10TH EDITION HIV PERSISTENCE DURING THERAPY™ Reservoirs & Eradication Strategies Workshop
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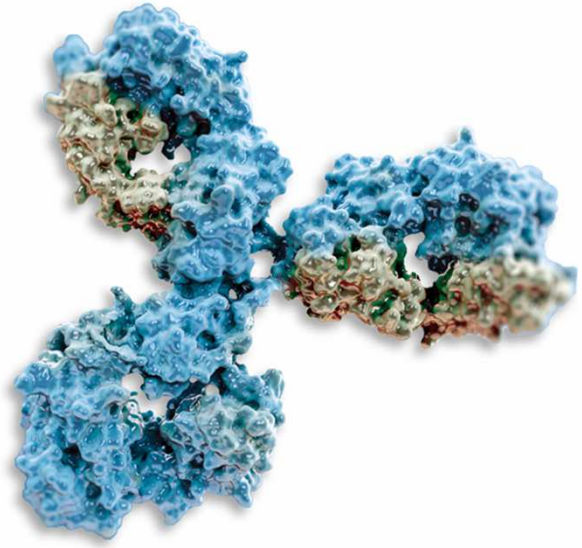
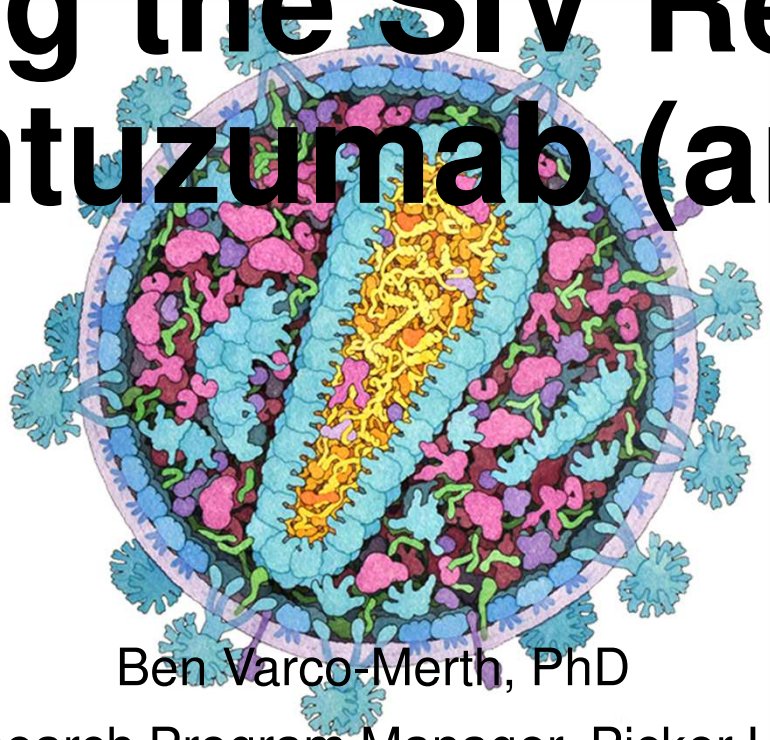
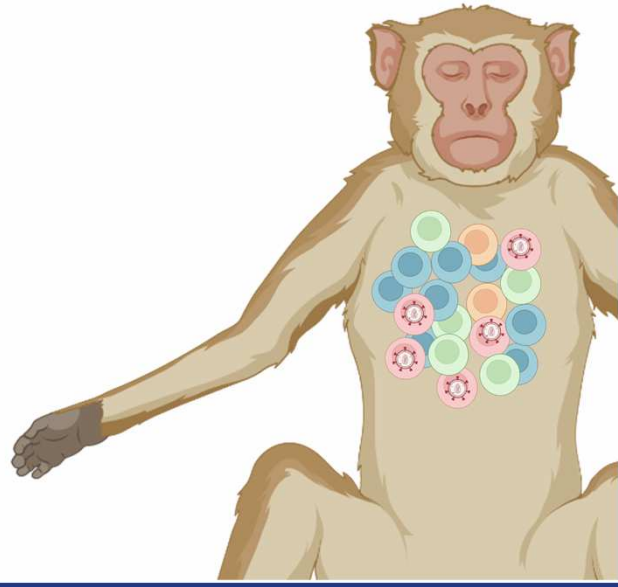
Targeting the SIV Reservoir with Alemtuzumab (anti-CD52)







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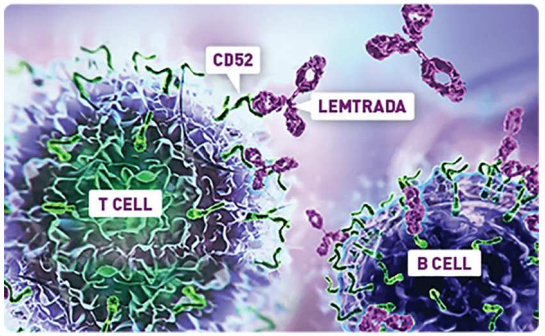
CONFLICTS OF INTEREST

No conflicts of interest to declare.

- **Key questions**
  - Can lymphocyte depletion reduce or eliminate the viral reservoir in SIV-infected ART-treated monkeys?
- **Key findings**
  - Alemtuzumab, a pan-lymphocyte depleting-antibody, induced massive depletion of CD4 T cells in the blood and tissues
  - However, this treatment did not delay time to viral rebound after ART interruption
- **Next steps**
  - Lymphocyte depletion, on it's own, is not sufficient to deplete the reservoir
  - Reservoir depletion strategies may need to account for the ability of the reservoir to reconstitute

Alemtuzumab is a licensed, humanized monoclonal antibody

- **Developed as a lymphocyte-targeting antibody**
  - Cambridge Univ Dept of Pathology (CAMPATH-1H)
- **Used to treat chronic lymphocytic leukemia and multiple sclerosis**
  - Currently marketed as Lemtrada
- **Recognizes CD52, a 12aa GPI-anchored glycoprotein**
  - Also known as “CAMPATH-1 antigen”
  - Expressed on lymphocytes, monocytes and spermatocytes. In monkeys it is sometimes expressed on erythrocytes
- **Depletes CD52+ cells mainly via ADCC and CDC.**



Alemtuzumab can deplete HIV-infected cells

Ex vivo

ORIGINAL RESEARCH

Journal of Virus Eradication 2016; 2: 12–18

Alemtuzumab-induced elimination of HIV-1-infected immune cells

Kiat Ruxrungtham[1,2a], Sunee Sirivichayakul[1a,2], Supranee Buranapraditkun[1,2] and Werner Krause[3*]

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[3] VivoTecc GmbH, Berlin, Germany
[a] These authors contributed equally to this work

In vivo

CLINICAL SCIENCE: CONCISE COMMUNICATIONS

Impact of alemtuzumab on HIV persistence in an HIV-infected individual on antiretroviral therapy with Sezary syndrome

Rasmussen, Thomas A.[a,b]; McMahon, James[c]; Chang, J. Judy[a]; Symons, Jori[a]; Roche, Michael[a]; Dantanarayana, Ashanti[a]; Okoye, Afam[d,e]; Hiener, Bonnie[f]; Palmer, Sarah[f]; Lee, Wen Shi[a]; Kent, Stephen J.[a]; Van Der Weyden, Carrie[g]; Prince, H. Miles[h]; Cameron, Paul U.[a,c]; Lewin, Sharon R.[a,c]

Author Information

AIDS: August 24, 2017 - Volume 31 - Issue 13 - p 1839-1845
doi: 10.1097/QAD.0000000000001540

As part of a HIV cure regimen

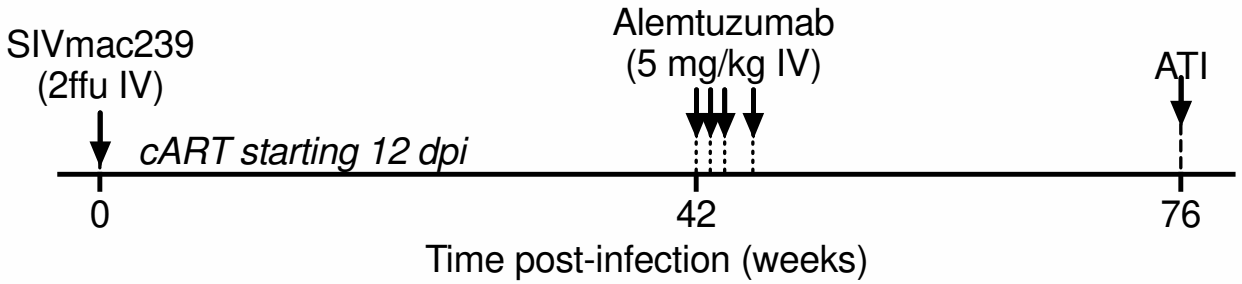
Evidence for HIV-1 cure after *CCR5*Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report

Ravindra Kumar Gupta, Dimitra Peppa, Alison L Hill, Cristina Gálvez, Maria Salgado, Matthew Pace, Laura E McCoy, Sarah A Griffith, John Thornhill, Aljawharah Alrubayyi, Laura E P Huyveneers, Eleni Nastouli, Paul Grant, Simon G Edwards, Andrew J Innes, John Frater, Monique Nijhuis, Anne Marie J Wensing, Javier Martinez-Picado, Eduardo Olavarria

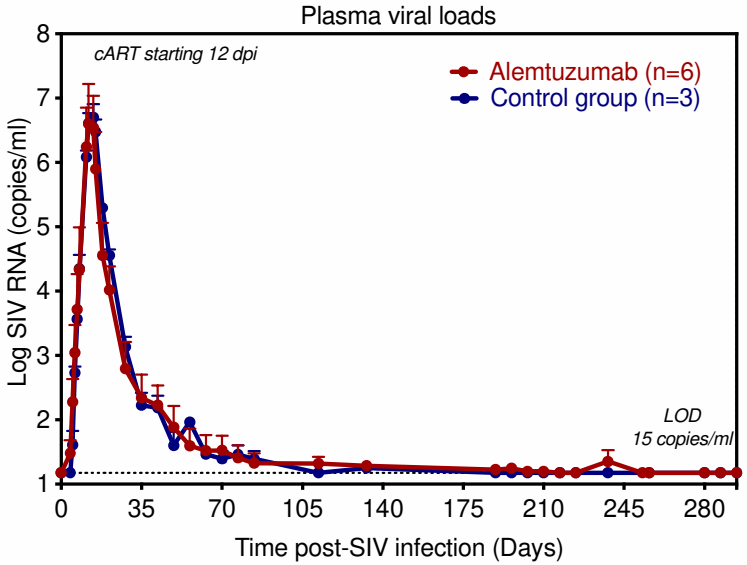
Adam Castillejo, the London Patient

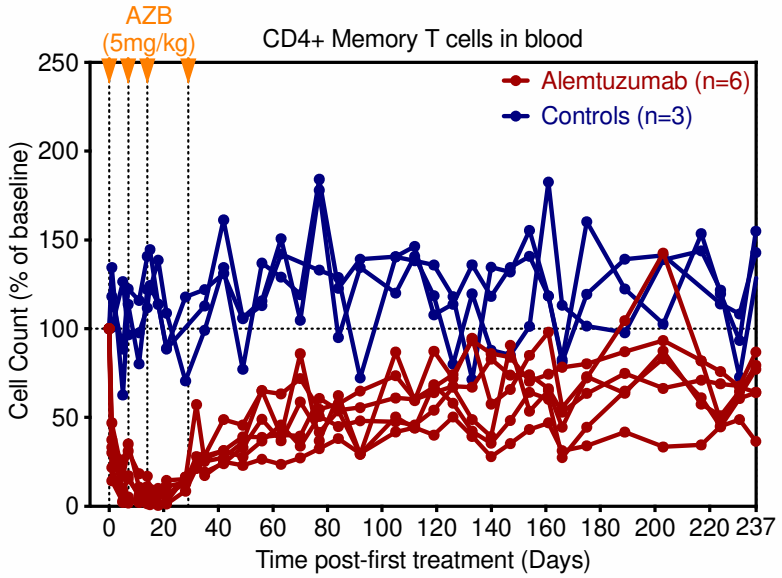
Gupta et al The Lancet HIV, Volume 7, Issue 5, 2020, Pages e340-e347,\

PILOT STUDY: Alemtuzumab effectively depleted CD4 T cells in blood and lymphoid tissues in SIV-infected ART-treated RM

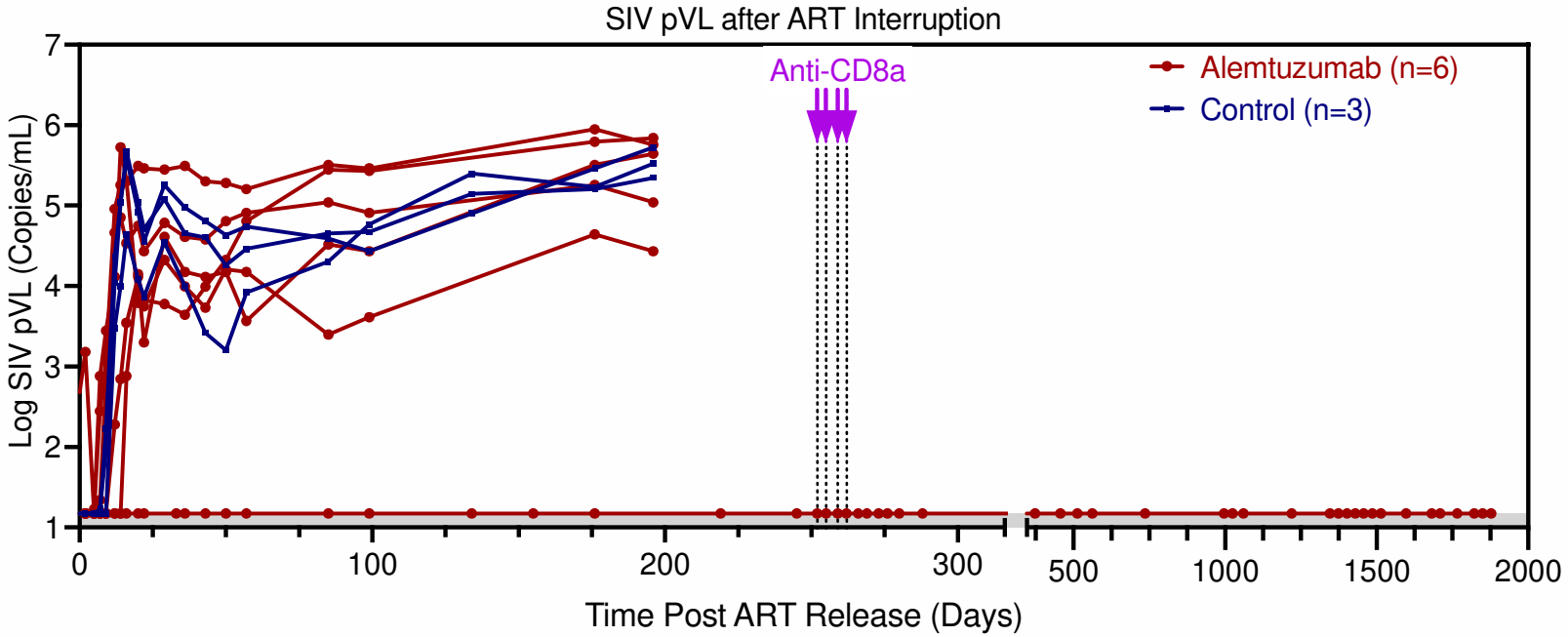


Alemtuzumab (n=6)
Untreated controls (n=3)





After ART interruption, most animals rebounded but one animal did not



This monkey remains aviremic ~1900 days later and we consider this a functional cure. We have nicknamed him the "Beaverton Monkey"

Key Questions

- Can alemtuzumab reduce or eliminate rebound-competent SIV reservoirs in ART-suppressed RM?

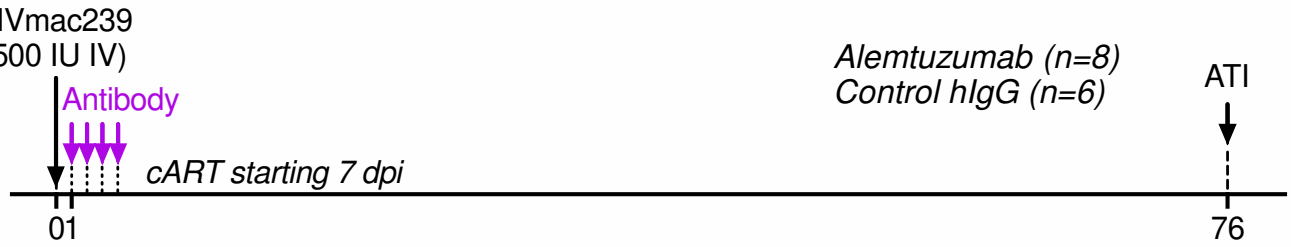
- When are SIV reservoirs most susceptible to depletion?

  "Early": At time of ART initiation (when the reservoir is more active)

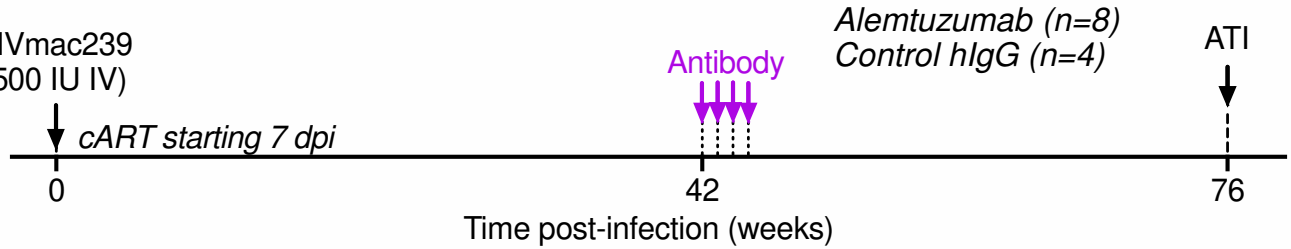
  "Late": Following full ART suppression (when the reservoir is more quiescent)

Experimental Overview

“Early”
(7 dpi)



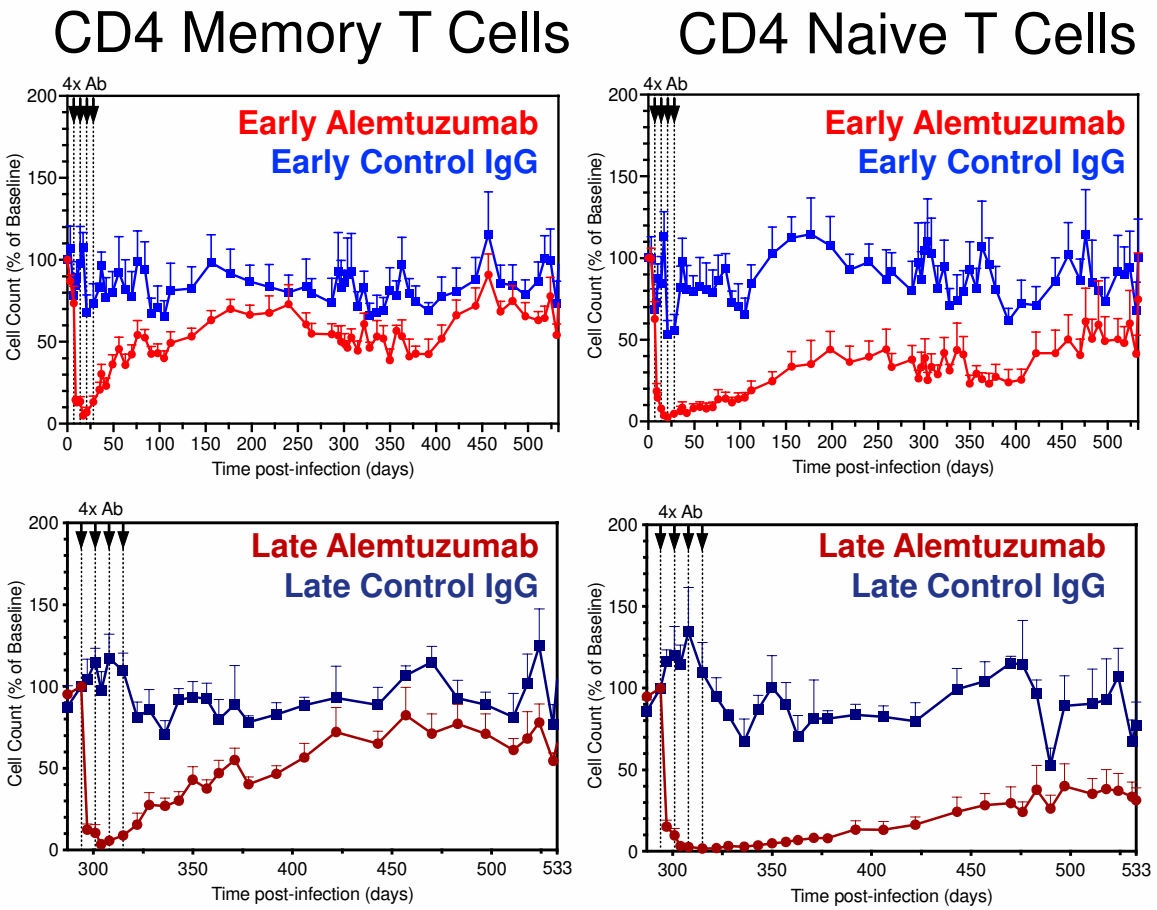
“Late”
(294 dpi)



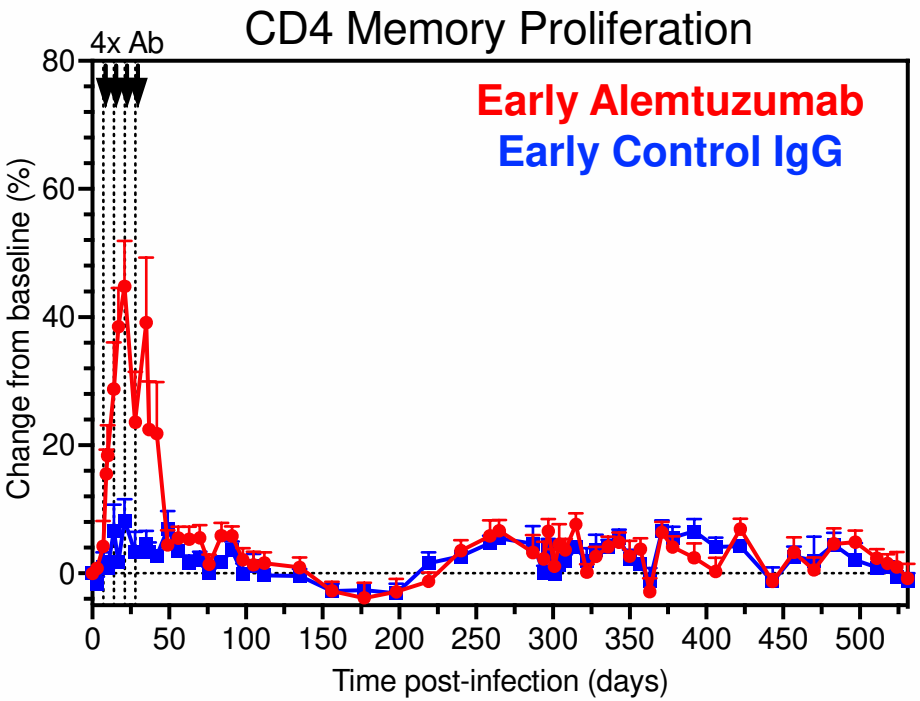
- *Prior to infection, RM were grouped based on screening for CD52 expression on RBCs.*
- *All RM inoculated with SIVmac239M (500 IU IV) and were treated with ART from 7 dpi through 533 dpi*
- *All RM received 4 doses of antibody @ 5mg/kg (either alemtuzumab or humanized control IgG)*

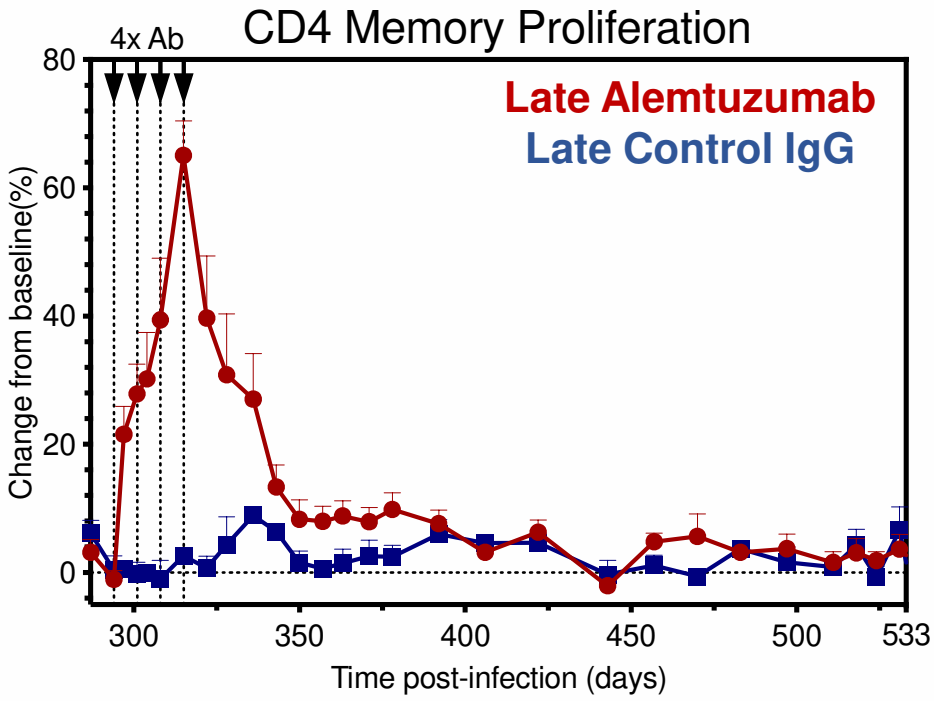
Alemtuzumab depletes CD4+ T cells in peripheral blood

- Alemtuzumab depleted >95% of circulating CD4 T cells
- Following depletion, CD4 T cells reconstituted



Following depletion, there was a significant increase in CD4 memory T cells proliferation



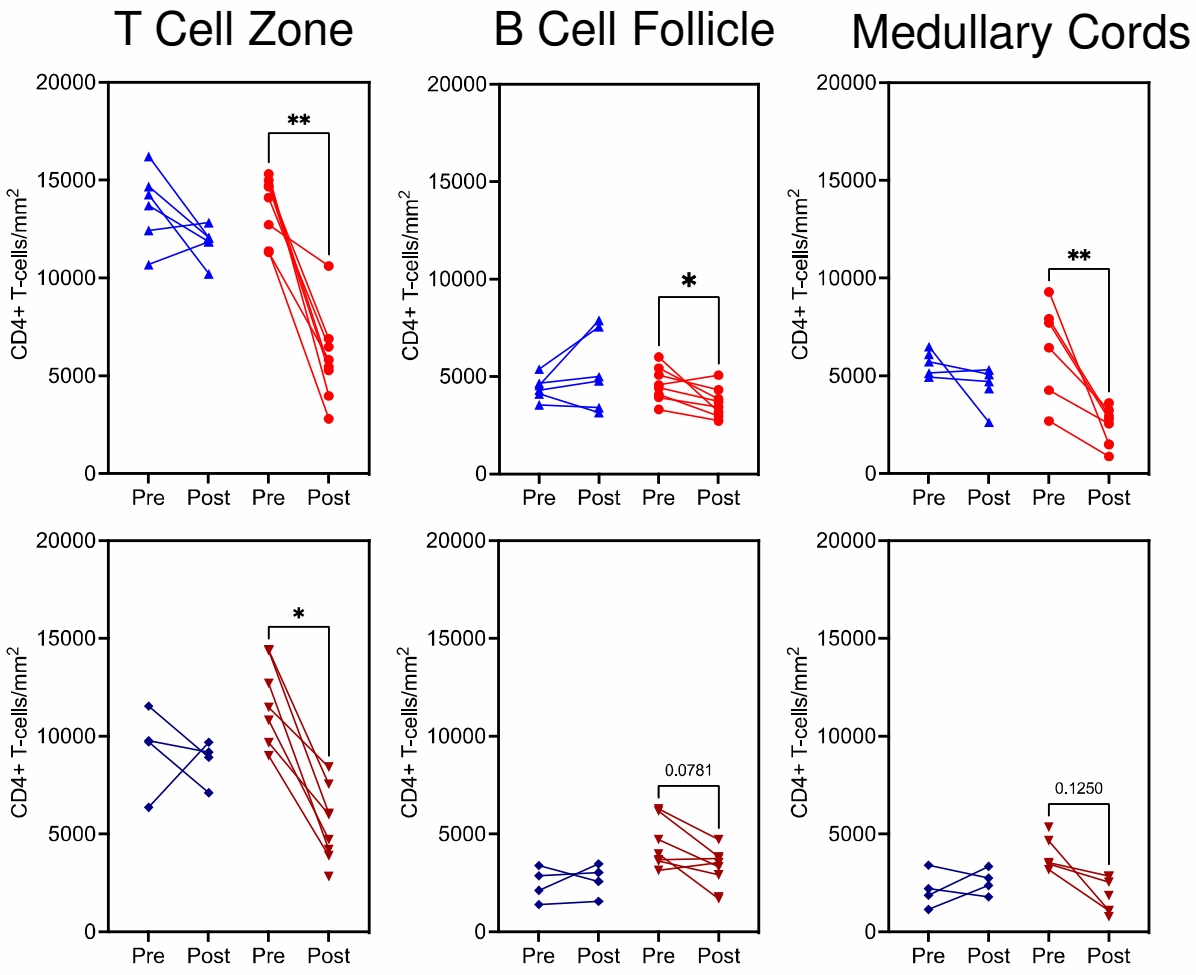


Alemtuzumab also depletes CD4 T cells in the lymph node

Early Alemtuzumab
Early Control IgG

Late Alemtuzumab
Late Control IgG

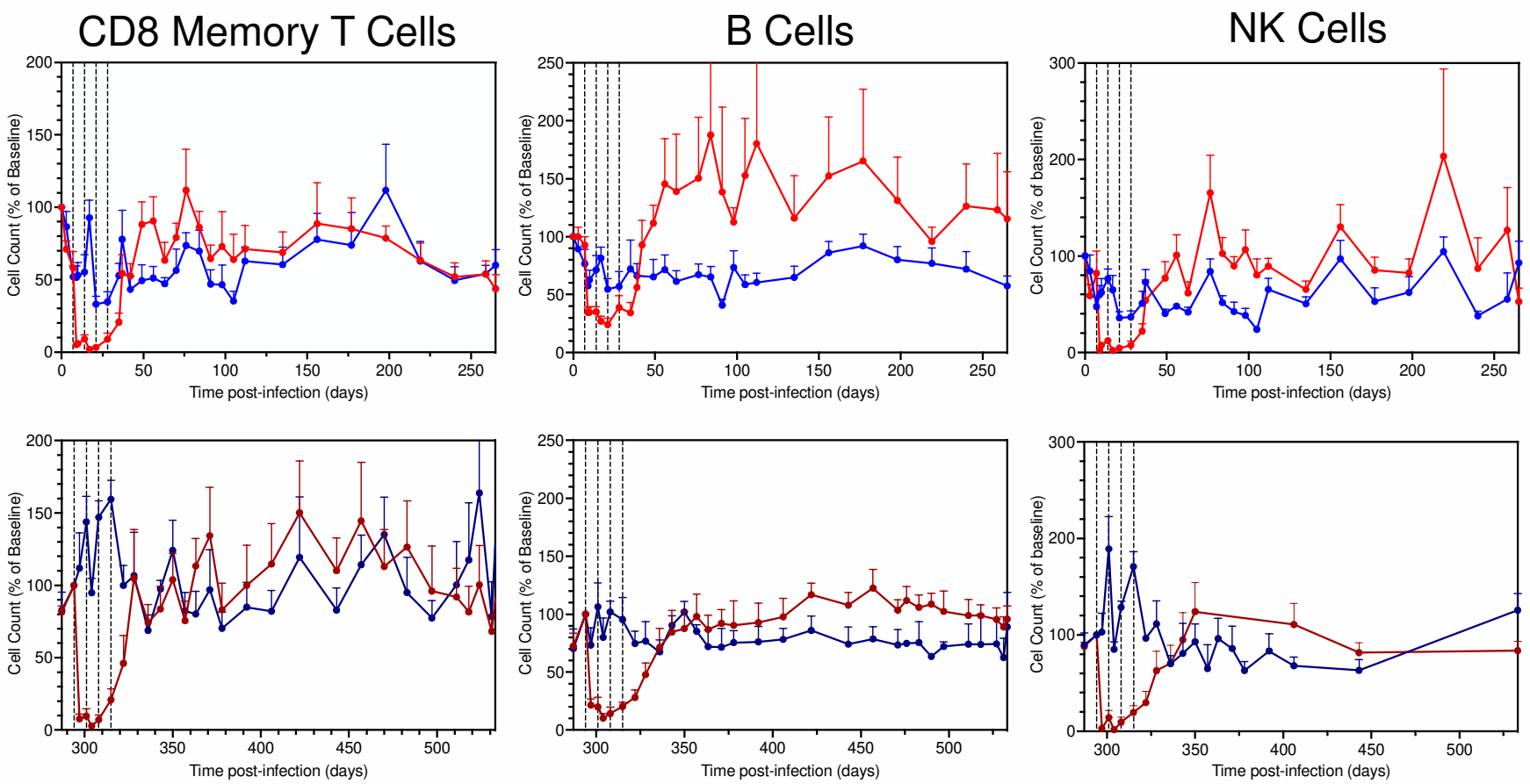
"Post" LN biopsies were collected 2 weeks after final dose of antibody, after the nadir of depletion of CD4 T cells in peripheral blood



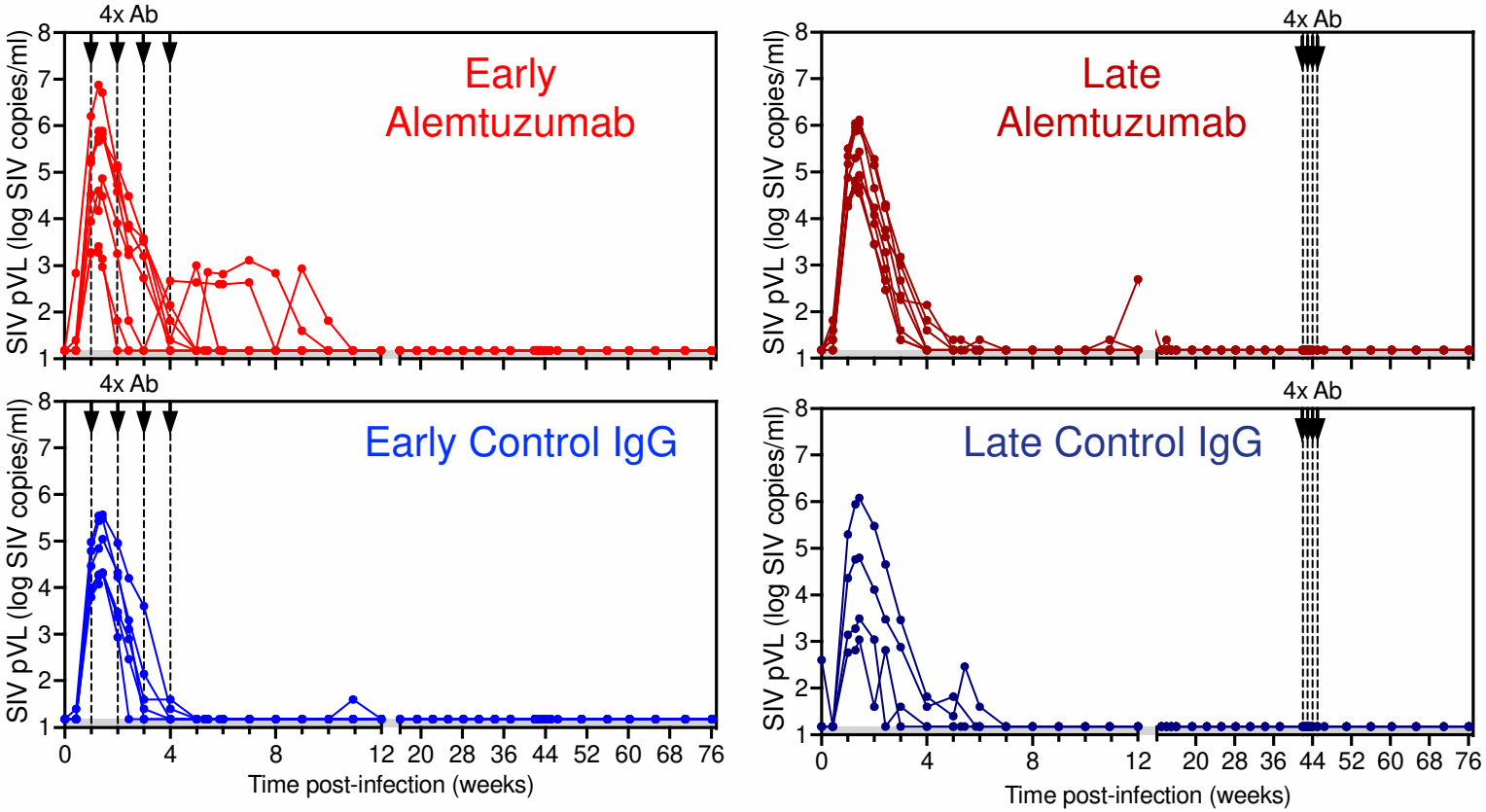
Alemtuzumab also depleted other lymphocyte subsets

Early Alemtuzumab
Early Control IgG

Late Alemtuzumab
Late Control IgG

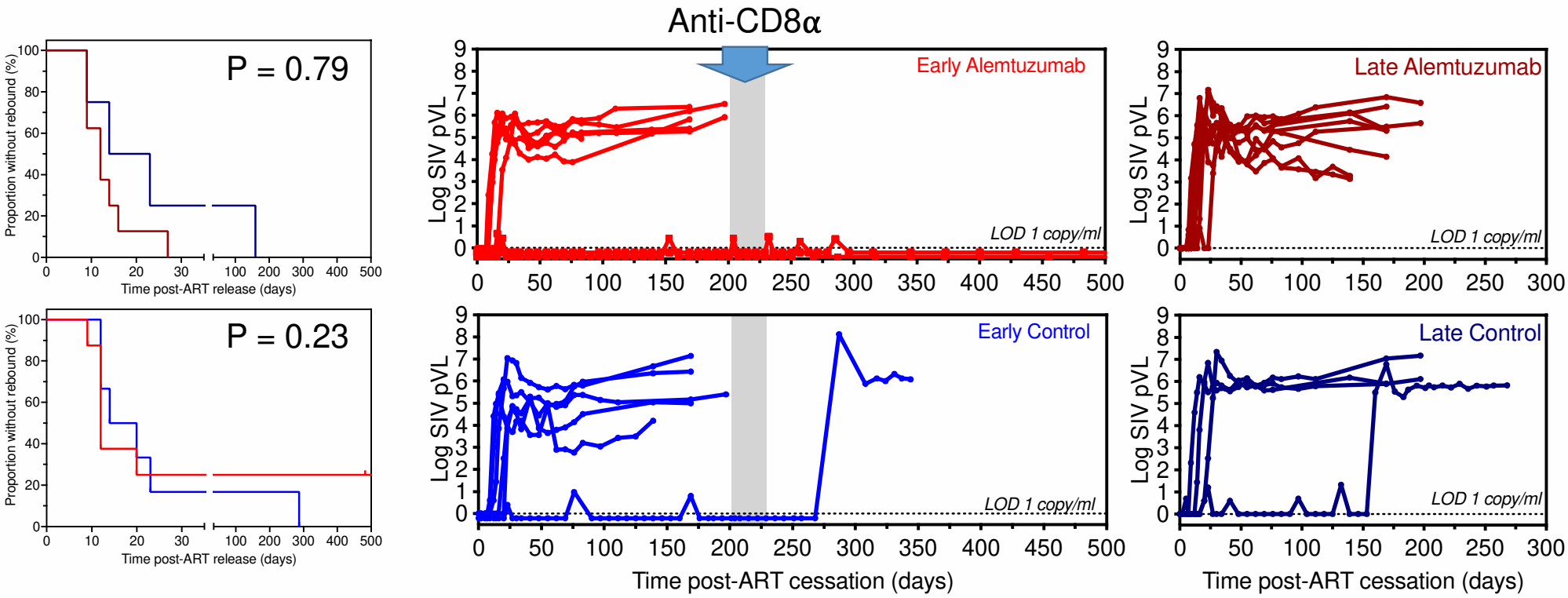


Plasma viremia was equivalent between groups and all RM were virologically suppressed from Week 12 through ATI at Week 76



There was no difference in pre-treatment viremia but some Early Alemtuzumab animals had delayed viral suppression

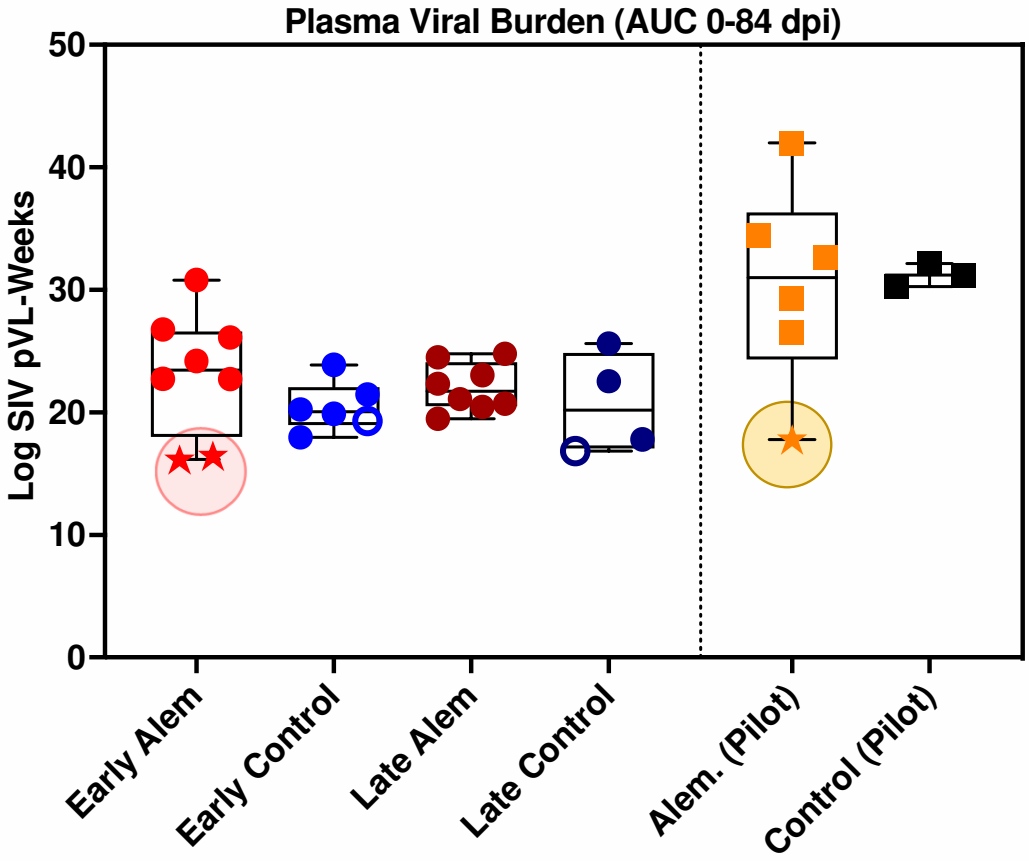
After ART interruption, Alemtuzumab did not delay average time to rebound



…however 2 Alemtuzumab-treated RM have not rebounded >500 days post-ATI

After 200 days post-ART interruption, 3 RM (2 early alemtuzumab, 1 early control) remained aviremic and underwent CD8a depletion (3 biweekly doses @ 50mg/kg)

Smaller viral reservoirs may be more susceptible to Alemtuzumab-mediated disruption



● = normal rebounder (<30 days)

○ = late rebounder (>150 days

★ = Non-rebounder (>500 days)

Summary

- Alemtuzumab depleted >95% of circulating CD4 T cells, and also depleted CD4 T cells in lymph nodes, before reconstitution
- Alemtuzumab treatment did not delay or prevent average time to post-ATI viral rebound
- However, 3 RM with smaller viral reservoirs did not rebound after ART release or subsequent CD8α depletion, suggesting smaller reservoirs may be more susceptible to disruption
- Broad depletion of CD4+ T cells may be inadequate to clear viral reservoirs as these reservoirs appear to rebound with CD4 T cell reconstitution (*consistent w/ Benner et al JCI Insight 2022*)

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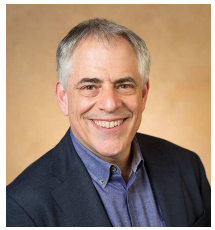
OREGON NATIONAL PRIMATE Research Center — OHSU



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