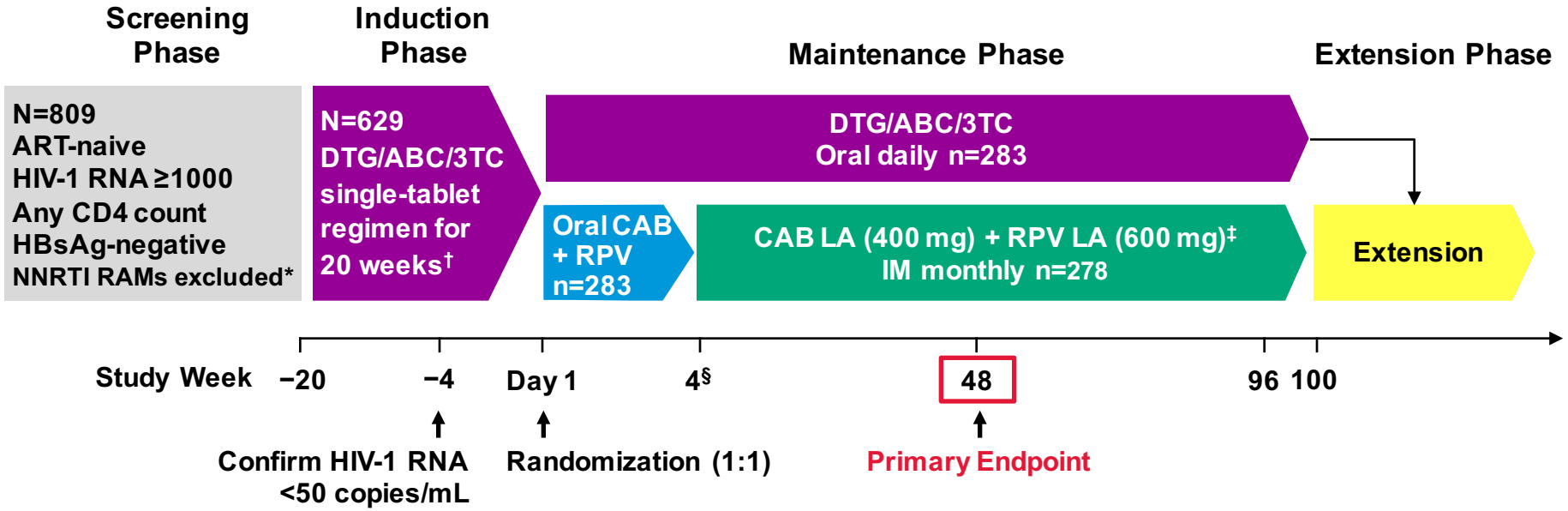
# FLAIR Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in ART-Naive Adults (Ongoing)




IM, intramuscular; HBsAg, hepatitis B surface antigen; LA, long-acting; RAM, resistance-associated mutation. *NNRTI RAMS but not K103N were exclusionary. †DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive (n=30 as last regimen during induction: n=2 discontinued during induction, n=14 randomized to CAB LA + RPV LA, n=14 randomized to DTG/ABC/3TC arm and continued on DTG plus 2 alternative non-ABC NRTIs in Maintenance Phase). ‡Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up. §Participants received initial loading doses of CAB LA 600 mg and RPV LA 900 mg at Week 4. Beginning Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections every 4 weeks.

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# FLAIR Objectives and Endpoints

## Objective

- Establish noninferior antiviral activity of monthly IM CAB LA + RPV LA vs continuing DTG/ABC/3TC

## Primary endpoint

- Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48 using the FDA Snapshot algorithm
  - 6% noninferiority margin on difference between groups

## Selected secondary endpoints

- HIV-1 RNA <50 copies/mL at Week 48 (Snapshot)*
- Safety and tolerability
- Viral resistance associated with CVF†
- Patient-reported outcomes‡

## Selected exploratory endpoint

- Participant-reported preferences of the LA regimen§

CVF, confirmed virologic failure; FDA, Food and Drug Administration; HIVTSQc, HIV Treatment Satisfaction Questionnaire (Change version); IM, intramuscular; LA, long-acting. *Predefined key secondary endpoint. †Defined as 2 consecutive HIV-1 RNA measurements ≥200 copies/mL. ‡HIVTSQc. §Single-item question for participant-reported preference on the LA and daily oral regimen.

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# FLAIR Baseline* Characteristics: ITT-E Population

| Parameter | CAB LA + RPV LA N=283 | DTG/ABC/3TC N=283 | Total N=566 |
|---|---|---|---|
| Median age (range), year | 34 (19-68) | 34 (18-68) | 34 (18-68) |
| Age ≥50 years, n (%) | 33 (12) | 29 (10) | 62 (11) |
| Female, n (%) | 63 (22) | 64 (23) | 127 (22) |
| Race, n (%) | | | |
| White | 216 (76) | 201 (71) | 417 (74) |
| Black or African American | 47 (17) | 56 (20) | 103 (18) |
| Other or missing | 20 (7) | 26 (9) | 46 (8) |
| Median body mass index (range), kg/m$^2$ | 24 (17-45) | 24 (13-47) | 24 (13-47) |
| HIV-1 RNA (copies/mL), n (%) | | | |
| <100,000 | 227 (80) | 227 (80) | 454 (80) |
| ≥100,000 | 56 (20) | 56 (20) | 112 (20) |
| Median baseline CD4+ cell count (IQR), cells/mm$^3$ | 437 (314-609) | 452 (321-604) | 444 (320-604) |
| <200, n (%) | 16 (6) | 23 (8) | 39 (7) |
| Median Day 1 CD4+ cell count (IQR), cells/mm$^3$ | 624 (473-839) | 625 (472-799) | 625 (473-818) |
| HIV-1–HCV co-infection, n (%) | 19 (7) | 9 (3) | 28 (5) |

HCV, hepatitis C virus; IQR, interquartile range; ITT-E, intention-to-treat–exposed; LA, long-acting. *Baseline was Week −20.

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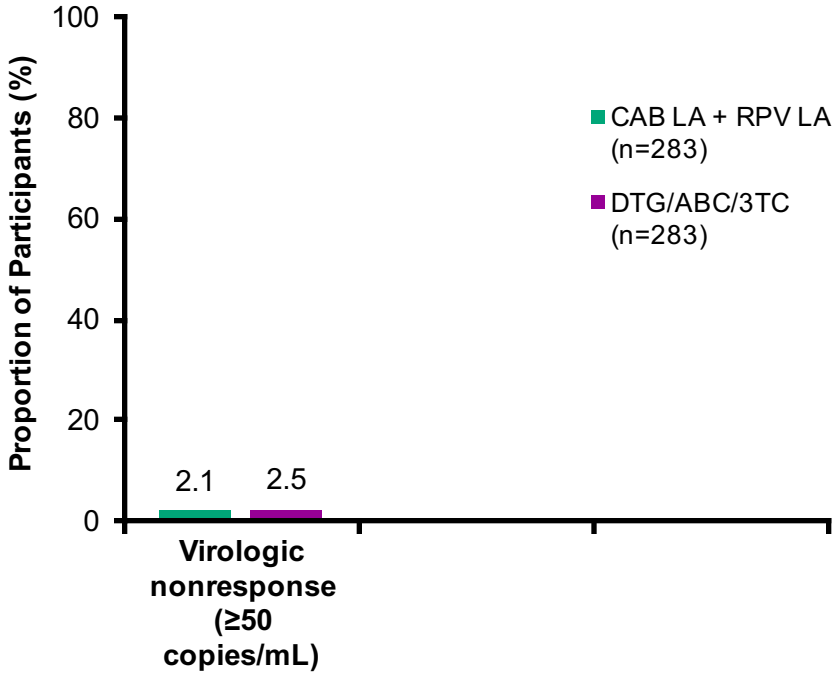
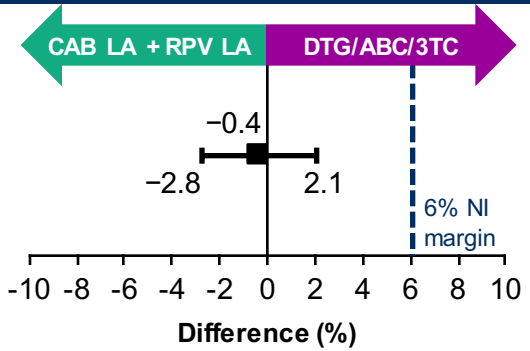
# FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E:
## Noninferiority Achieved for Primary and Secondary Endpoints

### Virologic Outcomes




### Adjusted Treatment Difference (95% CI)*




**Primary endpoint:**

**LA noninferior to DTG/ABC/3TC (≥50 copies/mL) at Week 48**

ITT-E, intention-to-treat–exposed; LA, long-acting; NI, noninferiority. *Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 copies/mL).

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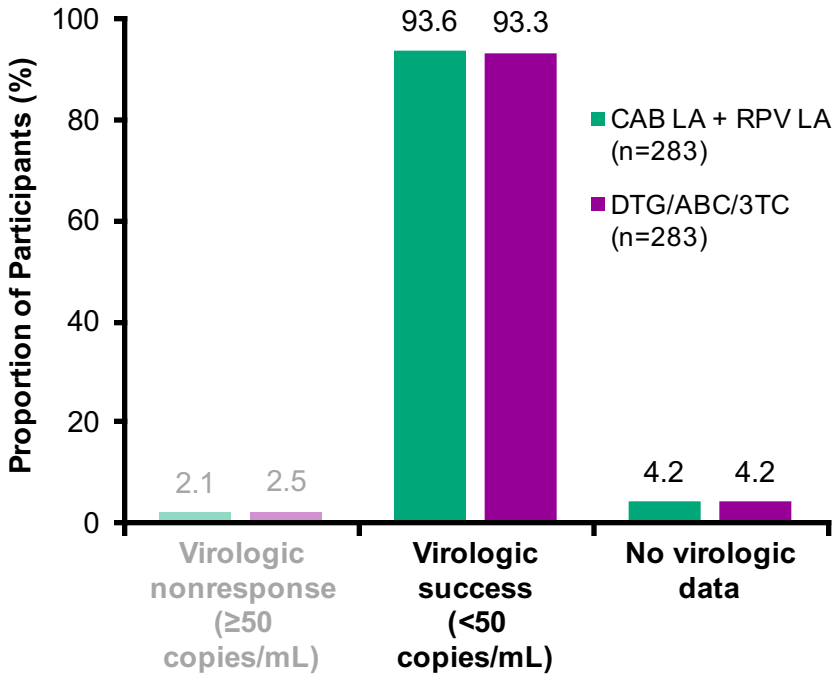
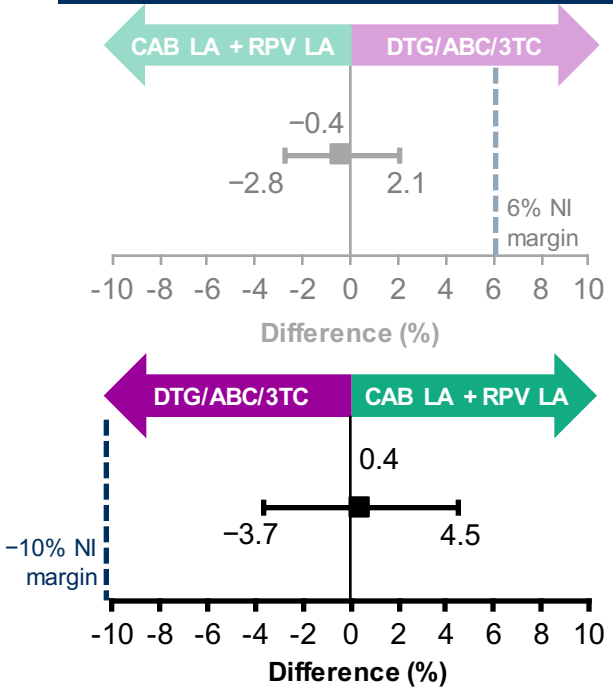
# FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E:
## Noninferiority Achieved for Primary and Secondary Endpoints (cont)

### Virologic Outcomes




### Adjusted Treatment Difference (95% CI)*




**Primary endpoint:**

**LA noninferior to DTG/ABC/3TC (≥50 copies/mL) at Week 48**

**Key secondary endpoint:**

**LA noninferior to DTG/ABC/3TC (<50 copies/mL) at Week 48**

ITT-E, intention-to-treat–exposed; LA, long-acting; NI, noninferiority. *Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 copies/mL).

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# FLAIR Snapshot Outcomes at Week 48 for ITT-E

| n (%) | CAB LA + RPV LA N=283 | DTG/ABC/3TC N=283 |
|---|---|---|
| **HIV-1 RNA <50 copies/mL** | **265 (93.6)** | **264 (93.3)** |
| **HIV-1 RNA ≥50 copies/mL** | **6 (2.1)** | **7 (2.5)** |
| Data in window not below threshold | 2 (0.7) | 2 (0.7) |
| Discontinued for lack of efficacy | 4 (1.4) | 3 (1.1) |
| Discontinued for other reason while not below threshold | 0 | 2 (0.7)* |
| **No virologic data** | **12 (4.2)** | **12 (4.2)** |
| Discontinued due to AE† | 8 (2.8) | 2 (0.7) |
| Discontinued for other reasons‡ | 4 (1.4) | 10 (3.5) |

ITT-E, intention-to-treat–exposed; LA, long-acting. *Relocation (1), lost to follow-up (1). †LA arm: hepatitis A (1), acute hepatitis B (1), acute hepatitis C (1), transaminases increase (1), hepatitis A/secondary syphilis (1), injection site pain (1), injection site pain/discomfort/diarrhea/vomiting (1), adenocarcinoma of colon (1). DTG/ABC/3TC arm: renal failure (1), suicide attempt (1). ‡ LA arm: Tolerability of injections (1), incarceration (1), lost to follow up (2). DTG/ABC/3TC arm: frequency of visits (participant decision [4]), noncompliance with study treatment and protocol procedures (2), relocation (1), participant decision to stop treatment (1), late to attend visits (1), lost to follow up (1).

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# FLAIR Confirmed Virologic Failures: CAB LA + RPV LA Arm

| Sex, Country, HIV-1 Subtype, Virologic Load (Baseline) | Baseline RAMs (HIV-1 RNA) | | SVF Timepoint | Viral Load at SVF/CVF (copies/mL) | SVF Timepoint RAMs (HIV-1 RNA) | | Drug Sensitivity at SVF† (Fold Change) |
|---|---|---|---|---|---|---|---|
| | NNRTI | INSTI* | | | NNRTI | INSTI* | |
| F, Russia, A1, 54K | | | Week 20 | 373 / 456 | E138E/A/K/T | L74I, Q148R | **RPV (7.1)**<br>**CAB (5.2)**<br>DTG (1.0) |
| M, Russia, A1, 23K | | | Week 28 | 287 / 299 | K101E | L74I, G140R | **RPV (2.6)**<br>**CAB (6.7)**<br>DTG (2.2) |
| F, Russia, A1, 20K | | | Week 48 | 488 / 440 | E138K | L74I, Q148R | RPV (1.0)<br>**CAB (9.4)**<br>DTG (1.1) |

- Plasma CAB and RPV concentrations at the time of failure were below the population means but within the range for the large majority of individuals who maintained virologic suppression
- One additional participant had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon reinitiation of oral therapy had suspected VF that was confirmed
- Three participants in the DTG/ABC/3TC arm had CVF at Weeks 8, 12, and 16, respectively; no drug resistance mutations were selected

CVF, confirmed virologic failure; LA, long-acting; RAM, resistance-associated mutation; SVF, suspected virologic failure; VF, virologic failure. *L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity. †Monogram biological /clinical cutoffs are: RPV=2.0, CAB=2.5, and DTG=4.0.

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# FLAIR Confirmed Virologic Failures: CAB LA + RPV LA Arm

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|---|---|---|---|---|---|---|---|
| | NNRTI | INSTI* | | | NNRTI | INSTI* | |
| F, Russia, A1, 54K | None | L74I | Week 20 | 373 / 456 | E138E/A/K/T | L74I, Q148R | **RPV (7.1)**<br>**CAB (5.2)**<br>DTG (1.0) |
| M, Russia, A1, 23K | None | L74I | Week 28 | 287 / 299 | K101E | L74I, G140R | **RPV (2.6)**<br>**CAB (6.7)**<br>DTG (2.2) |
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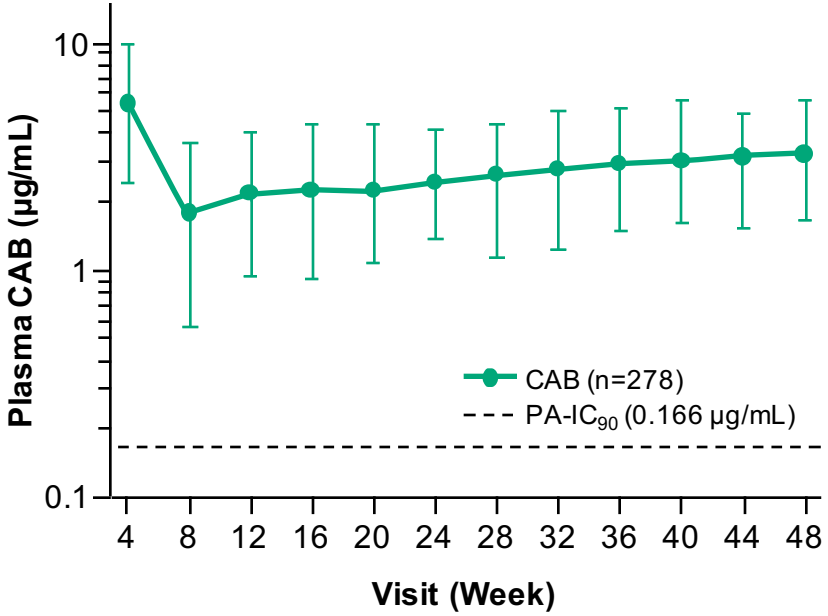
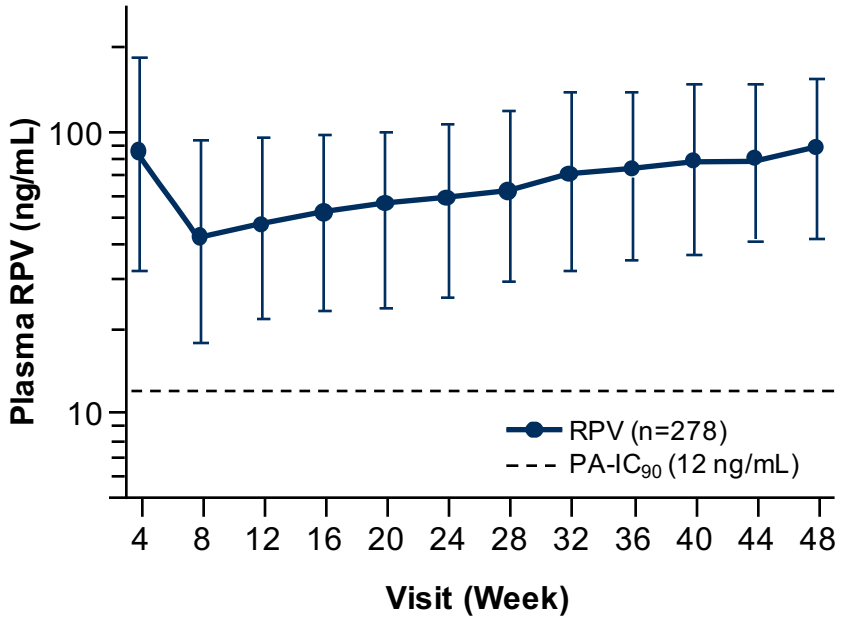
# FLAIR Plasma CAB and RPV Trough Concentrations by Visit Following CAB LA and RPV LA

- Plasma concentrations after IM CAB and RPV were comparable with those during efficacious oral regimens




IM, intramuscular; LA, long-acting; PA, protein-adjusted. Median (5th, 95th percentile) concentration–time data for CAB (left) and RPV (right) following monthly LA administration.

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# FLAIR Adverse Events (Excluding ISRs)

| | CAB LA + RPV LA N=283 | DTG/ABC/3TC N=283 |
|---|---|---|
| **Any AE (≥10%), n (%)** | | |
| Any event (per participant) | 246 (87) | 225 (80) |
| Nasopharyngitis | 56 (20) | 48 (17) |
| Headache | 39 (14) | 21 (7) |
| Upper respiratory tract infection | 38 (13) | 28 (10) |
| Diarrhea | 32 (11) | 25 (9) |
| **Drug-related AE (≥3%), n (%)** | | |
| Any event (per participant) | 79 (28) | 28 (10) |
| Headache | 14 (5) | 4 (1) |
| Pyrexia | 13 (5) | 0 |
| **All AEs leading to withdrawal*** | 9 (3) | 4 (1) |

- 74/79 (94%) CAB LA + RPV LA participants had drug-related AEs at maximum grade 1 or 2
  - One drug-related SAE on CAB LA + RPV LA (right knee monoarthritis)
    - None in DTG/ABC/3TC arm
  - No cases of drug hypersensitivity or drug-induced liver injury observed

ISR, injection-site reaction; LA, long-acting; SAE, serious AE. *Events leading to withdrawal included: CAB LA + RPV LA arm: acute hepatitis A (1), hepatitis B (2), hepatitis C (1), acute hepatitis A/secondary syphilis (1), injection site pain (1), injection site pain/general discomfort/diarrhea/vomiting (1), increased transaminases (1), and adenocarcinoma of colon (1); DTG/ABC/3TC arm: fatigue/nausea/dizziness (1), amnesia/disturbance in attention/dysarthria (1), suicide attempt (1), and renal failure (1).

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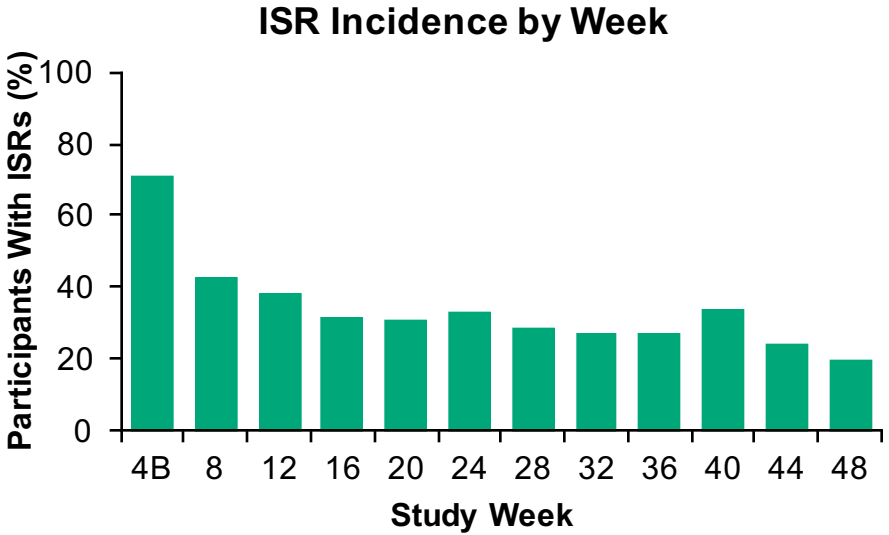
# FLAIR Injection-Site Reactions




- The majority (99%, 2189/2203) of ISRs were grade 1-2 and most (88%) resolved within ≤7 days

| Event | CAB LA + RPV LA N=283* |
|---|---|
| Participants receiving injections, n | 278 |
| Injections given, n | 7704 |
| ISR events, n (%) | 2203 (28.6) |
| Pain | 1879 (85.3) |
| Nodule | 86 (3.9) |
| Induration | 82 (3.7) |
| Swelling | 38 (1.7) |
| Warmth | 38 (1.7) |
| Grade 3 ISR pain | 12 (<1)† |
| Median duration of ISRs, days | 3 |
| Participants with ISR leading to withdrawal, n (%) | 2 (<1)‡ |

IM, intramuscular; ISR, injection-site reaction; LA, long-acting. Bars represent incidence of onset ISRs relative to the most recent IM injection visit. *Table shows data up to Week 72. †No events worse than grade 3 were reported. ‡ISR leading to withdrawal: 2 due to ISR pain. Two additional participants withdrew due to injection intolerability.

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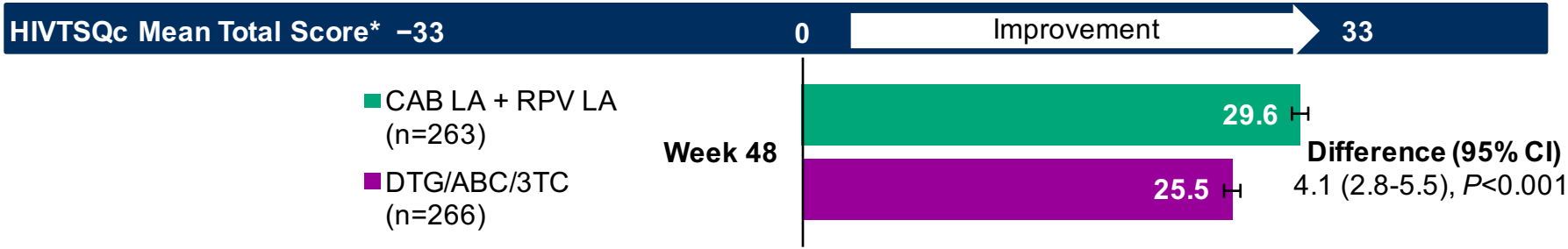
# FLAIR: High Participant Satisfaction (HIVTSQc) and Preference for Injectable Therapy




- Change in satisfaction with current treatment vs induction phase treatment was significantly higher for LA vs DTG/ABC/3TC
  - HIVTSQs exhibited a ceiling effect, with very high baseline satisfaction scores in both groups (data not shown)†

## Patient Preference Survey

Single-item question on participants' preference at Week 48:

- ITT-E population: 91% (257/283) preferred LA; 1% (2/283) preferred daily oral therapy
  - **Responding participants: 99% (257/259) preferred the LA regimen over previous oral therapy**

HIVTSQc, HIV Treatment Satisfaction Questionnaire (change version); HIVTSQs, HIV Treatment Satisfaction Questionnaire (status version); ITT-E, intention-to-treat–exposed; LA, long-acting; SE, standard error. *Adjusted for baseline HIV-1 RNA (< vs ≥100,000 copies/mL), sex, age, and race ± SE. Based on observed dataset of participants who completed the questionnaire at Week 48 or early withdrawal. †Maintenance (Day 1) HIVTSQs baseline mean score comparable between both arms with the same mean value of 59 out of 66 points.

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# FLAIR Conclusions

- Monthly CAB LA + RPV LA was noninferior to continued oral DTG/ABC/3TC at Week 48 for maintaining suppression of HIV-1
- Low confirmed virologic failure rate across both treatment arms: 1.4% vs 1.1%
  - Three participants on CAB LA + RPV LA had treatment-emergent resistance for NNRTI and INSTI at CVF
  - All harbored HIV-1 subtype A1, warranting further investigation
- ISRs in the LA arm were common but mainly grade 1 or 2, with few associated discontinuations
- Highly positive treatment satisfaction and preference outcomes with LA regimen
- Overall, these results support the therapeutic potential of monthly CAB LA + RPV LA for maintenance after oral induction in previously ART-naive individuals

CVF, confirmed virologic failure; ISR, injection-site reaction; LA, long-acting.

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# Acknowledgments


- We thank everyone who has contributed to the success of the study
  - All study participants and their families
  - The FLAIR clinical investigators and their staff in Canada, France, Germany, Italy, Japan, the Netherlands, the Russian Federation, South Africa, Spain, the United Kingdom, and the United States

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