Safety and anti-HIV activity of autologous T cells transduced with a lentiviral vector encoding bi-specific anti-gp120 CAR molecules (LVgp120duoCAR-T) in people living with HIV

California Institute of Regenerative Medicine

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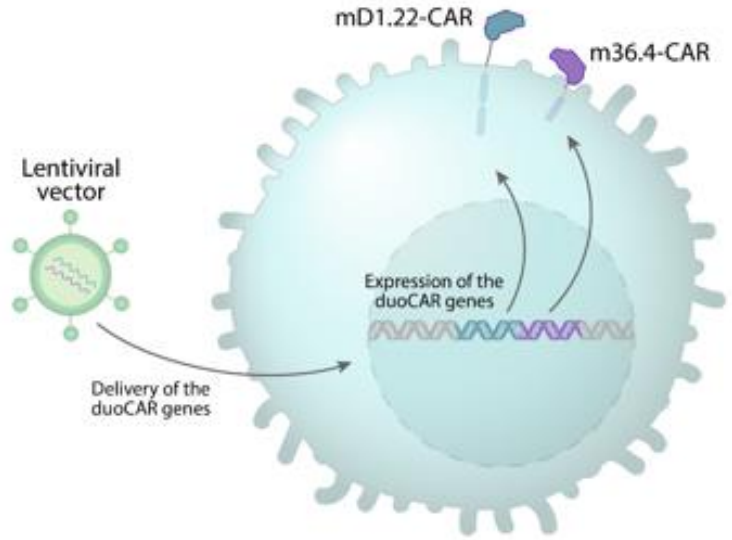

CaringCross

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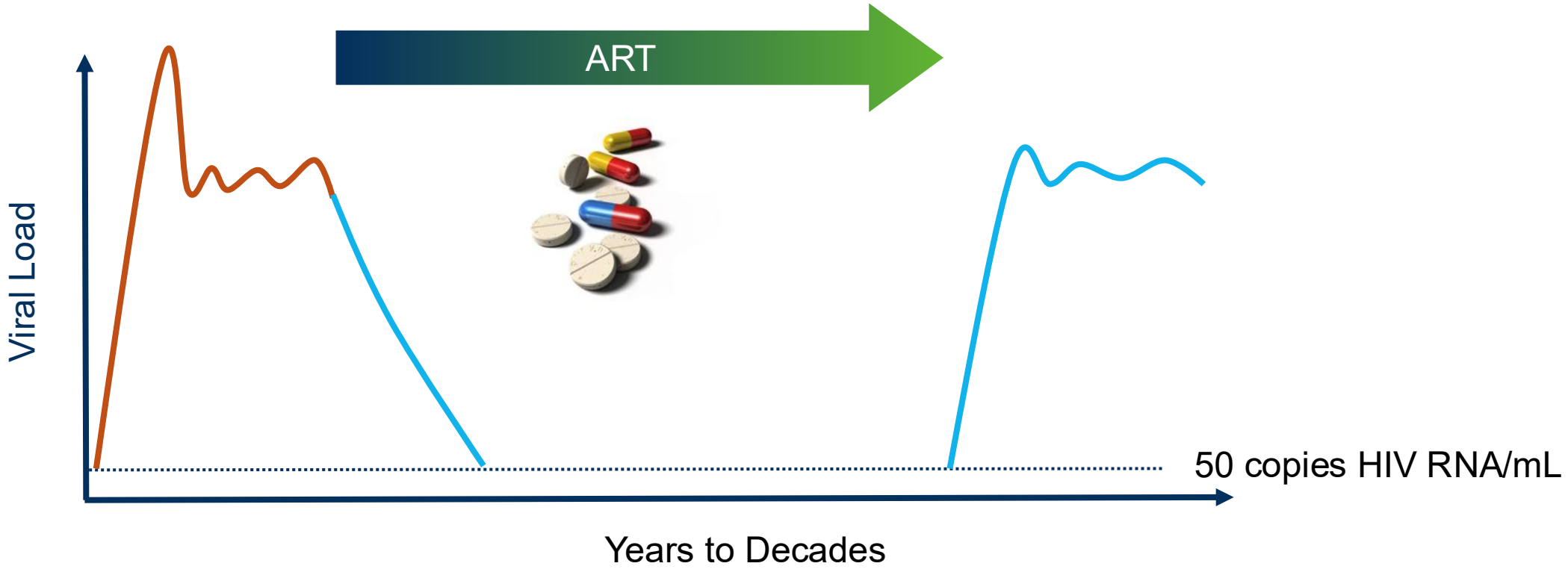
Antiretroviral therapy (ART) prevents active HIV replication but is not curative

Treatment must be given for life, which is challenging for many



Why do we need a cure in an era of effective antiretroviral therapy?

- Individual challenges
  - Adherence challenges
  - Stigma/discrimination of taking daily treatment
  - Long-term health: Obesity, polypharmacy
  - Multi-drug resistance
- Public health challenges
  - ART is lifelong and expensive: Total spent on HIV/AIDS: ~ $50 billion/year
  - Social disruptions affect access (COVID, PEPFAR)
  - Despite massive investments, many (~30%) not on effective ART

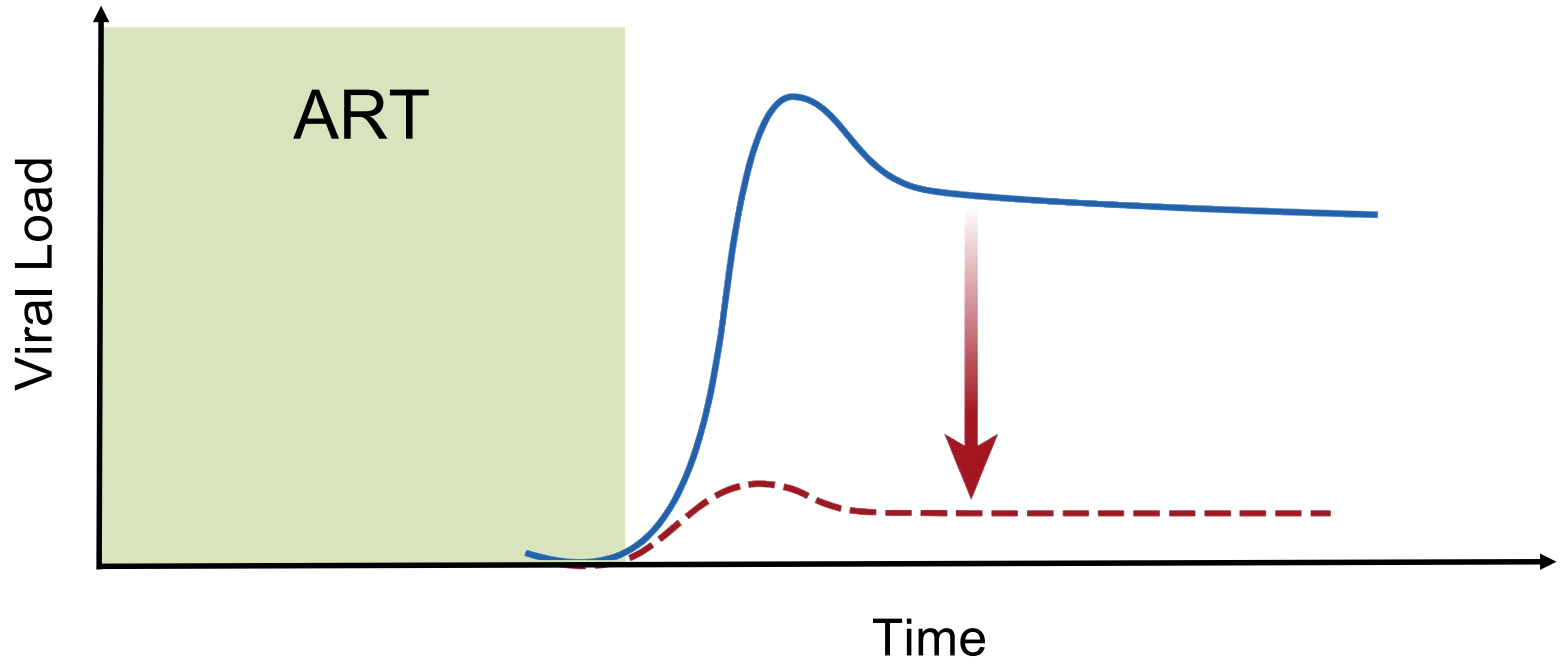
U.S. Plans to End AIDS Funding for South Africa

According to an unsigned statement from the State Department, the U.S. will phase out support for H.I.V. prevention and treatment in South Africa.

June 19, 2026

Immunotherapy: Enhance the capacity of the immune system to control HIV

Post-interventional control, similar to "elite" control



HIV control is consistently associated with CD8+ T cells that target conserved epitopes and have strong proliferative capacity ("stemness")

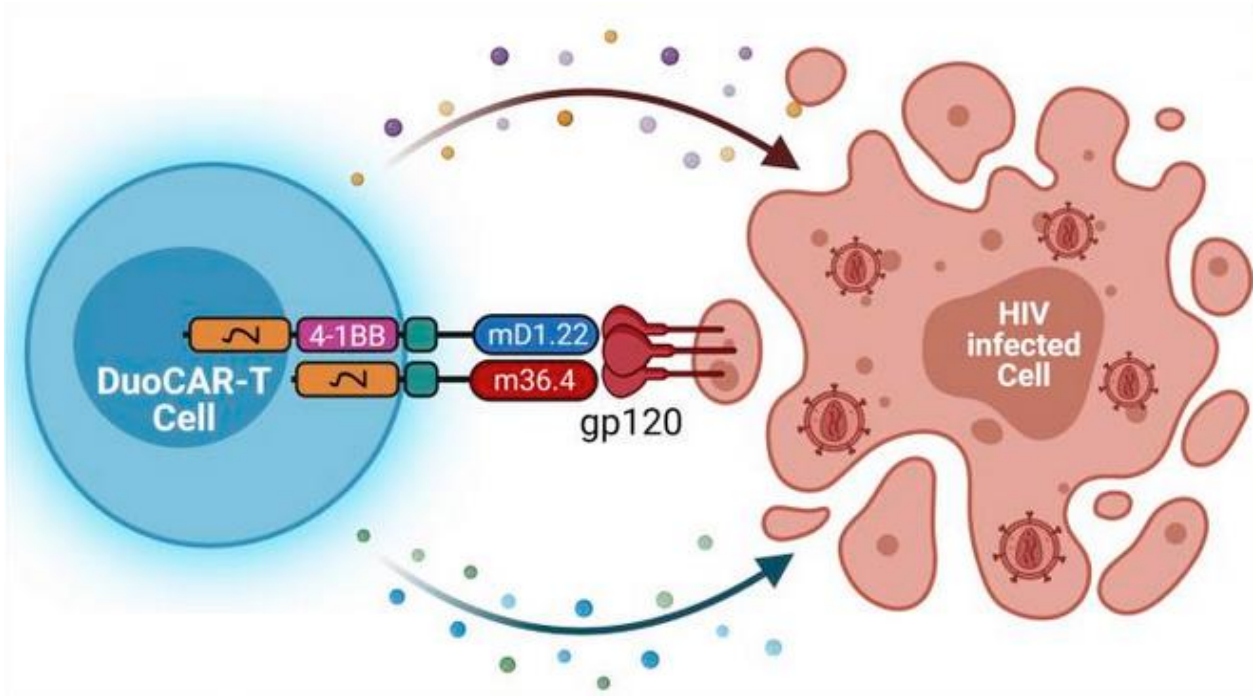
LVgp120duoCAR targets two conserved areas of the HIV Env protein

CARs bind HIV at entry and prevent infection of target cells

JCI insight

In vivo killing of primary HIV-infected cells by peripheral-injected early memory–enriched anti-HIV duoCAR T cells

Kim Anthony-Gonda,[1,2] Alex Ray,[3] Hang Su,[3] Yuge Wang,[2] Ying Xiong,[1,2] Danica Lee,[3] Ariele Block,[3] Vanessa Chilunda,[4] Jessica Weiselberg,[4] Lily Zemelko,[5] Yen Y. Wang,[5] Sarah Kleinsorge-Block,[6] Jane S. Reese,[6] Marcos de Lima,[6] Christina Ochsenbauer,[7] John C. Kappes,[7,8] Dimiter S. Dimitrov,[9] Rimas Orentas,[1,10] Steven G. Deeks,[5] Rachel L. Rutishauser,[5] Joan W. Berman,[3,4] Harris Goldstein,[3,11] and Boro Dropulić[1,2]



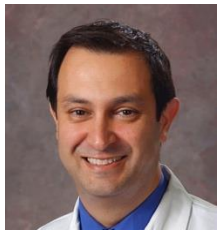
mD1.22 - engineered monomeric extracellular CD4 domain

m36.4 – derived from a neutralizing antibody targeting the co-receptor binding site

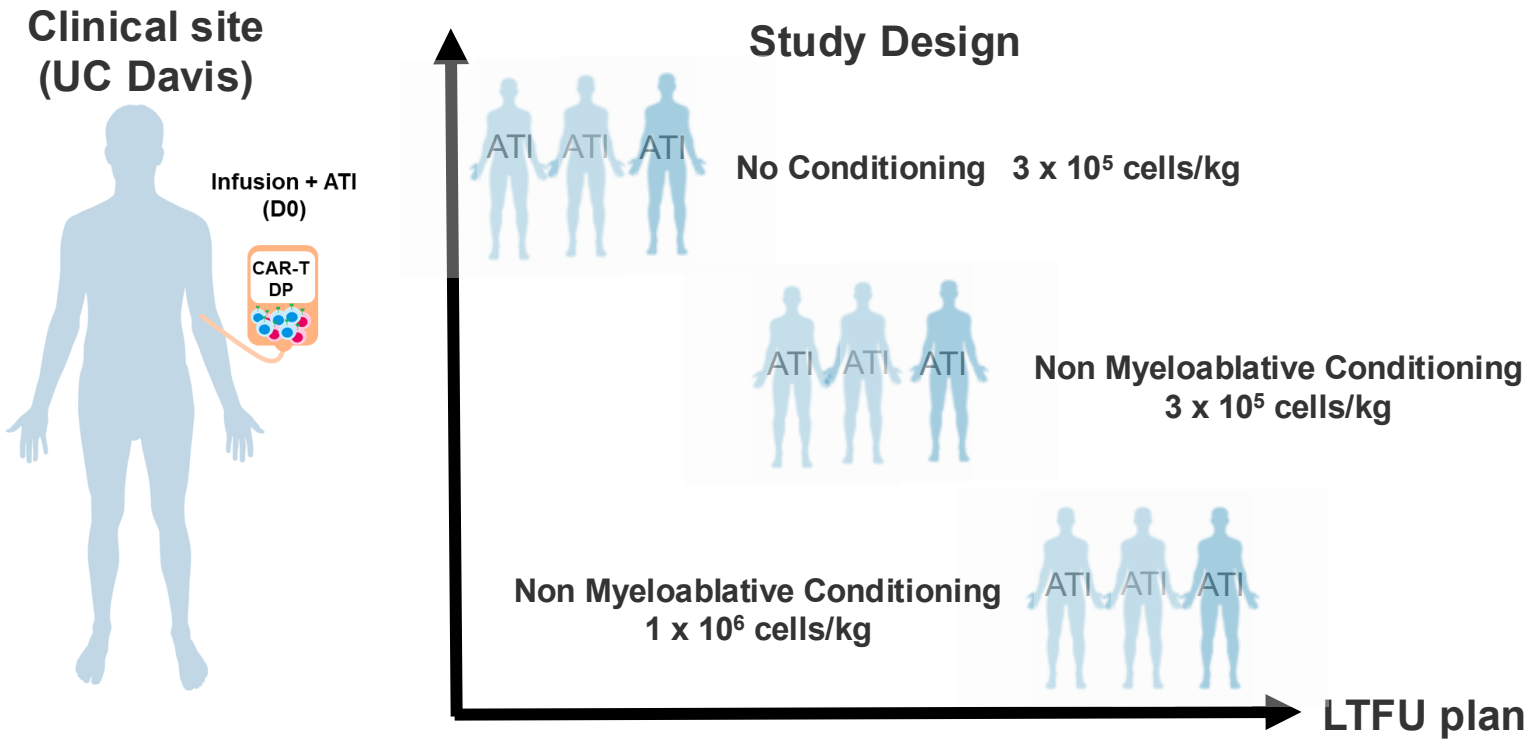
- LVgp120duoCAR cleared infected cells in a mouse model (Anthony-Gonda STM)
- Clinical pre-infusion duoCAR T cells enriched for CCR7+ stem cell–like/central memory T cells with expression of effector-like molecules

First-in-human, dose-escalation study (3+3 design)

ART interrupted at the same time as the CAR-T cells are infused



Mehrdad Abedi
Clinical PI

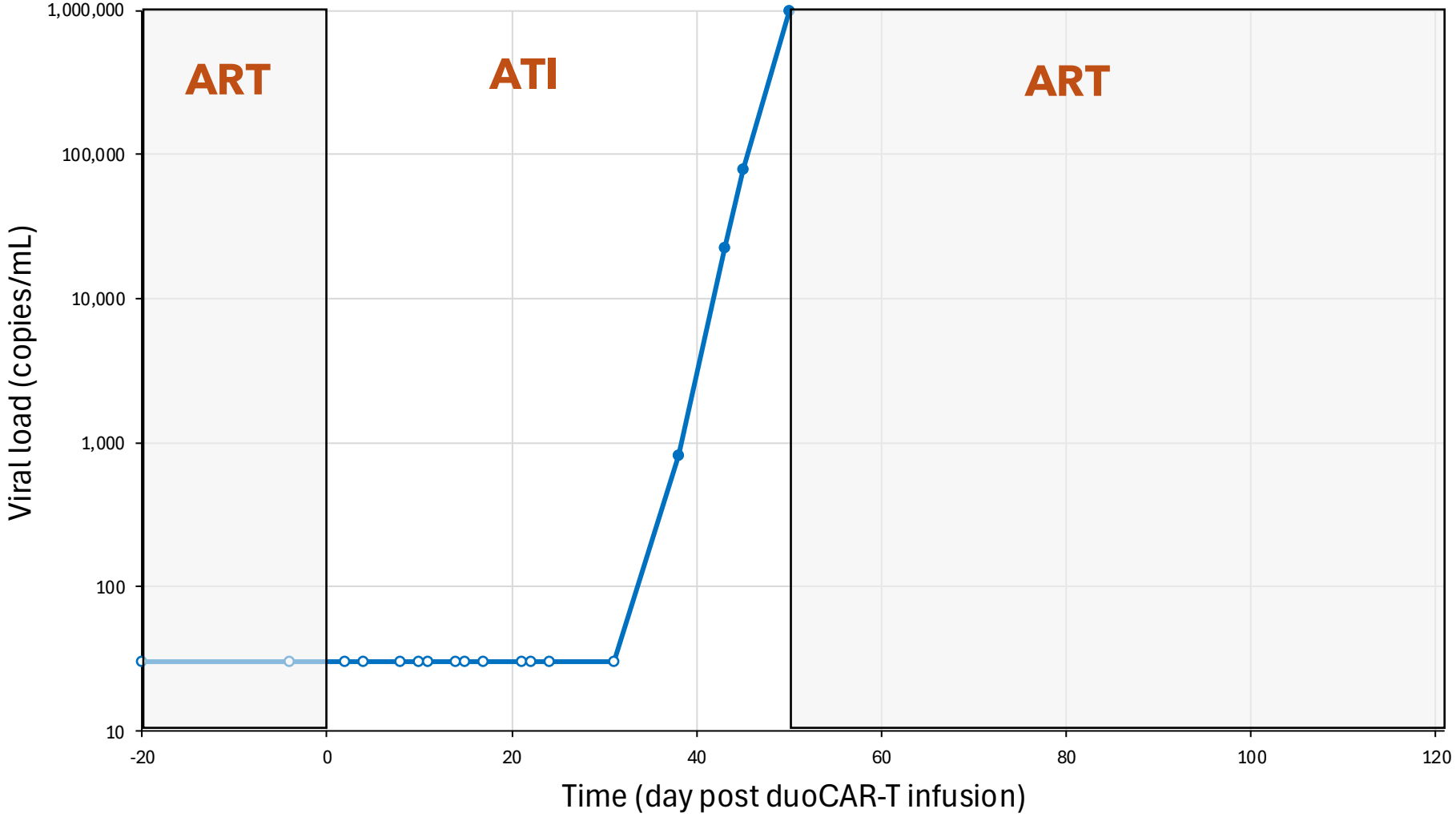


- 9 participants enrolled
- 2 in cohort 1 re-enrolled in later cohorts (11 total infusions)
- 9 interrupted ART and are the focus of the efficacy outcomes
- 2 remained on ART

Conditioning regimen: cyclophosphamide (1 gm/m^2)

NCT04648046

Typical post-treatment rebound dynamics



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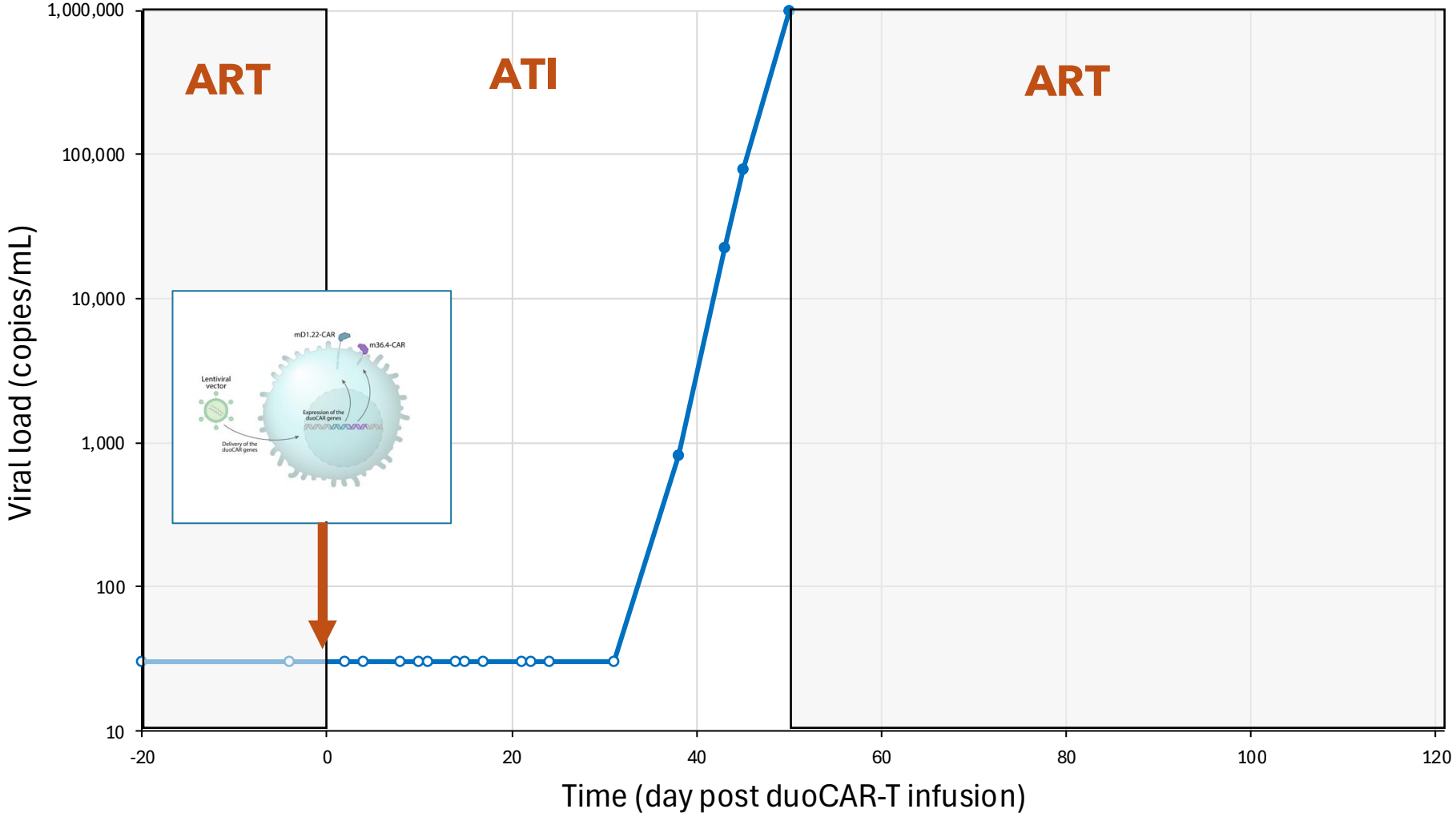
Study Design: CAR-T cells infused on the day ART is interrupted

Conditioning regimen given Day -3 (cohorts 2 and 3)



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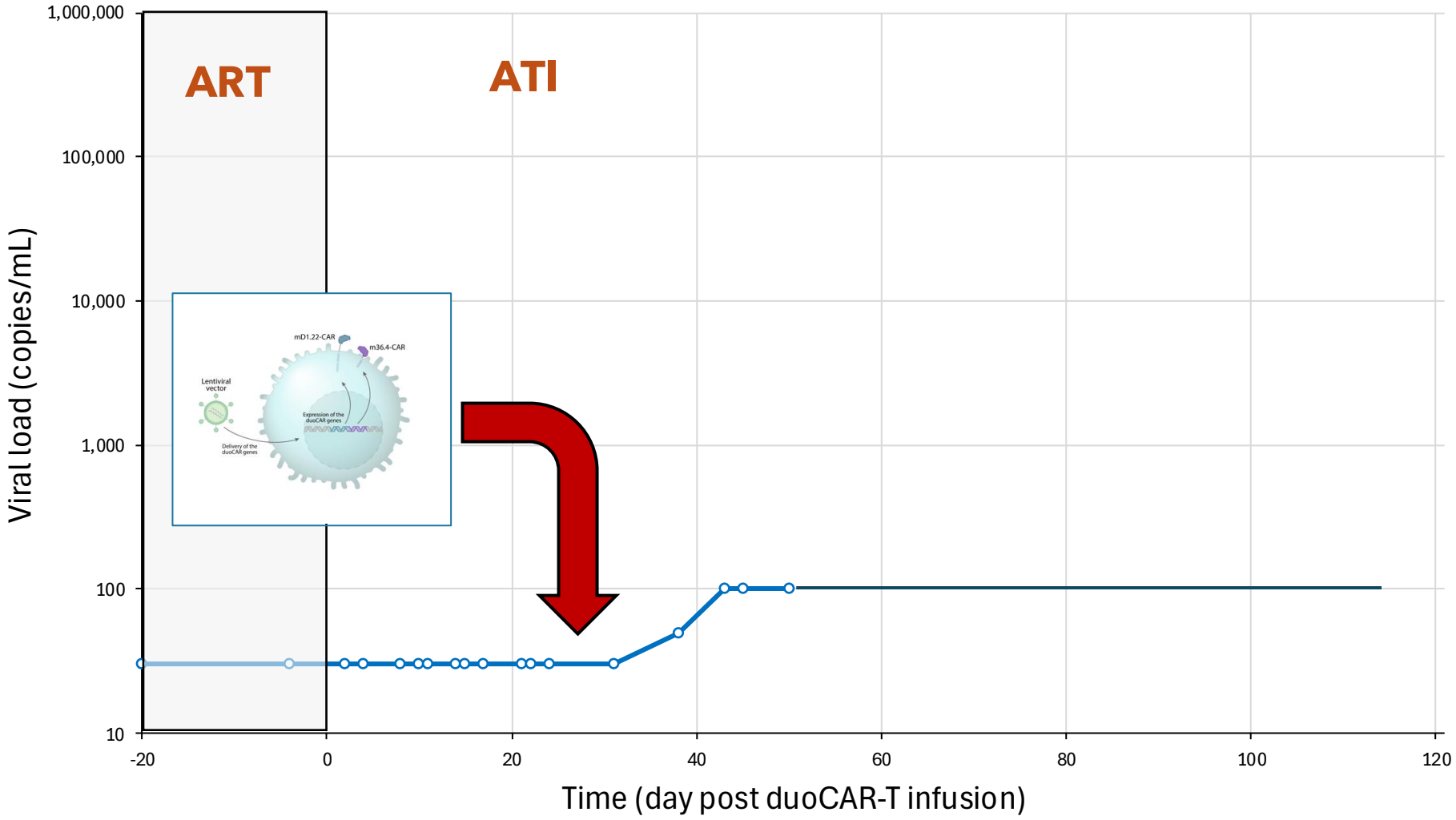
CAR-T cells infused at the virus-host intercept may allow the immune system to get ahead of the virus, leading to control



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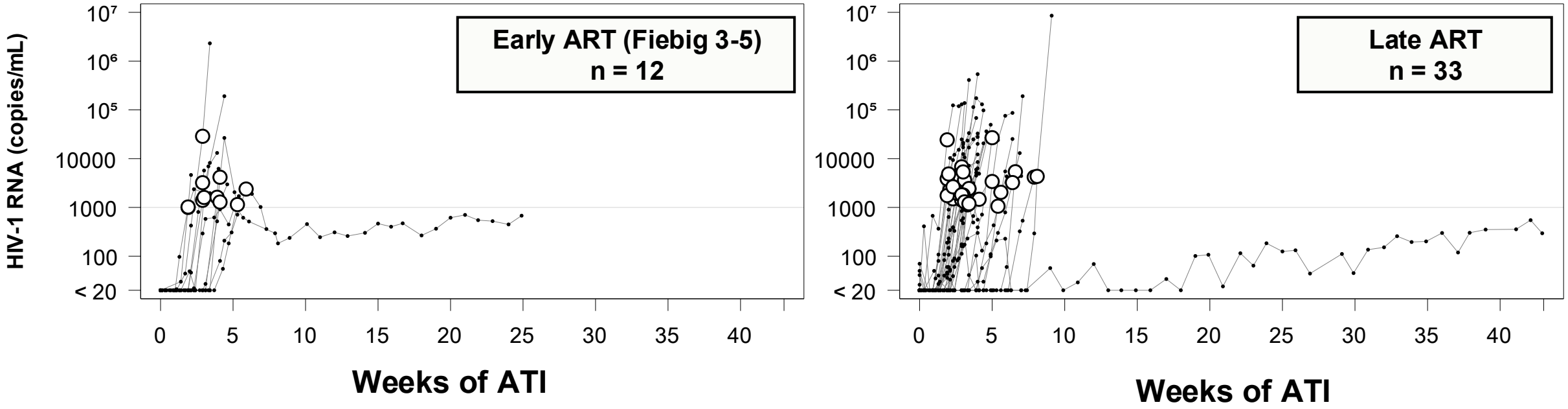
ACTG 5345: Prospective ATI study to define post-ART viral dynamics in the modern era

Clinical Infectious Diseases

Time to Viral Rebound After Interruption of Modern Antiretroviral Therapies

Jonathan Z. Li,[1] Evgenia Aga,[2] Ronald J. Bosch,[2] Mark Pilkinton,[3] Eugène Kroon,[4] Lynsay MacLaren,[5] Michael Keefer,[6] Lawrence Fox,[7] Liz Barr,[8] Edward Acosta,[9] Jintanat Ananworanich,[4,10] Robert Coombs,[11] John W. Mellors,[12] Alan L. Landay,[13] Bernard Macatangay,[12] Steven Deeks,[14] Rajesh T. Gandhi,[15] and Davey M. Smith[16]; and the AIDS Clinical Trials Group A5345 Study Team



- Rebound is typically rapid (14-21 days) and exponential
- Partial control (~ 1000 cpm) is uncommon
- Complete or near-complete control (< 50 cpm) is rare

ART resumed for VL > 1000 confirmed

Eligibility Criteria

- Age ≥ 18 and ≤ 70 years
- Continuous ART > 12 months without any interruptions of > 14 days
- Stable regimen that does not include an NNRTI or long-acting ART
- HIV RNA levels < 30 cpm (isolated blips allowed)
- Screening CD4+ T-cell count ≥ 350 cells/mm^3
- Capacity to construct an effective antiretroviral treatment regimen
- Not pregnant/breastfeeding
- Any history of an HIV-associated malignancy
- History of or current active hepatitis B; active HCV
- Active and poorly controlled atherosclerotic cardiovascular disease
- History of potential immune-mediated medical conditions

We enrolled people who started early or late

Baseline characteristics

Variable	Cohort 1	Cohort 2	Cohort 3
Age			
Age, Mean ± SD years	47.75 ± 12.92	45.5± 7.18	52 ± 15.52
Sex/Gender			
Cisgender man	4 (100%)	4 (100%)	3 (100%)
Cisgender woman	0	0	0
Transgender man	0	0	0
Transgender woman	0	0	0
Non-binary	0	0	0
Race/Ethnicity			
Hispanic or Latino	1 (25%)	2 (50%)	0
White	1 (25%)	1 (25%)	2(66.67%)
American Indian or Alaskan Native	0	0	0
African American or Black	0	0	0
Asian	0	1 (25%)	0
Native Hawaiian or other Pacific Islander	0	0	0
Mixed Race	2 (50%)	0	1 (33.33%)
Unknown/Not Reported/Declines to Answer	0	0	0

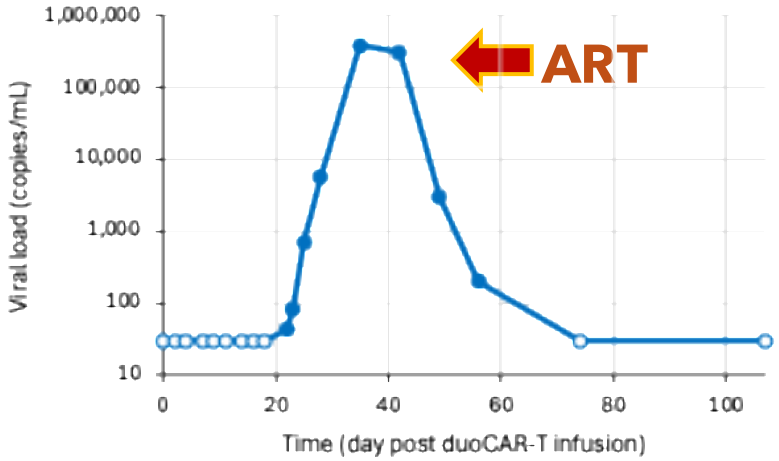
Cohort 1

No conditioning, low cell dose (3×10^5 cells/kg)

Cohort 1: Viral load rebound dynamics after ART is interrupted

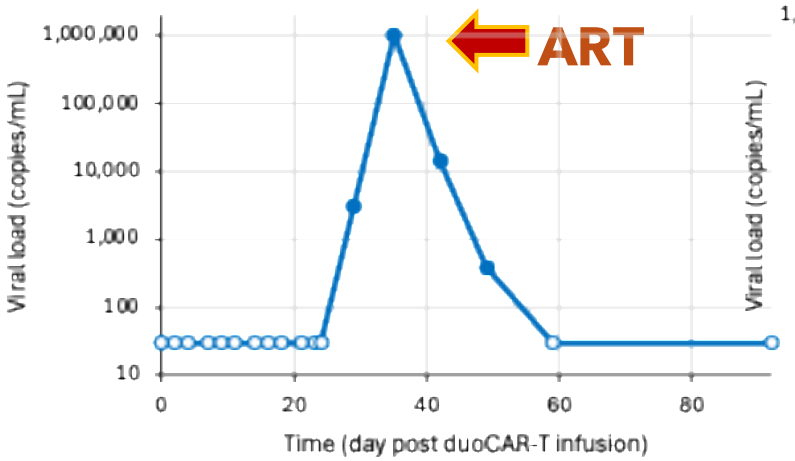
Viral load rebound exhibited typical dynamics

PID 91889



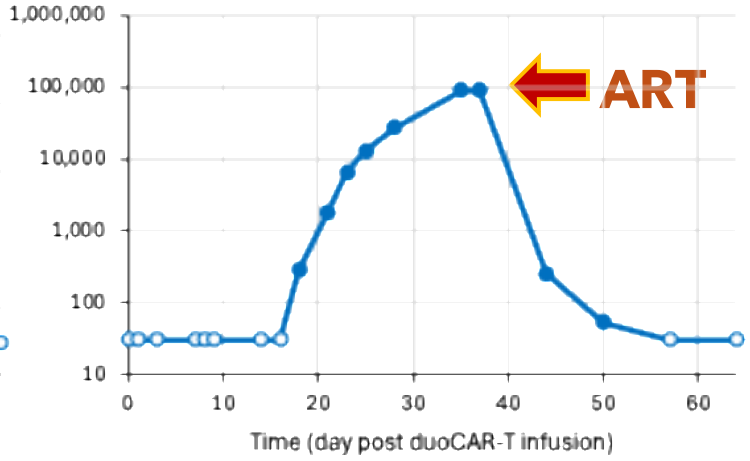
Chronic Infection

PID 84946



Chronic Infection

PID 31092



Chronic Infection

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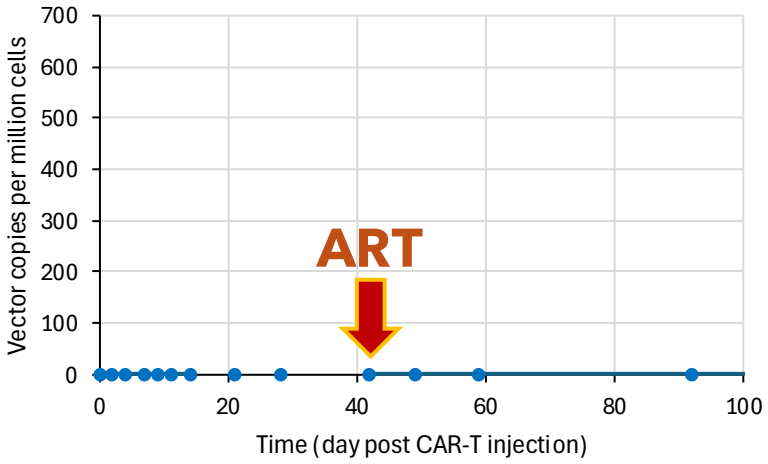
Cohort 1: No detectable CAR in 3 of 4 participants

Assay: qPCR of vector sequence normalized to housekeeping gene

PID 84946



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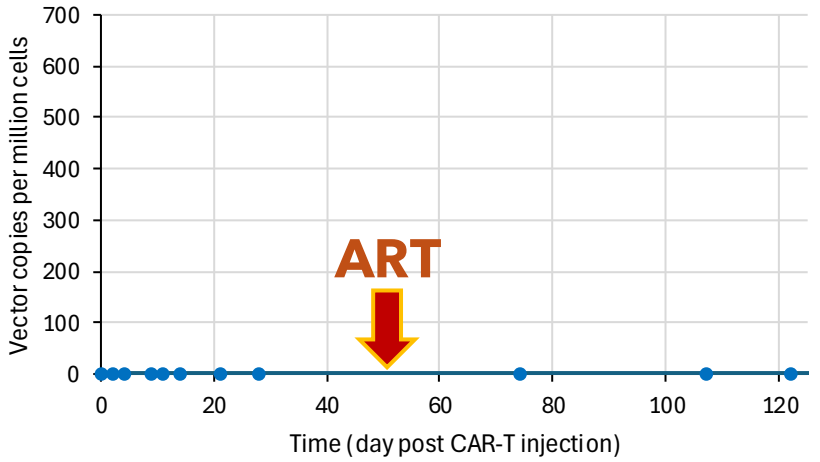

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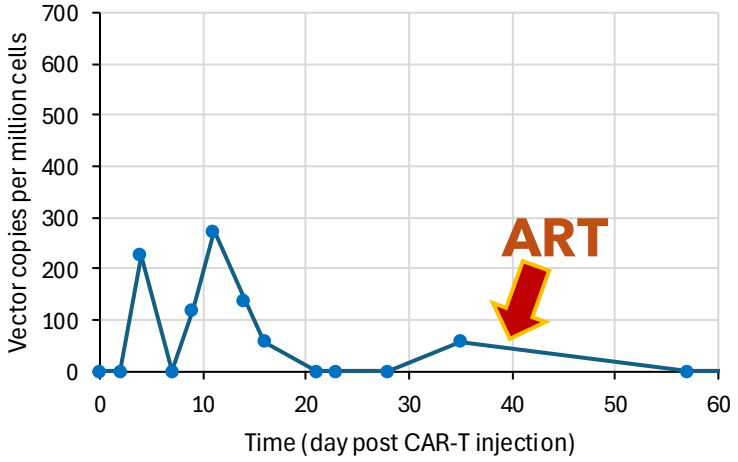
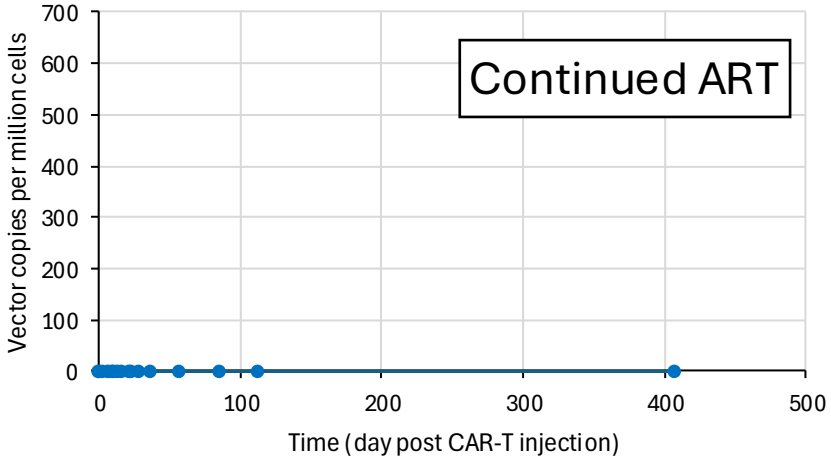


PID 39587

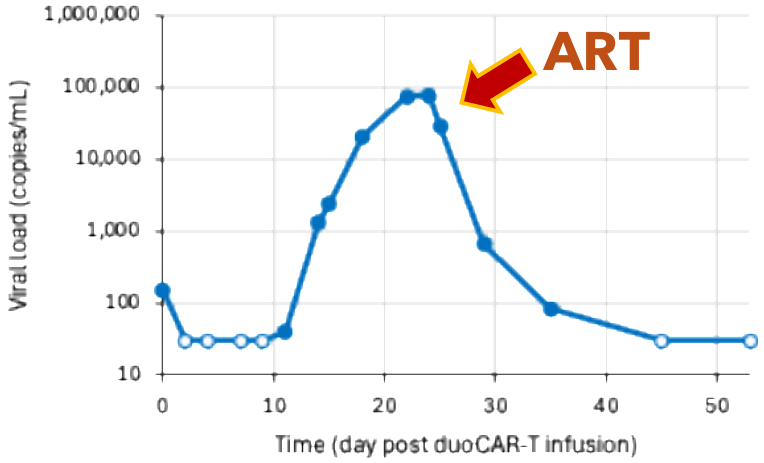


Cohort 2

Non-myeloablative conditioning, low cell dose (3 x 10^5 cells/kg)

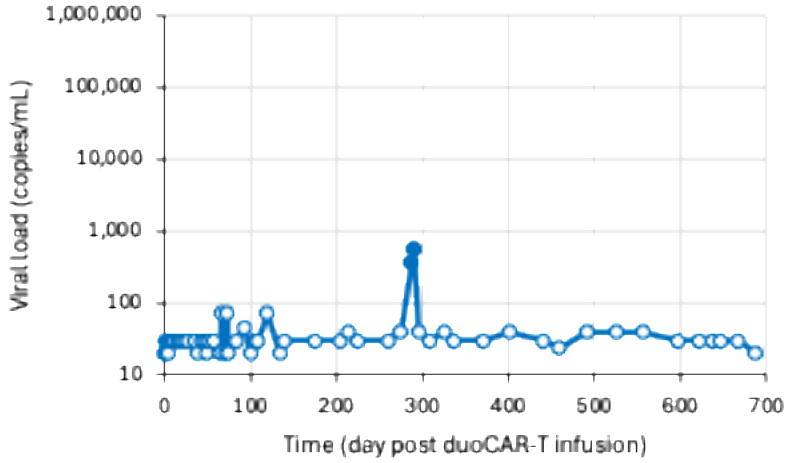
Cohort 2: Viral load rebound dynamics after ART is interrupted

PID 12233



Chronic Infection

PID 72528



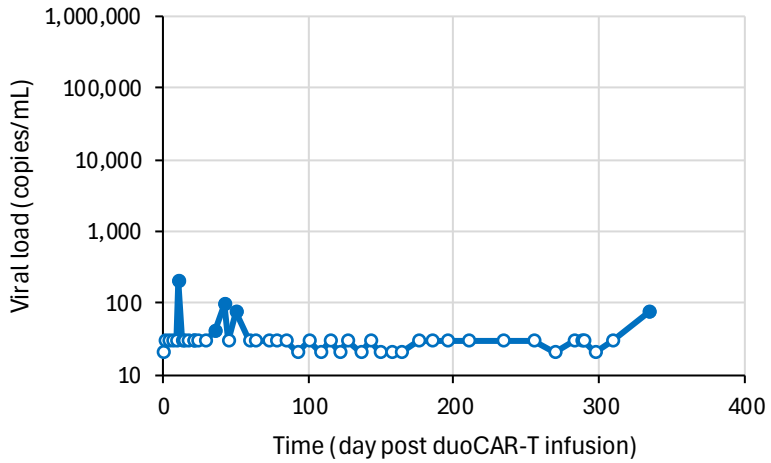
Acute/early infection (Fiebig 4)

HLA-B5701 Neg

No detectable ART at weeks 2, 6, 12, 20 and 48

Control > 96 weeks

PID 75682



Acute/early infection (Fiebig 4)

HLA-B5701 Neg

No detectable ART at weeks 2 and 8

Control > 44 weeks

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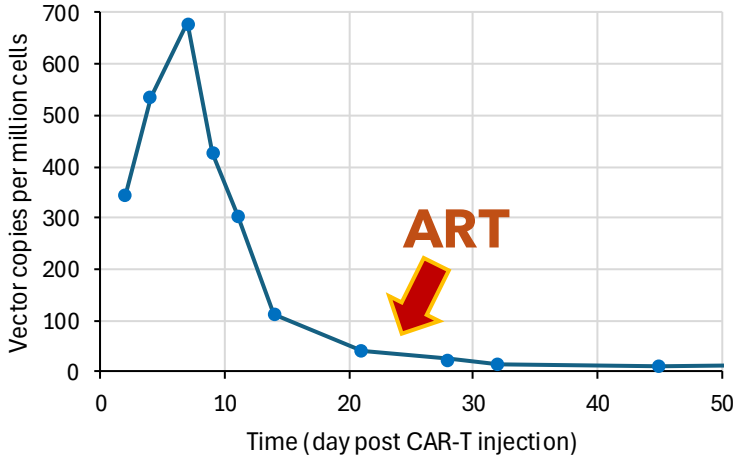
Cohort 2: CAR persistence

CAR-T cells during early post-infusion period, suggesting conditioning was needed

PID 12233



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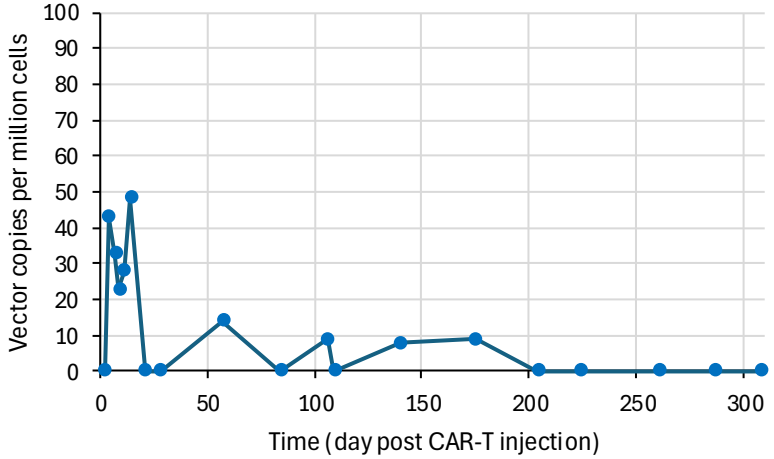
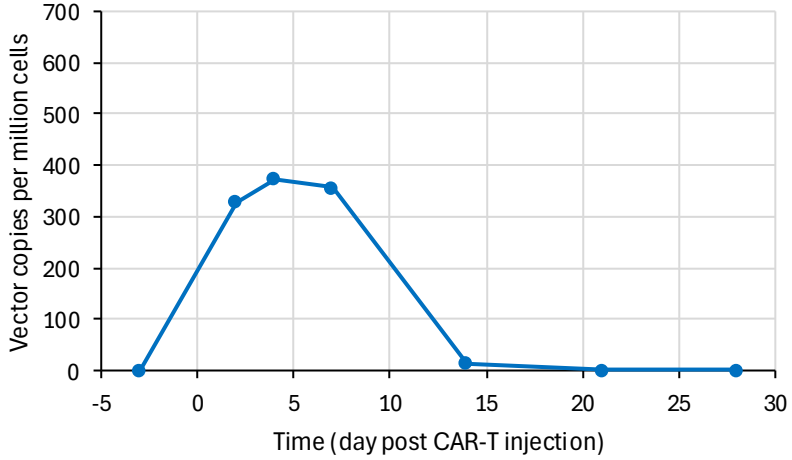
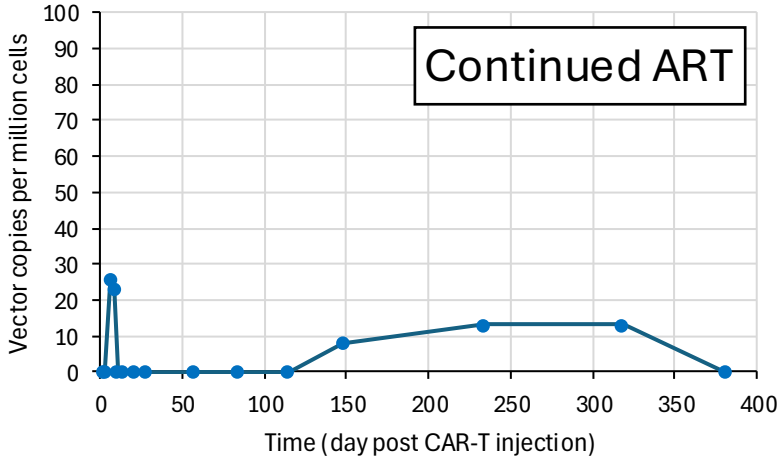


PID 75682



PID 89937



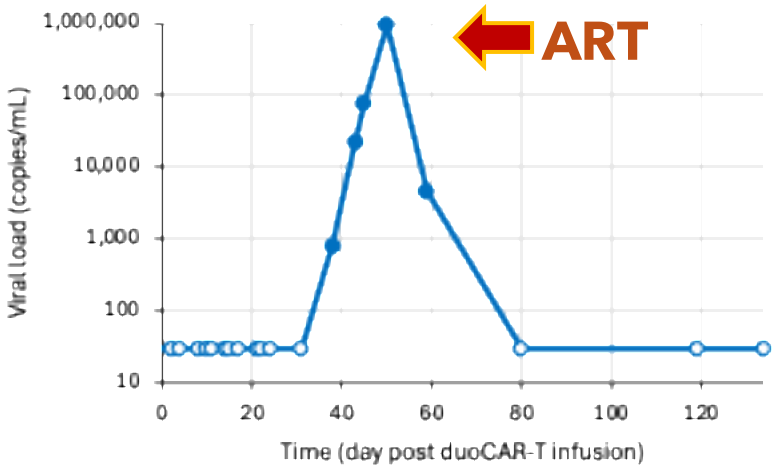
Cohort 3

Non-myeloablative conditioning, high cell dose (1 x 10^6 cells/kg)

Cohort 3: Viral load rebound dynamics after ART is interrupted

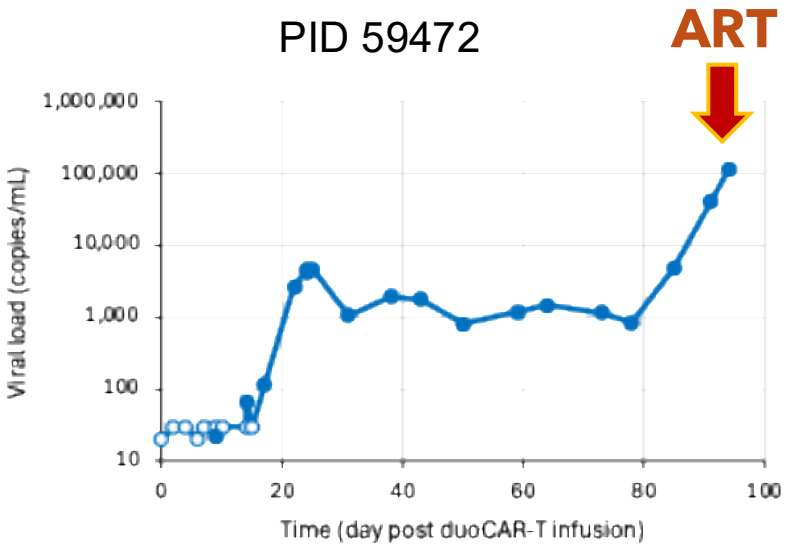
CAR persistence data pending

PID 91889



Chronic infection

PID 59472

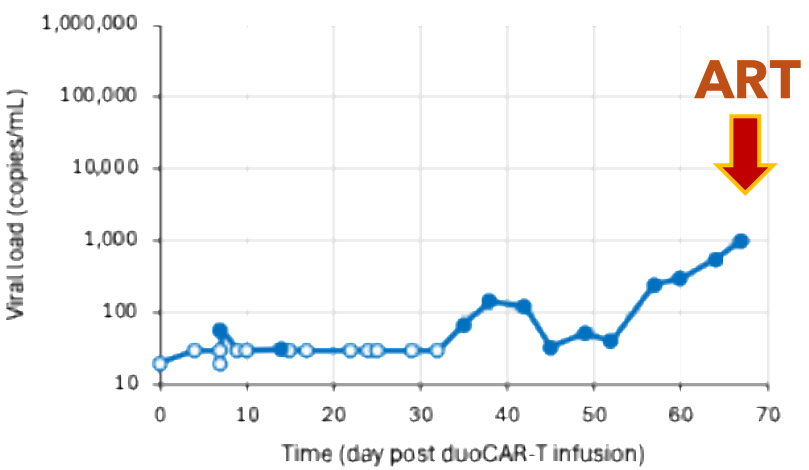


Acute/early infection (Fiebig 4-5)

HLA-B5701 Neg

Partial control ~ 12 weeks

PID 39587



Chronic infection

HLA-B5701 Neg

Partial control > 11 weeks

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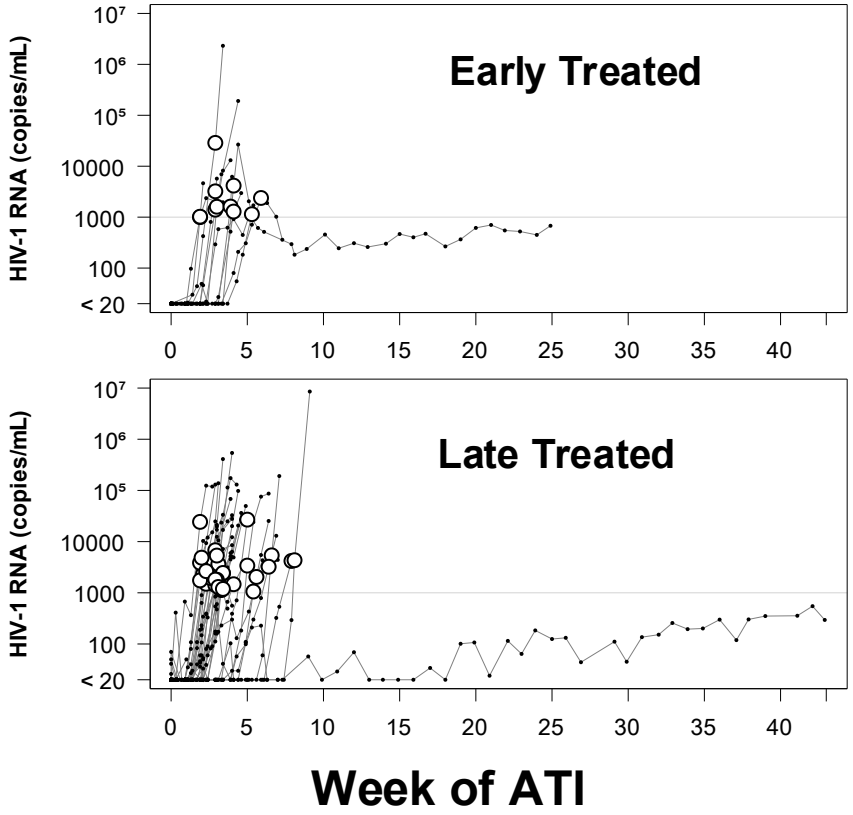
Time-to-rebound was longer than expected, suggesting CAR-T cells provided an early “brake” on the virus

A5345



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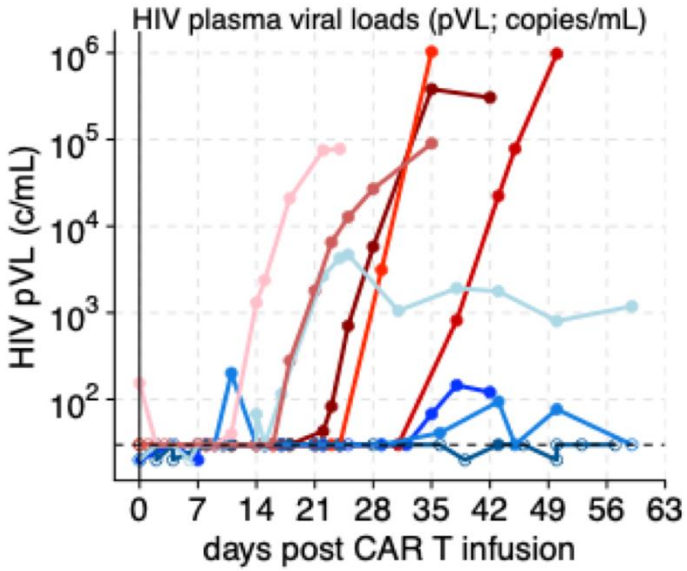

- Median time to a VL ≥ 50 cpm was 14 days (A5345) versus 23 days (CIRM) (P=0.02)
- Median time to a VL ≥ 1000 cpm was 21 days (A5345) versus 29 days (CIRM) P=0.01)

Safety Profile: Serious adverse events

- Product (LVgp120duoCAR-T cells)
  - No episodes of cytokine release syndrome
  - No episodes of neurotoxicity (ICANS)
  - No gradable toxicities related to the LVgp120duoCAR product
- Conditioning regimen (cyclophosphamide 1 gram/m^2)
  - Transient non-gradable lymphopenia common (expected)
  - Grade 4 neutropenia (day 10) and lymphopenia (day 14) in one individual; cell counts slowly improving
- Analytic treatment interruption (ATI)
  - Multiple expected grade 1 and 2 adverse events related to ATI
  - Transient drops in CD4+ T cells counts
  - No episodes of acute retroviral syndrome
  - No episodes of sexual transmission

Conclusions

- LVgp120duoCAR-T product was safe: No classic CAR-T cell toxicities observed (CRS, ICANS)
  - Conditioning regimen caused significant cytopenias in one person
- Transient low-level CAR levels observed in those with conditioning
- Post-ART control observed in those who started ART early
  - All who started ART (n=3) early and may have achieved control in absence of an intervention, although control at the level observed in two participants is rare
- Data provide encouraging evidence that a one-time treatment could offer a viable strategy for sustained, long-term HIV control
  - Randomized studies will be needed to prove effectiveness of this approach

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