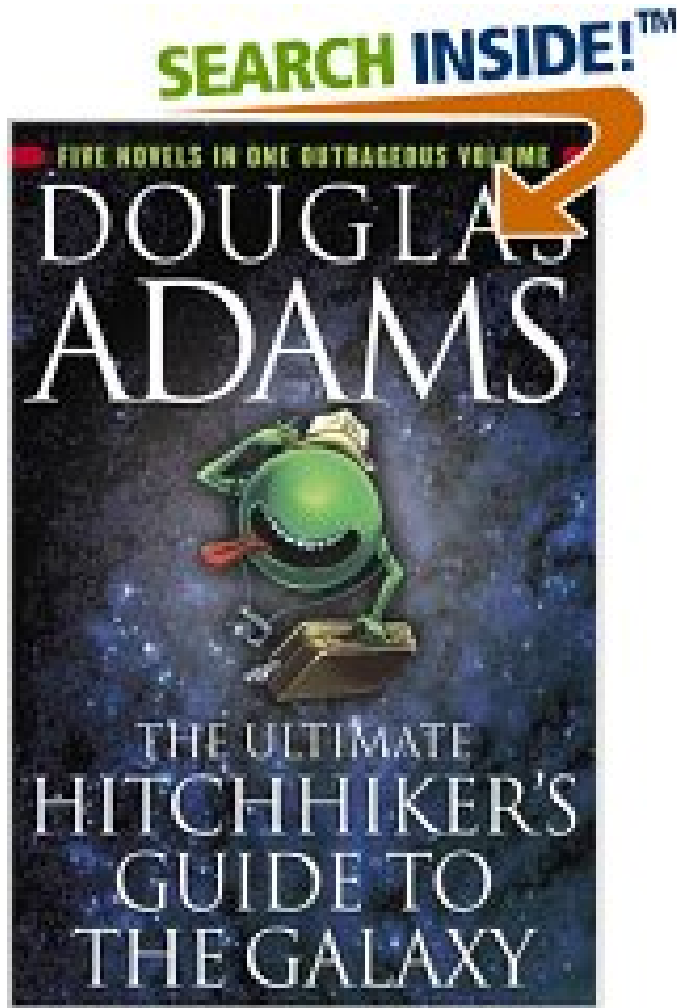


The Hitchhiker's Guide to AIDS Pathogenesis

Cristian Apetrei, MD, PhD

Tulane National Primate Research Center



“It is a curious fact, and one to which no one knows quite how much importance to attach, that something like 85% of all known worlds in the Galaxy, be they primitive or highly advanced, have invented a drink called: Jynnan tonnyx, Gel-N-N-T’N-ix, Jinond-onicks, Chinanto/mnings, Tzjin-anthony-ks”

Douglas Adams-The restaurant at the end of the universe

Gin and tonic

Pathogenic HIV/SIVmac/smm Infection of Humans and Rhesus Macaques

- **Massive, continuous viral replication, with viral load set-point being predictive for the duration of progression to AIDS**
- **Continuous depletion of CD4+ T-cells in peripheral blood that is more pronounced at mucosal sites**
- **High levels of immune activation, the magnitude of which has been reported to be predictive of disease progression**

The great question about life, the universe and everything regarding HIV pathogenesis: “How do the CD4+ T-cells go out of stock during HIV infection?”

The great question about life, the universe and everything: **“How do the CD4⁺ T-cells go out of stock during HIV infection?”**

www.sciencemag.org • SCIENCE • VOL. 280 • 17 APRIL 1998

Gastrointestinal Tract as a Major Site of CD4⁺ T Cell Depletion and Viral Replication in SIV Infection

Ronald S. Veazey, MaryAnn DeMaria, Laura V. Chalifoux, Daniel E. Shvetz, Douglas R. Pauley, Heather L. Knight, Michael Rosenzweig, R. Paul Johnson, Ronald C. Desrosiers, Andrew A. Lackner*

JOURNAL OF VIROLOGY, Aug. 1998, p. 6646–6656
0022-538X/98/\$04.00+0
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Vol. 72, No. 8

Gastrointestinal T Lymphocytes Retain High Potential for Cytokine Responses but Have Severe CD4⁺ T-Cell Depletion at All Stages of Simian Immunodeficiency Virus Infection Compared to Peripheral Lymphocytes

ZELJKA SMIT-McBRIDE,¹ JOSEPH J. MATTAPALLIL,¹ MICHAEL McCHESNEY,² DAVID FERRICK,³ AND SATYA DANDEKAR^{1*}

CD4⁺ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

Jason M. Brenchley,¹ Timothy W. Schacker,² Laura E. Ruff,¹ David A. Price,¹
Jodie H. Taylor,³ Gregory J. Beilman,³ Phuong L. Nguyen,⁵ Alexander Khoruts,²
Matthew Larson,² Ashley T. Haase,⁴ and Daniel C. Douek¹

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²*Department of Medicine, ³Department of Surgery, Division of Surgical Critical Care, and ⁴Department of Microbiology, University of Minnesota, Minneapolis, MN 55455*

⁵*Division of Hematopathology, Mayo Clinic, Rochester, MN 55905*

J. Exp. Med. © The Rockefeller University Press • 0022-1007/2004/09/761/10 \$8.00
Volume 200, Number 6, September 20, 2004 761–770
<http://www.jem.org/cgi/doi/10.1084/jem.20041196>

Primary HIV-1 Infection Is Associated with Preferential Depletion of CD4⁺ T Lymphocytes from Effector Sites in the Gastrointestinal Tract

Saurabh Mehandru,¹ Michael A. Poles,^{1,2} Klara Tenner-Racz,³
Amir Horowitz,^{1,2} Arlene Hurley,¹ Christine Hogan,¹ Daniel Boden,¹
Paul Racz,³ and Martin Markowitz¹

¹*Aaron Diamond AIDS Research Center and The Rockefeller University, New York, NY 10016*

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³*Bernhard-Nocht Institut Fur Tropenmedizin, 20359 Hamburg, Germany*

The Journal of Experimental Medicine • Volume 200, Number 10, November 15, 2004 1299–1314
http://www.jem.org/cgi/doi/10.1084/jem.20041049

Insufficient Production and Tissue Delivery of CD4⁺ Memory T Cells in Rapidly Progressive Simian Immunodeficiency Virus Infection

Louis J. Picker,¹ Shoko I. Hagen,¹ Richard Lum,¹ Edward F. Reed-Inderbitzin,¹ Lyn M. Daly,¹ Andrew W. Sylwester,¹ Joshua M. Walker,¹ Don C. Siess,¹ Michael Piatak Jr.,⁴ Chenxi Wang,² David B. Allison,² Vernon C. Maino,³ Jeffrey D. Lifson,⁴ Toshiaki Kodama,⁵ and Michael K. Axthelm¹

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³Becton Dickinson Biosciences, San Jose, CA 95131

⁴AIDS Vaccine Program, Science Applications International Corporation Frederick, Inc., National Cancer Institute (NCI), Frederick, MD 21702

⁵Department of Molecular Genetics and Biochemistry, University of Pittsburgh, Pittsburgh, PA 15260

Peak SIV replication in resting memory CD4⁺ T cells depletes gut lamina propria CD4⁺ T cells

Qingsheng Li¹, Lijie Duan¹, Jacob D. Estes¹, Zhong-Min Ma⁴, Tracy Rourke⁴, Yichuan Wang⁴, Cavan Reilly², John Carlis³, Christopher J. Miller^{4,5} & Ashley T. Haase¹

¹Department of Microbiology, Medical School, University of Minnesota, MMC 196, 420 Delaware Street S.E., ²Division of Biostatistics, School of Public Health, University of Minnesota, MMC 303, 420 Delaware Street S.E., and ³Department of Computer Science and Engineering, Institute of Technology, University of Minnesota, 200 Union Street S.E., Minneapolis, Minnesota 55455, USA

⁴California National Primate Research Center and Center for Comparative Medicine, and ⁵Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, and Division of Infectious Diseases, School of Medicine, University of California, Davis, California 95616, USA

articles

Massive infection and loss of memory CD4⁺ T cells in multiple tissues during acute SIV infection

Joseph J. Mattapallil¹, Daniel C. Douek², Brenna Hill², Yoshiaki Nishimura³, Malcolm Martin³ & Mario Roederer¹

¹ImmunoTechnology Section and ²Human Immunology Section, Vaccine Research Center, and ³Laboratory of Molecular Microbiology, NIAID, NIH, Bethesda, Maryland 20892, USA

HIV swiftly guts the immune system

Ronald S Veazey & Andrew A Lackner

Two studies show that SIV directly kills massive numbers of immune cells in the gut within days of infection. The results come on the heels of similarly dramatic findings for HIV, and could radically shift the focus of HIV research and therapy.

HIV pathogenesis: the first cut is the deepest

Louis J Picker & David I Watkins

HIV pathogenesis is thought of as a chronic infection involving slow degradation of immunity that ultimately leads to AIDS. This scenario, however, could reflect the decay of an immune system mortally wounded during acute HIV infection.

Viral blitzkrieg

R. Paul Johnson and Amitinder Kaur

It takes years for AIDS to develop from the damage inflicted on the immune system by HIV or its simian counterpart. Surprisingly, as many as half of the body's memory T cells may die at a very early stage of infection.

HIV disease: fallout from a mucosal catastrophe?

Jason M Brenchley, David A Price & Daniel C Douek

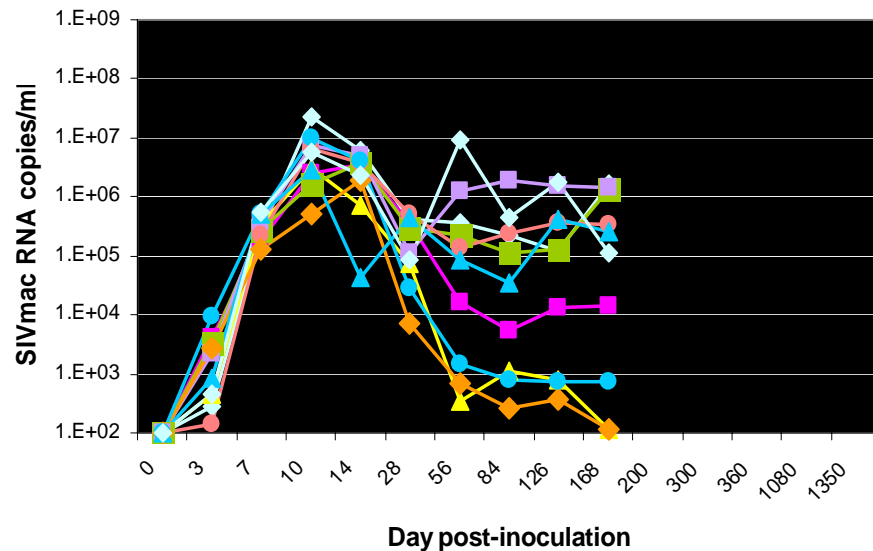
Pathogenesis of HIV infection: what the virus spares is as important as what it destroys

Zvi Grossman, Martin Meier-Schellersheim, William E Paul & Louis J Picker

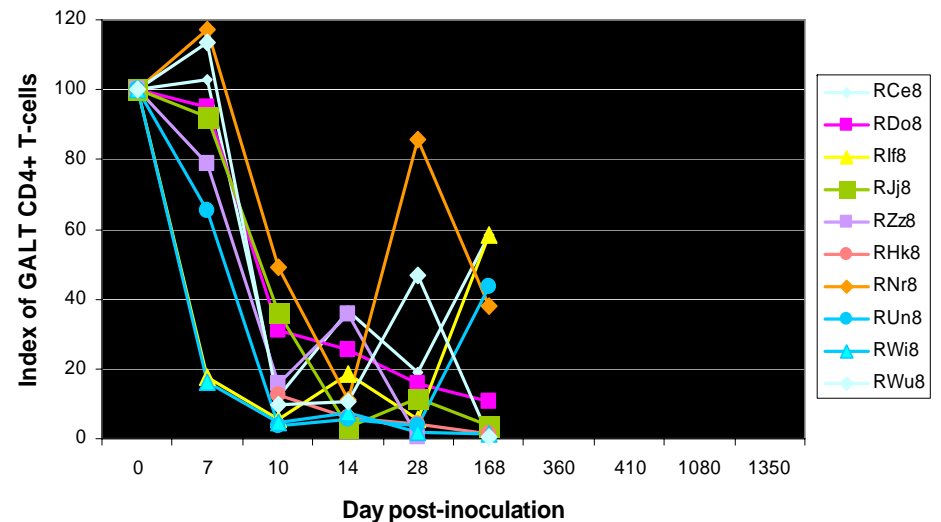
**Then why does it take 7-10 years
to get AIDS?**

Jynnan tonnyx: Highly pathogenic SIV Infection: SIVmac Infection in Vaccinated and Unvaccinated RMs

Dynamics of SIVmac viral load



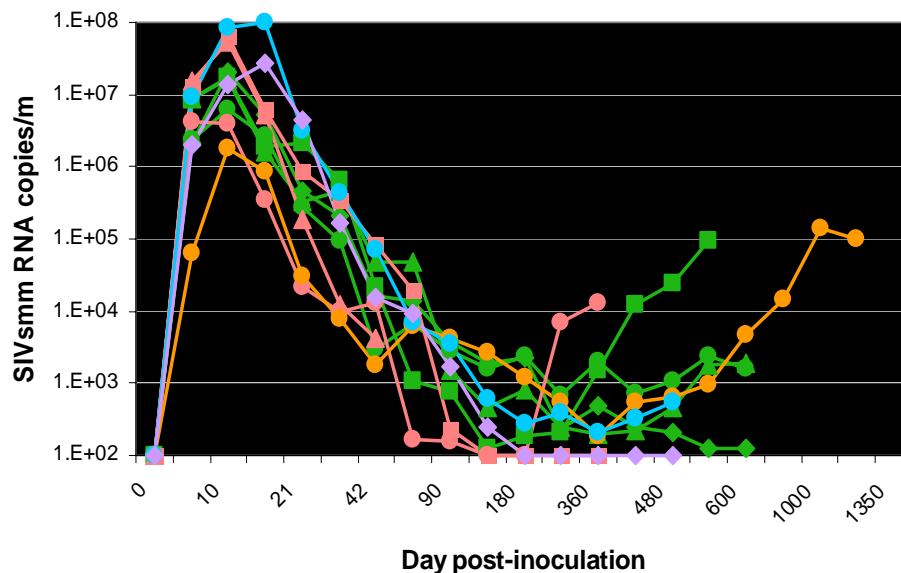
Dynamics of GALT CD4+ T-cells



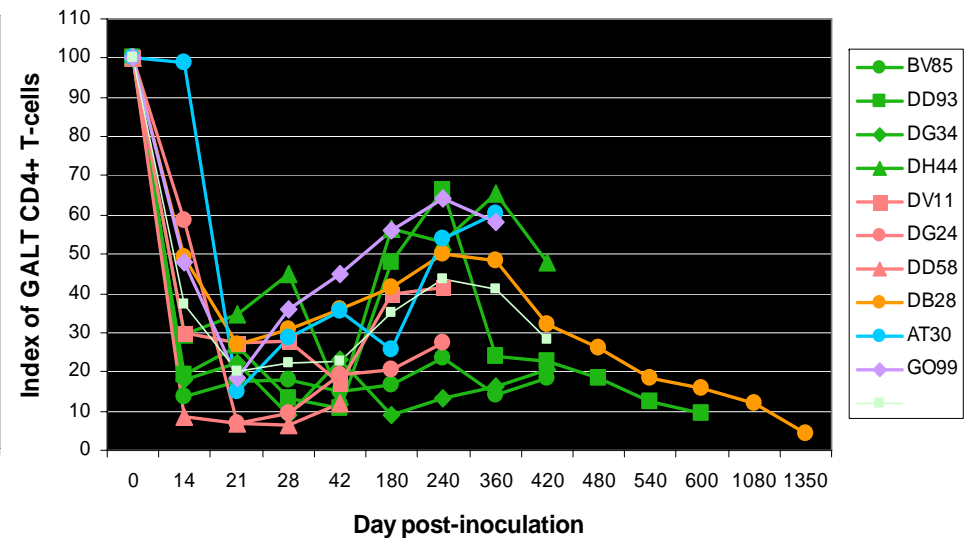
Similar levels of acute viral replication result in similar acute mucosal CD4+ T-cell depletion, irrespective of the dynamics of chronic infection

Jinond-o-nicks: Pathogenic SIV infection: RM Infection with Primary SIVsmm Isolates

Dynamics of SIVmac viral load



Dynamics of GALT CD4+ T-cells



- 60-90% of mucosal CD4+ T-cells are depleted during acute infection
- Magnitude of depletion depends on the levels of VL
- Mucosal CD4+ T-cell recovery can occur if viral replication is controlled

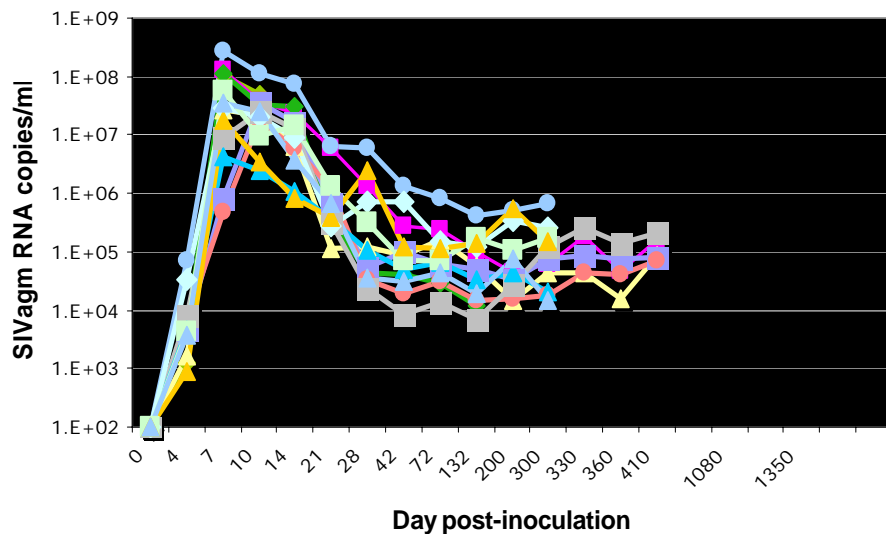
SIV Infection In Natural African NHP Hosts



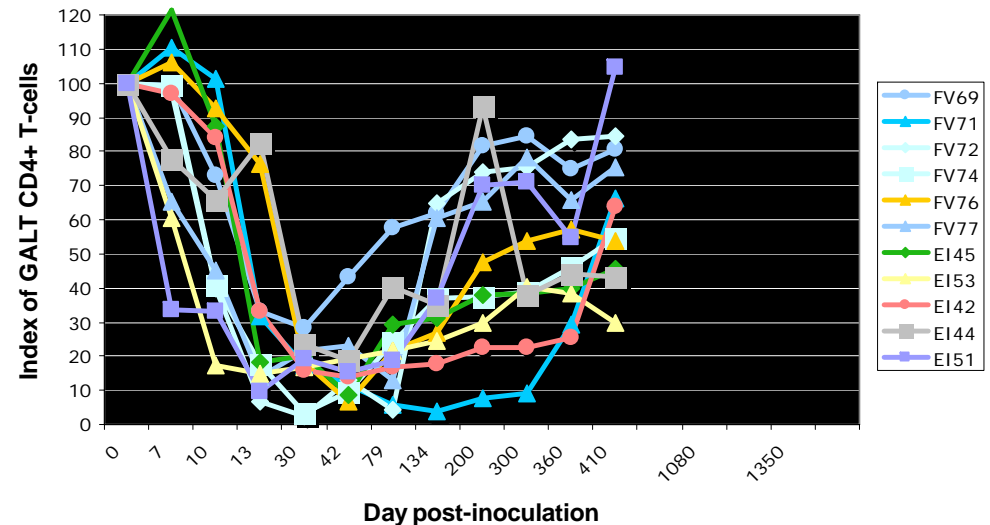
- **Active viral replication, set-points similar/higher than those reported in pathogenic infection**
- **Transient depletion of peripheral CD4+ T-cells during primary infection, which rebound to pre-infection levels during the chronic stage**
- **Transient or moderate increases in immune activation and proliferation during acute infection, with return to baseline levels during the chronic phase**
- **Muted immune responses**

Gel-N-N-T'N-ix: Natural Nonprogressive, Persistent SIV Infections: SIVagm Infection of AGMs

Dynamics of SIVagm viral load



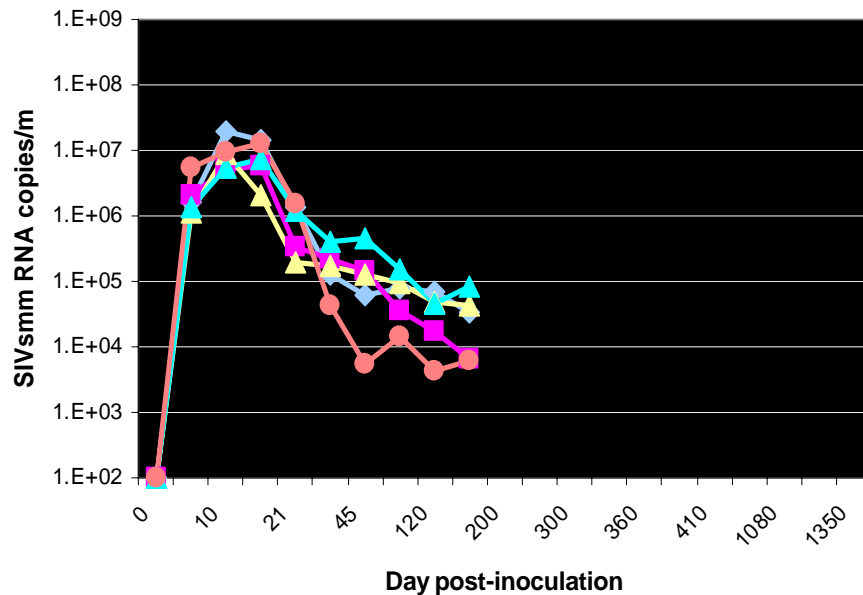
Dynamics of GALT CD4+ T-cells



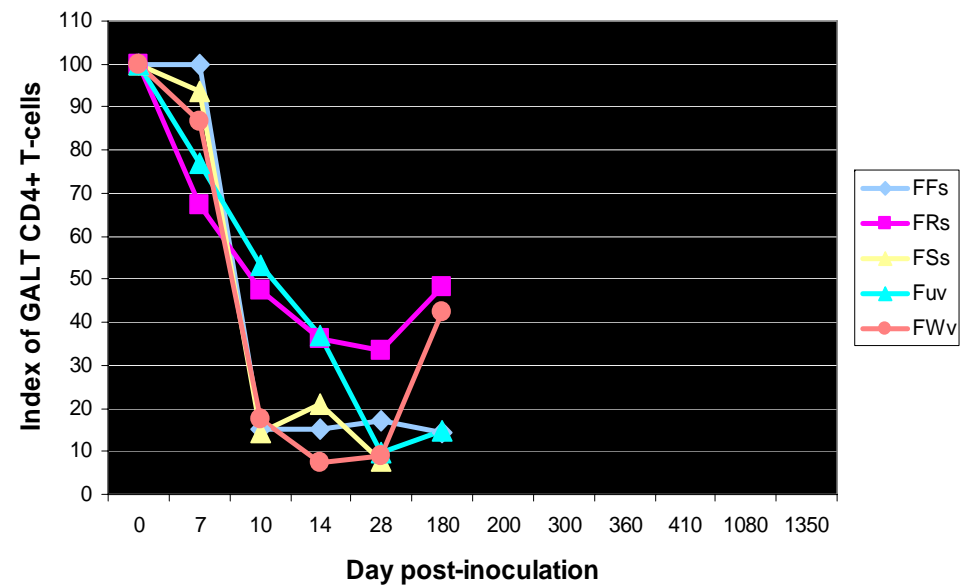
- Similar magnitude of acute mucosal CD4+ T-cell depletion as in pathogenic infections
- Significant recovery of GALT CD4+ T-cells during chronic infection **in the presence of high levels of viral replication (but in the context of normal levels of apoptosis, immune activation and CD4+ T-cell proliferation!!!)**

Ge-N-N-T'N-ix: Natural Nonprogressive, Persistent SIV Infections: SIVsmm Infection of SMs

Dynamics of SIVsmm viral load



Dynamics of GALT CD4+ T-cells



- Similar magnitude of acute mucosal CD4+ T-cell depletion as in pathogenic infections
- Significant recovery of GALT CD4+ T-cells during chronic infection **in the presence of high levels of viral replication (but in the context of normal levels of apoptosis, immune activation and CD4+ T-cell proliferation!!!)**

September 1st, 2007

The Journal of Immunology

Acute Loss of Intestinal CD4⁺ T Cells Is Not Predictive of Simian Immunodeficiency Virus Virulence¹

**Ivona Pandrea,^{2*†} Rajeev Gautam,* Ruy M. Ribeiro,[¶] Jason M. Brenchley,^{||} Isolde F. Butler,*
Melissa Pattison,* Terry Rasmussen,* Preston A. Marx,^{*§} Guido Silvestri,**
Andrew A. Lackner,^{*‡} Alan S. Perelson,[¶] Daniel C. Douek,^{||}
Ronald S. Veazey,^{*†} and Cristian Apetrei^{*§}**

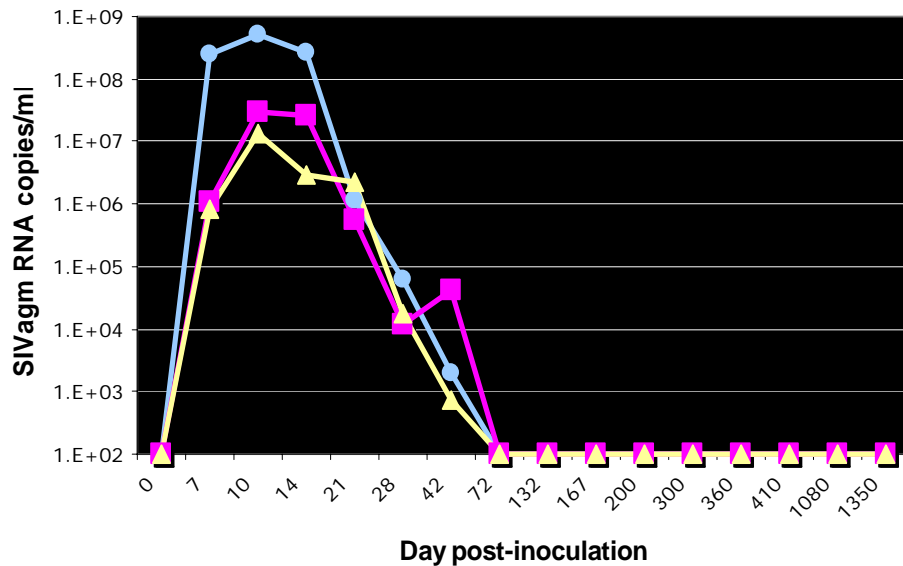
The Journal of Immunology

Severe Depletion of Mucosal CD4⁺ T Cells in AIDS-Free Simian Immunodeficiency Virus-Infected Sooty Mangabeys¹

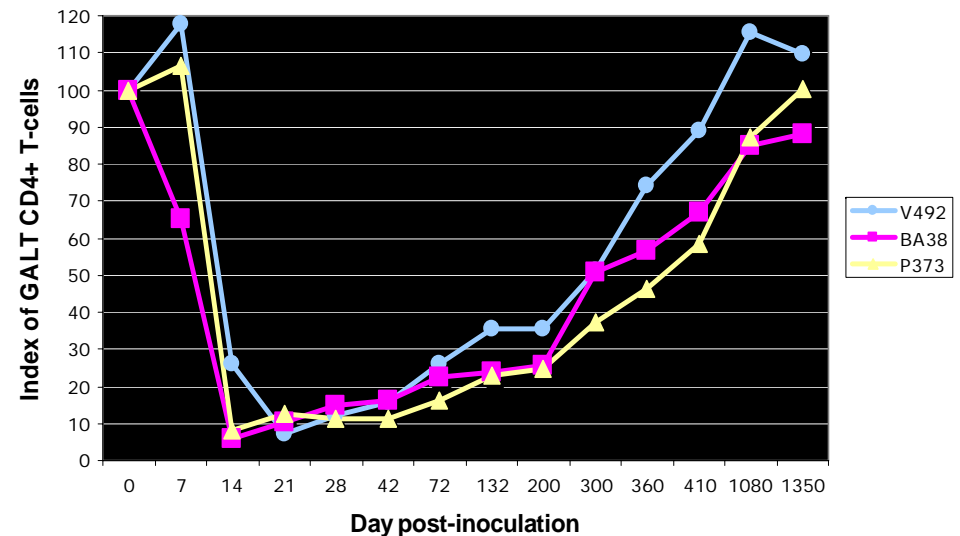
**Shari N. Gordon,^{*†} Nichole R. Klatt,^{*†} Steven E. Bosinger,[‡] Jason M. Brenchley,[§]
Jeffrey M. Milush,[¶] Jessica C. Engram,^{*†} Richard M. Dunham,^{*†} Mirko Paiardini,^{*†}
Sara Klucking,[†] Ali Danesh,[‡] Elizabeth A. Strobert,[†] Cristian Apetrei,^{||} Ivona V. Pandrea,^{||}
David Kelvin,[‡] Daniel C. Douek,[§] Silvija I. Staprans,[†] Donald L. Sodora,[¶] and Guido Silvestri^{2*†}**

Tzjin-anthony-ks: Controlled SIV Infections: **SIVagm Infection of RMs**

Dynamics of SIVmac viral load



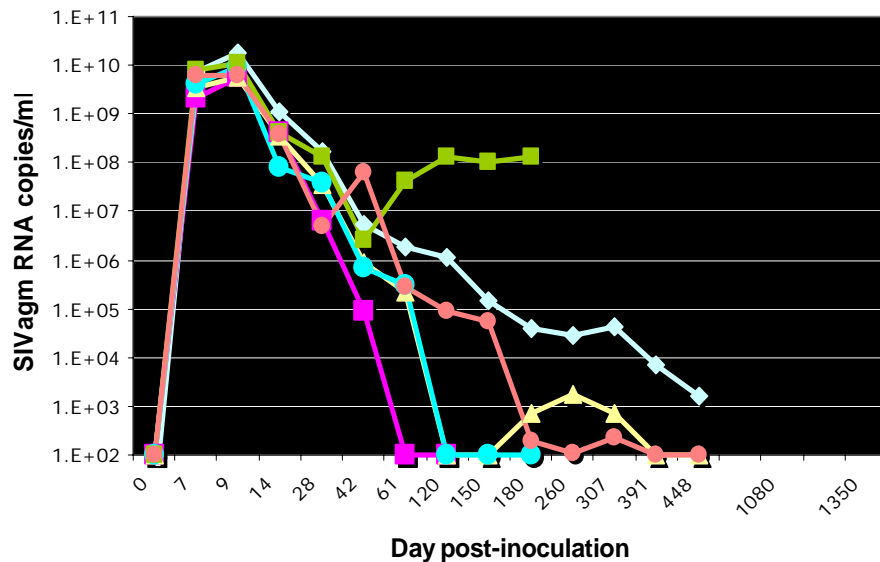
Dynamics of GALT CD4+ T-cells



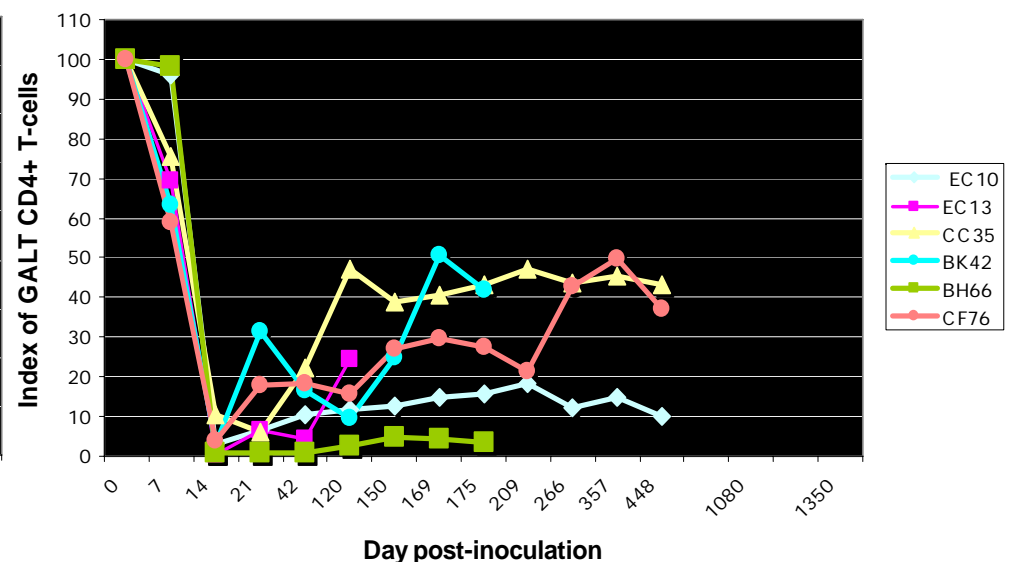
- **Massive (>90%) acute depletion of mucosal CD4+ T-cells**
- **Total recovery during the follow-up!!!!**
- **Demonstrates that mucosal barrier can be effectively restored if viral replication is completely controlled.**

Chinanto/mnings: Variable outcome of SIV Infection: PTM Infection with SIVagm

Dynamics of SIVmac viral load

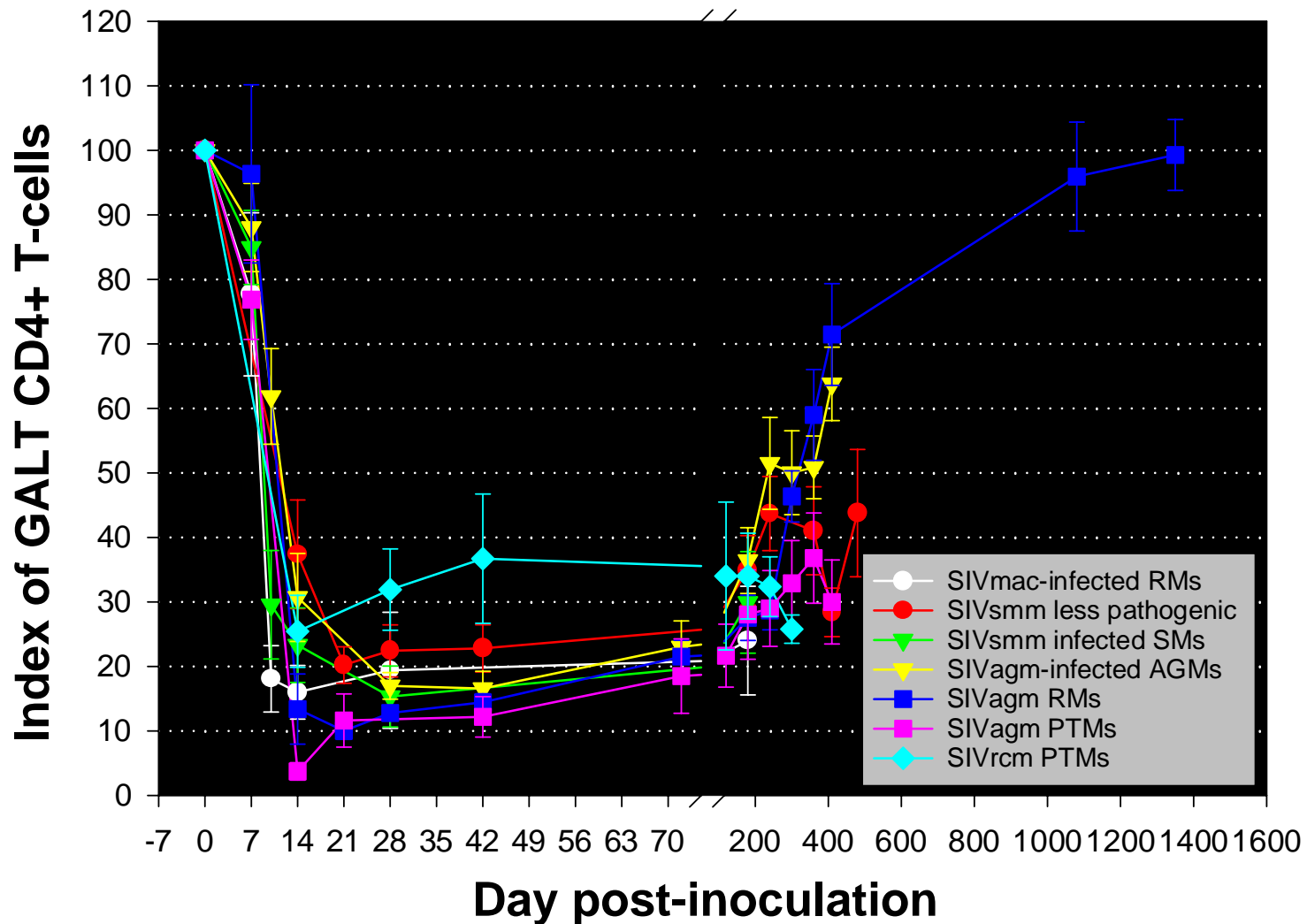


Dynamics of GALT CD4+ T-cells



- **>95% of mucosal CD4+ T-cells are depleted during acute infection**
- **No difference can be seen for acute depletion of mucosal CD4+ T-cells between progressors and controllers**
- **Limited mucosal CD4+ T-cell recovery with even intermittent viral replication.**

The Magnitude of Acute CD4+ T-Cell Depletion Does not Predict SIV Disease Progression



Conclusions

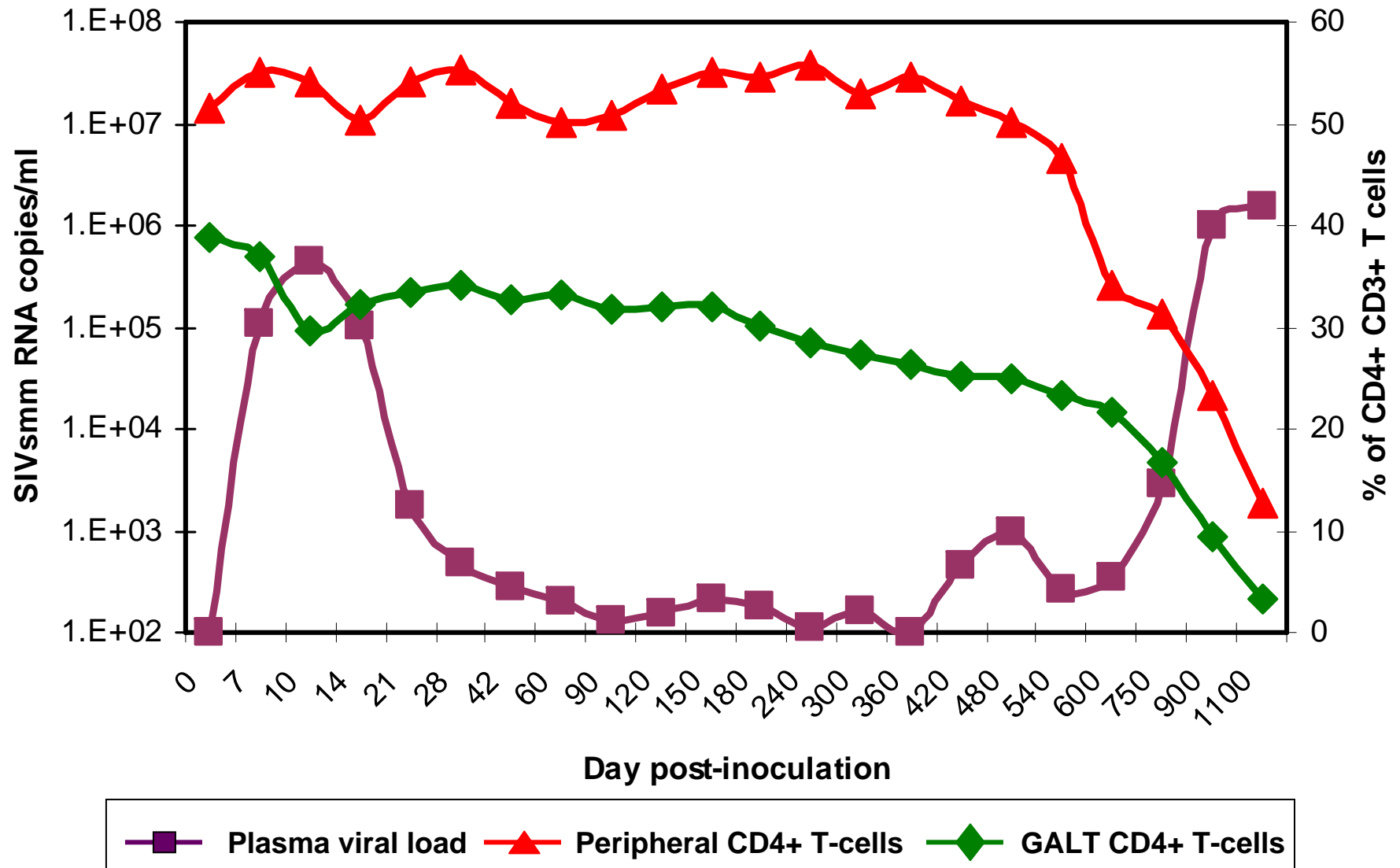
- **Acute mucosal CD4⁺ T-cell depletion is a common feature of SIV infection in pathogenic, persistent non-pathogenic or controlled infection.**
- **Therefore, acute mucosal CD4⁺ T-cell depletion may be necessary but it is not sufficient to result in disease progression.**
- **The outcome of chronic SIV infection is dependent on viral replication, other factors such as immune activation, and possibly other unknown factors.**

- **Acute mucosal CD4+ T- cell depletion not being predictive for disease progression, progression to AIDS is independent of acute CD4+ T-cell depletion.**

Is it?

Yes.

Dynamics of SIVsmmM951 infection in RM DB28



What is driving progression to AIDS?

**What is the answer to the Great
Question Of Life, the Universe and
Everything?**

“All right” said Deep Thought. “The answer to the Great Question...”

“Yes...!”

“Of life, the Universe and Everything...” said Deep Thought.

“Yes...!”

“Is...” said Deep Thought, and paused.

“Yes...!”

“Is...”

“Yes...!!!...?”



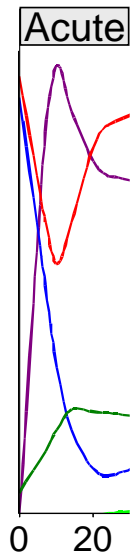
42

42

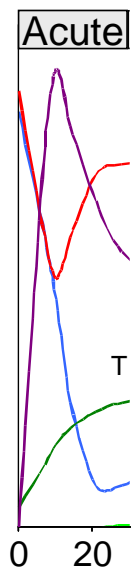
The set-point!!!!

Comparative dynamics of pathogenic and non-pathogenic HIV/SIV infection

Natural,
non-progressive
infection



Pathogenic
SIV/HIV
infection



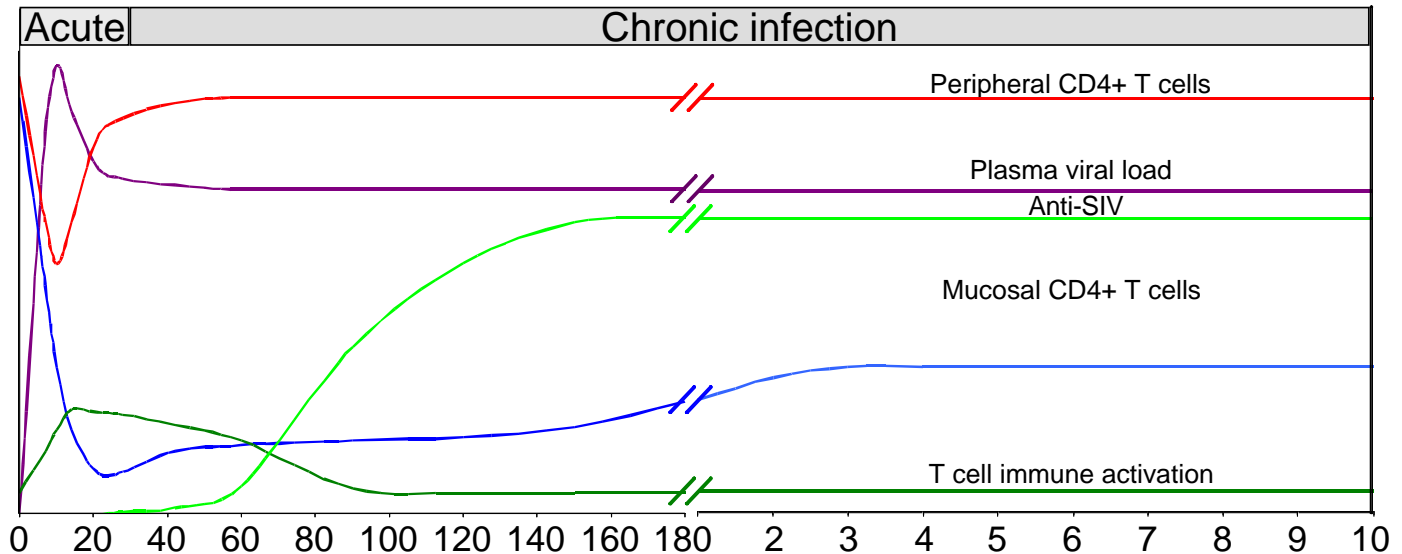
Days post-infection

Years post-infection

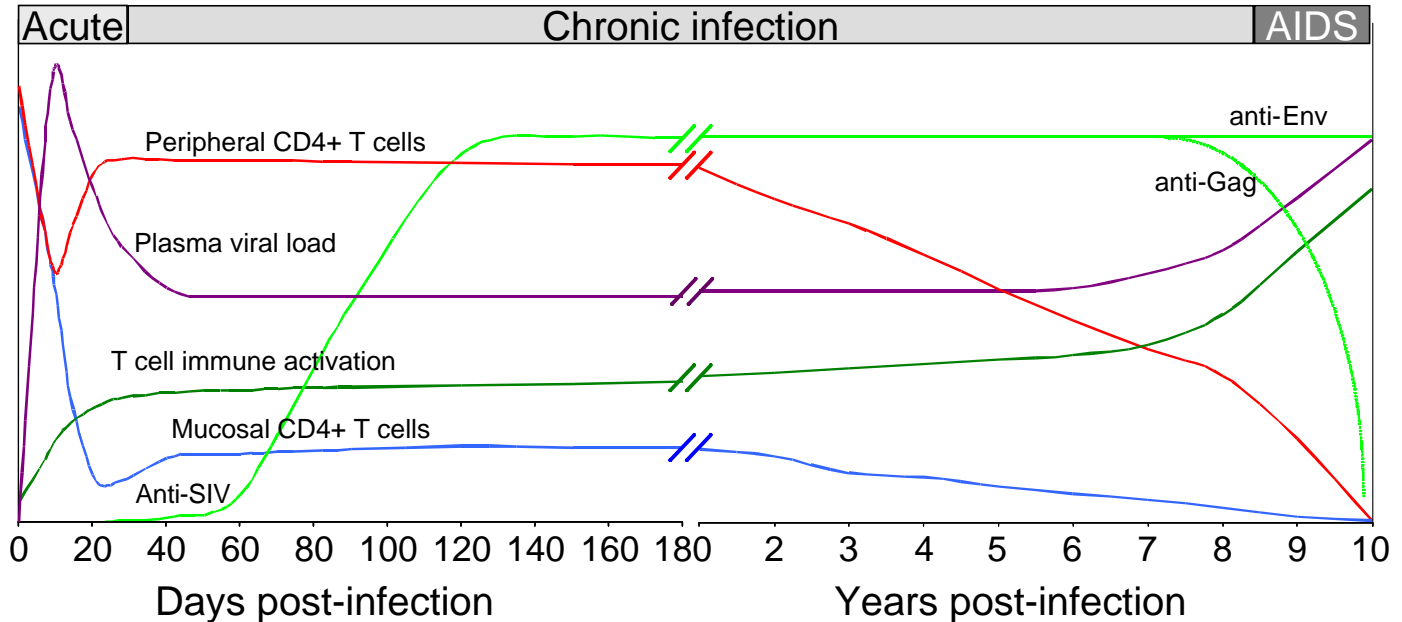
2 3 4 5 6 7 8 9 10

Comparative dynamics of pathogenic and non-pathogenic HIV/SIV infection

Natural, non-progressive infection



Pathogenic SIV/HIV infection





2005



2007

Dancing for the stars

Cristian Apetrei Lab

Rajeev Gautam

Isolde Krummrich

Thaidra Gaufin

Mary Barnes

Melissa Pattison

Chris Monjure

Nathalia Katz

Ivona Pandrea Lab

Crystal Stoulig

Chase Carter

Clint Coleman

Joseph Barbercheck

Aarti Gautam

Guido Silvestri Lab

Shari Gordon

Rick Dunham

LANL

Ruy Ribeiro

Alan Perelson

The stars

Preston Marx

Ronald Veazey

Andrew Lackner

Special guest appearance

Amitinder Kaur, NEPRC

David Montefiori, Duke

Vanessa Hirsch, NIH

**Produced by
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LOOK INSIDE!™

NEW YORK TIMES BESTSELLING AUTHOR OF
HITCHHIKER'S
GUIDE TO THE GALAXY

**DOUGLAS
ADAMS**

SO LONG, AND
THANKS
FOR ALL
THE **FISH**