Injection Site Reactions Associated with Long-Acting Cabotegravir and Rilpivirine in ATLAS, FLAIR, and ATLAS-2M

Summary

ATLAS and FLAIR

- Drug-related local injection site reactions (ISRs) were common, occurring in 83% (483/591) of patients in ATLAS and FLAIR. One percent of patients who received cabotegravir and rilpivirine (CAB + RPV LA) discontinued due to an ISR.[1]
    - Most were Grades 1 or 2 in severity.[1]
- The most common local ISR event was pain (77%).[1] Most local ISRs (94%) resolved within 14 days with a median (range) duration of 3 days (1–341). The incidence of local ISRs decreased over the course of the trials through Week 48.
- No specific treatments for local ISRs were evaluated in ATLAS and FLAIR.[1] Medical judgement should be used to determine how best to manage ISRs (e.g., oral analgesics, application of a hot or cold pack, etc.).

ATLAS-2M

- Through Week 48, 74% of patients in each treatment arm experienced a drug-related ISR.[2]
- In both arms, 86% of ISRs had a duration of 1 to 7 days.[3]
- As previously reported from ATLAS and FLAIR, ISRs were most commonly reported at treatment initiation and reports of ISRs tended to decrease over time.[2]

Pooled Analysis of ATLAS-2M and FLAIR

- Overall, the incidence, type, and severity of ISRs were generally comparable by dosing regimen, drug, sex at birth, baseline BMI, and race.[4]
- Nodules were reported in 19% of patients. Injection site nodules and induration events were reported to have taken the longest to resolve (9 and 8 days, respectively).[4]

ATLAS AND FLAIR: LOCAL INJECTION SITE REACTIONS AT WEEK 48

A total of 591 patients were included in both trials [ATLAS (N = 308) and FLAIR (N = 283)] and 581 received at least one round of injections with long-acting CAB + RPV LA.[1] Eighty-three percent (489/591) patients experienced a local ISR. Eighty-one percent (477/591) experienced a local ISR that the investigator determined was related to CAB + RPV LA. During the maintenance phase of ATLAS and FLAIR, local ISRs were the most commonly reported adverse event. See Table 1 below for more details.

Most local ISRs (94%) resolved within 14 days with a median (range) duration of 3 days (1 - 341).[1]

The most common local ISR event was pain (77%) followed by nodule formation (14%), induration (12%), swelling (8%), erythema (4%), and pruritis (4%).[1] Injection site abscess and cellulitis were reported in < 1% of patients for each event.

Specific to nodules, in the ATLAS trial, 37 patients (12%) reported nodules in the CAB + RPV LA group. All reports of nodules were a Grade 1 (n = 33) or Grade 2 (n = 4). The duration was as follows: 1–7 days, n = 16; 8–14 days, n = 5; > 14 days, n = 12; missing, n = 4.[5] In the FLAIR trial, 44 patients (16%) who received

CAB + RPV LA reported nodules. All reports were a Grade 1 (n = 39) or Grade 2 (n = 5). The duration was as follows: 1–7 days, n = 11; 8–14 days, n = 10; > 14 days, n = 23.[6]

The proportion of male and female patients with ISRs were similar. Injection site pain was reported less frequently by females than males (66% vs. 82%).[7]

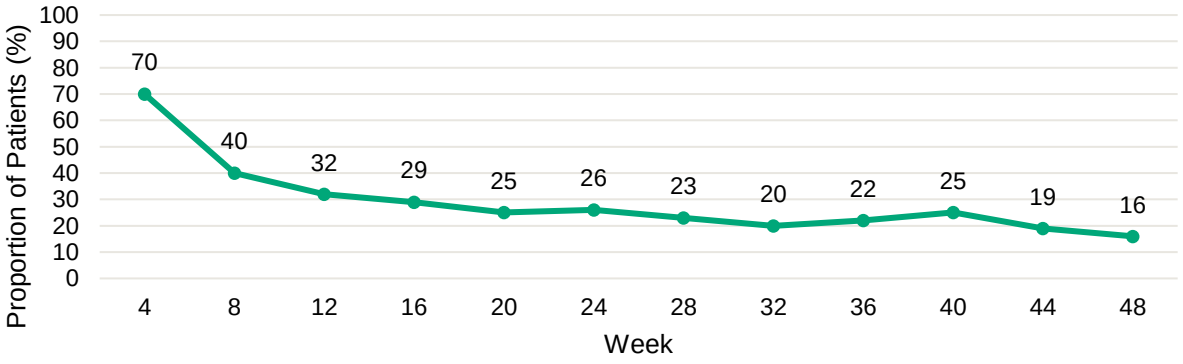
Table 1. Summary of Subject-Level Characteristics of Local ISR Adverse Events in the Maintenance Phase of ATLAS and FLAIR[1]

	ATLAS (N = 308) n (%)	FLAIR (N = 283) n (%)	Pooled (N = 591) n (%)
Subjects with injection	303 (98)	278 (98)	581 (98)
Subjects with ISR event	250 (83)	239 (86)	489 (84)
Event Grade			
Grade 1	215 (71)	222 (80)	437 (75)
Grade 2	110 (36)	101 (36)	211 (36)
Grade 3	11 (4)	11 (4)	22 (4)
Grade 4 or 5	0	0	0
Not applicable	0	1 (< 1)	1 (< 1)
Maximum duration, days			
1 to 7	158 (52)	133 (48)	291 (50)
8 to 14	44 (15)	51 (18)	95 (16)
>14	48 (16)	53 (19)	101 (17)
Not applicable	0	2 (< 1)	2 (< 1)
Event characteristics			
Drug-related	244 (81)	233 (84)	477 (82)
Leading to withdrawal	4 (1)	2 (< 1)	6 (1)

ISR = injection site reaction ATLAS = Antiretroviral Therapy Long-Acting Suppression; FLAIR = First Long-Acting HIV Injectable Regimen

The incidence of local ISRs reported at each time point decreased over the course of the studies (Figure 1).[1]

Figure 1. Incidence[a] of ISRs at Each Time Point Through Week 48[1]



[a] Bars represent incidence of onset ISRs relative to the most recent intramuscular injection visit

Six subjects (1%) withdrew during the maintenance phase of ATLAS and FLAIR due to ISRs through Week 48.[1] ISRs that led to discontinuation of CAB + RPV LA can be found in Table 2 below.

Table 2. Local ISRs Leading to Discontinuation in ATLAS and FLAIR Through Week 48[1]

System Organ Class Preferred Term	ATLAS (N = 308) n (%)	FLAIR (N = 283) n (%)	Pooled (N = 591) n (%)
Injection site pain	4 (1)	2 (< 1)	6 (1)
Injection site nodule	1 (< 1)	0	1 (< 1)
Discomfort	0	1 (< 1)	1 (< 1)
Injection site swelling	1 (< 1)	0	1 (< 1)

ISR = injection site reaction; ATLAS = Antiretroviral Therapy Long-Acting Suppression; FLAIR = First Long-Acting HIV Injectable Regimen

See Table 3 for a breakdown of ISR events relative to the number of injections given through Week 48.

Table 3. Injection Site Reactions Among Patients Who Received CAB + RPV LA in ATLAS and FLAIR Through Week 48[8]

Event	CAB + RPV LA (N = 591)*
ISR events	3663 (24.9)
Pain	3087 (21.0)
Grade 3 ISR pain	32 (0.2)
Nodule	140 (1.0)
Induration	136 (0.9)
Swelling	86 (0.6)

*the denominator used to calculate the percentages below is the total number of injections administered over 48 weeks (n = 14,682)

CAB + RPV LA = long-acting cabotegravir and rilpivirine; ATLAS = Antiretroviral Therapy Long-Acting Suppression; FLAIR = First Long-Acting HIV Injectable Regimen; ISR = injection site reaction

The protocols for ATLAS and FLAIR allowed for the use of longer needle lengths (≥ 2″) to accommodate for body type.[9,10] However, longer needles were used in a very small number of patients compared with the recommended 1.5” needles. As such, no comparisons can be made based on needle length.[1]

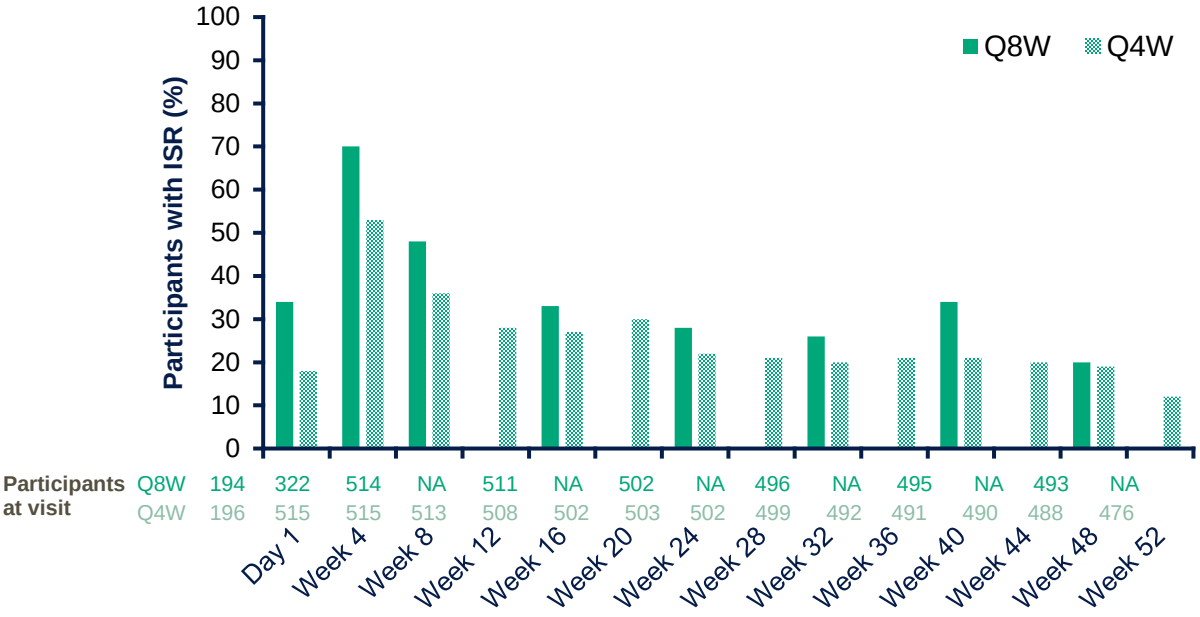
ATLAS-2M INJECTION SITE REACTIONS

Through Week 48, 74% of patients in each treatment arm experienced a drug-related ISR.[2] The median (min, max) duration of ISRs in the every-8-week and every-4-week arms were 3 days (1, 424) and 3 days (1, 281), respectively. In both arms, 86% of ISRs had a duration of 1 to 7 days.[3]

ISRs per injection tended to be lower in women than in men.[11]

As previously reported from ATLAS and FLAIR, ISRs were most commonly reported at treatment initiation and reports of ISRs tended to decrease over time.[12,13] See Figure 2 below.

Figure 2. Incidence of ISRs Reported by Patients Included in ATLAS-2M Through Week 48[2]



Q8W = every-8-week; Q4W = every-4-week

In the every-8-week arm and the every-4-week arm, 1% (n = 6) and 2% (n = 11) of patients, respectively, withdrew from the study for injection-related reasons.[2] In the every-8-week arm, 5 participants had an ISR leading to withdrawal and 1 participant withdrew consent from the study due to injection intolerability. In the every-4-week arm, 5 participants had an ISR leading to withdrawal and 6 participants withdrew consent from the study due to injection intolerability.

See Table 4 below for a breakdown of ISR events relative to the number of injections given through Week 48 of ATLAS-2M.[2]

Table 4. Incidence of ISRs Relative to the Number of Injections Administered through Week 48 of ATLAS-2M[2]

	Every-8-Week (n = 522)	Every-4-Week (n = 523)
Number of injections	8470	15,711
Number of ISR events (%)	2507 (30)	3152 (20)
Specific Adverse Events		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)

All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR.

ATLAS-2M AND FLAIR: POOLED 96-WEEK RESULTS

ISR characteristics including type, duration, and severity through 96 weeks were evaluated in a pooled analysis from ATLAS-2M (n = 654) and FLAIR (n = 283), where ISRs were analyzed by dosing regimen, drug, sex at birth, BMI, and race.[4] Overall, 937 patients naïve to CAB + RPV were included in the pooled analysis. Each ISR event was counted separately; thus, a patient may have had more than one ISR event following a single injection. Most participants were < 50 years of age (78%), male (sex at birth) (78%), white (76%), with a BMI < 30 kg/m² (84%).

Results

Injection site pain (20%), nodule (1%), and induration (1%) were the most commonly reported ISRs (% of injections).[4] The frequency, type, and severity of ISRs was generally comparable between CAB and RPV. Most ISRs were mild to moderate in severity (Grade 1, 83%; Grade 2, 16%; Grade 3, 1%). There were no Grade 4 or 5 ISRs. Slightly numerically more injection site pain events were reported with RPV (22%) vs. CAB (18%). See Table 5 below.

Table 5. ISR Events Through Week 96 by Dosing Regimen and Drug[4]

Parameter	CAB + RPV LA Dosing Regimen		Drug*	
	Q8W (n = 327)	Q4W (n = 610)	CAB (n = 937)	RPV (n = 937)
Number of participants receiving ≥ 1 injection (%)	321 (98)	599 (98)	920 (98)	920 (98)
Number of injections	7954	26,985	17,468	17,471
ISR events†, n	2345	6108	3836	4606
Pain, n (% of injections)	1904 (24)	5035 (19)	3142 (18)	3789 (22)
Nodule, n (% of injections)	107 (1)	355 (1)	213 (1)	249 (1)
Induration, n (% of injections)	61 (<1)	208 (<1)	130 (<1)	139 (<1)
Discomfort, n (% of injections)	113 (2)	107 (<1)	112 (<1)	107 (<1)
Swelling n (% of injections)	56 (<1)	85 (<1)	65 (<1)	76 (<1)

* CAB and RPV injections were administered on different sides of the body (e.g. left or right *gluteus medius*), or spaced approximately 2 cm from one another, from the site of any previous injection, or from any previous ISRs. The time, side, and location of CAB and RPV injections were reported. †Each ISR event was counted separately. Top five most common ISRs reported. Less common ISR events reported included: pruritus (n = 131), warmth (n = 81), erythema (n = 67), bruising (n = 43), anesthesia (n = 21), hematoma (n = 21), reaction (n = 18), discoloration (n = 10), hemorrhage (n = 5), abscess (n = 4), rash (n = 3), necrosis (n = 3), fibrosis (n = 2), discharge (n = 2), papule (n = 2), cyst (n = 2), movement impairment (n = 2), scar (n = 2), mass (n = 1), hypoesthesia(n = 1), granuloma (n = 1).
CAB = cabotegravir; ISR = injection site reaction; LA = long-acting; Q4W = every 4 weeks; Q8W = every 8 weeks; RPV = rilpivirine

The frequency and type of ISRs reported were generally similar across groups. There were slightly fewer injection site pain events reported in female (sex at birth) patients, BMI ≥ 30 kg/m², and Black or African

American patients. ISR severity was also generally similar across regimen, sex at birth, BMI, and race, with 97–99% of ISRs being Grade 1 or 2.[4]

The median (IQR) duration of ISRs was 3 days (2–4); the majority (87%) of ISR events lasted ≤ 7 days.[4] There was no difference in duration of ISR by dosing regimen. Almost all (99%) of ISRs were self-limited.

ISRs decreased in incidence over time: at Week 4, the incidence was 71%, falling to 24% by Week 48 and to 15% by Week 96.[4] Results were comparable between dosing regimens.

Events that took the longest to resolve were injection site nodule (median 9 days) and induration events (median 8 days).[4] These were mainly Grade 1 or 2 in severity.

Of the 462 reported injection site nodule events (reported by 19% [n = 178/920]) of all patients), reporting was similar by BMI and drug; however, nodule events were reported by a slightly higher proportion of female vs. male (sex at birth) patients (24% vs. 18%, respectively), patients of other race (44%, American Indian or Alaska Natives [n = 23/36, 64%], Native Hawaiian or other Pacific Islanders [n = 4/36, 11%], or of multiple races [n = 9/36, 25%]), and numerically more patients receiving Q4W vs. Q8W dosing (23% vs. 13%, respectively).

PATIENT REPORTED OUTCOMES

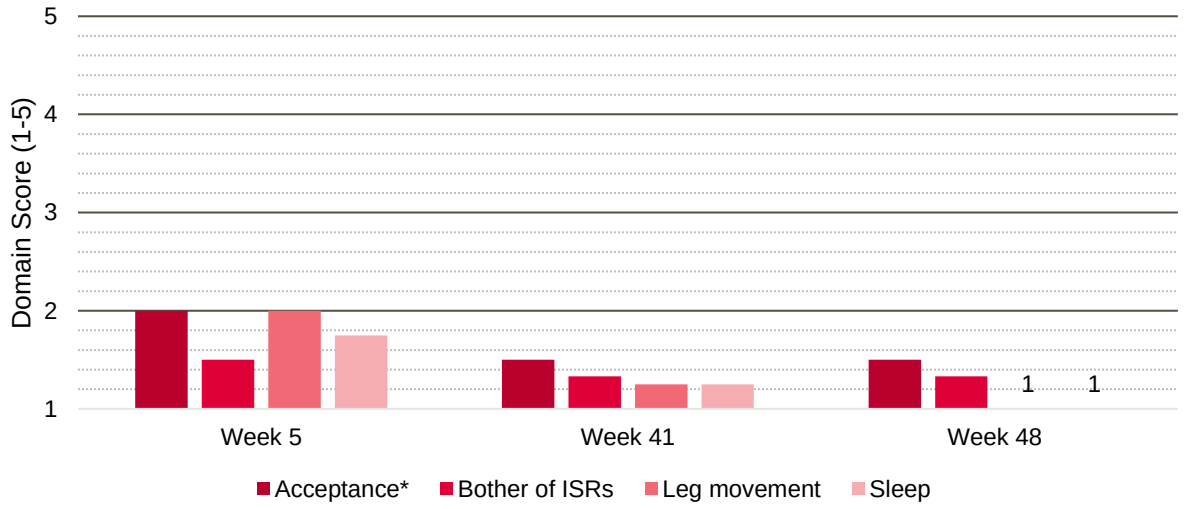
Perception of Injection (PiN)

The PiN questionnaire explores the bother of pain at the injection site and ISR, anxiety before and after injection, willingness to receive an HIV injectable treatment the following visit and satisfaction with the mode of treatment administration of individuals receiving injection and perceptions of individuals associated with receiving injections.[9,10] The PiN questionnaire was derived from the validated Vaccines' Perception of Injection (VAPI) questionnaire, and adapted for HIV-infected participants who received CAB + RPV LA.[14]

Four domains were assessed: Acceptance, Bother of ISRs, Leg Movement, and Sleep. Patients were asked to respond to 21 questions related to these domains, as well as 5 individual questions not part of the domains, on a scale of 1 to 5 where 1 = Totally Acceptable, 2 = Very Acceptable, 3 = Moderately Acceptable, 4 = A Little Acceptable, and 5 = Not at all Acceptable.[9,10] Only the change from Week 5 to Weeks 41 and 48 were analyzed statistically.

Results from the PiN can be found in Figure 1. Only Acceptance was analyzed statistically.[15] The differences between Week 5 and Weeks 41 and 48 were statistically significant ($P < 0.001$)

Figure 2. Median Domain Scores Assessed with the PiN Questionnaire[15]



*The differences between Week 5 and Weeks 41 and 48 were statistically significant ($P<0.001$)

OTHER NON-LOCAL INJECTION-ASSOCIATED REACTIONS

Other potential drug-related, non-local injection-associated reactions were reported by patients in ATLAS and FLAIR who were receiving CAB + RPV LA.[1] These include pyrexia, which includes feeling hot, chills, influenza-like illness and body temperature increased, and musculoskeletal pain/discomfort, which includes back pain, myalgia, and pain in extremity.

MANAGEMENT OF INJECTION SITE REACTIONS

No specific treatments for ISRs were evaluated in ATLAS, FLAIR, or ATLAS-2M.[1,2] Medical judgement should be used to determine how best to manage ISRs associated with CAB + RPV LA (e.g., oral analgesics, application of a hot or cold pack, spacing injections 2 cm apart from any previous injection or injection site reaction, etc.).

A survey was conducted amongst healthcare providers who administered CAB + RPV LA injections during the ATLAS, FLAIR, and ATLAS-2M trials to share optimal gluteal injection techniques and patient/provider experiences.[16] This voluntary, self-administered, online questionnaire, sent to 150 sites across 15 countries, revealed techniques to help optimize administration CAB + RPV LA administration. Findings that were ranked most effective in minimizing pain upon injection included: pushing the IM injection at a slower speed (66%), making sure the injection contents are at room temperature (58%), relaxing the gluteal muscle prior to injections (53%), and distracting the patient (34%). Administration of over-the-counter pain medications (74%) and a return to normal daily activities (30%) were ranked as top techniques to minimize post-injection pain.

This information is scientific and non-promotional in nature and is not intended for further distribution. Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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