Peptide Induced Apoptosis of Latently Infected Cells and Reduction of the HIV Reservoir in People with HIV

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CONFLICTS OF INTEREST

- Studies sponsored by GSK, ViiV, Gilead, MSD, Janssen, Abbivie
- Guest speaker for Gilead, Janssen, MSD, Abbott Diagnostics, Pfizer.
- Advisory boards: GSK, ViiV, MSD, Janssen, Gilead, Abbivie
- I have no shares in any pharmaceutical company.

"To control HIV we need to target the cells: the Infectious Diseases approach"

"To cure HIV we also need to target the cells: the oncology approach"

The drug

Gammora®

- 16-mer synthetic peptide
  - based on a short sequence of the HIV-1 integrase
- Peptide spans residues 174 – 188 of the integrase enzyme
  - Additional Tryptophan residue at N-terminus

Levin, A., Hayouka, Z., et al. (2010). " Biopolymers 93(8): 740 751

The *in vitro* evidence: what the peptides do

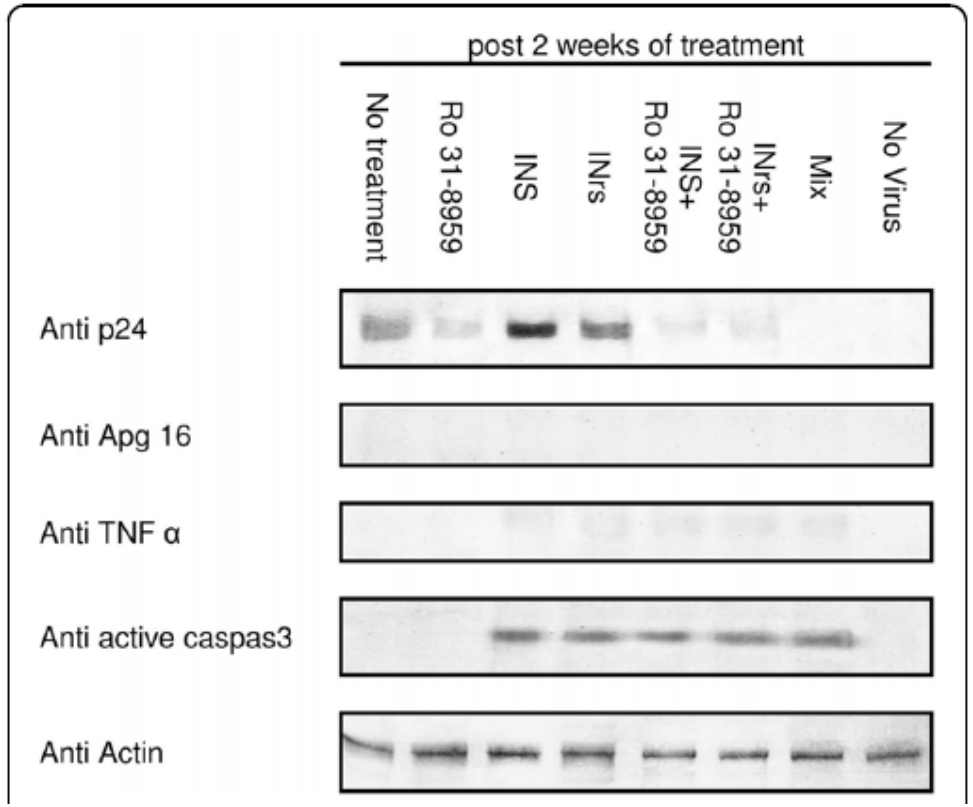
Levin *et al. AIDS Research and Therapy* 2010, **7**:31
http://www.aidsrestherapy.com/content/7/1/31

AIDS RESEARCH AND THERAPY

SHORT REPORT Open Access

Specific eradication of HIV-1 from infected cultured cells

Aviad Levin[1], Zvi Hayouka[2], Assaf Friedler[2], Abraham Loyter[1*]



Ro 31-8959 → SQV
INS → PEP1
Inrs→ PEP2

The *in vitro* evidence: what the association does.

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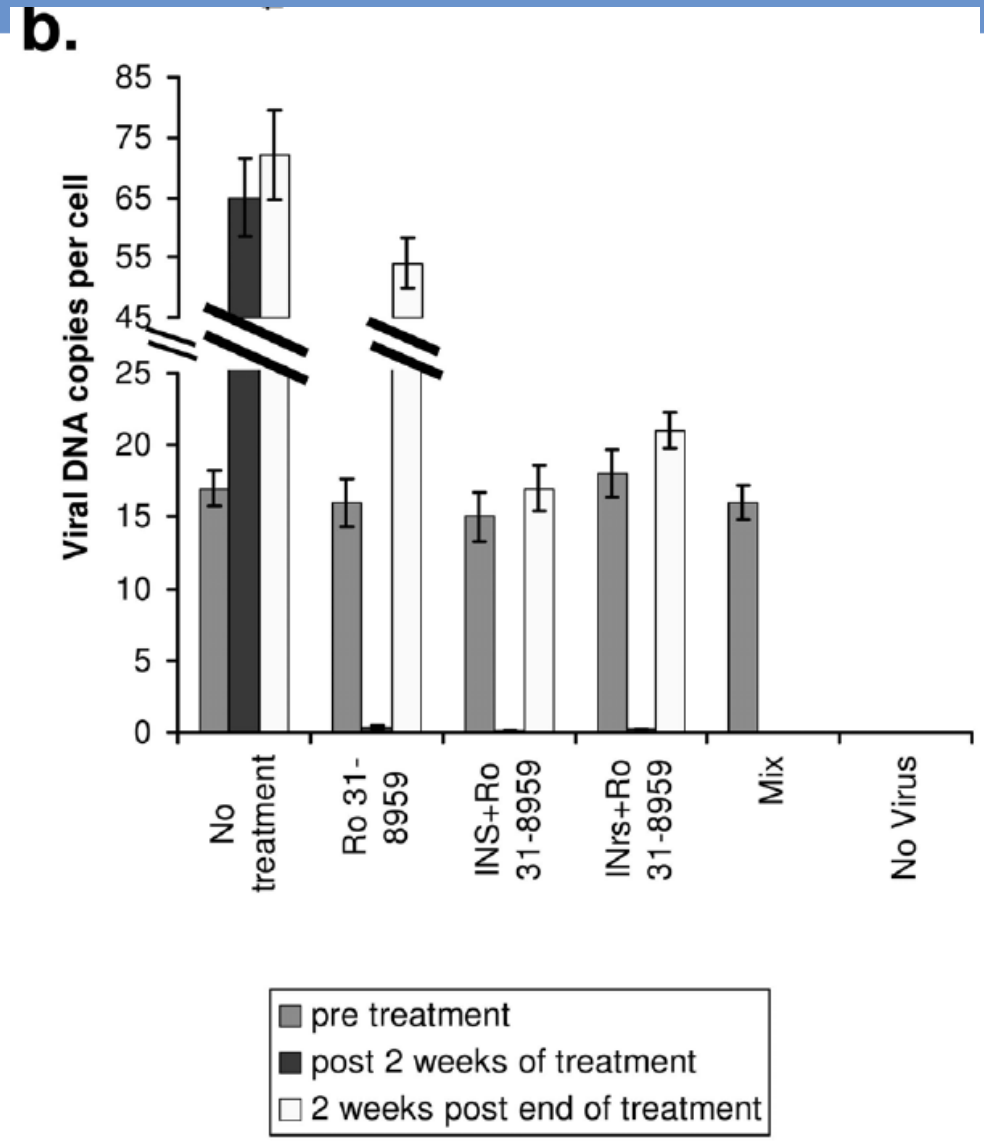

Ro 31-8959 → SQV
INS → PEP1
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The hypothesis

Integrase derived peptides

+

PI-based ARV regimen (TDF/3TC + darunavir-r)

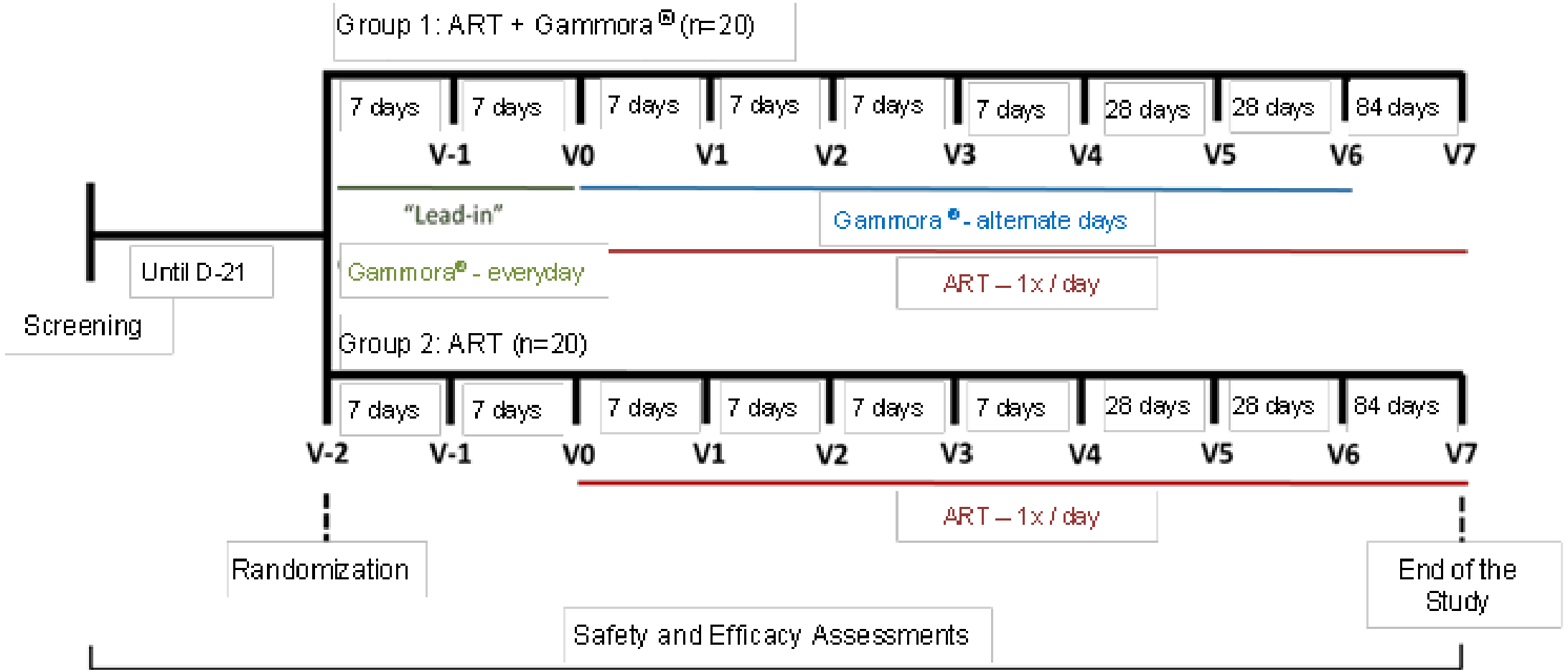
→ **Caspase 3 (apoptosis)** → **HIV-infected cell death (transient CD4 decrease)** → **Decrease of HIV proviral DNA**

Study Design

Pilot proof of concept open-label randomized clinical trial (n=40)

- Group 1. Gammora® + ART
  - Lead-in period: two weeks of Gammora® 2 mL SC daily
    - Gammora® 2 mL SC Monday, Wed, Friday for 12 weeks
    - Tenofovir/3TC 300/300 mg + Darunavir 800 mg + Ritonavir 100 mg OD
- Group 2. Control, ART only
  - Wait 2 weeks
    - Tenofovir/3TC 300/300 mg + Darunavir 800 mg + Ritonavir 100 mg OD

Treatment Strategy



Primary endpoints

- Reservoir size
- Apoptosis markers

Total DNA quantitation in PBMCs: as an estimate of the HIV reservoir by published qPCR techniques (triplicates).[1-3]

Statistical Analysis: non-parametric repeated measures ANOVA following an appropriate transformation where necessary.

Apoptosis determination: BD Pharmingen™ PE Annexin V Apoptosis Detection Kit (BD Biosciences) in PBMC by flow cytometry.

1. Komninakis, S. V. et al. J. Clin. Microbiol. 50, 2132–2133 (2012).
2. Buzón, M. J. et al. Nat. Med. 16, 460–465 (2010).
3. Kumar, A. M. et al. J. Neurovirol. 15, 257–274 (2009).

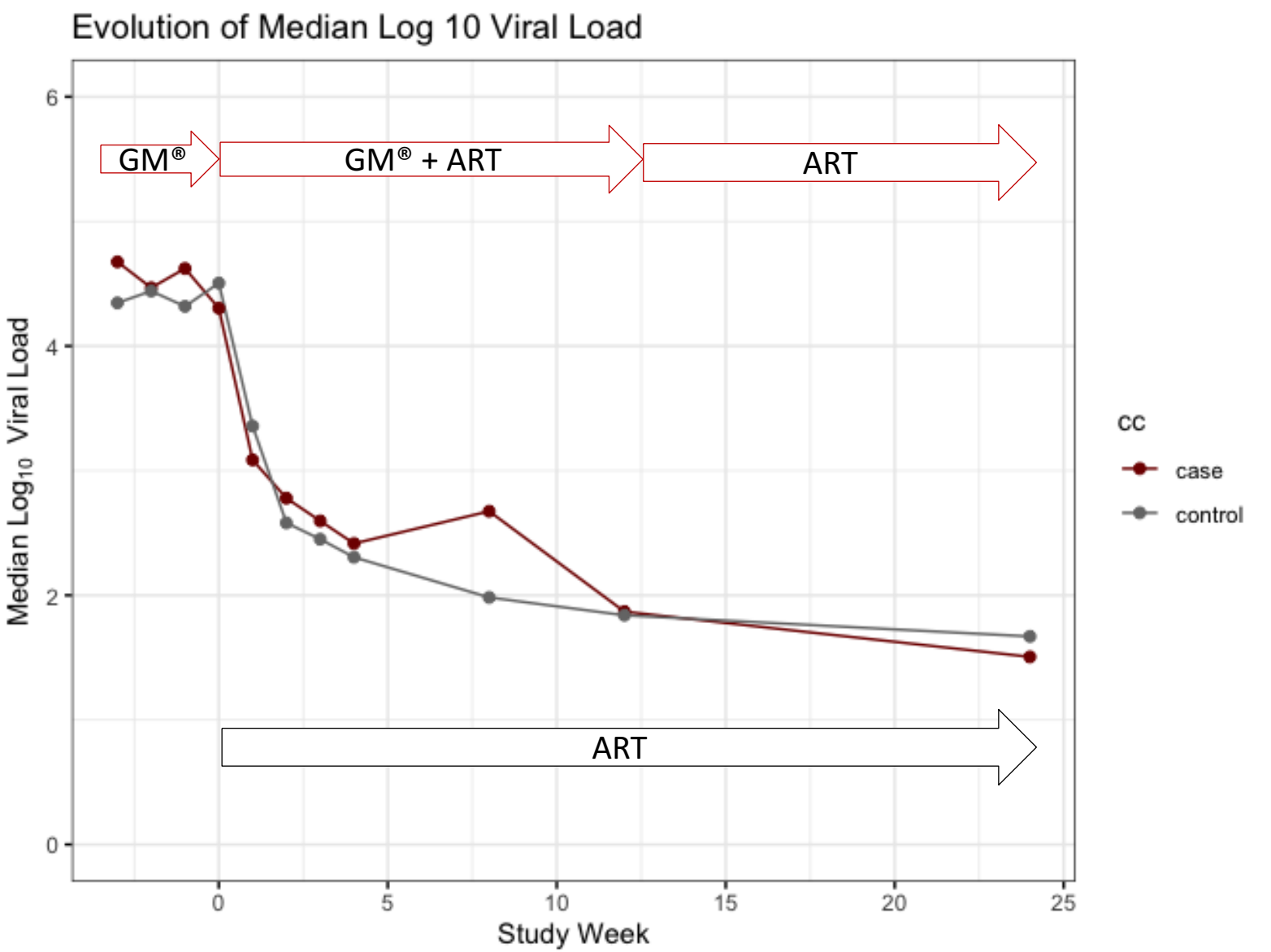
Interim analysis

- Results on a total of 13 PWH
  - Results for 12 available for DNA and Apoptosis analyses
  - 8 – Gammora® + ART
  - 5 – Controls (ART only)

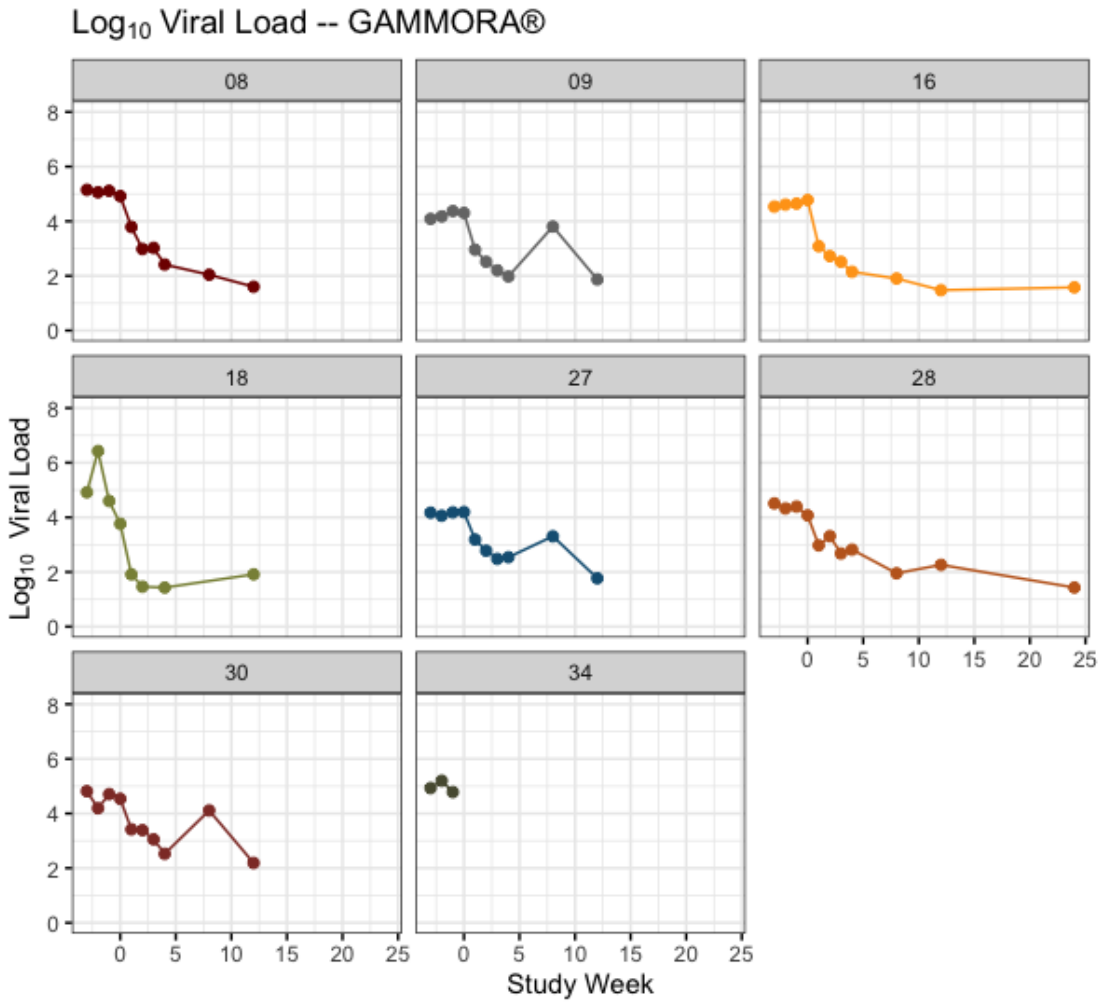
Demographics

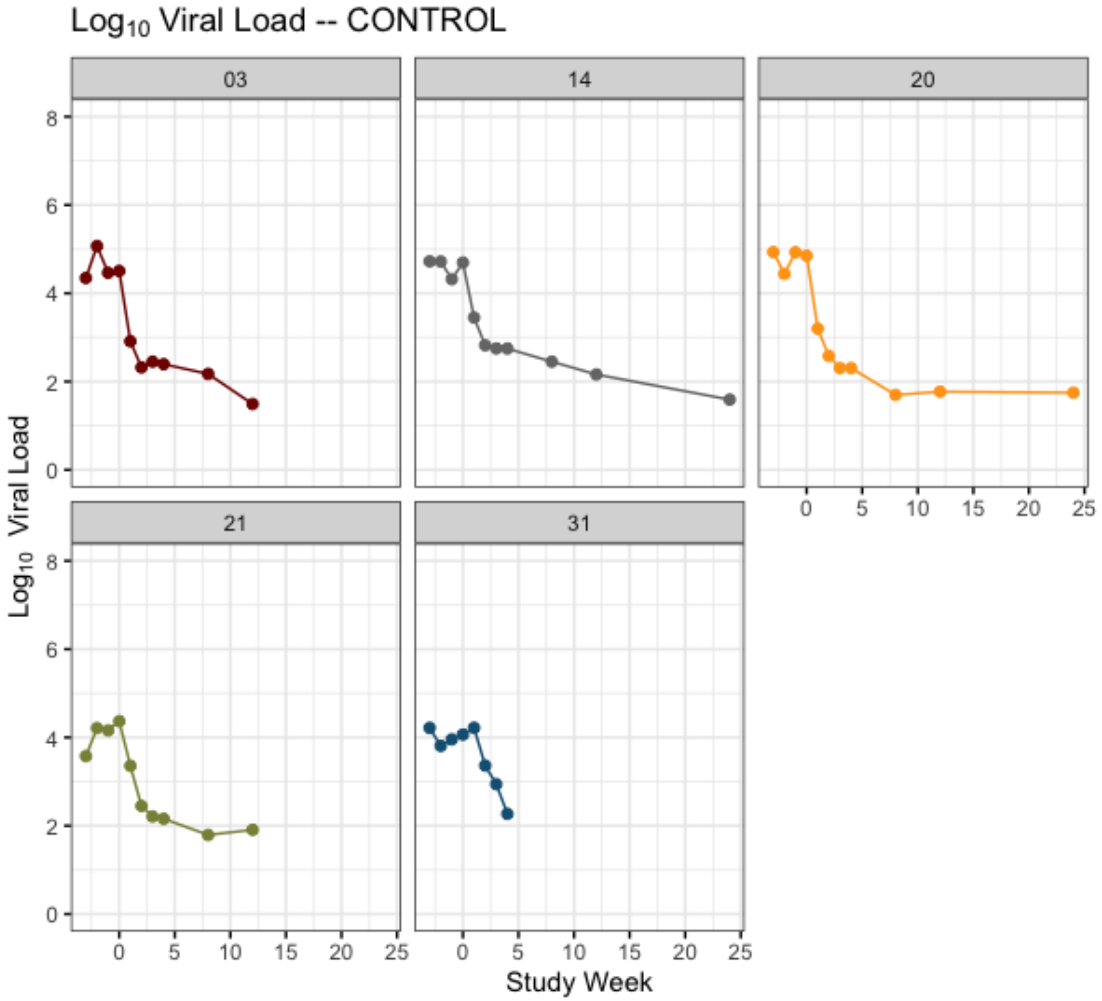
Characteristic	case N = 8[1]	control N = 5[1]	p-value[2]
age	27.8 (24.5, 31.2)	28.9 (27.8, 31.1)	0.5
gender			0.4
F	0 (0%)	1 (20%)	
M	8 (100%)	4 (80%)	
birth_state			0.6
MG	0 (0%)	1 (20%)	
PR	1 (13%)	0 (0%)	
SP	7 (88%)	4 (80%)	
race			>0.9
black	2 (25%)	1 (20%)	
mixed race	2 (25%)	2 (40%)	
white	4 (50%)	2 (40%)	

[1] Median (Q1, Q3); n (%)

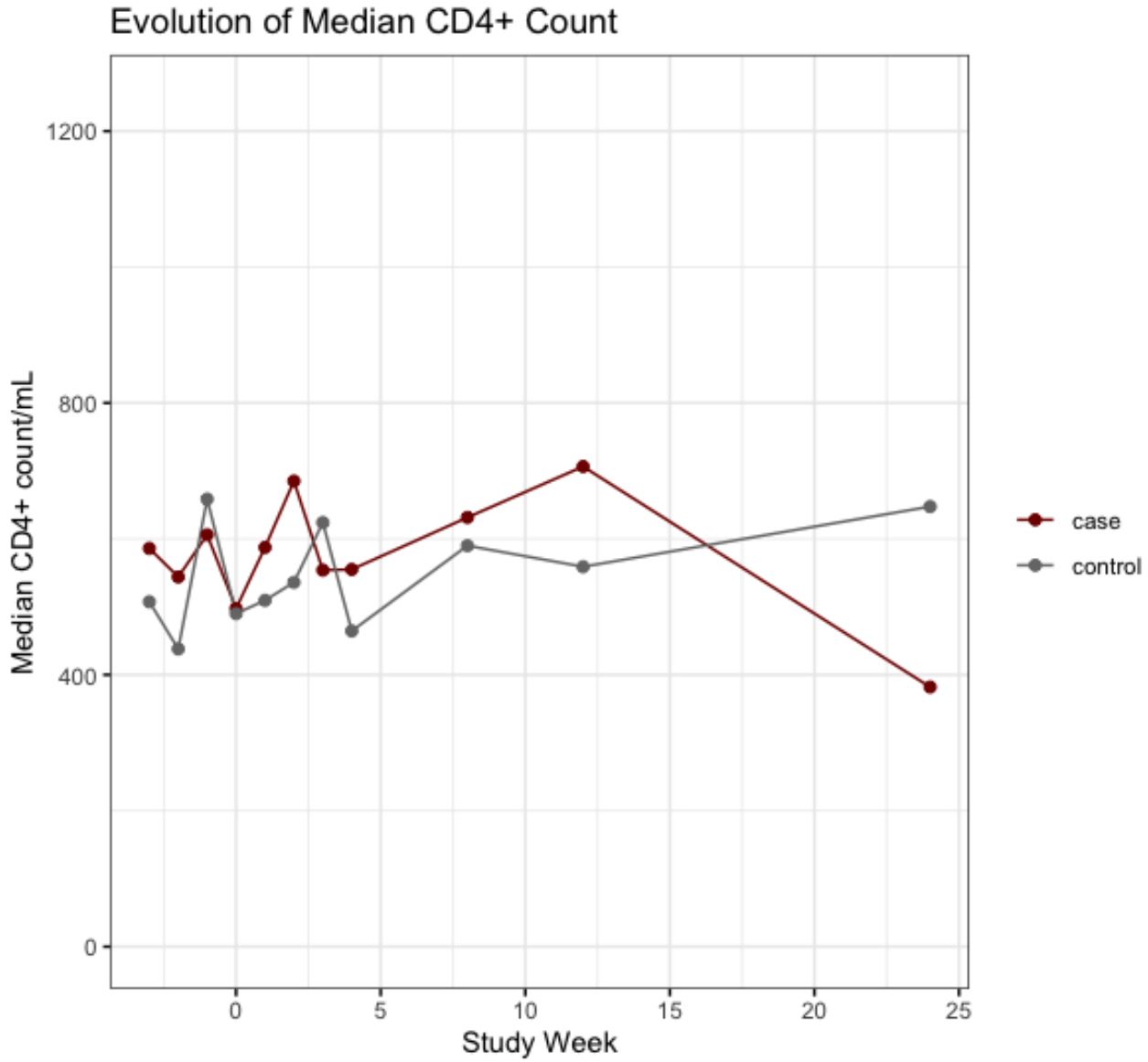

Evolution of Median Log 10 Viral Load
GM®
GM® + ART
ART
ART
Median Log10 Viral Load
Study Week
0
2
4
6
0
5
10
15
20
25
cc
case
control

Viral Load per Study Arm

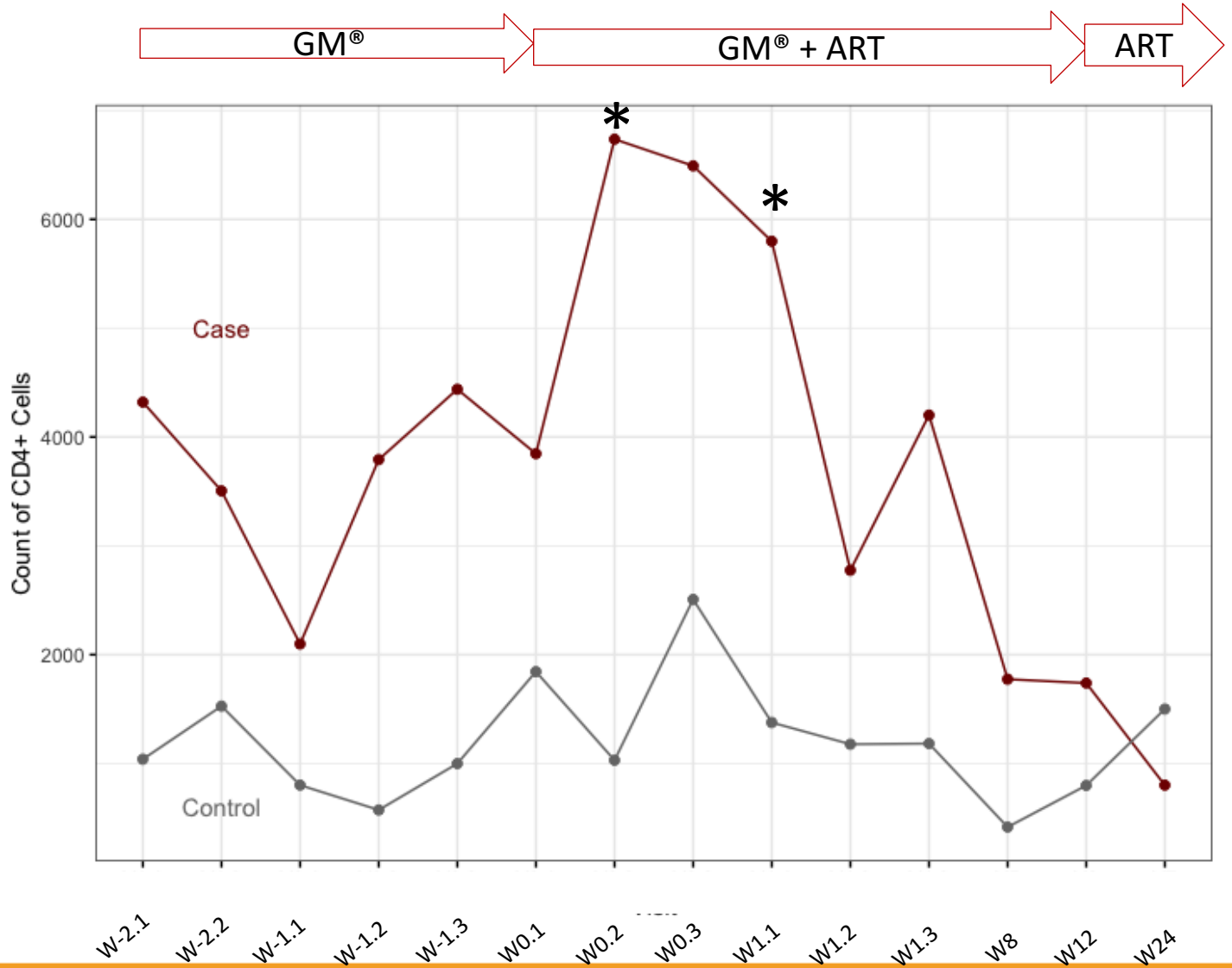




CD4+ T cells Evolution



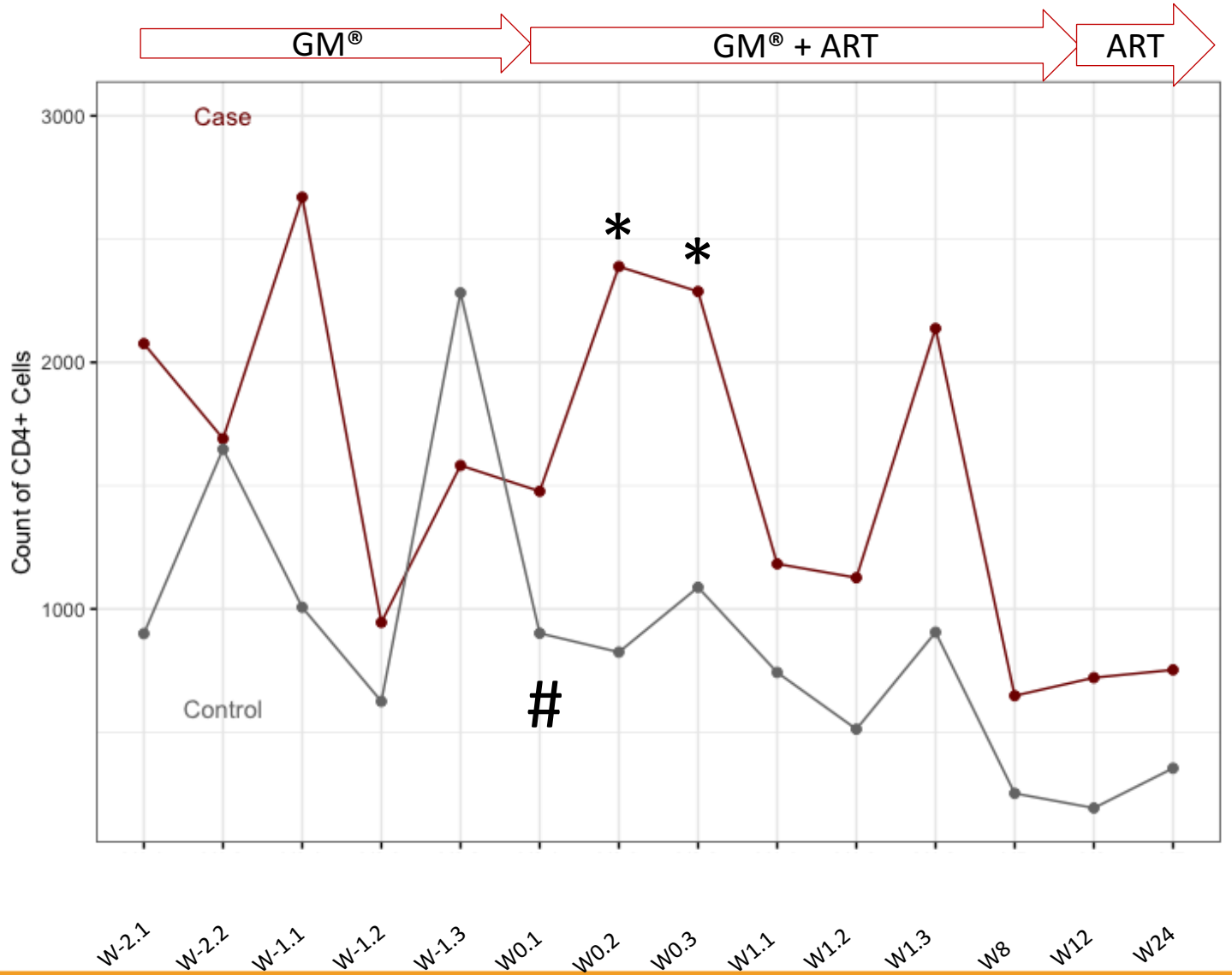
Early apoptosis – CD4+ T cells



* p<0.01

2 way Anova +
Bonferroni post test

Late apoptosis – CD4+ T cells

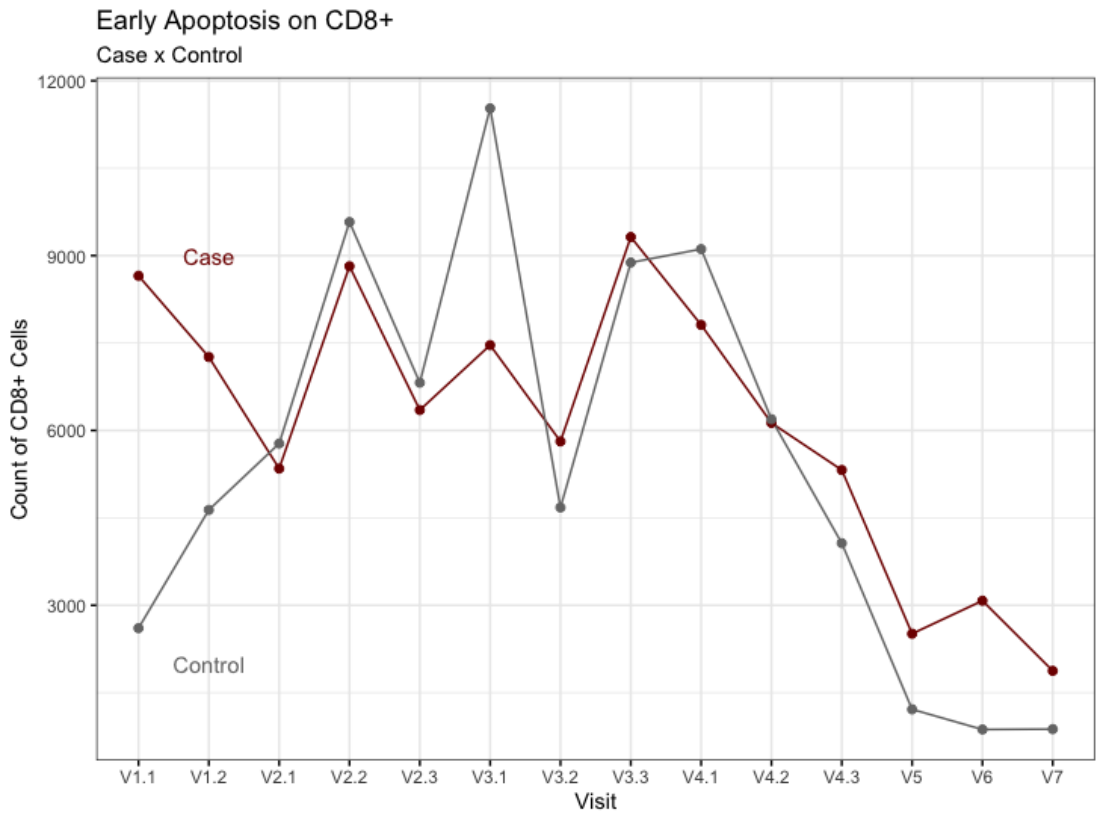


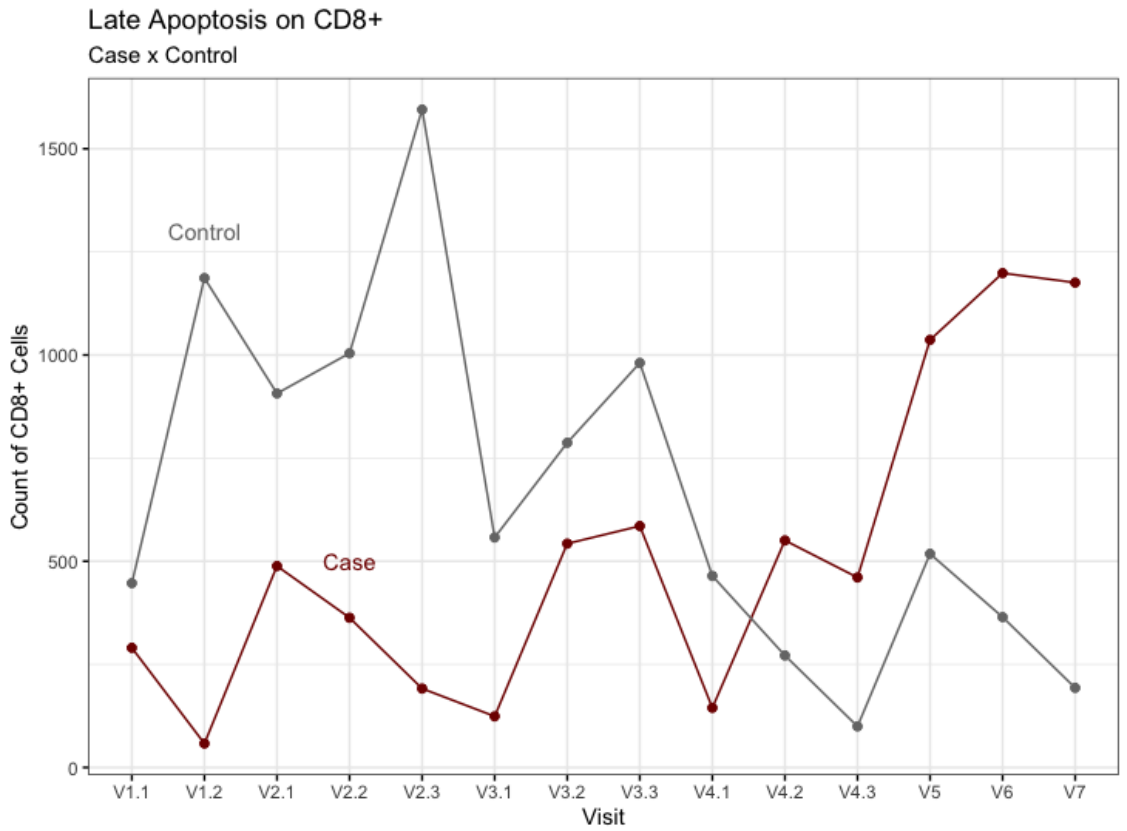
*p<0.01

2 way Anova + Bonferroni post test

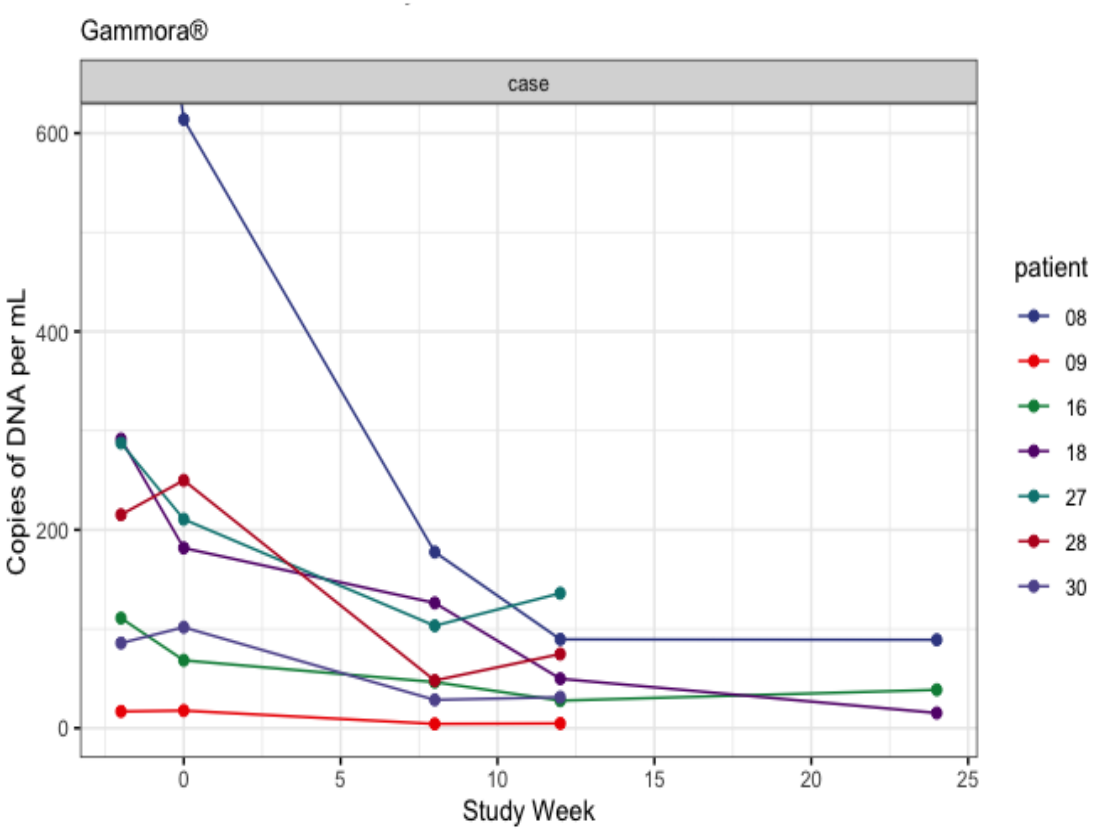
#decrease in apoptosis after ART in the control group

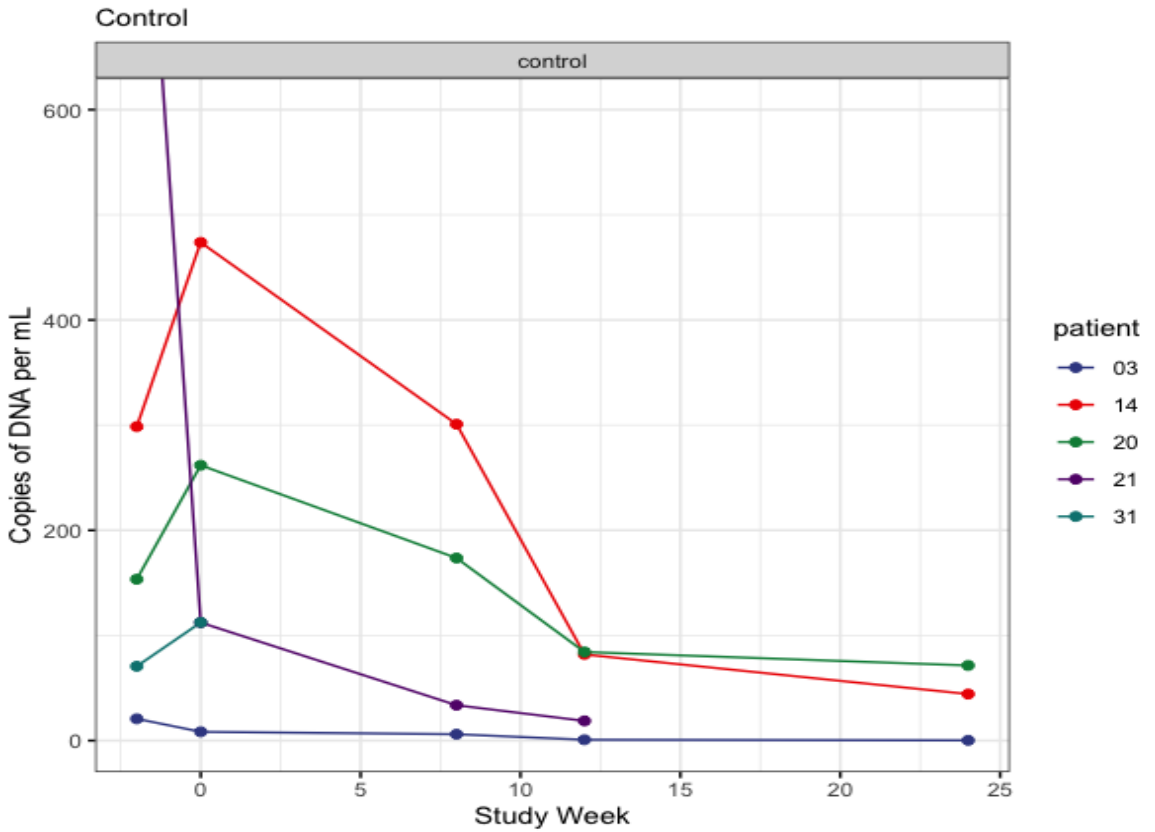
No changes in early or late apoptosis in CD8+ T cells



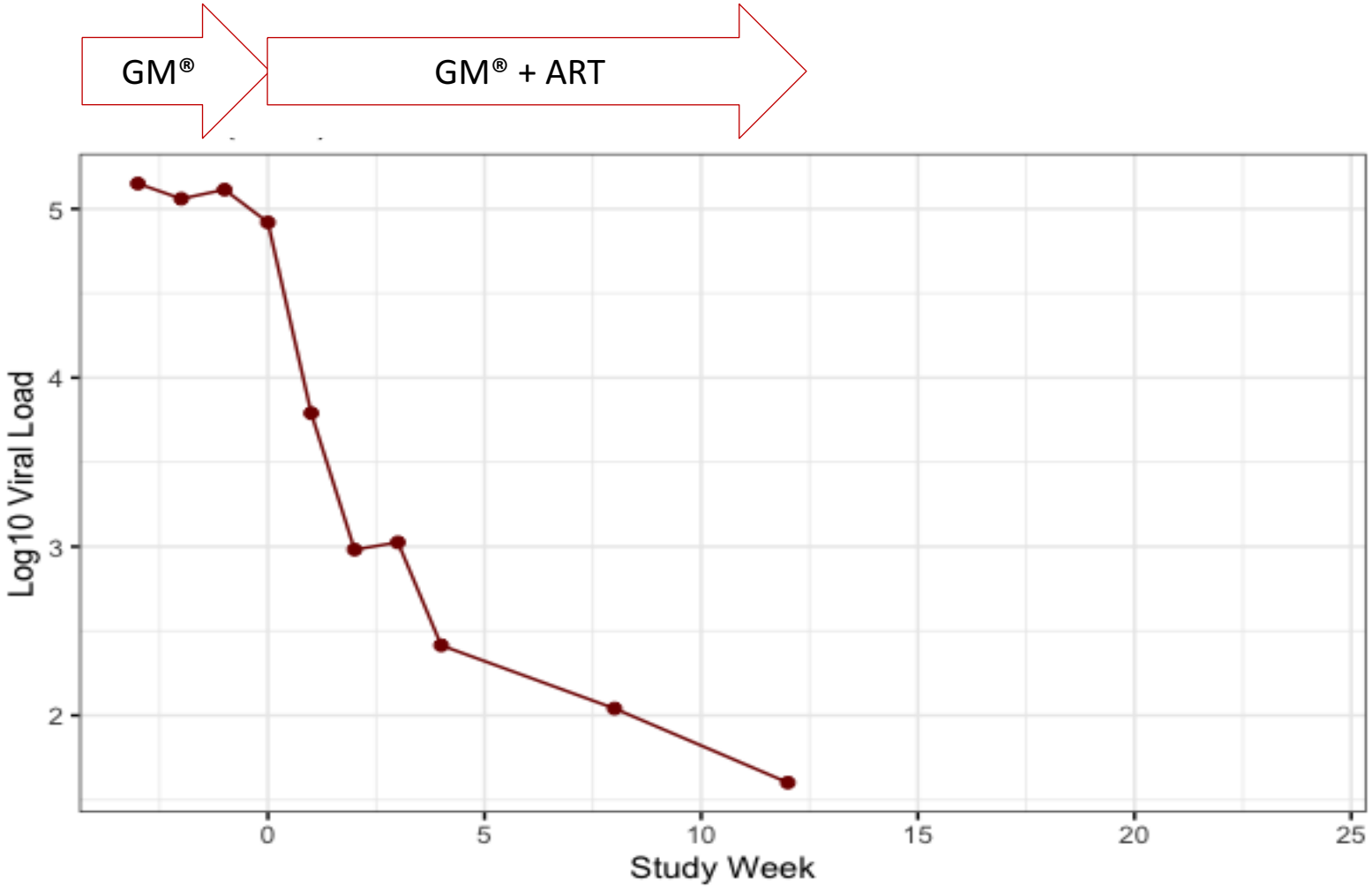


Total HIV DNA Dynamics

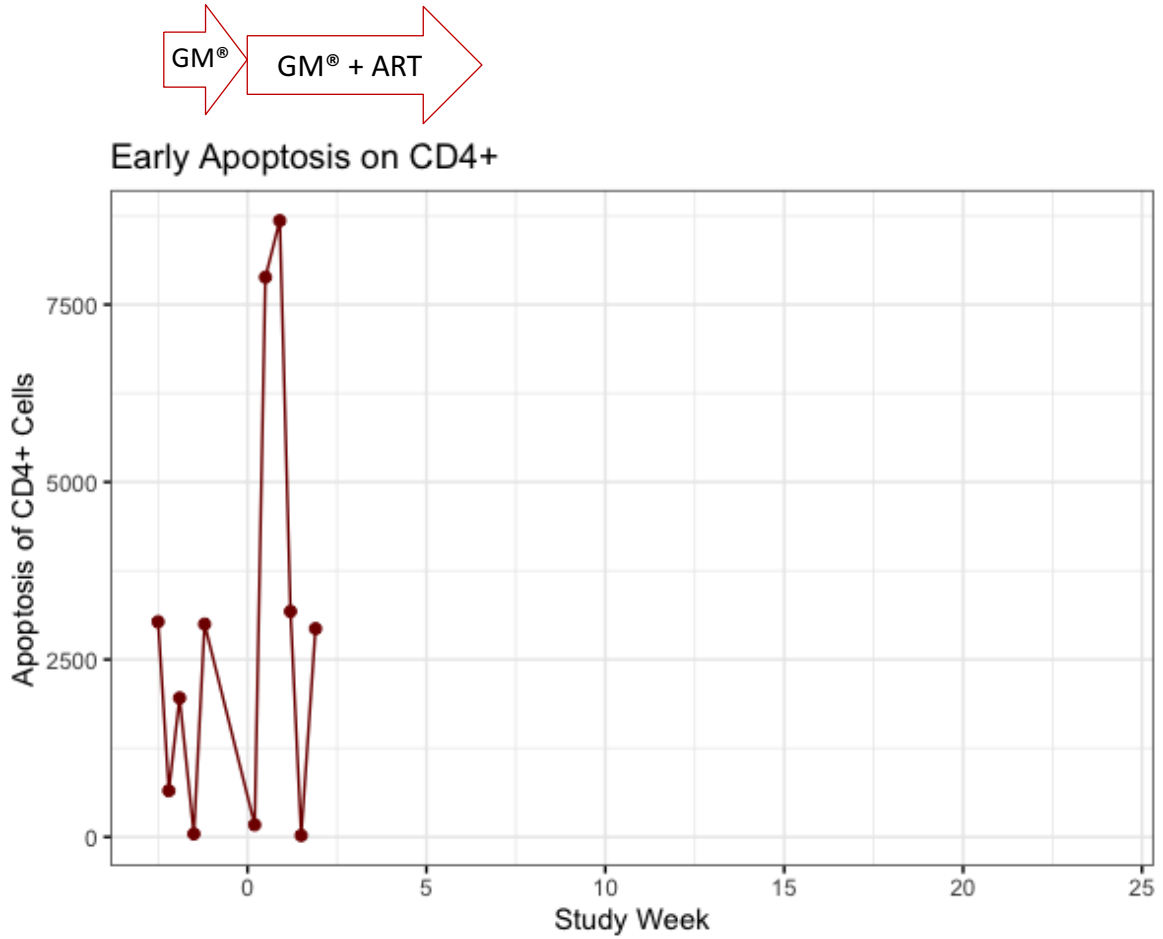


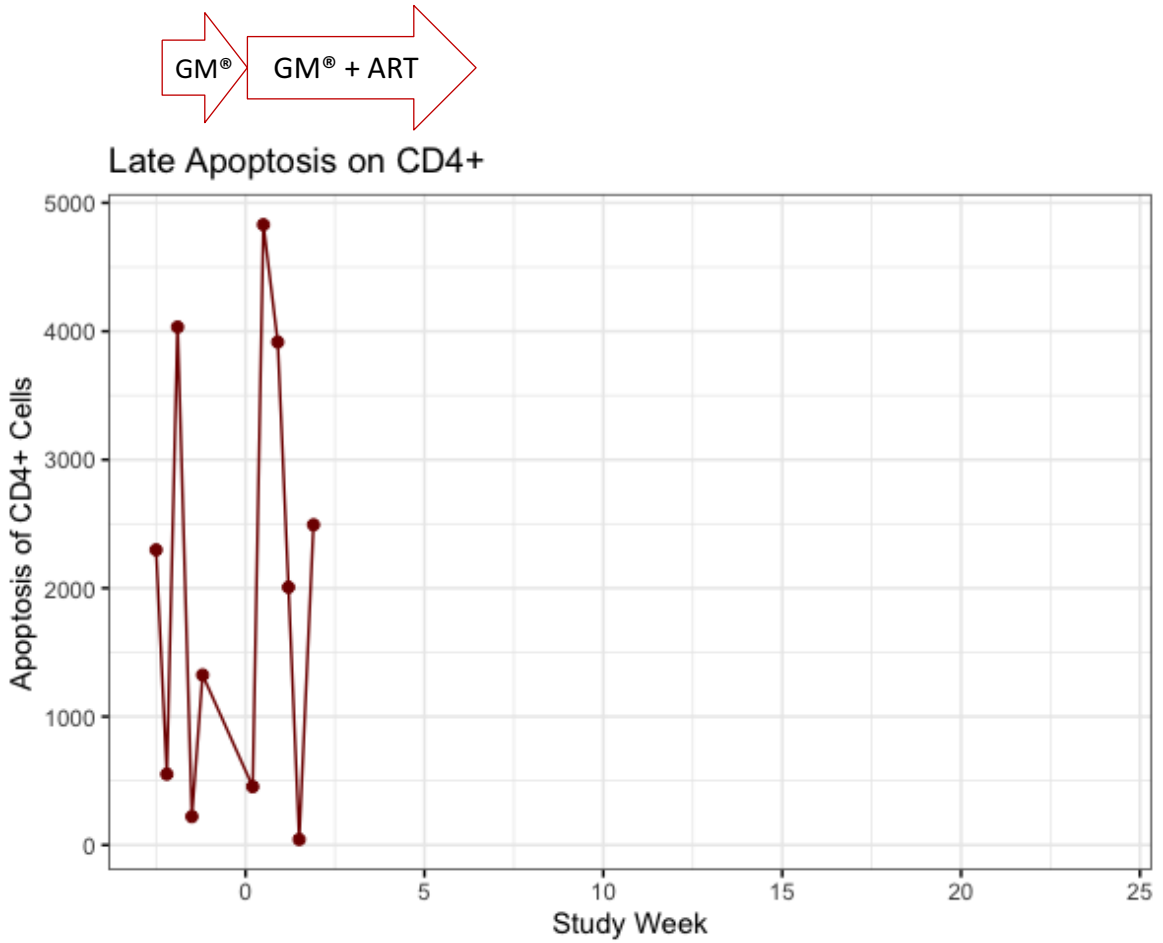


"Typical response": volunteer 08, case group, VL.

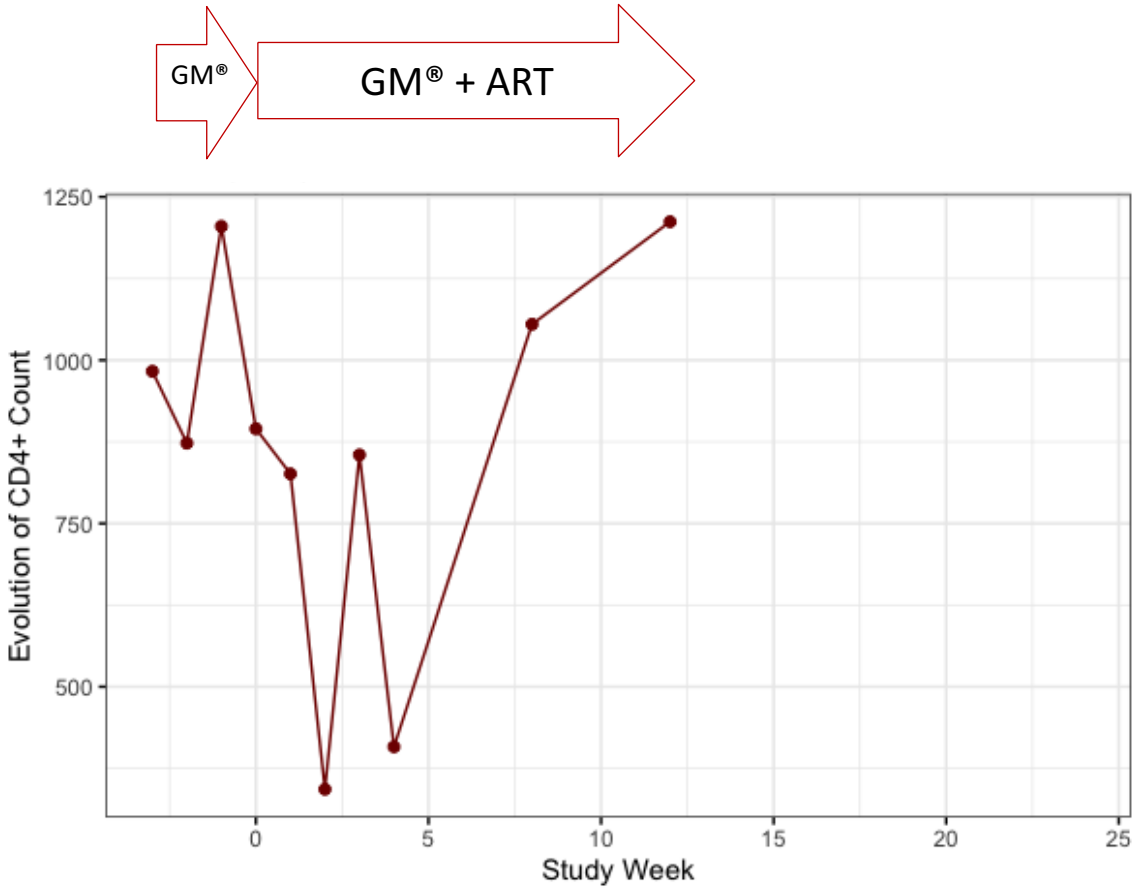


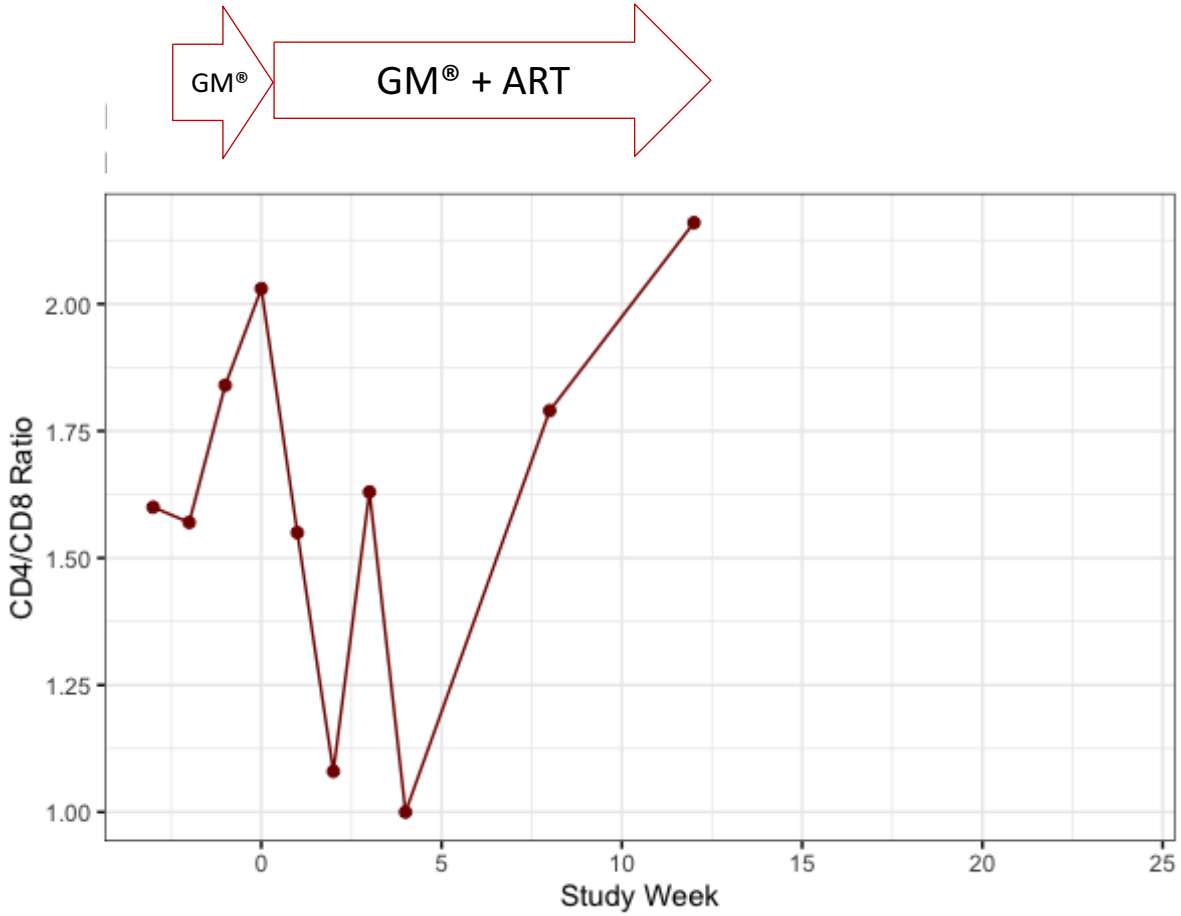
Typical response: volunteer 08, apoptosis



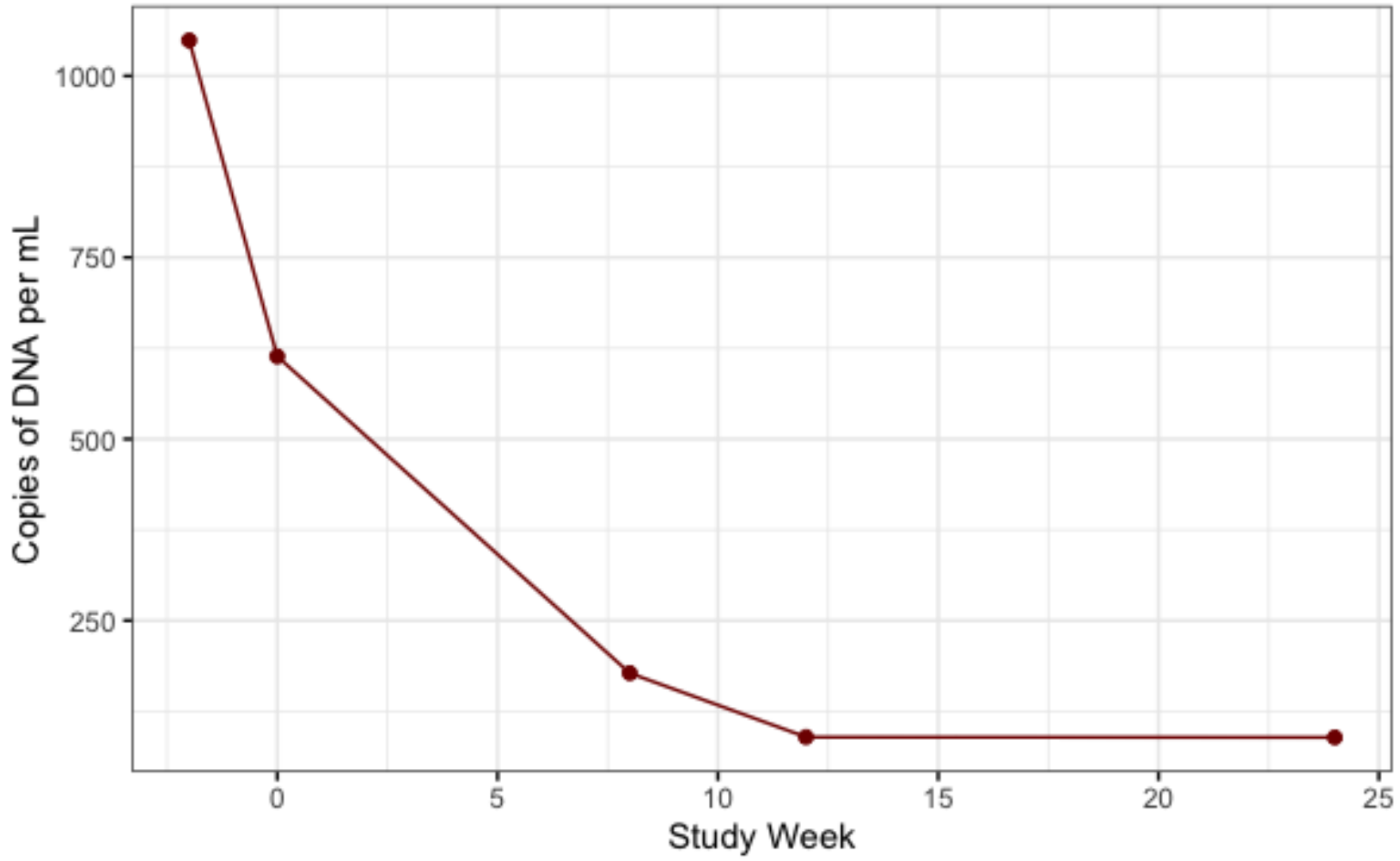


Typical response: volunteer 08, CD4+ T cells





Typical response: volunteer 08, Total DNA



Next steps

- Full enrollment and long-term F-U
- Next phase with two peptides
- ATI and roll over

Our Team – with Thanks!

- Retrovirology Laboratory, UNIFESP
  - Prof. Ricardo Sobhie Diaz, M.D.
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