T cell control of HIV:
A tale in six brief chapters

New England Cytometry Meeting
October 25, 2018

Ragon Institute of MGH, MIT and Harvard

hhmi
Howard Hughes Medical Institute

UNIVERSITY OF KWAZULU-NATAL

Chapter 1.
A New Disease

Learning from patients: 1981

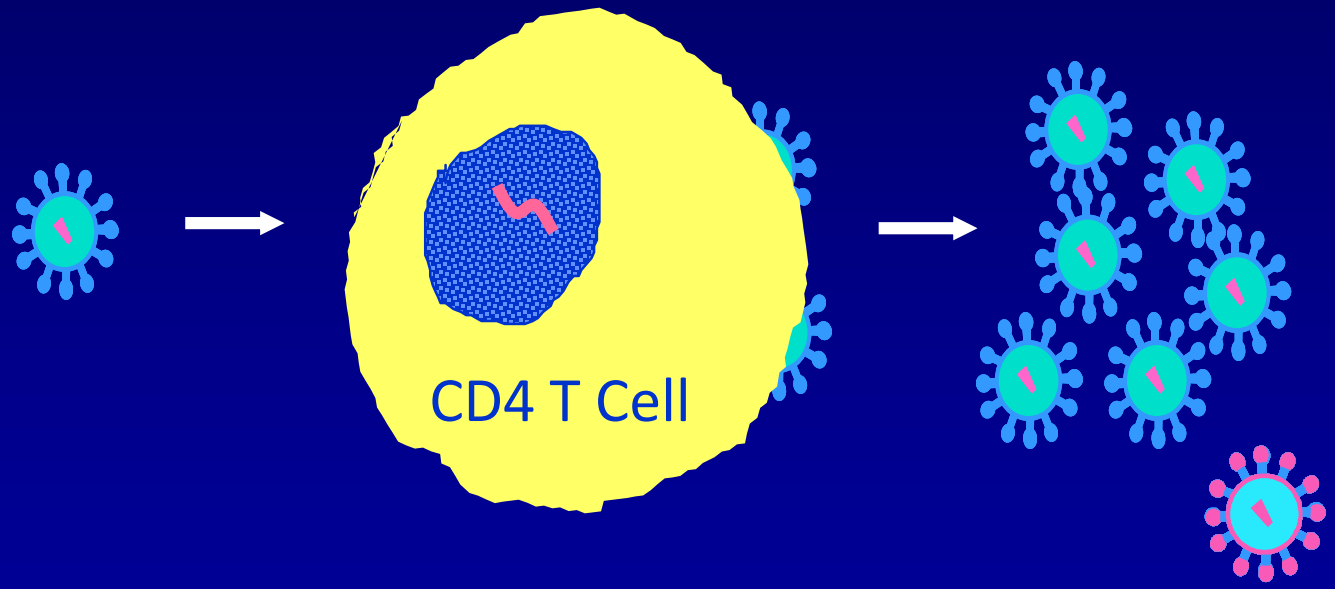
- 19 year old male transferred to MGH
  Previously well
  - Profound weight loss
  - TB in sputum, on Rx
  - Acute change in mental status
- Presumptive diagnosis on transfer:
  - Pulmonary TB with TB meningitis

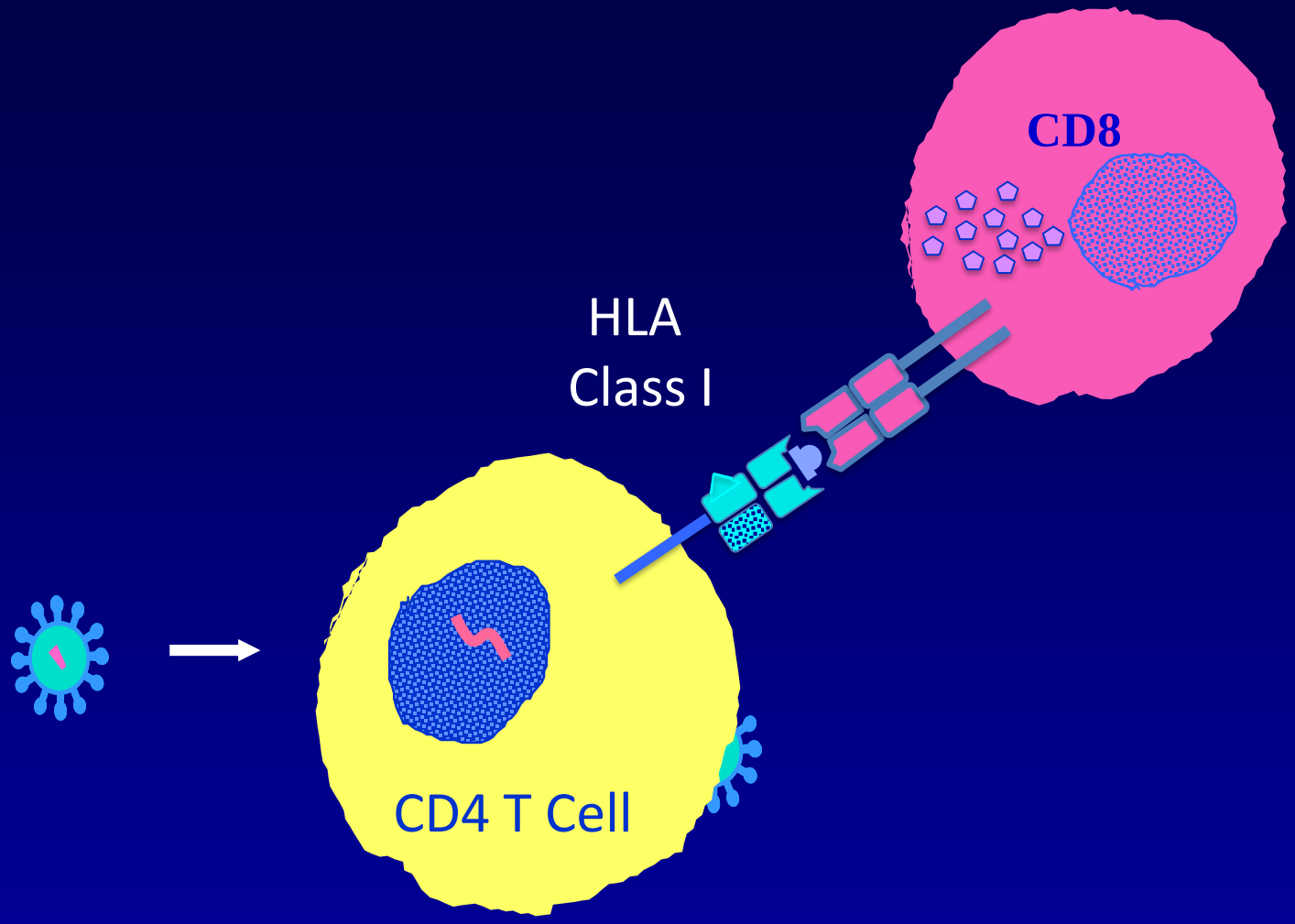
Diagnoses

- Brain:
  - No TB
  - Mass lesion: lymphoma
- Lung:
  - No TB
  - Multiple mass lesions : Kaposi's sarcoma and pneumocystis pneumonia
- Abdomen:
  - No TB
  - Multiple masses: Kaposi's sarcoma
  - Disseminated CMV infection of the colon

Chip Schooley
and Marty Hirsch,
ca. 1984

HIV is an infection of the immune system




CD8
HLA
Class I
CD4 T Cell

PART I *(Pages 1 to 5)*

OMB NO. 0925-

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD APPLICATION

FOLLOW INSTRUCTIONS CAREFULLY

☐ PREDOCTORAL ☒ POSTDOCTORAL ☐ OTHER:

LEAVE BLANK		
TYPE	ACTIVITY	NUMBER
REVIEW GROUP		FORMERLY
MEETING DATES		DATE RECEIVED

1. TITLE OF TRAINING PROPOSAL *(Do not exceed 56 typewriter spaces)*

CELL MEDIATED IMMUNE RESPONSE TO HTLV-III

2. PROGRAM ANNOUNCEMENT AREA

NATIONAL INSTITUTES OF HEALTH

3. APPLICANT

3a. NAME OF APPLICANT *(Last, first, middle initial)*

WALKER, BRUCE D.

3b. SOCIAL SECURITY NO. [redacted]

3c. PRESENT MAILING ADDRESS *(Street, city, state, zip code)*

INFECTIOUS DISEASE UNIT
MASSACHUSETTS GENERAL HOSPITAL
FRUIT STREET
BOSTON, MA 02114

3d. PERMANENT MAILING ADDRESS *(Street, city, state, zip code)*

MASSACHUSETTS GENERAL HOSPITAL
INFECTIOUS DISEASE UNIT
FRUIT STREET
BOSTON, MA 02114

3e. OFFICE TELEPHONE NO. *(Area code, no., and ext.)*

617-726-3812

3f. HOME TELEPHONE NO. *(Area code, no., and ext.)* [redacted]

3g. PERMANENT TELEPHONE NO. *(Area code, no., and ext.)*

617-726-3812

3h. ☒ U.S. CITIZEN OR U.S. NONCITIZEN NATIONAL OR ☐ PERMANENT RESIDENT OF U.S. *(Notarized statement required)*

NATIONAL RESEARCH SERVICE AWARD SUPPORT *(Individual and/or Institutional)*

HIV-specific CD8$^+$ T cells

HIV-specific cytotoxic T lymphocytes in seropositive individuals

Bruce D. Walker*, Sekhar Chakrabarti†, Bernard Moss†, Timothy J. Paradis*, Theresa Flynn*, Amy G. Durno*, Richard S. Blumberg*, Joan C. Kaplan*, Martin S. Hirsch* & Robert T. Schooley*

* Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA
† Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

AIDS virus-specific cytotoxic T lymphocytes in lung disorders

Fernando Plata*, Brigitte Autran†, Livia Pedroza Martins*, Simon Wain-Hobson*, Martine Raphaël†, Charles Mayaud‡, Michel Denis‡, Jean-Marc Guillon‡ & Patrice Debré†

* Laboratoire de Biologie et d'Immunologie Moléculaires des Rétrovirus, Institut Pasteur, 75724 Paris Cédex 15, France
† Laboratoire d'Immunologie Cellulaire et Tissulaire, Hôpital Pitié-Salpétrière, 75013 Paris, France
‡ Service de Pneumologie, Hôpital Tenon, 75010 Paris, France

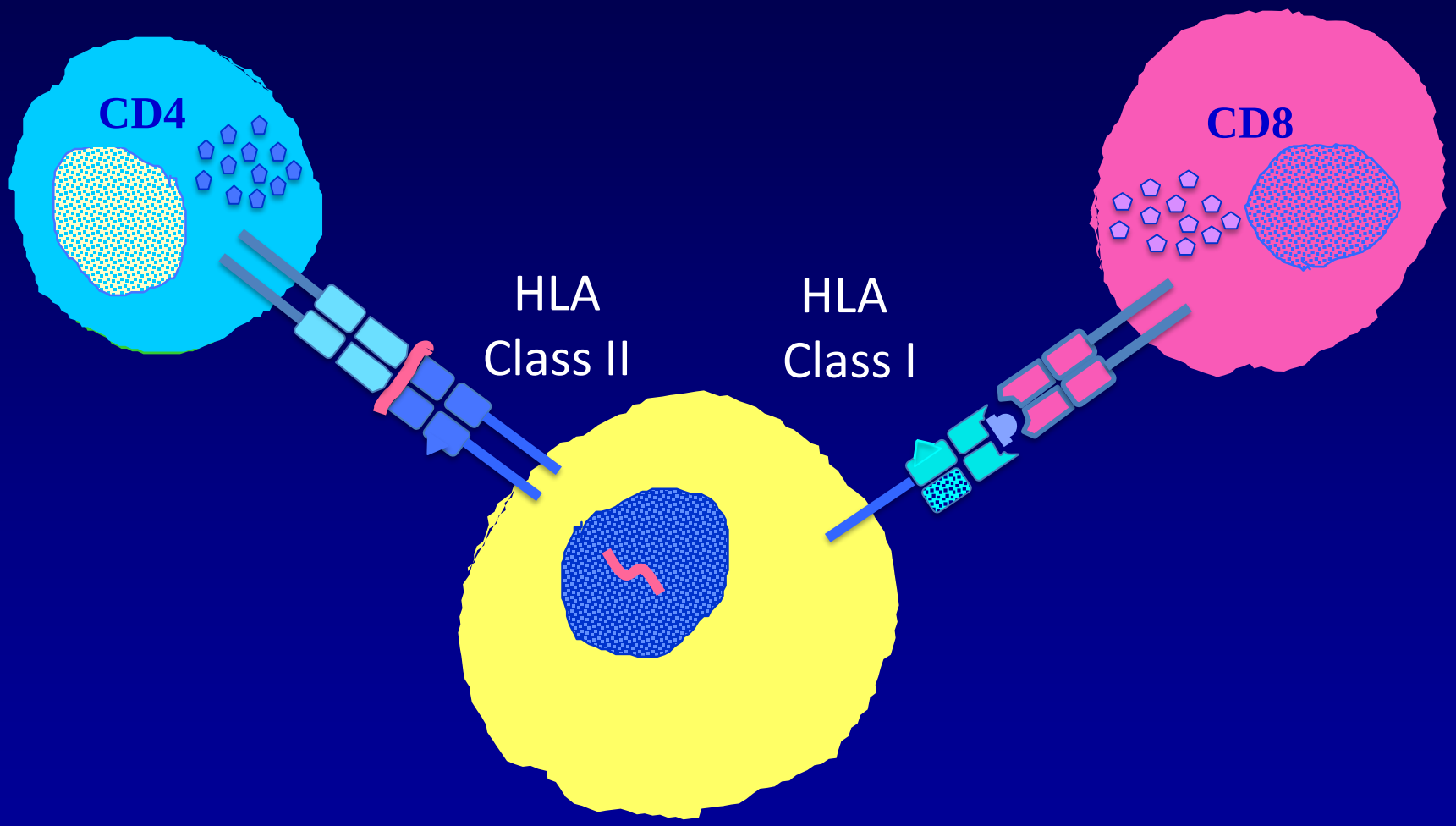
Nature 328:345, 1987
Nature 328:348, 1987

Chapter 2.
Outliers

Manic.

1978 2wk pre Thanksgiving
→ Sx hard to describe
Sudden onset very severe flu
Doing something at desk →
Sudden feeling of extreme fatigue
"frozen in mid"
Happened 2-3 times → over 1-2 d.
Called NY Hosp — ? cerebr hemorrhage
To hosp. w infusion
CT scan → R/O
Infusing factor
Worsening.
long diagnostic process
7-10 d in hosp.
samples.

HA
? Temp.
? swollen glands

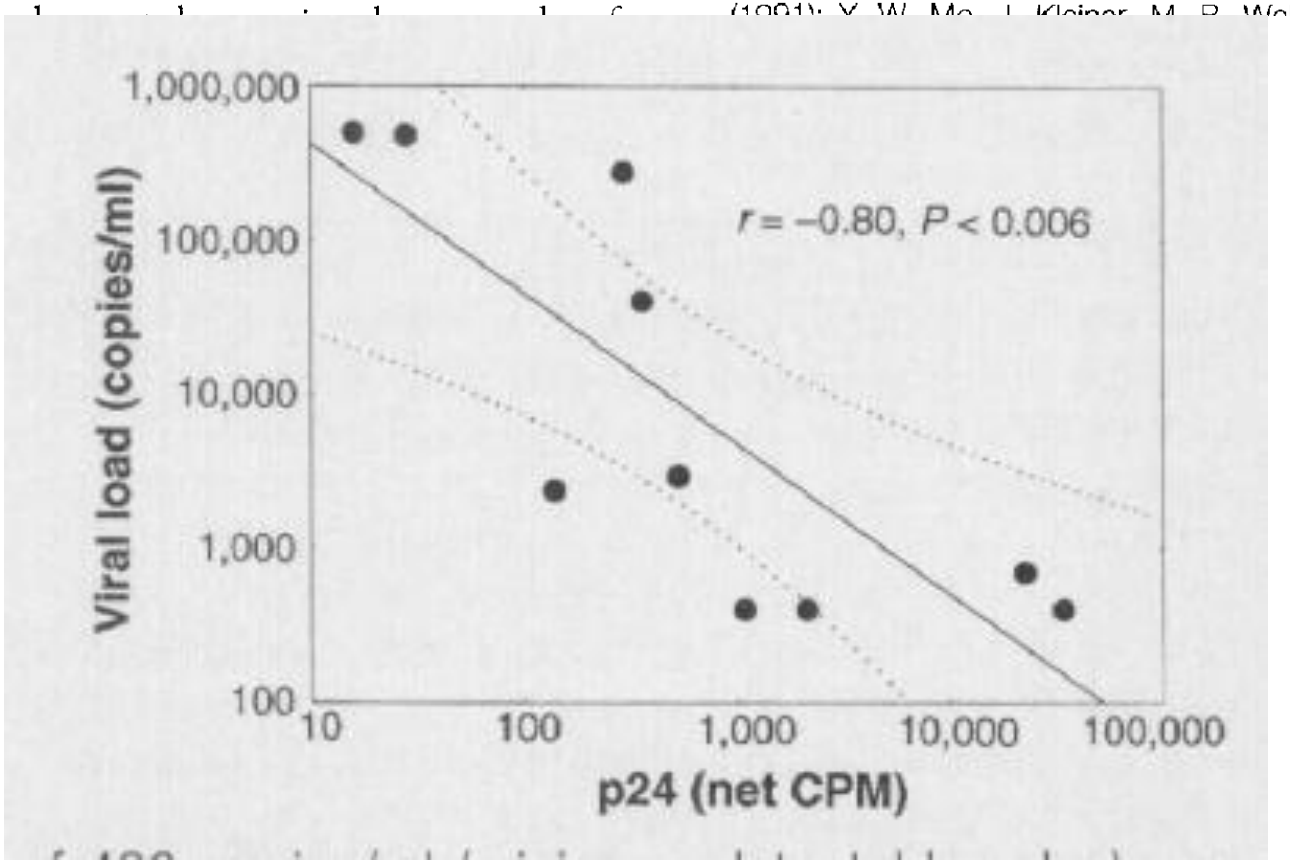

CD4
CD8
HLA
Class II
HLA
Class I

tion in Si(100) has intriguing consequences. Besides providing a logical pathway from adatom adsorption and diffusion to growth of islands, these chain structures and their prevalence suggest that the smallest and most obvious stable structure on the surface, the ad-dimer residing on top of the dimer rows, does not participate

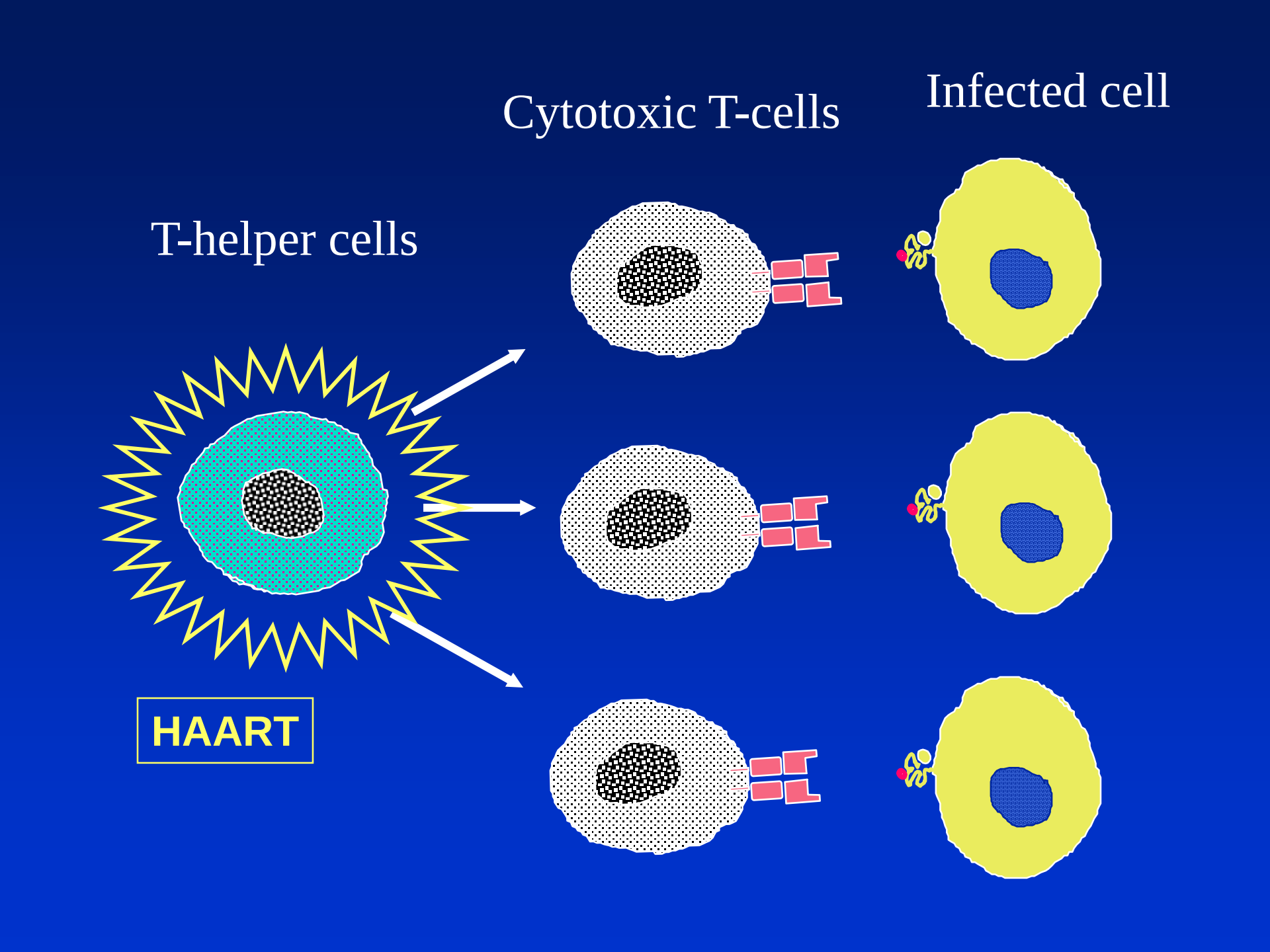
metastable structures that may have a variety of sizes.

REFERENCES AND NOTES

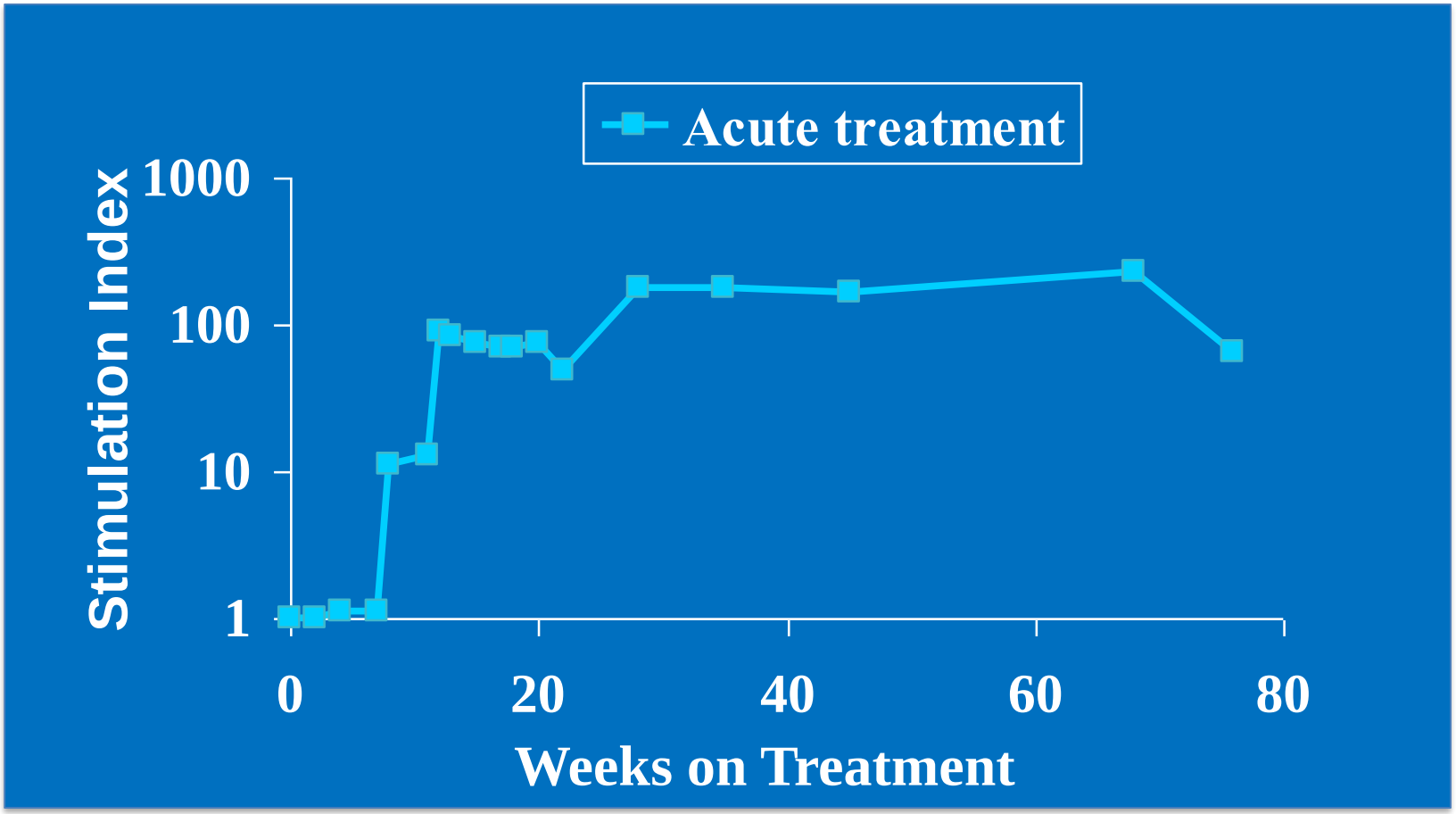
1. For a review and an extended list of references, see Z. Zhang and M. G. Lagally, *Science* **276**, 377 (1997).
2. Y.-W. Mo and M. G. Lagally, *Surf. Sci.* **248**, 313



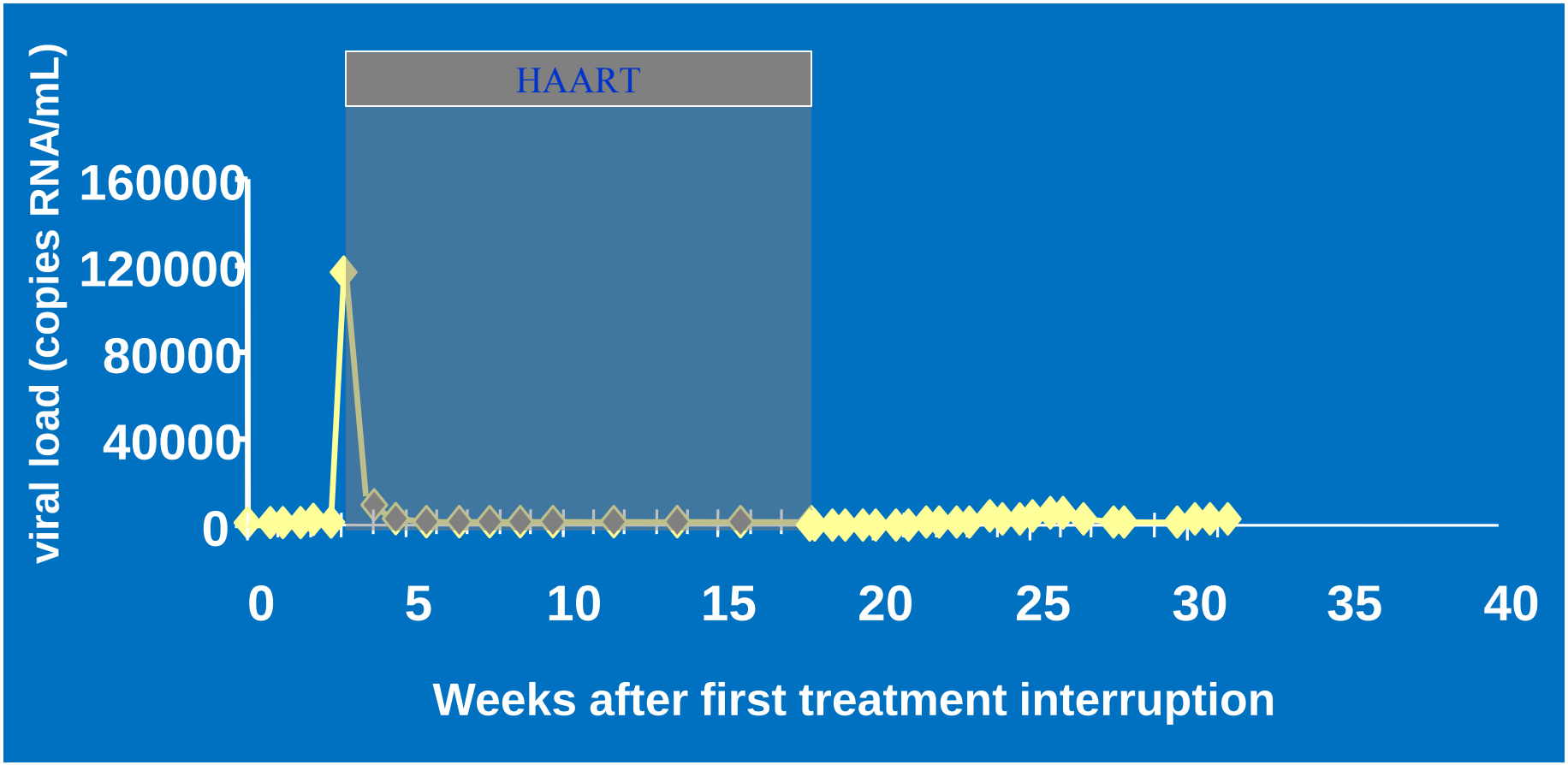
Science 1997


Cytotoxic T-cells
Infected cell
T-helper cells
HAART

HIV-Specific CD4+ T cell Responses following treatment in acute infection



Immune control:
Early treatment of acute HIV infection followed by treatment interruption



Immune control of HIV-1 after early treatment of acute infection

Eric S. Rosenberg, Marcus Altfeld, Samuel H. Poon, Mary N. Phillips, Barbara M. Wilkes, Robert L. Eldridge, Gregory K. Robbins, Richard T. D'Aquila, Philip J. R. Goulder & Bruce D. Walker

Partners AIDS Research Center and Infectious Disease Division, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA

Nature 2000

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Partners AIDS Research Center and Infectious Disease Division, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA

Nature 2000

Limited Durability of Viral Control following Treated Acute HIV Infection

Daniel E. Kaufmann[1☯], Mathias Lichterfeld[1☯], Marcus Altfeld[1], Marylyn M. Addo[1], Mary N. Johnston[1], Paul K. Lee[1], Bradford S. Wagner[1], Elizabeth T. Kalife[1], Daryld Strick[1], Eric S. Rosenberg[1], Bruce D. Walker[1,2*]

1 Partners AIDS Research Center, Infectious Disease Unit, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts, United States of America, 2 Howard Hughes Medical Institute, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts, United States of America

PLoS Medicine 2004

Chapter 3.
Insights from a raging epidemic


University of
KwaZulu-Natal

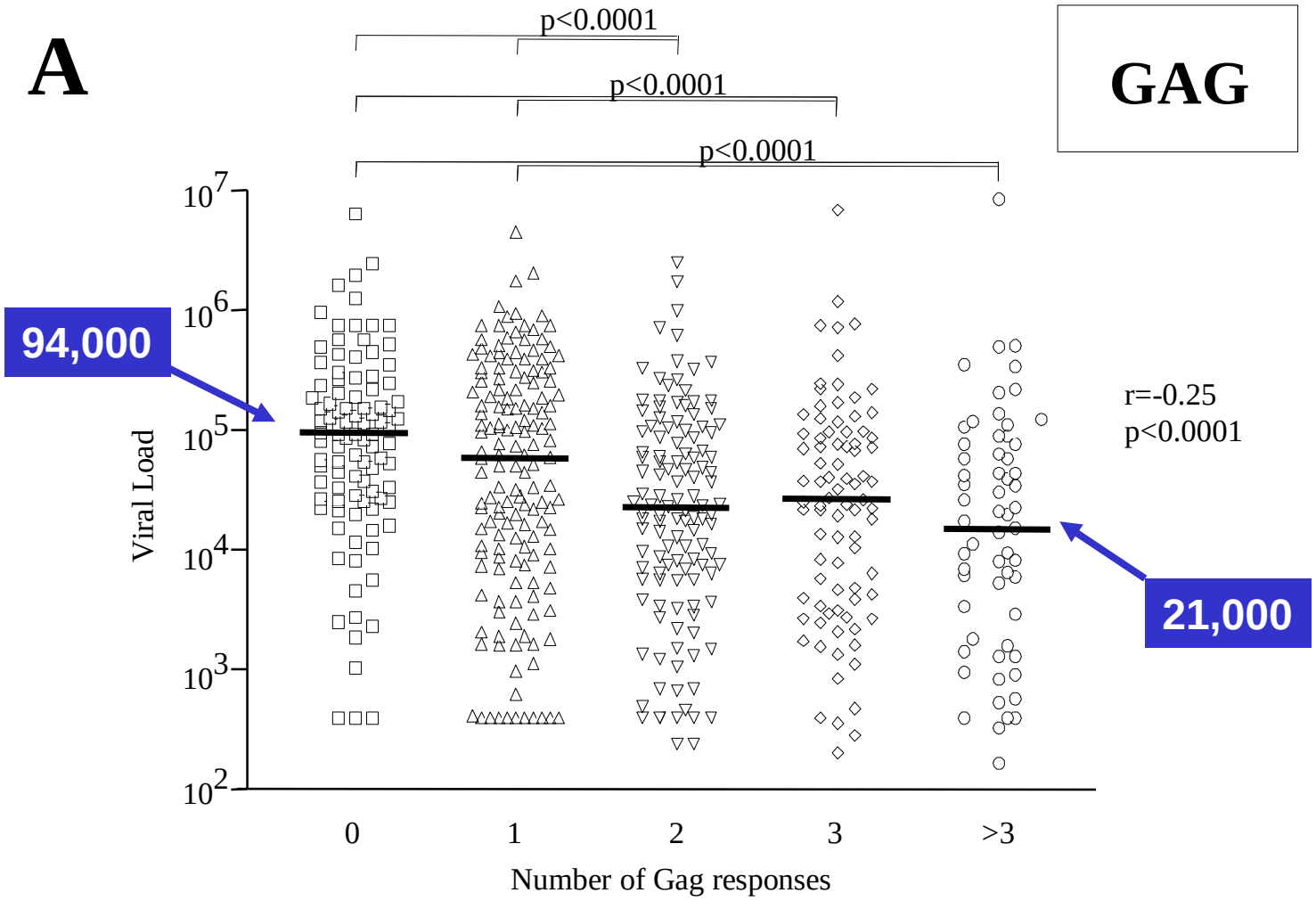

Kaye
Ajao
Krista
Dong


Doris Duke Medical Research Institute
Nelson R Mandela School of Medicine
KwaZulu Natal Province, South Africa

Emerging evidence from Africa of the importance of HIV-specific CTL

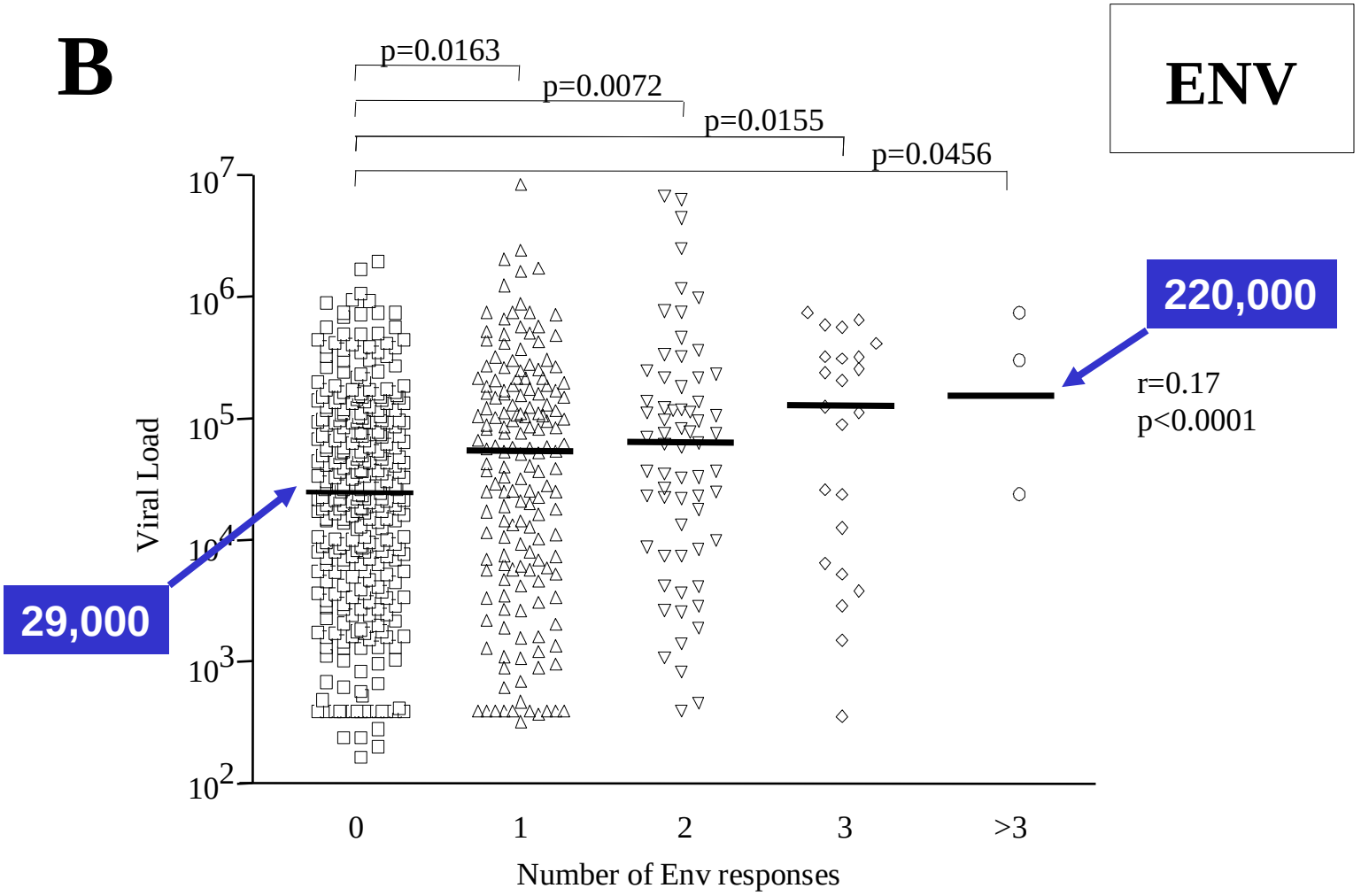
- Transmission of CTL escape variants to neonates
  - Goulder et al, *Nature* 2001
- Impact of HLA-B alleles on immune control
  - Kiepiela et al, *Nature* 2004
- PD-1 expression and HIV-specific T cell exhaustion
  - Day et al, *Nature* 2006
- Importance of Gag-specific T cell responses and control
  - Kiepiela et al, *Nature Medicine* 2007

The breadth of the Gag-specific CD8 response is associated with lower viral load



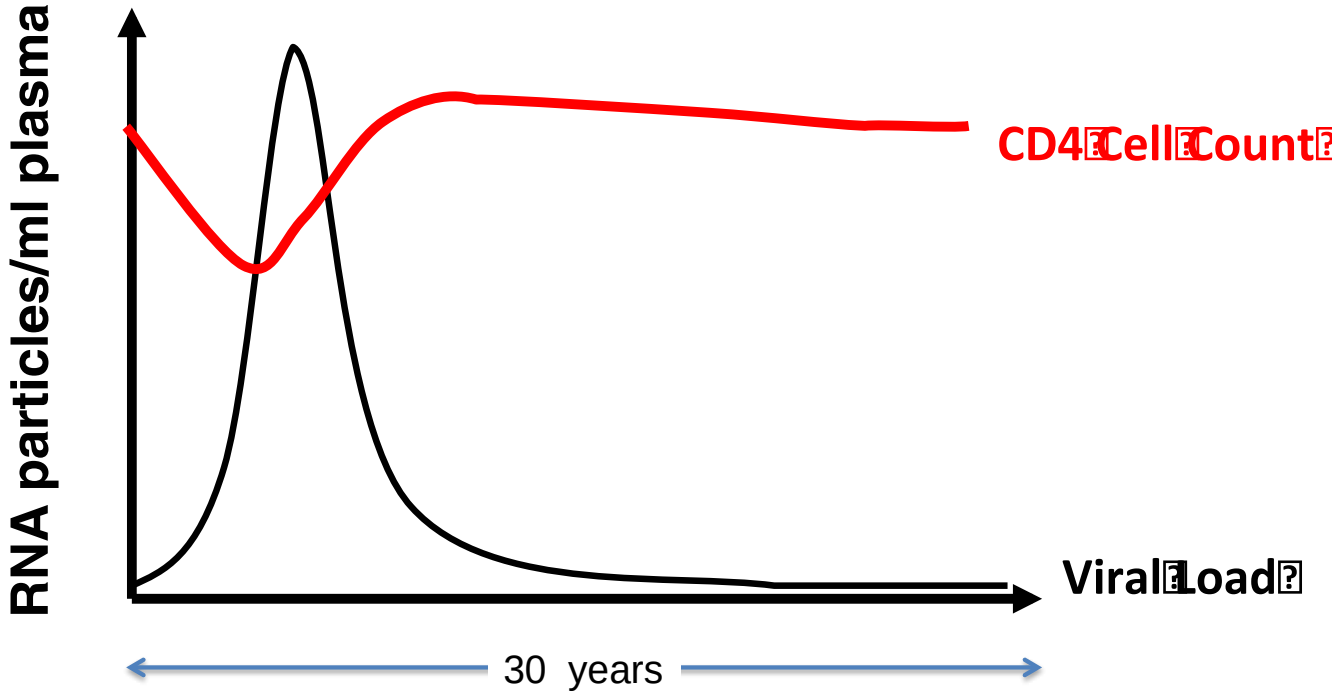
Kiepiela et al, *Nature Medicine* 2007

The breadth of the Env-specific CD8 response is associated with higher viral load



Kiepiela et al, *Nature Medicine* 2007

Chapter 4.
A late night conversation


RNA particles/ml plasma
CD4 Cell Count
Viral Load
30 years

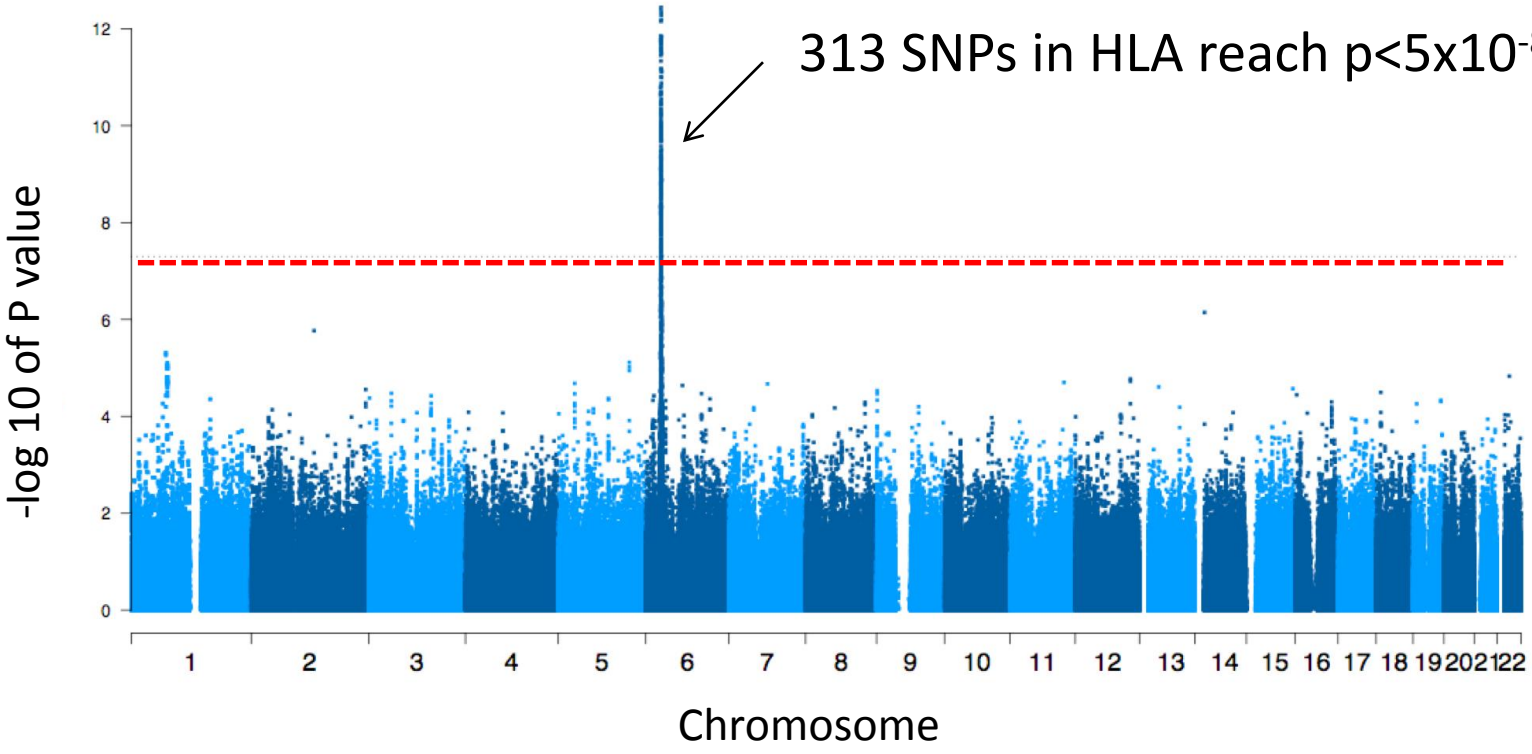
The International HIV Controllers Study

www.hivcontrollers.org

Genome-Wide Association Study:
HIV control is associated with chromosome 6 polymorphisms

974 controllers and 2648 progressors

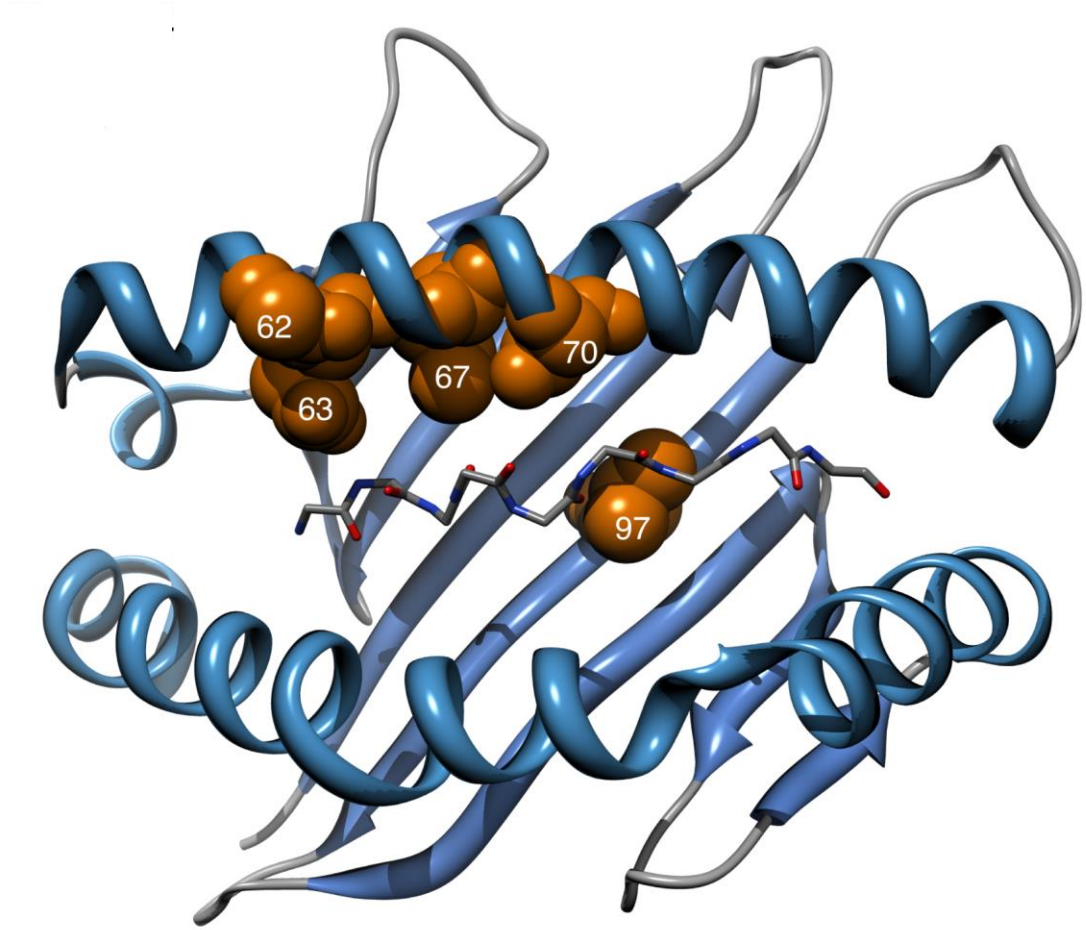
313 SNPs in HLA reach $p<5x10^{-8}$



Pereyra et al, *Science*, 2010

The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation

The International HIV Controllers Study*†

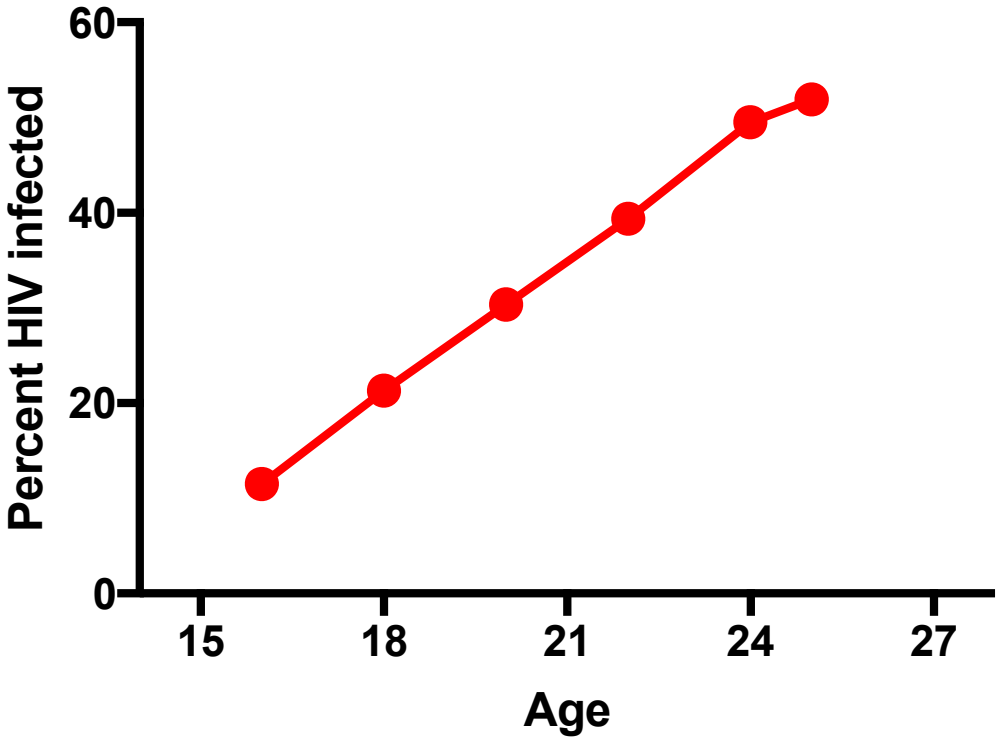


Pereyra et al, *Science*, 2010

Chapter 5.
Science and Social Good

Female HIV Prevalence by Age: KwaZulu Natal

Annual Incidence: 9.1%



Abdool Karim Q, et al. Science 2010;
Kharsany AB, et al. JAIDS 2015; 70(3): 289–95

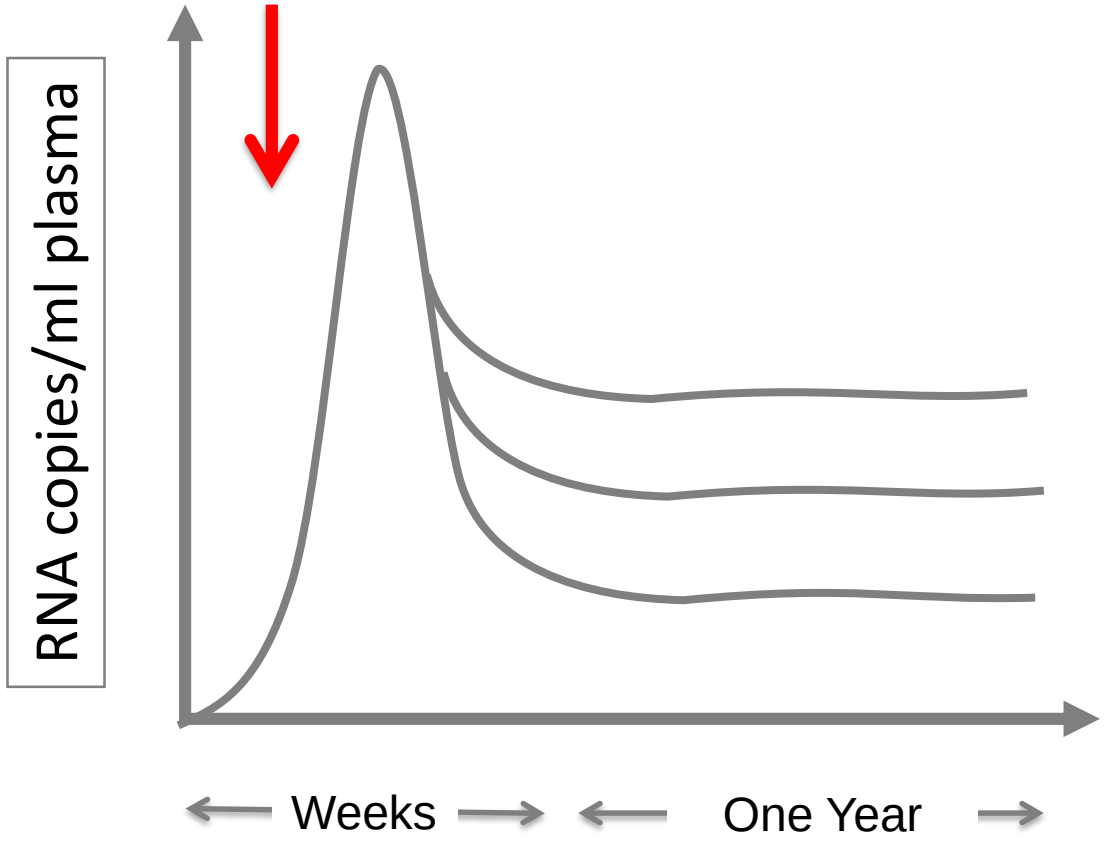
FRESH Study (2012-Present):

Females Rising through Education, Support and Health

Goals:
1. HIV prevention and poverty reduction
2. Immunology of hyperacute infection

http://www.ragoninstitute.org/international/fresh/

Learning from patients: Hyperacute HIV Infection



Set point viremia predicts disease outcome

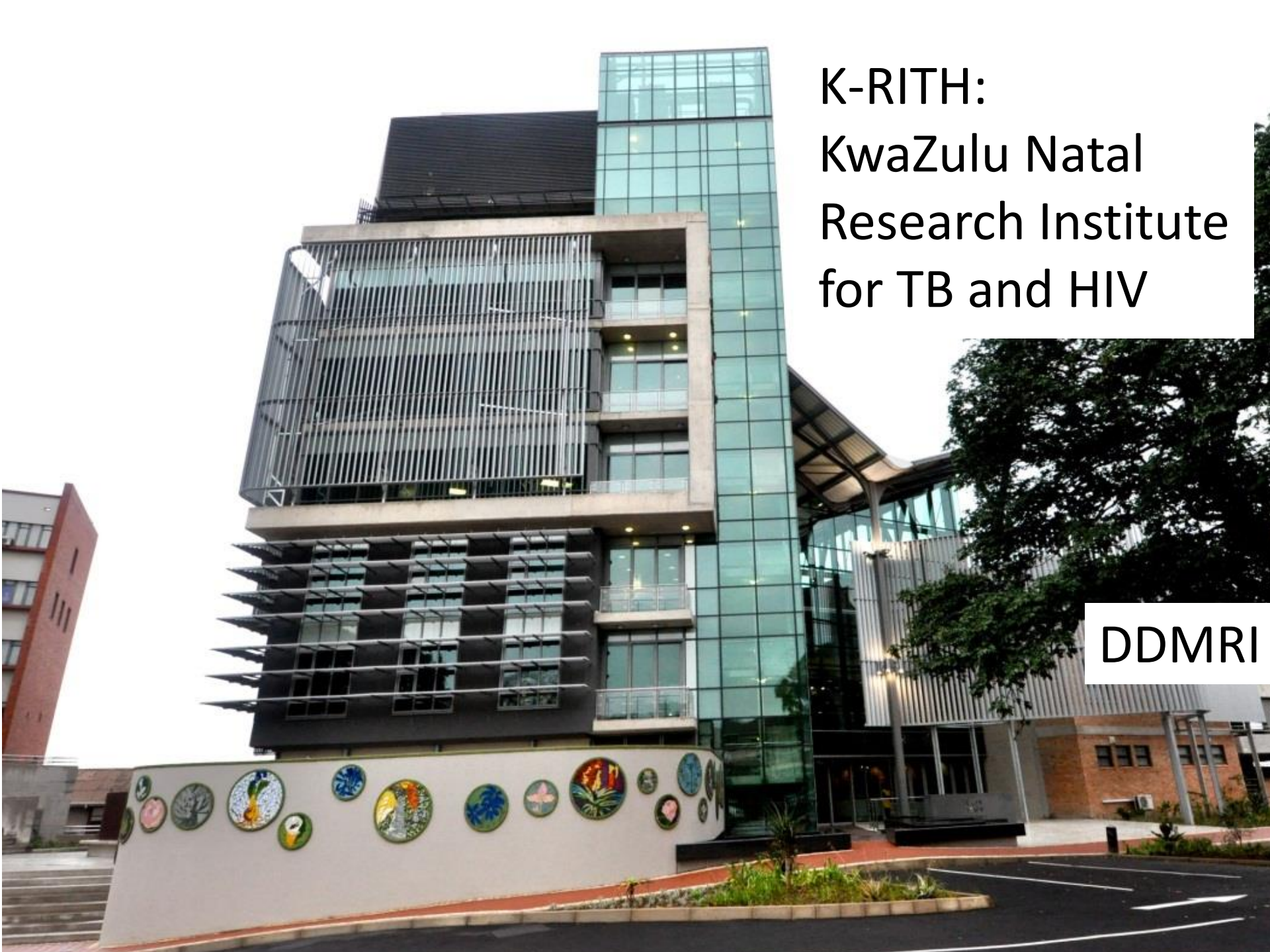
FRESH

Video linked in this article:

https://www.massgeneral.org/News/pressrelease.aspx?id=2290

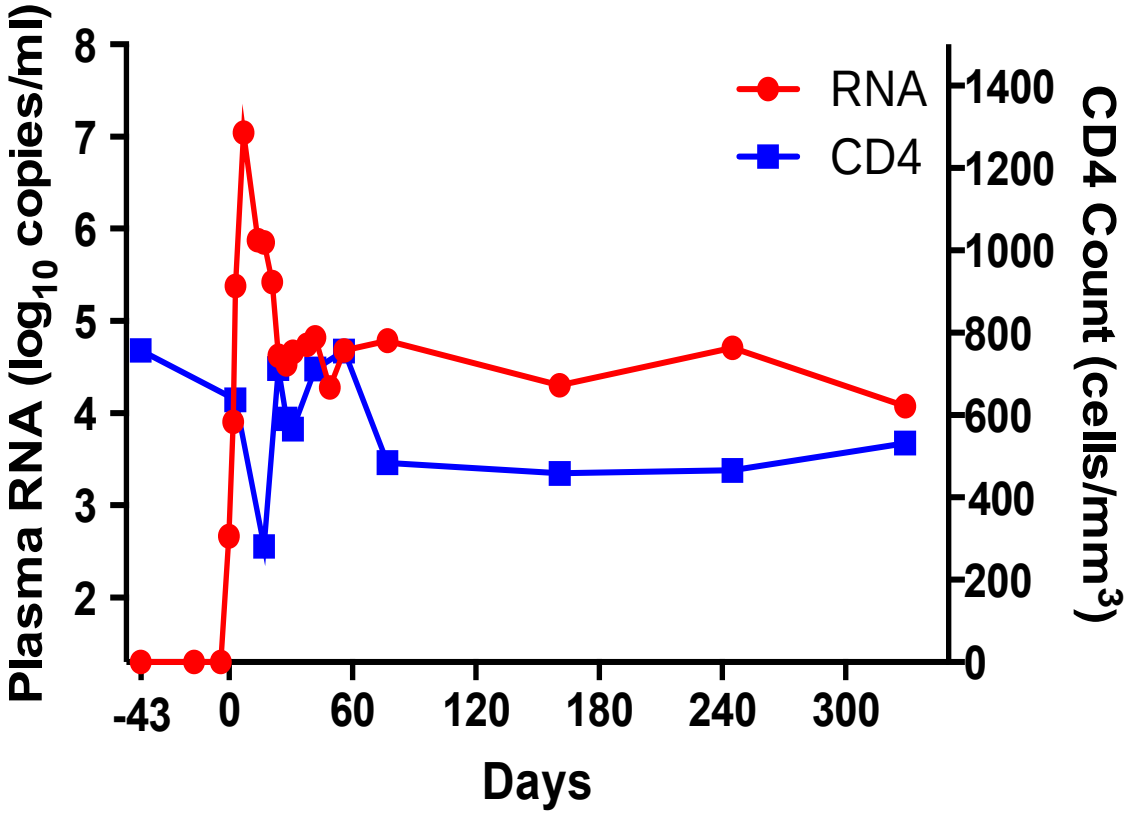
FRESH Study

- Subjects:
  - Uninfected 18-23 year old women at high risk of HIV infection in an impoverished township
- Methods:
  - Provide a twice weekly empowerment, life skills, job readiness and HIV prevention education with the goal of employment after one year
  - Test twice weekly for HIV RNA by finger prick


K-RITH:
KwaZulu Natal
Research Institute
for TB and HIV
DDMRI

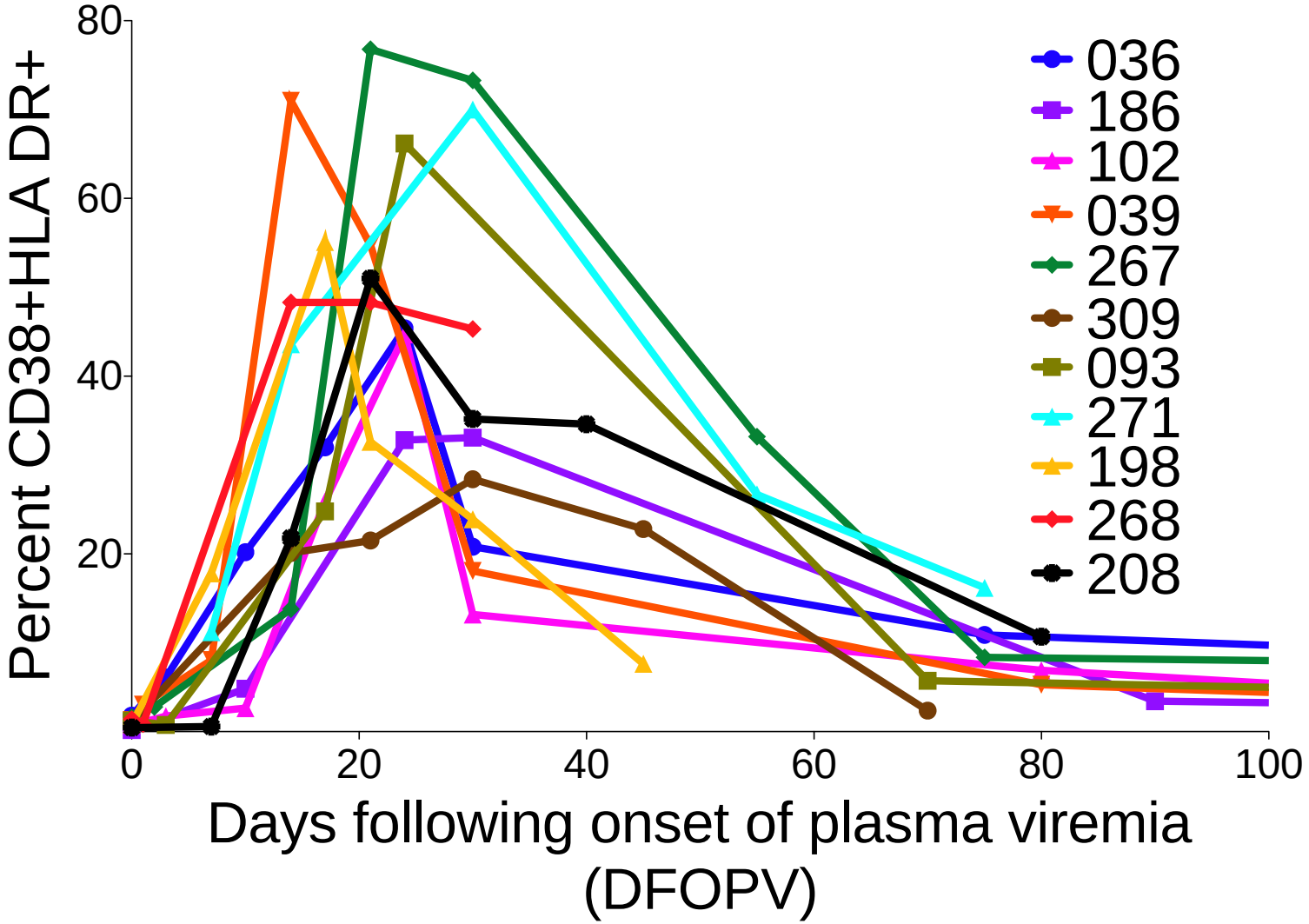

Zaza Ndhlovu
Thumbi Ndung’u

Kinetics of Hyperacute HIV Infection



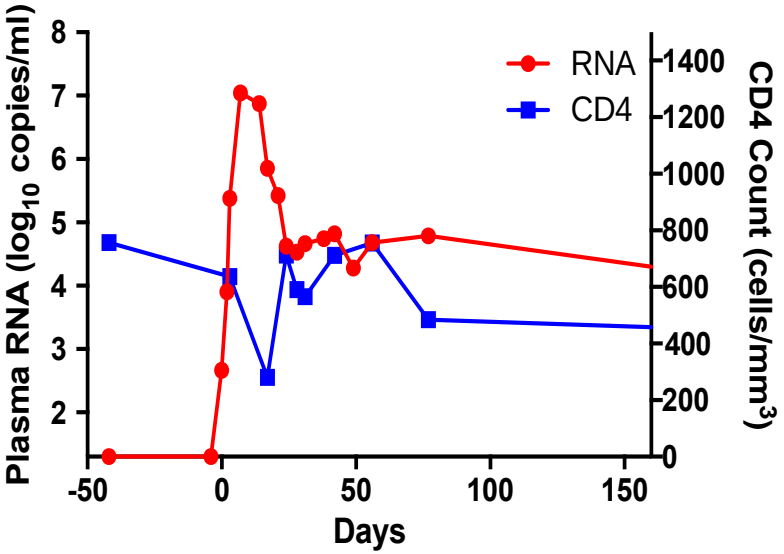
Ndhlovu et al, *Immunity* 2015
Dong et al, *Lancet HIV* 2017

Massive HIV-specific T cell activation in acute HIV infection

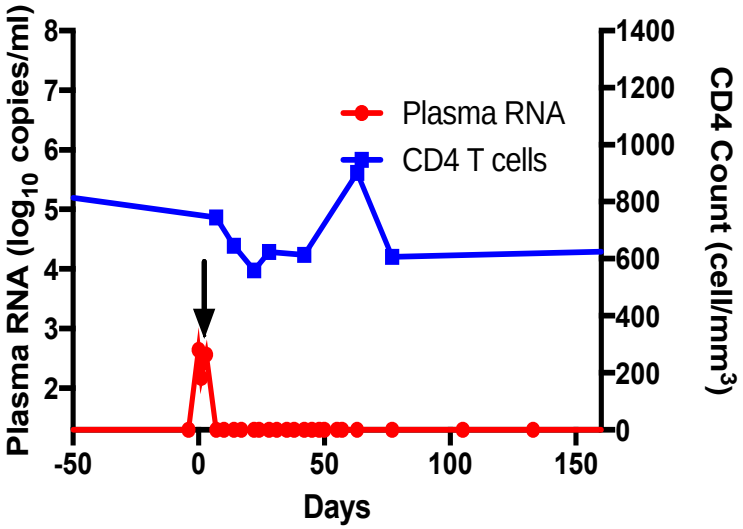


Hyperacute HIV Infection

No Treatment

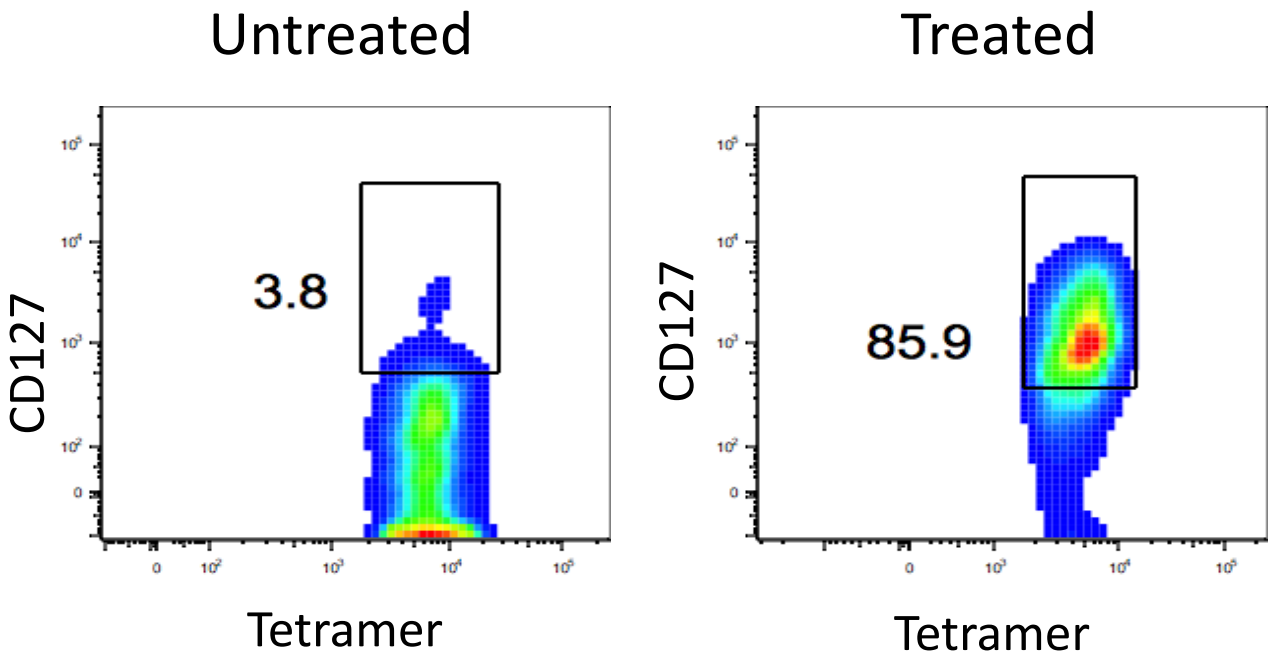


Atripla

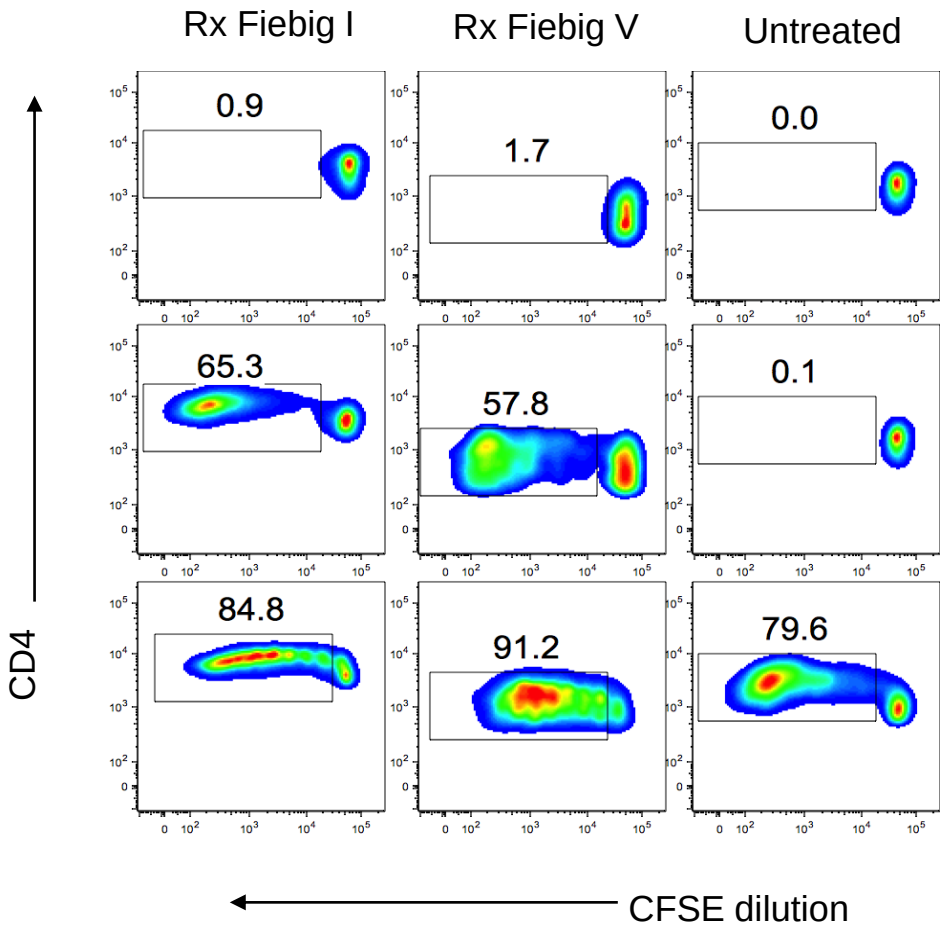


Ndhlovu et al, *Immunity* 2015
Dong et al, *Lancet HIV* 2017
Ndung'u et al, Science Immunology 2018

Early treatment leads to enhanced HIV-specific $CD8^+$ T cell function



Robust CD4+ T cell responses in treated acute HIV infection



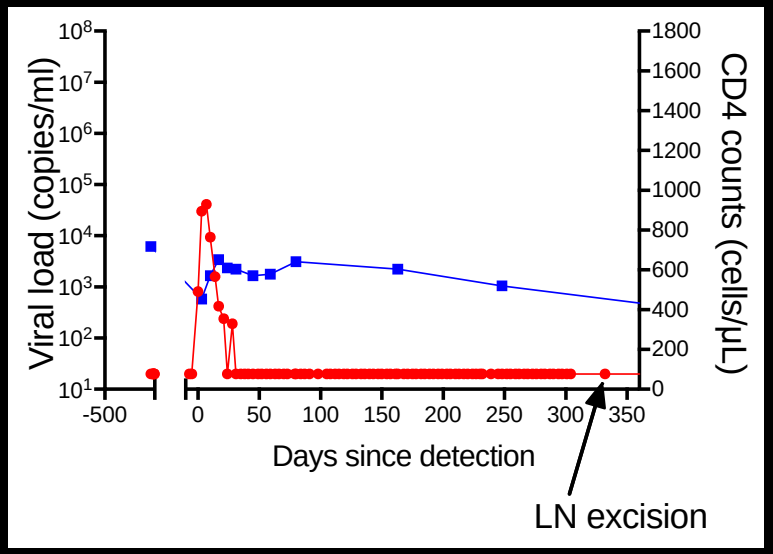
Unstimulated

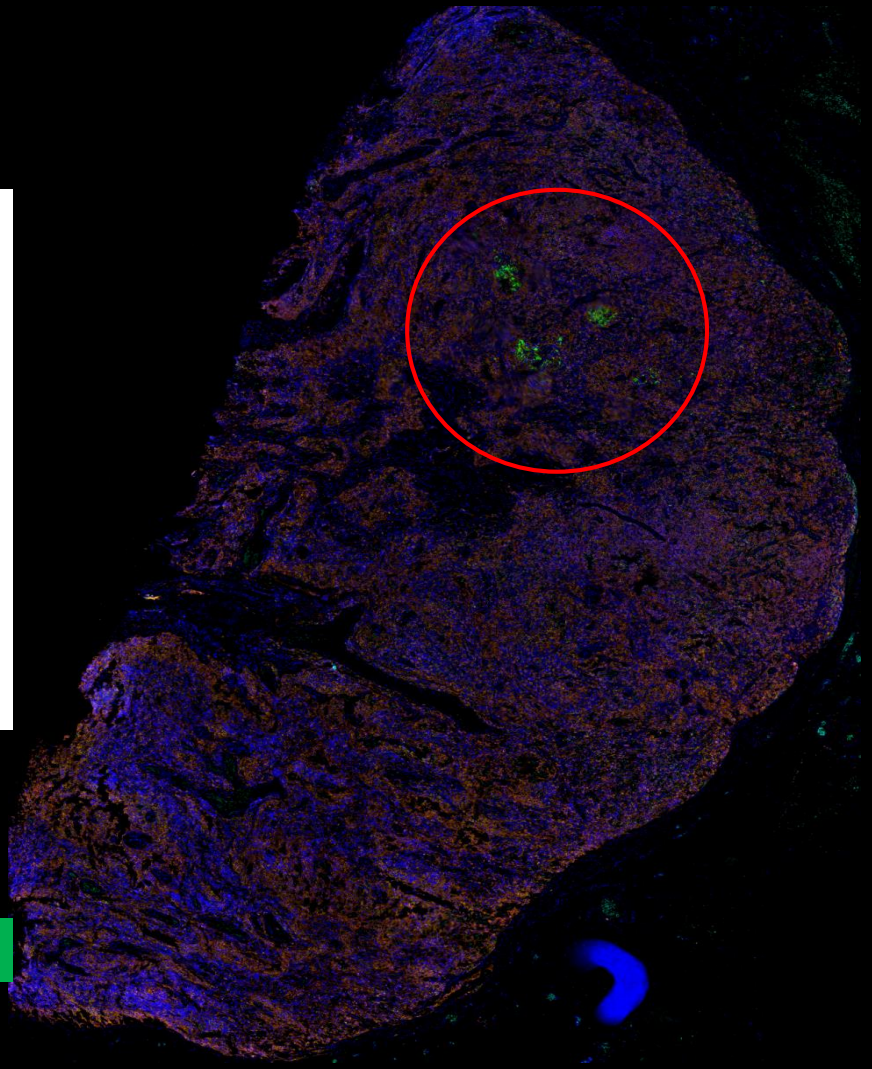
Gag Peptide Pool

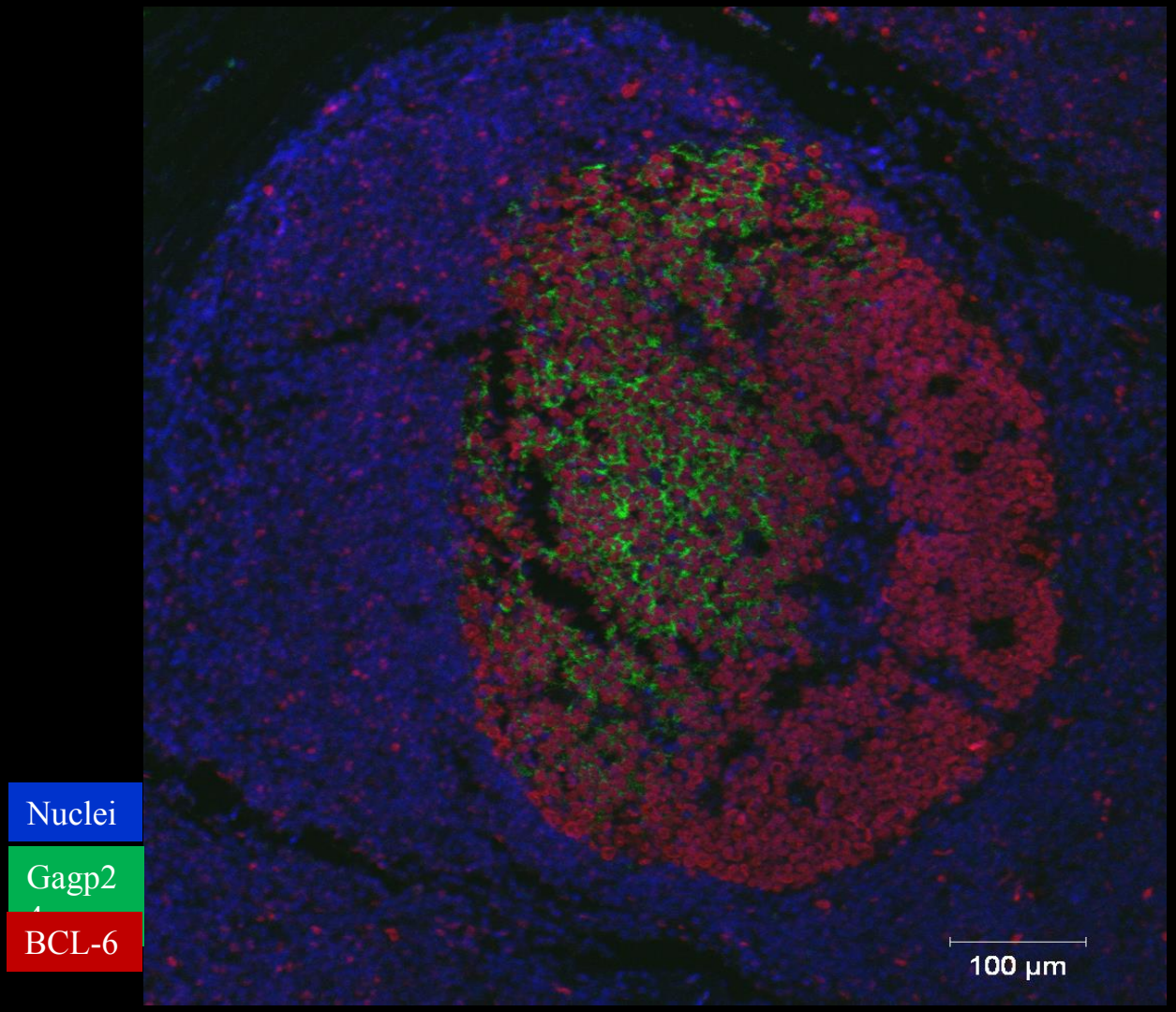
SEB

Ndhlovu et al, unpublished

HIV Gagp24 staining of a LN tissue from an early treated subject



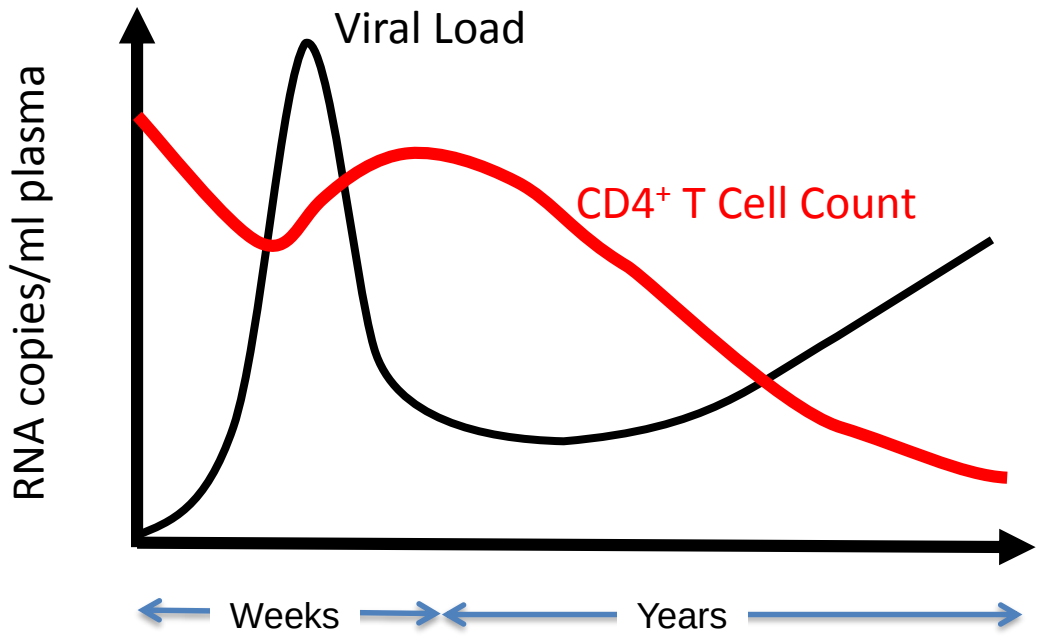



Nuclei
Gagp2
BCL-6
100 µm

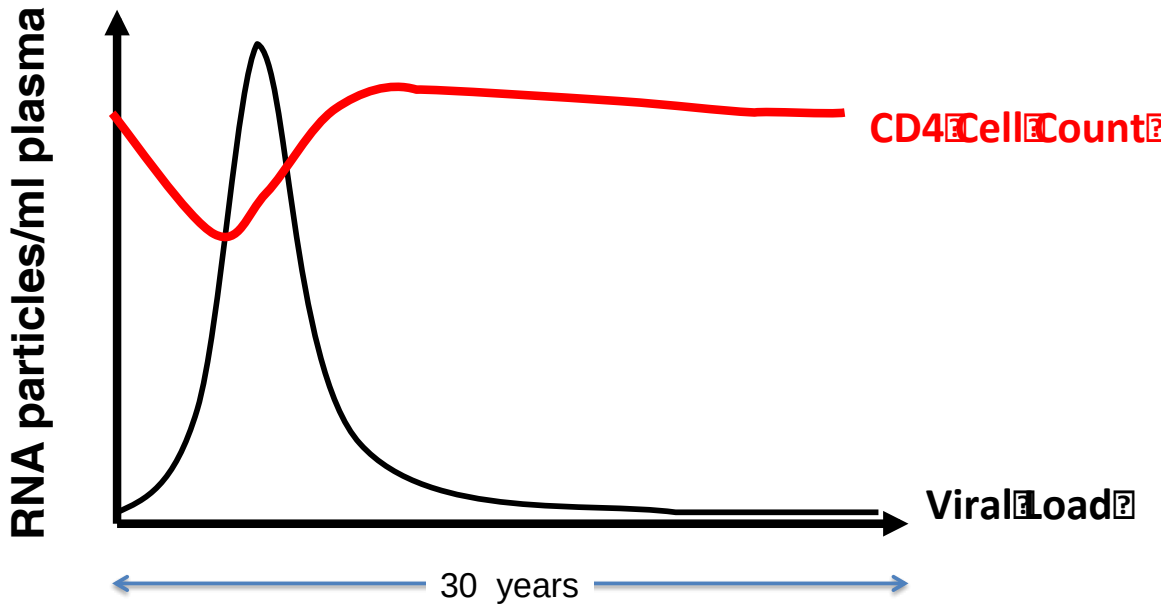
Chapter 6.
Stock Markets and Social Networks


EXIT

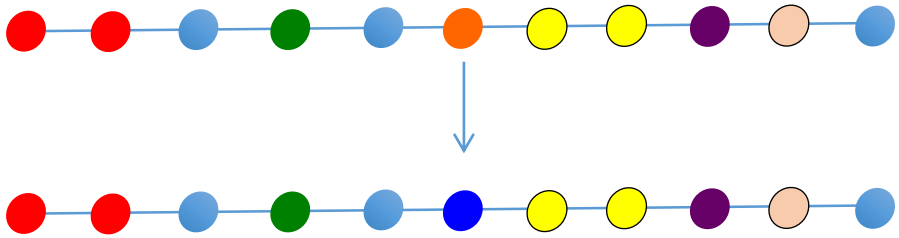
“A successful vaccine must do better than natural immunity to HIV”



"A successful vaccine must do as well as the best natural immunity to HIV"

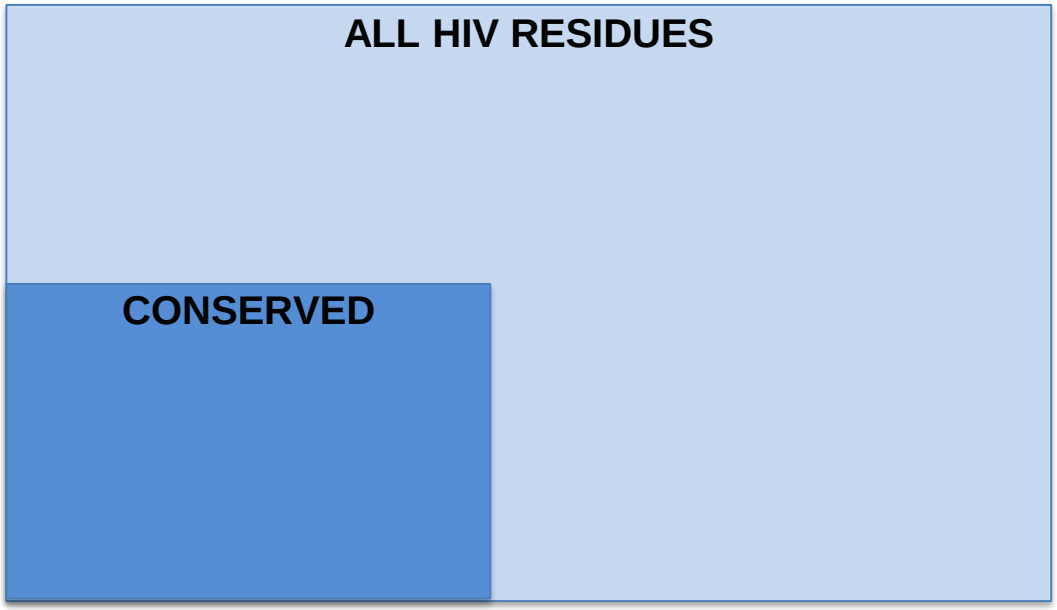


Measures of conservation: Sequence analysis

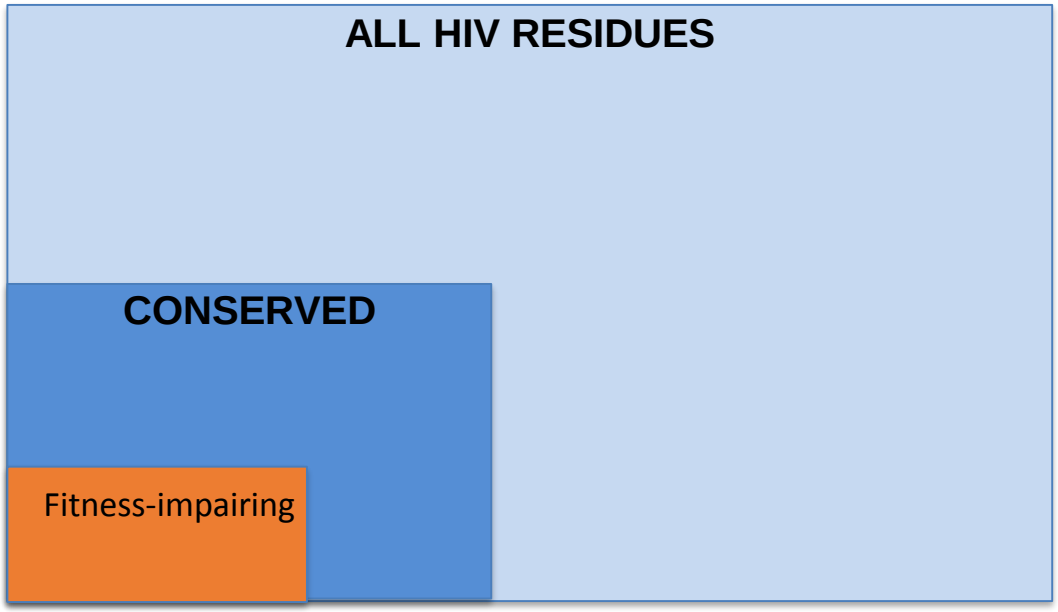


- Based on available sequence data
- Measures mutability of single amino acids
- Does not incorporate amino acid interactions or protein structure
- Does not correlate with fitness

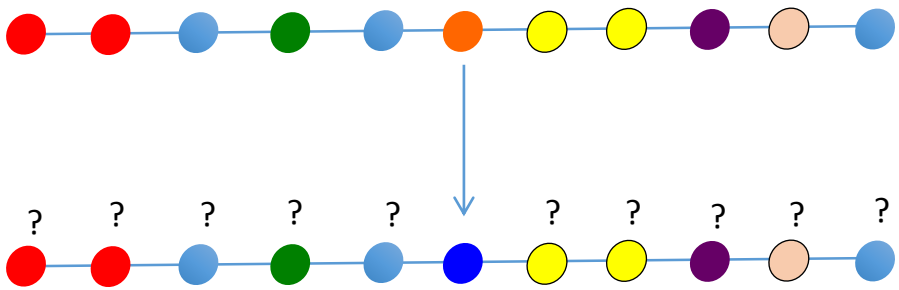
Can we identify a subset of conserved residues that incur a maximal viral fitness cost?



Can we identify a subset of conserved residues that incur a maximal viral fitness cost?



Measures of conservation:
Fitness Landscapes



- Based on available sequence data
- Employs analysis tools used in the stock market
- Measures interdependence of amino acid mutations
- Suggests structural features are linked to fitness (Gag Capsid)

Dahriel et al, *PNAS* 2011
Ferguson et al, *Immunity* 2013

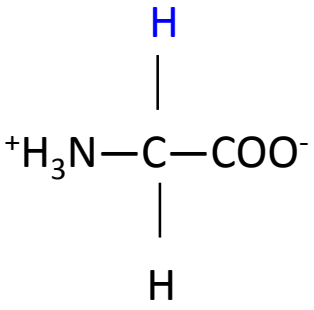
What can we learn from protein structure?

Structure-based Network Analysis (Think social networks)

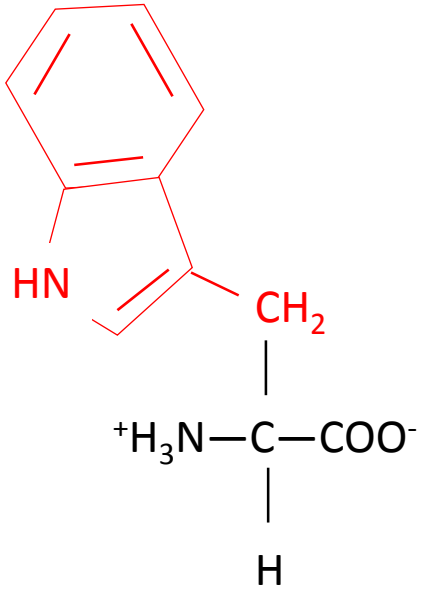
Gaurav Gaiha, MD, PhD

Elizabeth Rossin, MD, PhD

Amino acid properties affect protein folding

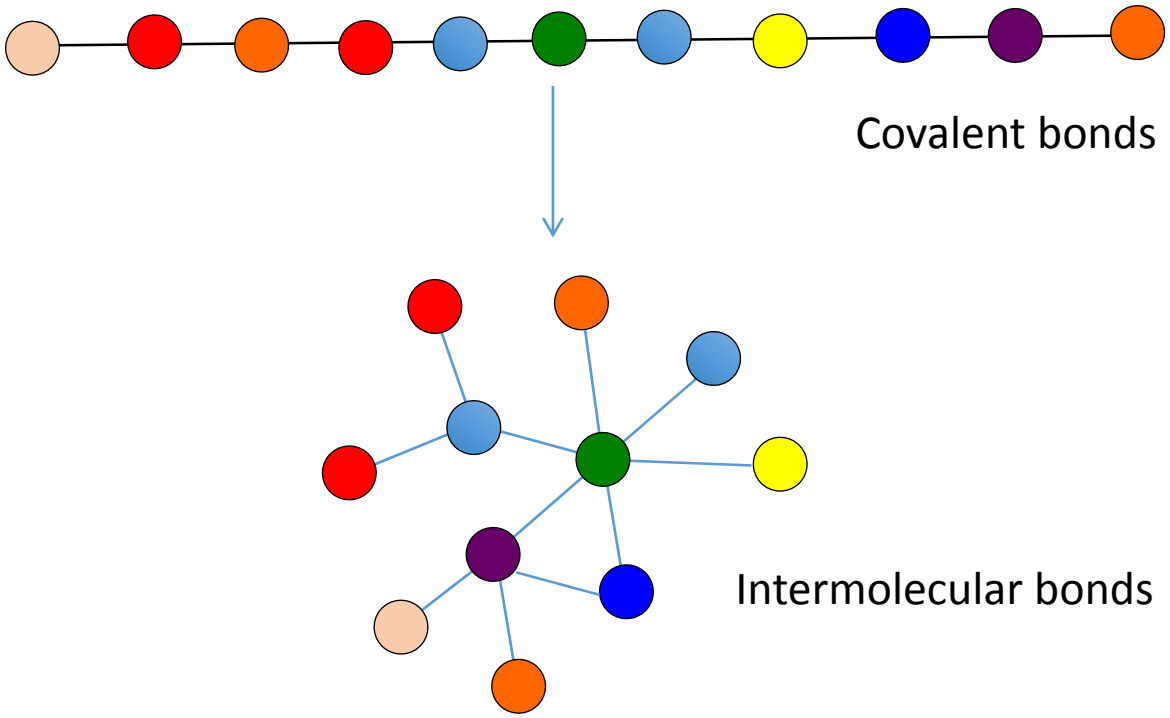


Glycine
G



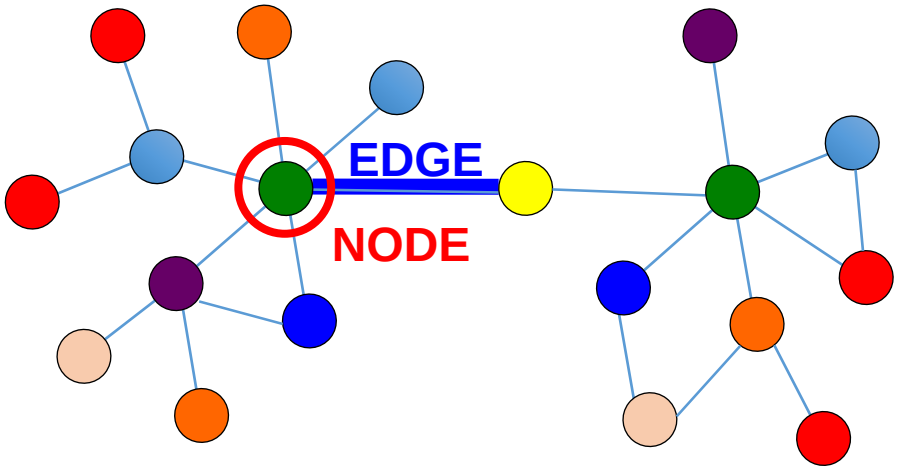
Tryptophan
W

Amino acid side chains influence structure



Proteins act as networks

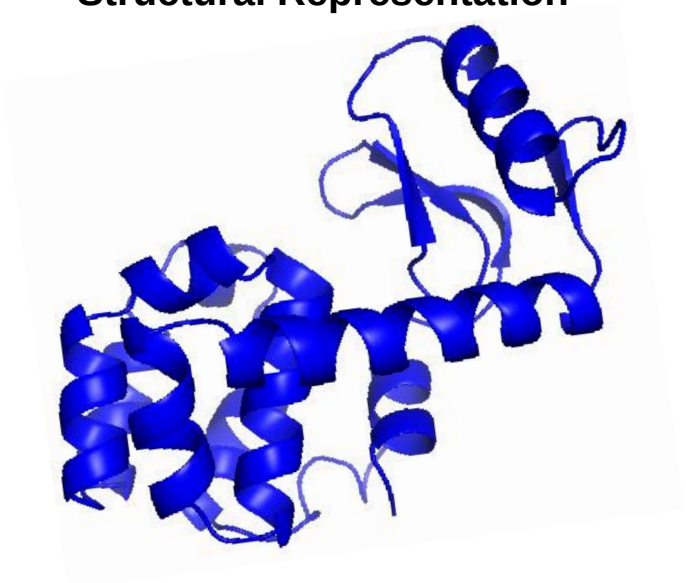
Provides LOCAL and GLOBAL insight by transforming the system to NODES and EDGES



NODE = Amino Acid
EDGE = Intermolecular Interaction

Structure-based Network Analysis

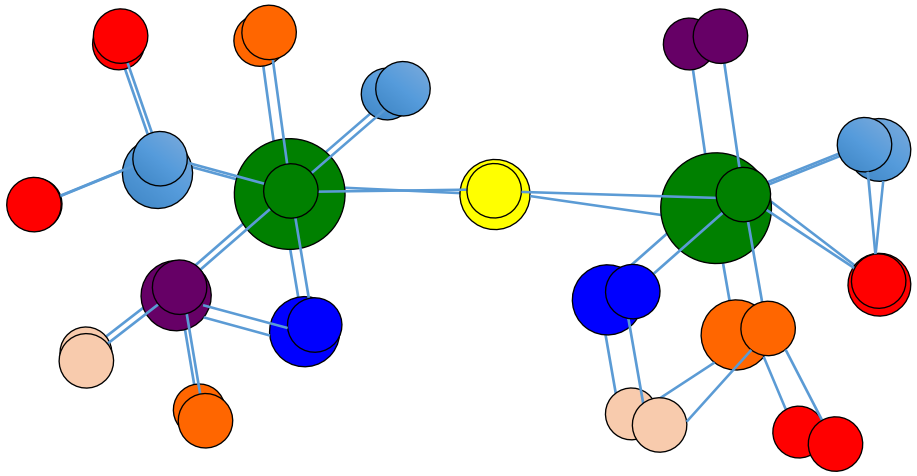
Structural Representation



INPUT: 3-dimensional atomic level data from PDB file

Concepts from Network Theory – Degree Centrality

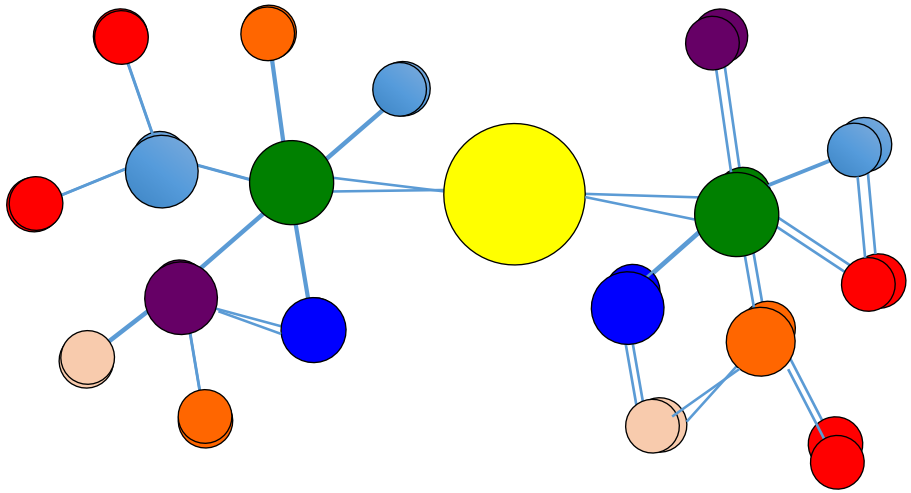
A measure of LOCAL Importance – # of Connections



Greater size = greater magnitude

Concepts from Network Theory– Betweenness Centrality

A measure of GLOBAL Importance – Involvement in Bridges



Greater size = greater magnitude

Consortia for HIV/AIDS Vaccine Development (CHAVD) RFA-AI-18-001

The purpose of this Funding Opportunity Announcement (FOA) is to solicit grant applications that propose to establish Consortia for HIV/AIDS Vaccine Development (CHAVD) to support a coordinated, multidisciplinary team(s) of researchers focused on iterative approaches to accelerate HIV vaccine development by addressing key immunogen design roadblocks to the discovery and development of a safe and effective antibody-mediated preventive HIV vaccine.

The following activities will NOT be supported by this FOA:

- Vaccine protection where the major mechanism of protection is not antibody-mediated

T cell-directed therapy in Melanoma

Conclusions

- Durable natural immune control and possibly cure of HIV is achievable
- Durable immune control is mediated by CTL targeting of highly networked epitopes, providing a rational approach for HIV immunogen design
- Immediate treatment of hyperacute infection leads to induction of HIV-specific CD4 and CD8 T cells with enhanced function, and provides an ideal model for iterative immunotherapeutic intervention studies


The Mountain Club on Loo

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Sjabulile Ngcobo
Zandile Dlamini
Zandile Jali
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BILL & MELINDA GATES foundation

GILEAD

CFAR
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iavi
International AIDS Vaccine Initiative

Ragon Institute
of MGH, MIT and Harvard