Nuevos factores implicados en el pronóstico de la infección por VIH-1

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Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol

Institut de Recerca de la SIDA IrsiCaixa *(www.irsicaixa.es)*

Fundación privada sin ánimo de lucro cuyo principal objetivo es investigación científica multidisciplinaria del VIH/SIDA

- Patogénesis Viral
- Biología Molecular y Celular
- Genética e Inmunología
- Retrovirología clínica
- Farmacología
- Vacunas

AIDS could become a leading cause of illness and death worldwide by 2030

Leading Causes of Burden of Disease Worldwide in 2030

1st HIV/AIDS

2nd Unipolar depressive disorders

3rd Ischaemic heart disease

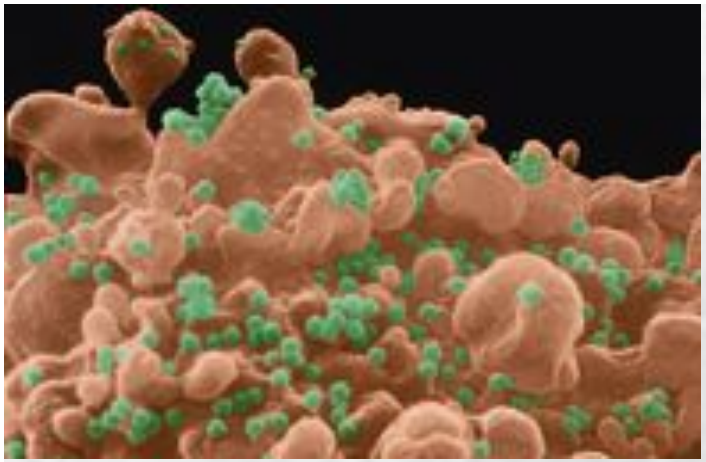
Leading Causes of Death Worldwide in 2030

1st Ischaemic heart disease

2nd Cerebrovascular disease

3rd HIV/AIDS

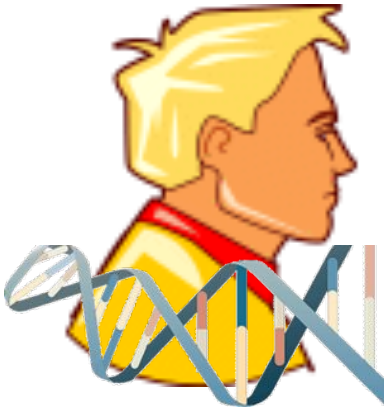
Mathers & Loncar, PLOS 2006
Projections of Global Mortality and Burden of Disease from 2002 to 2030
UNAIDS & WHO



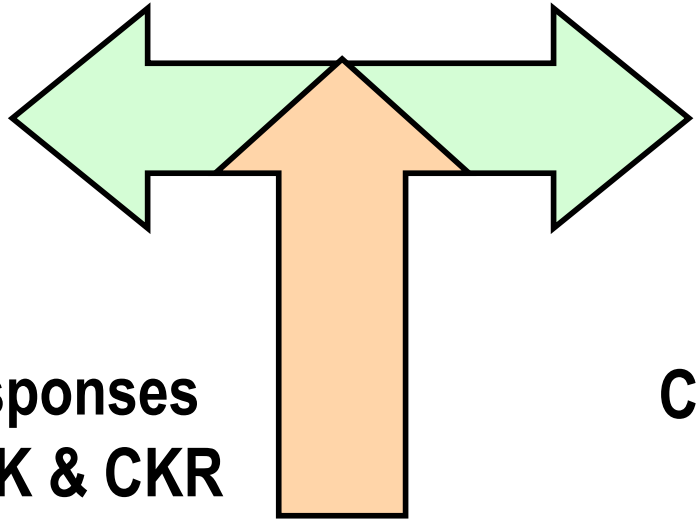
- **High degree of variability**
- **Viral persistence:**
  - **Limited cytopathic potencial**
  - **Escaping adaptive immune responses**

Courtesy of Dr. J Blanco

Factors affecting disease progression



CD4 and CD8 T-cell responses
Altered expression of CK & CKR
HLA type



Coreceptor tropism
Δnef, vpr R77Q
Viral subtypes

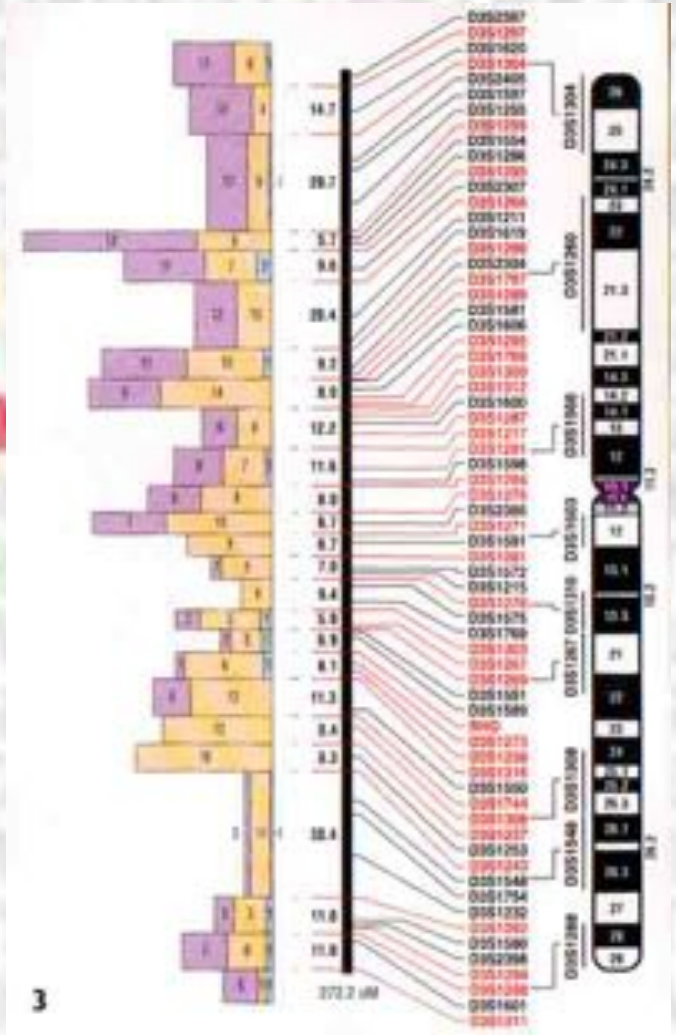
Antiviral Rx

Human Genome Project

- ✓ *15 years, 6 countries, 20 centers.*
- ✓ *3 billion $, 3 billion letters. 1 $ per letter—such a deal!*
- ✓ *23 chromosomes. Supposed to contain 100,000 genes. Turns out to only have 30,000 genes—or maybe 25,000. But it could be 40,000—check back with us next year.*
- ✓ *Said to have the answer to everything, absolutely everything. Diabetes, Asthma, Cancer, Evolution, Populations, Migrations, Life, Death, Taxes*

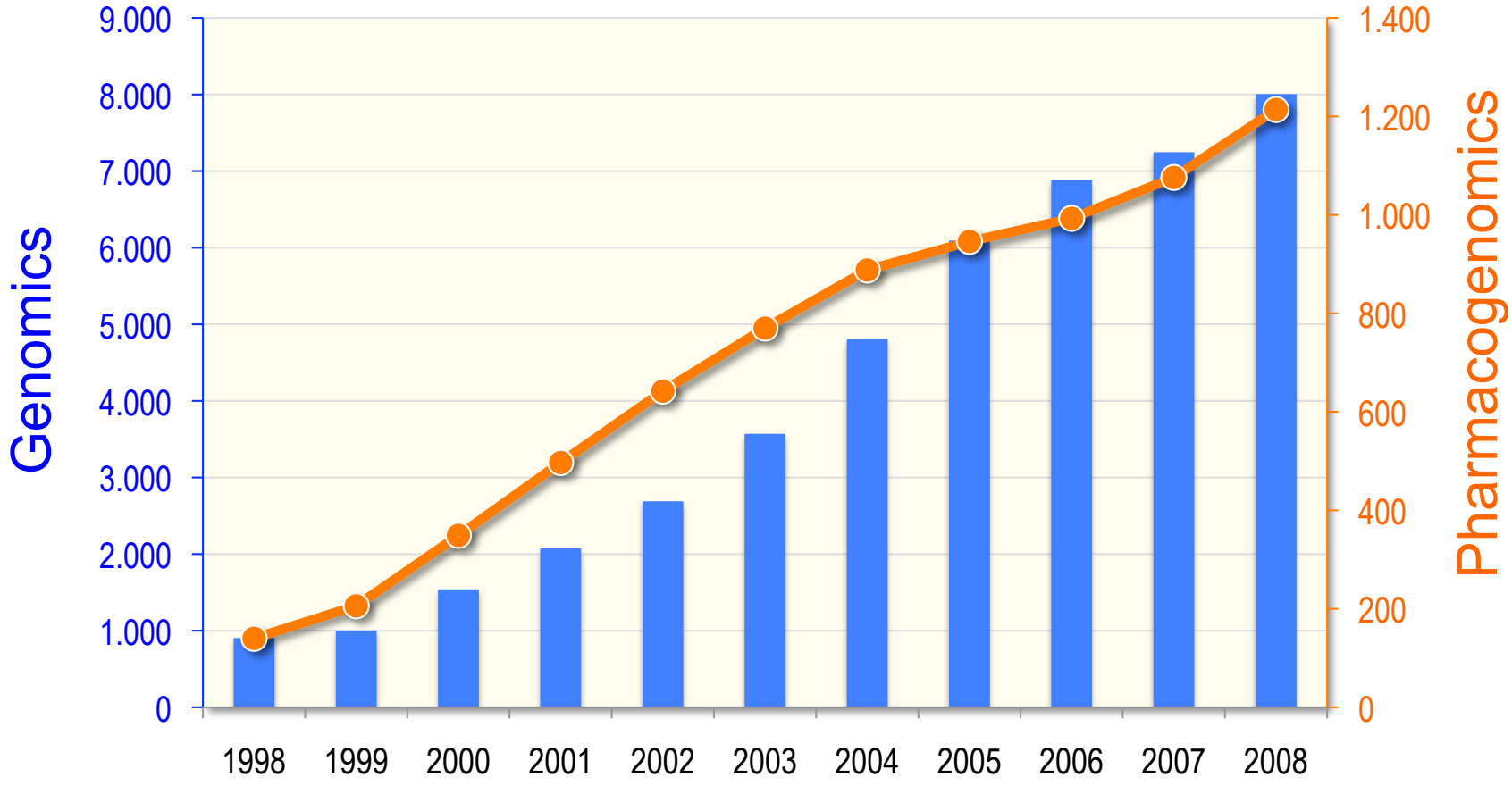
But ... the human genome is harder to read than expected

- *~30,000 genes*
- *3.7 proteins per gene*
- *3 billion base pairs*
- *"Junk DNA"*
- *Differential splicing*



Is genomics interesting ?

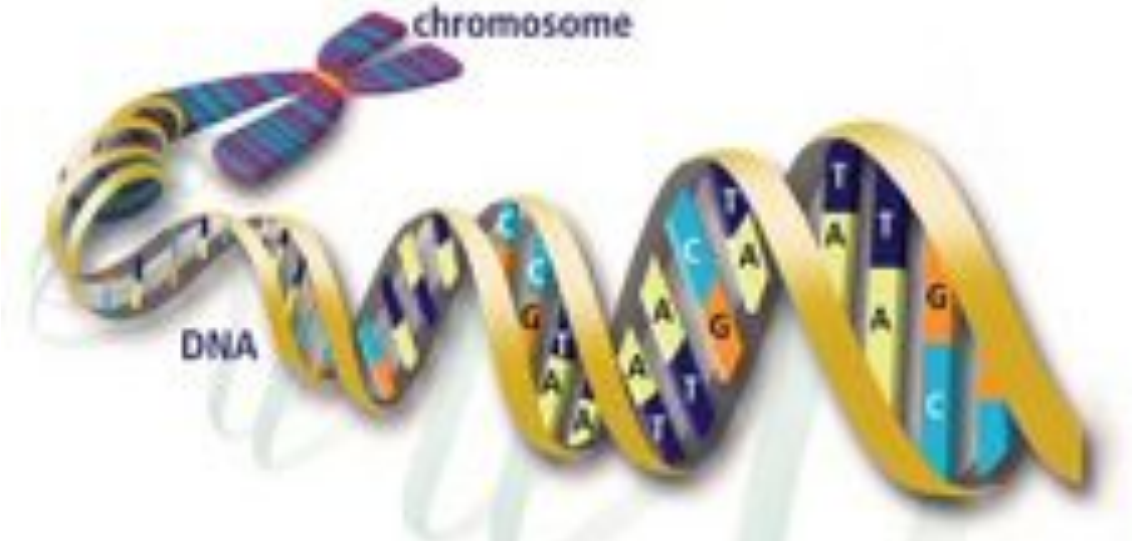
PubMed references containing the terms ...



Why now ? ⇨ Unprecedent Progress

1. High-throughput genotyping and sequencing
2. Knowledge about genetic variation in humans
3. Evolutionary genomics

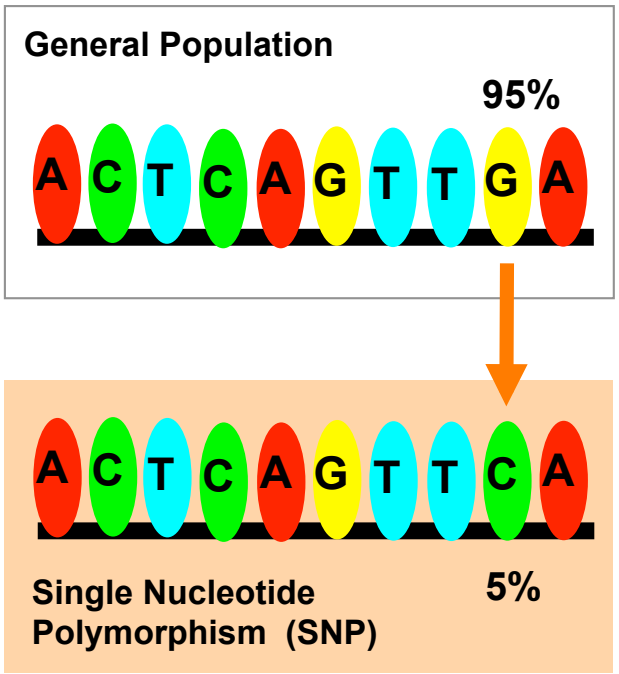
Genetic variations



Human genome: <u>3000 million</u> nucleotides

- We share 99.9% of our DNA
- We are different in 0.1% (1/1000)

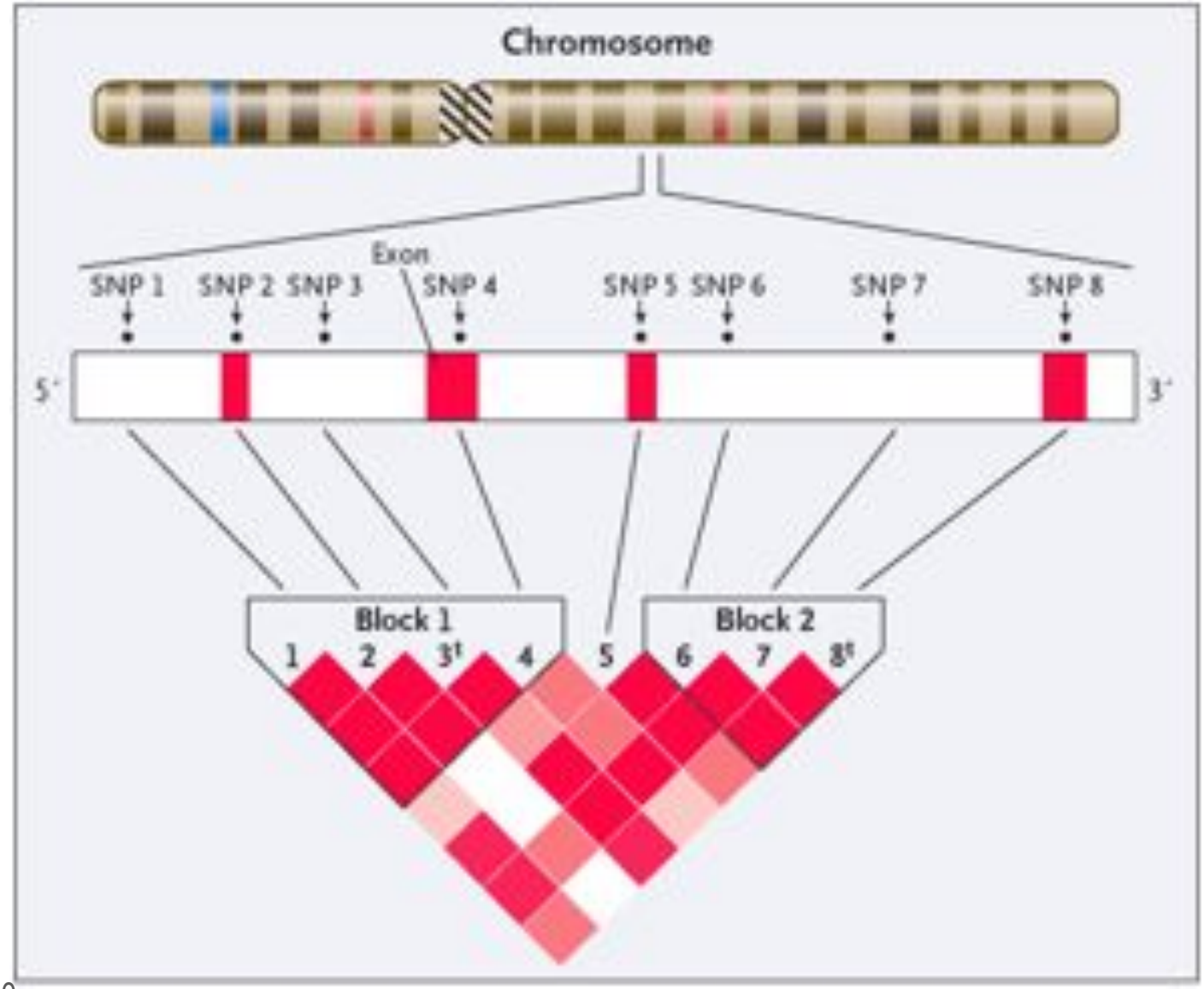
3 milion differences!



International HapMap Project

Haplotype Map

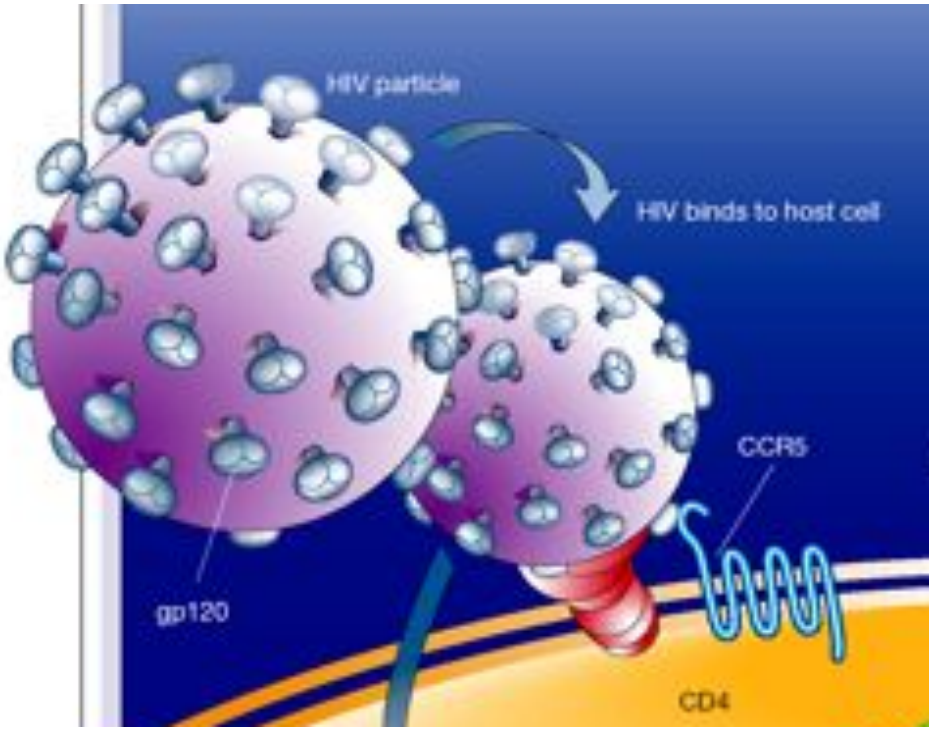
define patterns of genetic variation across human genome

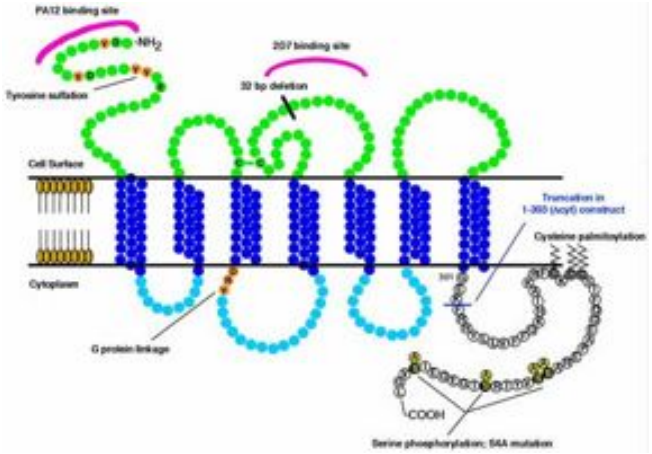


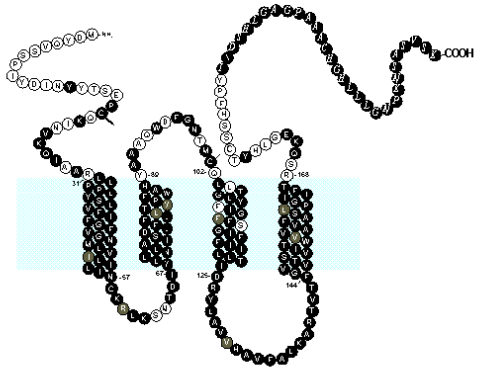
Human gene polymorphisms that influence HIV-1 disease

Susceptibility to Infection and Natural History

Chemokine receptor/ligand system

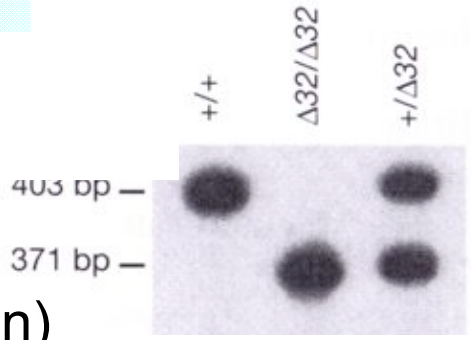






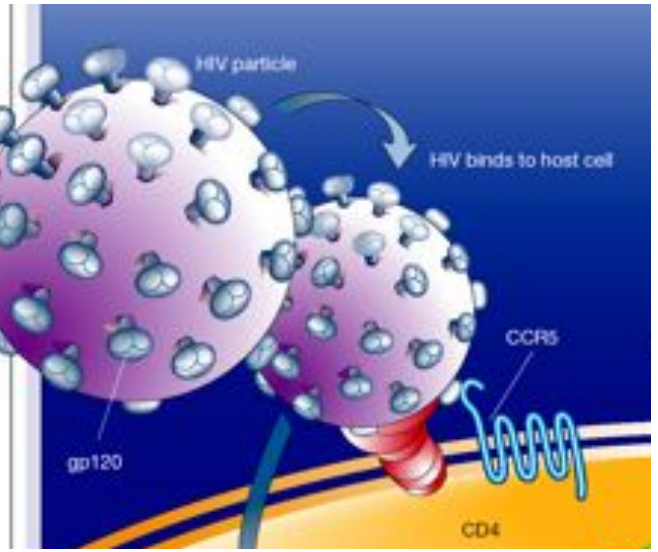
CCR5 Δ32 (HHG*2)

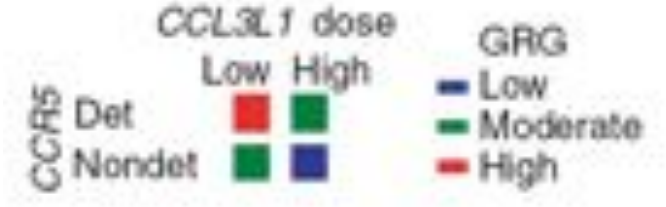
- 32-bp deletion in the region coding for a portion of a transmembrane domain of the receptor
- allele frequency of ~9% among white population
- Homozygous subjects (1%–2% of the white population)
  - ↳ nearly complete protection
- Heterozygous subjects ⇨ slight protection *(HR: 0.5 to 0.8)*

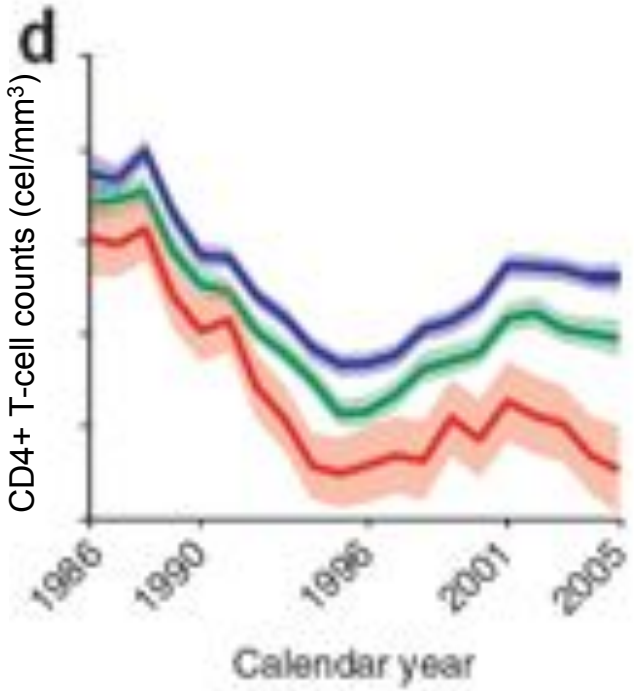


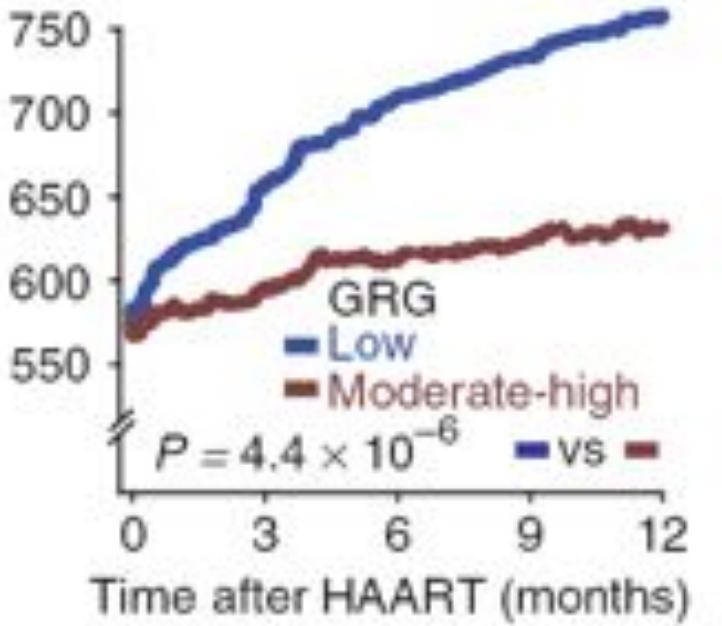
Chemokine receptor/ligand system

CCL3L1 (MIP-1α): copy number variation
CCR5: Δ32 + polymorphisms in promotor







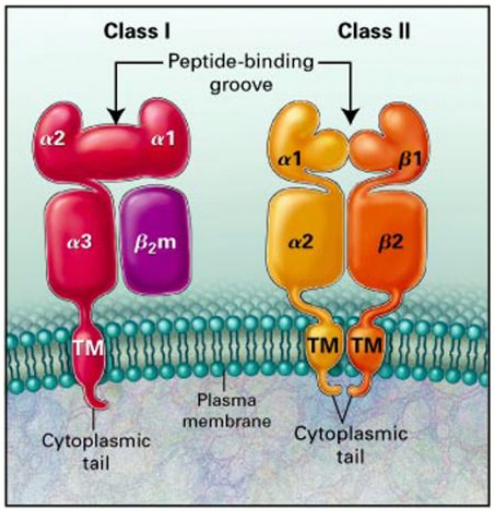


Ahuja *et al.* 2008. Nat Med

HLA and the Ag-Presenting System

HLA class I homozygosity

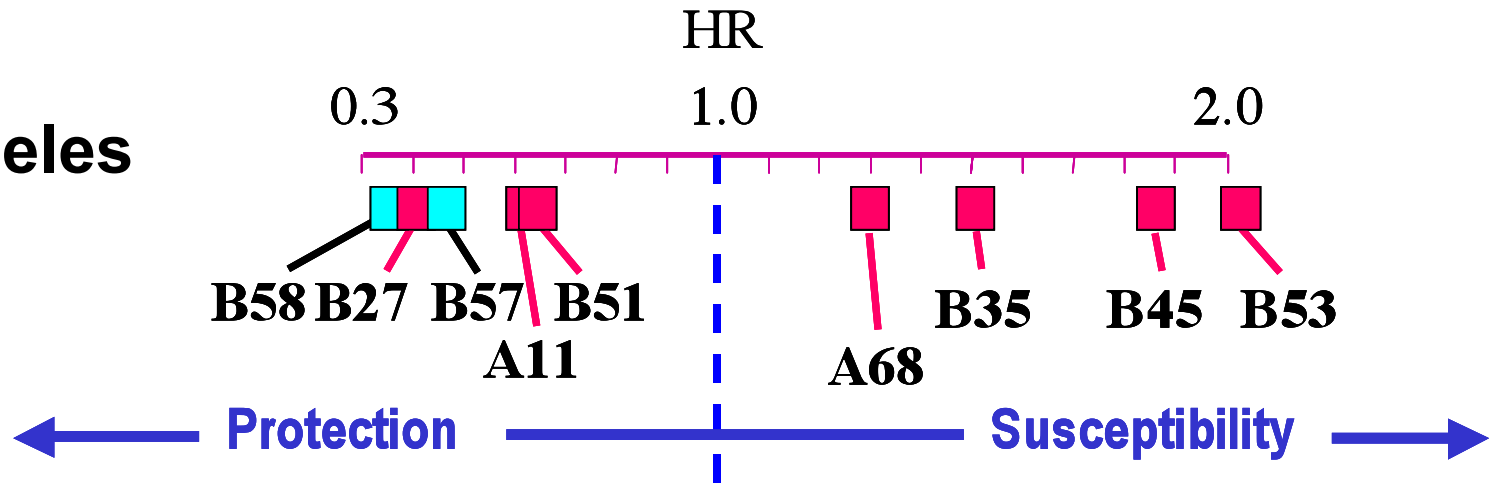
- homozygosity at class I loci strongly associated with
  - ⇨ poor control of infection
  - ⇨ relatively rapid disease progression



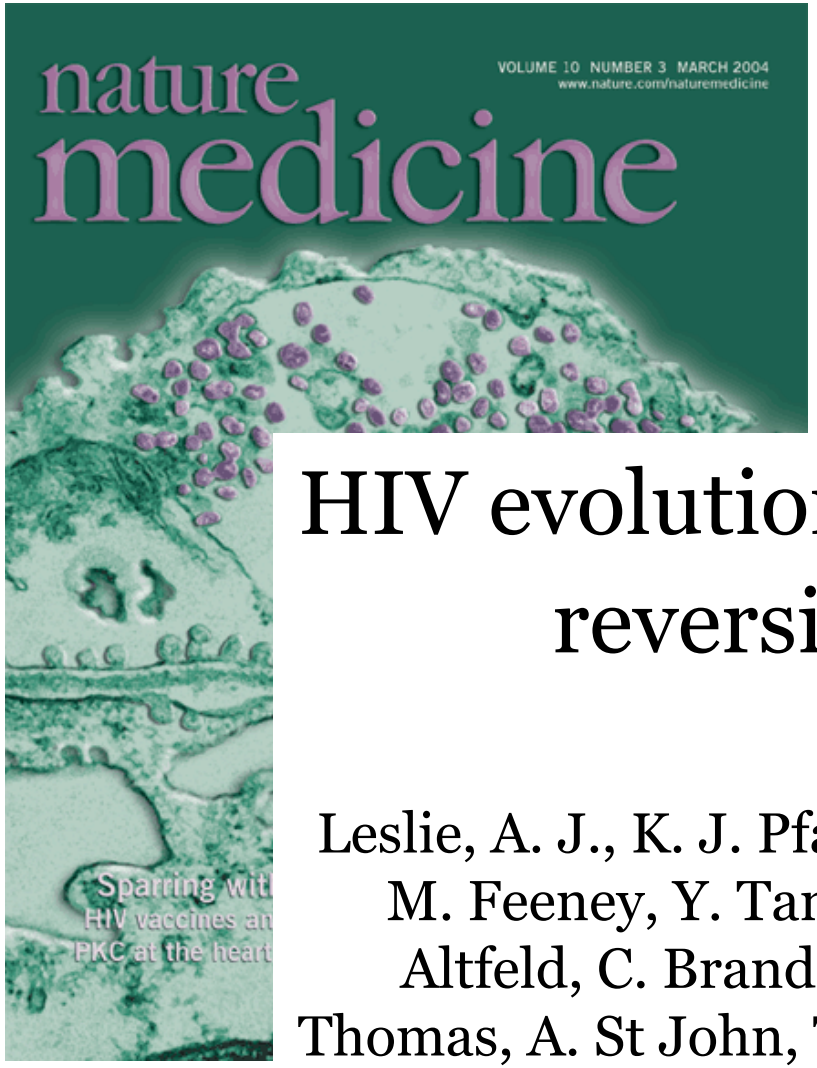
HLA class I allele sharing (MTC transmission)

- identity of HLA class I alleles between potential virus donors and recipients ⇨ increases the susceptibility of the latter

Individual HLA class I alleles



Example 1

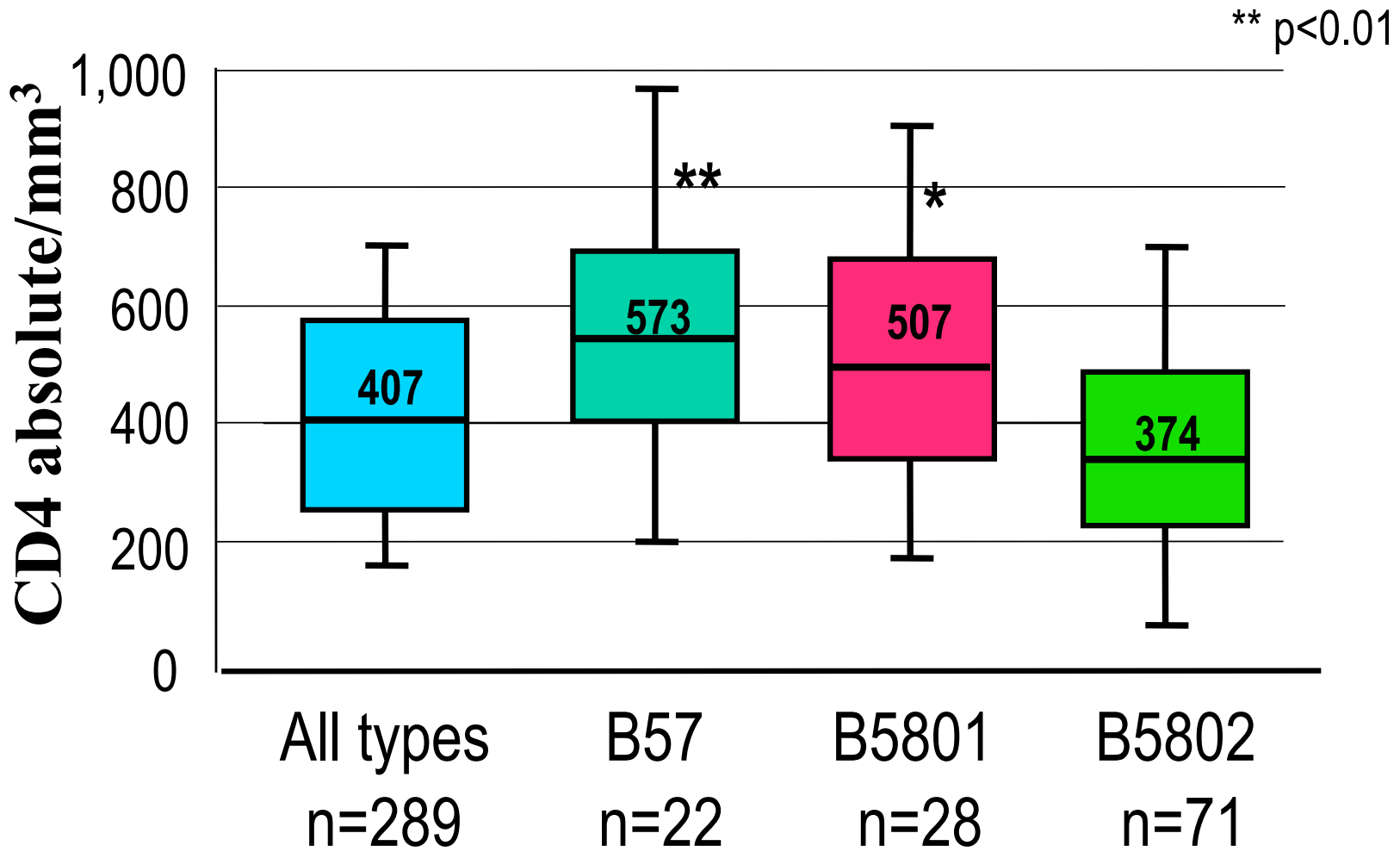


HIV evolution: CTL escape mutation and reversion after transmission

Leslie, A. J., K. J. Pfafferott, P. Chetty, R. Draenert, M. M. Addo, M. Feeney, Y. Tang, E. C. Holmes, T. Allen, J. G. Prado, M. Altfeld, C. Brander, C. Dixon, D. Ramduth, P. Jeena, S. A. Thomas, A. St John, T. A. Roach, B. Kupfer, G. Luzzi, A. Edwards, G. Taylor, H. Lyall, G. Tudor-Williams, V. Novelli, J. Martinez-Picado, P. Kiepiela, B. D. Walker, and P. J. Goulder

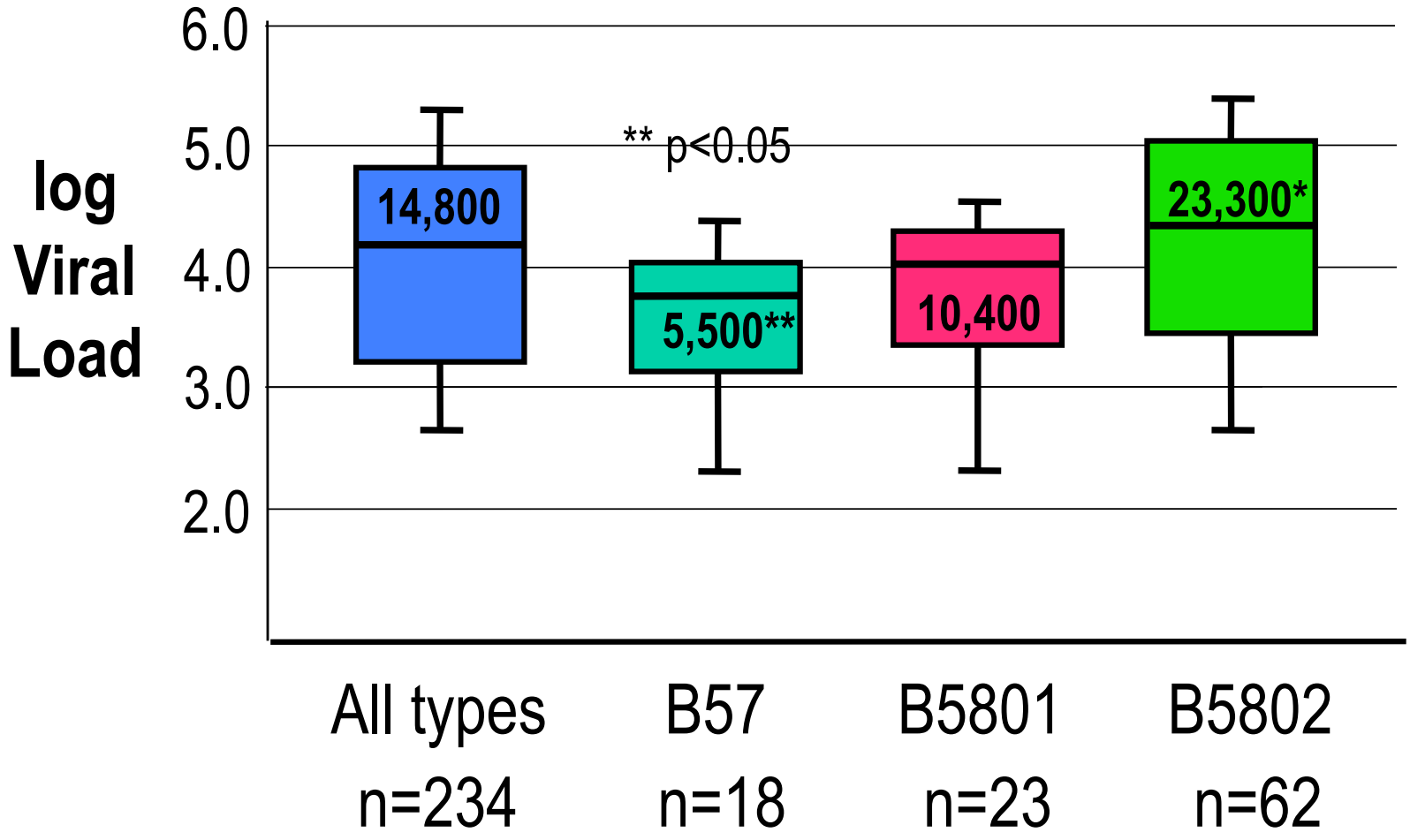
Leslie *et al.* Nat Med 2004

HLA-B57 is associated with higher absolute CD4 counts in C-clade infected people



Nat Med 2004 vol. 10

HLA-B57 is associated with low pVL in C-clade infected people



Nat Med 2004 vol. 10

Example 2

ARTICLE

Constraints on HIV-1 evolution and immunodominance revealed in monozygotic adult twins infected with the same virus

Rika Draenert,[1,2] Todd M. Allen,[1] Yang Liu,[3] Terri Wrin,[3] Colombe Chappey,[3] Cori L. Verrill,[1] Guillem Sirera,[4] Robert L. Eldridge,[1] Matthew P. Lahaie,[1] Lidia Ruiz,[4] Bonaventura Clotet,[4] Christos J. Petropoulos,[3] Bruce D. Walker,[1,2] and Javier Martinez-Picado[4]

[1]Howard Hughes Medical Institute and [2]Partners AIDS Research Center, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129
[3]Monogram Biosciences, South San Francisco, CA 94080
[4]Fundació irsiCaixa, Hospital Universitari Germans Trias i Pujol, Badalona, Spain 08916

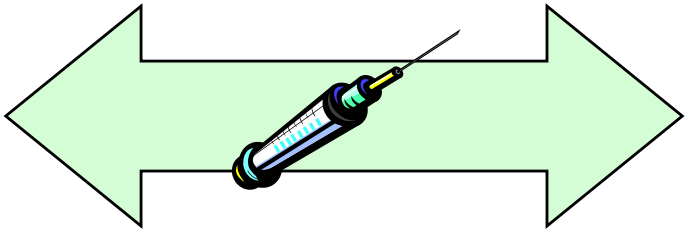
J Exp Med 2006 vol 203:529–539

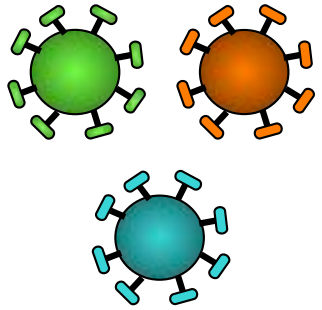
Patients: zygosity identity and HLA Class I

21 year old identical twins

12/98 Last HIV-

9/99 First HIV+



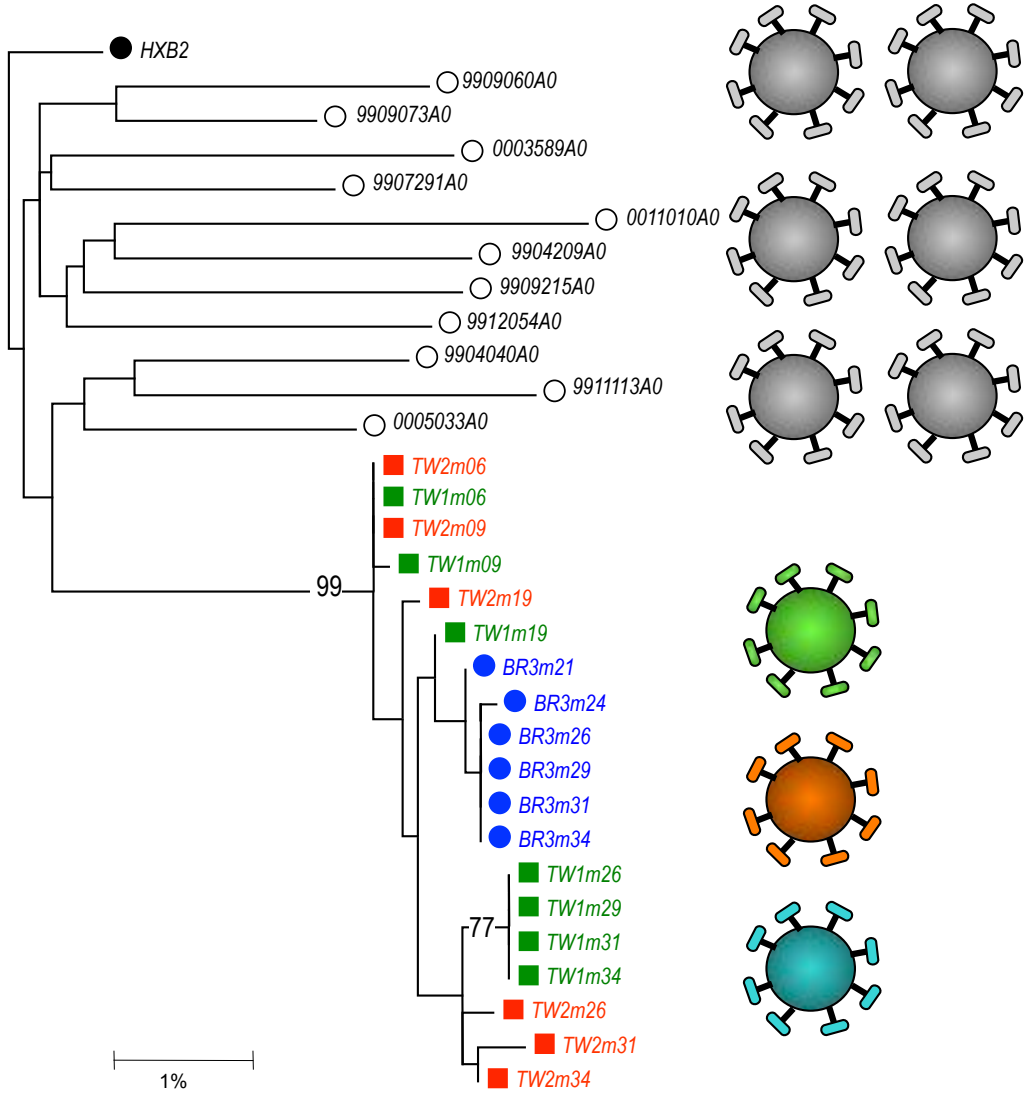


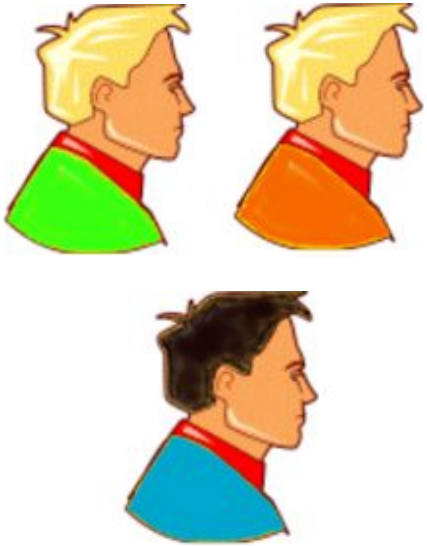
Sibling infected

13 months later

Zygotic identification ↓ polymorphic STR	
HLA Class I	
TW1 & TW2	BR3
A0201, 2402	A0201, 0201
B4001, 5001	B4001, 44
Cw03, 04	Cw03, 05

Genetic identity of infecting HIV

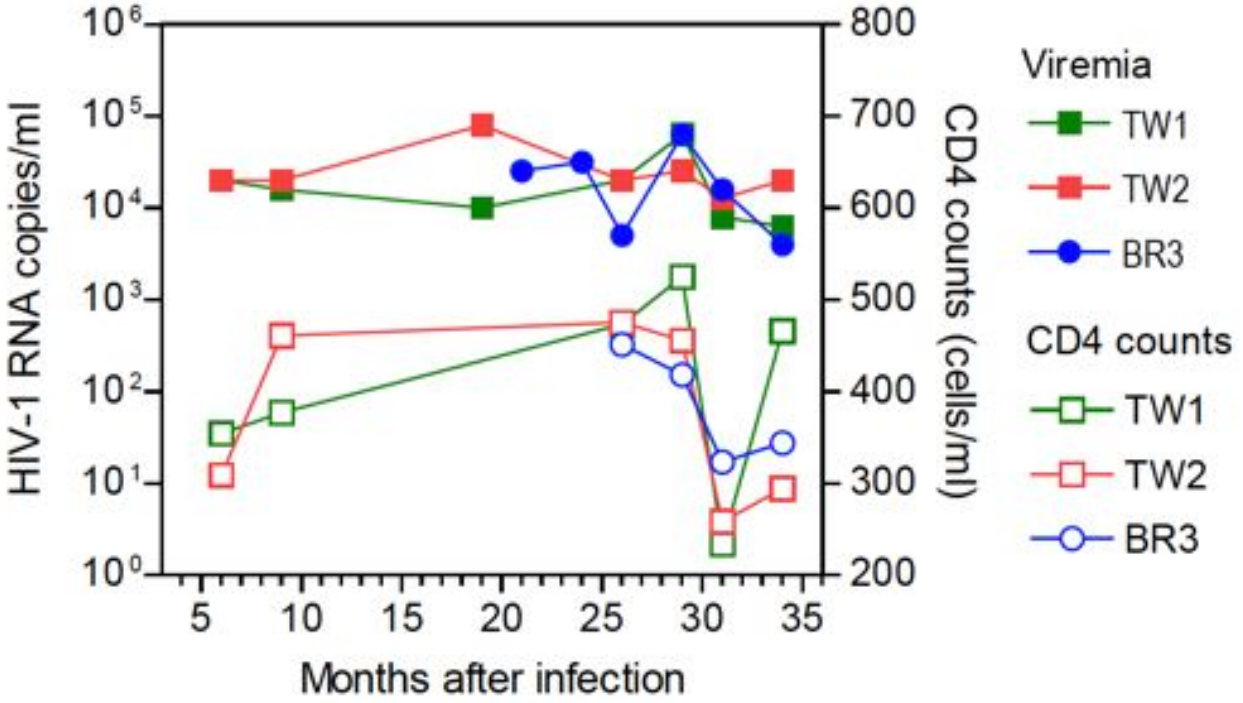




J Exp Med 2006 vol 203:529–539

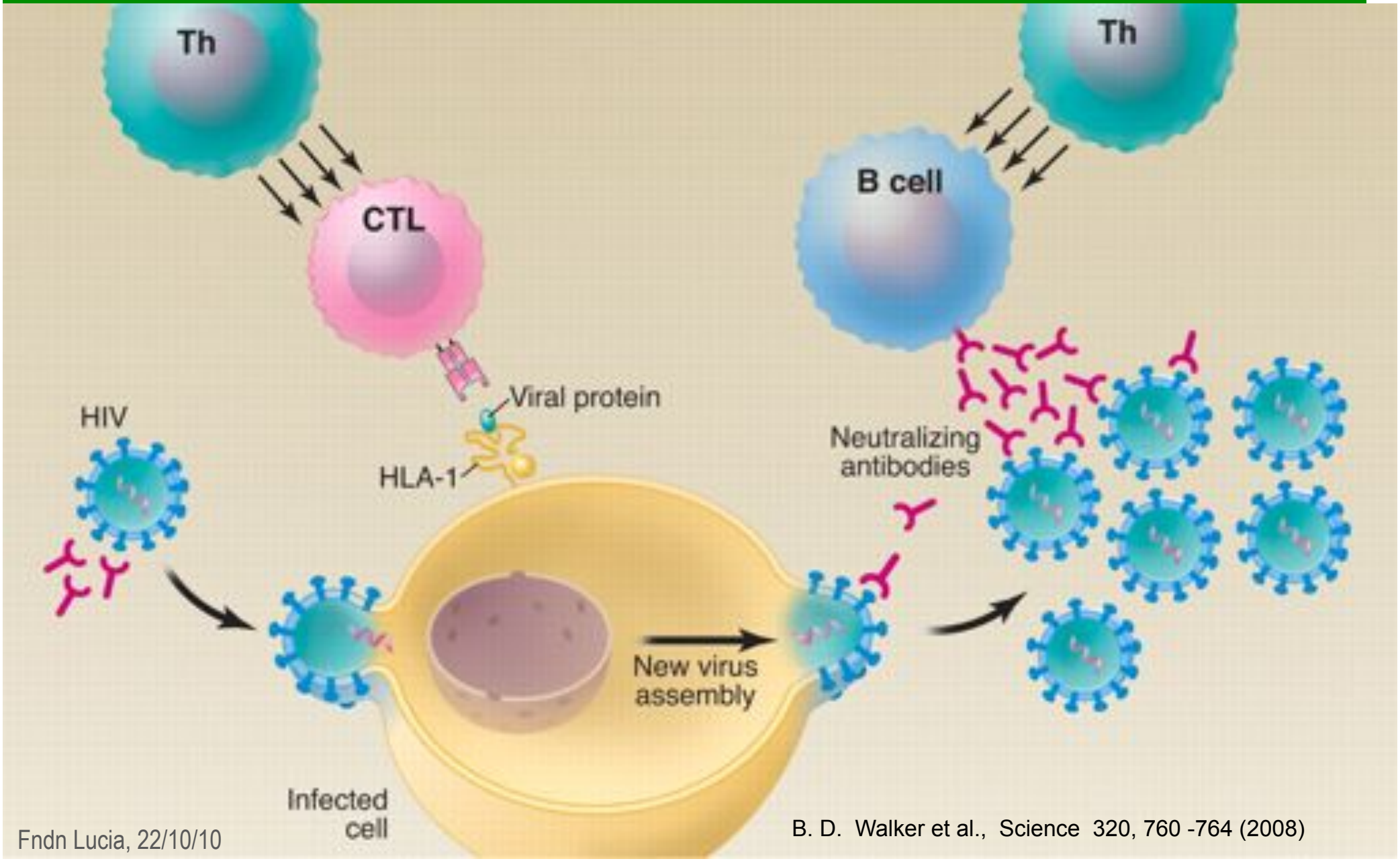
Similar clinical course

Plasma viremia
CD4+ T-cell counts



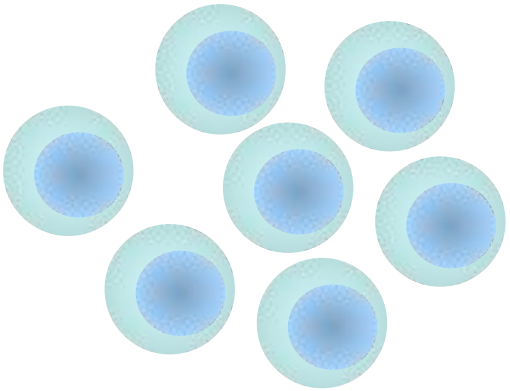
J Exp Med 2006 vol 203:529–539

Adaptive immune responses in HIV infection



B. D. Walker et al., Science 320, 760 -764 (2008)

ELISPOT assay for T-cell responses

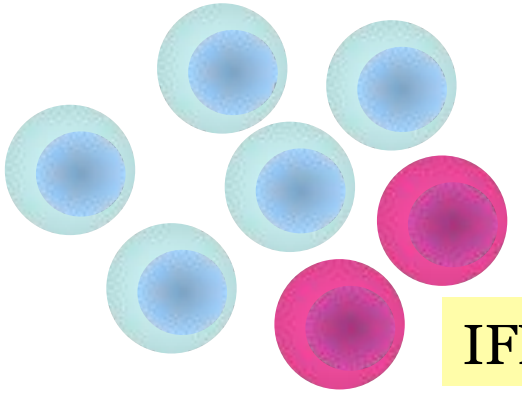


peripheral blood
mononuclear cells

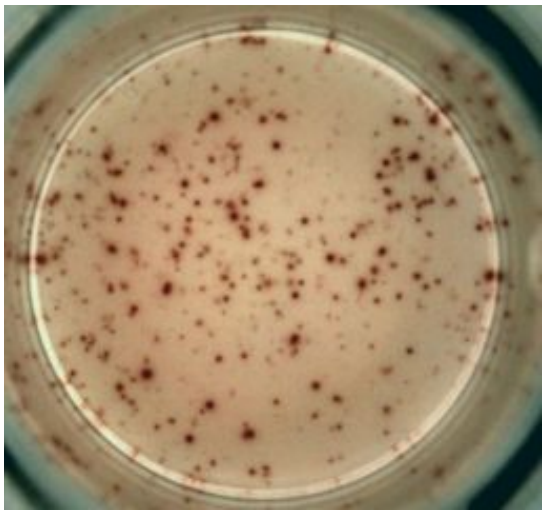
+

P1
P2
P3
P4
P5
P6
P7
P8
P9

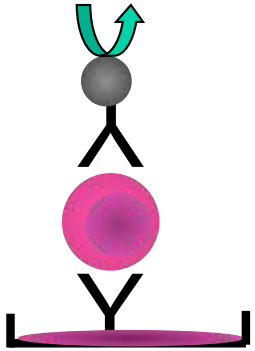
Overlapping peptides
Gag, Pol, Nef, Env etc



IFN- γ

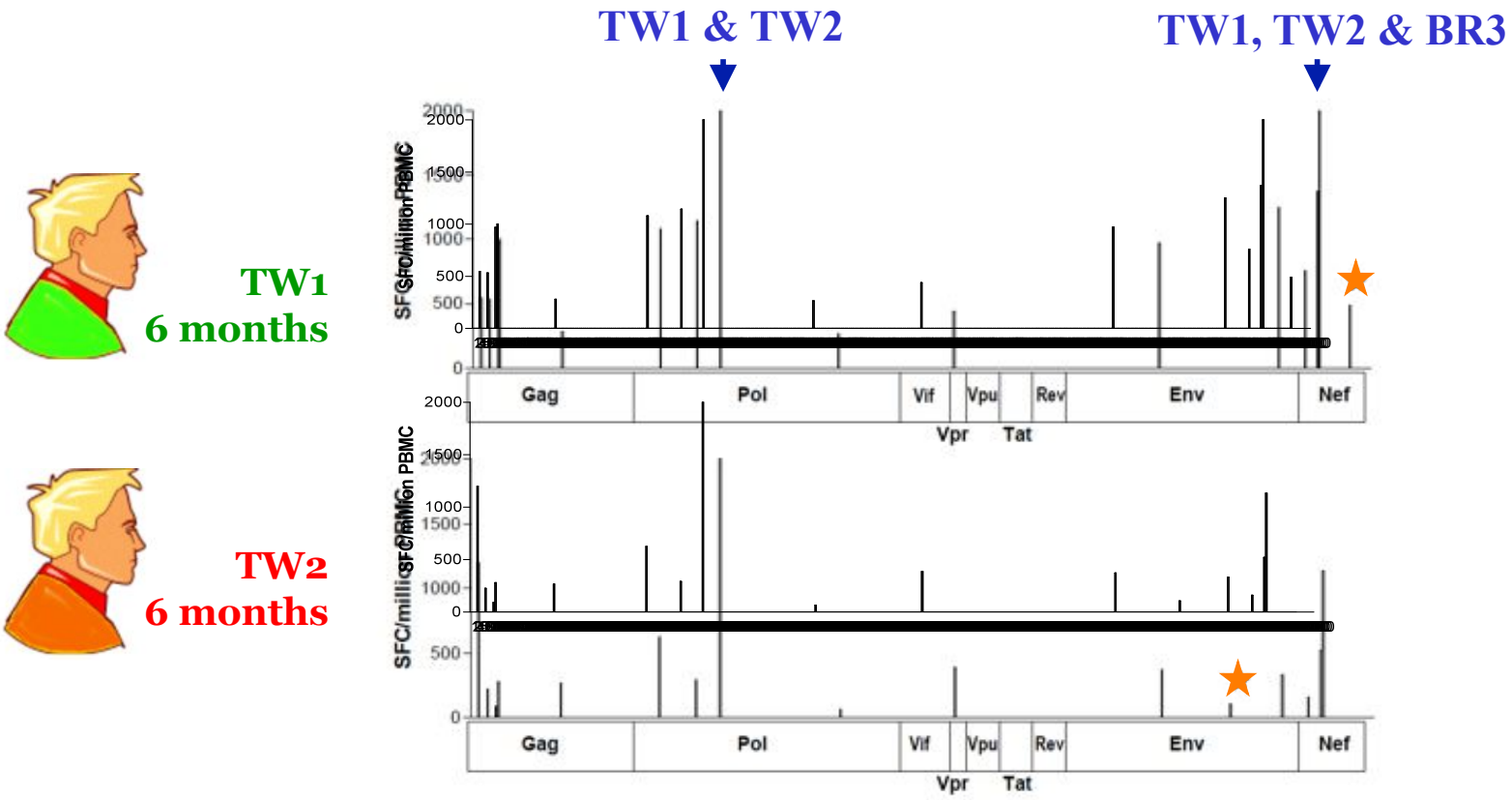


Elispot read-out



IFN-γ T cell responses in the twins

- ELISPOT with overlapping peptides all throughtout the viral genome
- 15/17 initial responses were shared between twins, including immunodominant responses.



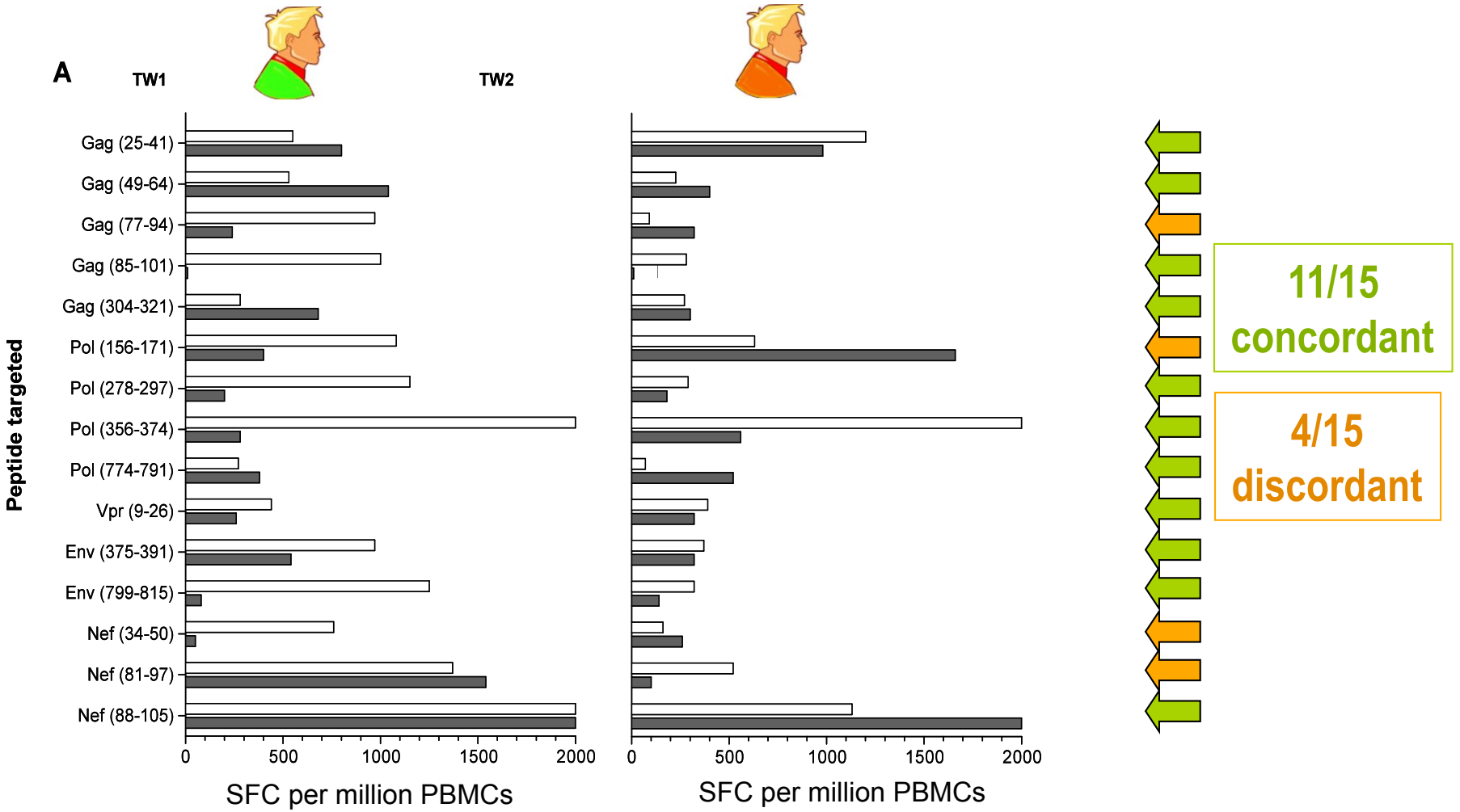
▼ *immune-dominant response*

★ *response in only one twin*

J Exp Med 2006 vol 203:529–539

T cell responses during the course of the study

Responses targeted by both twins at the first and last study time points
15/17 initial responses were common



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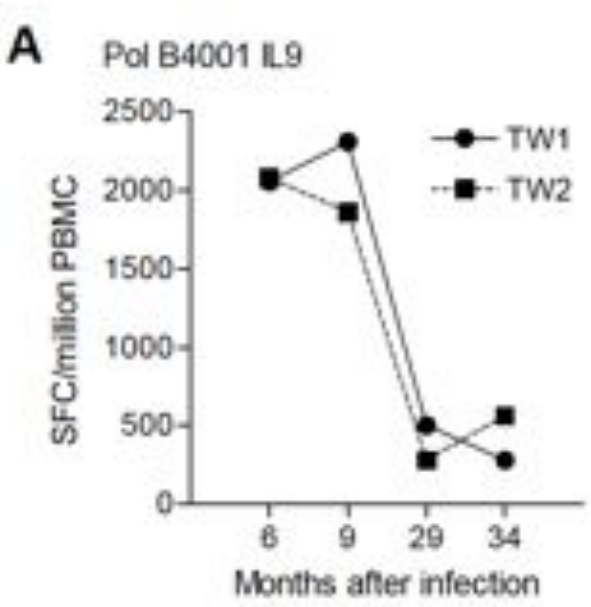
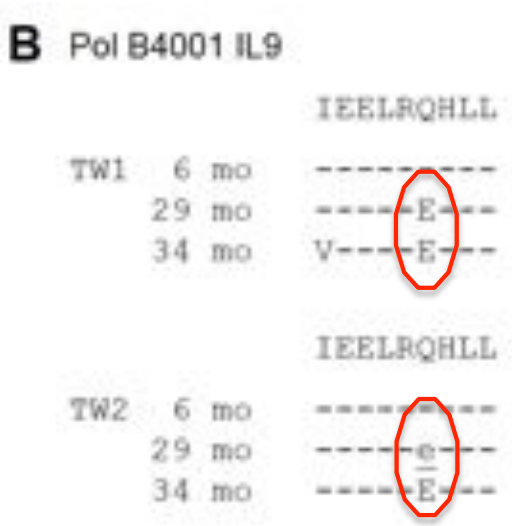
Concordant CD8 T cell responses and viral evolution

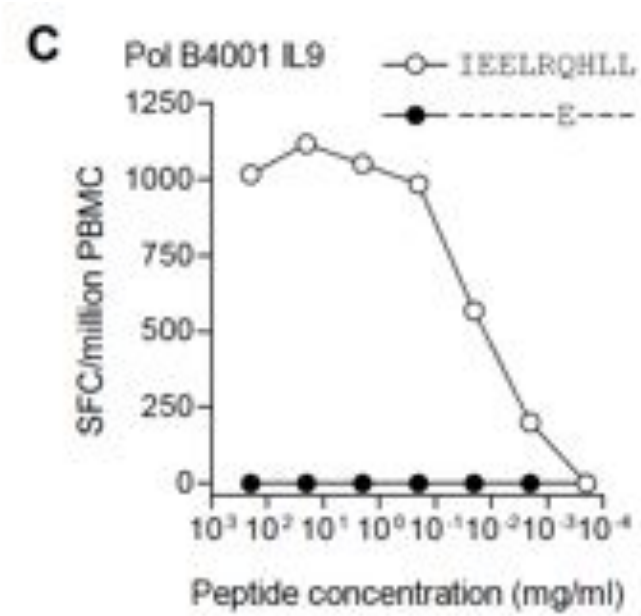
T-cell response over time



Viral evolution at the epitope



Peptide titration assay



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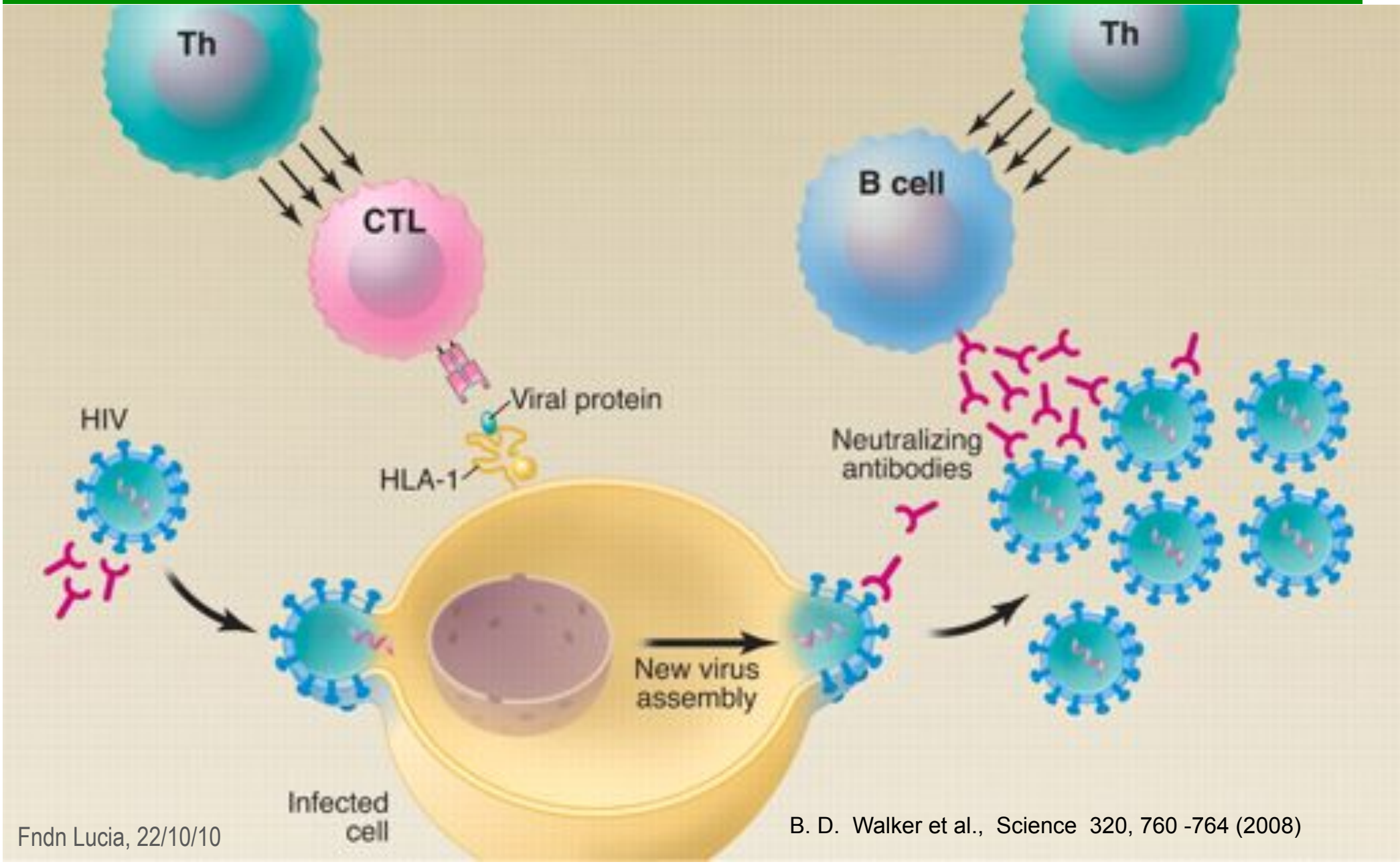
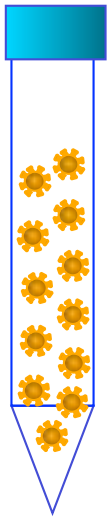
Adaptive immune responses in HIV infection

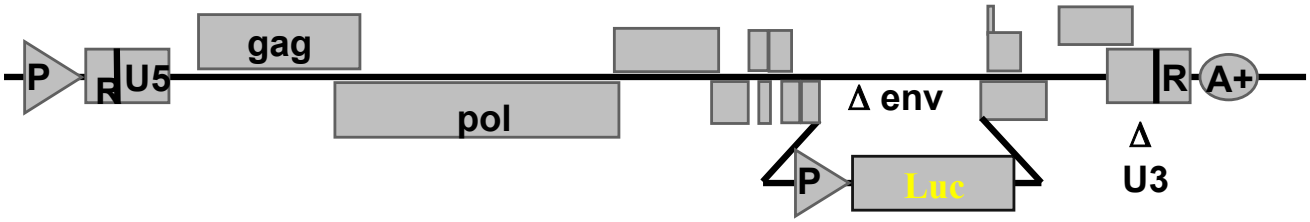


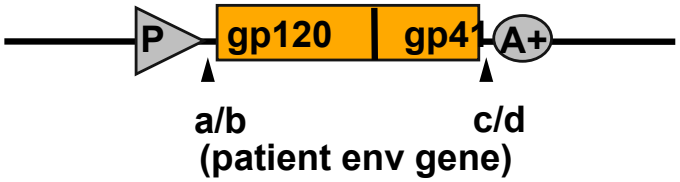
B. D. Walker et al., Science 320, 760 -764 (2008)

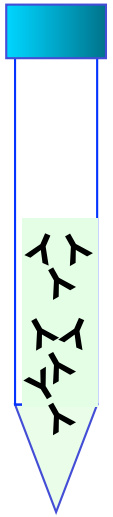
Antibody neutralizing assay



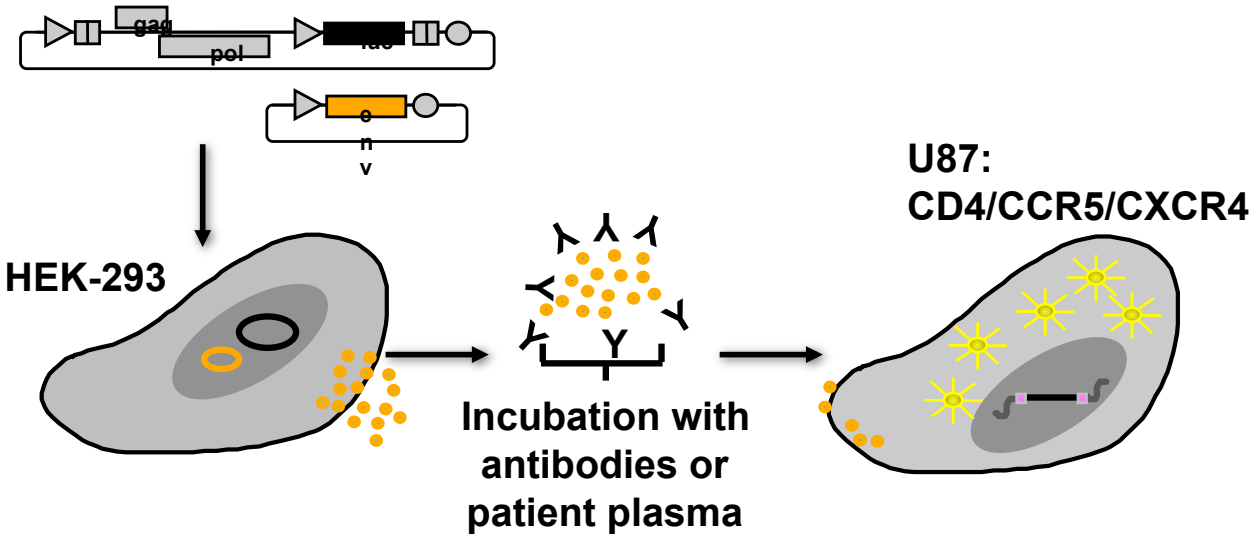
rec HIV-1
TW1



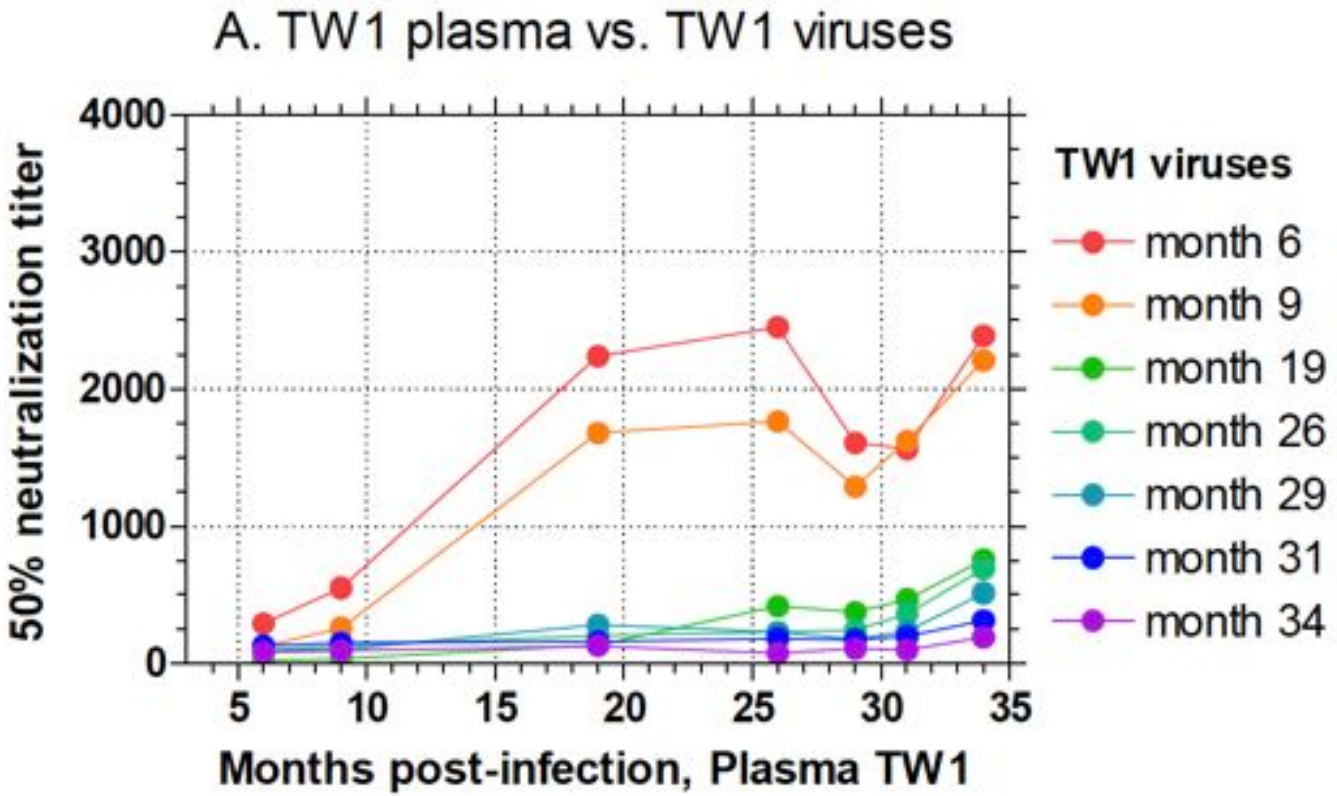


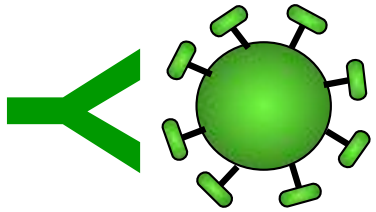


Plasma
With NAb
TW1



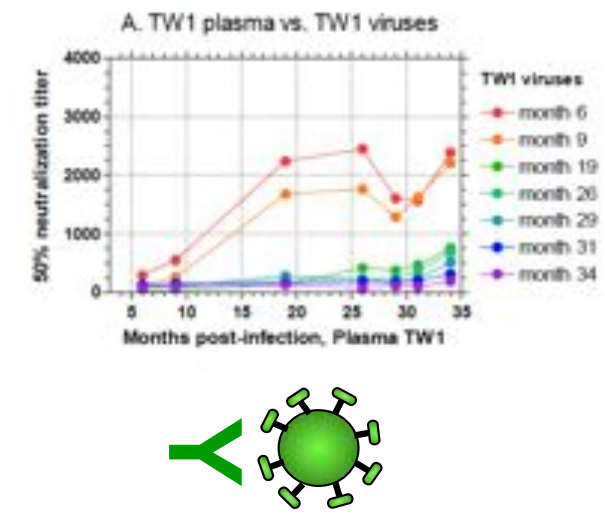
Antibody neutralizing titers of TW1 against autologous viruses

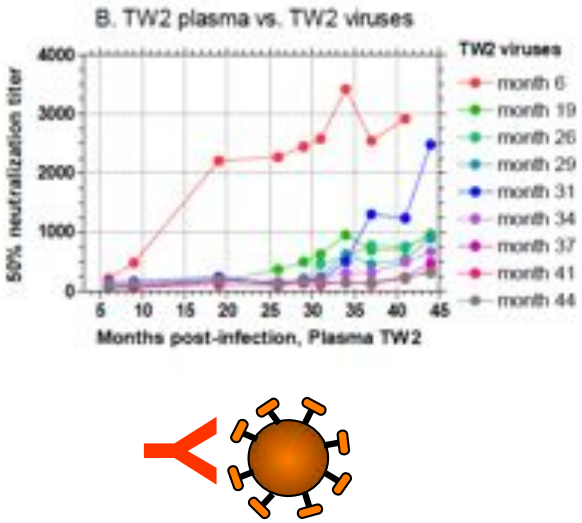


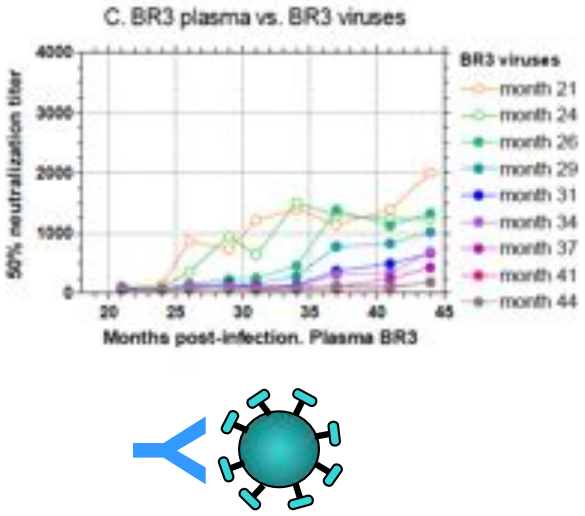


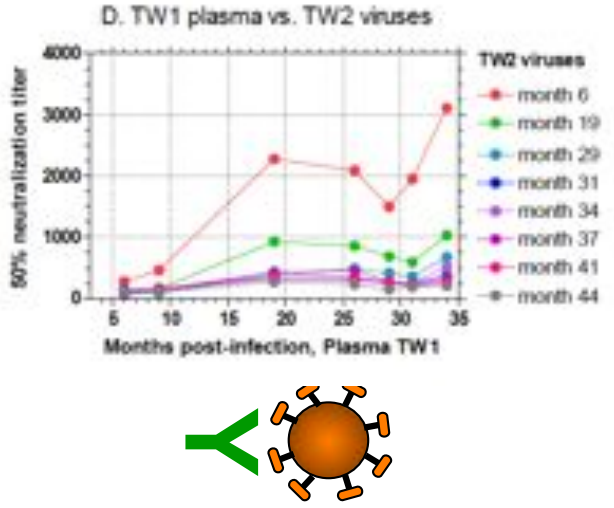
J Exp Med 2006 vol 203:529–539

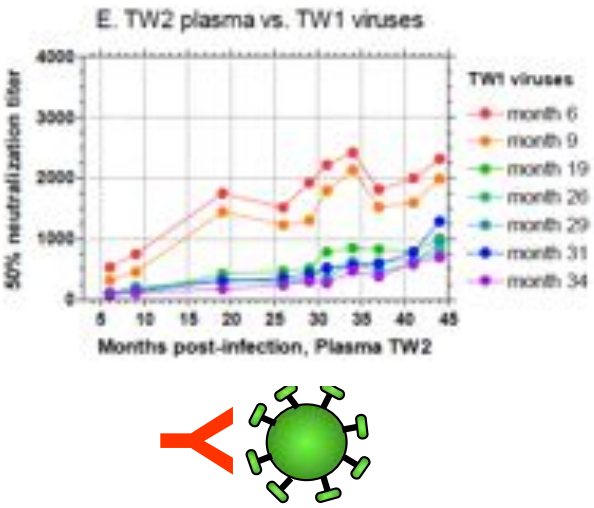
Antibody neutralizing titers of TW1, TW2 and BR3 plasma against autologous and heterologous viruses

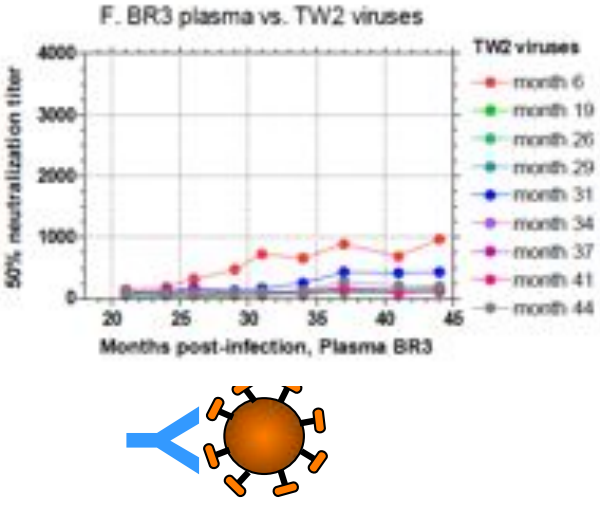










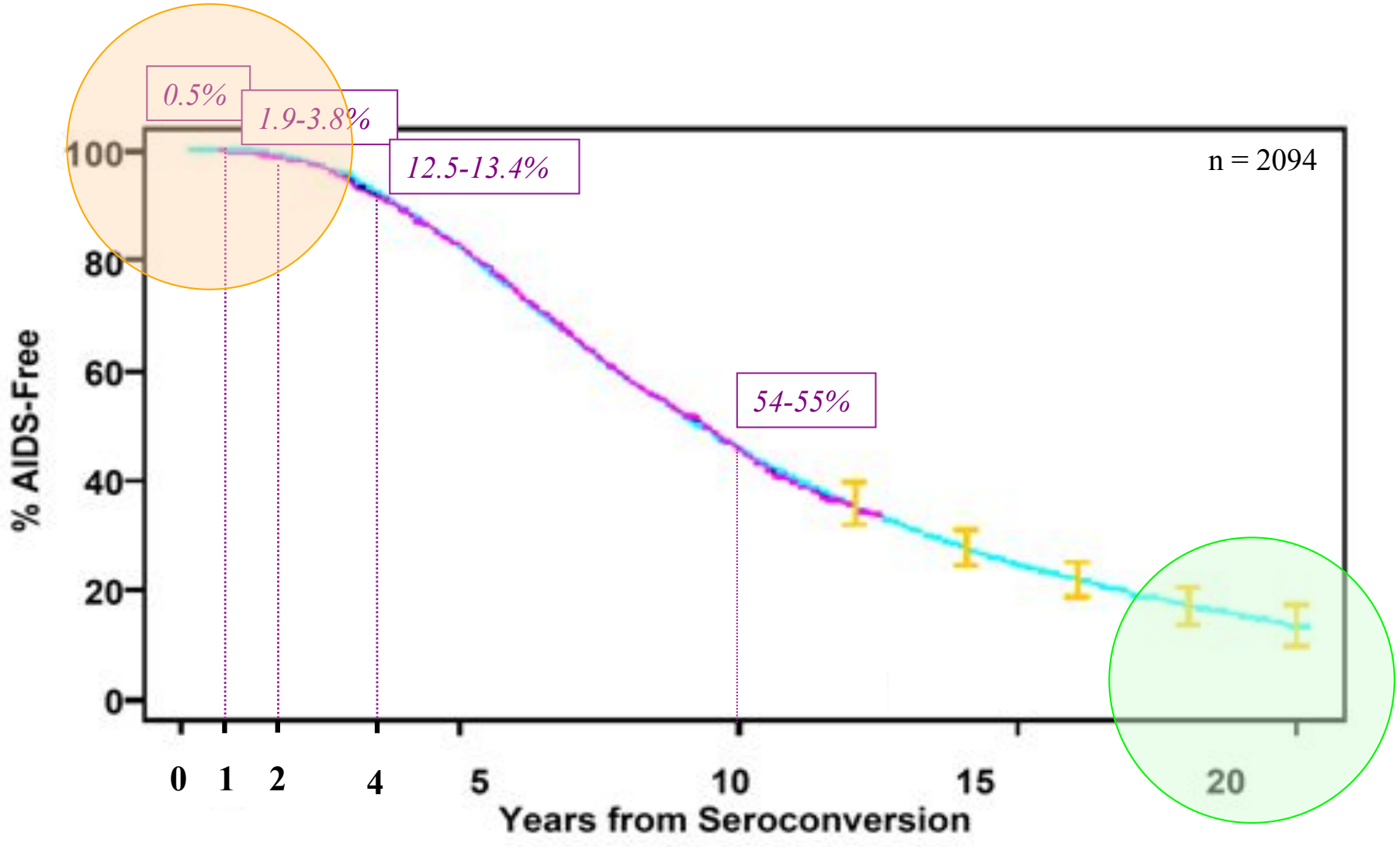


J Exp Med 2006 vol 203:529–539

Summary

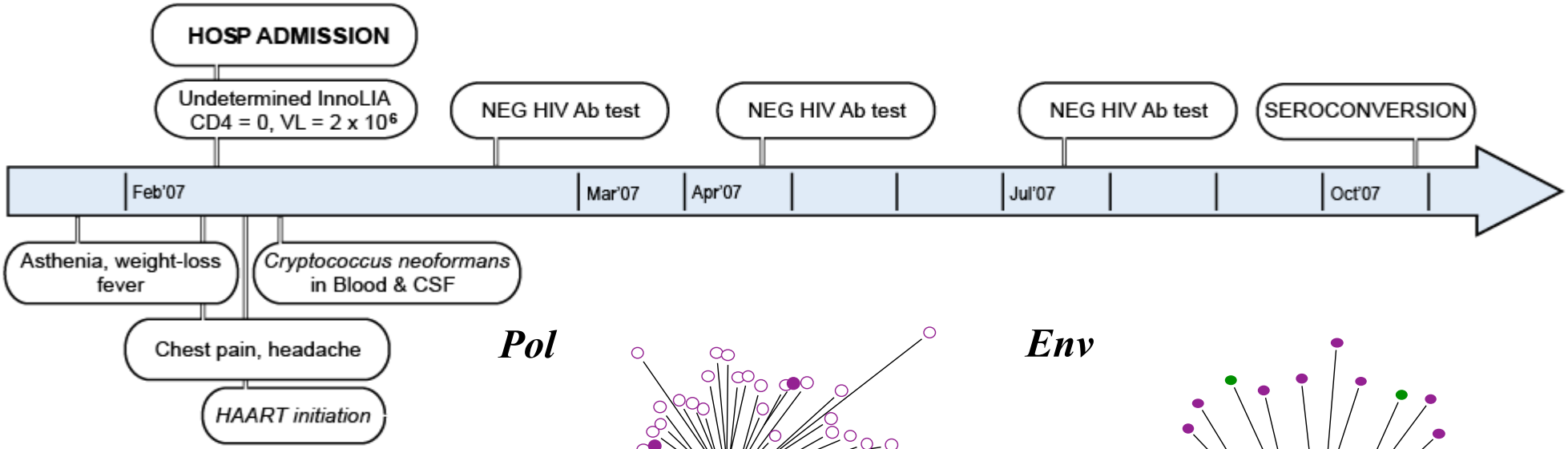
- These twins experienced a similar ...
  - clinical course
  - breadth and magnitude of CD8 T cell responses
  - neutralizing Ab responses
  - constrains on HIV evolution under adaptative humoral and cellular immune selection pressure

Estimated long term AIDS-free proportions prior to potent ART

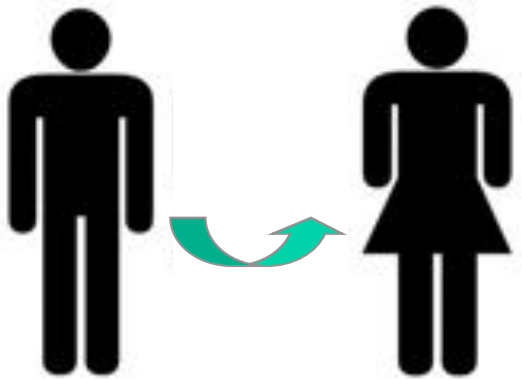


Muñoz et al. 1995. JAIDS 8:496-505
Muñoz et al. 1989, Am J Epidemiol 130: 530-9

Sexual Transmission of Severe PHI

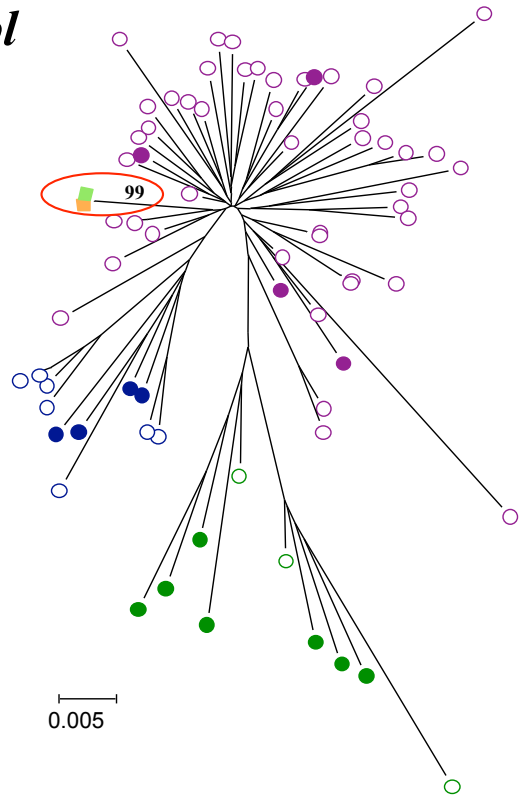


15-yrs

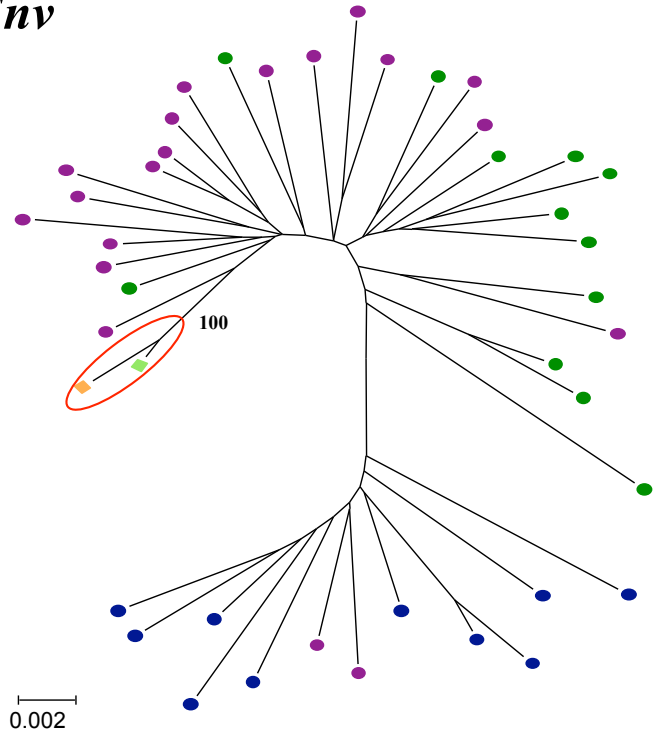


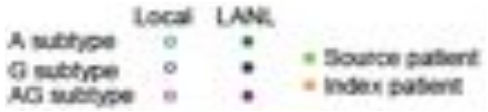
CRF02-A/G subtype
No drug resistance-associated mutations

Pol



Env

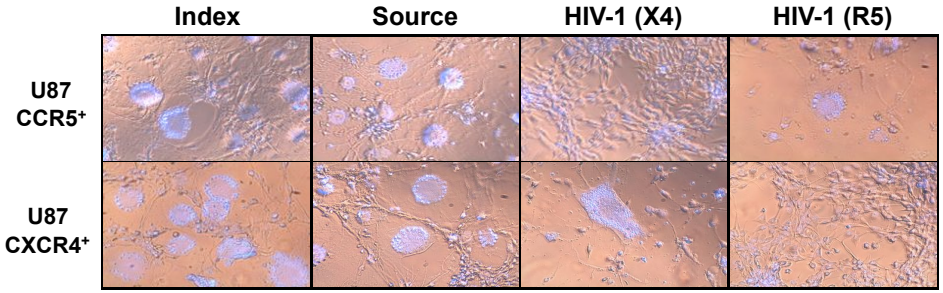


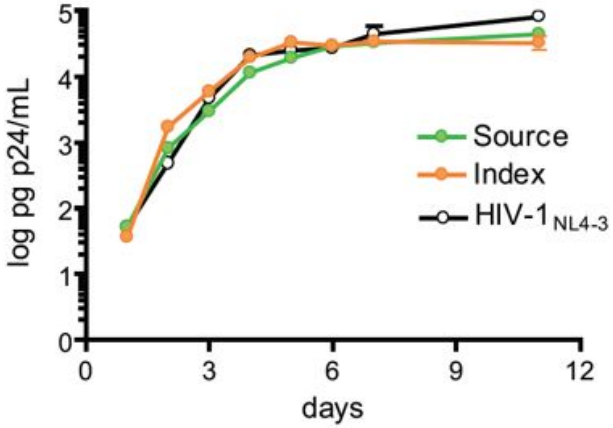


Dalmau et al. 2009. Clin Infect Dis 48:229-38

Severe Primary Infections

Dual- Tropic highly replicative virus

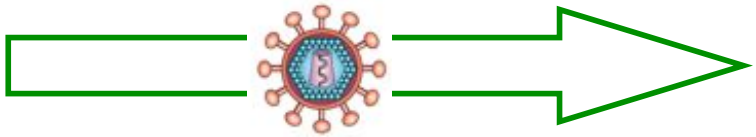




Sharing same HLA-supertypes ⇨ lack of CTL responses

CTL responses to 3 epitopes in Gag, Nef, Pol

escaped



HIV-1

Weak CTL responses to 1 epitope in Env

Dalmau et al. 2009. Clin Infect Dis 48:229-38

Severe PHI: humoral immune responses

- HIV-1-specific antibody tests did not become positive until 9 months after the initiation of ART
  - *Related to slow CD4+ T cell recovery upon ART ?*

- Low mean diversity of index patient-derived Env clones: 1.8%
  - *Due to limited humoral pressure ?*

- Serum levels of IgG, IgM and IgA were within the reference range or higher: potential polyclonal B cell activation

- Positive IgG responses to CMV, *T. Gondii* and HAV: ability of ab to maintain an appropriate response against microorganisms that cause persistent infections

Dalmau et al. 2009. Clin Infect Dis 48:229-38

Severe PHI: conclusions

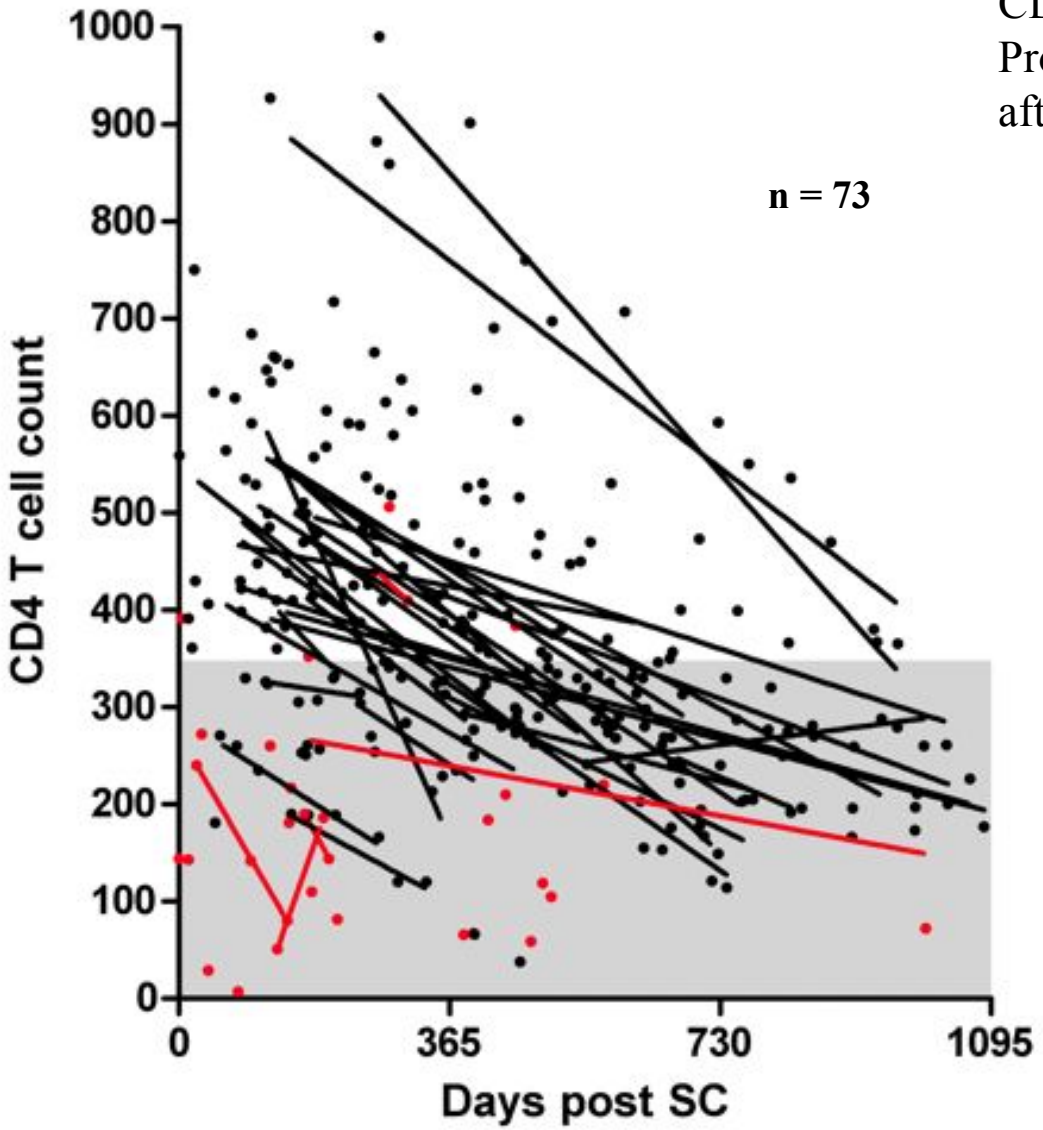
- Concurrence of viral and host factors contribute to the clinical severity of primary HIV-1 infection

- Patients infected with highly replicative, dual-tropic viruses are more prone to develop AIDS-defining symptoms during acute infection if they are unable to mount humoral and cellular HIV- 1–specific immune responses.

- The presence of concordant HLA supertypes might facilitate the preferential transmission of HLA-adapted viral variants, further accelerating disease progression.

Way to go …

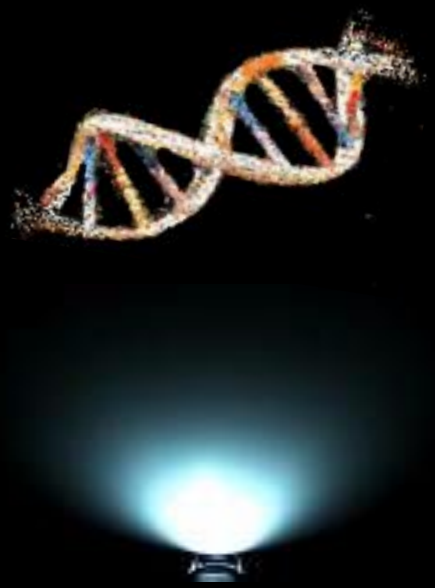
CoRP



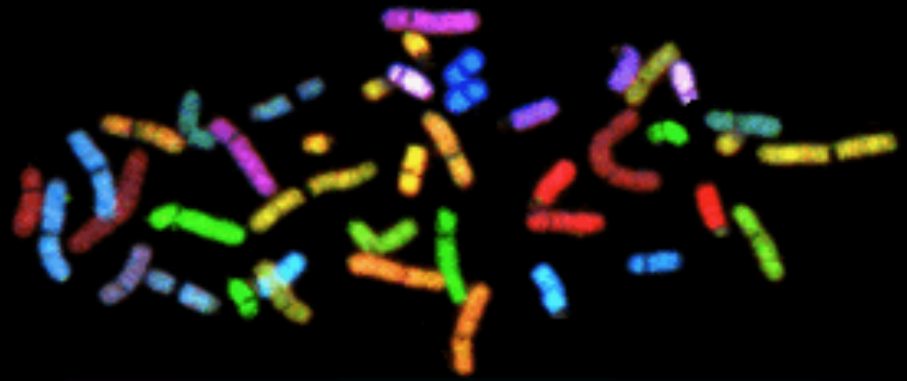
CD4 evolution of Rapid Progression during 3 years after seroconversion

***Red**: accompanied with an AIDS event/death*

Genetics

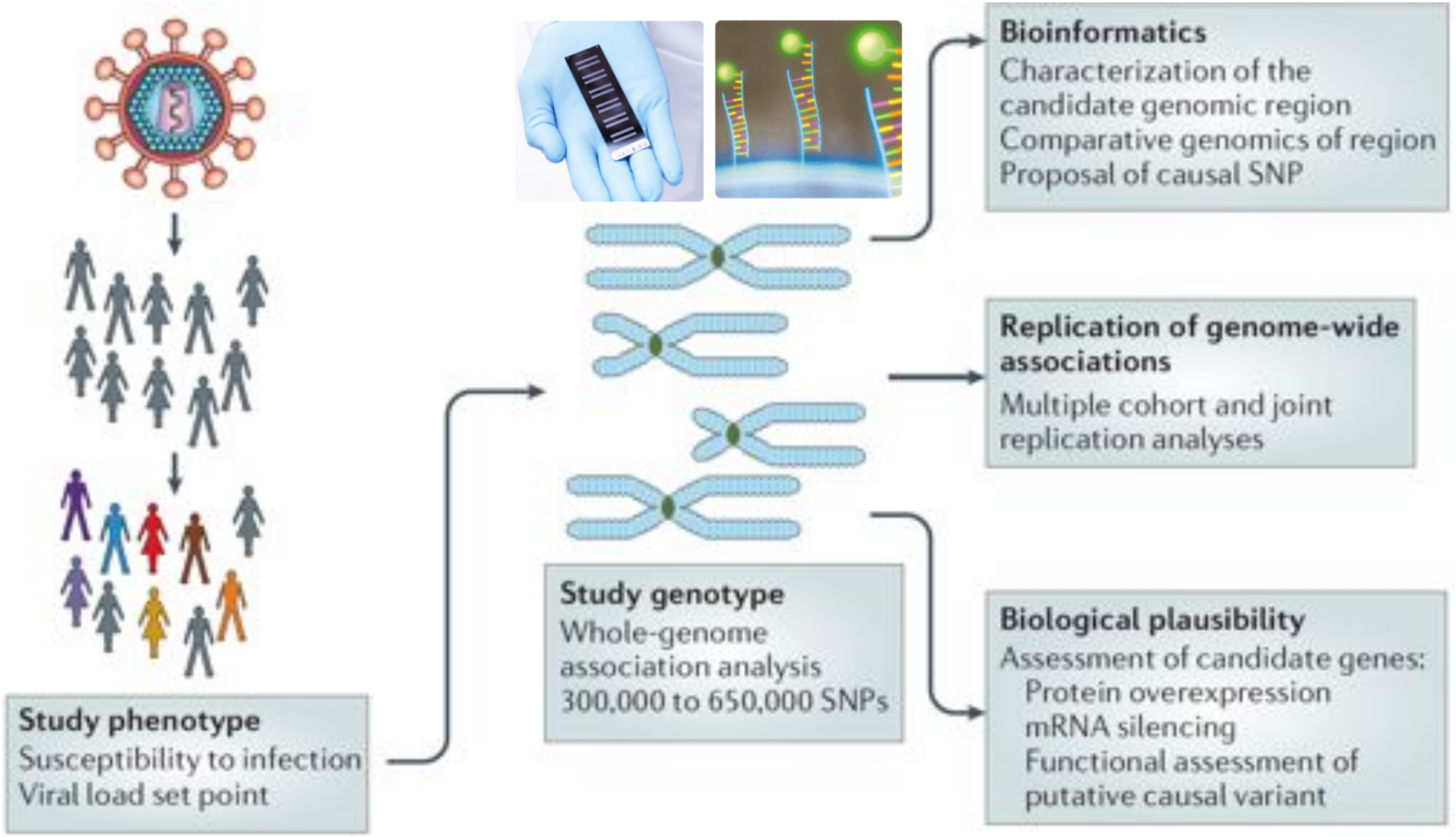


Genomics



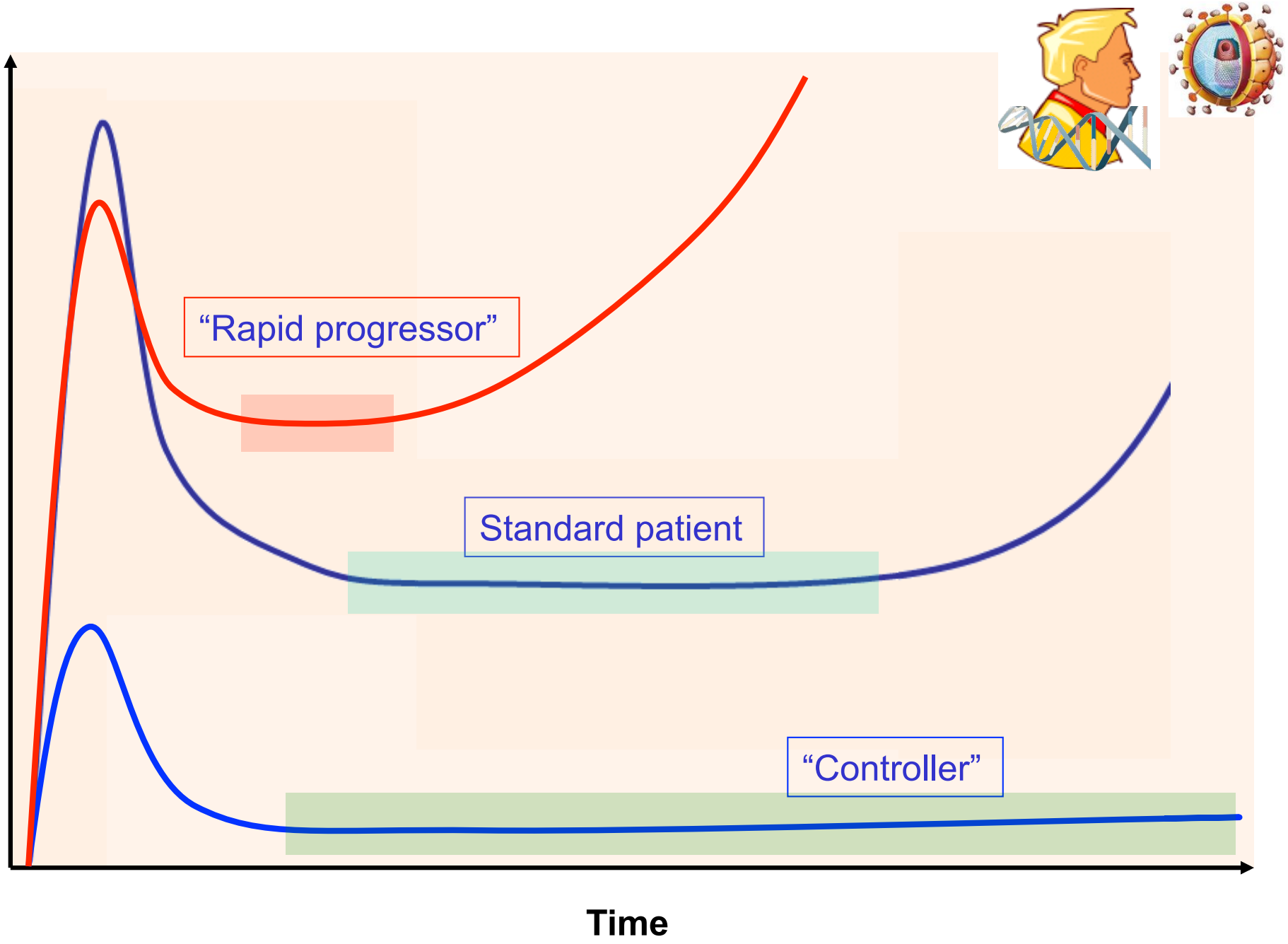
it is now possible to scan the *whole genome* to find the genetic determinants of key differences amongst people

EuroCHAVI: Genome-wide association analysis strategy

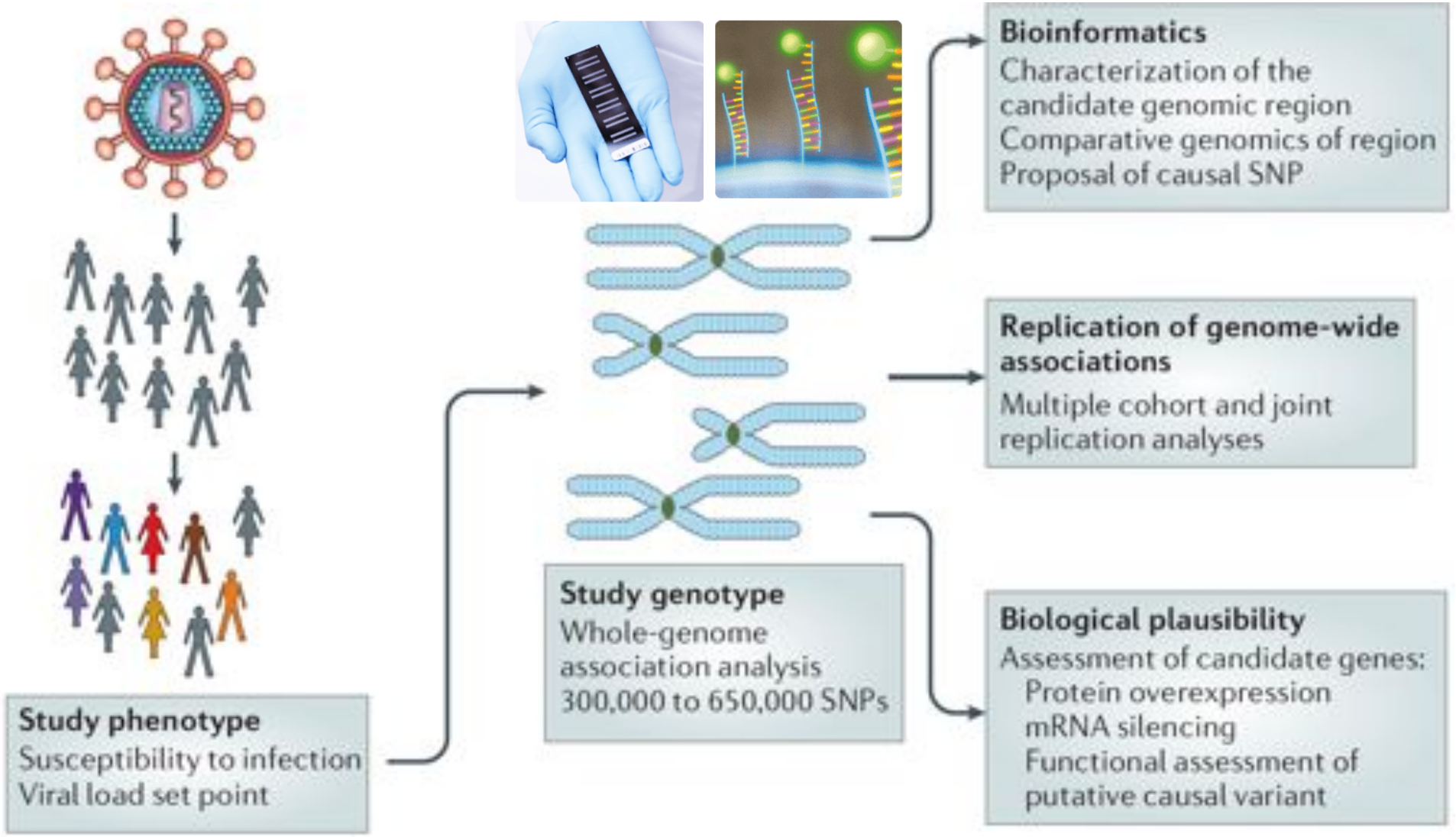


Telenti & Goldstein. 2006 Nature Reviews in Microbiology 2005. Genomics meets HIV.

Variability in natural control of HIV-1

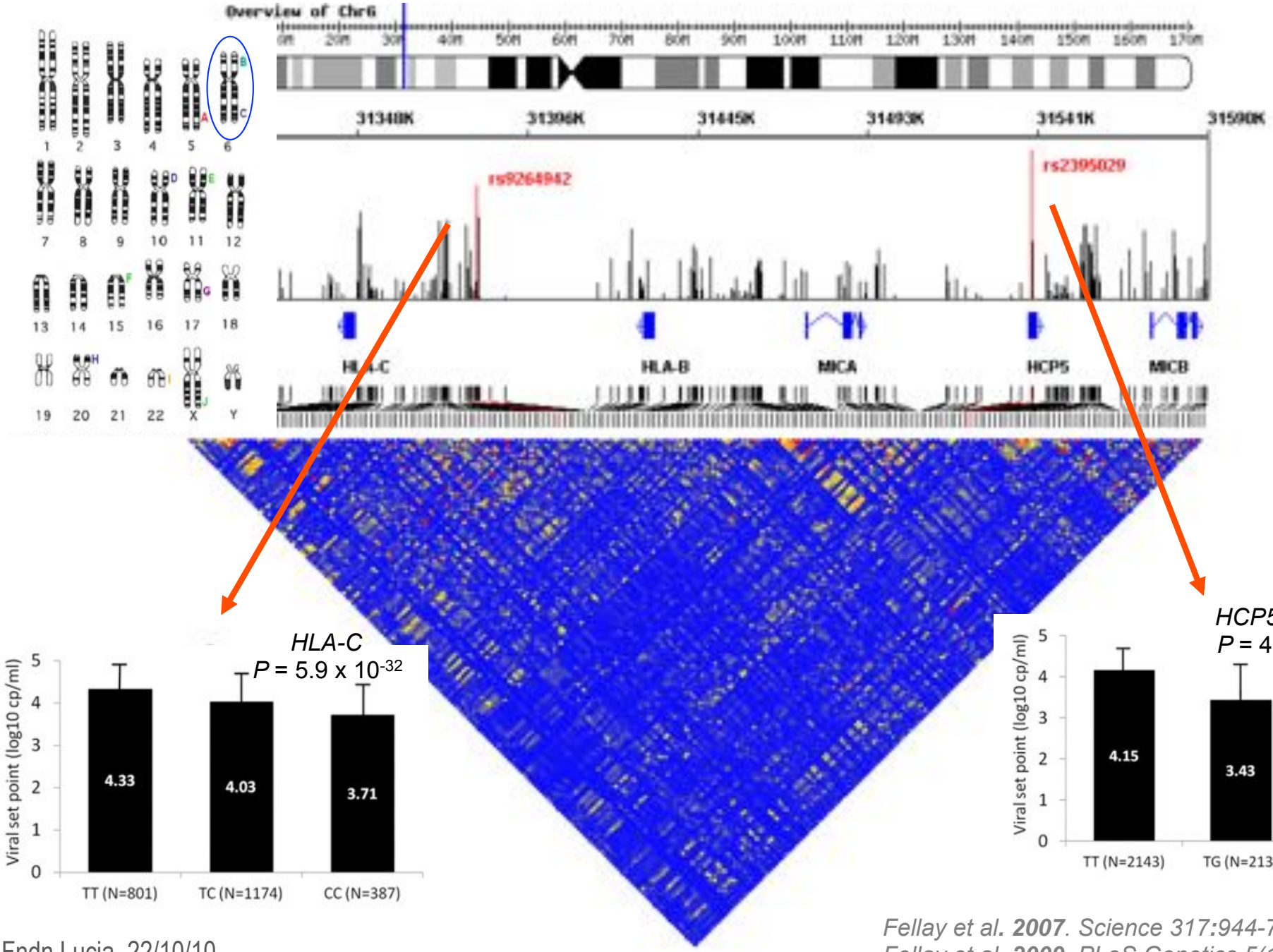


EuroCHAVI: Genome-wide association analysis strategy



Telenti & Goldstein. 2006 Nature Reviews in Microbiology 2005. Genomics meets HIV.

Chromosome 6 p21.3, HLA complex

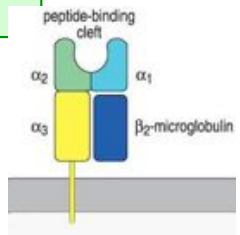


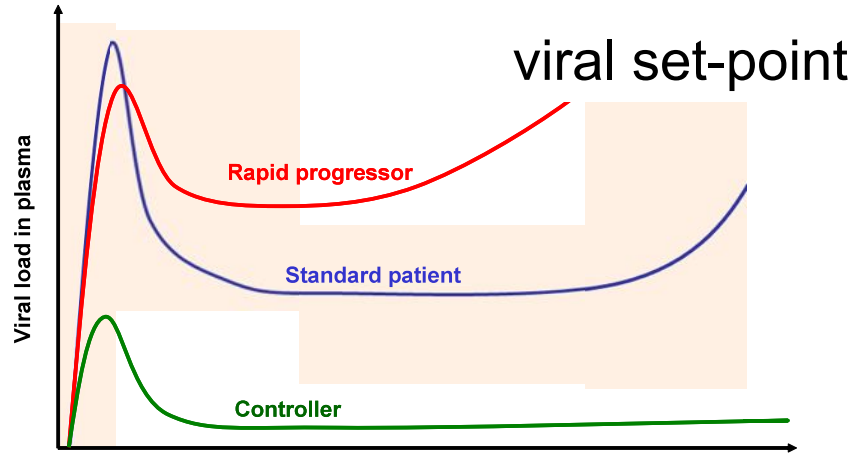
*Fellay et al. **2007**. Science 317:944-7*
*Fellay et al. **2009**. PLoS Genetics 5(12):e1000791*

Human gene polymorphisms that influence HIV-1 disease (1st genome-wide analysis)

➡ HLA-B*5701
➡ HLA-C

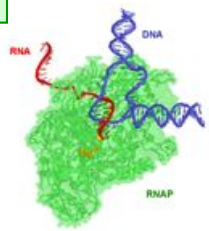
15%

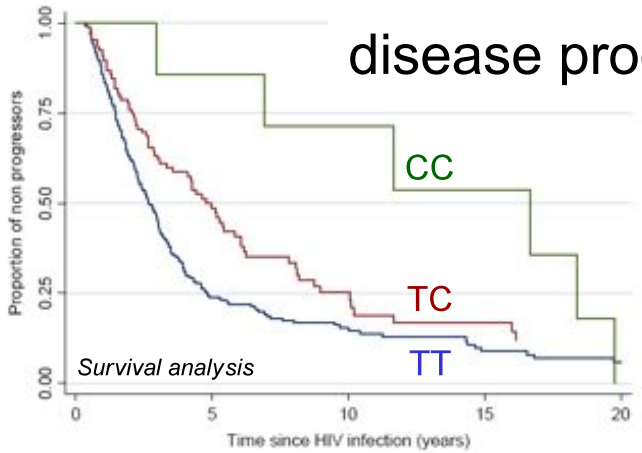


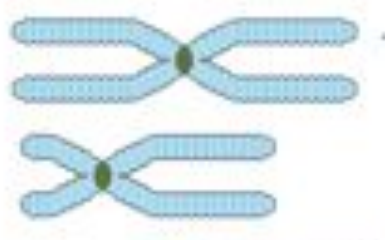


➡ ZNRD1

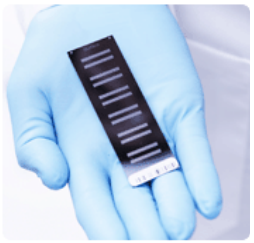
6%

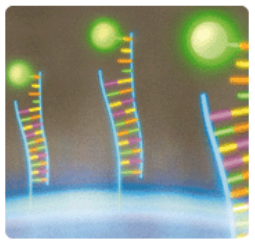




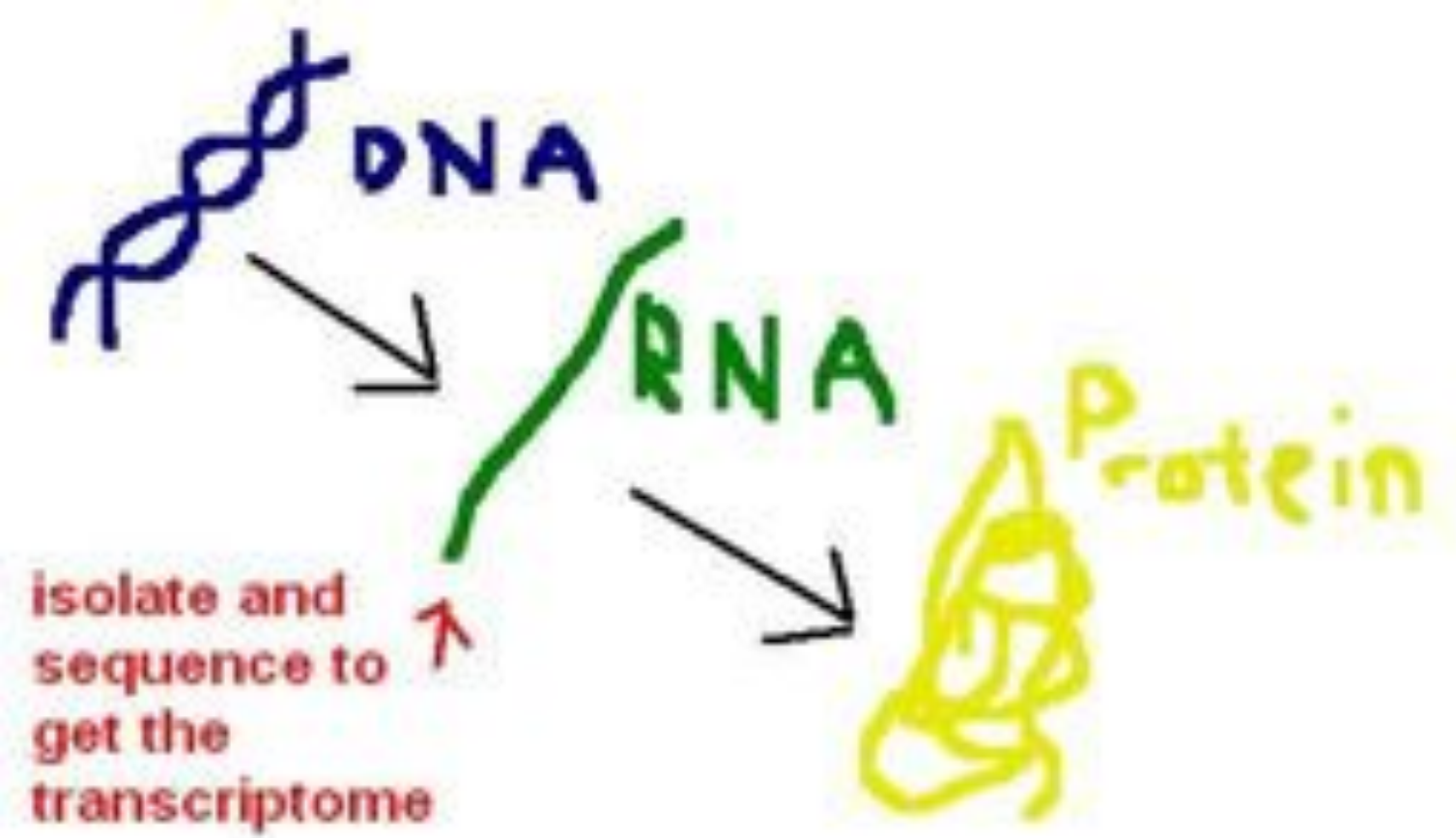


GWA

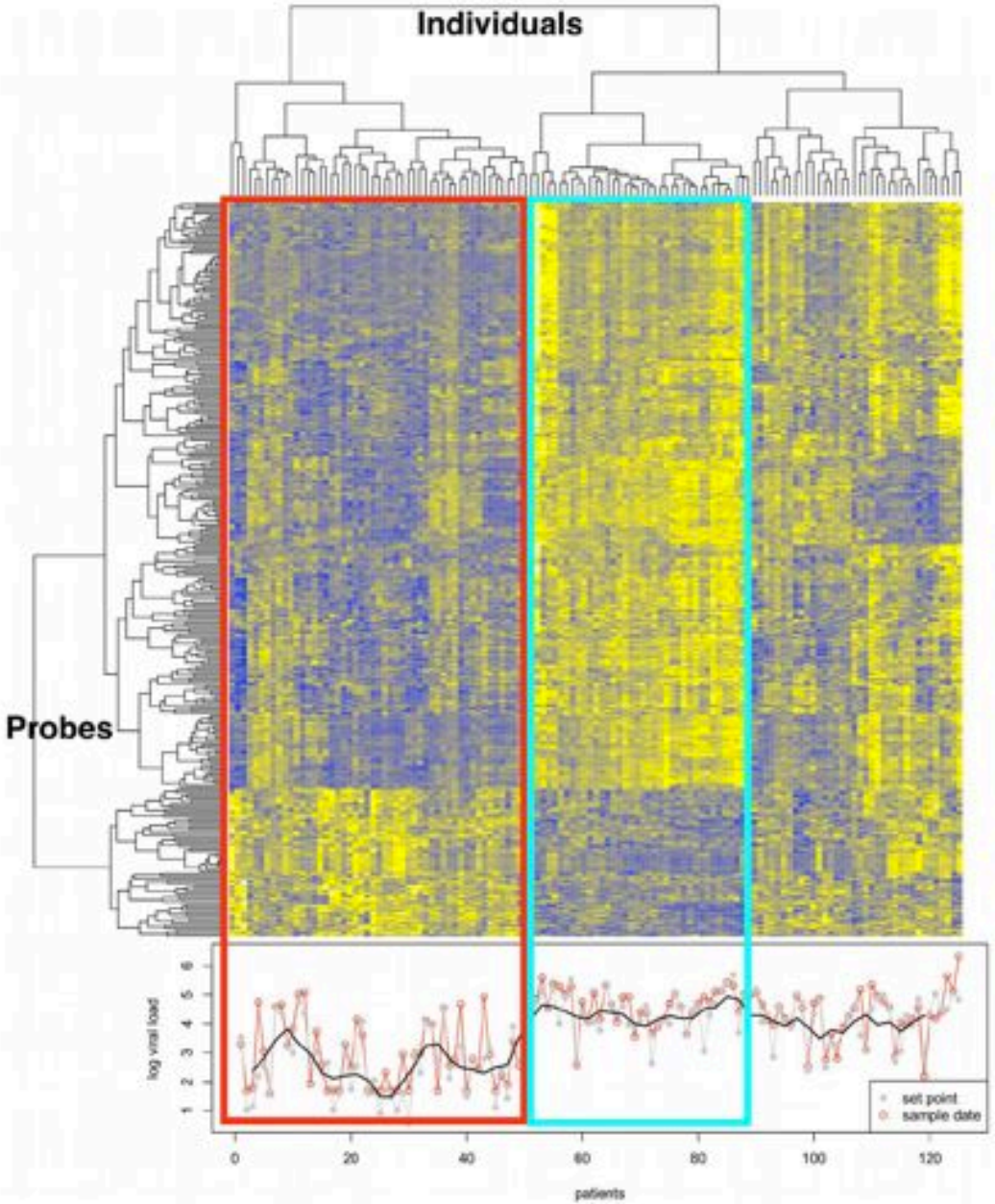




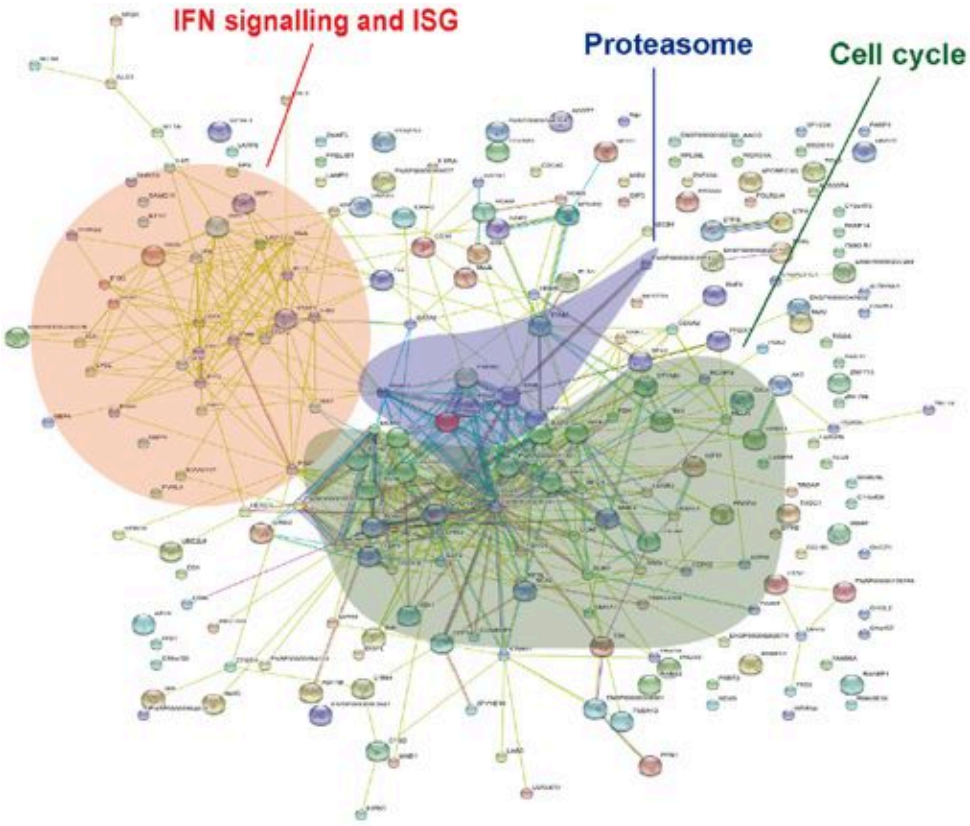
EuroCHAVI, Fellay *et al.* Science 2007


DNA
RNA
Protein
isolate and
sequence to
get the
transcriptome

Genome-Wide mRNA Expression Correlates of Viral Control in CD4+ T-Cells from HIV-1-Infected Individuals



Predicted interaction networks of genes differentially expressed during HIV-1 infection

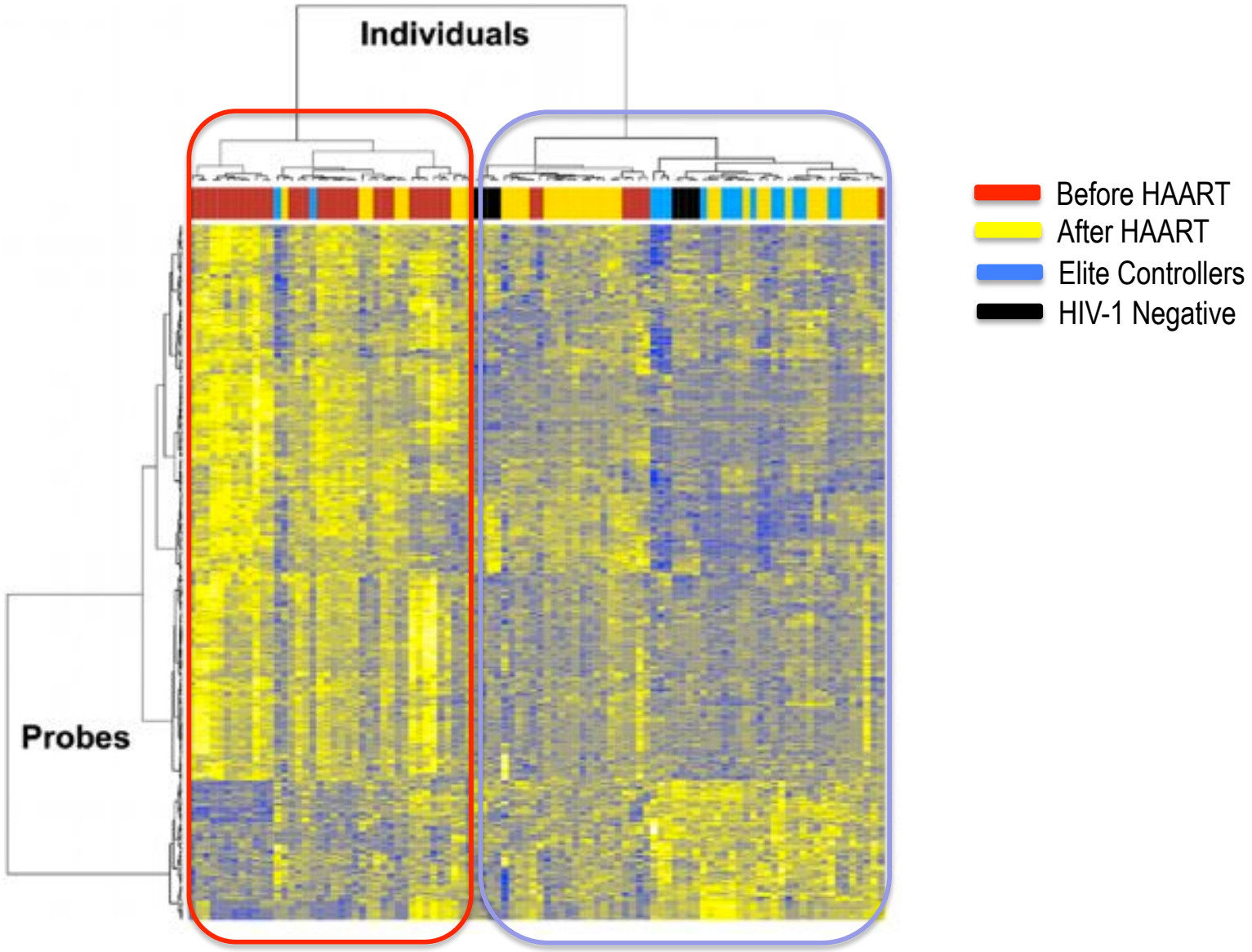


Fndn Lucia, 22/10/10

48,000 mRNA transcripts

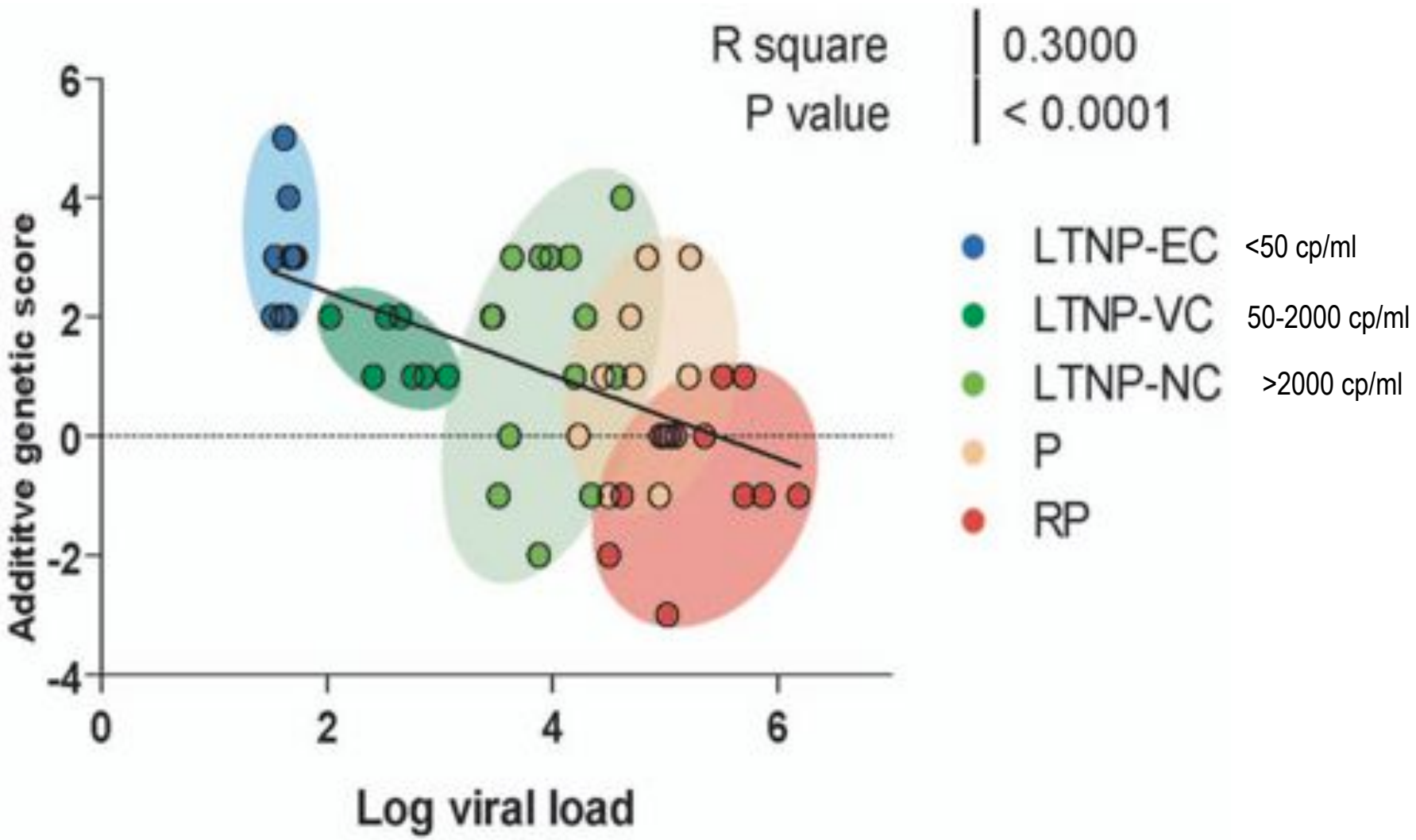
*Rotger et al. **2010**. PLoS Pathog. 6(2):e100078*

Transcriptome analysis in CD4+ T cells from HIV-infected individuals before and after viral suppression



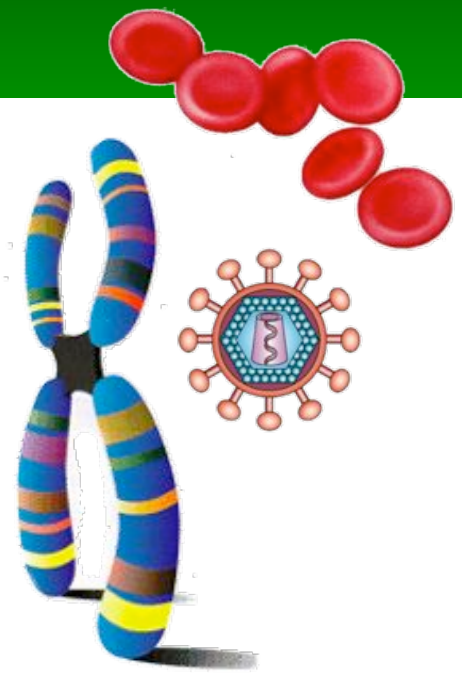
*Rotger et al. **2010**. PLoS Pathog. 6(2):e100078*

Host and Viral Genetic Correlates of Clinical Definitions of HIV-1 Disease Progression



*Casado et al. **2010**. PLoS One. 5(6):e11079*

Why some HIV-1 exposed people never get infected ?



- Purpose:
  - To identify gene variants* that influence susceptibility or resistance to HIV infection among highly exposed yet uninfected haemophilia subjects

- CHAVI 014:
  - GWA in haemophiliacs exposed before systematic blood screening for HIV-1 and that never got infected
  - International study