Antiretrovirals and immune-based approaches: data from clinical trials

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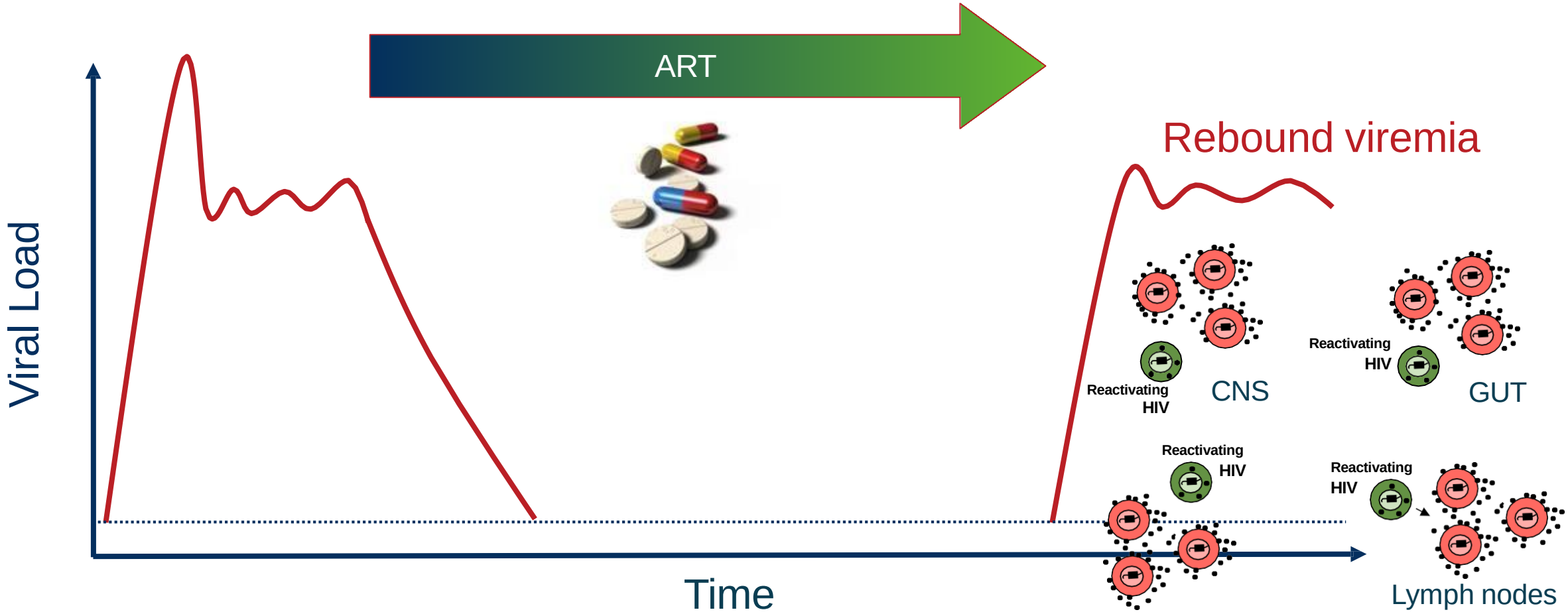
COI

La sottoscritto **NOZZA SILVIA**
in qualità di relatore
ai sensi dell’art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

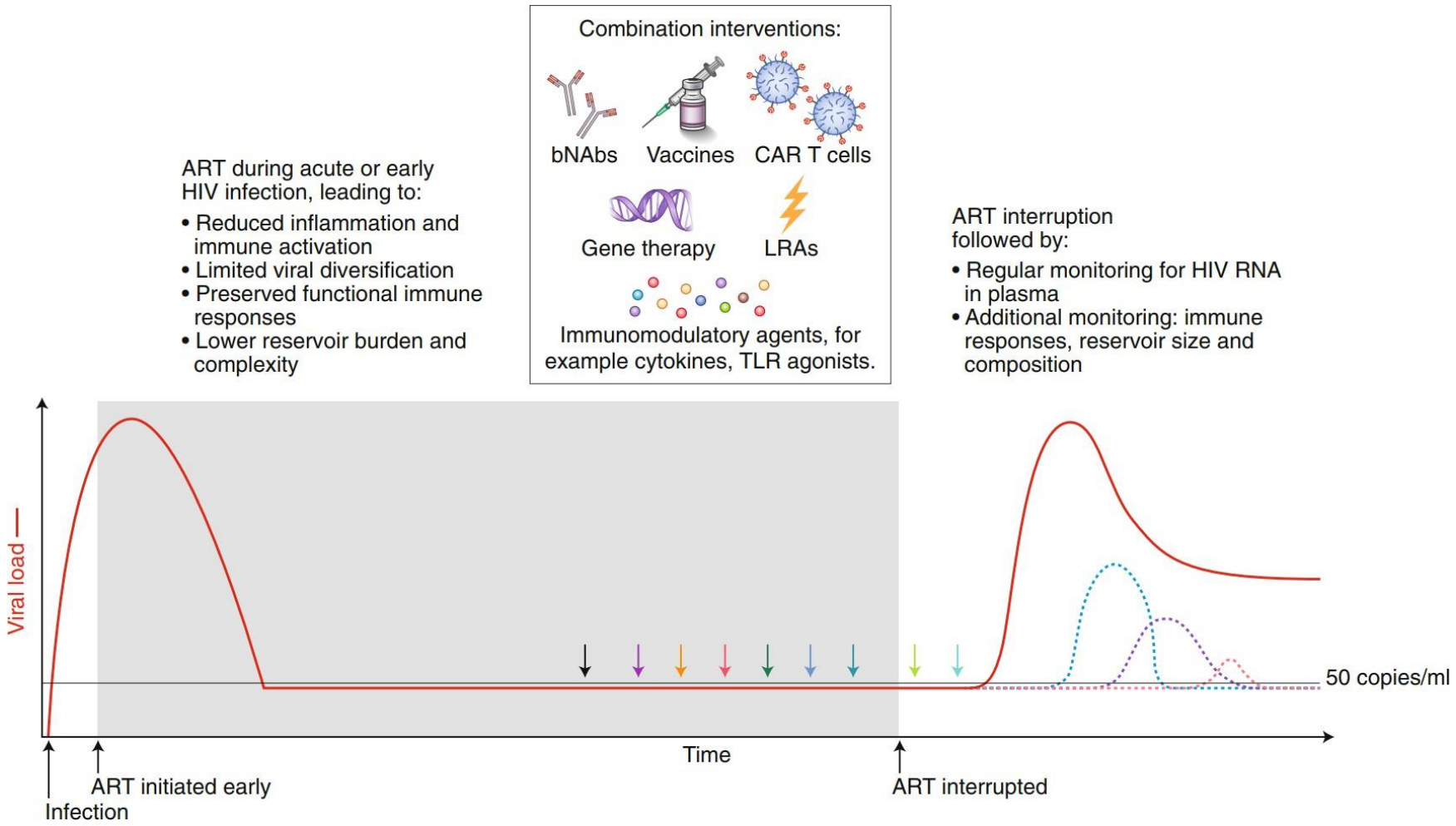
dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

ViiV HEALTHCARE
GILEAD SCIENCES
JANSSEN CILAG
MSD

RATIONALE


ART
Viral Load
Time
Rebound viremia
Reactivating
HIV
CNS
Reactivating
HIV
GUT
Reactivating
HIV
Reactivating
HIV
Lymph nodes

Multiple approaches are being pursued in the clinic



Courtesy of Steven Deeks

ART-Free HIV-1 Remission in Very Early Treated Children: Results From IMPAACT P1115

54 neonates with confirmed in utero HIV-1 received very early ART≠ within 48 hours of life

↓

6 children met eligibility criteria and discontinued ART for analytic treatment interruption **(ATI)**

Year of Enrollment:
2015-2017

Age at ATI:
Median 5.5 years instead of at least 2 years as planned due to delays with COVID-19

ATI is needed as there is no known biomarker predictive of ART-free remission

≠Very early nevirapine-based ART or a three-drug nevirapine (NVP) prophylactic regimen with transition to three-drug NVP-ART regimen within 10 days of birth;
LPV/r added when age-appropriate ([min, max]: ***15-29 days of age***
NVP discontinued 12 weeks after achieving two consecutive HIV-1 RNA <LOD [min, max]:***17-29 weeks of age***

CROI 2024

Lancet HIV 2020, 2023

Pre-ATI Criteria

Plasma viral load <200 c/mL by study week 24

Sustained undetectable plasma HIV-1 RNA from week 48 onwards

- No subsequent HIV-1 RNA detected through time to ATI

Cessation of breastfeeding

- At least six weeks prior to evaluation for ATI

Parent or legal guardian willing and able to provide informed consent

Pre-ATI Biomarker Profile

Normal CD4+ T cell count for age and CD4+ T cell percentage ≥25

Negative HIV-1 antibody status

- Tested on two consecutive samples collected at least 8 weeks apart
- Determined with 4th generation ELISA

No HIV-1 DNA detected in ≥850,000 PBMCs

- Tested on two consecutive samples collected at least 8 weeks apart
- Determined with a CLIA-certified, pan-subtype droplet digital PCR HIV-1 DNA assay

ART-free remission: *no confirmed plasma HIV-1 RNA above the limit of detection (LOD) of the assay for ≥48 weeks off ART*

CROI 2024

Lancet HIV 2020, 2023

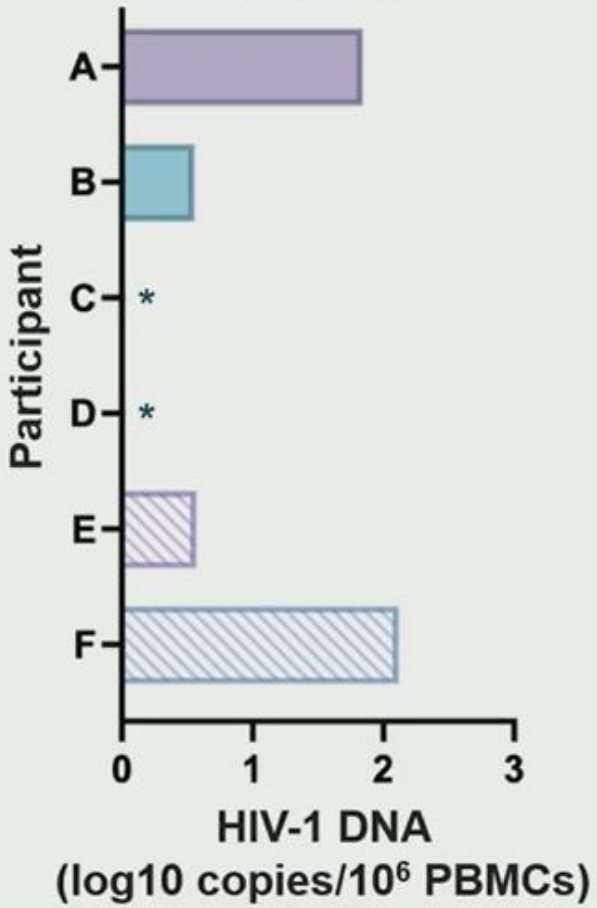
Participant	Country of Birth	Sex at Birth	Age at First Positive HIV Nucleic Acid Test (Hours)	Age at Triple ARV Initiation (Days)	Age at ATI (Years)
A*	Tanzania	F	8	1	5.6
B*	Uganda	F	18.7	2	5.5
C	Uganda	M	8.9	1	5.3
D	Zimbabwe	F	40	2	5.7
E*	Uganda	M	6.3	1	5.4
F	Uganda	F	8.5	1	5.5

**Maternal Receipt Of Antenatal ARV*

Participant A through F sorted by longest to shortest duration of ATI

Hatched bars indicate children who did not achieve ART-free remission

CROI 2024



[min, max]:
[*not detected, 2.11]

Hatched bars indicate children who did not achieve ART-free remission

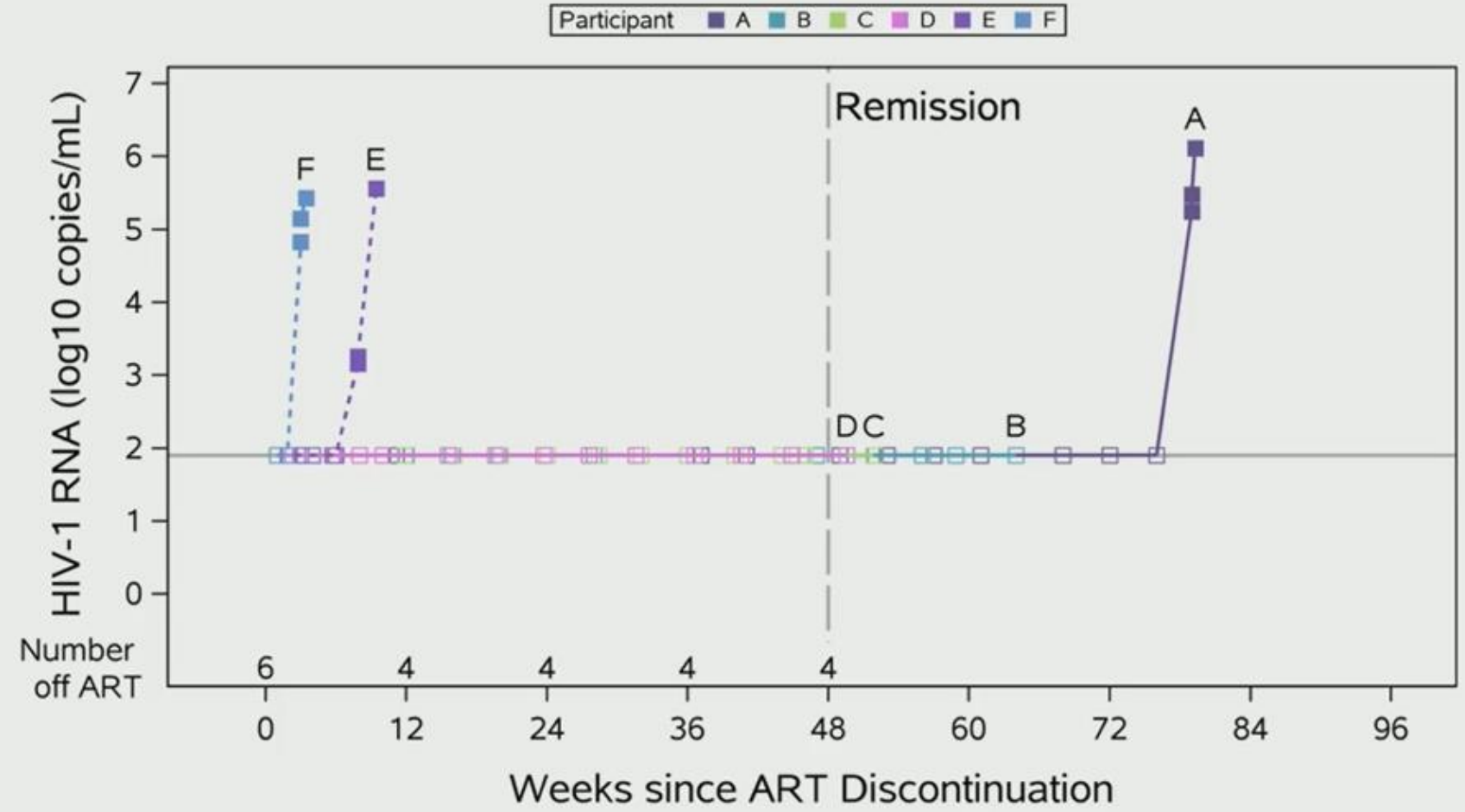
Age at Testing (Days)	Earliest Age HIV-1 DNA Not Detected (Weeks)
6	12.1
9	12.1
8	1.1
2	0.3
9	25.1
8	49.0

No. cells analyzed [min, max]:
[307200, 1068000]

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Study Weeks off ART
(no detectable plasma HIV-1 RNA)

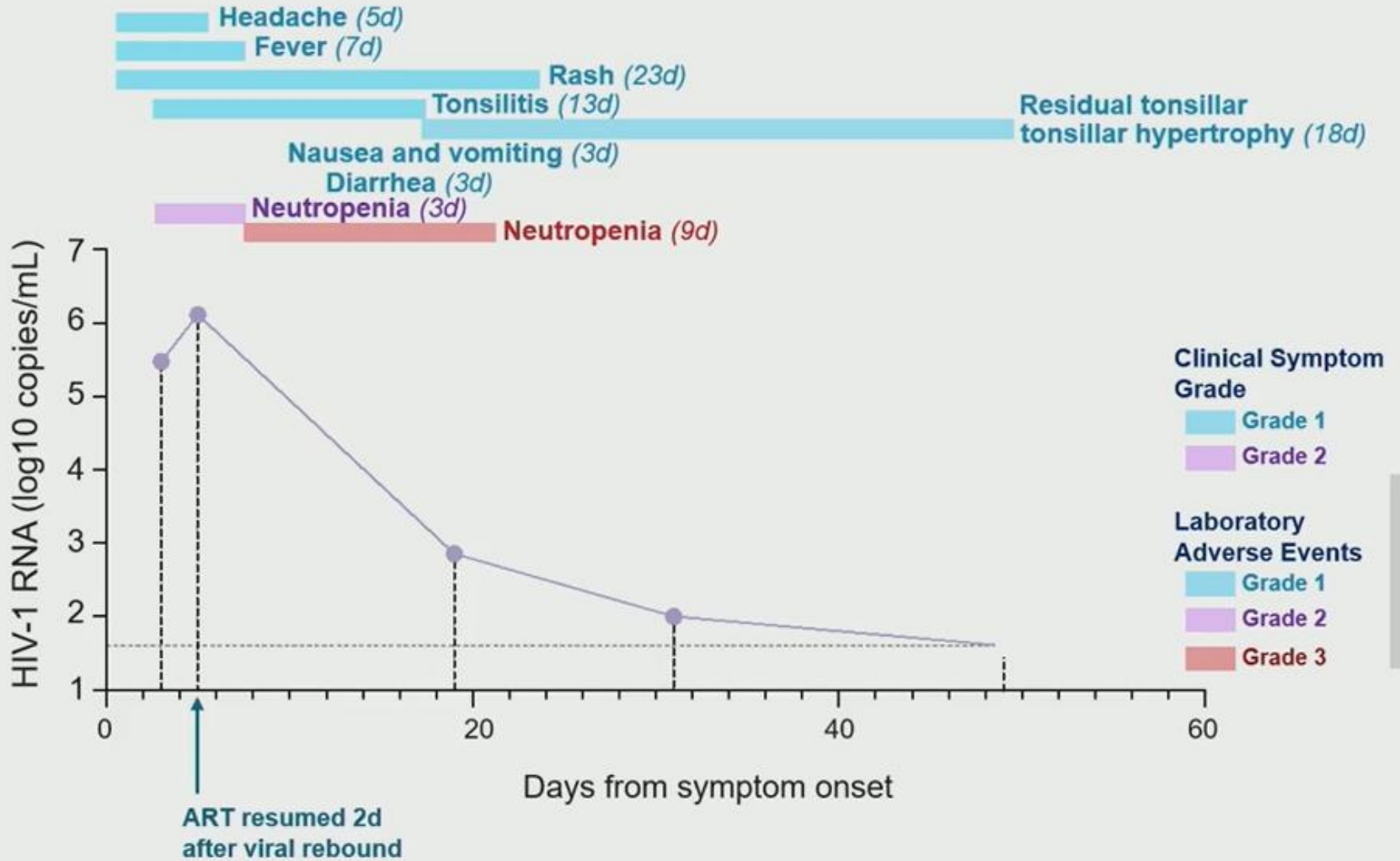
A	80
B	>64
C	>52
D	>48
E	8
F	3



4 of 6 very early treated children with durable virologic suppression achieved ART-free remission with **no viremic rebound for ≥48 weeks** (exact 95% CI 22%-96%)

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Participant A: Acute Retroviral Syndrome after 80 weeks of ART-free Remission



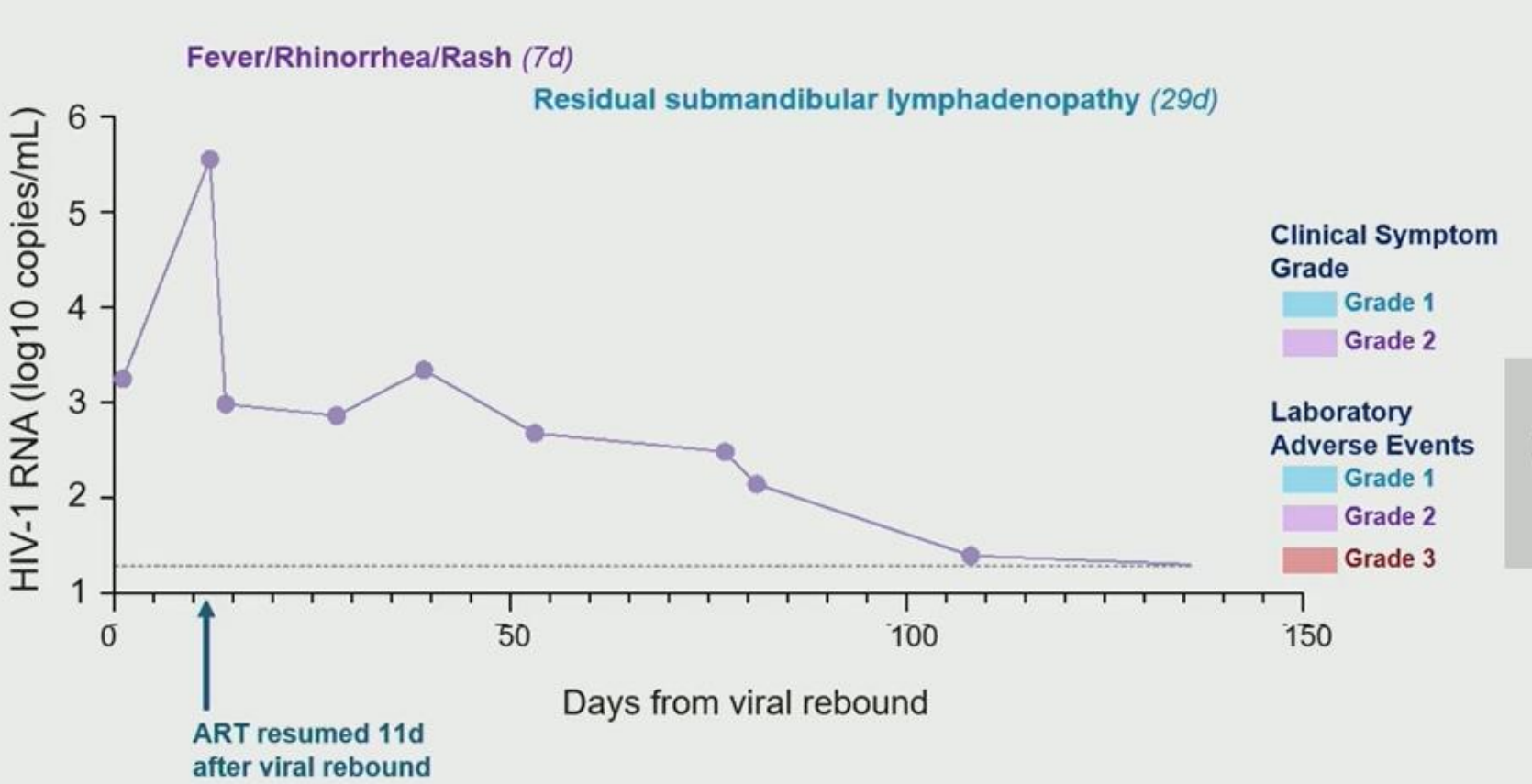
Grade 1 clinical signs and symptoms

Grade 3 neutropenia (transient)

Re-suppression to plasma viral load below the LOD (<40 c/mL) by 6.7 weeks

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Participant E: Acute Retroviral Syndrome after 8 Weeks of ART Discontinuation

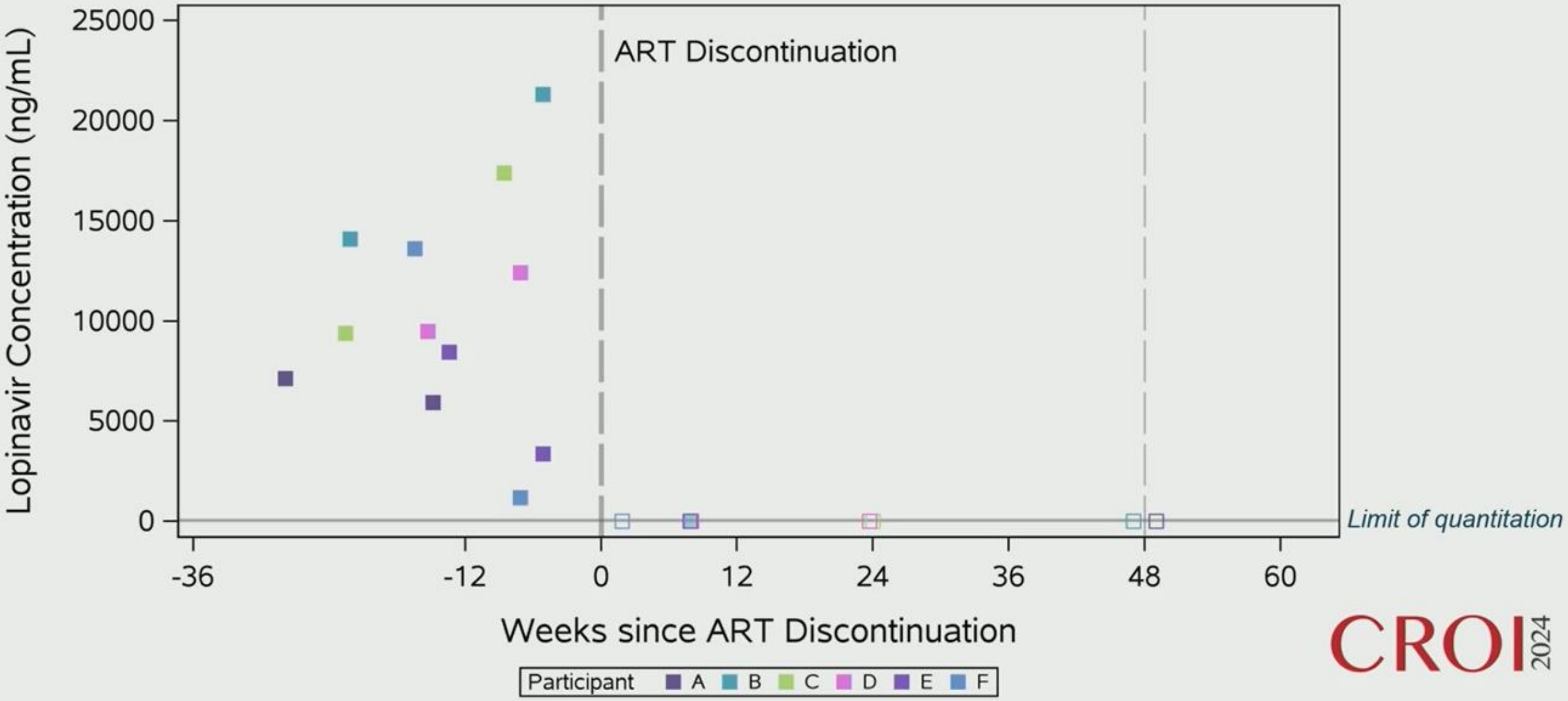


Grade 1 & 2 clinical signs and symptoms

Re-suppression to plasma viral load below the LOD (<20 c/mL) by 20 weeks

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Lack of Quantifiable Lopinavir Confirms ART Discontinuation



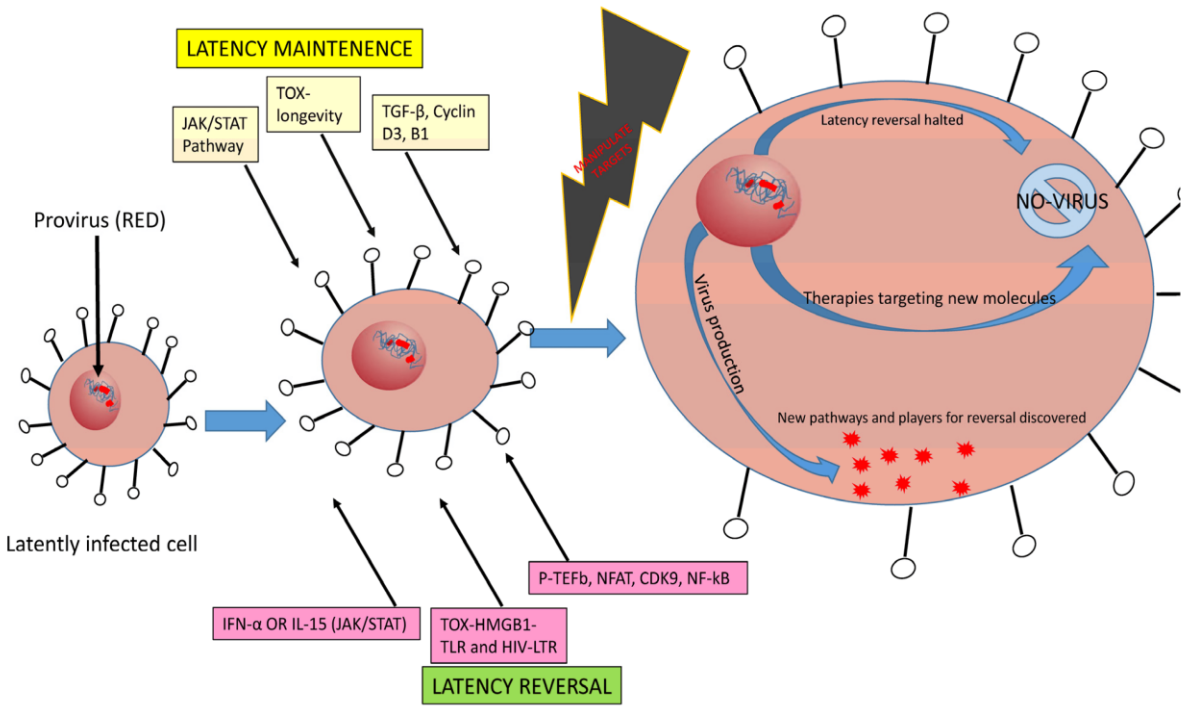
CROI 2024

Conclusions

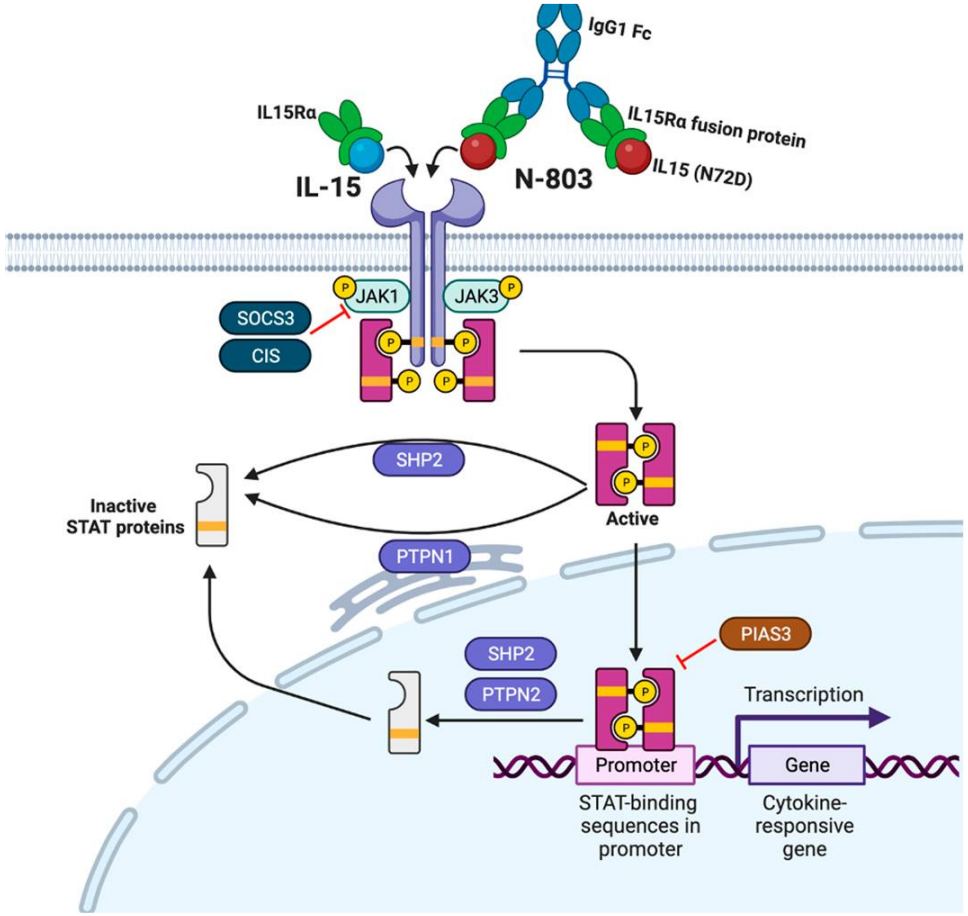
- This study provides **proof-of-concept** that very early ART in neonates with in utero HIV-1 significantly curtailed viral reservoirs and enabled ART-free remission.
  - The proposed eligibility criteria and biomarker profiling was not fully predictive of ART-free remission, as evidenced by rebound in two of six children who underwent ATI.
  - The occurrence of acute retroviral syndrome with rebound viremia warrants careful clinical oversight during ATI.

Immunomodulatory agents

HIV Latency Reversal Agents



Interleukins



VACCINATION

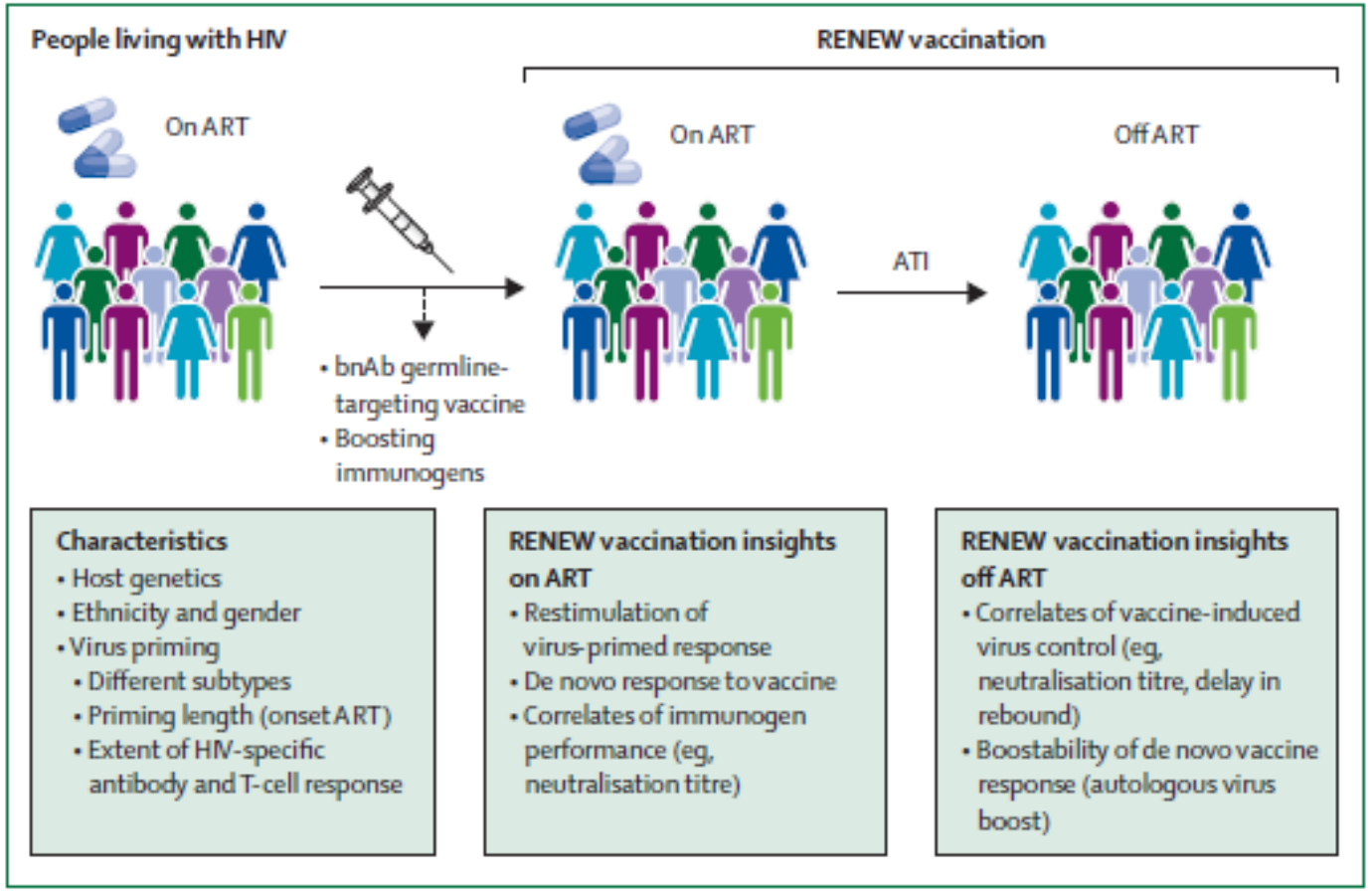


Figure: **RENEW vaccination approach**
Involving people living with HIV in HIV vaccine evaluation provides a wide range of possibilities to simultaneously assess restimulated and de novo responses to immunogens. We refer to this approach as RENEW vaccination. ATI=analytic treatment interruption. bnAbs=broadly neutralising antibodies. RENEW vaccination=restimulating and new priming of antibody responses through vaccination. ART=antiretroviral therapy.

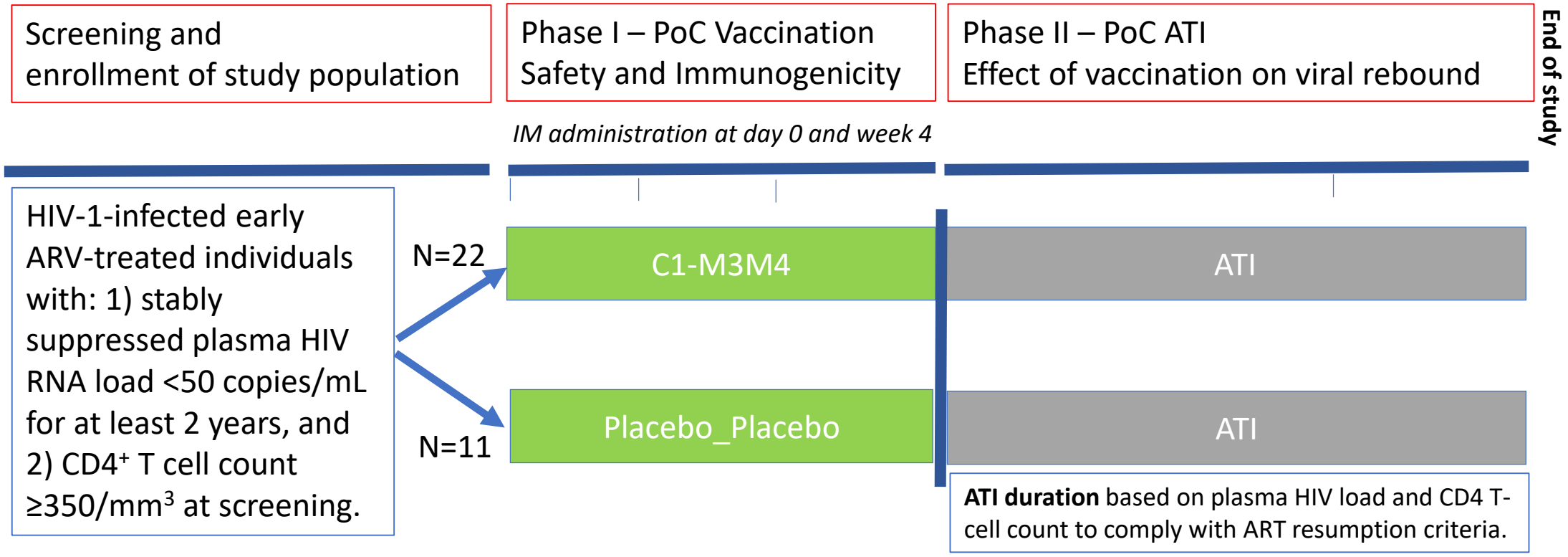
We argue that RENEW trials in people living with HIV would most usefully advance vaccine development if conducted in parallel with, rather than after, ongoing trials of candidate immunogens in unprimed non-human primates and classic phase 1 and 2 and emerging experimental medicine vaccine trials in HIV-naive populations.[37] A vaccine failing to trigger responses in well primed people living with HIV would bring into question the utility of testing such an immunogen in large phase 3 trials with HIV-naive participants

Trkola A, Moore PL, *Lancet ID 2024*

Therapeutic vaccines: HIV-CORE 007 _ Study Scheme

Phase I : Randomized, placebo-controlled, single-blind vaccination study with ChAdOx1.HIVconsv1 - MVA.HIVconsv3 and 4.
Phase II : Open-label study with an ARV treatment interruption (ATI).

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EAVI2020

Courtesy of Elena Bruzzesi

Ministero della Salute

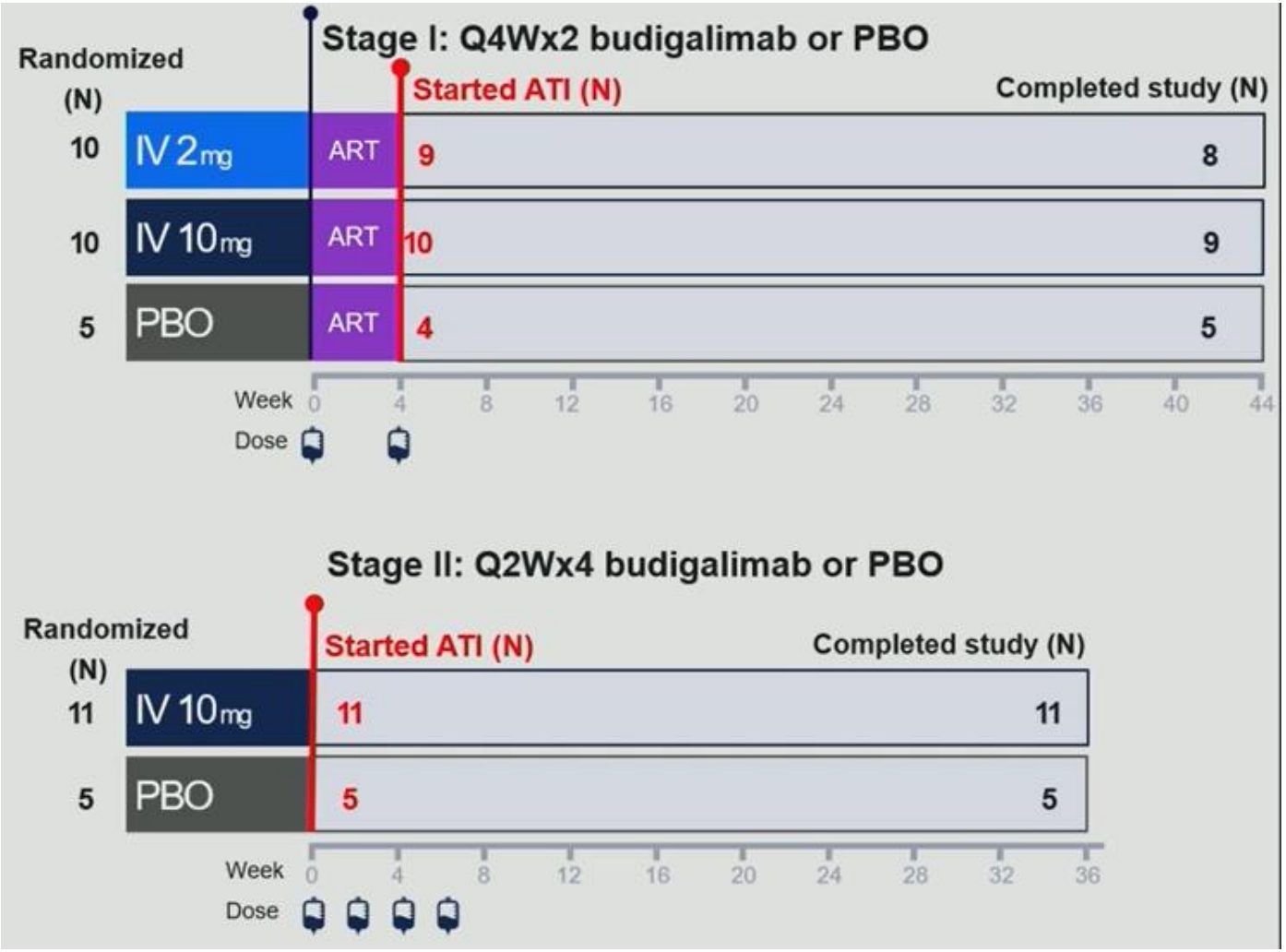
Phase Ib Study With Budigalimab in PLWH

- Chronic HIV-1 disease results in immune exhaustion and dampens T-cell responses through upregulation of inhibitory co-receptors or "immune checkpoints," such as PD-1[1]
- PD-1 inhibitors are approved as cancer immunotherapies, and in HIV-1 infection, offer a potential approach to enable durable viral control without ART through reversal of T-cell exhaustion and restoration of T-cell functionality[2-4]
- Budigalimab is an investigational humanized, recombinant IgG1 L234A L235A mAb
  - Phase 1 trials in solid tumors show multi-round 250 mg IV Q2W or 500 mg IV Q4W dosing has similar efficacy and safety profile for patients with cancer as that of approved PD-1 inhibitors[5,6]
- Study M19-939 (NCT04223804) is a phase 1b randomized double-blind study to investigate a shorter course of low-dose budigalimab in PLWH undergoing analytical treatment interruption (ATI)

Objective: Identify potential efficacious dose and regimen of budigalimab with a favorable safety in PLWH

Outcomes: Safety, pharmacokinetics, PD-1 receptor saturation, biomarkers, viral kinetics

Study design and baseline characteristics



Baseline Characteristics	Stage I: Q4W×2			Stage II: Q2W×4	
	Placebo N=5	2 mg IV N=10	10 mg IV N=10	Placebo N=5	10 mg IV N=11
Male	5 (100)	10 (100)	10 (100)	5 (100)	10 (91)
Age, y	44 (14)	42 (13)	47 (14)	49 (11)	47 (14)
HIV-1 disease, y	11 (13)	9 (8)	13 (9)	19 (6)	11 (7)
CD4+ cell count, cells/μL	652 (143)	887 (263)	785 (175)	680 (160)	775 (203)
Viral suppression on ART, y	10 (12)	7 (5)	13 (9)	16 (5)	11 (6)
%CD8+ PD-1+ cells	**45 (14)**	**39 (16)**	**42 (15)**	**42 (23)**	**41 (7)**

Data are expressed as number (%) or mean [SD]

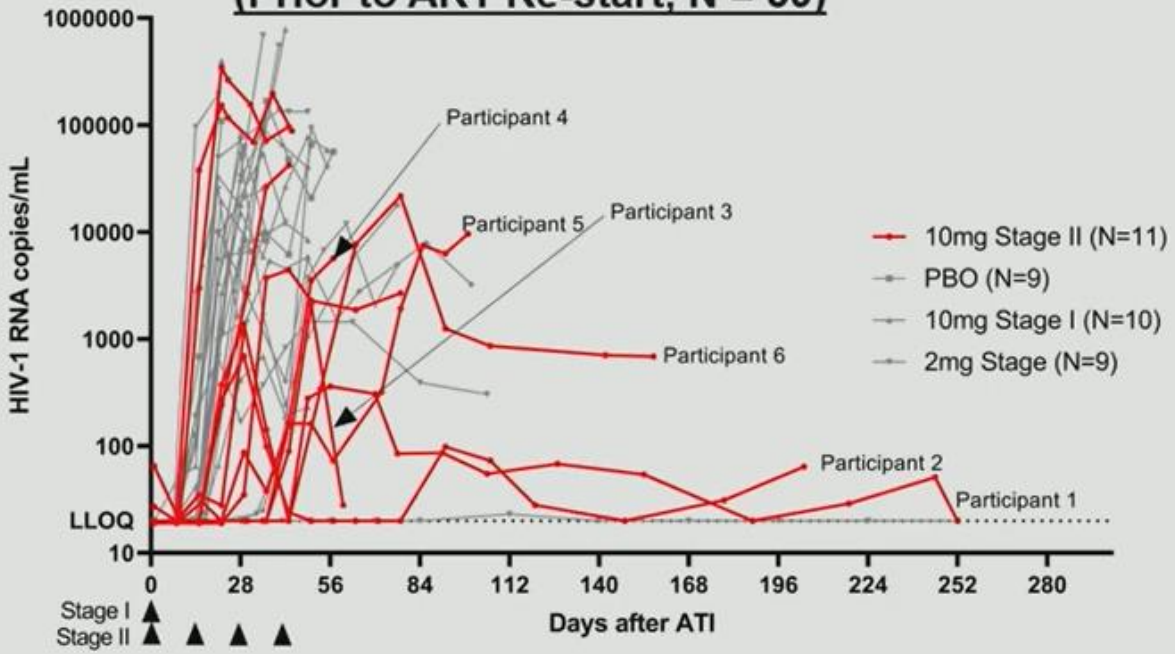
Safety[1]:

- No Grade ≥3 or serious AEs related to study drug reported
- 2 Grade 1 immune-related AE reported, both reversible

Target engagement (peripheral blood)[1]:

- 2 mg IV: duration of >95% PD-1 receptor saturation (RS) < 15d
- 10 mg IV: duration of >95% PD-1 RS was 30d, with total period of > 95 % RS around 70d with 10 mg Q2Wx4 doses

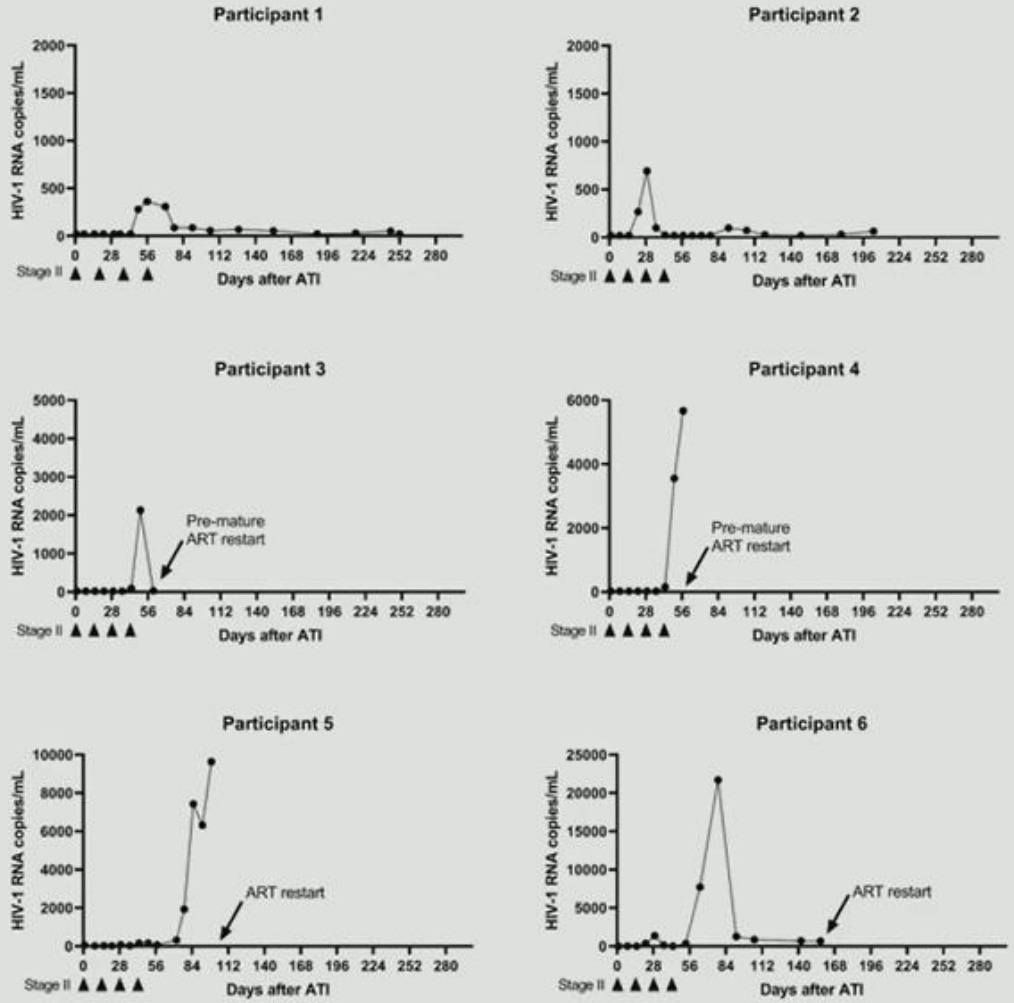
Viral Load in All Participants Undergoing ATI (Prior to ART Re-start, N = 39)



ATI, analytical treatment interruption; LLOQ, 20 copies/mL; Q2W, every 2 weeks

	HLA-A	HLA-B
Participant 1	02:01:01:01, 31:01:02:01	14:01:01:01, 35:01:01:42
Participant 2	25:01:01:01, 30:02:01:01	40:02:01:08, 57:01:01:01
Participant 3	01:01:01:01, 02:01:01:01	35:17:01, 52:01:01:02
Participant 4	03:01:01:01, 24:02:01:01	18:01:01:45, 53:01:01:01
Participant 5	03:01:01:01, 24:02:01:01	07:02:01:01, 18:01:01:45
Participant 6	02:01:01:01, 32:01:01:01	39:01:01, 40:01:02

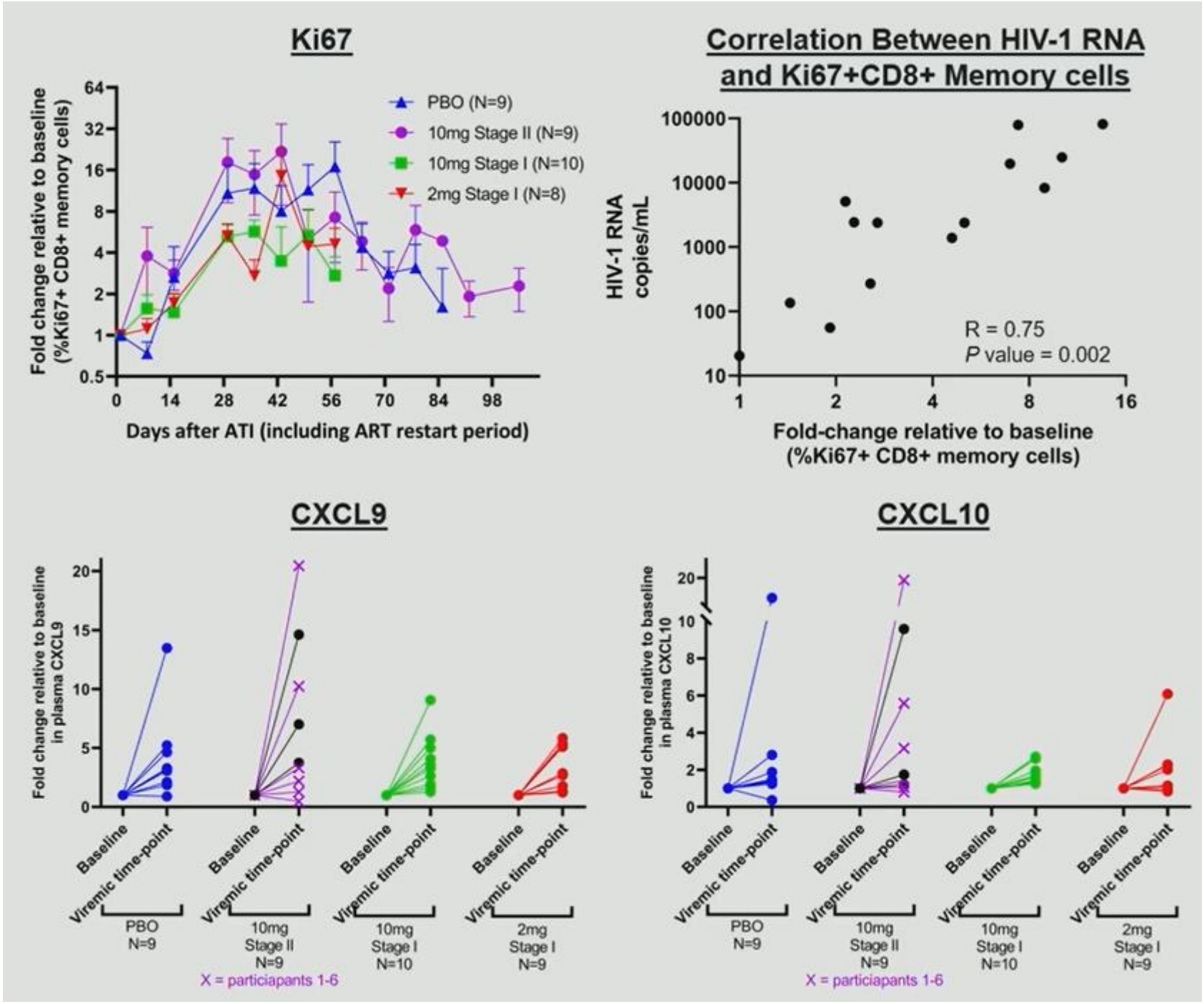
10 mg Q2W×4 Budigalimab: Participants With Delayed Viral Rebound and/or Off-ART Viral Control[a] (N = 6 of 9[b])



[a]Defined as experiencing delayed viral rebound (>21 days) and/or off-ART viral control (<1000 cp/mL)

[b]2 of 11 participants in 10mg Stage II did not complete dosing

CRC


Ki67
Fold change relative to baseline (%Ki67+ CD8+ memory cells)
64
32
16
8
4
2
1
0.5
0
14
28
42
56
70
84
98
Days after ATI (including ART restart period)
PBO (N=9)
10mg Stage II (N=9)
10mg Stage I (N=10)
2mg Stage I (N=8)
Correlation Between HIV-1 RNA and Ki67+CD8+ Memory cells
HIV-1 RNA copies/mL
100000
10000
1000
100
10
1
2
4
8
16
R = 0.75
P value = 0.002
Fold-change relative to baseline (%Ki67+ CD8+ memory cells)
CXCL9
Fold change relative to baseline in plasma CXCL9
20
15
10
5
0
Baseline
Viremic time-point
PBO N=9
10mg Stage II N=9
10mg Stage I N=10
2mg Stage I N=9
X = particiapants 1-6
CXCL10
Fold change relative to baseline in plasma CXCL10
20
10
8
6
4
2
0
Baseline
Viremic time-point
PBO N=9
10mg Stage II N=9
10mg Stage I N=10
2mg Stage I N=9
X = particiapants 1-6

Safety and PD

- Budigalimab administered for short duration at low doses was well tolerated in PLWH. Target engagement was observed at all doses with near-complete PD-1 receptor saturation for ~10 weeks post-ATI with four 10 mg biweekly IV doses

Exploratory Efficacy

- Biweekly administration of budigalimab 10 mg IV for 4 doses led to delayed viral rebound and/or ART-free viral control in 6 of 9 participants who completed dosing, with 2 participants remaining off ART until the end of the study

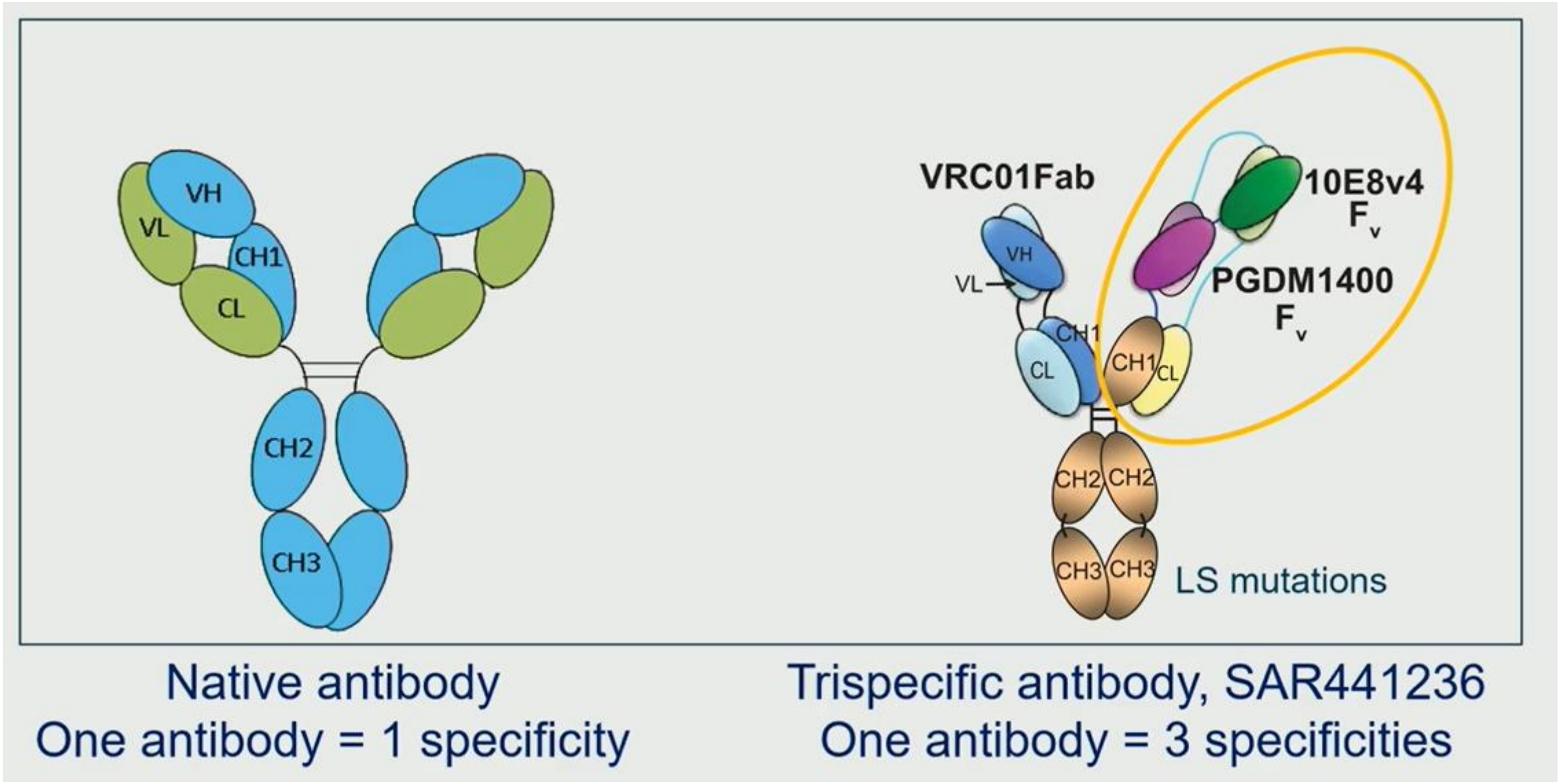
Exploratory Biomarkers

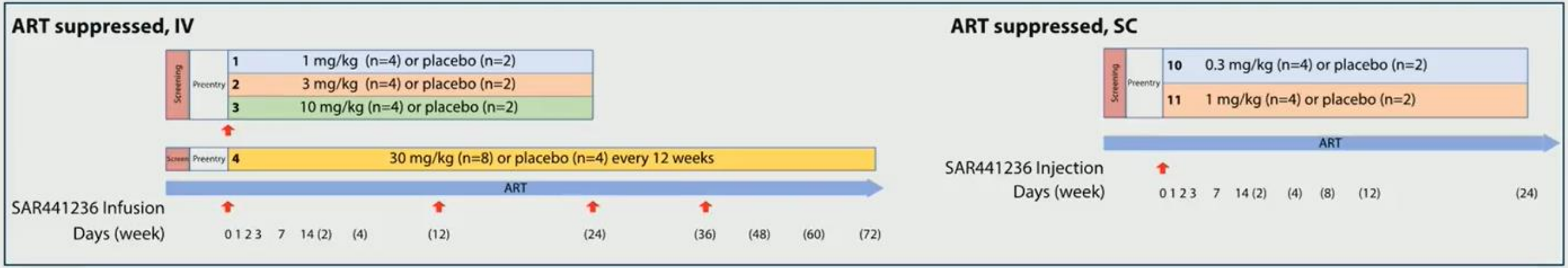
- Trends in budigalimab-dependent increase in T follicular helper-like cells, CD8+CXCR5+ cells and CD4+CCR6+ cells were observed in participants with low viral load
- Viremia during ATI was associated with increased CD8+ T cell activation, proliferation, differential transcriptomic trajectories, and TCR clonality/diversity

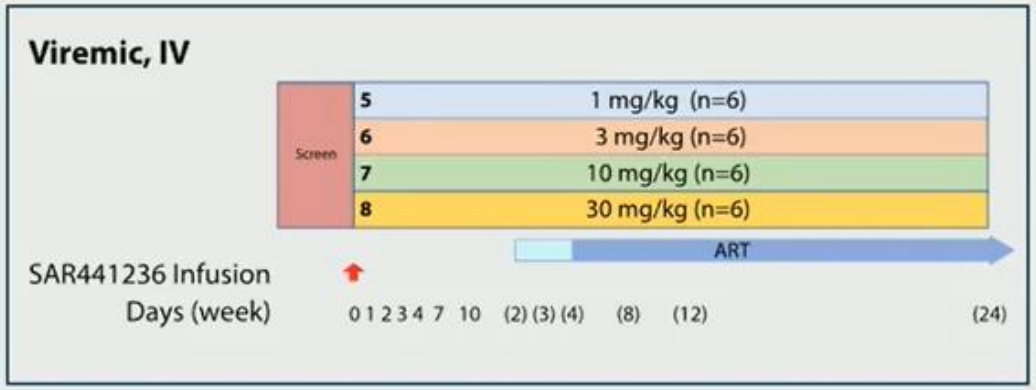
Next Steps

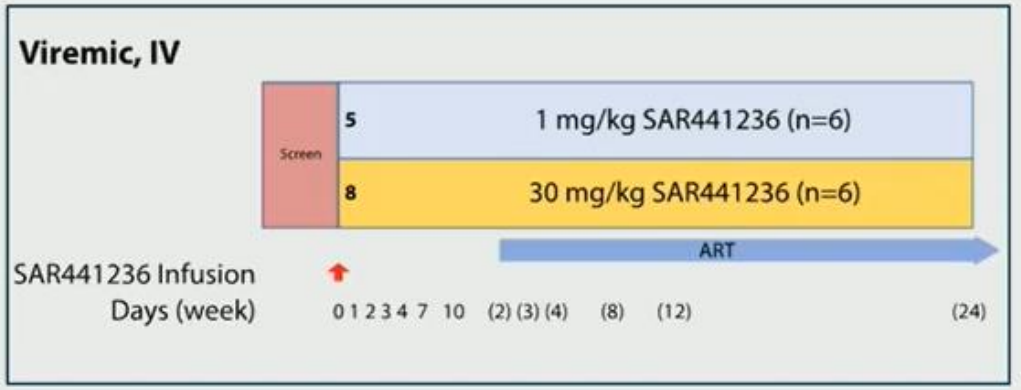
- Phase 2 study (NCT06032546) examining ART-free viral control with budigalimab and ABBV-382 is ongoing (Poster #411)

A First-in-Human Study of the Trispecific HIV-1 Broadly Neutralizing Antibody









ART suppressed, IV/SC dosing

- Age 18-70
- On ART > 12 months
- CD4 >200
- pVL < 50 c/mL for >1 year; one blip <200 allowed

Viremic, IV dosing

- Age 18-70
- Treatment naïve –or– no ART in preceding 8 weeks
- pVL > 5,000 and ≤ 200,000 c/mL; CD4 > 350
- No active opportunistic infections

Baseline characteristics

Characteristic	ART suppressed IV	Viremic IV	ART suppressed SC	Total
Participants, N	32	7	12	51
Age				
Median years (IQR)	54 (46, 58)	26 (24, 30)	53 (49, 59)	48 (37, 57)
Sex				
Female N (%)	4	0	1	5
Male N (%)	28 (88%)	7 (100%)	11 (92%)	46 (90%)
Race/Ethnicity				
Black N (%)	12 (38%)	3 (43%)	4 (33%)	19 (37%)
White N (%)	16 (50%)	3 (43%)	5 (42%)	24 (47%)
Hispanic/Latino N (%)	3 (9%)	1 (14%)	2 (17%)	6 (12%)
Other	1 (3%)	0	1 (8%)	2 (4%)
Baseline CD4				
Median (IQR)	743 (518, 855)	458 (364, 782)	849 (564, 1063)	

Treatment-induced ADA

		N	Treatment-induced ADA*	Specificity	Titer Median (min, max)
On ART IV	1 mg/kg	4	0		
	3 mg/kg	4	1	CODV+Fv3+Fc-	22.5 (5, 40)
	10 mg/kg	4	1 (transient)	week 2/4: CODV+Fv3-Fc- Week 12: CODV+Fv3+Fc-	5 (5, 5)
	30 mg/kg (4 doses)	9	2 (1 transient)	CODV+Fv3+Fc- CODV+Fv3-Fc-	12.5 (5, 20)
On ART SC	0.3 mg/kg	4	0		
	1 mg/kg	4	2	CODV-Fv3-Fc- CODV+Fv3+Fc-	7.5 (5, 40)
Viremic IV	1 mg/kg	5	4	CODV+Fv3+Fc- CODV+Fv3-Fc-	7.5 (5, 640)
	30 mg/kg	2	1 (transient)	CODV-Fv3-Fc-	5 (5, 5)

Conclusions

- SAR441236 administration was safe and well tolerated. Serious injection site reactions were not observed.
- The PK of SAR441236 was similar to monospecific HIV-1 LS bnAbs
- Treatment-induced ADA in aviremic participants were uncommon, transient, low-titer, and did not affect PK
- Antiviral activity of SAR441236 was modest; levels of intact provirus did not change over 72 weeks of follow-up. Additional analyses are pending.
- These findings, coupled with the convenience of administering a single biologic, support the evaluation of novel tri- or multi-specific bnAbs for HIV-1 treatment or prevention

Key questions to mitigate potential harms related to HIV cure-related research with analytical treatment interruptions



Dubé K et al. Lancet HIV. 2024 March ; 11(3): e137–e139

Thank you

Tutte le persone che partecipano ai trials clinici

