National HIV Curriculum

Cabotegravir plus Rilpivirine Extended Release Injectable Suspension

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Last Updated: October 6, 2023

Cabotegravir and Rilpivirine Oral and Injectable Preparations

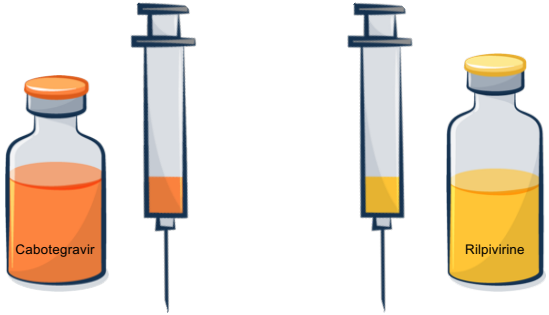
Optional Lead-In Oral Components

Cabotegravir + Rilpivirine

30 mg → INSTI

25 mg → NNRTI

Intramuscular Injection Components



Cabotegravir + Rilpivirine

200 mg/mL → INSTI

300 mg/mL → NNRTI

Source: Cabotegravir-Rilpivirine Prescribing Information

Cabotegravir and Rilpivirine Extended Release Injectable Suspension Indications

- **Complete regimen to treat HIV-1**
- **For adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - On stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine
- **Oral Lead-In**
  - Lead-in is optional
- **Continuation Phase Injections**
  - Approved for every 1-month and every 2-month injections
  - Doses are different with every 1-month and every 2-month injections
  - Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information

Cabotegravir and Rilpivirine
Oral Preparations and Extended Release Injectable Suspension

- **Optional Oral Lead-in (Cabotegravir and Rilpivirine)**
  - Cabotegravir: 30 mg once daily (take with food)
  - Rilpivirine: 25 mg once daily (take with food)
  - Given to assess tolerability to cabotegravir and rilpivirine
- **Cabotegravir and Rilpivirine Extended-Release Injectable Suspension**
  - Cabotegravir: 200 mg/mL (given as 2 mL or 3 mL dose)
  - Rilpivirine LA: 300 mg/mL (given as 2 mL or 3 mL dose)
  - Administered as intramuscular gluteal injections
  - Injections given on opposite gluteal sites (or ≥2 cm apart on same site)
  - Consider using long needle for persons with BMI ≥30 kg/m^2

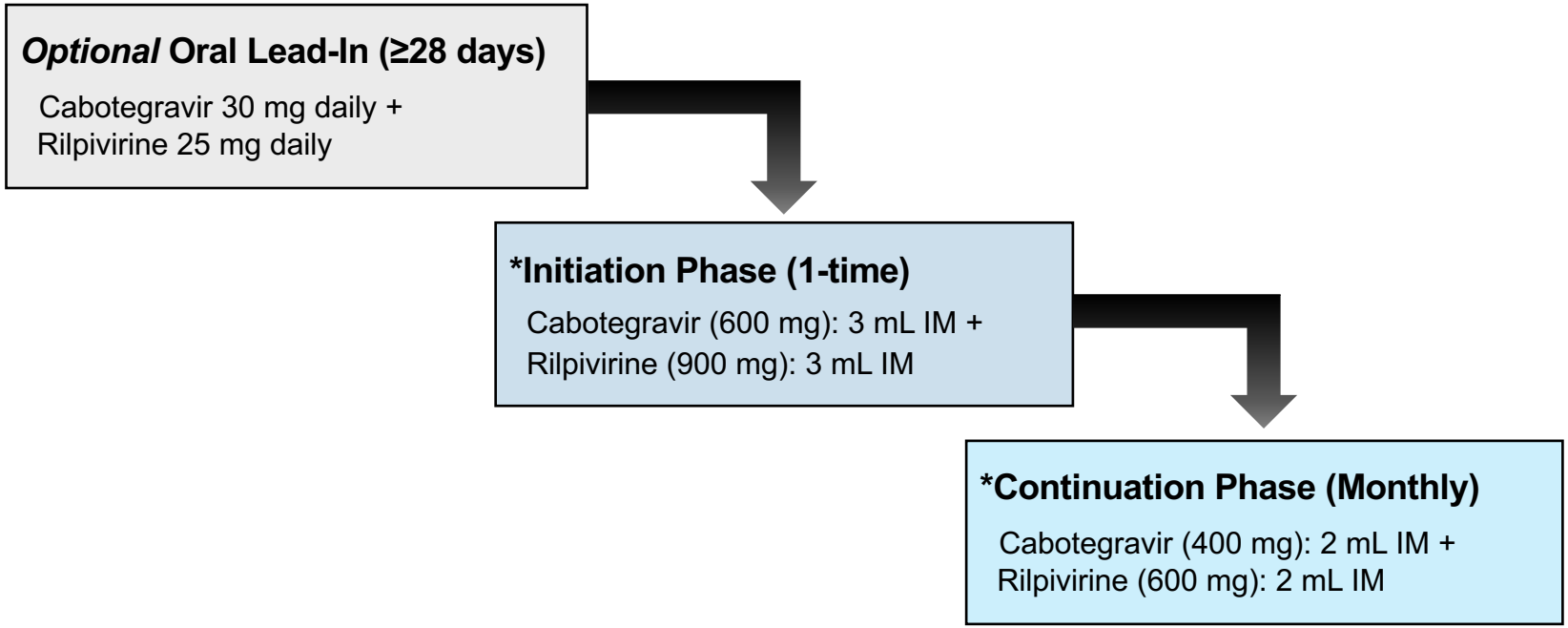
Source: Cabotegravir-Rilpivirine Prescribing Information

Dosing Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

Recommended Dosing Schedule in Adults for Every 1-Month Cabotegravir and Rilpivirine			
Drug	**Optional Oral Lead-In**	**Initiation Phase Injections** (One-Time Dosing)	**Continuation Phase Injections** (Once-Monthly Dosing)
	If used, administer for ≥28 days	Administer on the last day of current antiretroviral therapy or last day of oral lead-in (if used)	Administer Monthly
Cabotegravir	30 mg orally once daily with a meal	600 mg IM (3 mL)	400 mg IM (2 mL)
Rilpivirine	25 mg orally once daily with a meal	900 mg IM (3 mL)	600 mg IM (2 mL)

Source: Cabotegravir-Rilpivirine Prescribing Information

Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine



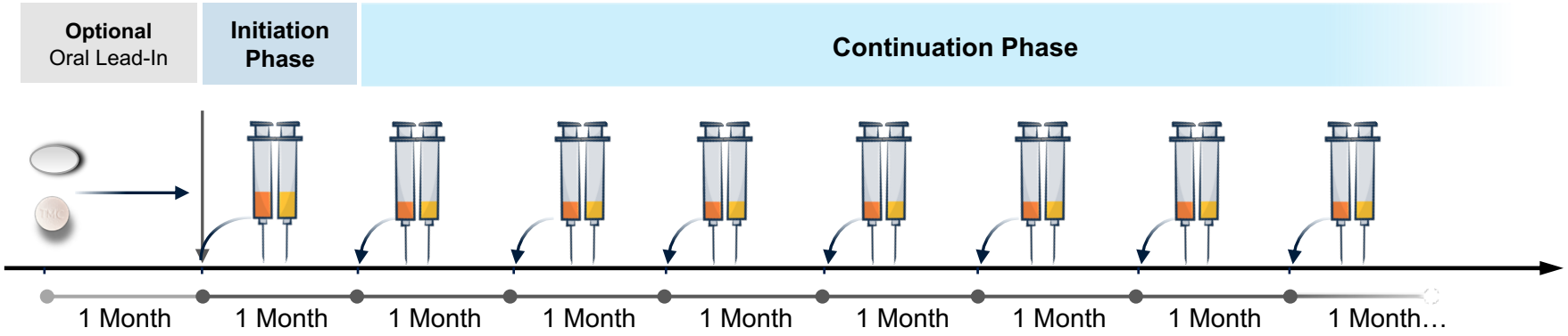
*Administer injections at opposite gluteal sites (or at least 2 cm apart) and give both during the same visit.

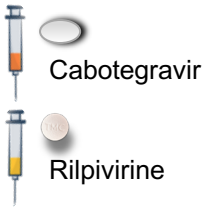
Source: Cabotegravir-Rilpivirine Prescribing Information

Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: One-time initiation phase injections then monthly continuation phase injections thereafter

Administer first injections on the last day of current fully suppressive antiretroviral therapy or last day of oral lead-in (if used)





Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

***Dosing for 1-time Initiation Phase Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

***Dosing for Continuation Phase Injections** = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Management of Missed Injections in Persons on Every 1-Month Dosing

Management for Planned and Unplanned Missed Injections in Patients on Every 1-Month Dosing	
Time Since Last Injection	**Recommendation for Oral Bridging**
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 30 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 1 month (+/- 7 days) after the last injection dose of cabotegravir and rilpivirine. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time from last injections is >1 month + 7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

Recommendations for Restarting Injection Doses after Missed Injections with Every 1-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-1-Month Dosing Schedule	
Time Since Last Injection	**Recommendation**
Less than or equal to 2 months	Resume with cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injections as soon as possible.
Greater than 2 months	Reinitiate with with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) then continue to follow the monthly cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injection dosing schedule.

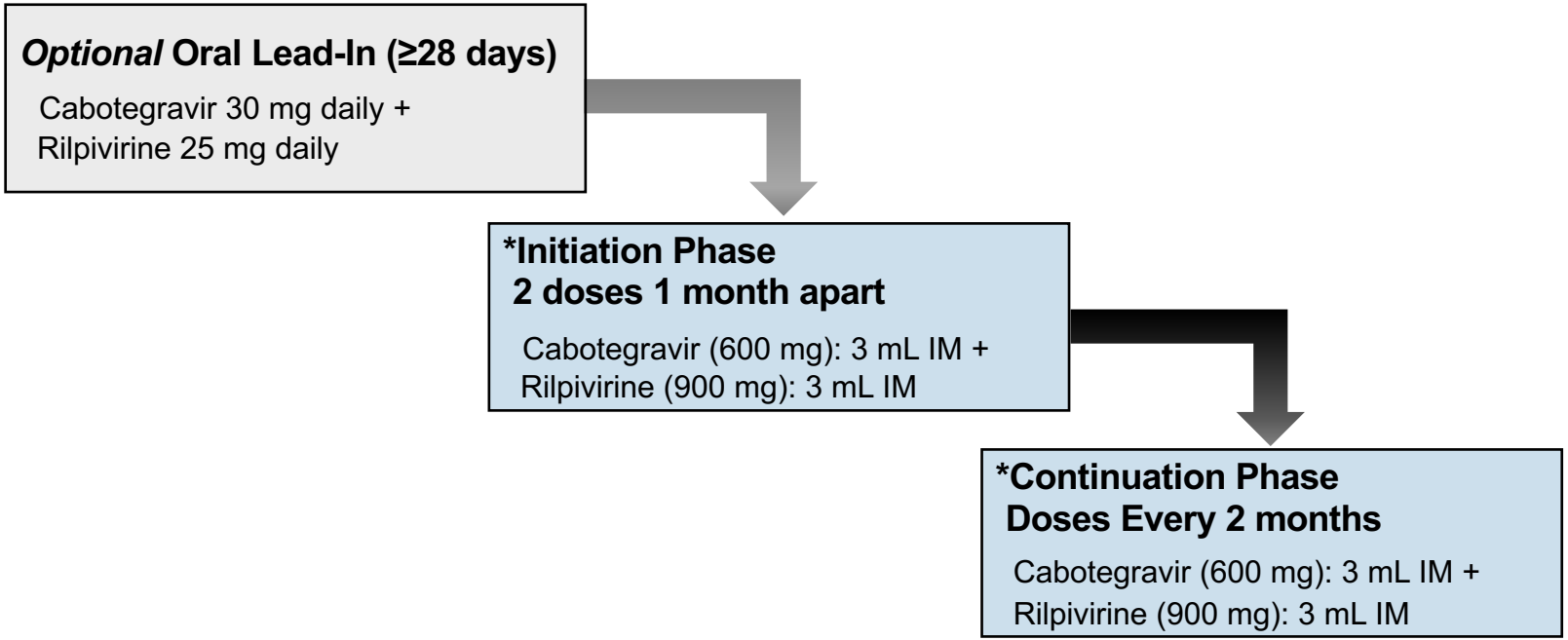
Source: Cabotegravir-Rilpivirine Prescribing Information

Dosing Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

Recommended Dosing Schedule in Adults for Every 2-Month Cabotegravir and Rilpivirine		
Drug	**Optional Oral Lead-In** If used, administer for ≥28 days	**Injections** Give 2 doses 1 month apart, then administer every 2 months Administer first dose on the last day of current antiretroviral therapy or on the last day of the oral lead-in (if used)
Cabotegravir	30 mg orally once daily with a meal	600 mg IM (3 mL)
Rilpivirine	25 mg orally once daily with a meal	900 mg IM (3 mL)

Source: Cabotegravir-Rilpivirine Prescribing Information

Dosing Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine



*Administer injections at opposite gluteal sites (or at least 2 cm apart) and give both during the same visit.

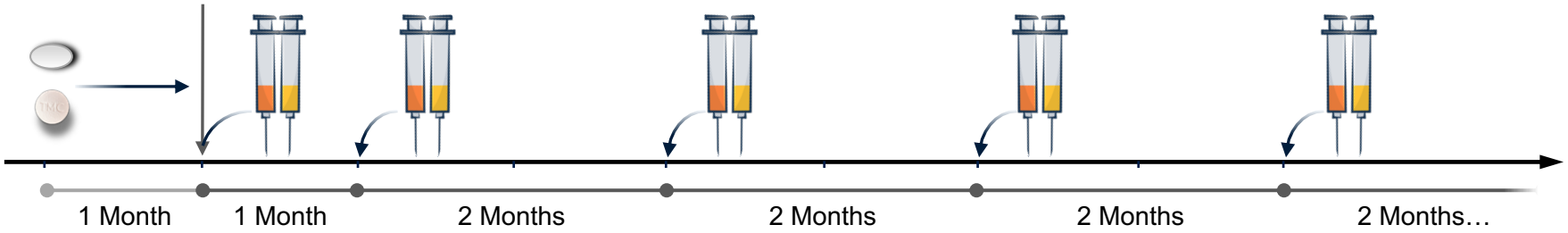
Source: Cabotegravir-Rilpivirine Prescribing Information

Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: First two injections given 1 month apart then every 2 months thereafter

Administer first injections on the last day of current antiretroviral therapy or last day of oral lead-in (if used)

Optional Oral Lead-In	**Initiation Phase**	**Continuation Phase**



Cabotegravir

Rilpivirine

Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

***First Two Injections (Initiation Phase):** given 1 month apart, before transitioning to every 2-month dosing

***Dosing for All Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Management of Missed Injections in Persons on Every 2-Month Dosing

Oral Bridge Therapy for Planned and Unplanned Missed Injections in Patients on 2-Month Dosing

Time Since Last Injection	Recommendation for Oral Bridging
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 50 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 2 months (+/- 7 days) after the last injection doses. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time for scheduled injection is missed or delayed by >7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

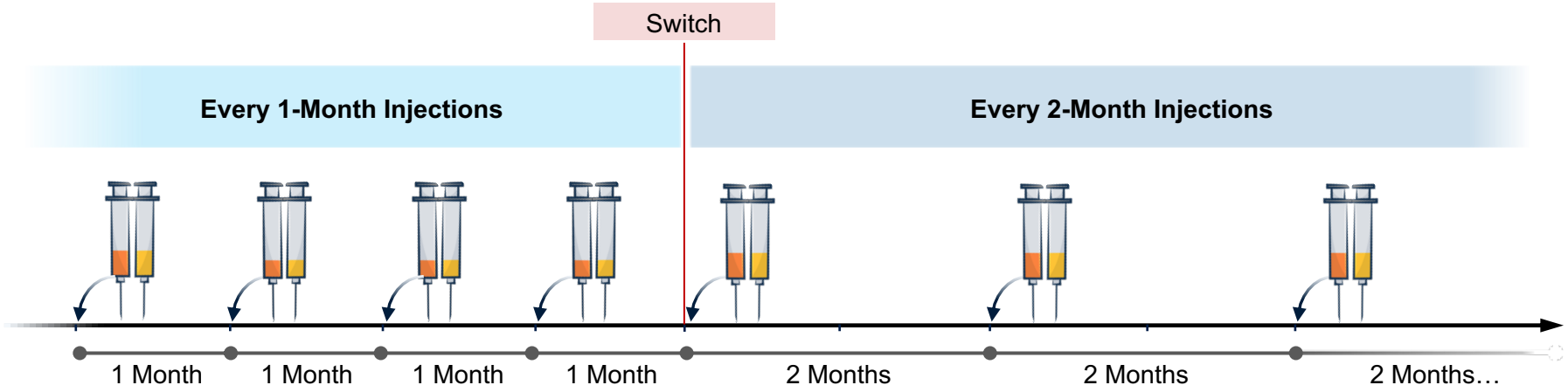
Recommendations for Restarting Injection Doses after Missed Injections with Every 2-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-2-Month Dosing Schedule

Missed Injection Visit	Recommendation
Injection 2	• **Time since last injection ≤2 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible, then continue to follow the every-2-month injection dosing schedule. • **Time since last injection >2 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
Injection 3 or Later	• **Time since last injection ≤3 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible and continue with the every-2-month injection dosing schedule. • **Time since last injection >3 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

Source: Cabotegravir-Rilpivirine Prescribing Information

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 1-Month to Every 2-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

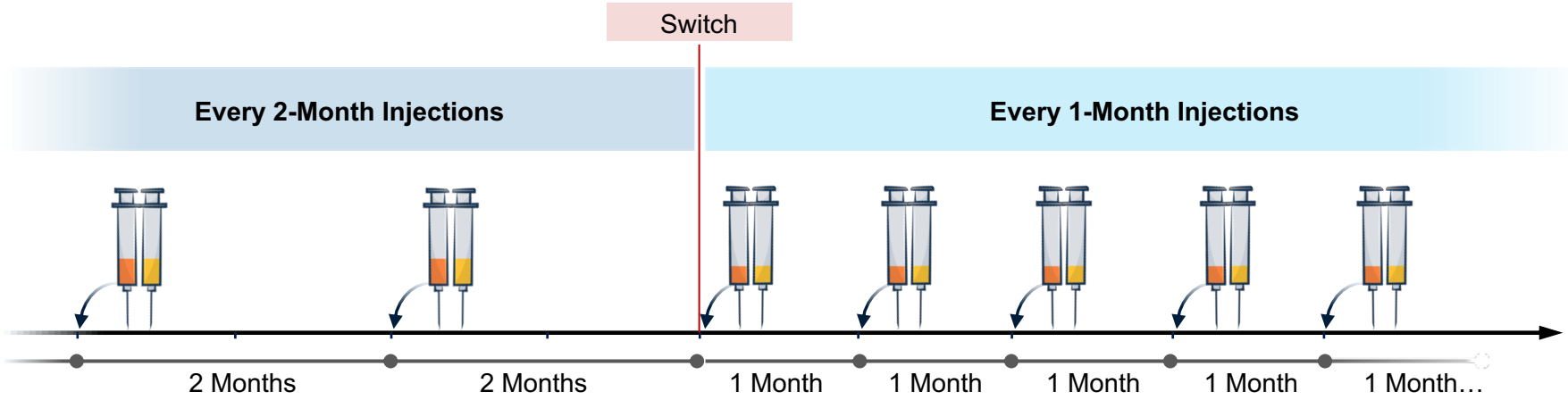
*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 2-Month to Every 1-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM + Rilpivirine (900 mg): 3 mL IM

*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM + Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

Summary of Key Studies

Cabotegravir and Rilpivirine Long-Acting Injectable

- **Phase 3 Trials in Treatment Naïve**
  - FLAIR: IM CAB + IM RPV monthly versus oral DTG-ABC-3TC: 48 weeks
  - FLAIR: IM CAB + IM RPV monthly versus oral DTG-ABC-3TC: 96 weeks
  - FLAIR: IM CAB + IM RPV with or without oral lead in: 124-week extension

- **Phase 3 Trials in Treatment Experienced**
  - ATLAS: switch to monthly IM CAB + IM RPV or continue 3-drug oral ART
  - ATLAS-2M: switch to IM CAB + IM RPV taken every 1 or 2 months: 48 weeks
  - ATLAS-2M: switch to IM CAB + IM RPV taken every 1 or 2 months: 96 weeks
  - SOLAR: switch to every 2 months IM CAB + IM RPV or continue BIC-TAF-FTC

Summary of Key Studies

Cabotegravir and Rilpivirine Long-Acting Injectable

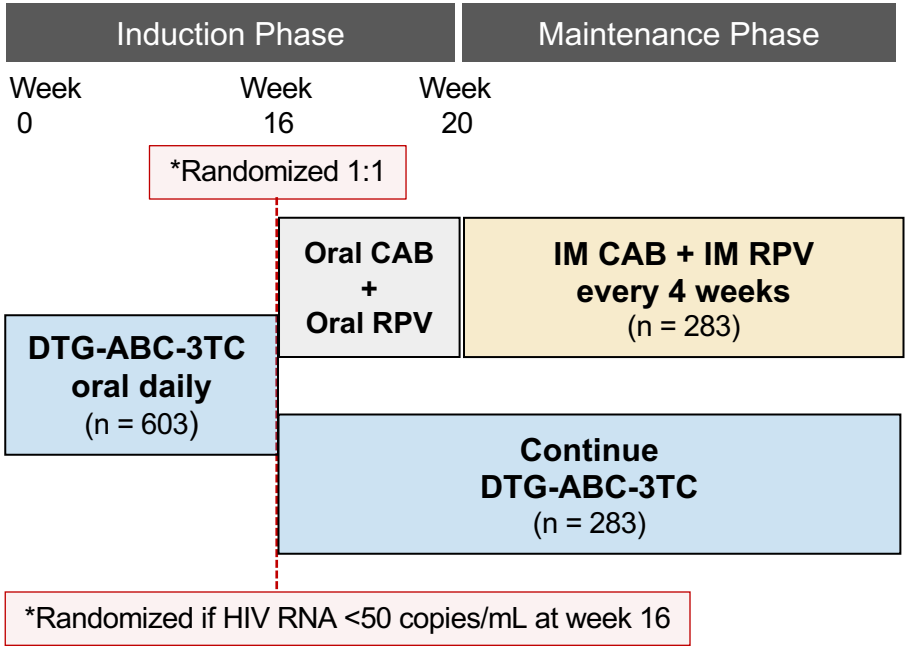
- **Phase 2 Trials**
  - LATTE: oral CAB + oral RPV daily versus oral EFV plus 2 NRTIs
  - LATTE-2: IM CAB + IM RPV every 1 or 2 months versus oral CAB + oral ABC-3TC
  - POLAR: every 2-month IM CAB + IM RPV after 5 years or oral CAB + oral RPV

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction

FLAIR Study: 48-Week Data

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Design

- **Background**: Phase 3, randomized, open-label, trial assessing IM CAB + RPV after oral induction for treatment-naïve adults
- **Inclusion Criteria**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥1,000 copies/mL
  - Any CD4 cell count
  - No chronic hepatitis B
  - No NNRTI resistance



Oral lead in dosing: cabotegravir 30 mg daily and rilpivirine 25 mg daily x 4 weeks
Loading injections: cabotegravir 600 mg IM and 900 mg rilpivirine IM x 1
Maintenance injections: cabotegravir 400 mg IM and 600 mg rilpivirine IM monthly

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Baseline Characteristics

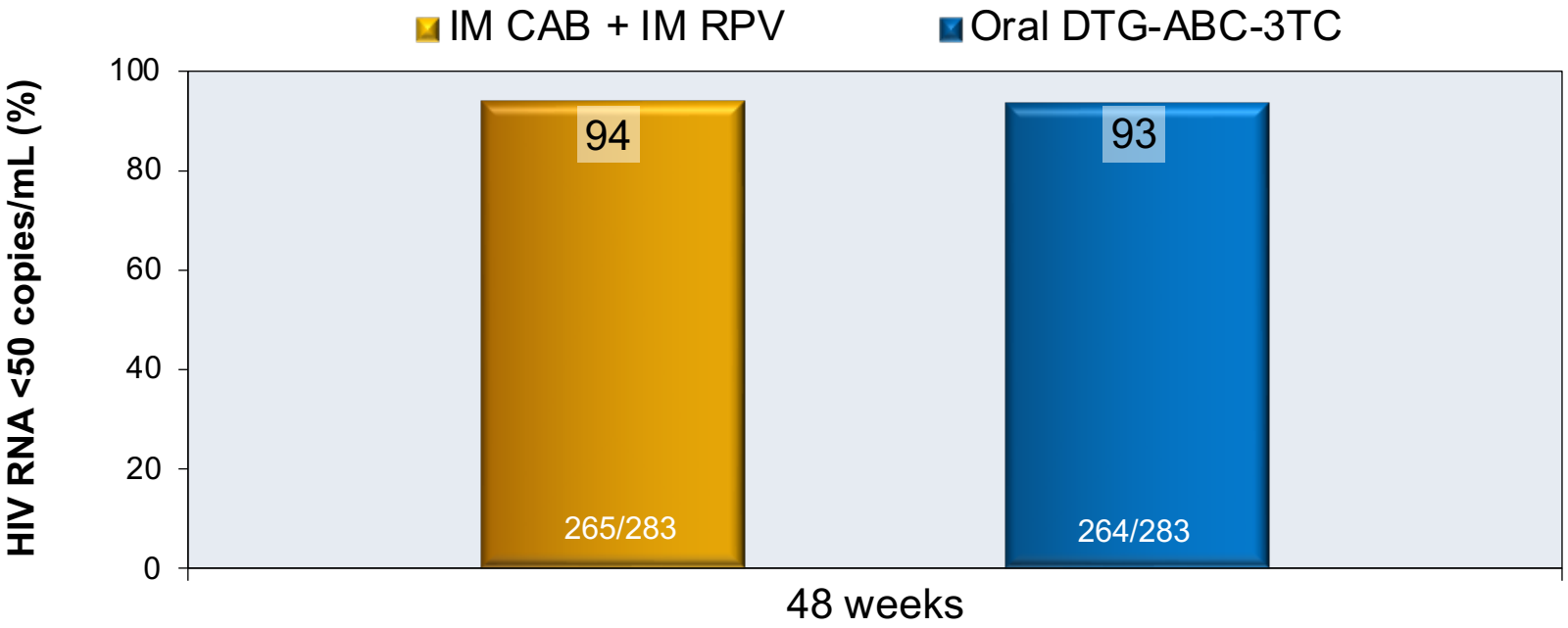
FLAIR: Baseline Characteristics

Characteristic	IM CAB + IM RPV (n = 283)	DTG-ABC-3TC (n = 283)	Overall (n = 566)
Age, years, median	34	34	34
Female, n, %	63 (22)	64 (23)	127 (22)
White, n, %	216 (76)	201 (71)	417 (74)
Black, n, %	47 (17)	56 (20)	103 (18)
Median body-mass index	24	24	24
CD4 count <200 cells/mm^3, n, %	16 (6)	23 (8)	39 (7)
CD4 count ≥500 cells/mm^3, n, %	108 (38)	108 (38)	216 (38)
HIV RNA ≥200k copies/mL, n, %	26 (9)	23 (8)	39 (7)
HIV RNA 10k-50k copies/mL, n, %	95 (34)	113 (40)	208 (37)

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



*HIV RNA ≥50 copies/mL at 48 weeks: 2.1 % CAB-RPV, 2.5% DTG-ABC-3TC

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Results

Resistance Data for Participants in the IM CAB + IM RPV arm with Viral Rebound Meeting Protocol-Defined Criteria for Genotype Resistance Testing

Country; HIV-1 Subtype	At Baseline		At Virologic Failure	
	HIV RNA	INSTI RAMs	HIV RNA	INSTI RAMs
Russia; A1	54,000 copies/mL	L74I	456 copies/mL	L74I, Q148R
Russia; A1	23,000 copies/mL	L74I	299 copies/mL	L74I, G140R
Russia; A1	20,000 copies/mL	L74I	440 copies/mL	L74I, Q148R

There were no baseline NNRTI RAMs
There were also 3 virologic failures in the DTG-ABC-3TC arm; no new RAMs detected
Abbreviations: F = female; M = male; RAMs = resistance associated mutations

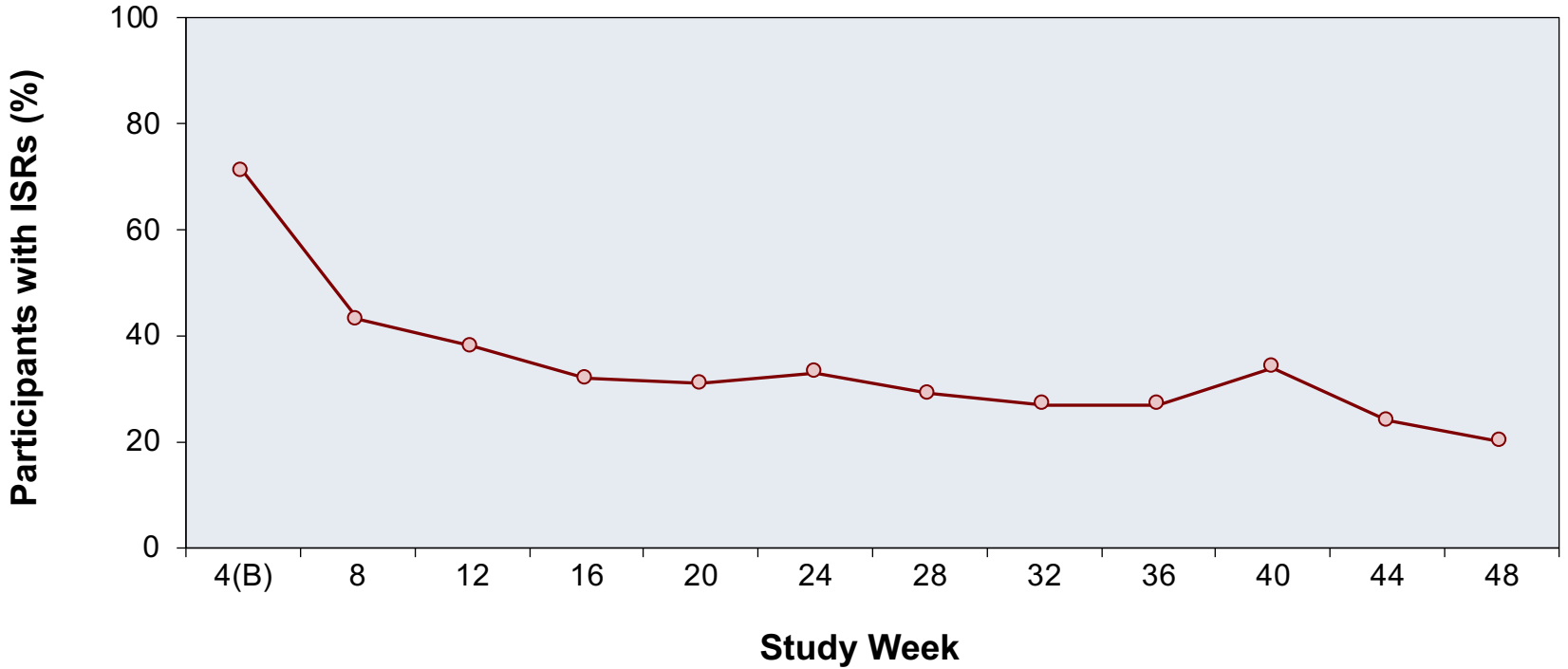
Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Adverse Events

Drug-Related Adverse Events and Injection Site Reactions (ISR)		
Drug-Related Adverse Event (AE) All reported as: n (%)	**IM CAB + IM RPV** (n = 283)	**DTG-ABC-3TC** (n = 283)
Any AE	236 (83)	28 (10)
Any AE, excluding ISR	79 (28)	28 (10)
Grade 3 or 4 AE	14 (5)	0
Grade 3 or 4 AE, excluding ISR	4 (1)	0
Any injection site pain	227 (80)	NA
Grade 3 or 4 injection site pain	11 (4)	NA

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Injection Site Reactions (ISRs)



99% of ISRs mild to moderate in severity. Median duration 3 days. 4 participants withdrew due to ISR.

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (48-Week Data): Conclusions

Conclusions: “Therapy with long-acting cabotegravir plus rilpivirine was noninferior to oral therapy with dolutegravir–abacavir–lamivudine with regard to maintaining HIV-1 suppression. Injection-site reactions were common.”

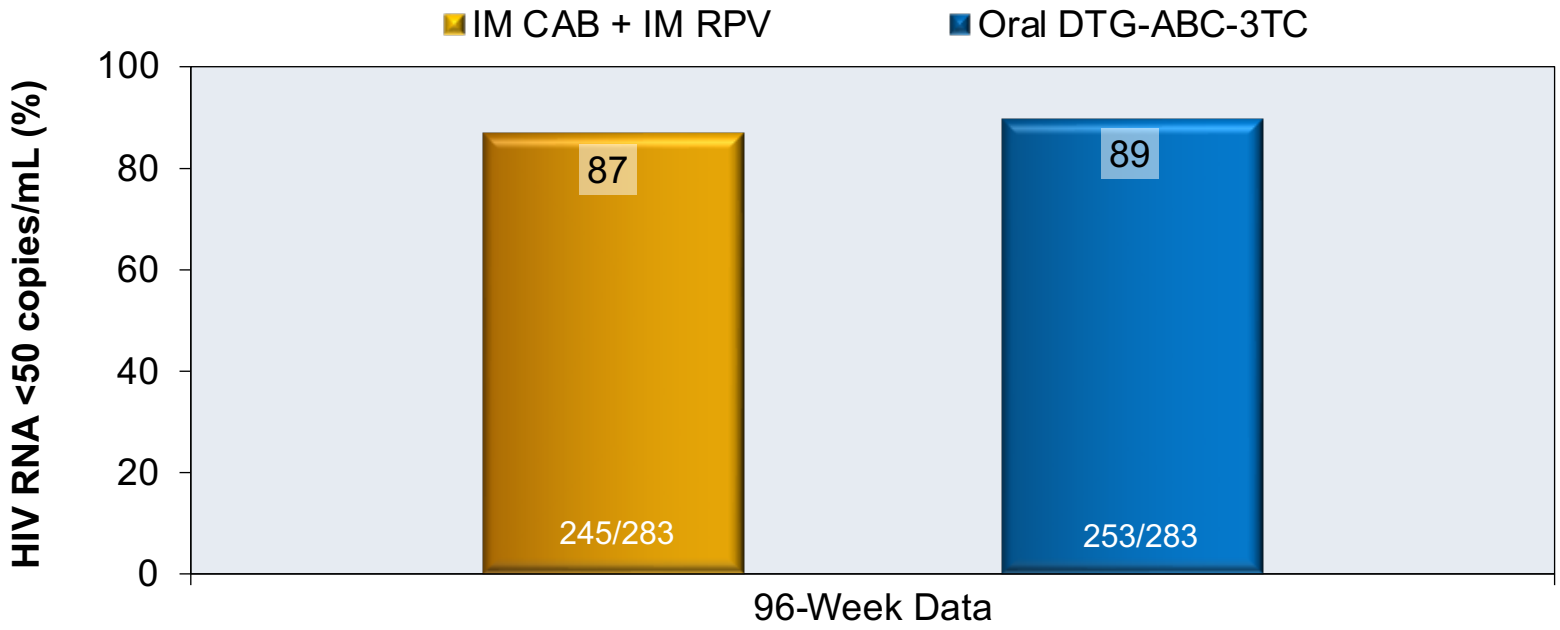
Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction

FLAIR Study: 96-Week Data

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (96-Week Data): Results

Week 96: Virologic Response by Snapshot Outcomes (Intention-to-Treat Population)

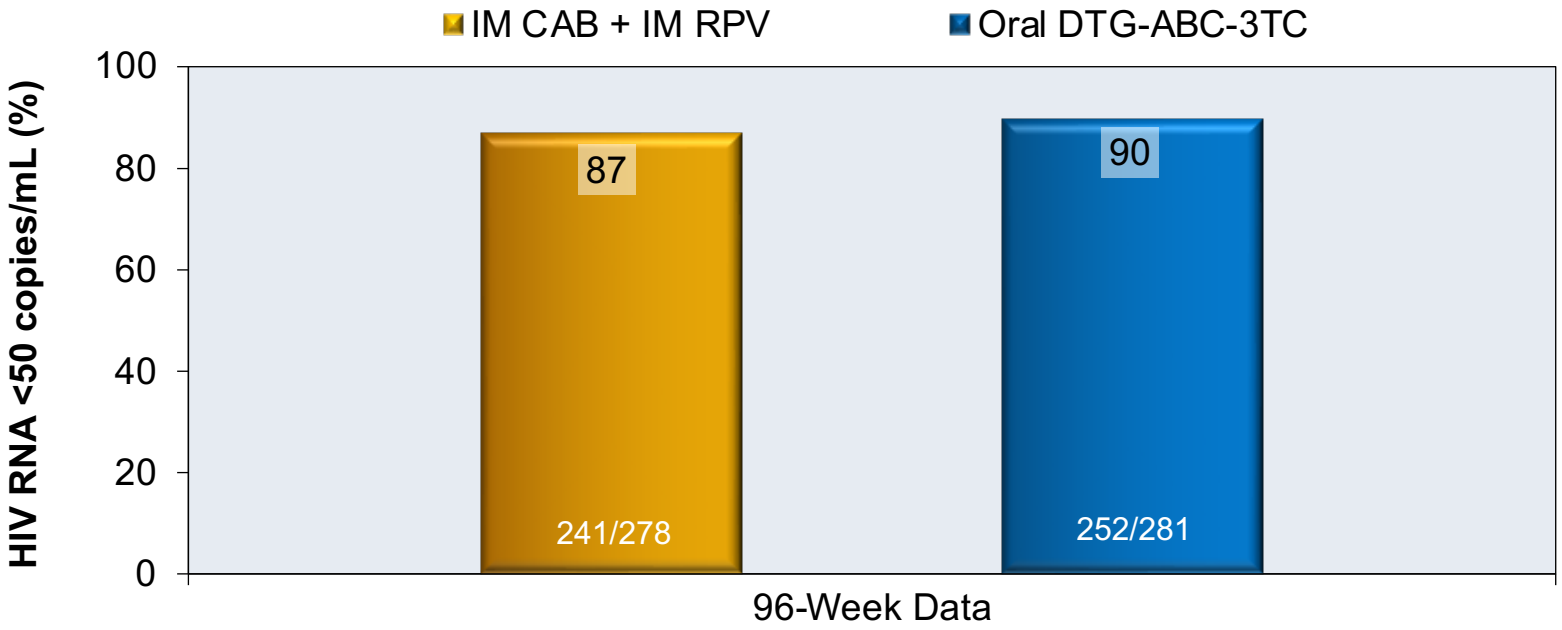


*HIV RNA ≥50 copies/mL at 96 weeks: n = 9 (3%) CAB-RPV, n = 9 (3%) DTG-ABC-3TC
*Only 1 virologic failure occurred between weeks 48 and 96 (in the DTG-ABC-3TC group)

Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (96-Week Data): Results

Week 96: Virologic Response by Snapshot Outcomes (Per Protocol Population)



*HIV RNA ≥50 copies/mL at 96 weeks: n = 9 (3%) CAB-RPV, n = 9 (3%) DTG-ABC-3TC

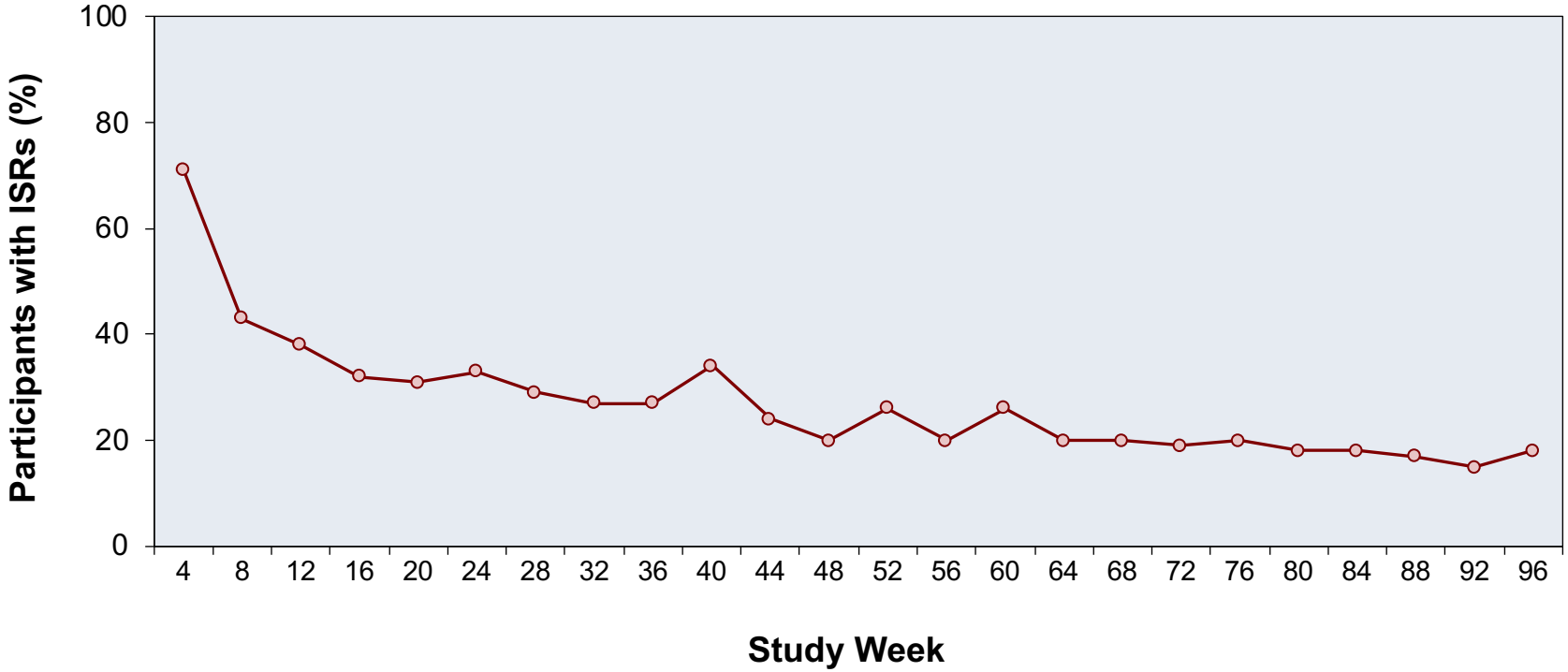
Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (96-Week Data): Adverse Events

Drug-Related Adverse Events and Injection Site Reactions (ISR)		
Drug-Related Adverse Event (AE)	**IM CAB + IM RPV** (n = 283)	**DTG-ABC-3TC** (n = 283)
Any AE, n (%)	246 (87)	33 (12)
Any AE, excluding ISR, n (%)	95 (34)	33 (12)
Grade 3 or 4 AE, n (%)	16 (6)	0
Serious AE, n (%)	1 (<1)	0
AE leading to withdrawal, n (%)	3 (1)	4 (1)

Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (96-Week Data): Injection Site Reactions (ISRs)



Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM Cabotegravir and IM Rilpivirine after Oral Induction FLAIR Study (96-Week Data): Conclusions

Interpretation: “The 96-week results reaffirm the 48-week results, showing long-acting cabotegravir and rilpivirine continued to be non-inferior compared with continuing a standard care regimen in adults with HIV-1 for the maintenance of viral suppression. These results support the durability of long-acting cabotegravir and rilpivirine, over an almost 2-year-long period, as a therapeutic option for virally suppressed adults with HIV-1.”

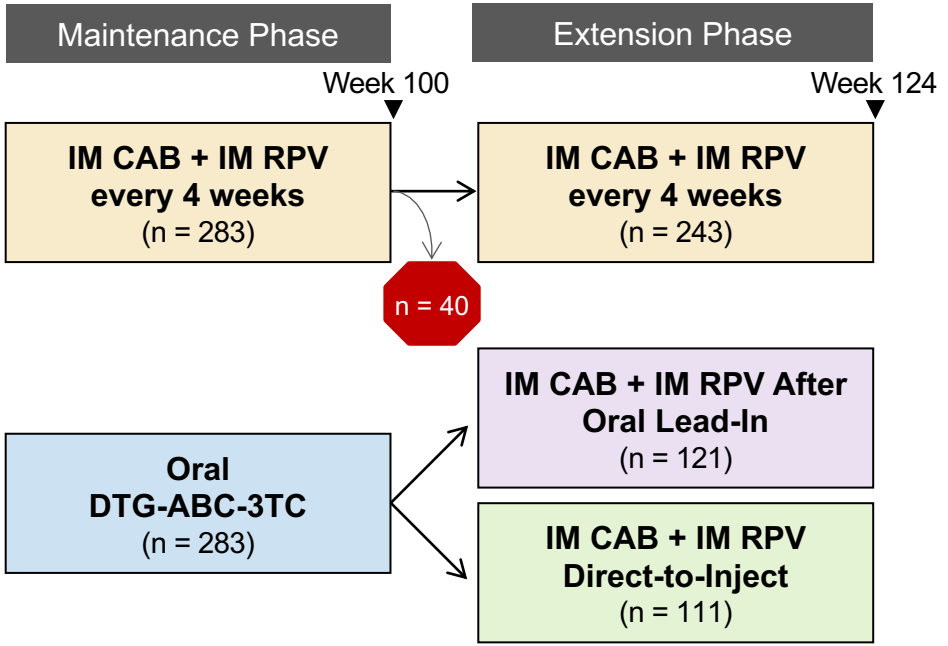
Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting Cabotegravir and Rilpivirine with Oral Lead In versus Direct-to-Inject

FLAIR Study: Week 124 Extension Phase

Long-Acting IM CAB and IM RPV With or Without Oral Lead In FLAIR Study (124-Week Extension): Design

- **Background**: Extension of phase 3, randomized, open-label trial assessing IM CAB + IM RPV compared to DTG-ABC-3TC for treatment-naïve adults
- **Inclusion Criteria**: After 100-week maintenance phase, participants receiving IM CAB + IM RPV every 4 weeks could choose to continue (*Continuation Group*) or withdraw; those assigned to oral ART could choose to transition (*Switch Group*) to IM CAB + IM RPV after oral lead in or without oral lead in ("direct to inject")

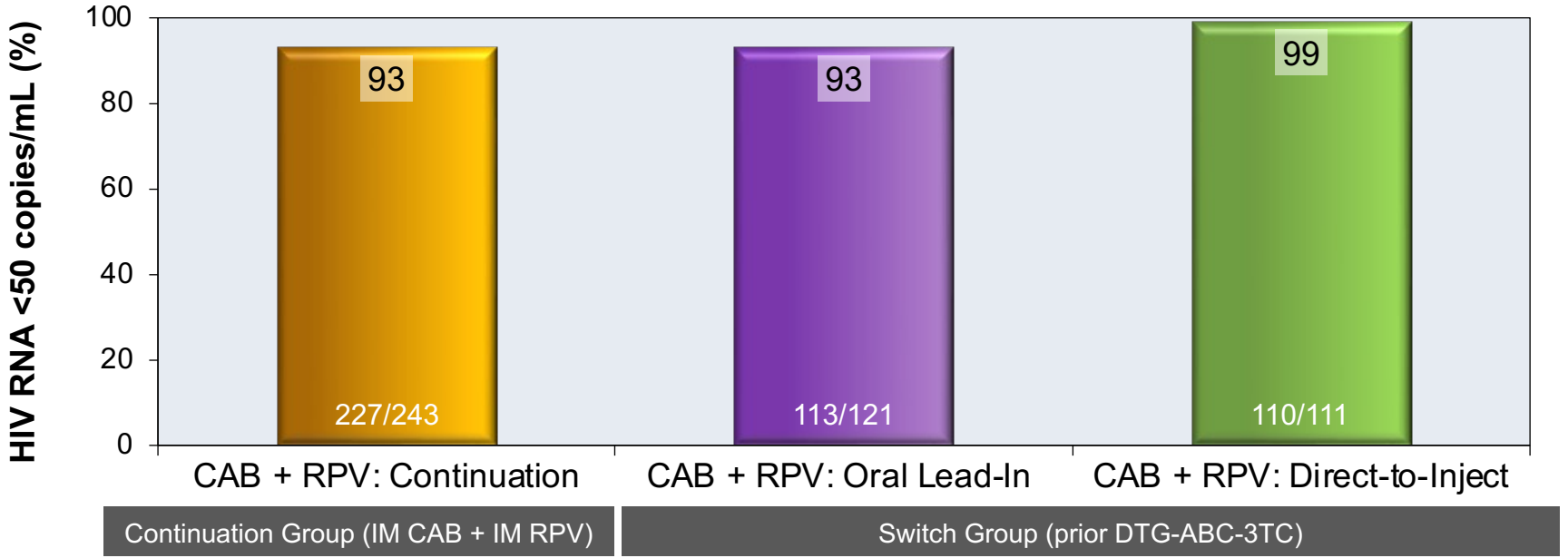


Oral lead in dosing: cabotegravir 30 mg daily and rilpivirine 25 mg daily x 4 weeks
Loading injections: cabotegravir 600 mg IM and 900 mg rilpivirine IM x 1
Maintenance injections: cabotegravir 400 mg IM and 600 mg rilpivirine IM monthly

Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM CAB and RPV With or Without Oral Lead In FLAIR Study (124-Week Extension): Results in Extension Phase

Virologic Responses During 24-Week Extension Phase



Continuation group: randomized to IM CAB + IM RPV at baseline and at week 100 opted to continue IM CAB + IM RPV until week 124.
Switch group: randomized to DTG-ABC-3TC and at week 100 switched to IM CAB + IM RPV with either oral lead in or direct-to-inject strategy

Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

Long-Acting IM CAB and RPV With or Without Oral Lead In FLAIR Study (124-Week Extension): Conclusion

Interpretation: “After 24 weeks of follow-up, switching to long-acting treatment with or without an oral lead-in phase had similar safety, tolerability, and efficacy, supporting future evaluation of the simpler direct-to-injection approach. The week 124 results for participants randomly assigned originally to the long-acting therapy show long-acting cabotegravir plus rilpivirine remains a durable maintenance therapy with a favourable safety profile.”

Source: Orkin C, et al. Lancet HIV. 2021;8:e185-e196.

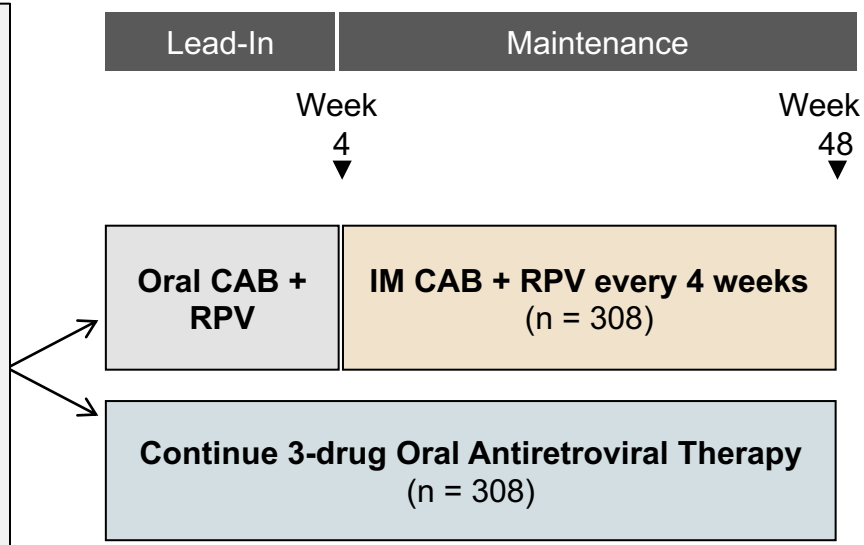
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance

ATLAS Study

National HIV Curriculum

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance ATLAS Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking 2NRTIs+INSTI, NNRTI, or PI
  - Stable ARV regimen ≥6 months
  - HIV RNA <50 copies/mL ≥6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance, except that K103N mutation allowed
  - No chronic hepatitis B



Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Baseline Characteristics

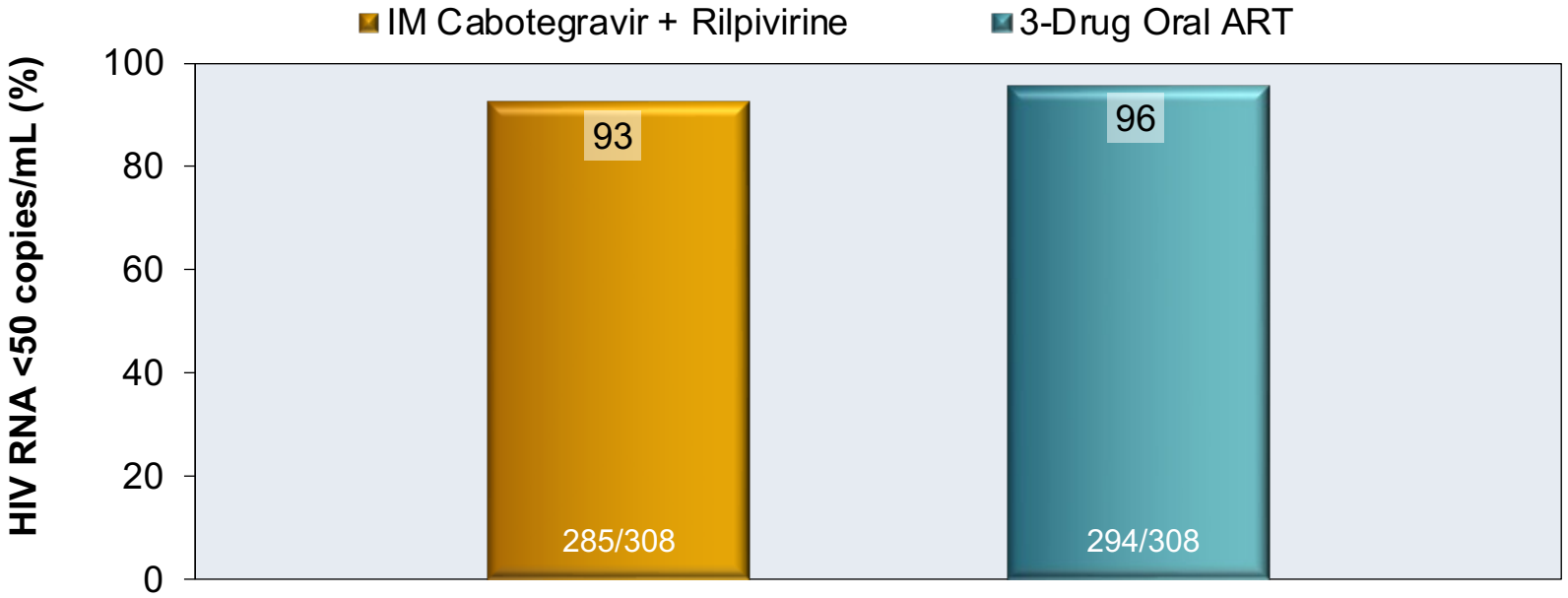
ATLAS: Baseline Characteristics

Characteristic	IM CAB + RPV (n = 308)	Oral ART (n = 308)	Overall (n = 616)
Age, years, median	40	43	42
Female, n, %	99 (32)	104 (34)	203 (33)
White, n, %	214 (69)	207 (67)	421 (68)
Black, n, %	62 (20)	77 (25)	139 (23)
Median body-mass index	26	26	26
CD4 count <350 cells/mm^3, n, %	23 (7)	27 (9)	50 (8)
Time since first ART (months), median, range	52 (7-222)	52 (7-257)	52 (7-257)
Third class agent, n, %	6	6	6
NNRTI	155 (50)	155 (50)	310 (50)
INSTI	102 (33)	99 (32)	201 (33)
PI	51 (17)	54 (18)	105 (17)

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 2 % CAB + RPV, 1% 3-drug oral ART

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance

ATLAS Study: Results

Participants in the IM CAB-RPV arm with Viral Rebound Meeting Protocol-Defined Criteria for Genotype Resistance Testing

Country, HIV-1 Subtype	At Baseline		At Virologic Failure	
	INSTI RAMs	NNRTI RAMs	HIV RNA	INSTI RAMs
Russia, A/A1	L74I	E138E/A	25,745 copies/mL	L74I
F, France, AG	None	V108V/I, E138K	258 copies/mL	None
M, Russia, A/A1	L74I	None	1841 copies/mL	N155H, L74I

There were also 4 virologic failures in the oral ART arm; new RAMs detected included one G190S, one M184I, and one M230M/I.

Abbreviations: RAMs = resistance associated mutations

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23..

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Adverse Events

Injection Site Reactions (ISRs)	
Type of Reactions	**Participants (%) with Reaction**
Participants who received injections, n	303
Any reaction, n (%)	250 (81)
Pain, n (%)	231 (75)
Grade 3 pain, n, (%)	10 (3)
Pain leading to withdrawal	4 (1)
Nodule, n (%)	37 (12)
Induration, n (%)	30 (10)
Swelling, n (%)	23 (7)
Median duration of reaction, days	3
The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.	

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Conclusions

Conclusions: “Monthly injections of long-acting cabotegravir and rilpivirine were noninferior to standard oral therapy for maintaining HIV-1 suppression. Injection-related adverse events were common but only infrequently led to medication withdrawal.”

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

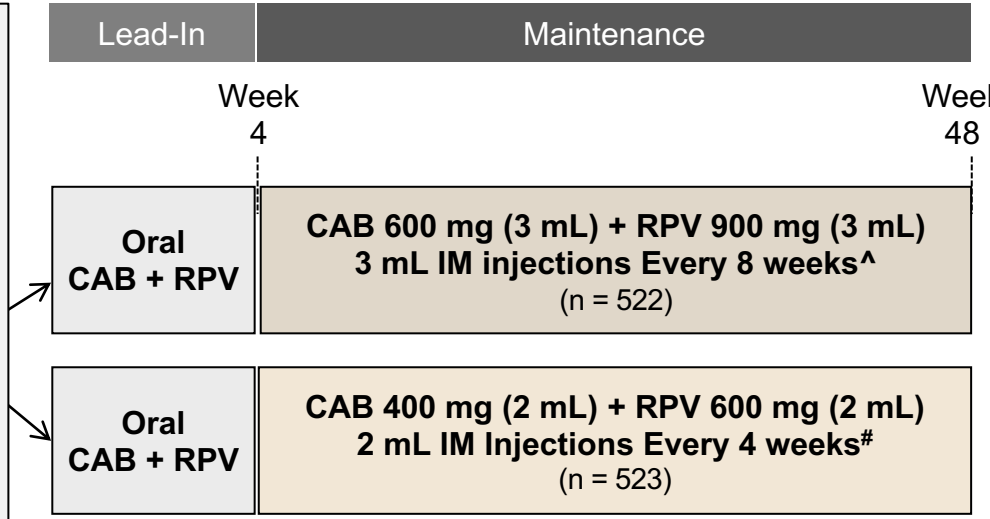
IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M

National HIV Curriculum

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB plus IM RPV maintenance ART administered every 8 weeks versus every 4 weeks
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an uninterrupted first or second oral standard of care ART regimen for ≥6 months
  - HIV RNA <50 copies/mL ≥6 months at screening and >2x in prior year
  - No history of virologic failure
  - No INSTI or NNRTI resistance, except that K103N mutation allowed



*Some individuals enrolled from ATLAS trial; those already receiving IM CAB + RPV through ATLAS did not require oral lead-in for ATLAS-2M

^Participants first received loading doses of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study weeks 4 and 8

#Participants first received loading dose of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study week 4

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Baseline Characteristics

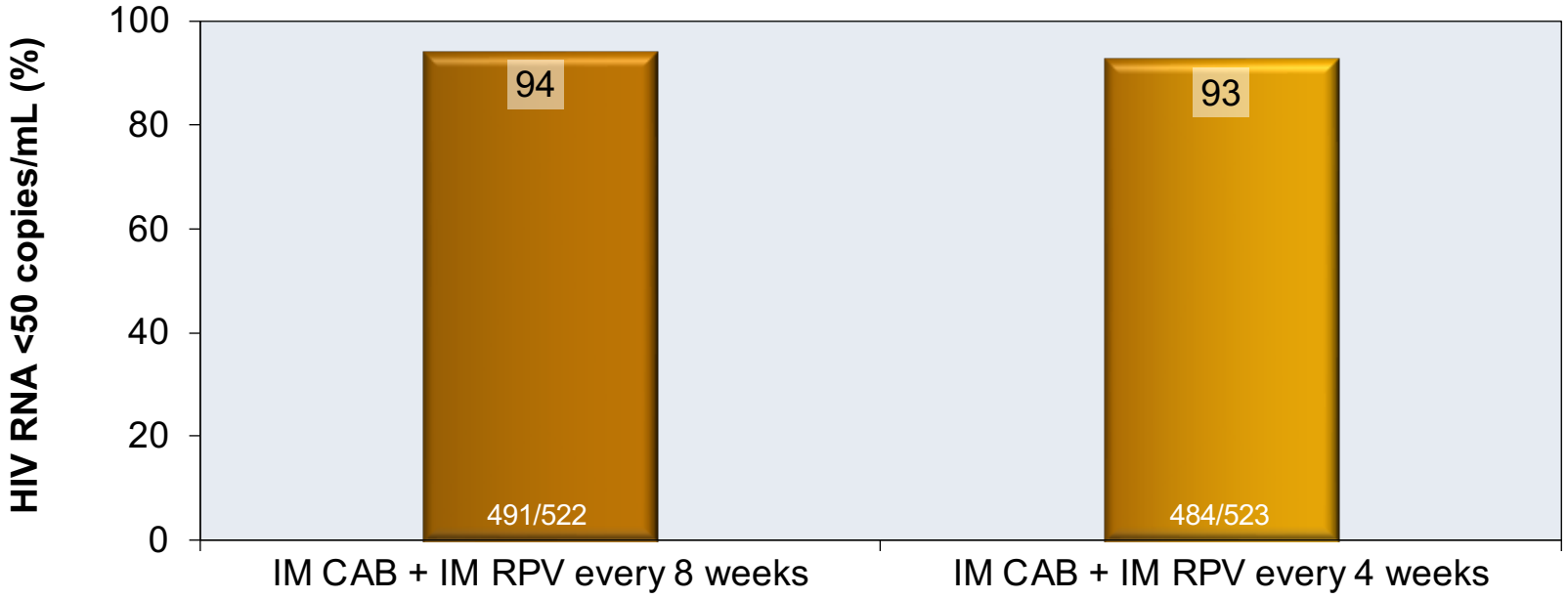
ATLAS-2M: Baseline Characteristics

Characteristic	IM CAB + RPV Every 8 Weeks (n = 522)	IM CAB + RPV Every 4 Weeks (n = 523)
Age, years, median	42	42
Female sex at birth, n, %	137 (26)	143 (27)
White, n, %	370 (71)	393 (75)
Black, n, %	101 (19)	90 (17)
Median body-mass index	25.7	25.9
Median CD4 T-cell count	642	688
Previous exposure to long-acting CAB+RPV, n, %		
None	327 (63)	327 (63)
1-24 weeks	69 (13)	68 (13)
>24 weeks	126 (24)	128 (24)

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results

Participants with Viral Rebound Meeting Protocol-Defined Criteria for Genotype Resistance Testing

	Total Number of Participants	Archived (Baseline) RPV RAMs*	Archived (Baseline) INSTI RAMs*	RPV RAMs Detected at Time of VF	INSTI RAMs Detected at Time of VF
Q8 Weeks	8	5/8	1/8	6/8	5/8
Q4 Weeks	2	0/2	0/2	1/2**	2/2

*Detected by archive (DNA) genotype

**One participant had RPV RAMs; the other an NNRTI polymorphism that reduced RPV activity >100-fold

Abbreviations: RAMs = resistance associated mutations; VF = virologic failure

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results

Injection Site Reactions (ISRs)*		
Types of Reactions	**IM CAB + RPV Every 8 Weeks, n (%)**	**IM CAB + RPV Every 4 Weeks, n, %**
Participants who received injections, n	516	517
Any reaction, n (%)	392 (76)	390 (75)
Serious reaction, n (%)	1 (<10)	0 (0)
Reaction leading to discontinuation, n (%)	6 (1)	11 (2)
Pain, n (%)	371 (72)	363 (70)
Nodule, n (%)	54 (10)	89 (17)
Induration, n (%)	41 (8)	39 (8)
Swelling, n (%)	32 (6)	27 (5)

*The majority of ISRs (98%) were grade 1-2.

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Conclusions

Conclusions: “The efficacy and safety profiles of dosing every 8 weeks and dosing every 4 weeks were similar. These results support the use of cabotegravir plus rilpivirine long-acting administered every 2 months as a therapeutic option for people living with HIV-1.”

Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

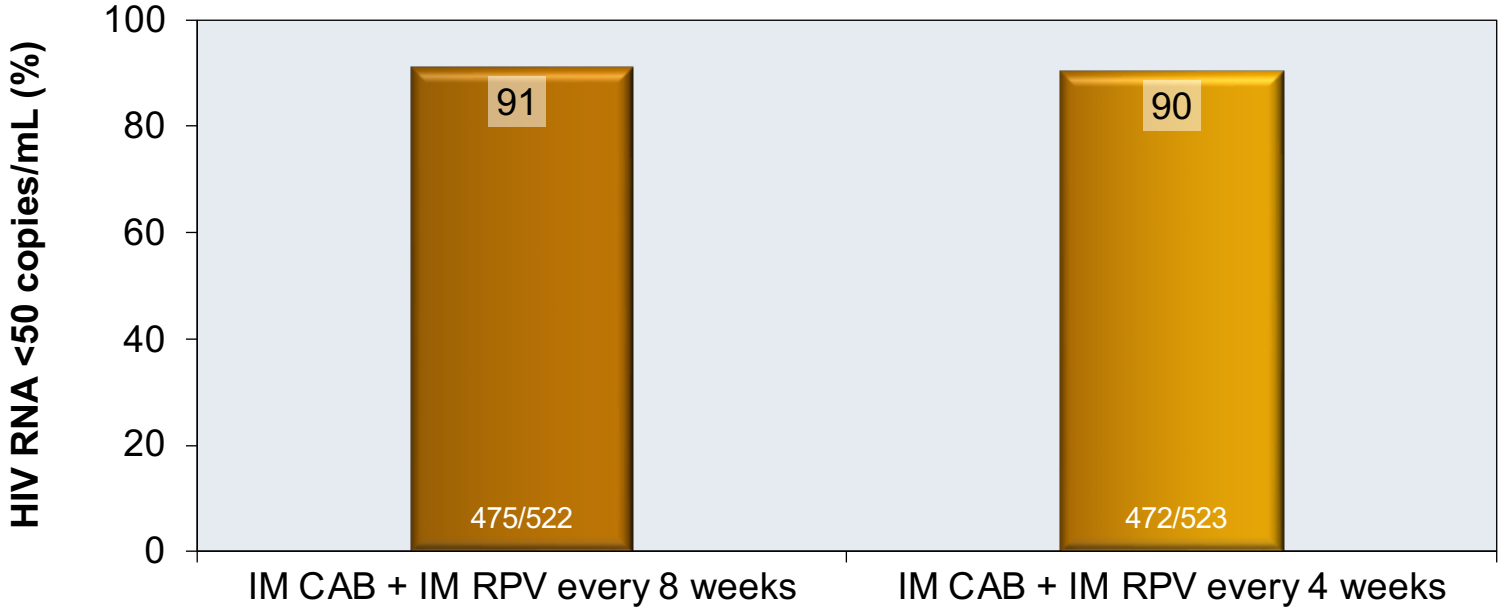
IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M: 96-Week Results

National HIV Curriculum

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results (Week 96)

Weeks 96: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 96 weeks: 11/522 (2%) in q8-week arm, 6/523 (1%) in q4-week arm

Source: Jaeger H, et al. Lancet HIV. 2021;8:e679-e689.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results (Week 96)

Injection Site Reactions (ISRs)*		
Types of Reactions	**IM CAB + RPV Every 8 Weeks, n (%)**	**IM CAB + RPV Every 4 Weeks, n, %**
Number of injections	12,832	23,855
Injection site pain	2,662/12,832 (21%)	3,295/23,855 (14%)
Injection site nodule	188/12,832 (2%)	297/23,855 (1%)
Injection site discomfort	134/12,832 (1%)	148/23,855 (1%)
Total number of ISRs	3,400	4,157
Grade 1	2,745/3,400 (81%)	3,446/4,157 (83%)
Grade 2	601/3,400 (18%)	661/4,157 (16%)
Grade 3	54/3,400 (2%)	50/4,157 (1%)
Withdrawal due to ISR	7/516 (1%)	11/517 (2%)
Median duration of ISR: 3 days (IQR 2 – 5)		

Source: Jaeger H, et al. Lancet HIV. 2021;8:e679-e689.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance ATLAS-2M Study: Results (Week 96)

Interpretation: “Long-acting cabotegravir and rilpivirine dosed every 8 weeks had non-inferior efficacy compared with that of every 4 weeks through the 96-week analysis, with both regimens maintaining high levels of virological suppression. These results show the durable safety, efficacy, and acceptability of dosing long-acting cabotegravir and rilpivirine monthly and every 2 months as maintenance therapy for people living with HIV-1.

Source: Jaeger H, et al. Lancet HIV. 2021;8:e679-e689.

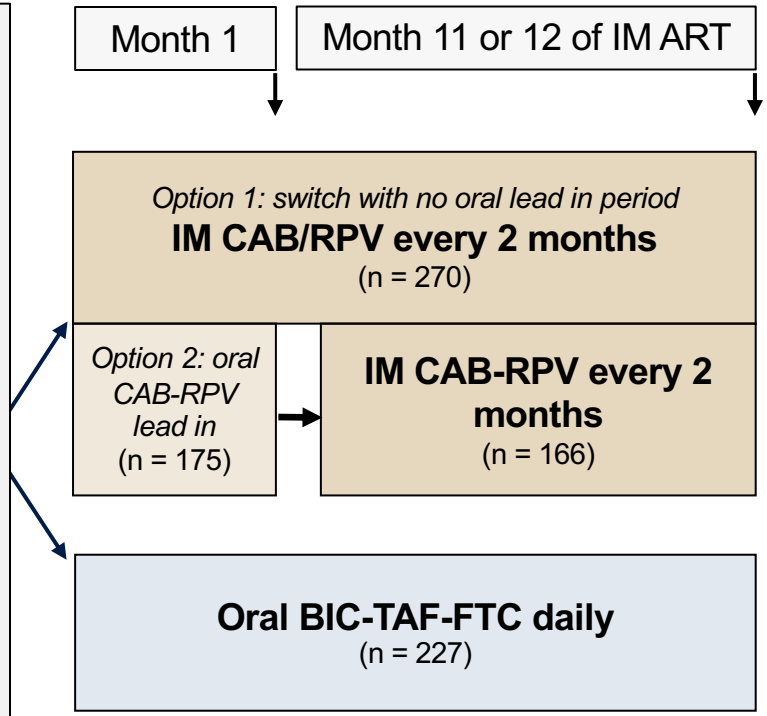
Switch to IM CAB and RPV Every 2 Months vs. Continued Oral BIC-TAF-FTC

SOLAR

National HIV Curriculum

Switch to IM CAB and RPV versus Continued BIC-TAF-FTC
SOLAR: Study Design

- **Background:** Randomized, multicenter, active-controlled, open-label, phase 3b, non-inferiority study designed to evaluate the efficacy and safety of switching to long-acting, intramuscular cabotegravir and rilpivirine versus continuing daily, oral, fixed-dose bictegravir-TAF-FTC
- **Inclusion Criteria**
  - Age >18 years
  - Taking bictegravir-TAF-FTC as a first or second regimen
  - No history of non-INSTI-based ART
  - No known or suspected resistance to study drugs
  - HIV RNA <50 copies/mL for at least 6 months
  - If pregnancy potential, agreed to contraception
- **Regimens (2:1 randomization)**
  - Bictegravir-TAF-FTC (50/25/200 mg) daily
  - CAB-RPV (600/900 mg) IM (oral lead-in period optional)



Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

Switch to IM CAB and RPV versus Continued BIC-TAF-FTC
SOLAR: Baseline Characteristics

SOLAR Study Baseline Characteristics		
Characteristic	**IM CAB-RPV** (n = 447)	**BIC-TAF-FTC** (n = 223)
Median age, years (range)	37 (18-74)	37 (18-66)
Age ≥50 years, n (%)	86 (19%)	42 (19%)
Cisgender female, n (%)	76 (17%)	41 (18%)
Cisgender male, n (%)	359 (80%)	178 (80%)
Transgender female, n (%)	9 (2%)	3 (1%)
Transgender male, n (%)	1 (<1%)	0
Gender non-binary, n (%)	1 (<1%)	0
Other gender, n (%)	1 (<1%)	1 (<1%)

Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

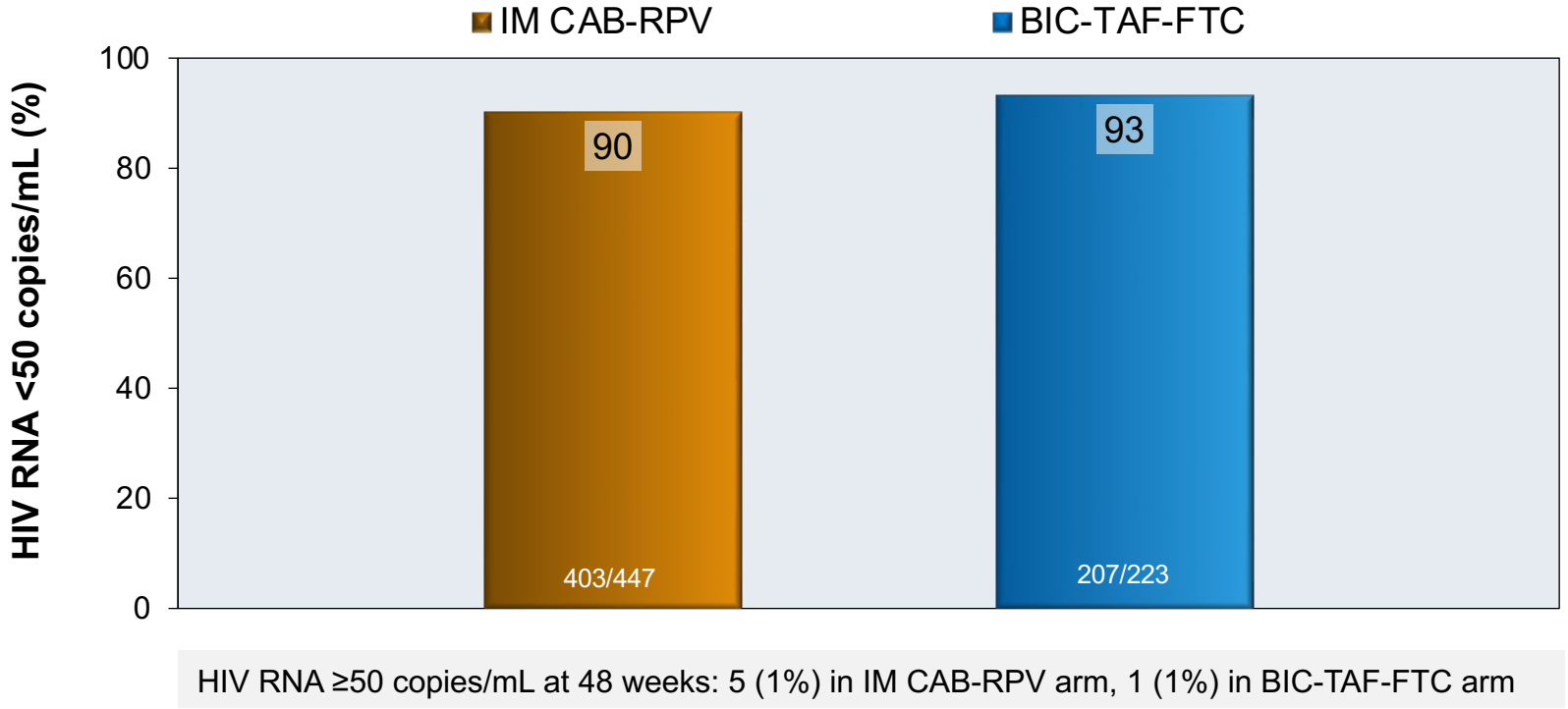
Switch to IM CAB and RPV versus Continued BIC-TAF-FTC
SOLAR: Baseline Characteristics

SOLAR Study Baseline Characteristics: Continued		
Characteristic	**IM CAB-RPV** (n = 447)	**BIC-TAF-FTC** (n = 223)
White race, n (%)	307 (69%)	156 (70%)
Black or African American race, n (%)	95 (21%)	49 (22%)
Asian race, n (%)	23 (5%)	11 (5%)
Other race, n (%)	22 (5%)	7 (3%)
Hispanic or Latinx ethnicity, n (%)	93 (21%)	38 (17%)
BMI, kg/m^2, median (IQR)	26.0 (23.2-29.4)	25.4 (23.4-29.6)
BMI ≥30, n (%)	93 (21%)	52 (23%)
Duration previous ART, years (median)	2.58	2.47
CD4 count, cells/mm^3, median (IQR)	649 (447-850)	640 (459-846)

Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

Switch to IM CAB and RPV versus Continued BIC-TAF-FTC SOLAR: Results

Virologic Response (Modified Intention-to-Treat Analysis) at Month 11-12



HIV RNA ≥50 copies/mL at 48 weeks: 5 (1%) in IM CAB-RPV arm, 1 (1%) in BIC-TAF-FTC arm

Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

Switch to IM CAB and RPV versus Continued BIC-TAF-FTC SOLAR: Results

Treatment Emergent Adverse Events (AEs) Through Month 11-12		
	IM CAB-RPV (n = 447)	**BIC-TAF-FTC** (n = 223)
Any drug-related AE	327 (72%)	2 (1%)
Excluding ISR*	90 (20%)	NA
Any ≥grade 3 drug-related AE	22 (5%)	0
Excluding ISR*	7 (2%)	NA
Drug-related serious AE	4 (1%)	0
Drug-related AE in >2%		
Pyrexia	13 (3%)	0
Headache	11 (2%)	0
Fatigue	10 (2%)	0
Diarrhea	9 (2%)	0
Drug-related AE leading to withdrawal	19 (4%)	0

*Injection site reactions (ISRs) were reported by 70% of long-acting CAB-RPV participants; 98% were grade 1 or 2

Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

Switch to IM CAB and RPV versus Continued BIC-TAF-FTC
SOLAR: Conclusion

Interpretation: “These data support the use of long-acting cabotegravir plus rilpivirine dosed every 2 months as a complete antiretroviral regimen that has similar efficacy to a commonly used integrase strand transfer inhibitor-based first-line regimen, while addressing unmet psychosocial issues associated with daily oral treatment.”

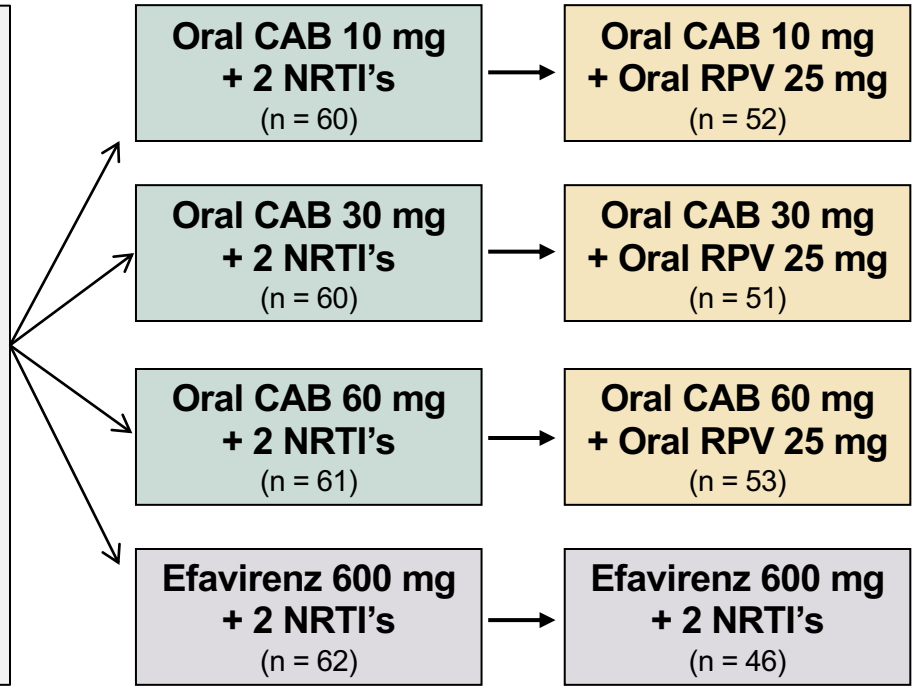
Source: Ramgopal MN, et al. Lancet HIV. 2023;10:e566-77.

Oral Cabotegravir + Oral Rilpivirine versus Efavirenz + 2 NRTI's

LATTE Study

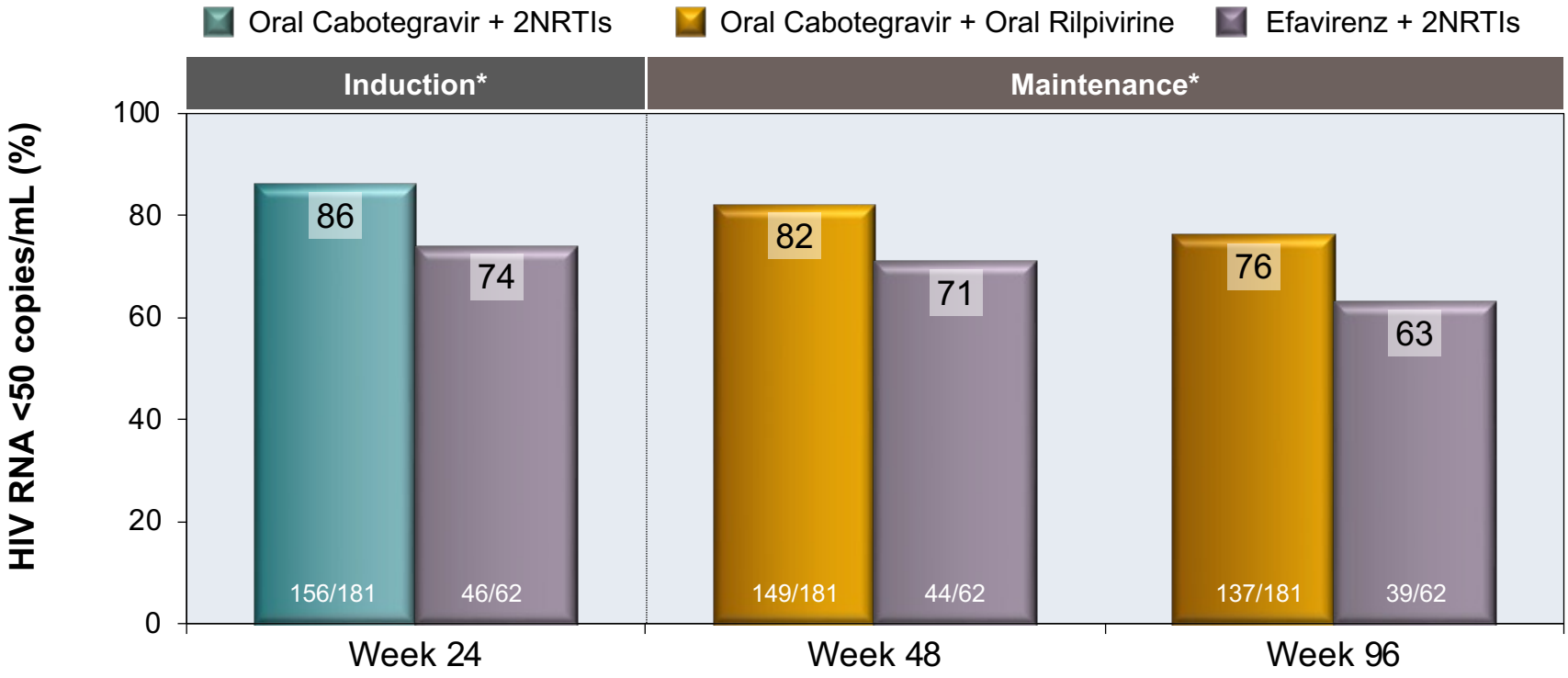
Oral Cabotegravir + Oral Rilpivirine versus Efavirenz + 2 NRTI's
LATTE Study: Design

- **Background**: Phase 2b, randomized, partially blinded study done at multiple centers in the U.S. and Canada
- **Inclusion Criteria**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA >1,000 copies/mL
  - CD4 count >200 cells/mm^3
  - CrCl >50 mL/min
  - No hepatitis B
  - No significant transaminitis



Source: Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-55.

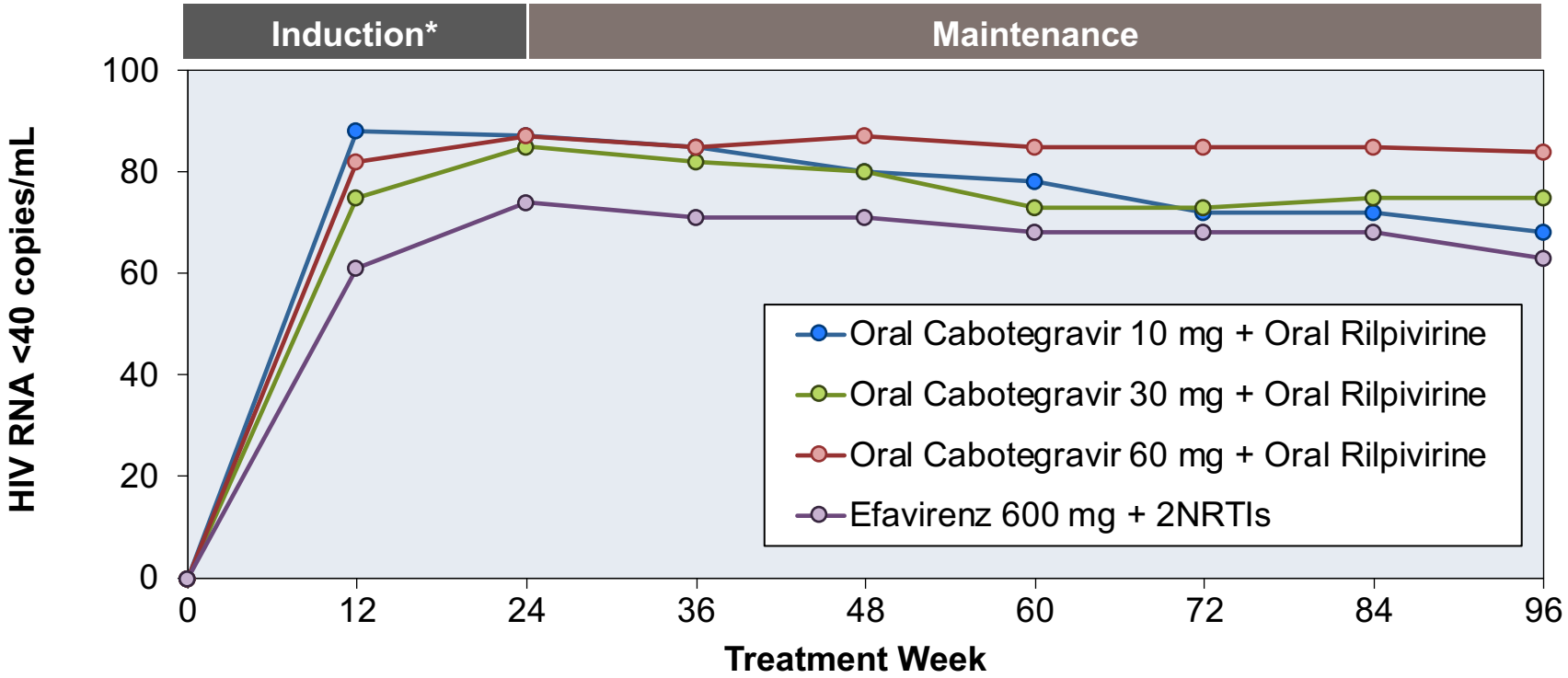
Oral Cabotegravir + Oral Rilpivirine versus Efavirenz + 2 NRTI's LATTE Study: Results



*Cabotegravir data is composite of all cabotegravir doses

Source: Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-55.

Oral Cabotegravir + Oral Rilpivirine versus Efavirenz + 2 NRTI's LATTE Study: Results



*During induction phase cabotegravir administered with investigator chosen 2NRTIs

Source: Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-55.

National HIV Curriculum

Oral Cabotegravir + Oral Rilpivirine versus Efavirenz + 2 NRTI's LATTE Study: Conclusions

Conclusions: "Cabotegravir plus dual NRTI therapy had potent antiviral activity during the induction phase. As a two drug maintenance therapy, cabotegravir plus rilpivirine provided antiviral activity similar to efavirenz plus dual NRTIs until the end of week 96. Combined efficacy and safety results lend support to our selection of oral cabotegravir 30 mg once a day for further assessment. LATTE precedes studies of the assessment of long-acting injectable formulations of both drugs as a two-drug regimen for the treatment of HIV-1 infection."

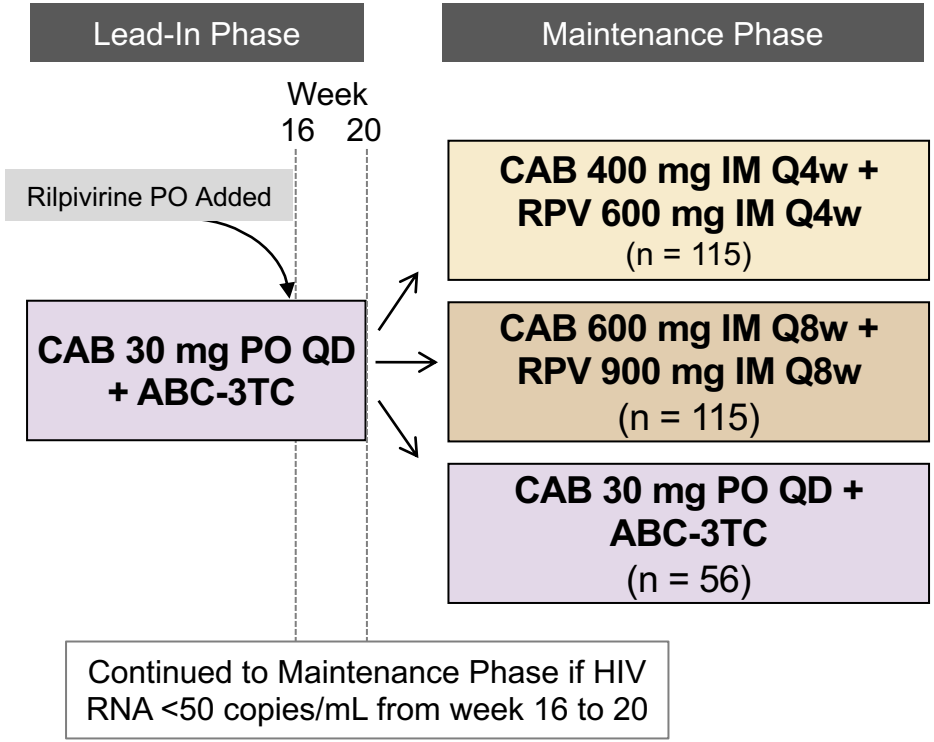
Source: Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-55.

Cabotegravir IM + Rilpivirine IM Every One or Two Months versus Oral CAB + ABC-3TC

LATTE-2

IM Cabotegravir + IM Rilpivirine versus Cabotegravir + ABC-3TC
LATTE-2 Study: Design

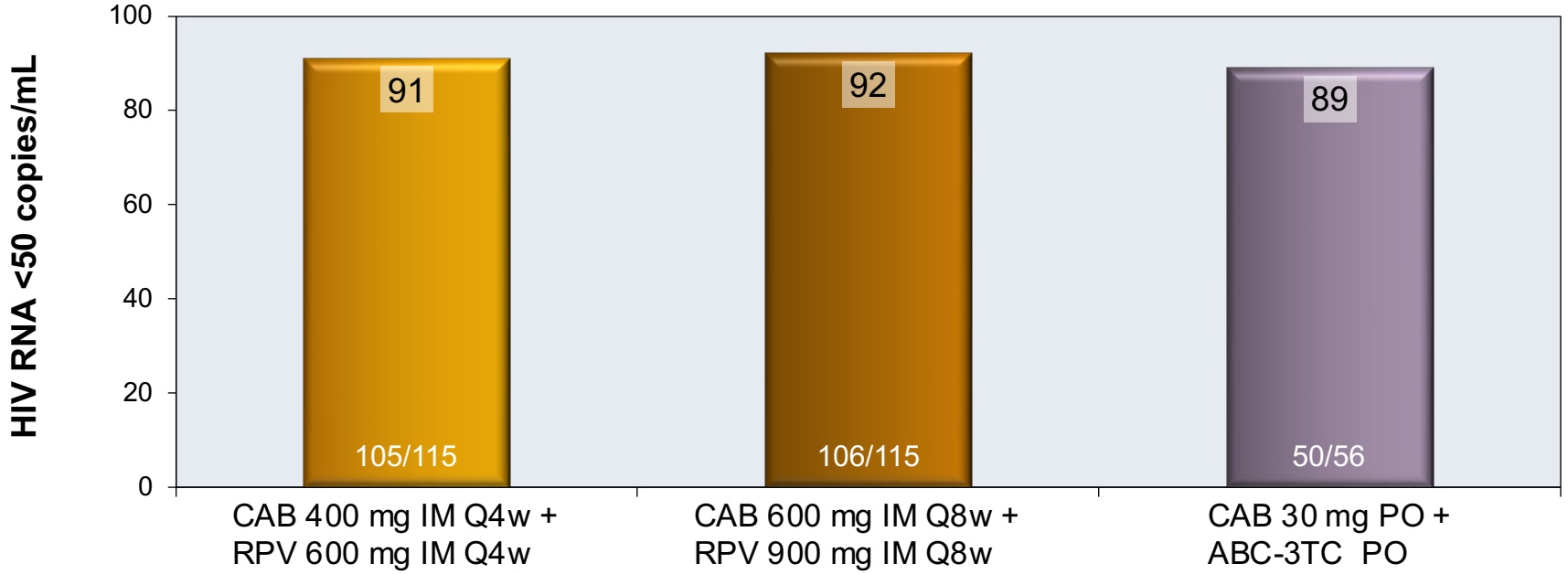
- **Background**
  - Phase 2b, randomized, open-label trial assessing dual therapy with long-acting, injectable agents for maintenance
- **Inclusion Criteria**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA >1,000 copies/mL
  - CD4 count >200 cells/mm^3
  - CrCl >50 mL/min
- **Exclusions**
  - Major resistance mutations
  - Pregnancy
  - Significant hepatic impairment
  - AIDS-defining condition



Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

IM Cabotegravir + IM Rilpivirine versus Cabotegravir + ABC-3TC LATTE-2 Study: Results

Week 48 Virologic Results (by FDA Snapshot Algorithm)

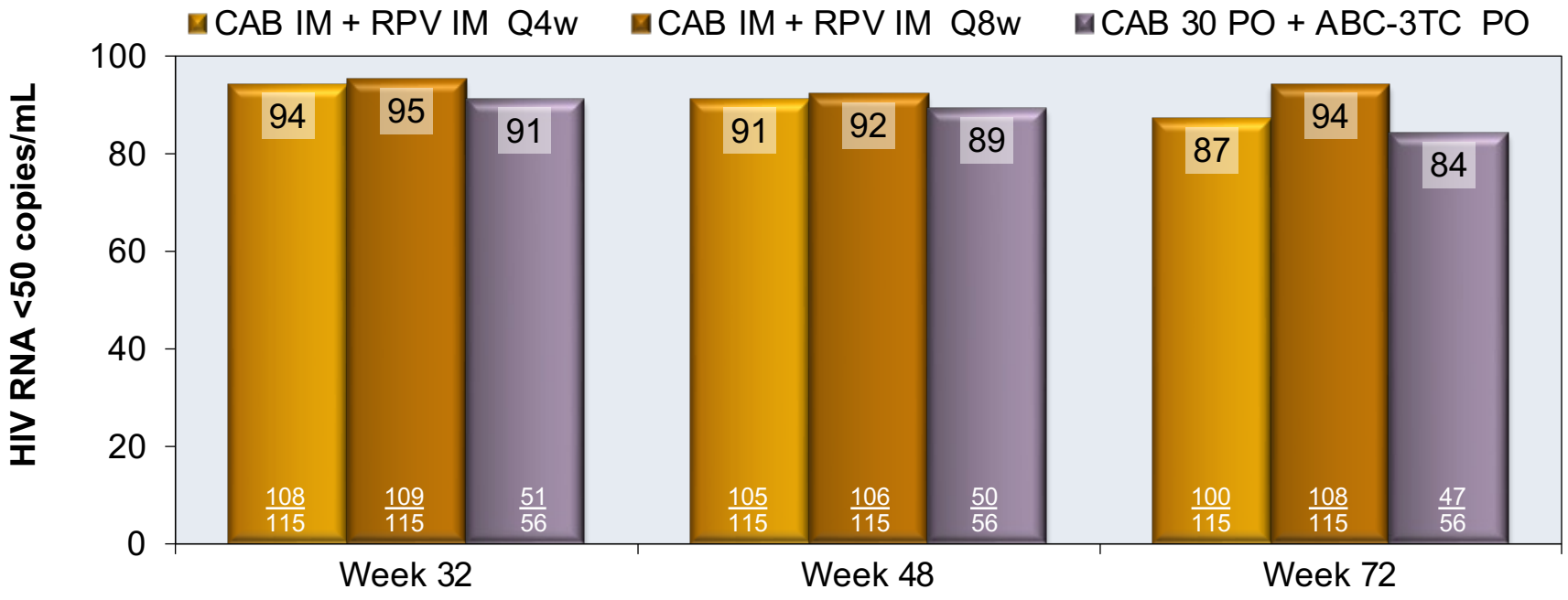


Abbreviations: CAB = cabotegravir; RPV = rilpivirine; ABC-3TC = abacavir-lamivudine

Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

IM Cabotegravir + IM Rilpivirine versus Cabotegravir + ABC-3TC LATTE-2 Study: Results

Week 96 virologic results by FDA snapshot analysis



Abbreviations: CAB = cabotegravir; RPV = rilpivirine; ABC-3TC = abacavir-lamivudine

Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

IM Cabotegravir + IM Rilpivirine versus Oral Cabotegravir + ABC-3TC LATTE-2 Study: Adverse Events

Treatment-related adverse events at 96 weeks (excluding injection site reactions)

	Q4 Weeks CAB IM + RPV IM (n = 115)	Q8 Weeks CAB IM + RPV IM (n = 115)	Oral CAB PO + ABC-3TC (n=56)
Pyrexia	7 (6%)	5 (4%)	0 (0%)
Nausea	12 (10%)	8 (7%)	5 (9%)
Headache	7 (6%)	6 (5%)	4 (7%)
Dyspepsia	6 (5%)	1 (<1%)	1 (2%)
Asthenia	3 (3%)	2 (2%)	3 (5%)

*All of the above treatment-related adverse reactions were grade 1-2.

Abbreviations: Q = every; IM = intramuscular; CAB = Cabotegravir; RPV = rilpivirine; ABC-3TC = abacavir-lamivudine

Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

IM Cabotegravir + IM Rilpivirine versus Cabotegravir + ABC-3TC
LATTE-2 Study: Adverse Events

Treatment-Related Injection Site Reactions

	Q4 Weeks IM CAB + IM RPV (n = 115)		Q8 Weeks IM CAB + IM RPV (n = 115)	
	Any	Grade 3-4	Any	Grade 3-4
Pain	112 (97%)	6 (5%)	109 (95%)	8 (7%)
Nodule	35 (30%)	1 (<1%)	29 (25%)	1 (<1%)
Swelling	34 (30%)	0	29 (25%)	1 (<1%)
Pruritis	33 (29%)	0	24 (21%)	0
Induration	25 (22%)	0	28 (24%)	1 (<1%)
Warmth	21 (18%)	0	22 (19%)	1 (<1%)
Bruising	14 (12%)	0	19 (17%)	0
Erythema	19 (17%)	0	12 (10%)	1 (<1%)
Discoloration	6 (5%)	0	3 (3%)	0

Abbreviations: Q = every; IM = intramuscular; CAB = Cabotegravir; RPV = Rilpivirine

Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

IM Cabotegravir + IM Rilpivirine versus Oral Cabotegravir + ABC-3TC LATTE-2 Study: Conclusions

Conclusions: “The two-drug combination of all-injectable, long-acting cabotegravir plus rilpivirine every 4 weeks or every 8 weeks was as effective as daily three-drug oral therapy at maintaining HIV-1 viral suppression through 96 weeks and was well accepted and tolerated.”

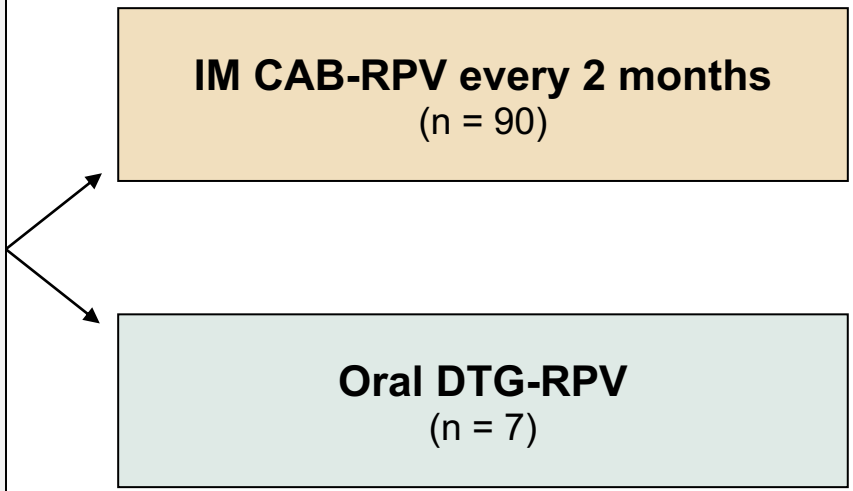
Source: Margolis DA, et al. Lancet 2017;390:1499-1510.

Every 2-Month IM CAB plus IM RPV After 5 Years of Oral CAB plus Oral RPV

POLAR Study

Every 2-Month IM CAB + IM RPV after 5 Years of Oral CAB + Oral RPV Polar Study: Design

- **Background**
  - Phase 2b, multicenter, non-randomized, rollover study; LATTE participants who completed 300 weeks of oral CAB + oral RPV and had HIV RNA <50 copies/mL were eligible
- **Design**
  - Eligible participants could elect to switch to every 2-month IM CAB-RPV or switch to dolutegravir (DTG) with RPV as 2-drug oral maintenance ART



Source: Mills A, et al. AIDS. 2022;36:195–203.

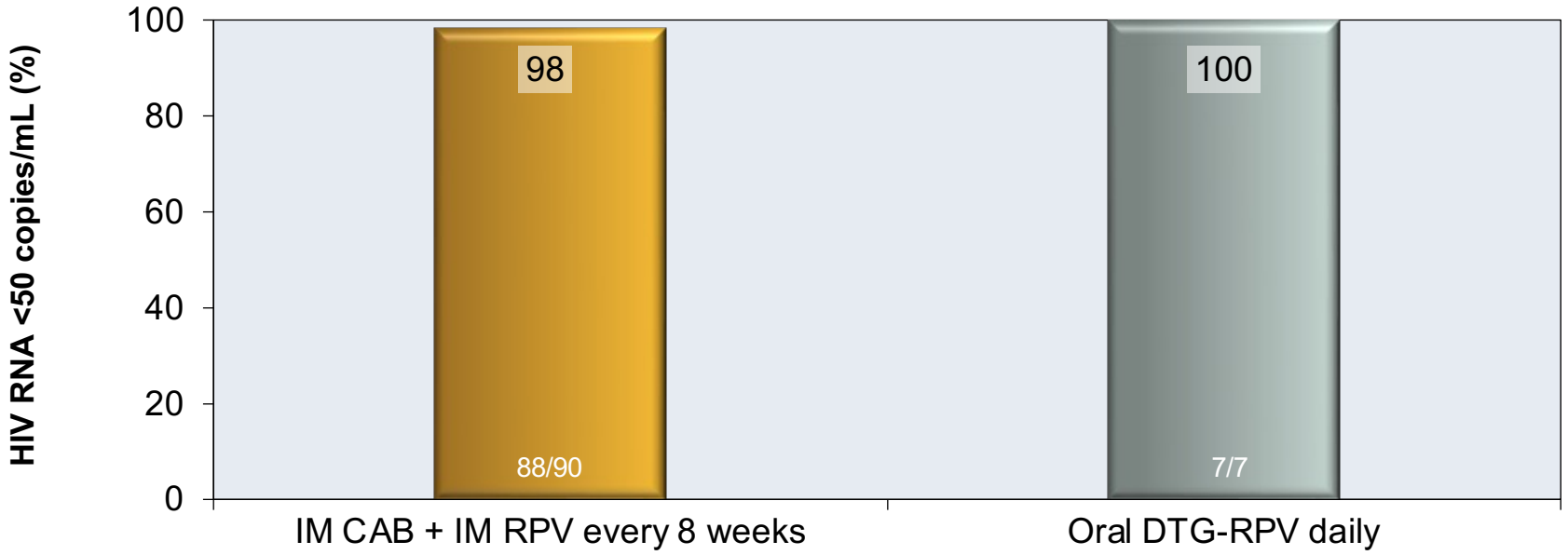
Every 2-Month IM CAB + IM RPV after 5 Years of Oral CAB + Oral RPV Polar Study: Baseline Characteristics

POLAR: Baseline Characteristics		
Characteristic	**IM CAB-RPV Every 8 Weeks** (n = 90)	**Oral DTG-RPV Daily** (n = 7)
Age, median, years	41	53
Age ≥50 years, n (%)	16 (18)	4 (57)
Female sex at birth, n (%)	2 (2)	0
Female self-reported sex, n (%)	3 (3)	0
White, n (%)	63 (70)	4 (57)
Black, n (%)	21 (23)	3 (43)
Other, n (%)	6 (7)	0
BMI, median, kg/m2	27	27
CD4 T-cell count, median	851	779

Source: Mills A, et al. AIDS. 2022;36:195–203.

Every 2-Month IM CAB + IM RPV after 5 Years of Oral CAB + Oral RPV Polar Study: Results

12 Months: Virologic Response by FDA Snapshot Analysis (ITT)

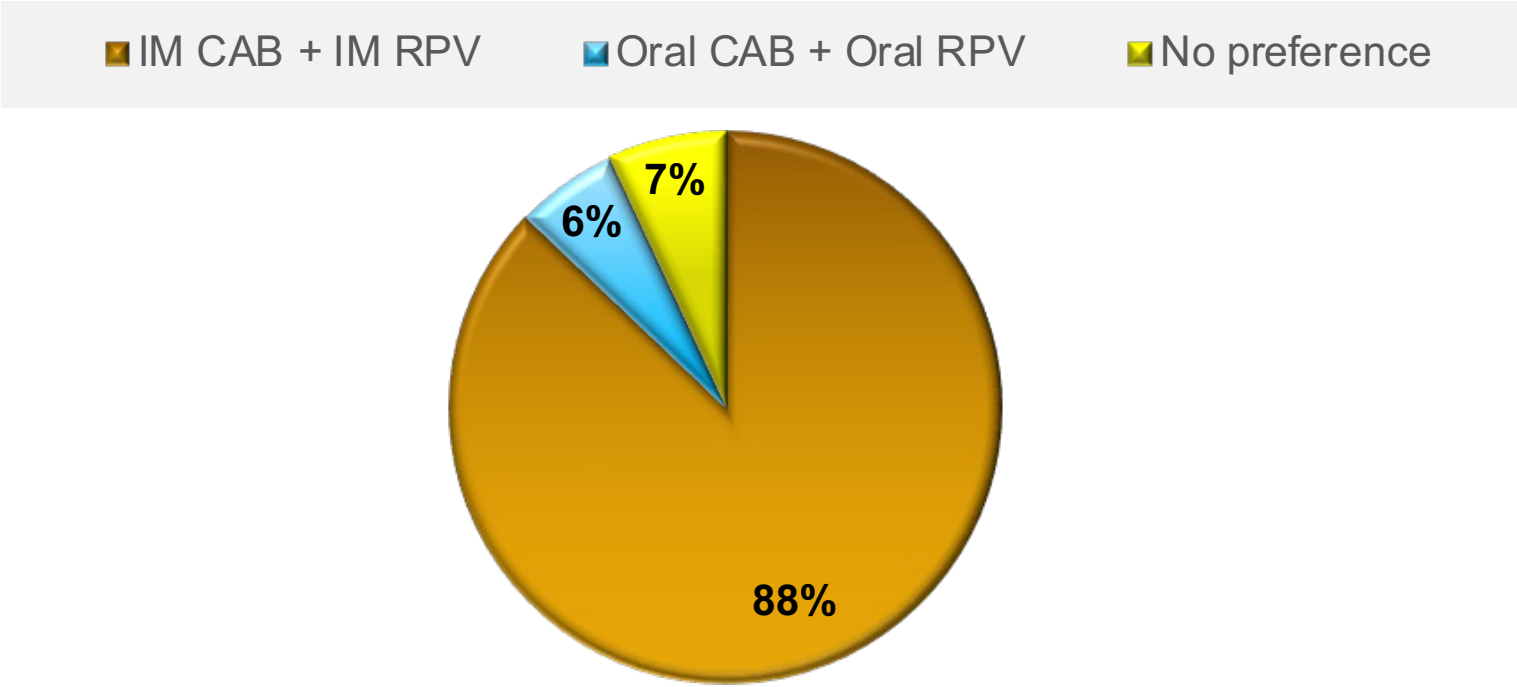


*2 participants in IM CAB-RPV arm had no virologic data at month 12 so were counted as failures
*No participant in either arm had HIV RNA >50 copies/mL at month 12

Source: Mills A, et al. AIDS. 2022;36:195–203.

Every 2-Month IM CAB + IM RPV after 5 Years of Oral CAB + Oral RPV Polar Study: Results

12 Months: Participant Reported Treatment Preferences



Source: Mills A, et al. AIDS. 2022;36:195–203.

Every 2-Month IM CAB + IM RPV After 5 Years Oral CAB + RPV Polar Study: Conclusions

Conclusions: “Cabotegravir plus rilpivirine (CAB + RPV) long-acting maintained virologic suppression in participants who had previously received daily oral CAB + RPV for at least 5 years in LATTE, with a favorable safety profile. Most participants preferred CAB + RPV long-acting to their prior oral CAB + RPV regimen at month 12.”

Source: Mills A, et al. AIDS. 2022;36:195–203.

Acknowledgments

The **National HIV Curriculum** is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totaling $1,332,044 with 0% financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov. This project is led by the University of Washington's Infectious Diseases Education and Assessment (IDEA) Program.

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