CROI 2020 Review: Long-Acting ART

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April 2, 2020

Disclosures

No conflicts of interests or relationships to disclose.

Outline

- Today: update on long-acting ART
  - IM cabotegravir + rilpivirine: FLAIR, ATLAS, ATLAS-2M
  - SubQ GS-6207 (capsid inhibitor)

- Next week: update on dual ART and HIV cure
  - DTG/3TC initial ART: 96-week results
  - Islatravir + doravirine metabolic outcomes
  - Sustained HIV remission in the London Patient

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Long-Acting IM Cabotegravir + Rilpivirine

Long-Acting IM Cabotegravir-Rilpivirine (*Cabenuva*)
General Administration Strategy and Outstanding Questions

Oral (Daily) Lead-In
Cabotegravir 30 mg QD
+ Rilpivirine 25 mg QD

Loading (Injectable) x 1
Cabotegravir (600 mg)
Rilpivirine (900 mg)

Maintenance (Injectable)
Cabotegravir (400 mg)
Rilpivine (600 mg)

Questions:
- Optimal lead-in time?
- Maintenance frequency?
- Necessary oral bridge/tail?

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Summary of Key Studies
Cabotegravir-Rilpivirine

- Phase 2 Trials in Treatment Naïve
  - LATTE: Oral CAB-RPV daily versus EFV plus 2 NRTI's
  - LATTE-2: IM CAB-RPV q1 or 2 months vs. oral CAB + ABC-3TC
- Phase 3 Trials in Treatment Naïve
  - FLAIR: IM CAB-RPV every month versus oral DTG-ABC-3TC
- Phase 3 Trials in Treatment Experienced
  - ATLAS: Switch to monthly IM CAB-RPV or stay on 3-drug ART
  - ATLAS-2M: switch to IM CAB-RPV every one or two months
  - LATITUDE: IM CAB-RPV for persons with detectable HIV RNA

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Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction

FLAIR Study

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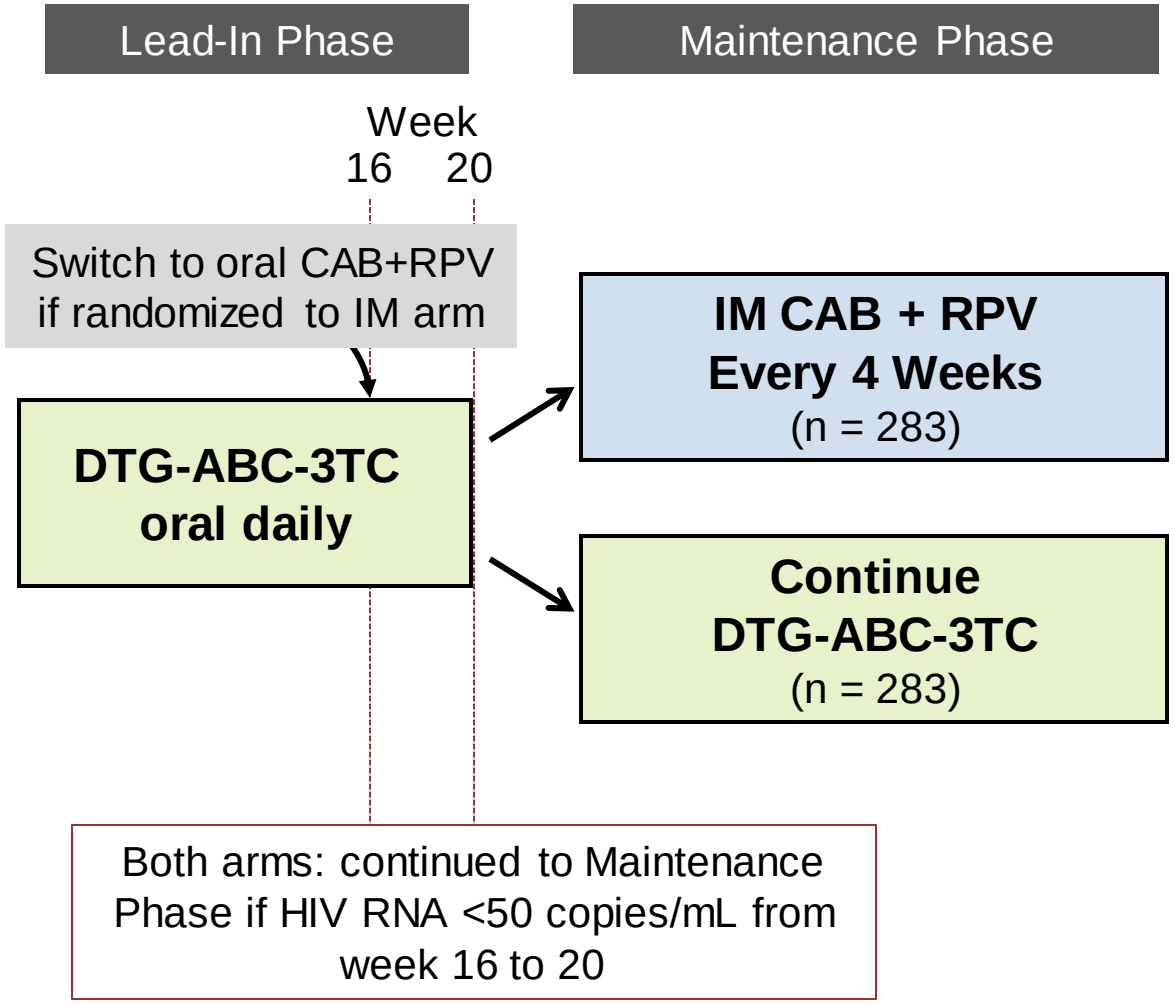
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Design

Study Design: FLAIR

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



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

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Baseline Characteristics

FLAIR: Baseline Characteristics			
Characteristic	**IM CAB + RPV** (n = 283)	**Oral ART** (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.

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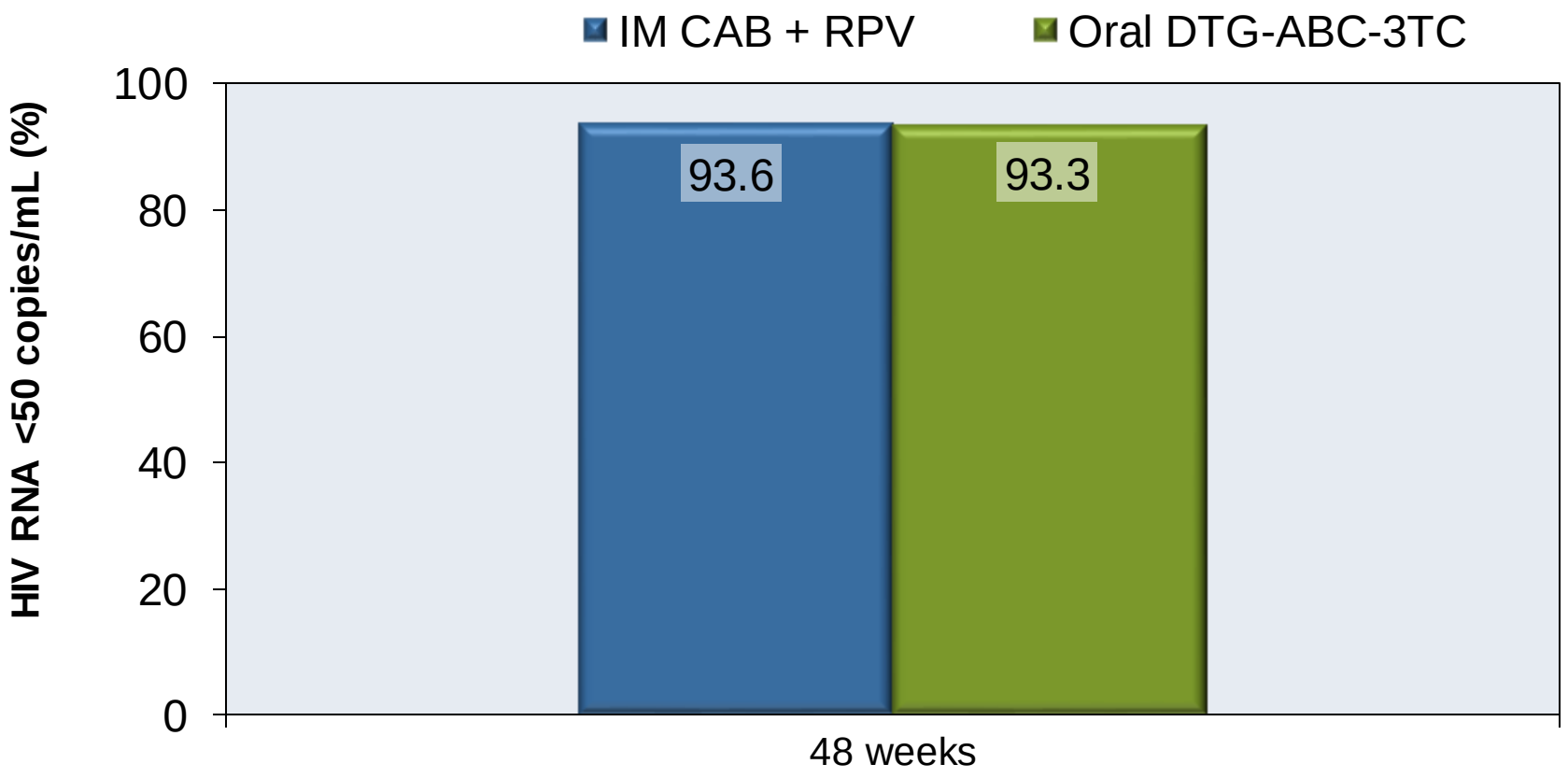
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)



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.

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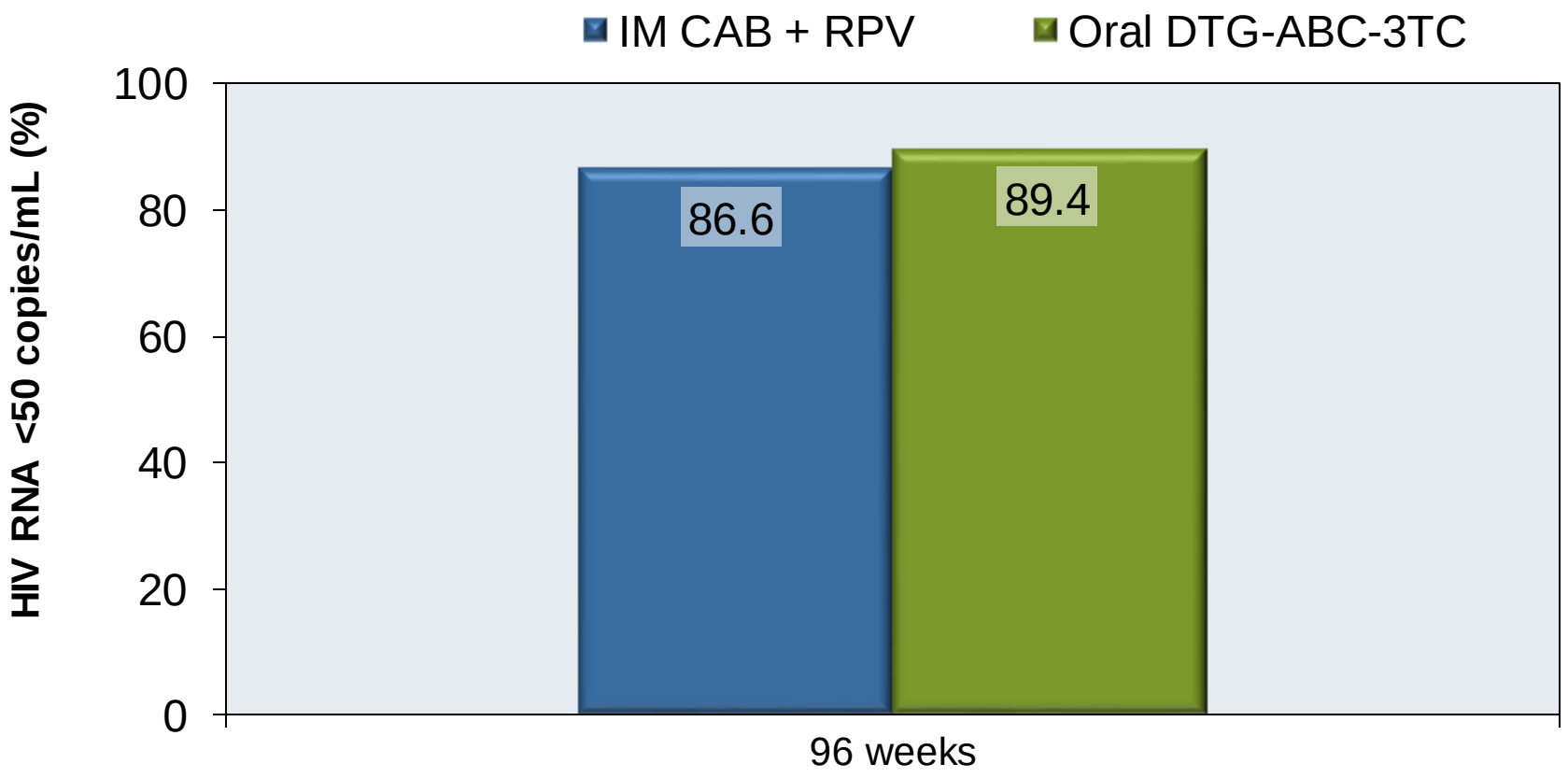
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Results

Week 96: Virologic Response by FDA Snapshot Analysis (ITT)



HIV RNA ≥50 copies/mL at 96 weeks: 3.2% CAB-RPV, 2.5% DTG-ABC-3TC

Source: Orkin C, et al. CROI 2020, Abstract 482.

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Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Results

Participants in the IM CAB + RPV arm with viral rebound meeting protocol-defined criteria for genotype resistance testing				
Sex, Country, HIV-1 Subtype, Viral Load (Baseline)	**Baseline INSTI RAMs**	**Baseline NNRTI RAMs**	**Viral Load at Confirmed Virologic Failure**	**INSTI RAMs at Virologic Failure**
F, Russia, A1, 54,000 copies/mL	L74I	None	456 copies/mL	L74I, Q148R
M, Russia, A1, 23,000 copies/mL	L74I	None	299 copies/mL	L74I, G140R
F, Russia, A1, 20,000 copies/mL	L74I	None	440 copies/mL	L74I, Q148R
There were also 3 virologic failures in the DTG-ABC/3TC arm; no new RAM's detected Abbreviations: RAMs = resistance associated mutations				

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

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Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Adverse Events

Drug-Related Adverse Events and Injection Site Reactions (ISRs)		
Adverse Events (AEs)	**IM CAB + RPV** (N = 283)	**Oral ART** (N = 283)
Any AE	236	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.

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Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: 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.

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Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS Study

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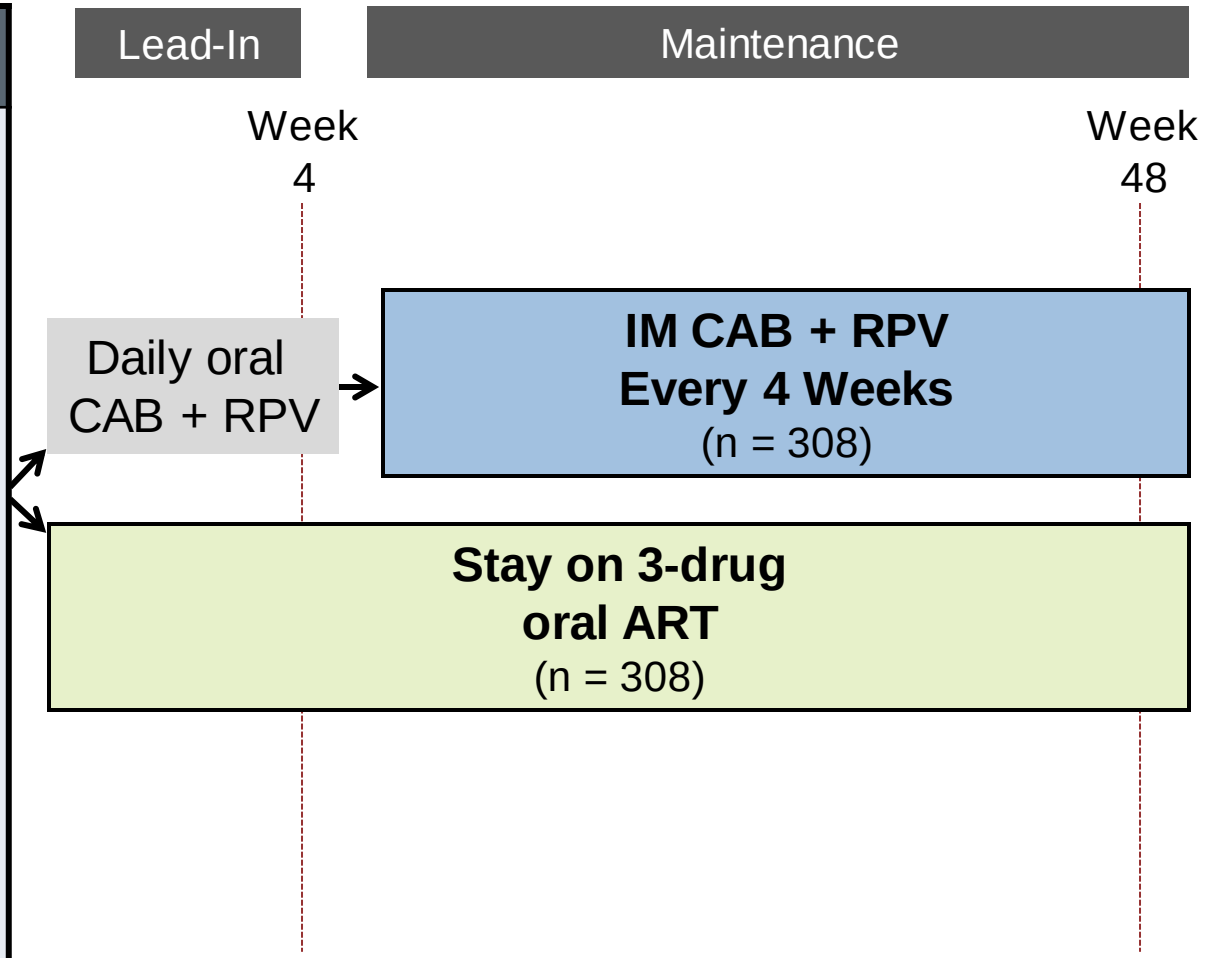
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Design

Study Design: ATLAS

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB-RPV after oral induction for adults taking 3-drug oral ART
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an INSTI, NNRTI, boosted PI, or unboosted atazanavir, plus 2 NRTI's
  - Stable regimen & HIV RNA <50 copies/mL for ≥ 6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)
  - No chronic hepatitis B



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

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Long-Acting IM Cabotegravir and 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.

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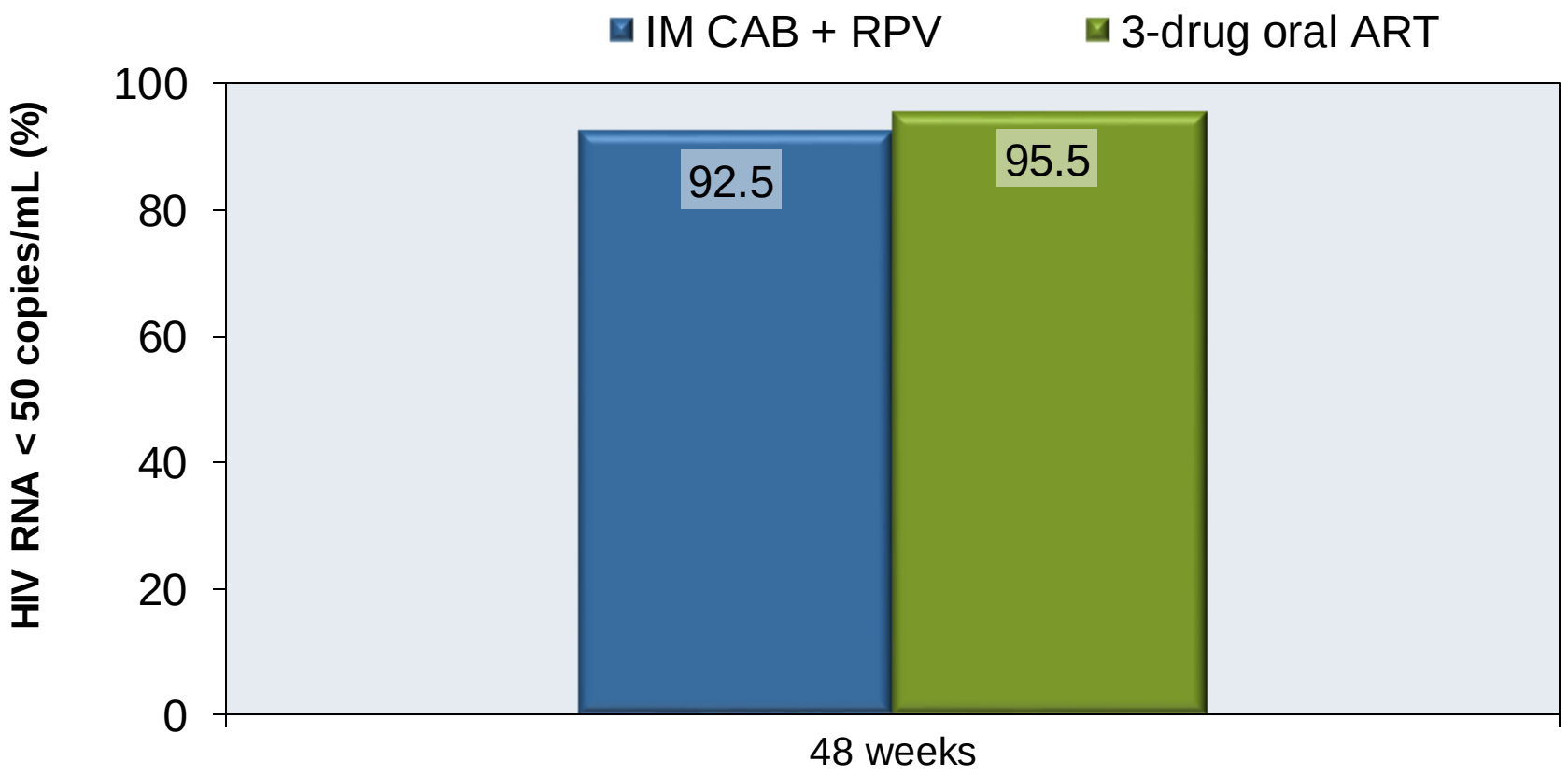
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥ 50 copies/mL at 48 weeks: 1.6% CAB-RPV, 1.0% 3-drug oral ART

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

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Long-Acting IM Cabotegravir and 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

Sex, Country, HIV-1 Subtype	Baseline INSTI RAMs	Baseline NNRTI RAMs	Viral Load at Confirmed Virologic Failure	INSTI RAMs at Virologic Failure
F, 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 instance of 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.

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

Injection Site Reactions (ISRs)	
Reactions	**Baseline N = 308**
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.

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Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS-2M Study

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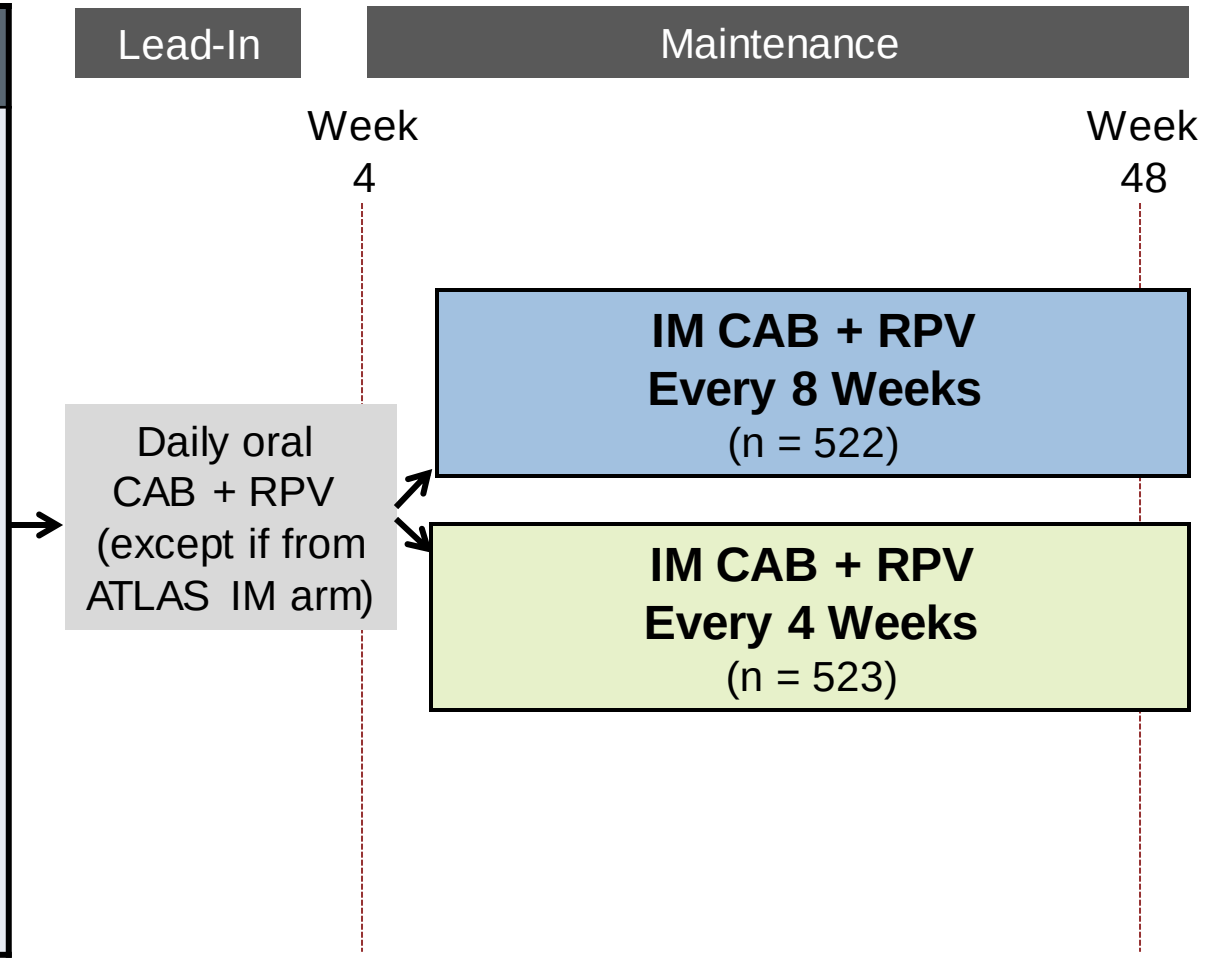
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS-2M Study: Design

Study Design: ATLAS-2M

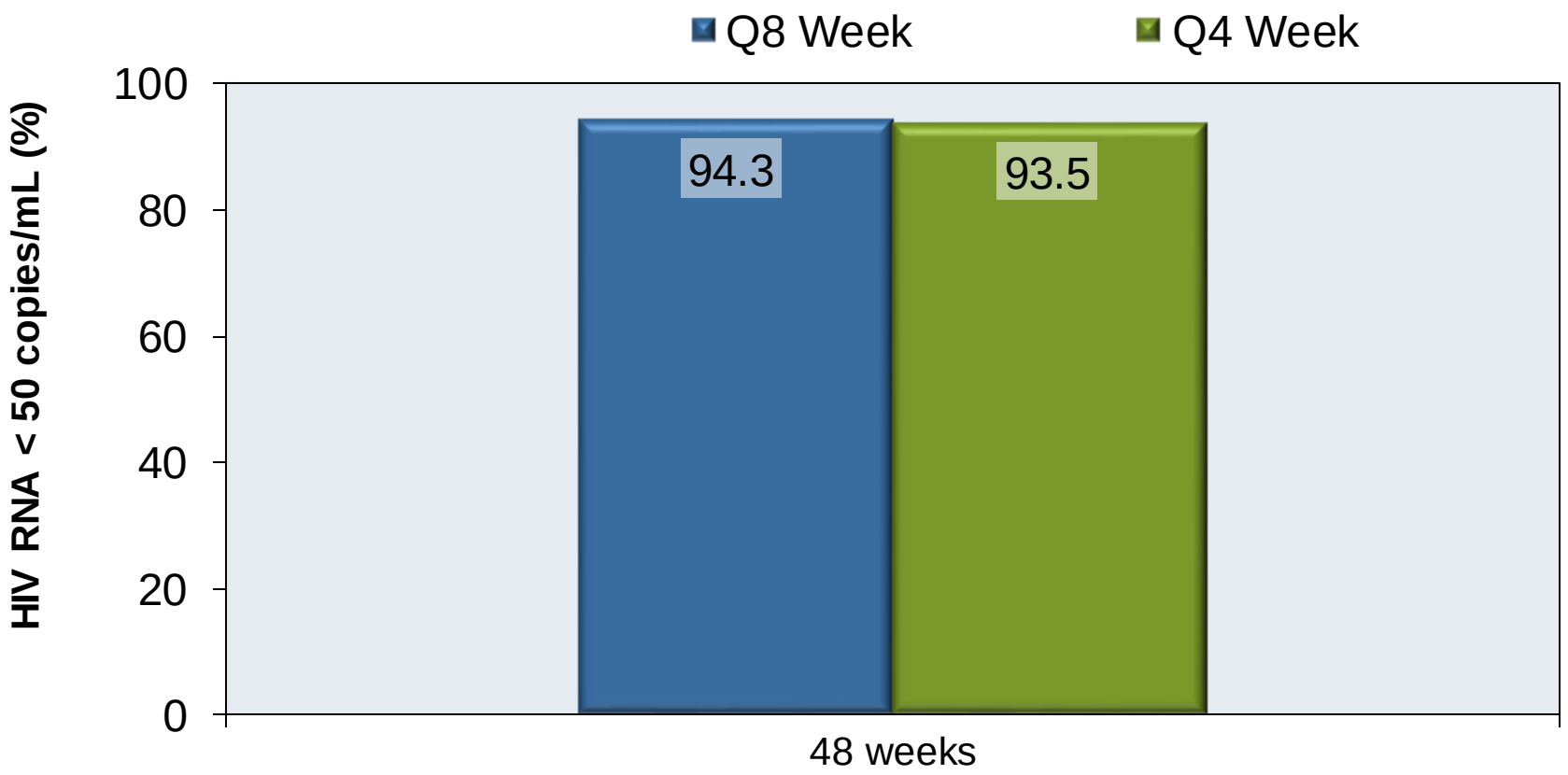
- **Background**: Phase 3, randomized, open-label trial assessing IM CAB-RPV q2 months after oral induction for adults taking 3-drug oral ART
- **Inclusion Criteria**
  - Adults from ATLAS receiving monthly IM CAB + RPV or oral ART with HIV RNA <50 copies/mL at 52 weeks
  - Adults receiving standard oral ART outside of ATLAS with HIV RNA <50 copies/mL for ≥6 months; no prior virologic failure (K103N ok)



Source: Overton et al, CROI 2020. Abstract 34.

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS-2M Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)



HIV RNA ≥ 50 copies/mL at 48 weeks: 1.7% Q8 week arm, 1.0% Q4 week arm

Source: Overton et al, CROI 2020. Abstract 34.

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Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS-2M Study: Results

Virologic Failures and Resistance-Associated Mutations (RAMs)		
Outcome	**Q8 Week** (n = 522)	**Q4 Week** (n = 523)
Confirmed VF, n, %	8 (1.5)	2 (0.4)
Rilpivirine RAMs detected at VF, n	6/8	1/2
Specific rilpivirine RAMs detected at VF	K101E, E138E/K, E138A, Y188L	K101E, M230L
Pre-existing rilpivirine RAM's detected, n	5/6	0/2
INSTI RAMs detected at VF, n	5/8	2/2
Specific INSTI RAMs detected at VF	Q148R, N155H	E138E/K, Q148R, N155N/H
Pre-existing INTI RAMs detected, n	1/5	0/2

5/8 in Q8 week arm had L74I polymorphism at baseline (3 subtype A)
9/10 VF's in study re-suppressed on fully active oral ART; all 10 retained phenotypic susceptibility to DTG
Injection site reactions frequent but 98% grade 1/3; median duration 3 days

Source: Overton et al, CROI 2020. Abstract 34.

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Reflections on Long-Acting CAB-RPV

- May be an excellent option for carefully selected individuals
  - No resistance, likely to adhere to regular injections, no hep B
  - Struggling with pill fatigue, swallowing pills, stigma, transitions out of hospital/corrections setting
- Many operational & clinical questions
  - Burden on clinic staff if injections must be given in clinic
  - Risk of missed doses
  - Optimal oral bridge for missed doses, tail for stopping
  - Role for persons with imperfect adherence/detectable VL
  - Injection site reaction fatigue over time
  - Metabolic/weight gain differences over standard oral ART

See also: Currier J. NEJM. March 2020;382(23)

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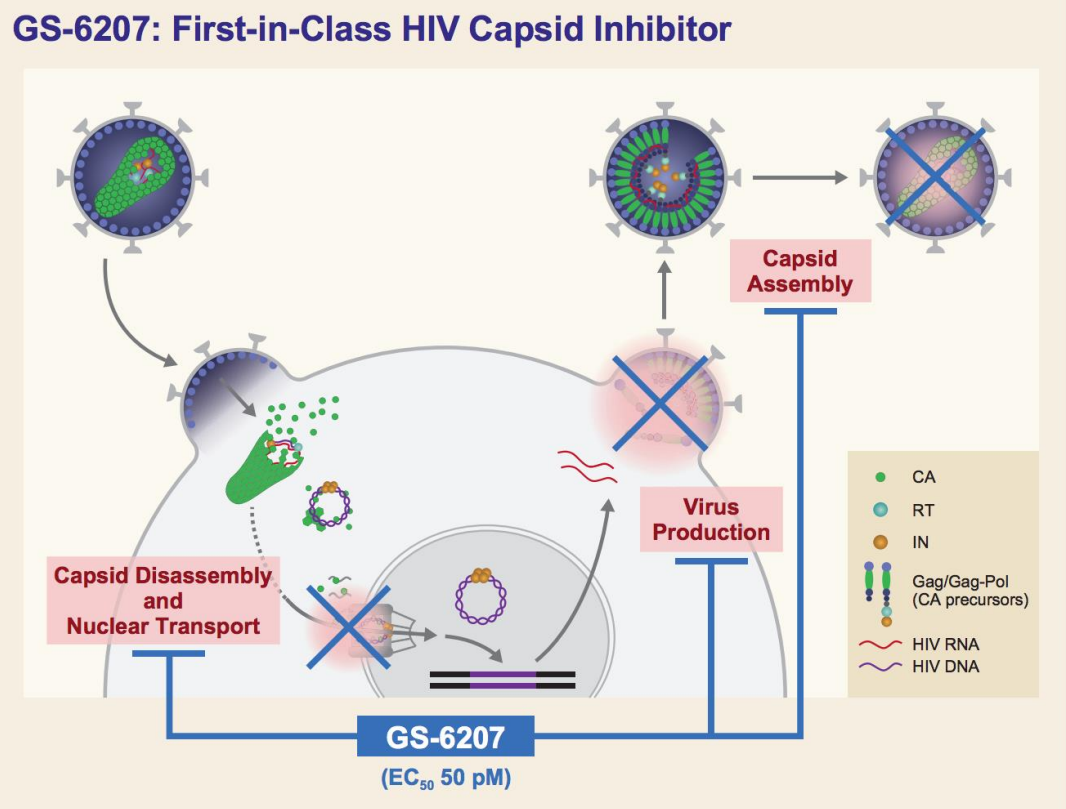
Subcutaneous GS-6207 (Capsid Inhibitor)

Dose-Ranging Study

Dose Response Relationship of SubQ Capsid Inhibitor

- Novel mechanism of action; active with RAM's to other ART
- SubQ dosing q≥12 weeks likely maintains adequate levels



Source: Daar E, et al. CROI 2020. Abstract 3691.

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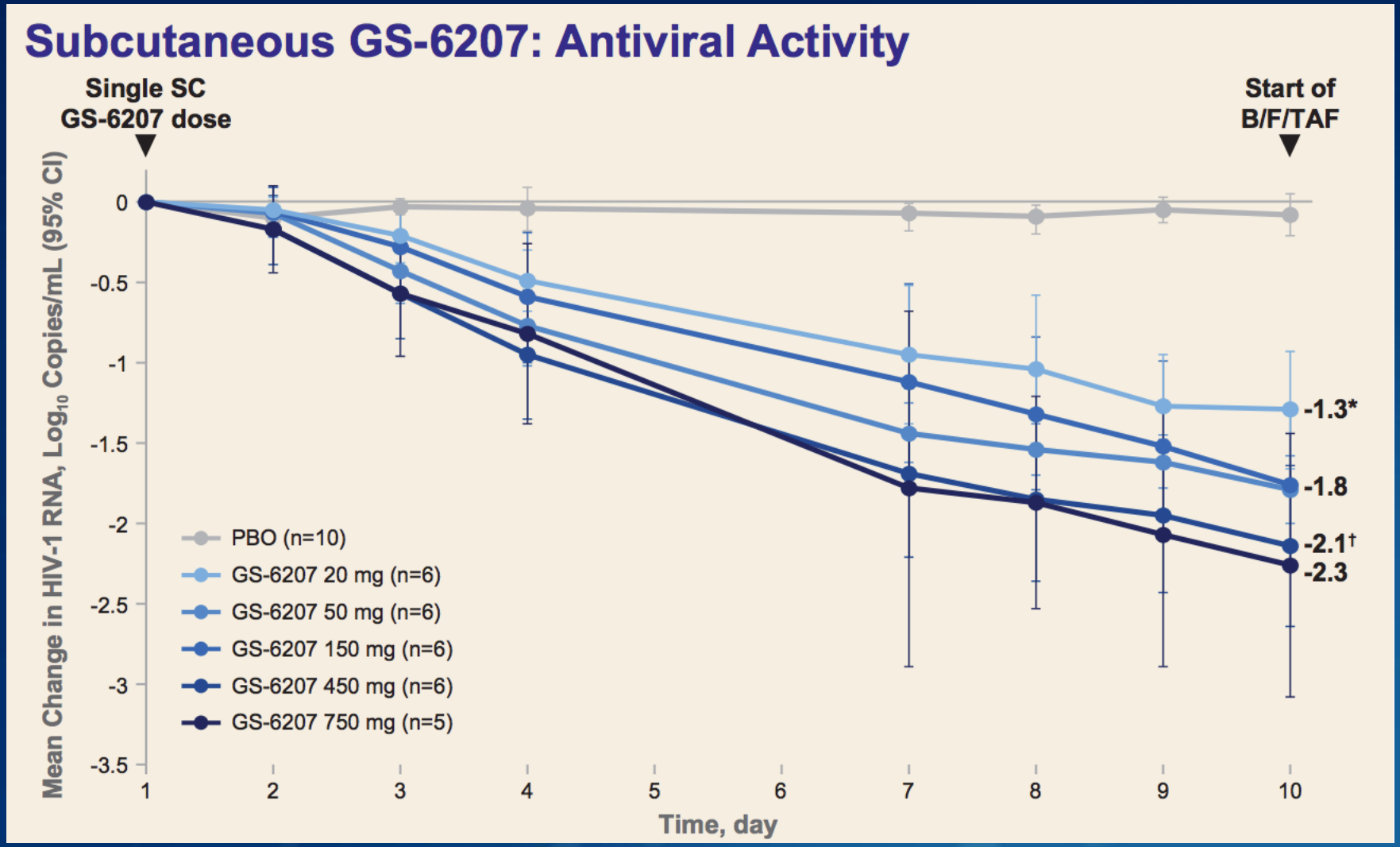
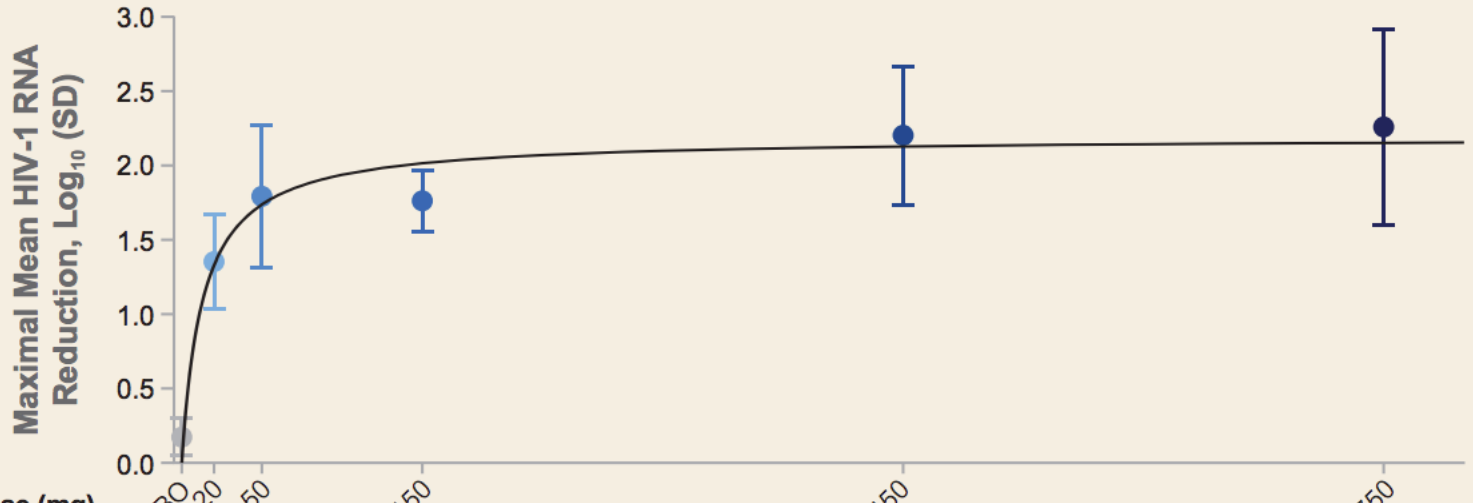
Dose Response Relationship of SubQ Capsid Inhibitor



Source: Daar E, et al. CROI 2020. Abstract 3691.

Dose Response Relationship of SubQ Capsid Inhibitor

Dose-response Relationship Between GS-6207 and Antiviral Activity: E_{max} Model*



Each dot represents mean HIV-1 RNA reduction in each dosed group. CV, coefficient of variation; E_{max}, maximal effect.

Source: Daar E, et al. CROI 2020. Abstract 3691.

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Dose Response Relationship of SubQ Capsid Inhibitor Investigator Conclusions

- Single subQ doses of GS-6207 had potent antiviral activity
- In a blinded safety review, GS-6207 was safe
- Most common AEs were self-limiting, mild to moderate injection-site reactions
- Results support further evaluation of GS-6207 as a long-acting ARV agent with a q6 month dosing interval
- Two clinical trials planned – treatment-naïve & experienced

Source: Daar E, et al. CROI 2020. Abstract 3691.

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Acknowledgment

The Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2,972,660 with 0% financed with non-governmental sources.

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AETC AIDS Education & Training Center Program Mountain West