INTRODUCTION TO PATHOPHYSIOLOGY OF HIV AND VIRAL HEPATITIS

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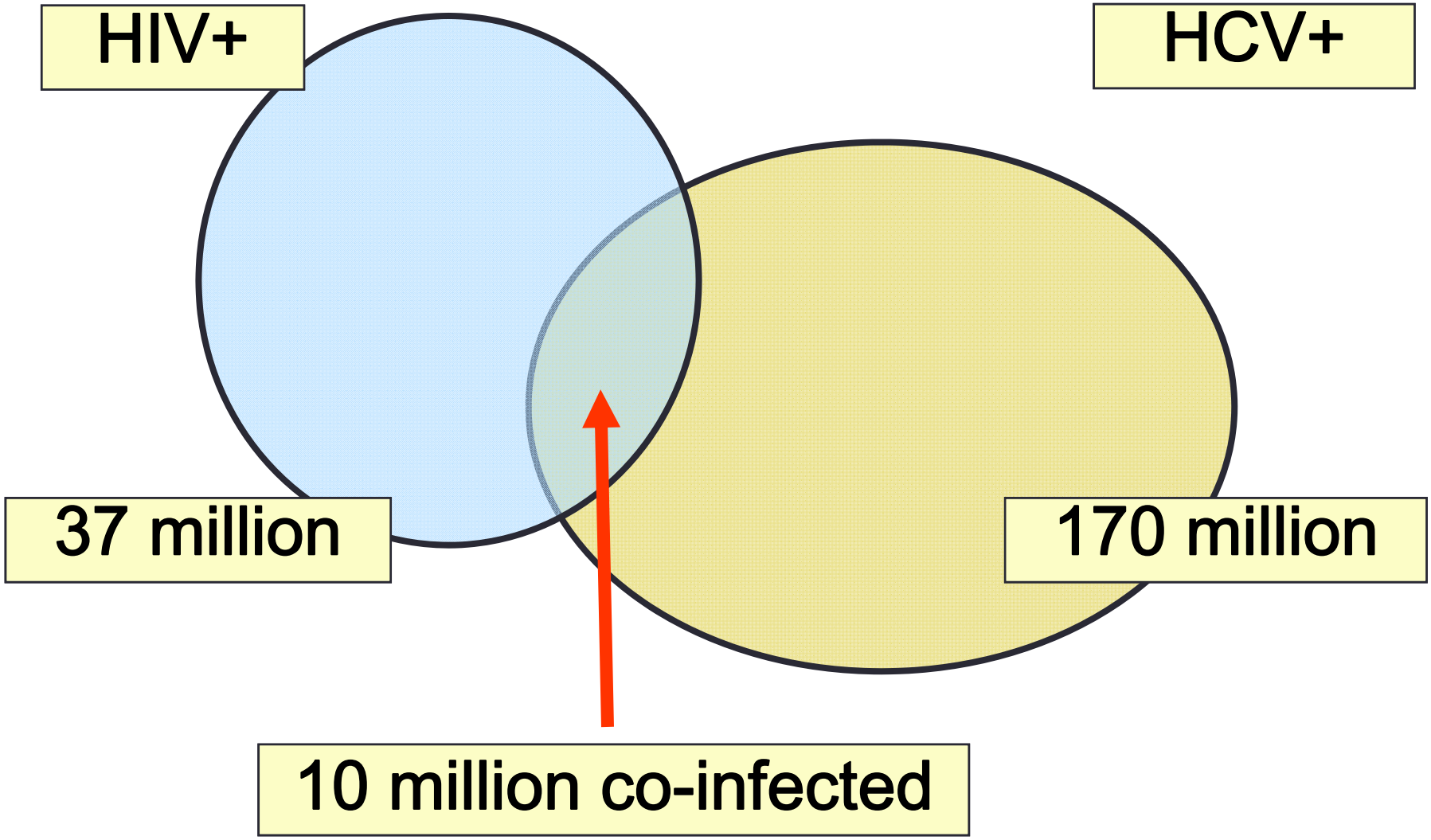
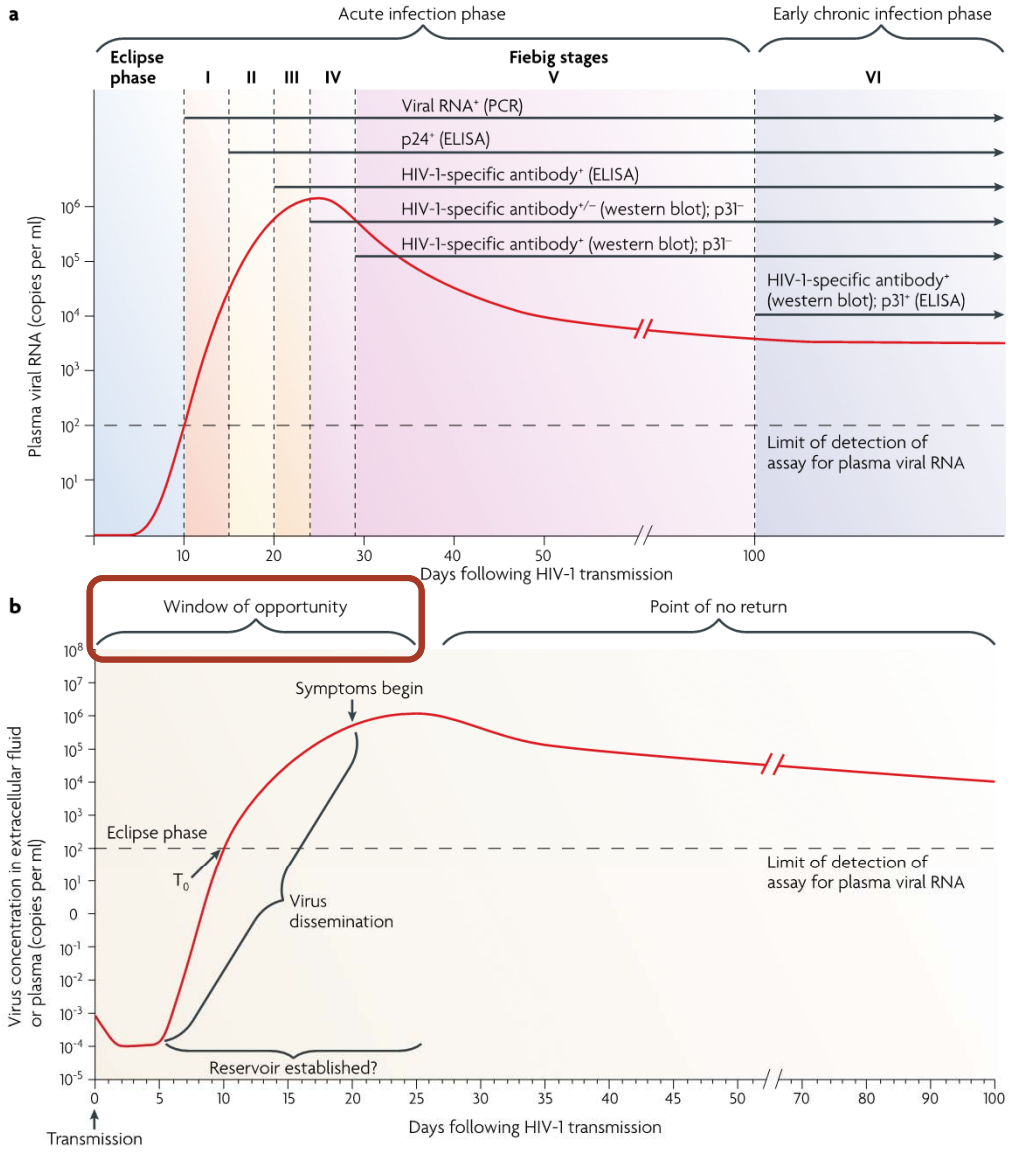
Disclosures

- I have received research grants from MSD, ViiV and Gilead
- I have participated in advisory boards for MSD and ViiV
- I don’t have stock options

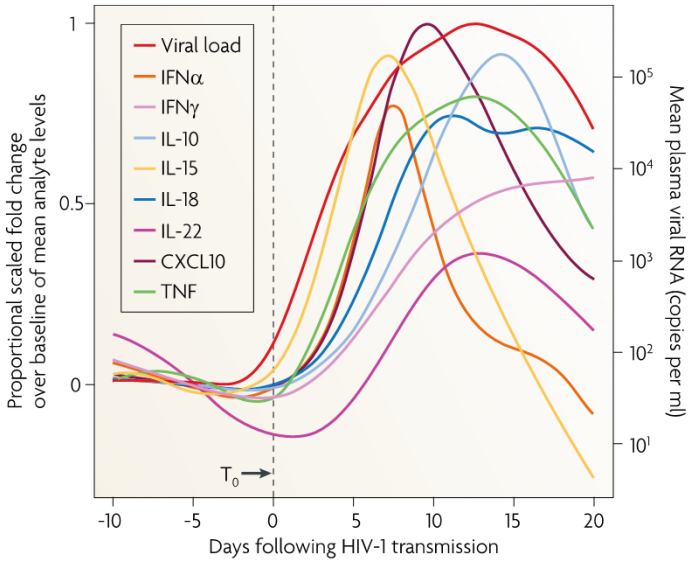
HIV and HCV Infections Overlap



ACUTE HIV-1 INFECTION



Cytokines during AHI



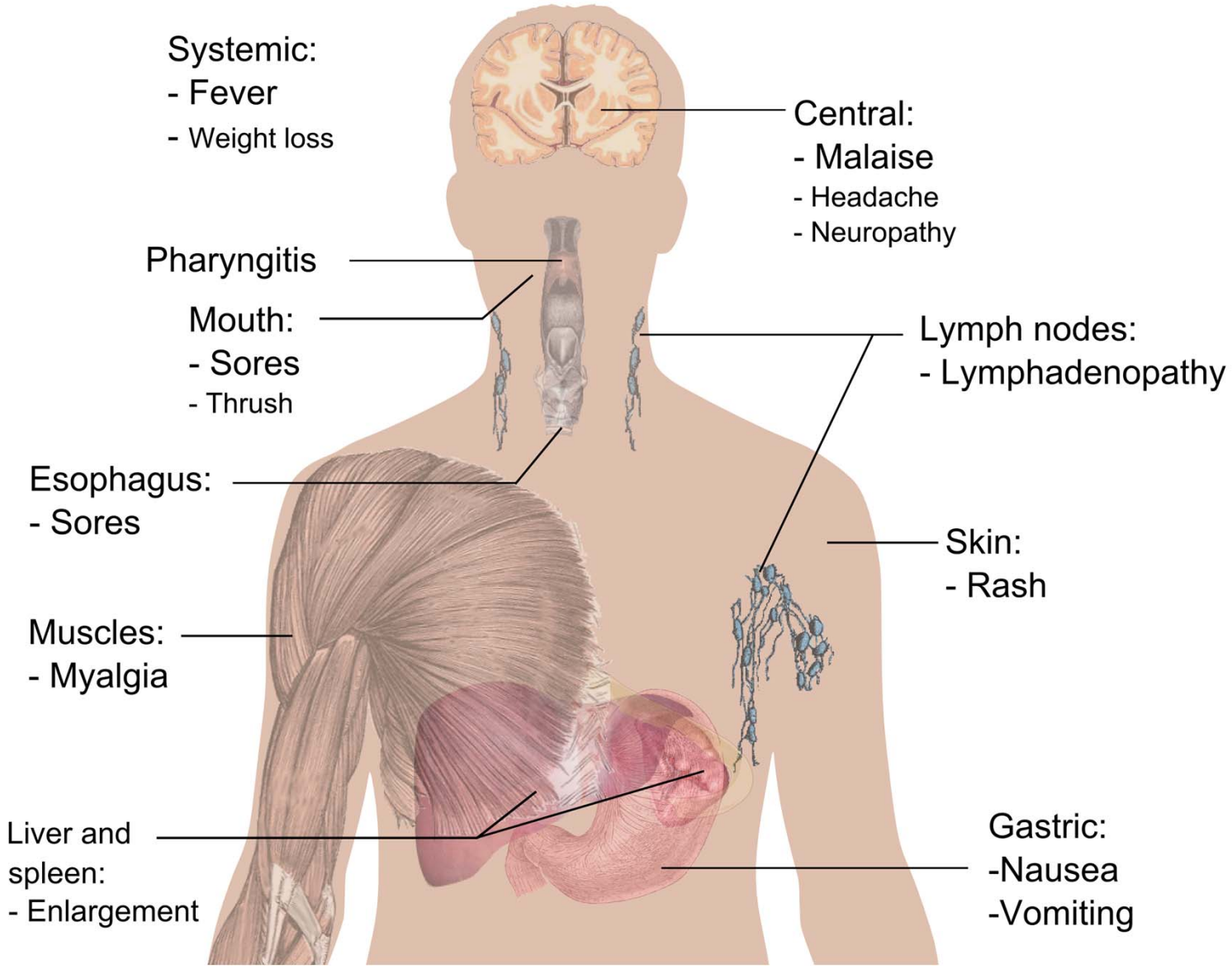
Acute: 0 - 100 days

Recent: 0 - 6 months

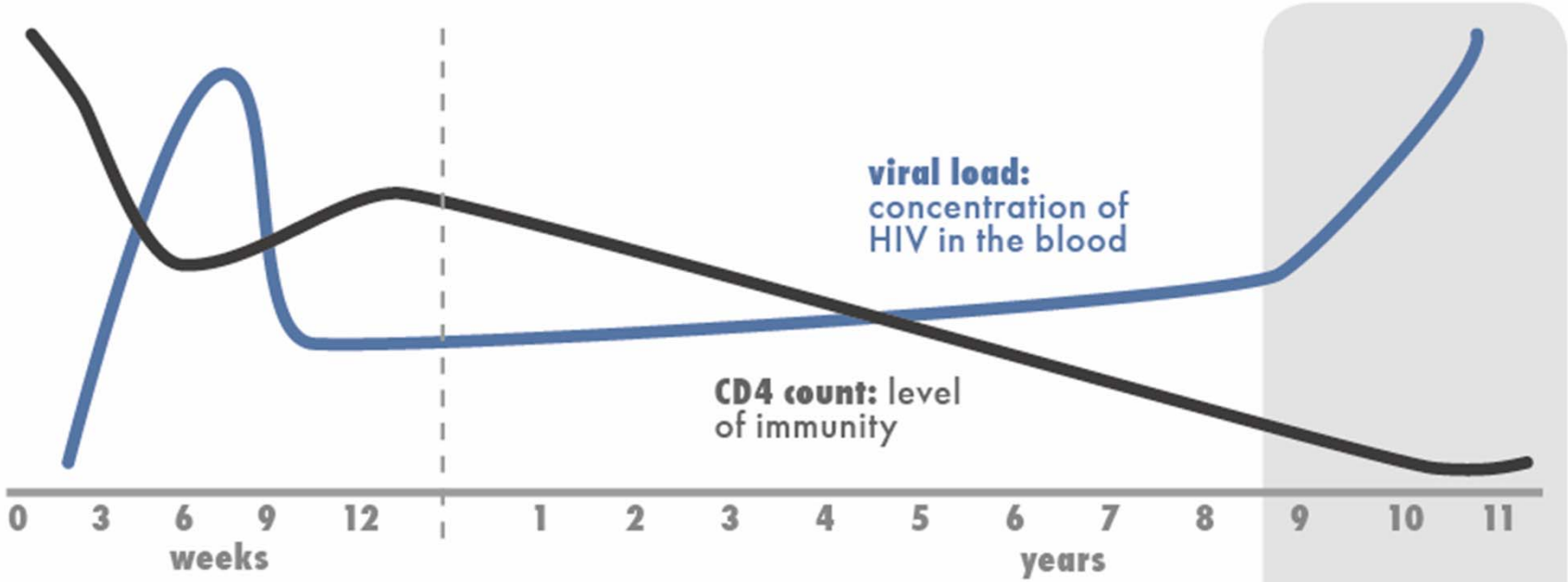
McMichael A, et al. 2010, Nat Rev Immunol

Main symptoms of

Acute HIV infection



HIV progression, CD4 count and viral load



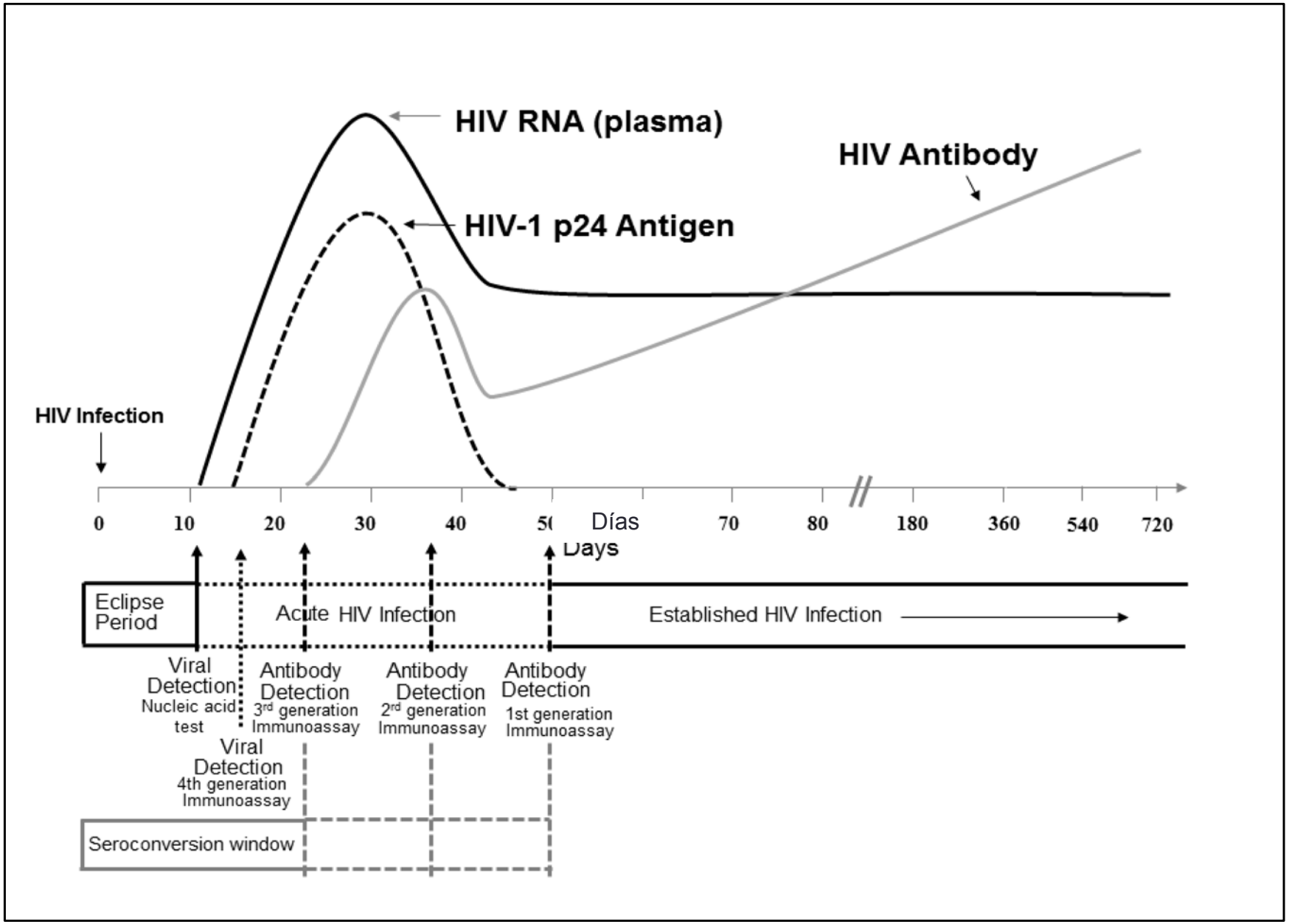
HIV INFECTION
3-6 weeks after infection the level of HIV in the body rises

HIV-POSITIVE
9-12 weeks later HIV reproduces at a very low

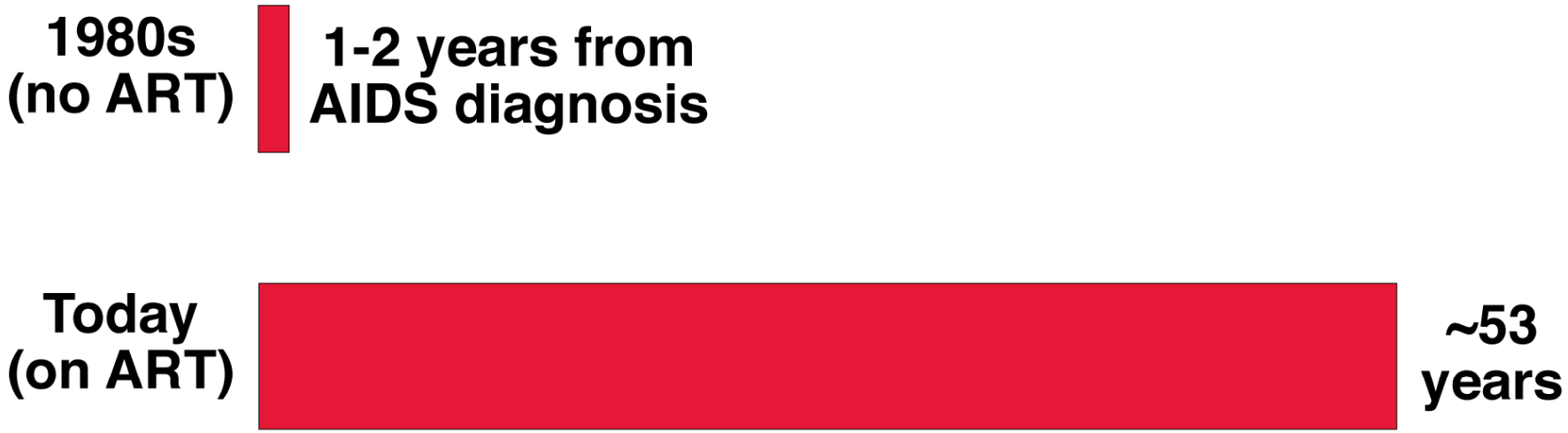
HIV-POSITIVE
During the latent stage of HIV infection no symptoms are experienced

HIV-POSITIVE
After many years HIV has killed many of the CD4 cells because it uses them to make copies of itself

AIDS
The immune system is weakened and opportunistic diseases can now invade the defenseless body

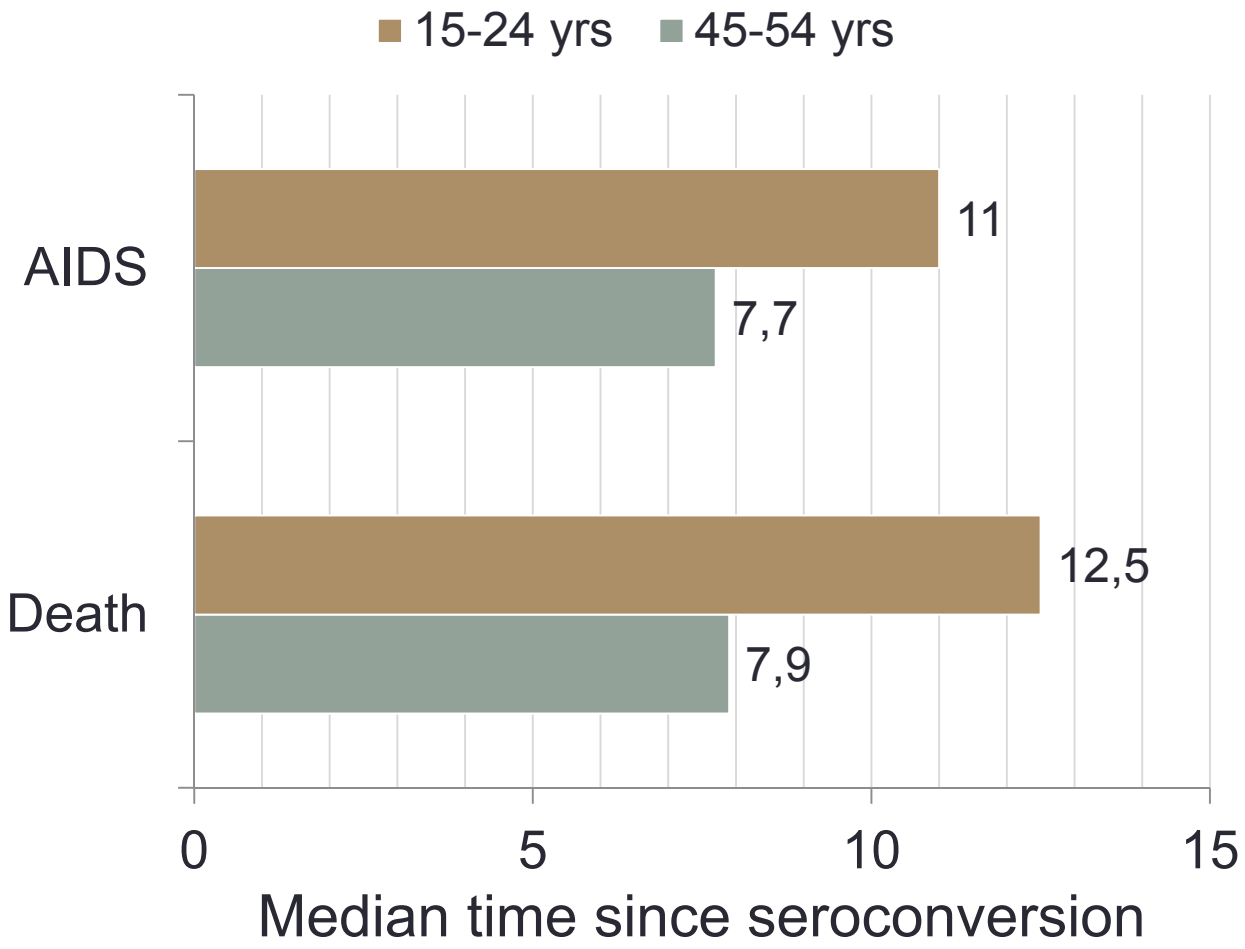

HIV RNA (plasma)
HIV Antibody
HIV-1 p24 Antigen
HIV Infection
0
10
20
30
40
50
Días
70
80
180
360
540
720
Days
Eclipse Period
Acute HIV Infection
Established HIV Infection
Viral Detection
Nucleic acid test
Antibody Detection
3rd generation Immunoassay
Antibody Detection
2nd generation Immunoassay
Antibody Detection
1st generation Immunoassay
Viral Detection
4th generation Immunoassay
Seroconversion window

Life Expectancy for 20-Year-Old Newly Diagnosed with HIV, 1980s and Today



Source: JL Marcus et al., *JAIDS*, 2016.

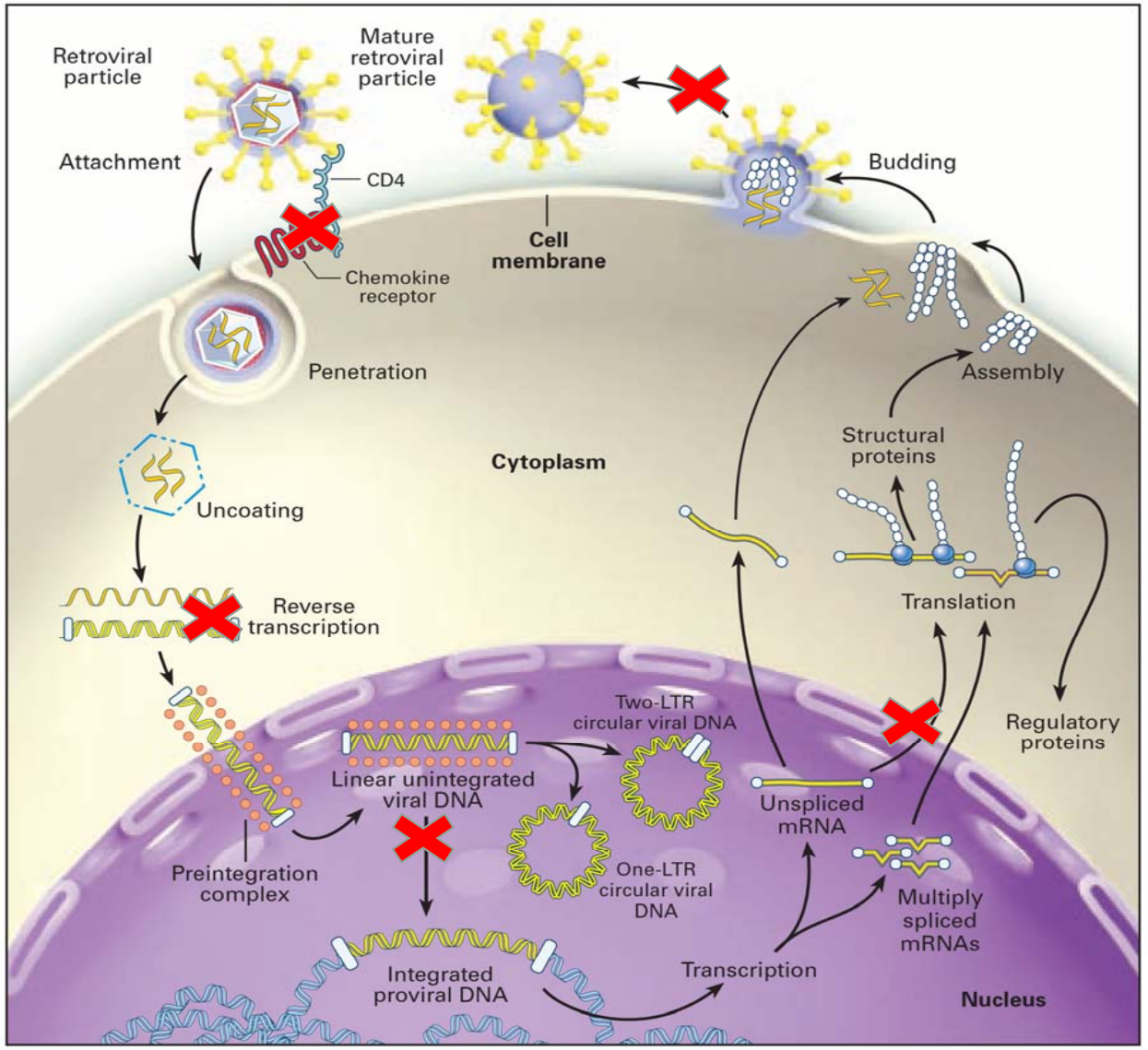
HIV-1 disease progression



n = 13,030 HIV-1- infected individuals from 15 countries

Cascade collaboration, Lancet 2002

HIV life cycle and ART

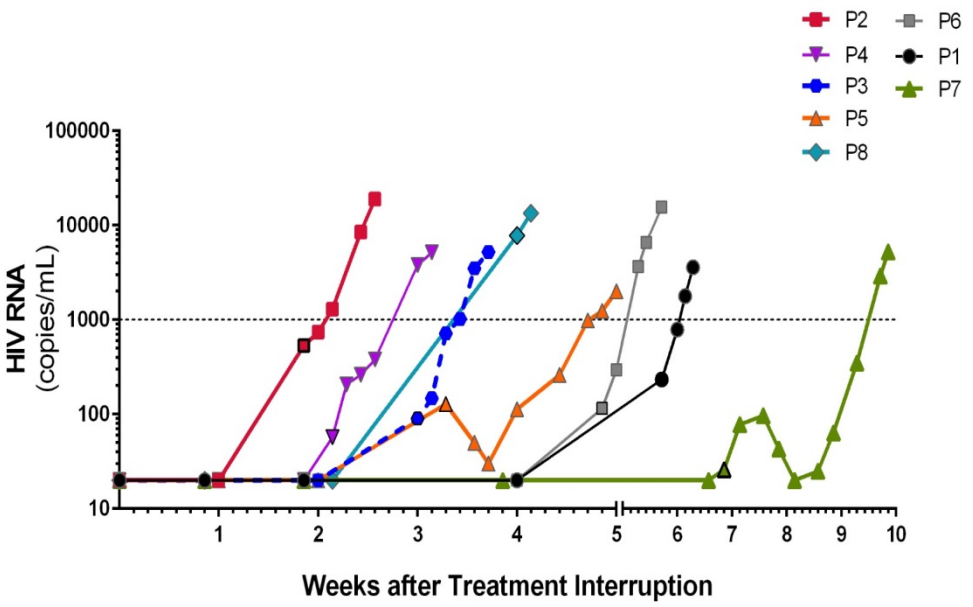


Viral Load Following Treatment Interruption

- N=8
- **ART started at Fiebig I** (HIV RNA+, p24 Ag-, Ab-) for ≥ 96 w.
- VL <50 c/mL ≥48 w & CD4 >400 cells.
- Resume ART if two VL >1000 c/ml or two CD4 <350 cells.
- TI for 24 w. VL every 3-7 days.

Hypothesis.

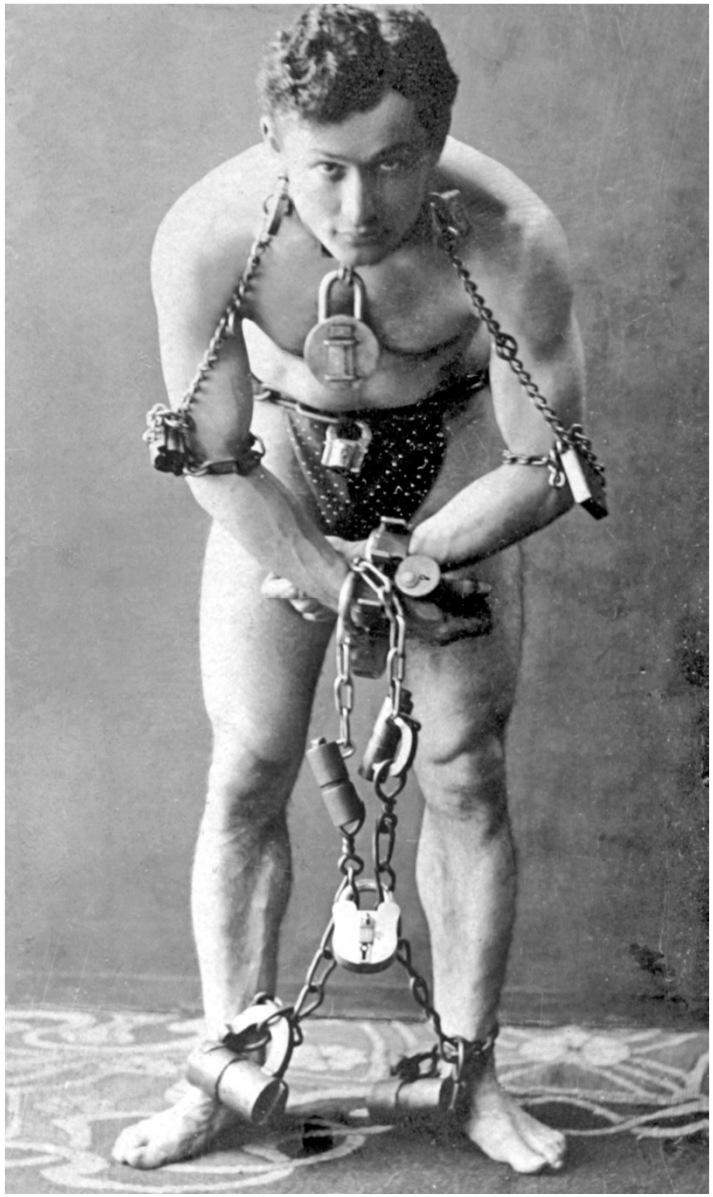
- At least 30% of individuals will have delayed time to VL rebound (VL<50 at 24 w).
- Proceed to stage 2 if ≥ 1 person has VL <50 c/ml at week 12.



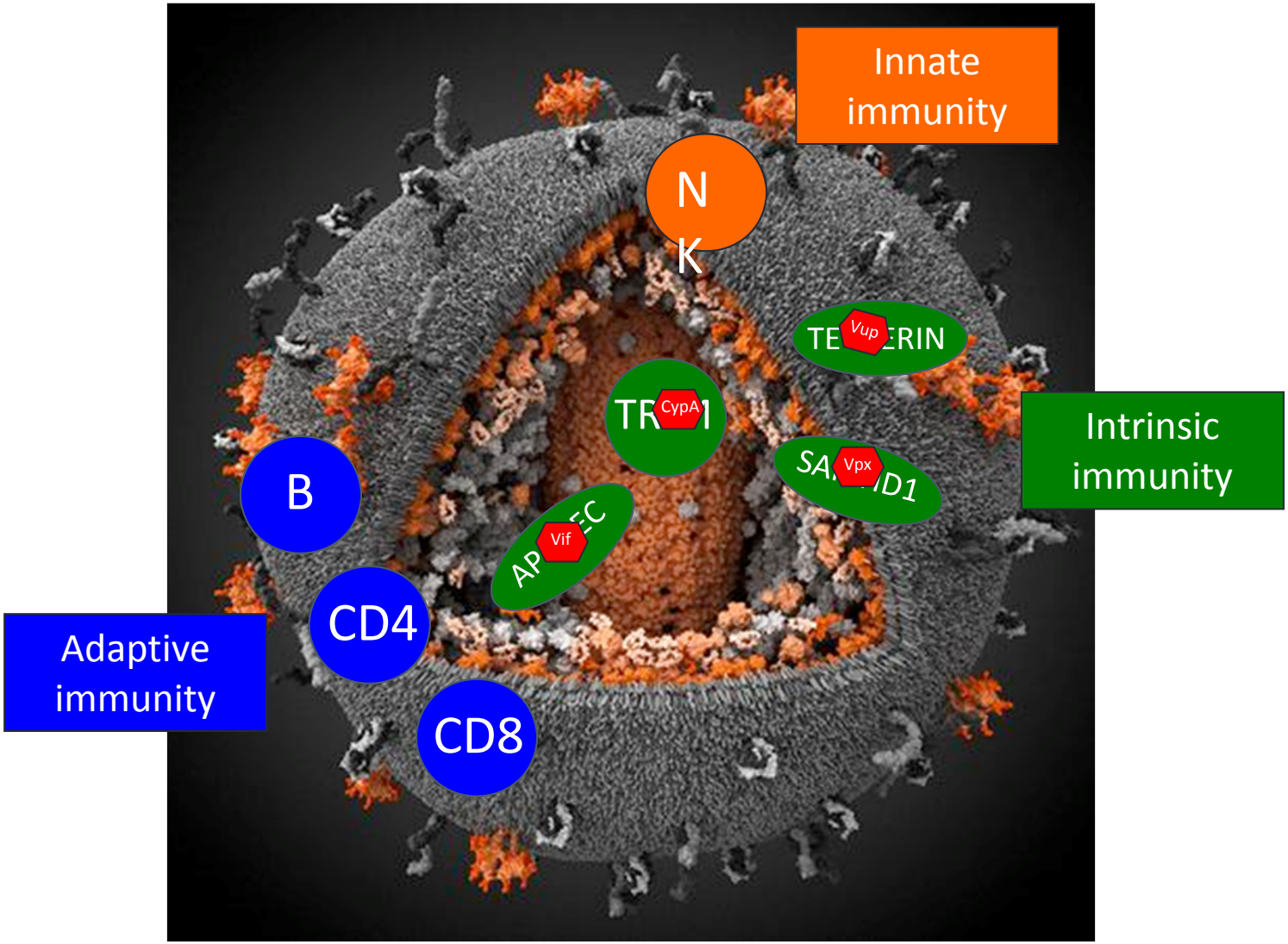
Median time to viral rebound: 26 days (range 13-48)
Highest VL at rebound (median): 5169 (2005 – 13462)

Ananworanich J. CROI 2017, Seattle, WA. #124.

HIV is an escapist… just like Harry Houdini

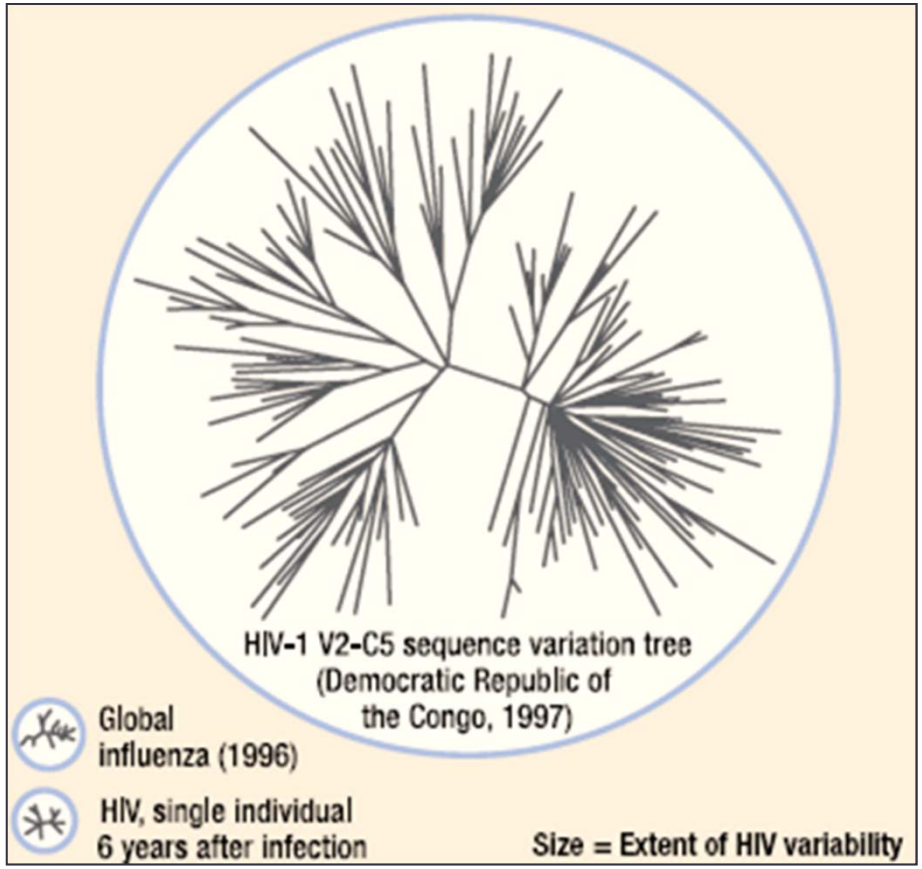


HIV-1 Strategies to counteract host immunity

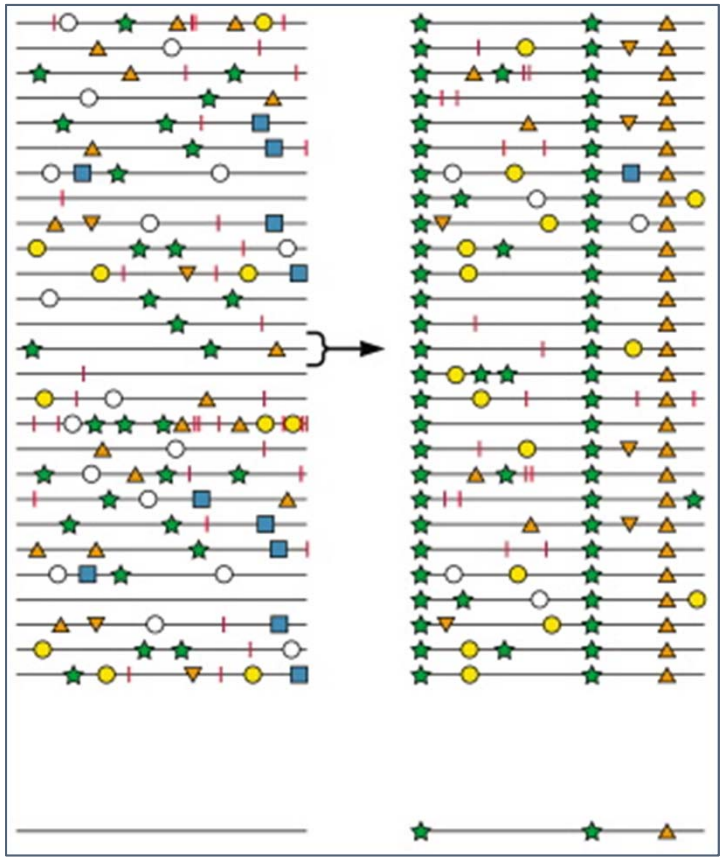


Huge genetic diversity

Population level

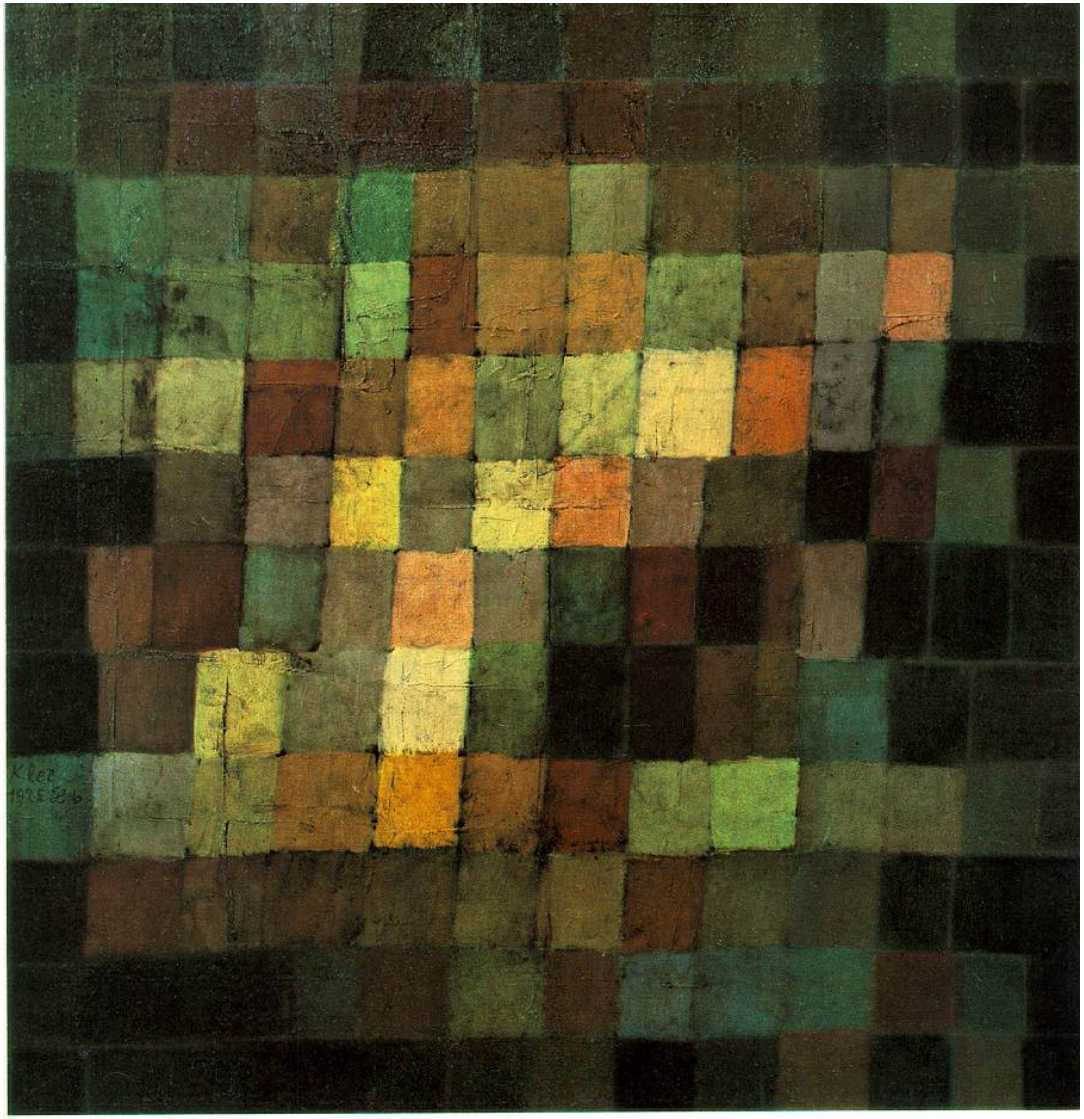


Individual level



- Balance between **mutation rate**, **drift** and **selection**

1. High replication rate: $10^{9\text{-}12}$ new virions/day
2. Error-prone polymerase:
    - 1 mutation / 10,000 bp
    - 3-8 recombination events / mutation event
3. Cellular mechanisms: MDR1 gene codes for P-glycoprotein
4. Role of RNAseH
5. Selective pressure of Abs & CTLs against HIV epitopes
6. Viral pool size and availability of target cells

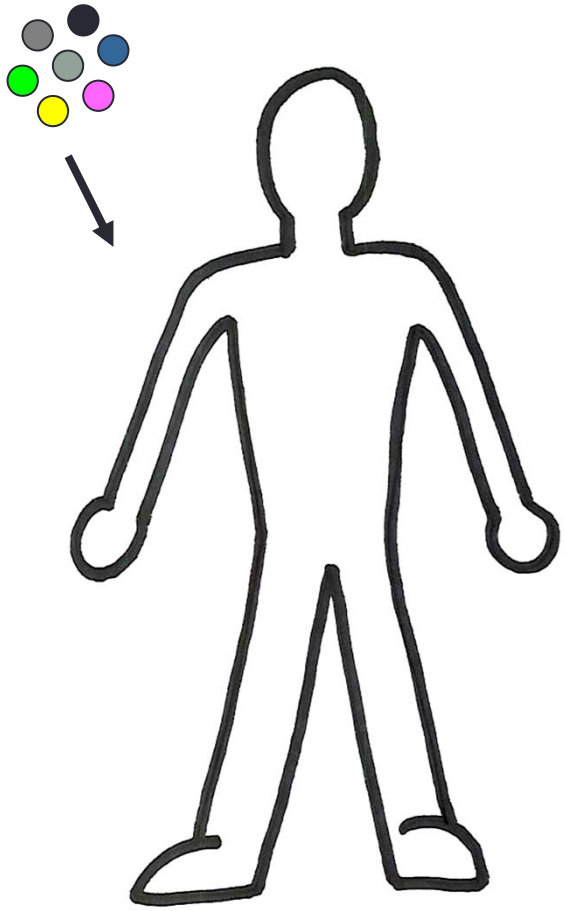


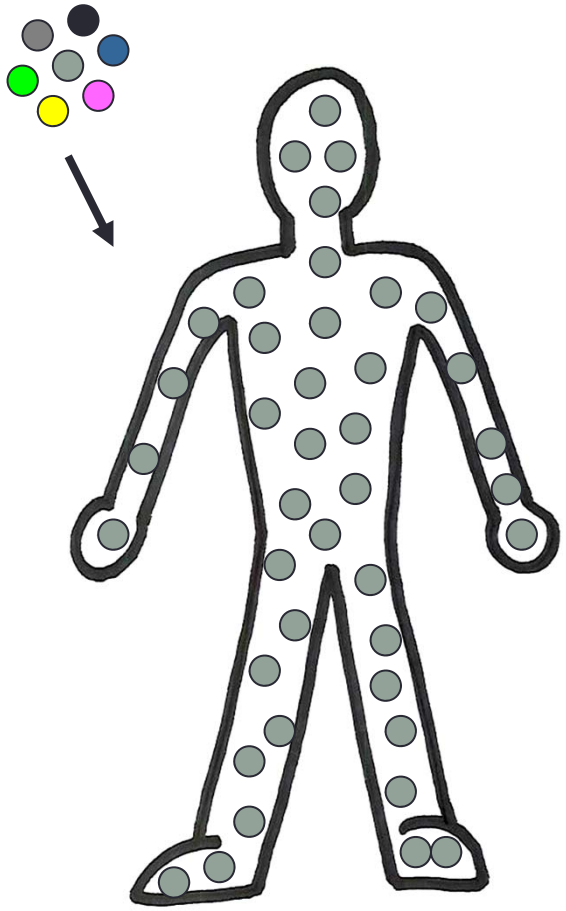
QUASISPECIES

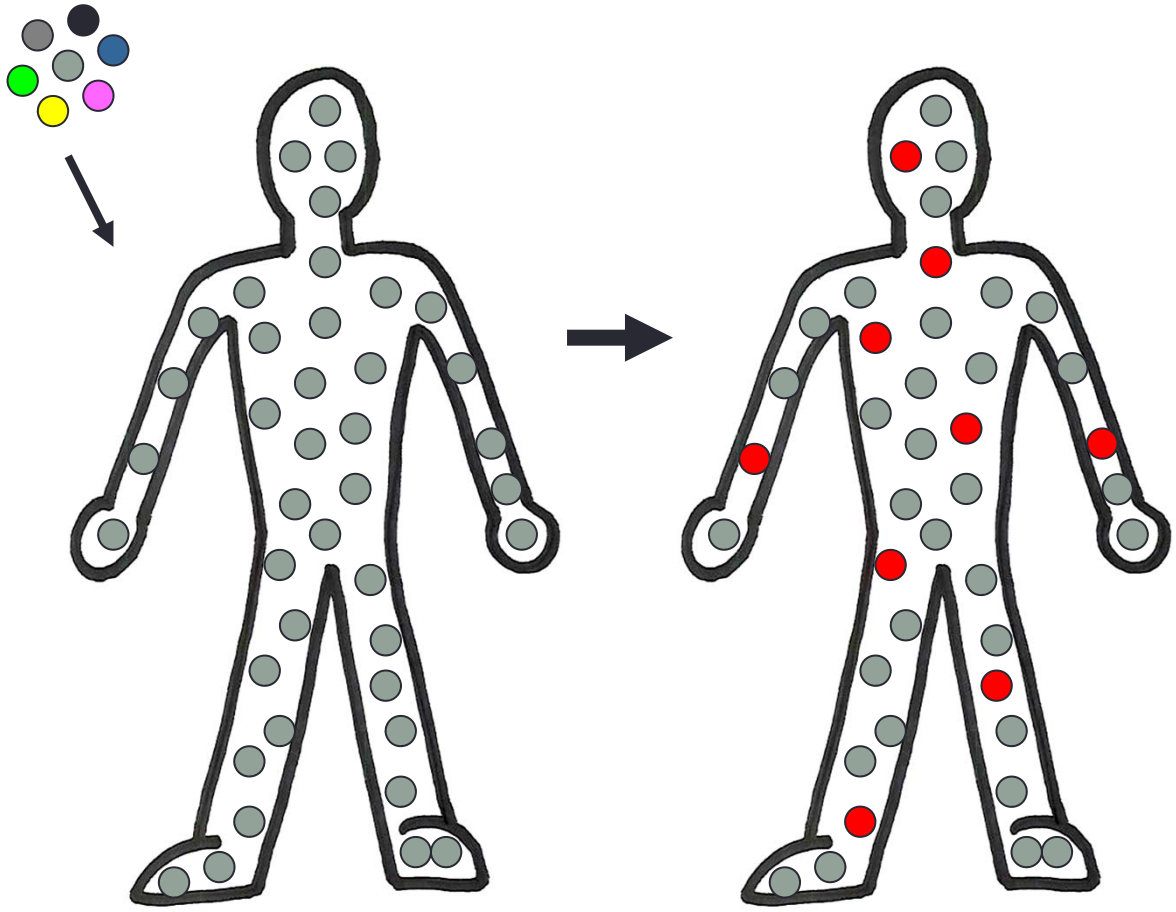
"A population of viruses that share a common origin but which have distinct genomic sequences as a result from mutation, drift and the impact of selection"

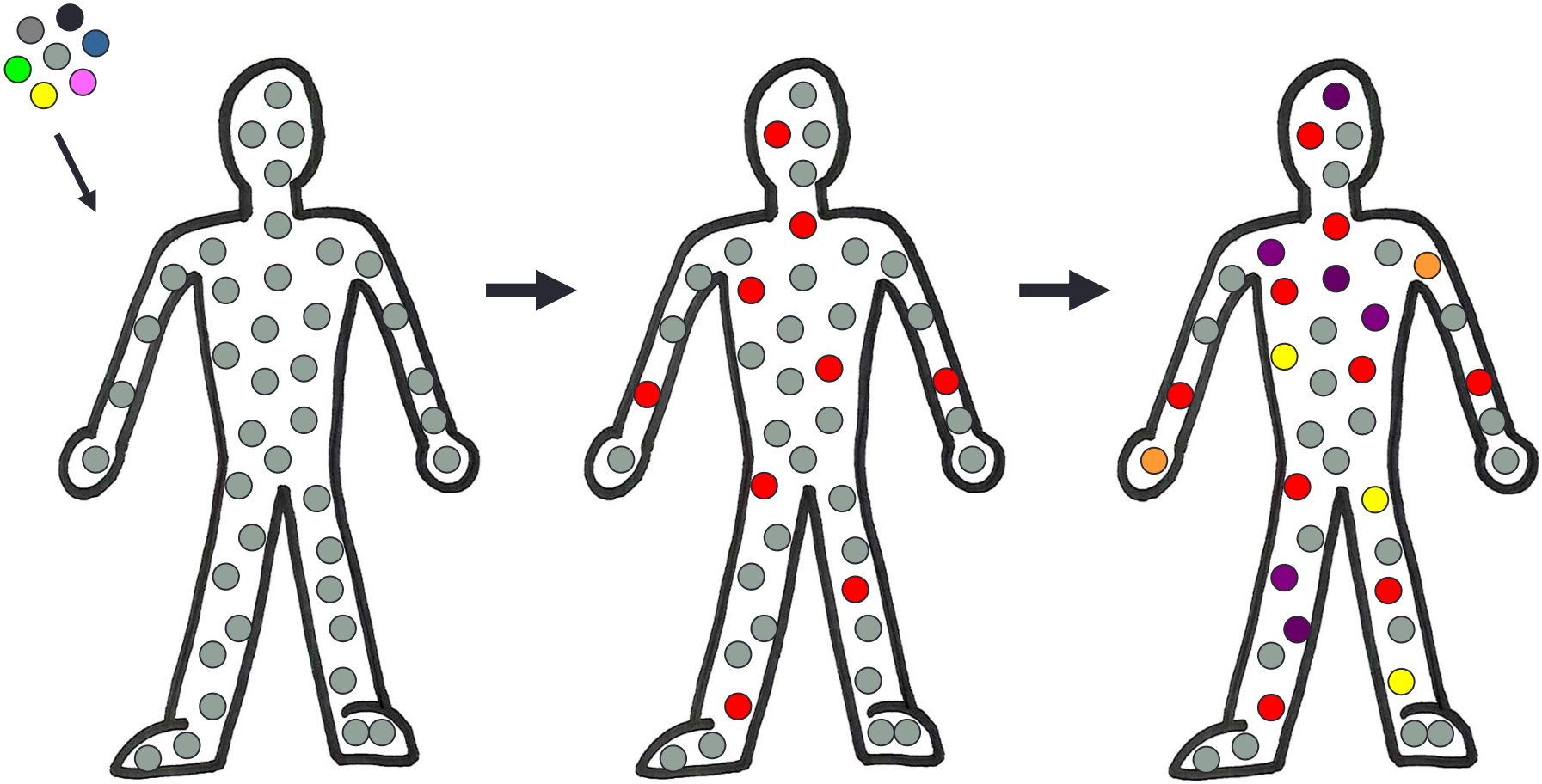
In ARV-naïve subjects chronically infected with a “wild-type” HIV-1

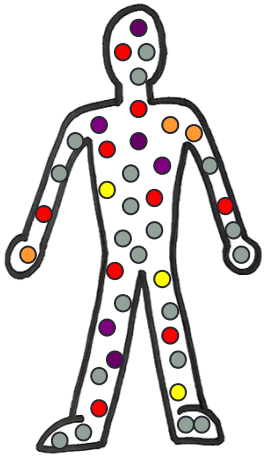
- All non-deletereous single mutants likely preexist
- Few double mutants preexist
- Almost no triple mutants are expected

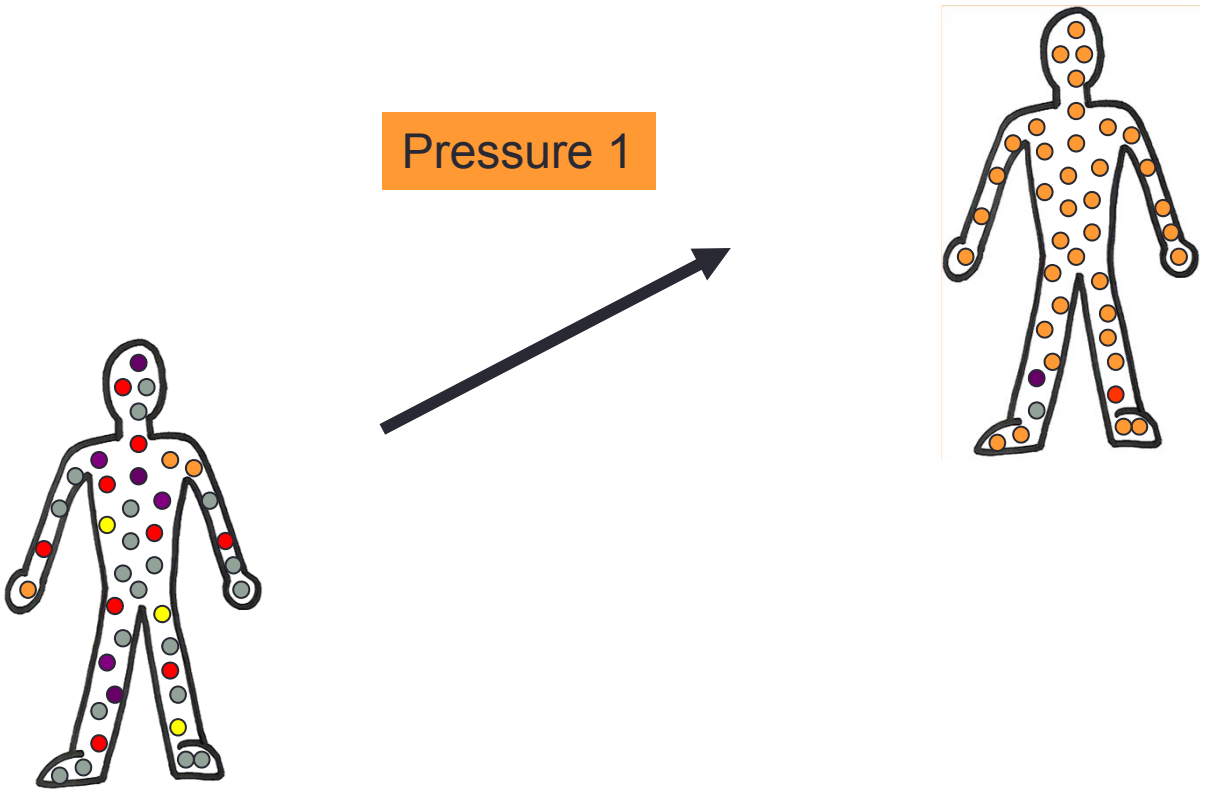


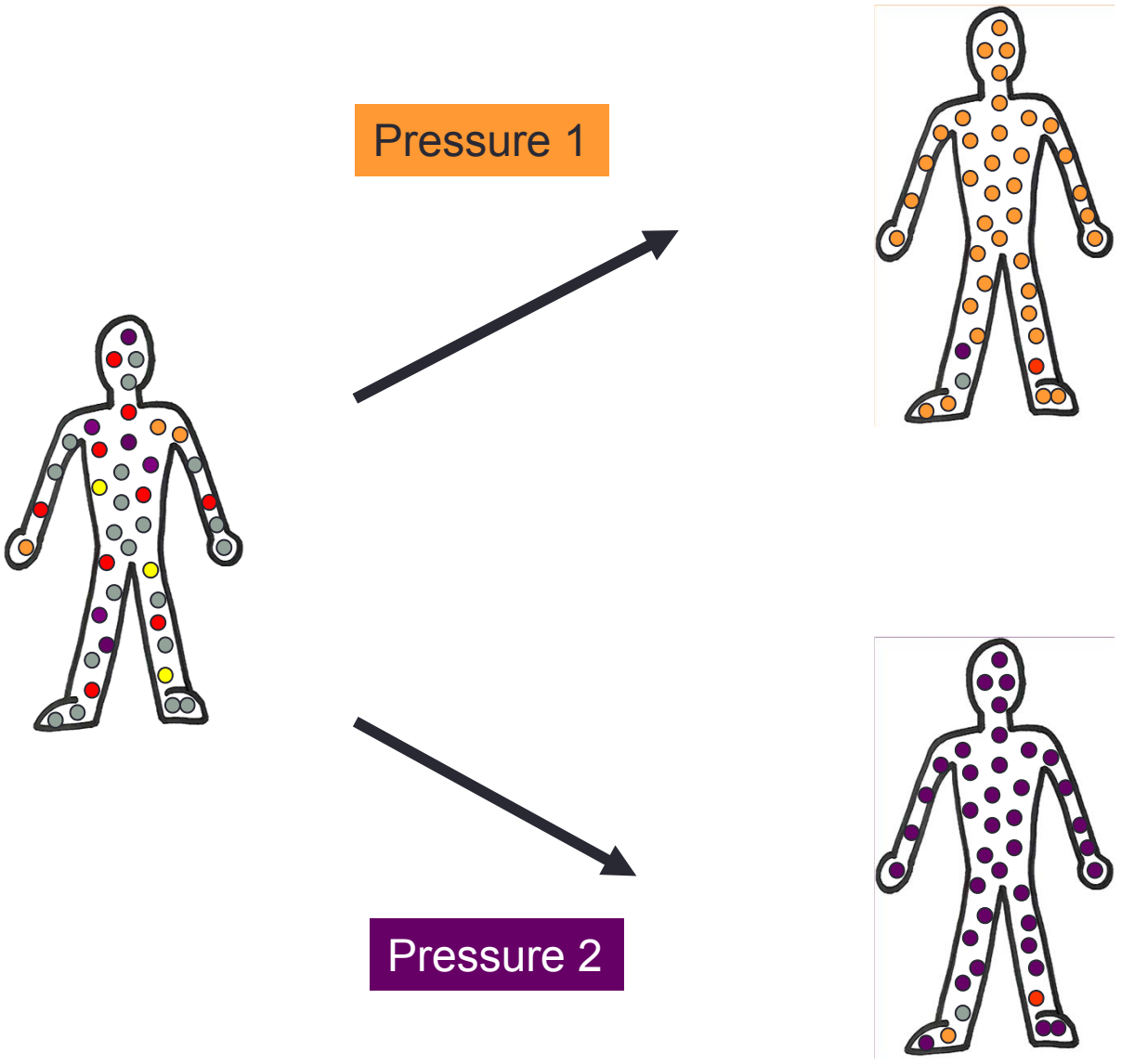


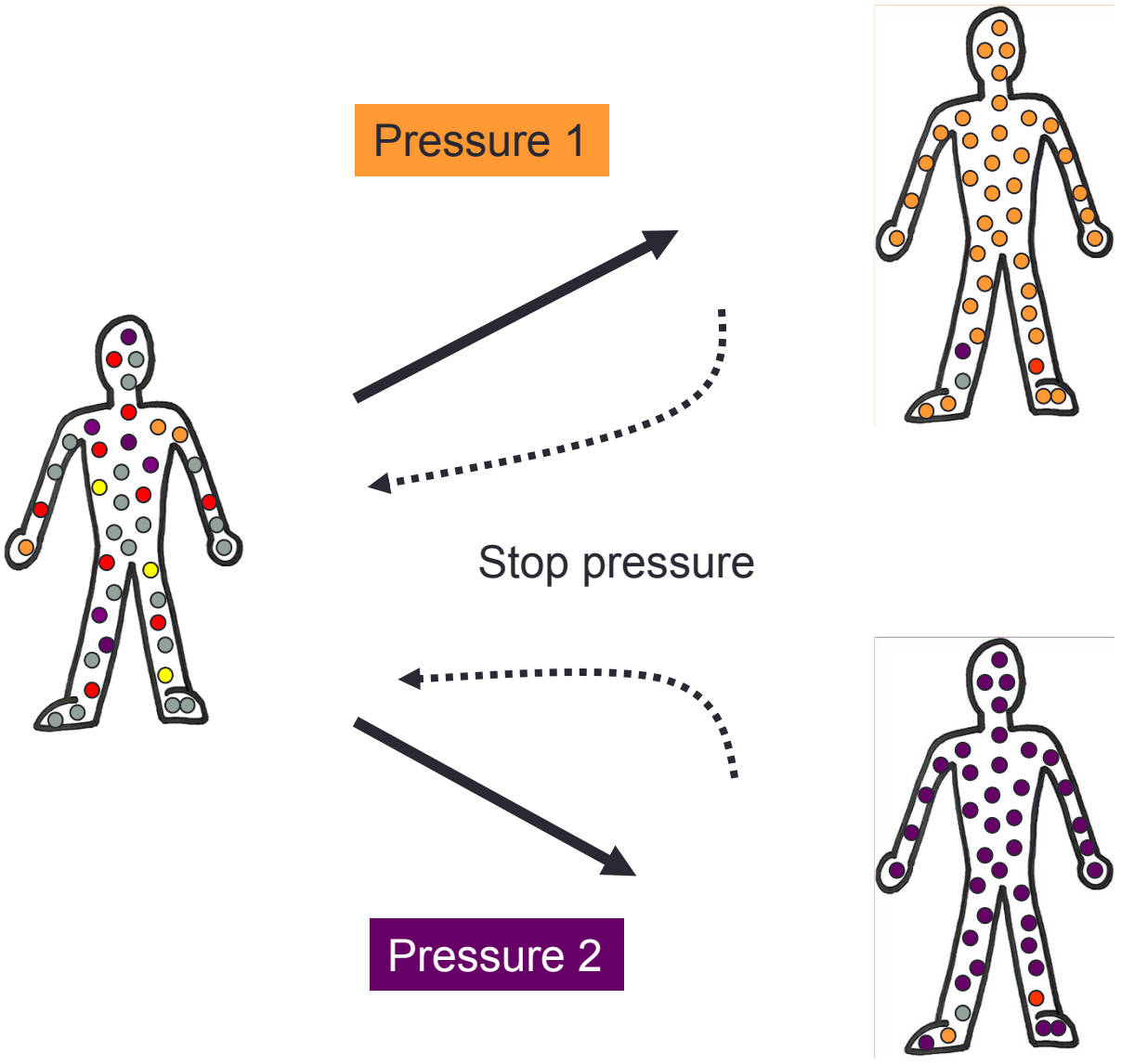


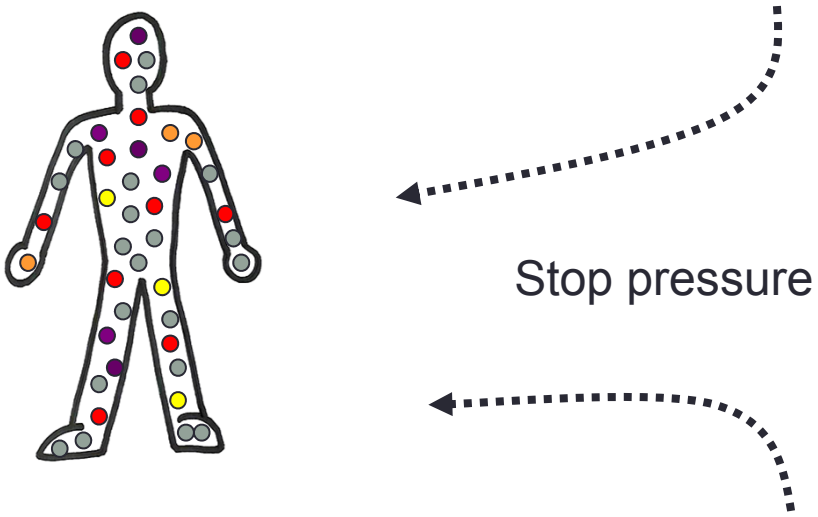




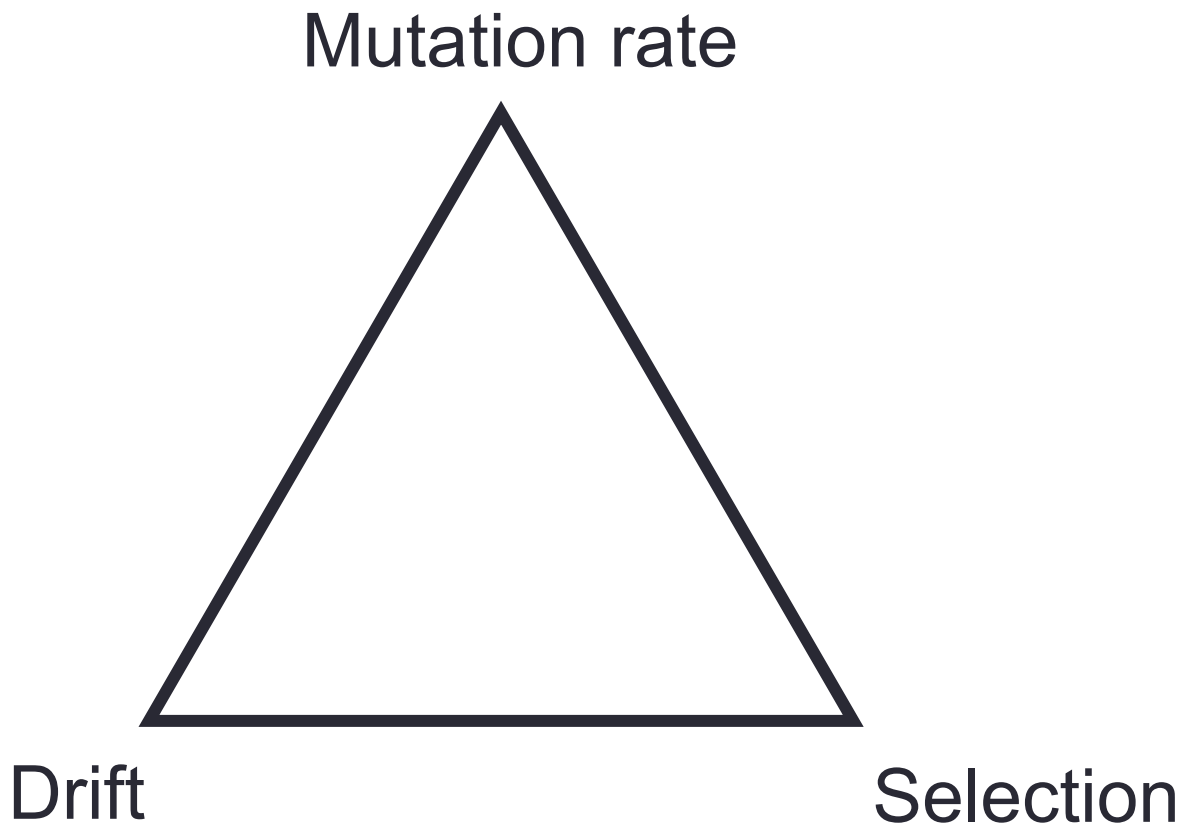

Pressure 1


Pressure 1
Pressure 2

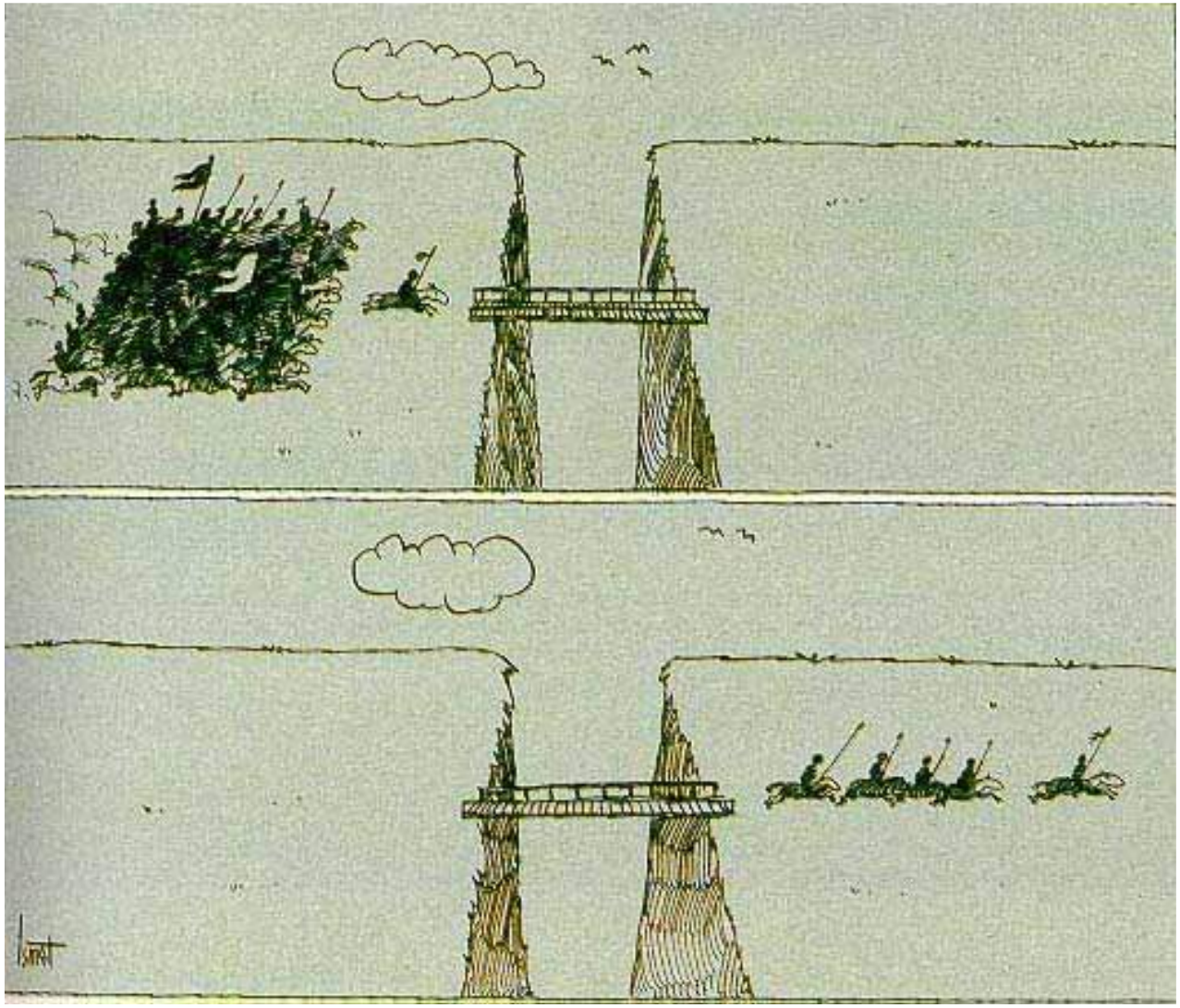

Pressure 1
Stop pressure
Pressure 2


Stop pressure

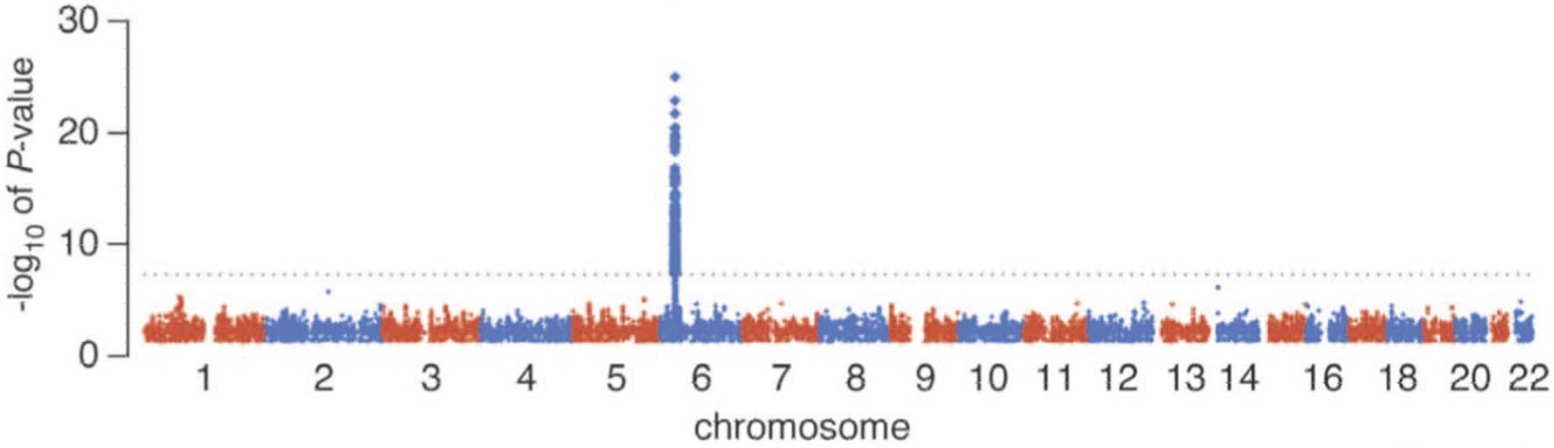
Diversity



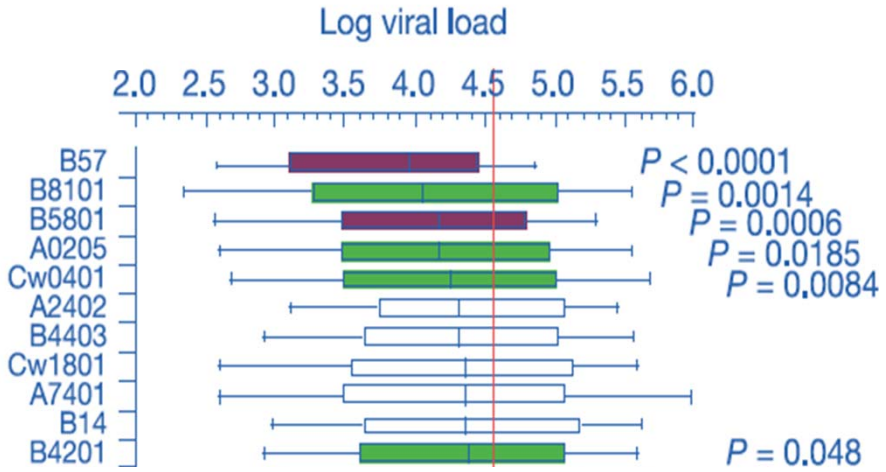
Drift



HLA-I molecules are a major driving force of HIV-1 evolution

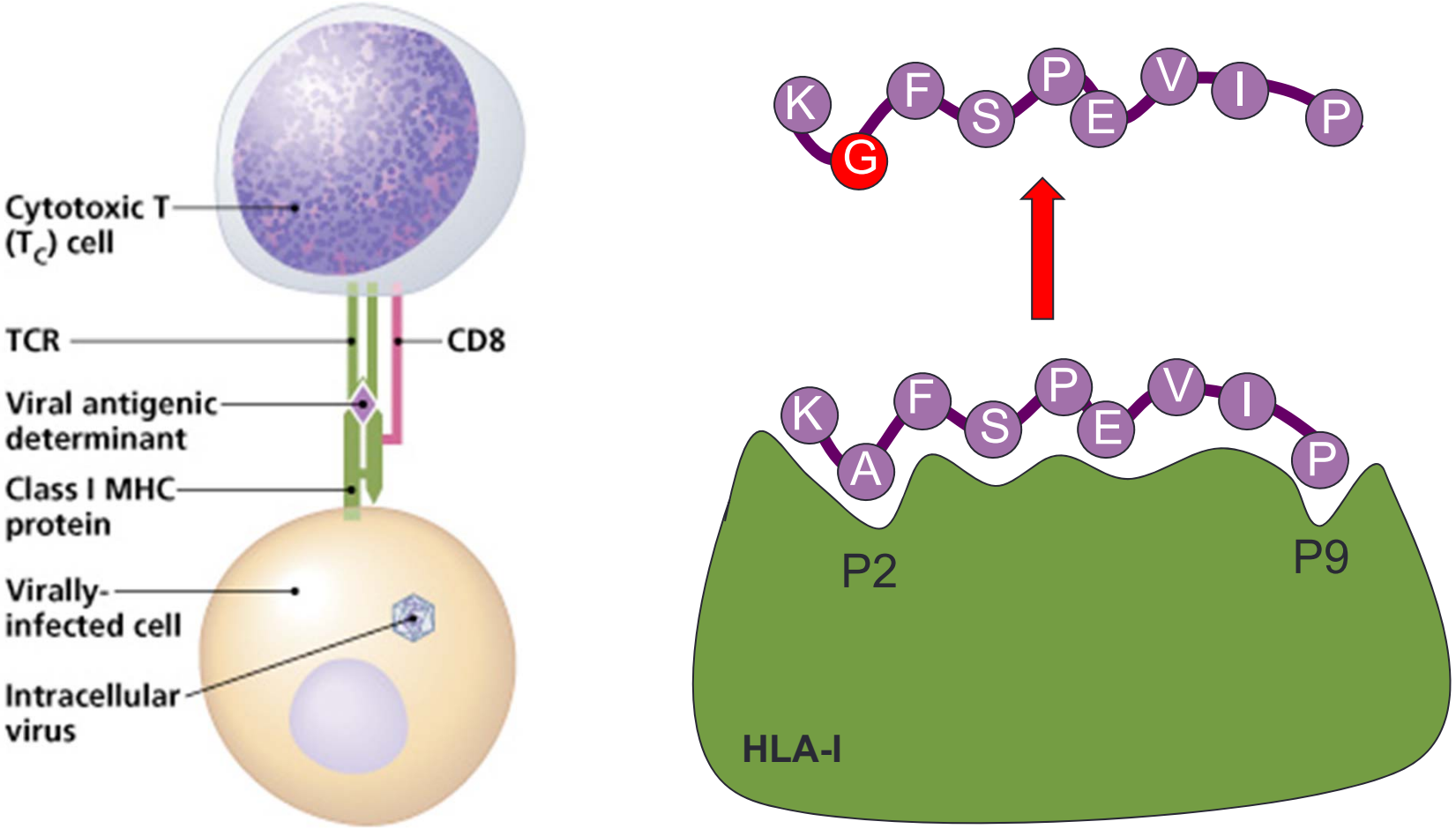


Pereyra et al, Science 2010

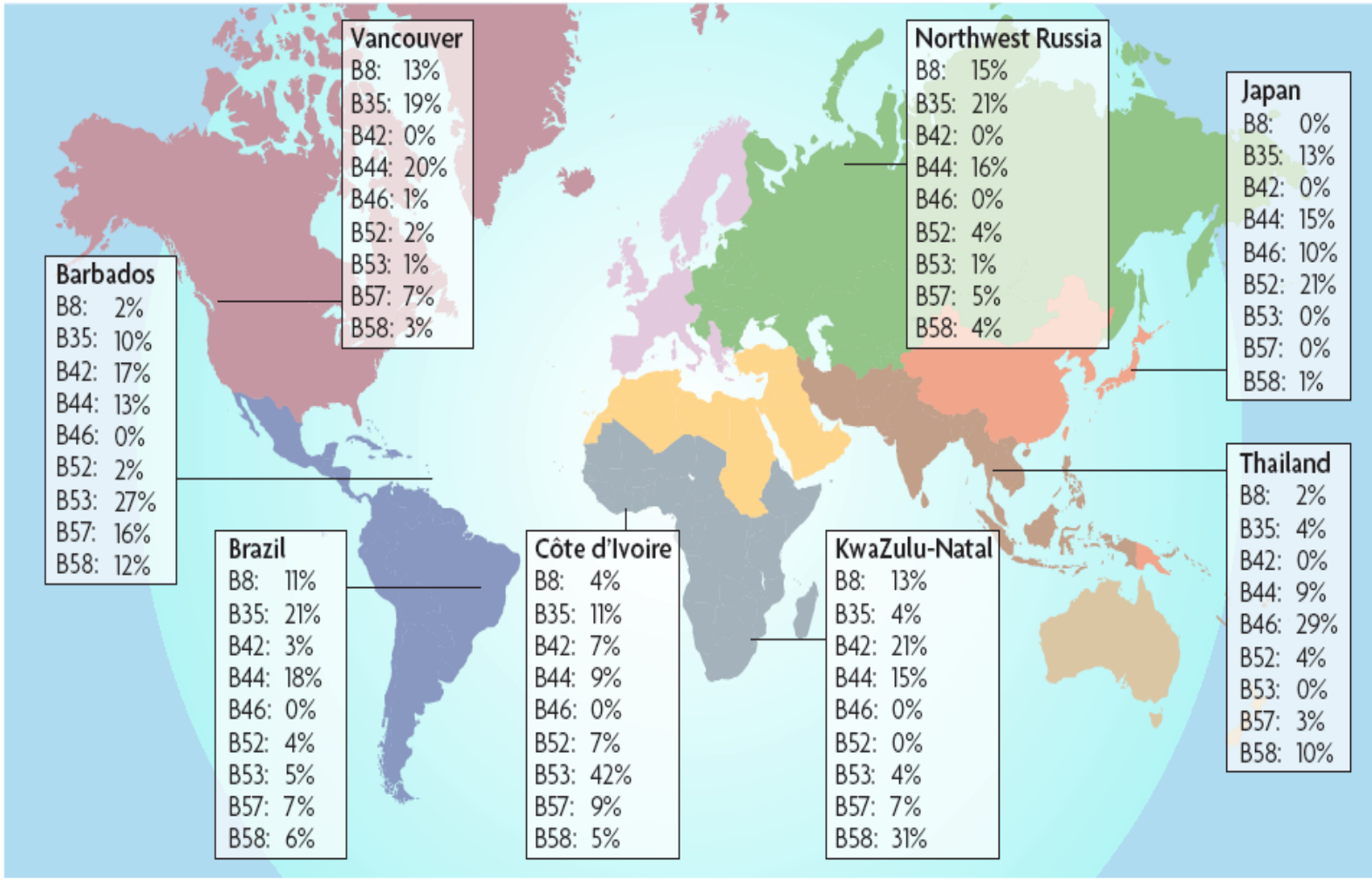


Kiepiela et al, Nature 2004

CD8+ T-cell responses and HIV-1 escape



HLA class I alleles are also highly diverse



Host HLA genetics and HIV diversity: frequent transmission of escaped epitopes and epitope loss over time

JOURNAL OF VIROLOGY, Aug. 2004, p. 8437–8445 Vol. 78, No. 16
0022-538X/04/$08.00+0 DOI: 10.1128/JVI.78.16.8437–8445.2004

Frequent Transmission of Cytotoxic-T-Lymphocyte Escape Mutants of Human Immunodeficiency Virus Type 1 in the Highly HLA-A24-Positive Japanese Population

Tae Furutsuki,[1,2]† Noriaki Hosoya,[1]† Ai Kawana-Tachikawa,[1]† Mariko Tomizawa,[1] Takashi Odawara,[3] Mieko Goto,[1] Yoshihiro Kitamura,[1] Tetsuya Nakamura,[3] Anthony D. Kelleher,[4] David A. Cooper,[4] and Aikichi Iwamoto[1,3]*

Division of Infectious Diseases, Advanced Clinical Research Center, Department of Infectious Diseases and Applied Immunology, Research Hospital,[1] and Institute of Medical Science,[3] University of Tokyo, Minato-ku, Tokyo 108-8639, and Department of Applied Biochemistry, Tokai University, Hiratsuka-shi, Kanagawa,[2] Japan, and National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia[4]

A

A24-positive Japanese hemophiliacs

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
A24-J041	---------V	-F--------	---------M
A24-J033	-----R---T	-F-------Y	-------D--
A24-J031	-H-------T	-F--------	-
A24-J030	---------T	-F--C-----	----------
A24-J034	---------T	-F--------	-----DQ-Q-
A24-J038	----------	-----C----	-----D-D--
A24-J005	-D/E-------T	-F--------	-
A24-J029	---------V/T	-F--------	--------Q-
A24-J037	--C------T	-F--------	-----D----
A24-J035	---------T	-F--------	----------
A24-J036	--C------T	-F--------	----------

A24-negative Japanese hemophiliacs

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
NA24-J037	----------	----------	----------
NA24-J035	----------	----------	----M-----
NA24-J031	----------	----------	-------G/E-V/I
NA24-J041	----------	----------	--------DE
NA24-J032	----------	----------	----M-----
NA24-J030	--S------V	----C-----	----------
NA24-J040	----------	----------	---------I
NA24-J033	----------	----------	-L/V-------
NA24-J029	-H--------	----------	--------D-
NA24-J034	----------	----------	----V/L----
NA24-J039	----------	----C-----	-----D-D--
NA24-J006	---------V	----C-----	-----D----

B

A24-positive Japanese infected through USI

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
A24-J006	---------V	-F--------	-----E/D--Q-
A24-J007	---------T	-F--C-----	----A---E-
A24-J009	---------T	-F--------	-
A24-J010	---------T	-F--------	-------QR-
A24-J012	---------T	-F--------	-------D--
A24-J013	---------T	-F--------	-----D-DQ-
A24-J016	-D-------V	----C-----	-----DQD--
A24-J017	-D-------T	-F--C-----	---------I
A24-J018	---------T	-F--------	---------I
A24-J023	---------T	-F--------	----L--GBA
A24-J021	---------T	-F--------	-----D-DQ-
A24-J024	---------T	-F--------	-----D-D--
A24-J025	-D-------T	-F--------	-----DQDQ-
A24-J026	---------T	-F--------	-------KQ-

A24-negative Japanese infected through USI

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
NA24-J025	-H-------V	----C-----	-----D-D/AQ-
NA24-J023*	---------T	-Y/W/F----------	----------I Y
NA24-J021	----------	----------	-----M--Q-
NA24-J018*	---------T	-Y/F--C-----	---------- Y
NA24-J017*	---------T	-Y/F---------	----L----- Y
NA24-J016	---------V	----------	----L---Q-
NA24-J015	---------T	-F--------	-----D-DQ-
NA24-J012	-H/QS------T	----------	-----D-DQ-
NA24-J011	---------T	-F--------	-------NQ-
NA24-J010	-	----------	-
NA24-J009	---------T	-F--------	-------NQ-
NA24-J008	-D-------T	-F--------	----L---Q-
NA24-J007	---------T	-F--------	-------NQ-
NA24-J005	-G/D-------T	-F--------	-----DQDQ-
NA24-J003	-H--------	----------	-----DQ---
NA24-J002	-Q/HG-------	----------	-----D-DQ-

C

A24-positive Australian infected through USI

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
A24-A001	---------T	-F--------	----------
A24-A002	---------T	-F--------	----M-----

A24-negative Australian infected through USI

Patient ID	flanking WQNYTPGPGI	CTL epitope RYPLTFGWCF	flanking KLVPVEPEKV
NA24-A007	---------V	----------	-
NA24-A005	---------V	----------	----------
NA24-A013	----------	----------	----------
NA24-A008	-H--------	----------	----M-P/Q---
NA24-A003	-H--------	----------	-----D-D--
NA24-A006	----------	----C-----	--------E-

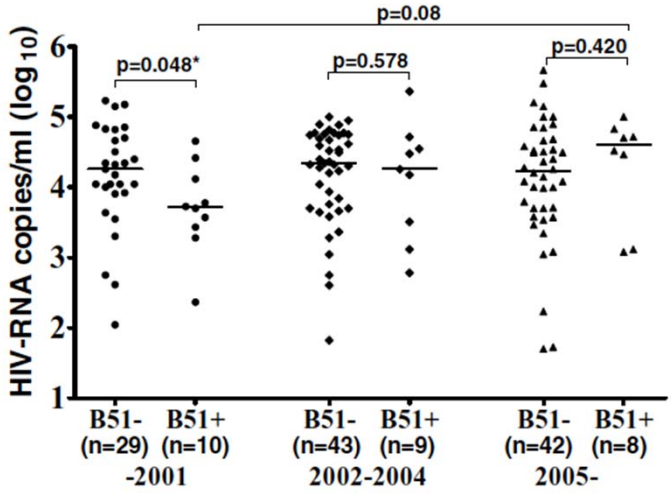
Microbiol Immunol 2010; **54**: 196–205
doi:10.1111/j.1348-0421.2010.00206.x

ORIGINAL ARTICLE

Changes in impact of HLA class I allele expression on HIV-1 plasma virus loads at a population level over time

Michiko Koga[1], Ai Kawana-Tachikawa[1], David Heckerman[2], Takashi Odawara[1], Hitomi Nakamura[1], Tomohiko Koibuchi[3], Takeshi Fujii[3], Toshiyuki Miura[4] and Aikichi Iwamoto[1,5,6]

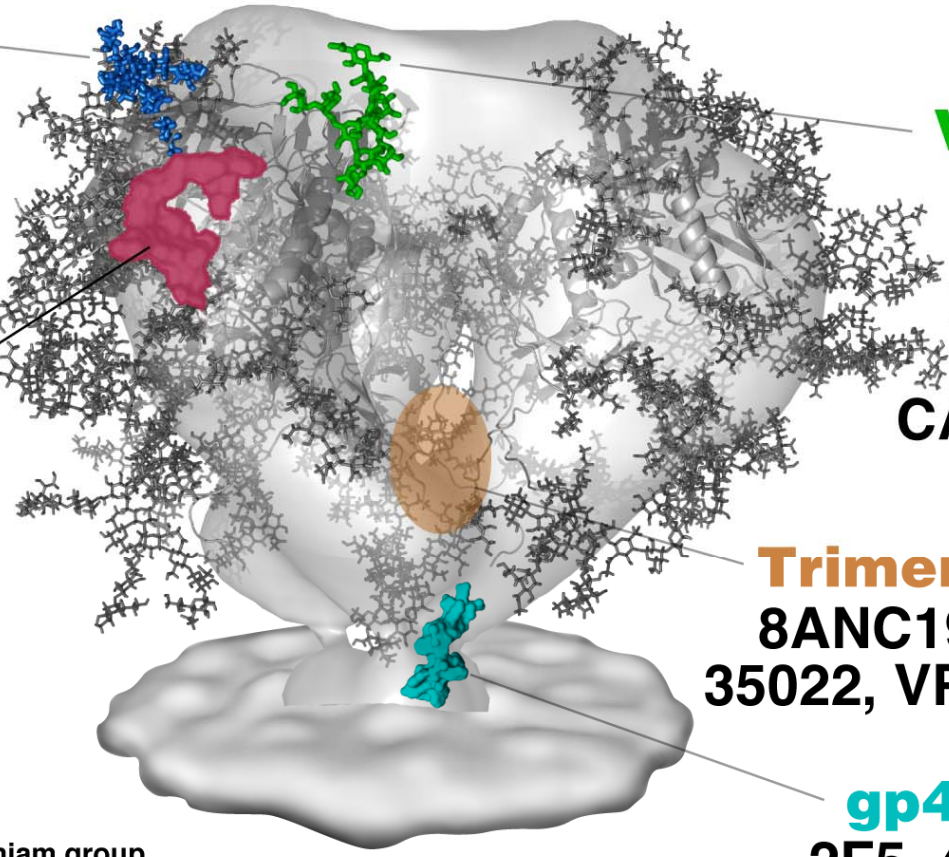
[1]Division of Infectious Disease, Advanced Clinical Research Center, [3]Department of Infectious Diseases and Applied Immunology, Research Hospital, [4]Department of Infectious Disease Control, International Research Center for Infectious Diseases, [5]Department of infectious Disease and Applied Immunology, and [6]Research Center for Asian Infectious Diseases, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, 108-8639, Japan and [2]Microsoft Research, Redmond, Washington 98052



Broadly Neutralizing Antibodies Binding to Neutralization Epitopes on HIV Trimer

N332 Glycan Supersite
PGT121, PGT128, 10-1074

CD4 Binding Site
VRC01, PG04, CH31, 3BNC117, 12A12, CH103, VRC07-523, N6



V1V2 Apex
PG9, PG16, CH01-04, PGT141-45, PGDM1400, CAP256-VRC26

Trimer Interface
8ANC195, PGT151, 35022, VRC34, ACS202

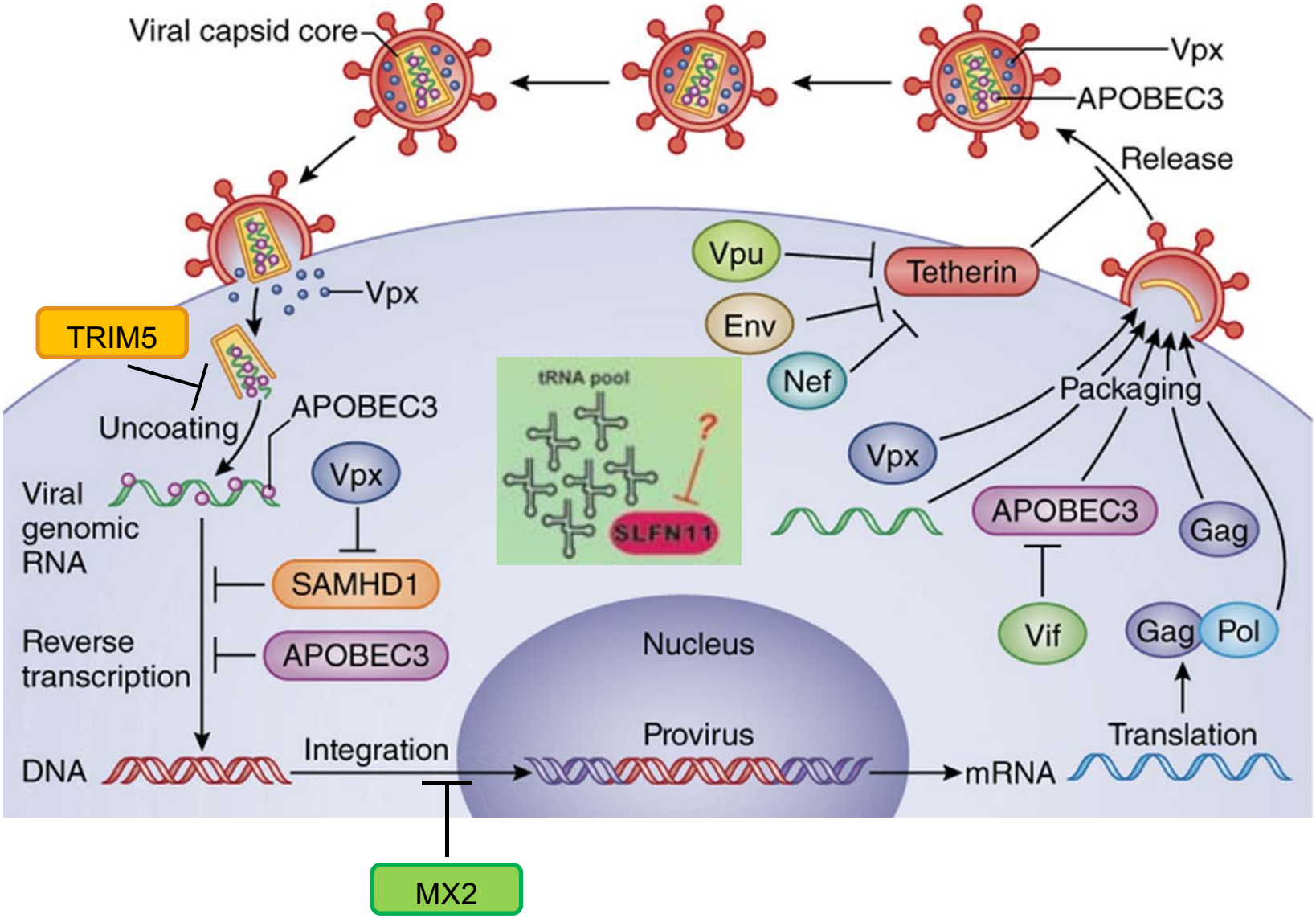
gp41 MPER
2F5, 4E10, 10E8

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson group

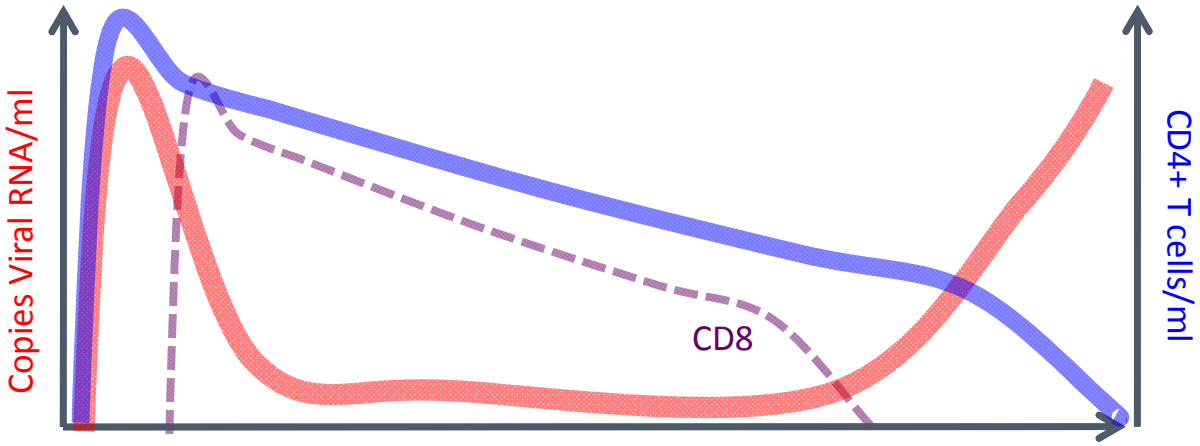
Courtesy of John Mascola

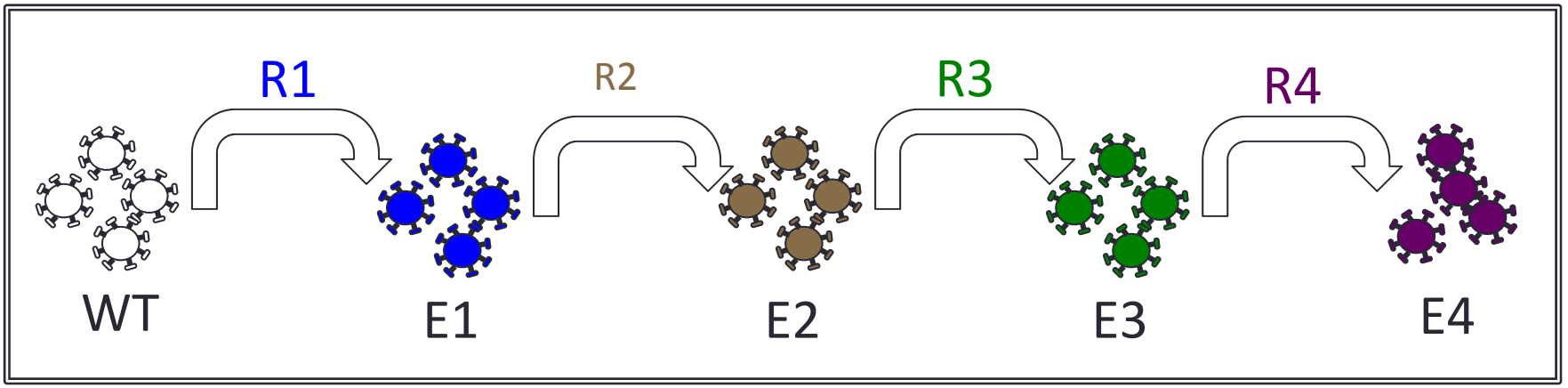
Gp160 from the outside

Restriction factors

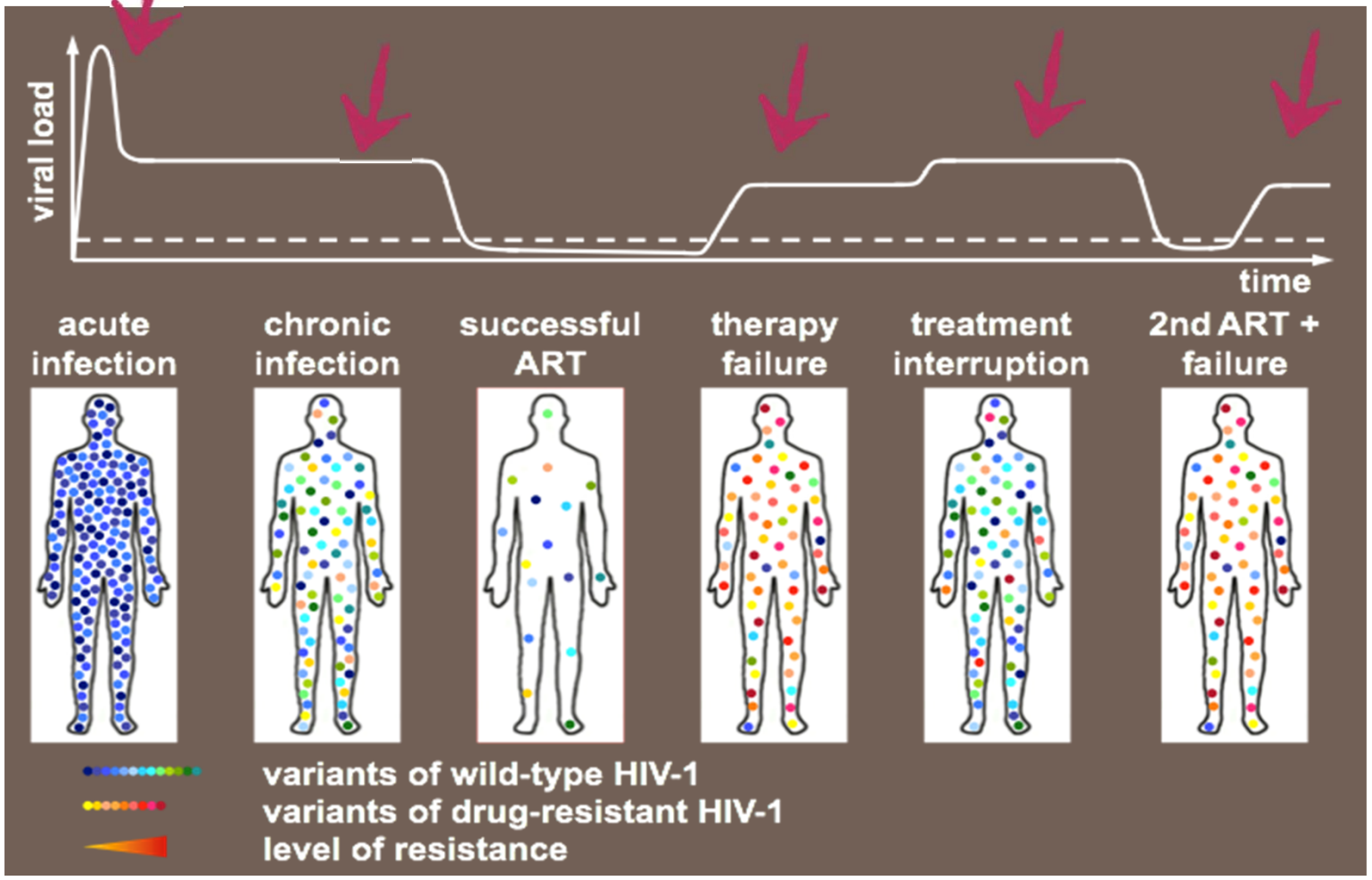


HOST RACE HIV EVOLUTION



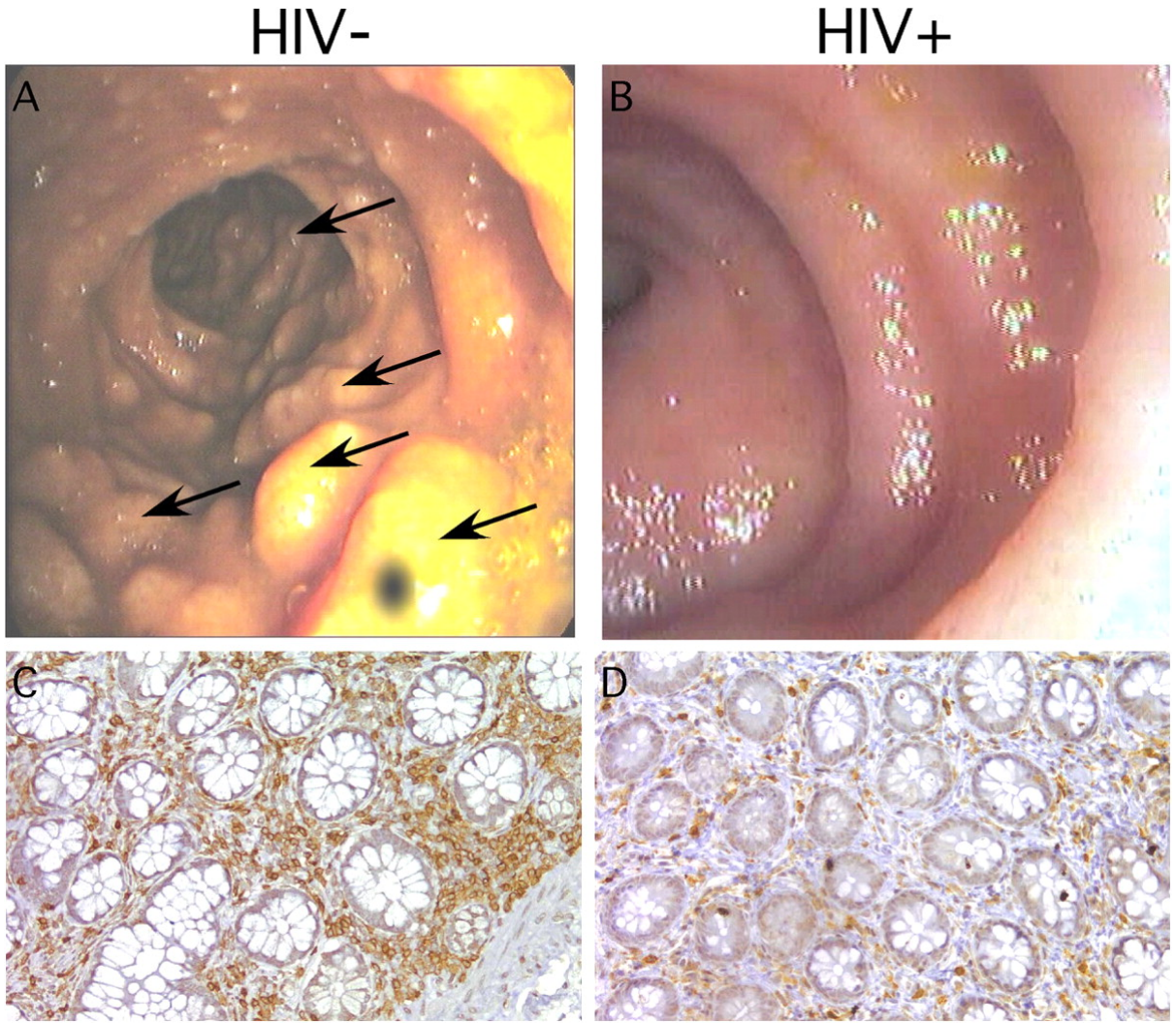


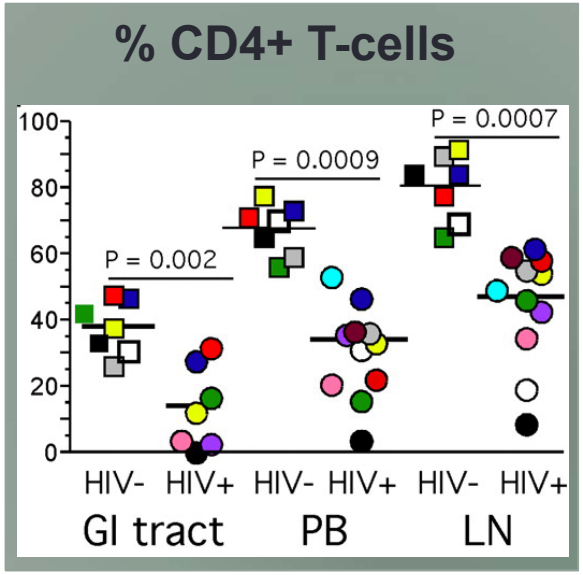
Quasispecies as a survival strategy



Metzner K, Paredes R, CHAIN Training slide

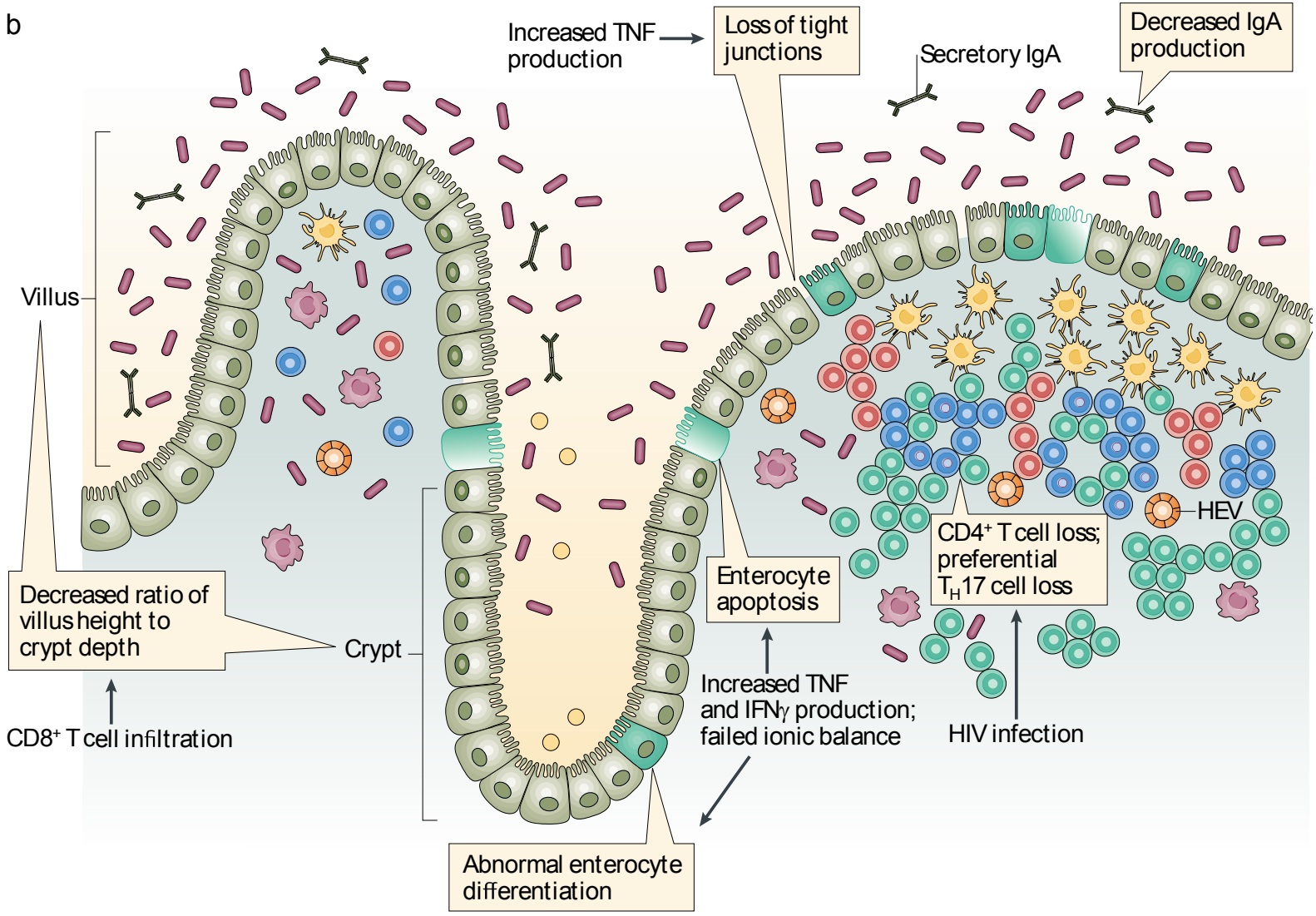
HIV infection damages the GALT



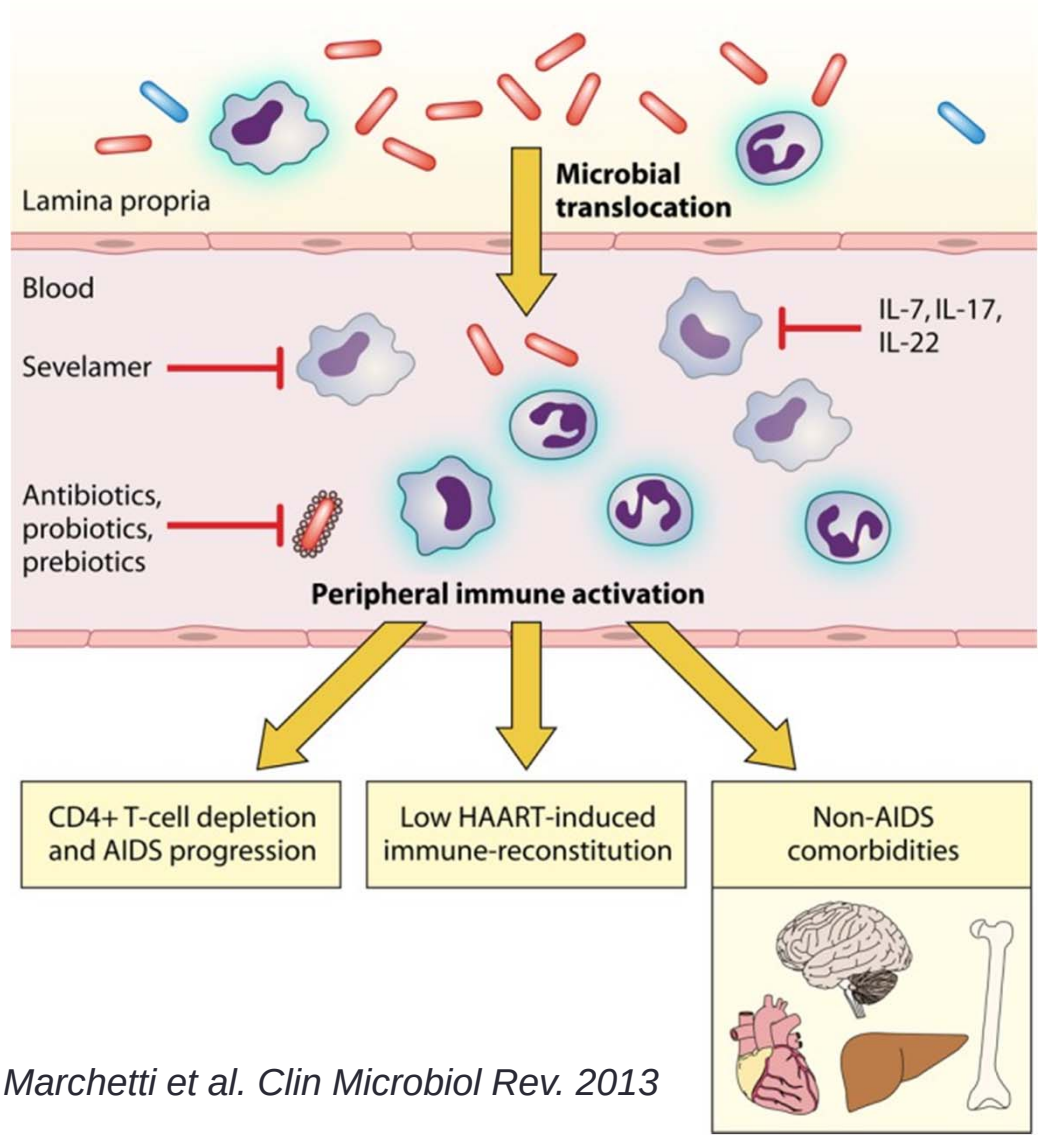


Brenchley J M et al. J Exp Med 2004;200:749-759

Microbial translocation in HIV



Microbial translocation in HIV pathogenesis



Marchetti et al. Clin Microbiol Rev. 2013

Bacterial translocation and clinical progression

AIDS. 2011 Jul 17;25(11):1385-94.

Microbial translocation predicts disease progression of HIV-infected antiretroviral-naive patients with high CD4+ cell count.

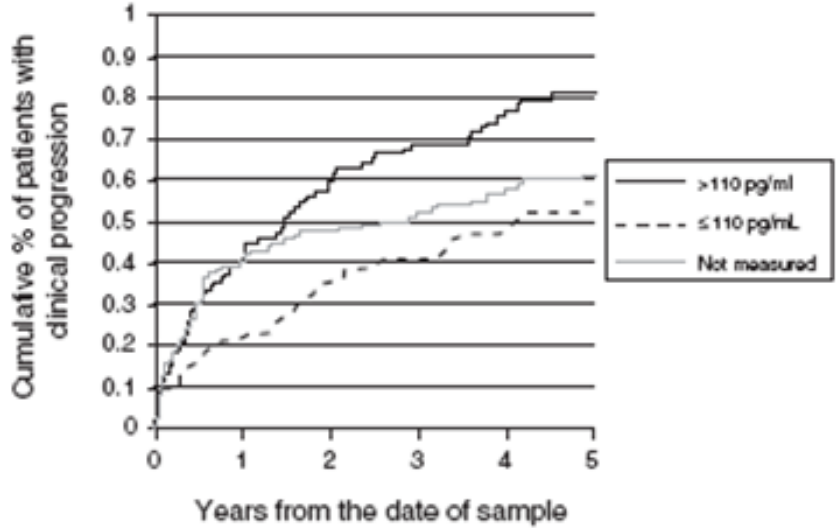
Marchetti G, Cozzi-Lepri A, Merlini E, Bellistrì GM, Castagna A, Galli M, Verucchi G, Antinori A, Costantini A, Giacometti A, di Caro A, D'arminio Monforte A; ICONA Foundation Study Group.

ICONA Cohort

- Documented last HIV-negative test and first HIV-positive

- Plasma sample stored while ART-naive

N=379.

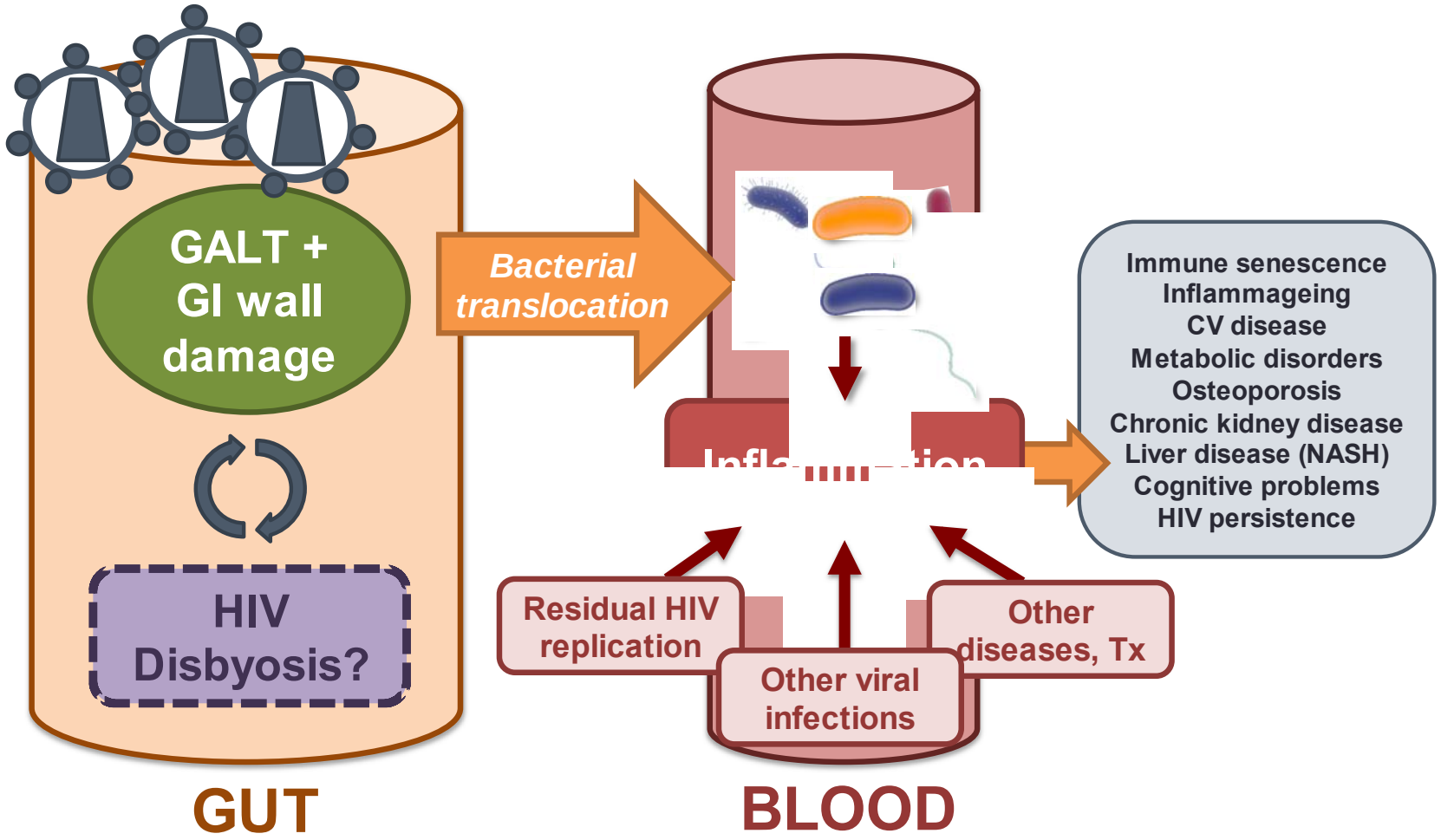


LPS groups	Number at risk at each year					
>110 pg/ml	123	61	36	26	16	11
≤110 pg/ml	124	90	70	61	52	42
Not measured	132	75	61	51	40	32

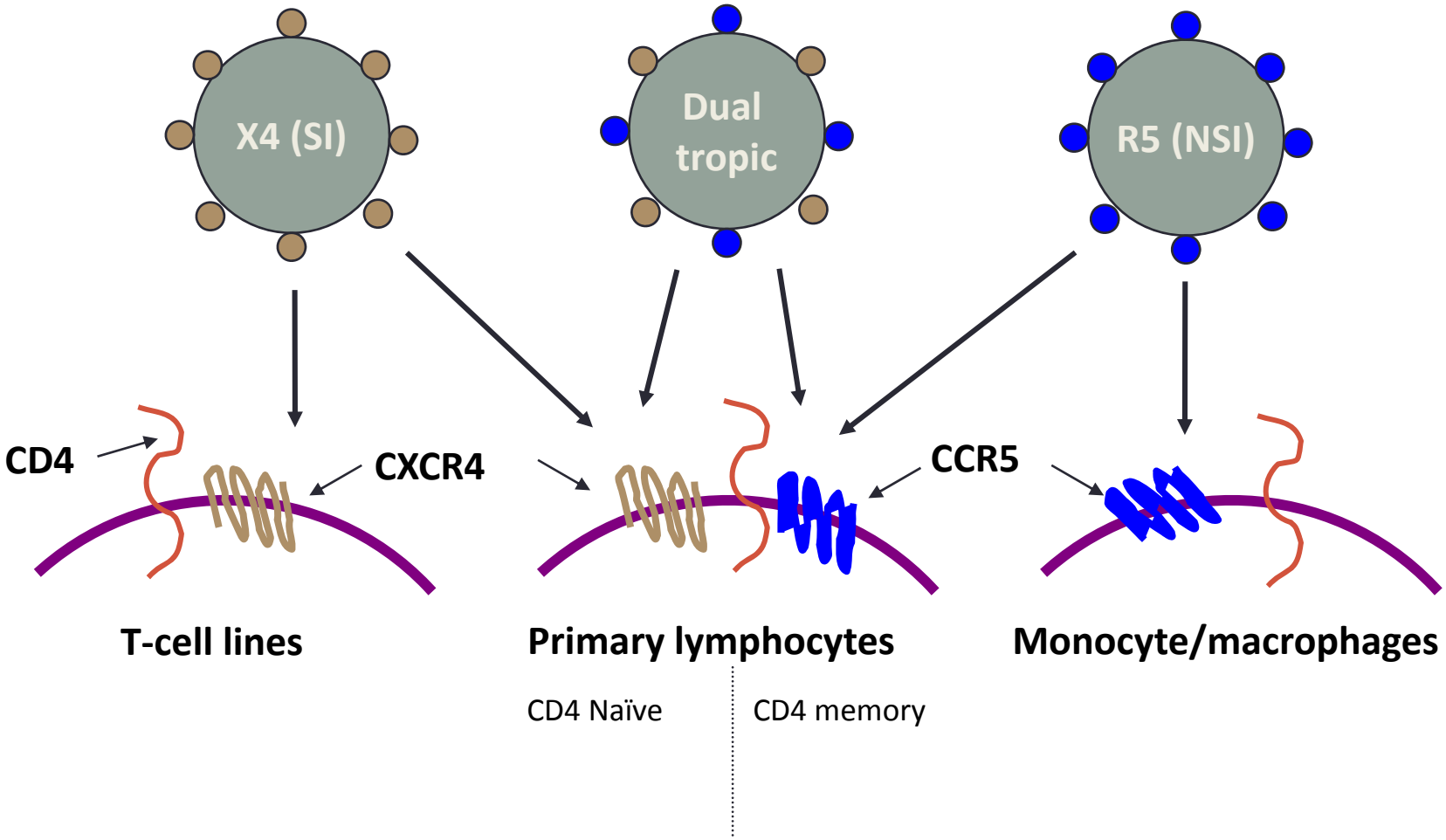
Circulating LPS in the first year of infection is a good predictor of progression

Marchetti G, et al. AIDS 2011;25(11):1385-94.

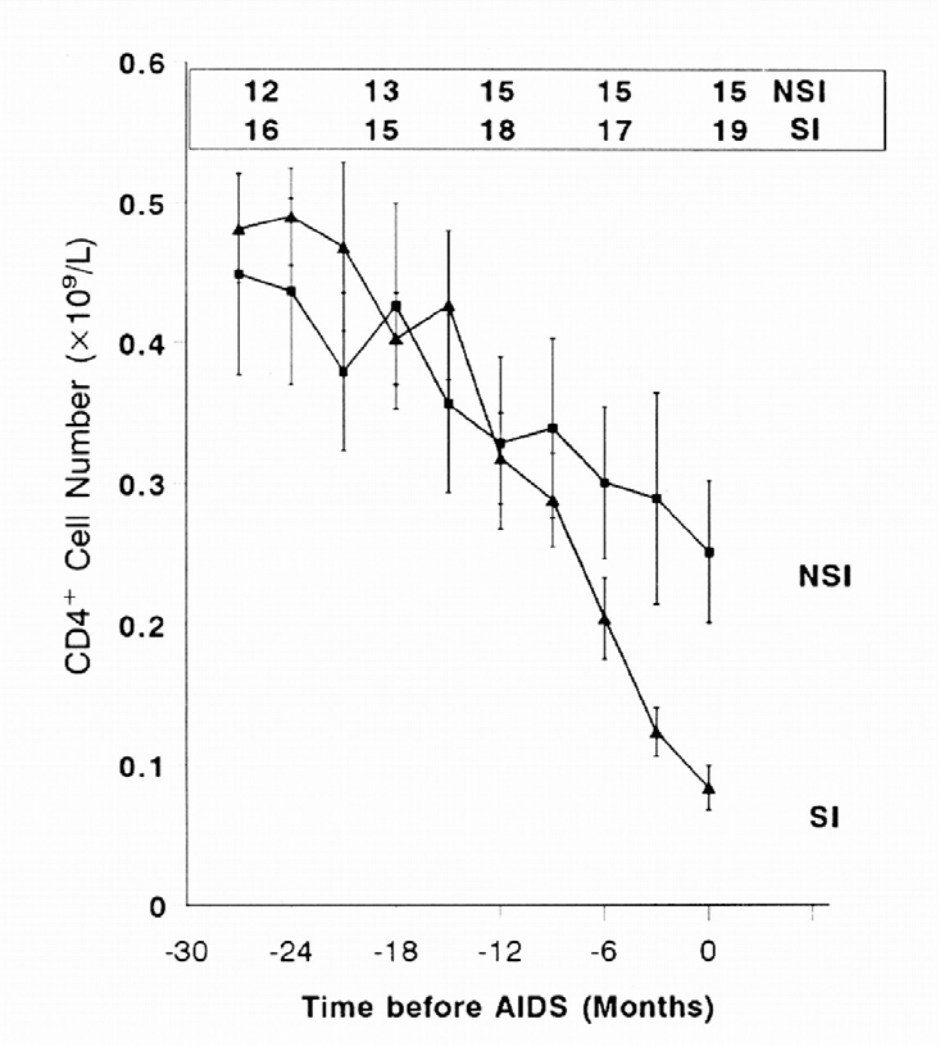
INFLAMMAEGING



Tropism prediction

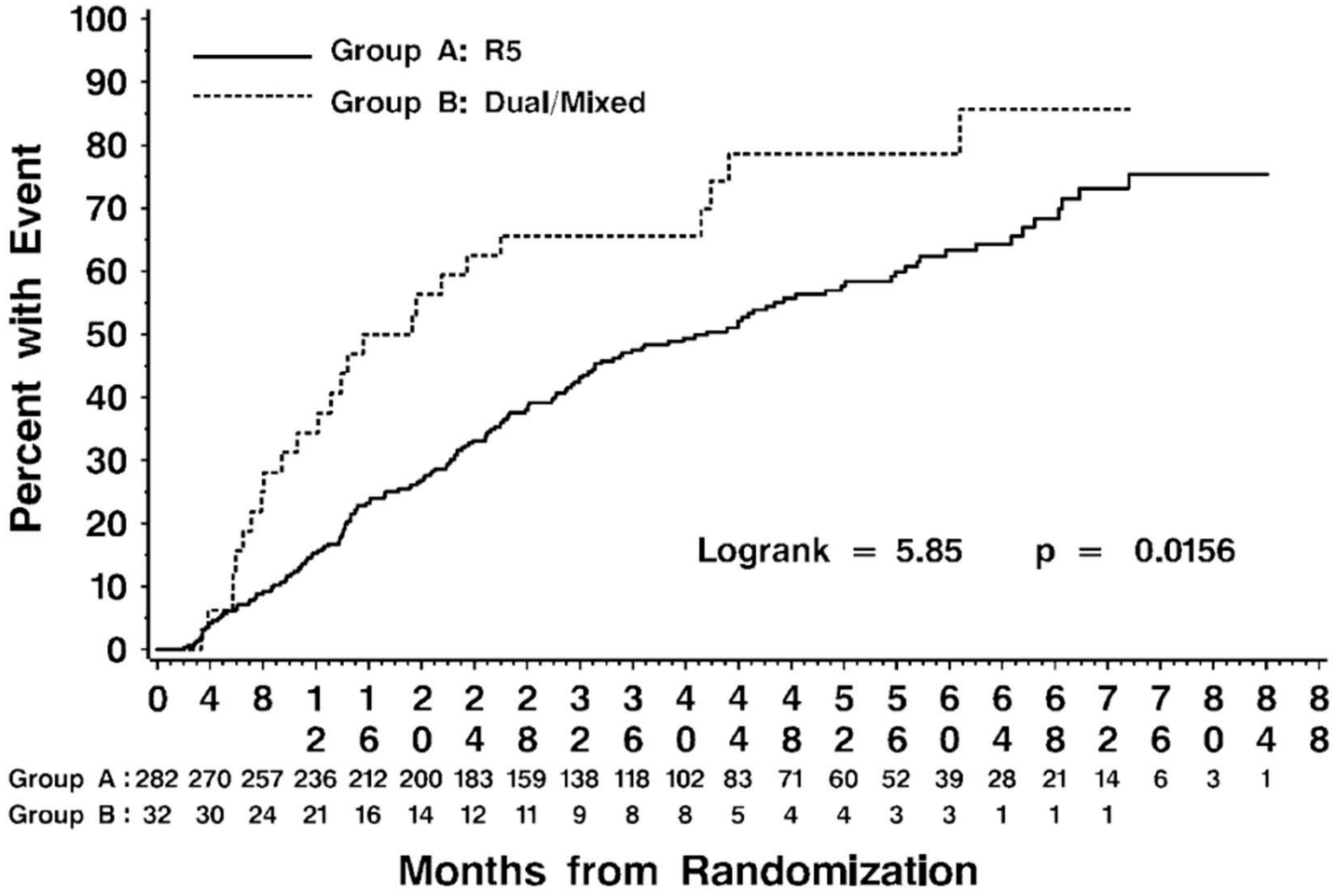


Tropism



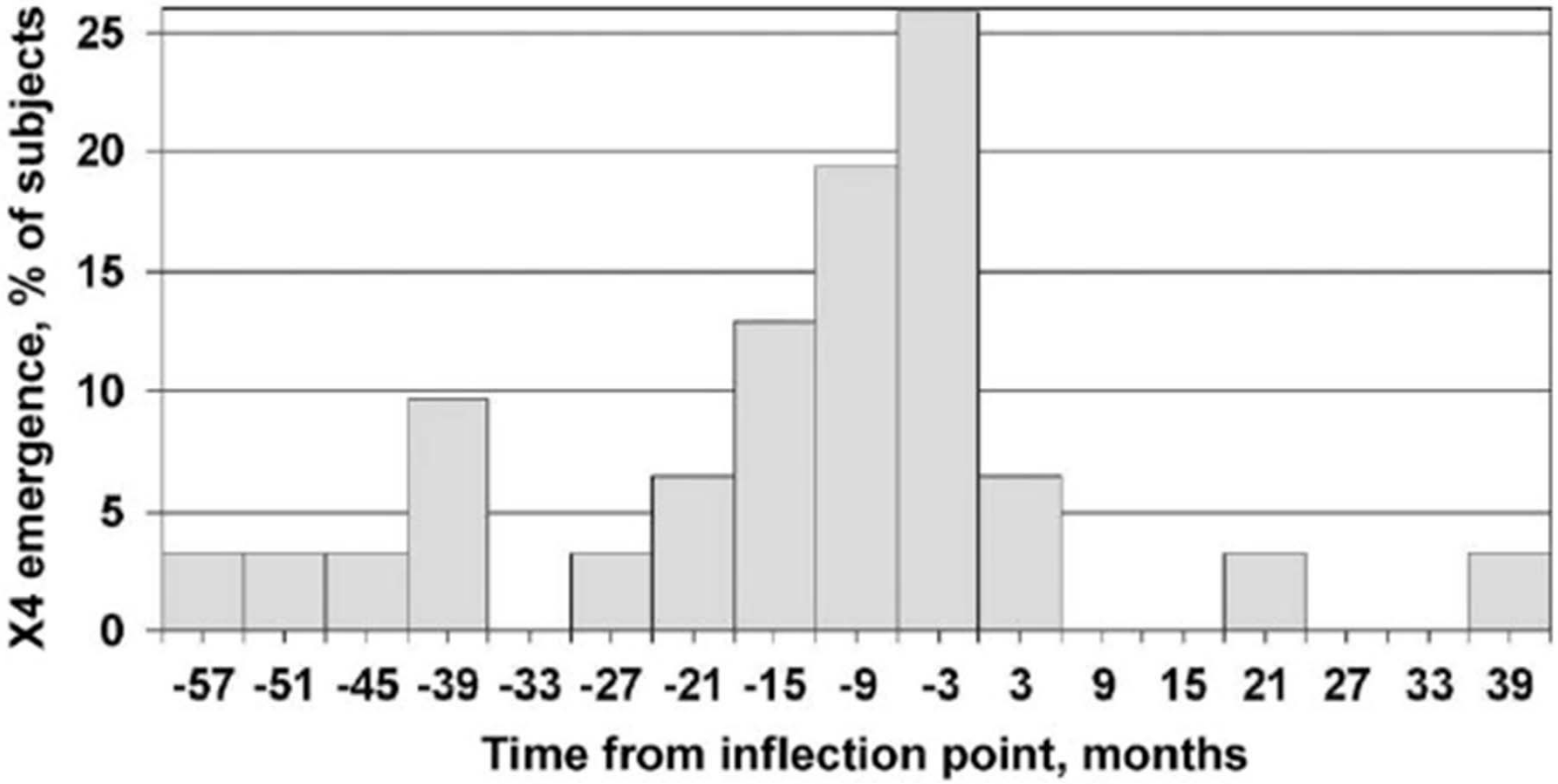
Koot M, et al: Prognostic Value of HIV-1 Syncytium-Inducing Phenotype for Rate of CD4+ Cell Depletion and Progression to AIDS. Annals Int Med 1993

Rate of progression to CD4+<350, initiation of ART or death



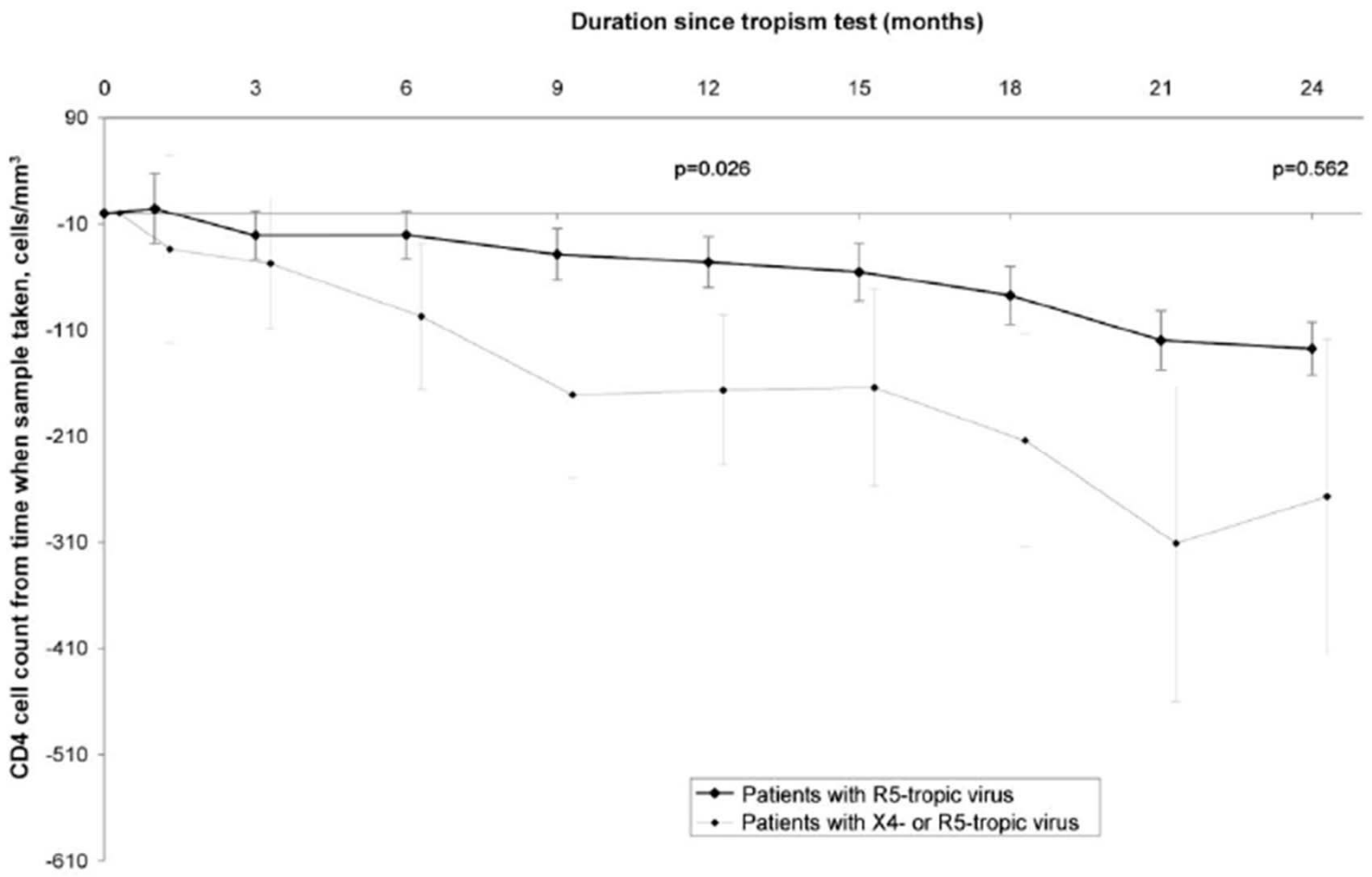
Goetz. JAIDS 2009

Time of X4 virus emergence in relation to CD3 inflection point



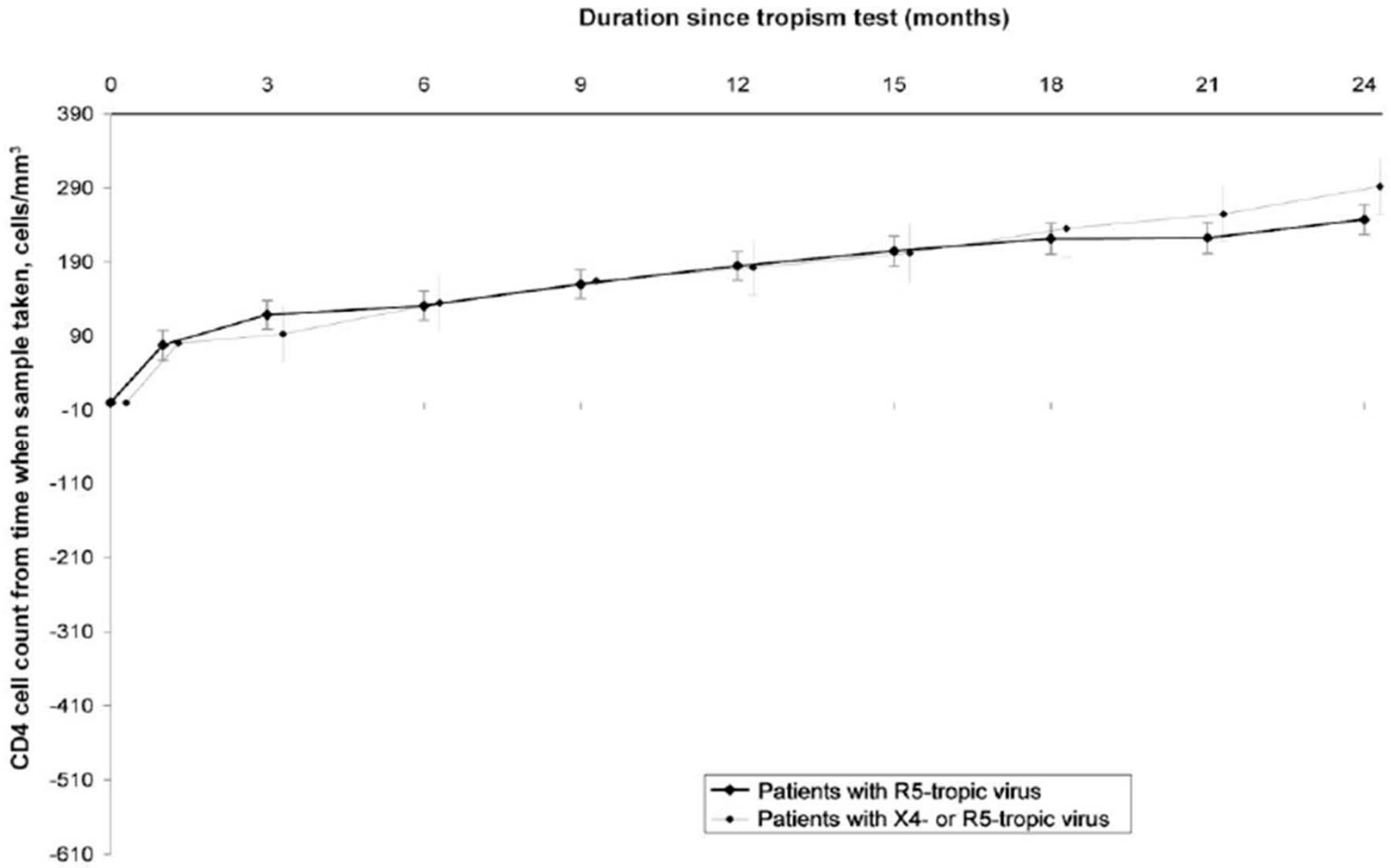
Shepherd. MACS cohort, JID 2008

Tropism & CD4 loss **before ART**



Waters CID 2008

Tropism & CD4 gain **after ART**



Waters CID 2008

Why do we need to cure HIV?

- **Life expectancy** remains reduced on cART
- Ongoing **morbidity** on cART
- Prevent HIV **transmission**
- Substantial **stigma** and **discrimination**
- **Lifelong** cART:
  - adherence
  - toxicity
  - long term-cost

Estimated **2015** AIDS investment for universal prevention, treatment, care and support

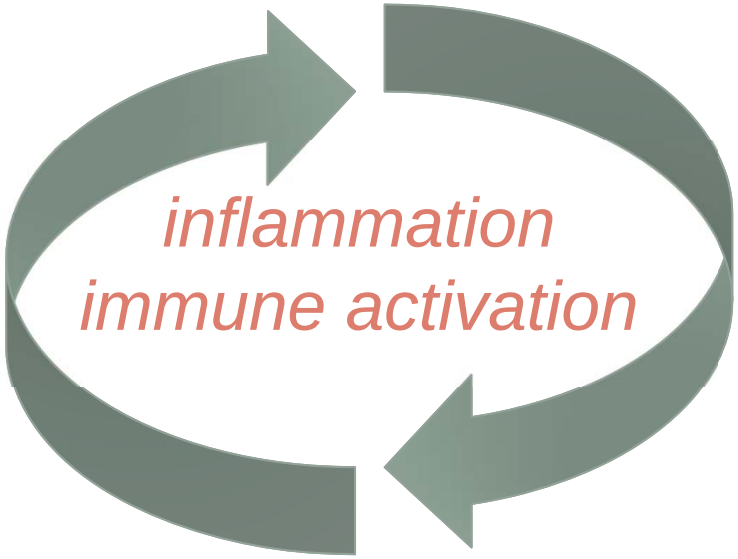
22 billion USD

Lohse, Ann Int Med 2007; Hogg. Lancet 2008; Deeks & Phillips, BMJ 2009; May, BMJ 2011

Barriers to cure HIV infection

Where is the virus and how is it maintained in the face of suppressive therapy?

Residual replication



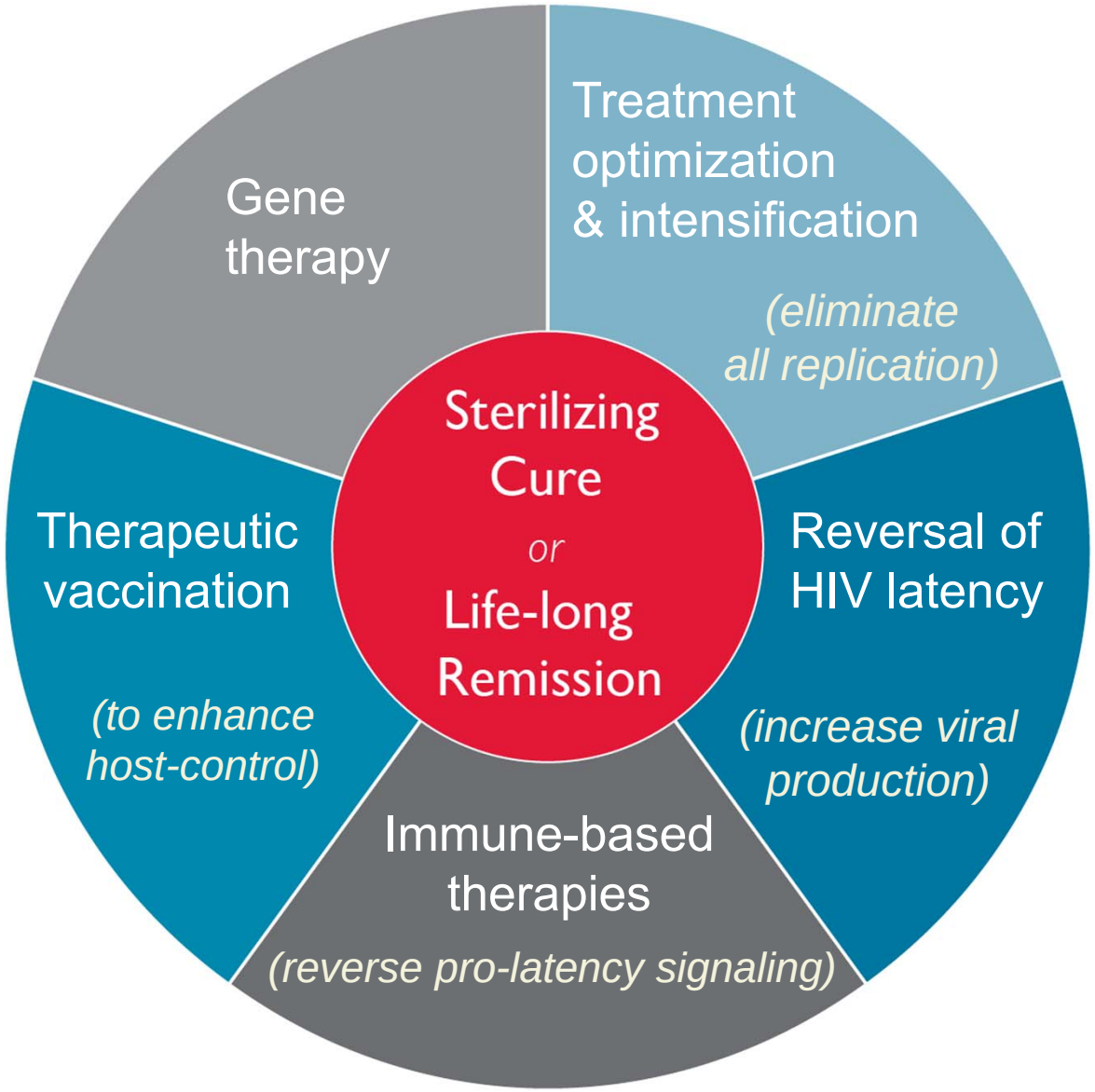
Latent infection

HIV cure: 2-models

Eradication	Remission
Sterilizing cure	Functional cure
Elimination of all HIV-infected cells	Long-term health without cART
HIV RNA < 1 cop/mL	HIV RNA <50 cop/mL
Berlin Patient post-BMT	Elite controllers Post-cART controllers

J.Martinez-Picado

Strategies to cure HIV



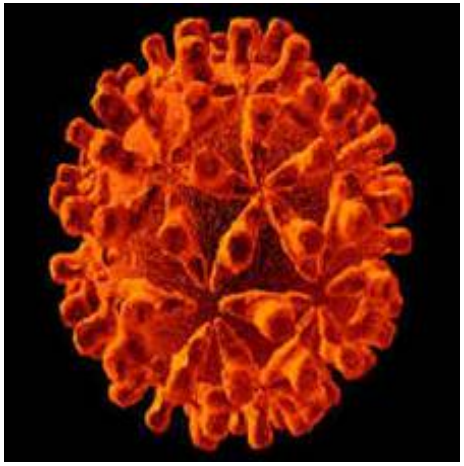
J.Martinez-Picado

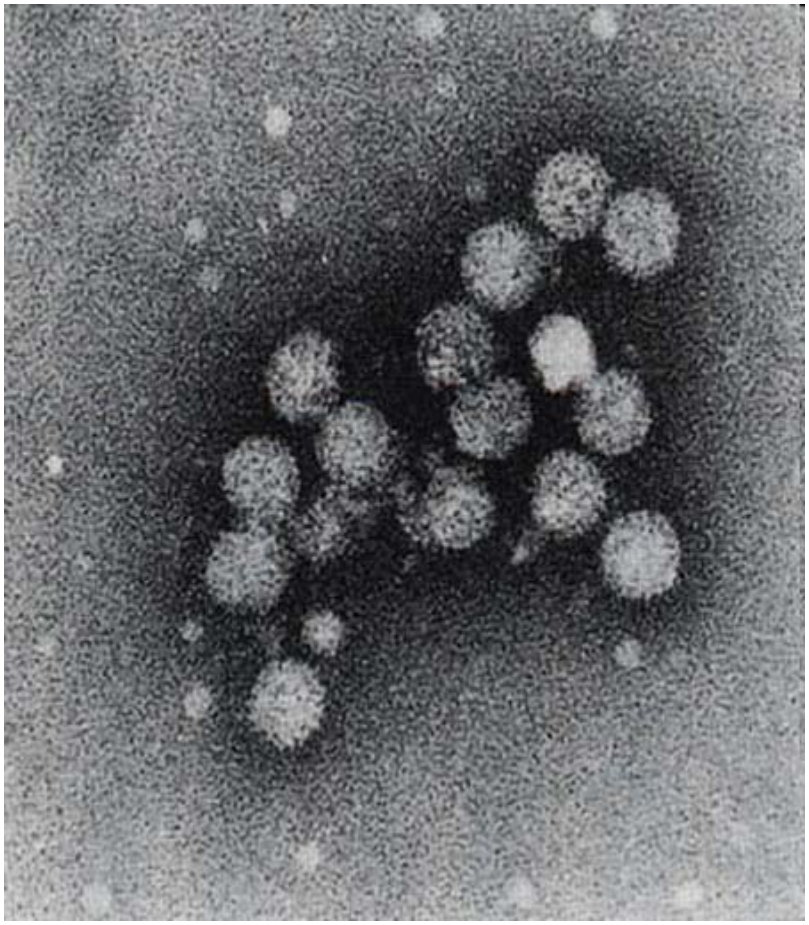
VIRAL HEPATITIS

HCV

Properties

Single strand RNA
Enveloped
Spheroidal: 40-60 nm in diameter.
Surface projections (appears rough)
3 structural proteins
6 non-structural proteins





Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

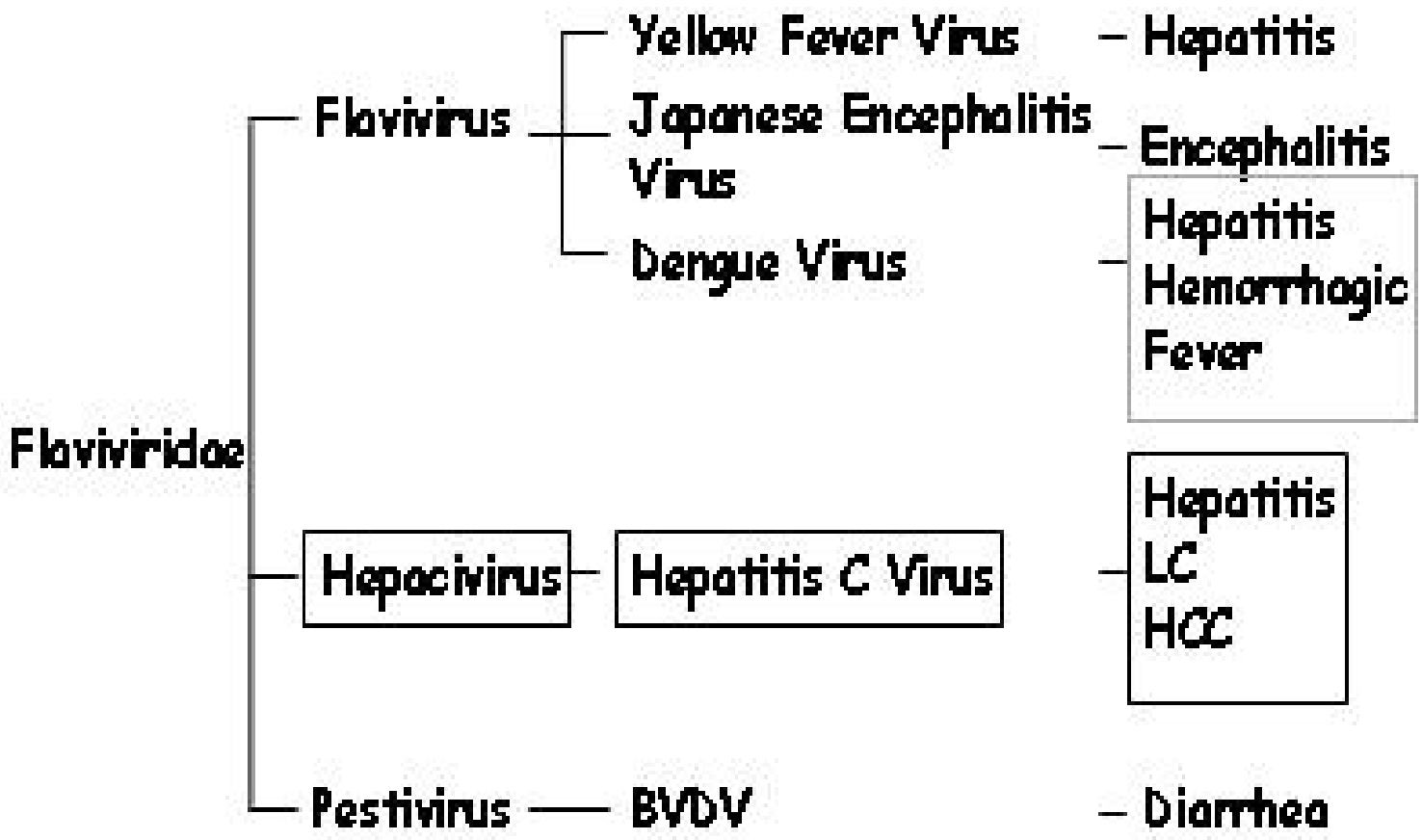
A random-primed complementary DNA library was constructed from plasma containing the uncharacterized non-A, non-B hepatitis (NANBH) agent and screened with serum from a patient diagnosed with NANBH. A complementary DNA clone was isolated that was shown to encode an antigen associated specifically with NANBH infections. This clone is not derived from host DNA but from an RNA molecule present in NANBH infections that consists of at least 10,000 nucleotides and that is positive-stranded with respect to the encoded NANBH antigen. These data indicate that this clone is derived from the genome of the NANBH agent and are consistent with the agent being similar to the togaviridae or flaviviridae. This molecular approach should be of great value in the isolation and characterization of other unidentified infectious agents.

WITH THE DEVELOPMENT OF SPECIFIC diagnostics for the hepatitis A virus (HAV) and the hepatitis B virus (HBV) in the 1970s, it became clear that most cases of hepatitis arising from blood transfusion were not caused by infections with these or other known viral agents (*1–4*). Despite over a decade of research, the agent or agents responsible for this so-called non-A, non-B hepatitis (NANBH) remains unidentified (*5, 6*), although there is evidence that one blood-borne NANBH agent may be a small, enveloped virus that is readily transmissible to chimpanzees (*7, 8*). A major impediment to progress in studies of this virus has been that despite intensive work, conventional immunological methods have consistently failed to identify specific viral antibodies and antigens (*5, 6*). Although this failure could be interpreted in terms of a lack of viral antibody, we consid-

Q.-L. Choo, G. Kuo, A. J. Weiner, L. R. Overby, M. Houghton, Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608.
D. W. Bradley, Hepatitis Branch, Centers for Disease Control, 1600 Clifton Road NE, Atlanta, GA 30333.

MA Martinez

HCV belongs to Flavivirus

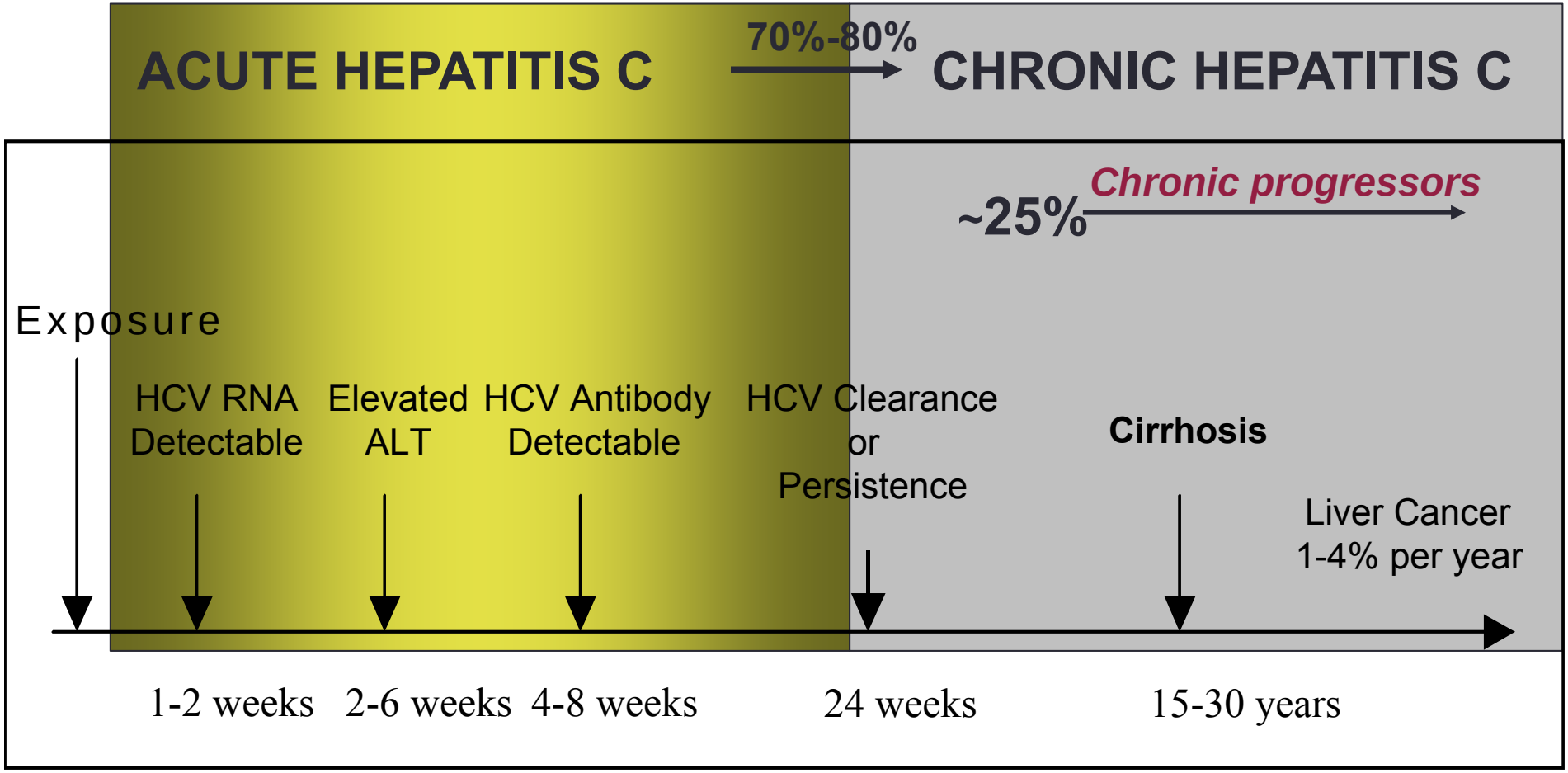


Relative Infectivity

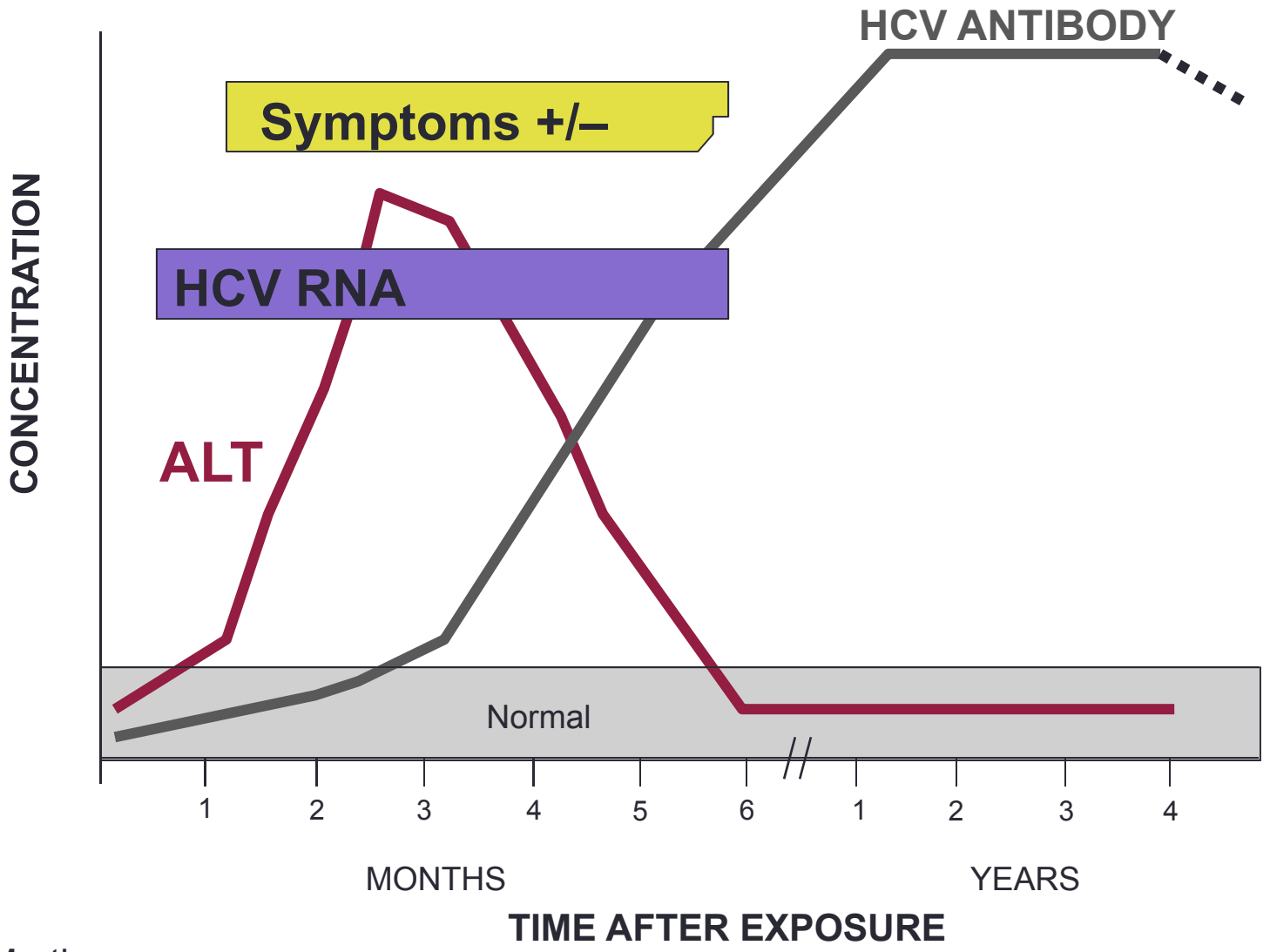
Transmission Route	HCV Risk	HBV Risk	HIV Risk
IDU	~ 30%/yr ≥60% acute/yr	~ 12-30% acute/yr	~30%/yr
Blood Tx	Now rare	Rare	Rare
Sporadic	10% cases	20-30%	
Needle-stick	0.44-10%	3-40%	0.3%
Tattoos/Piercing	1-5%	?	? 0%
Sexual	≤5%	Highest	Higher
Vertical	≤6%	~40%	~26%
Snorting	?	~2.5% NA cases	?

MA Martinez

Natural History of HCV Infection

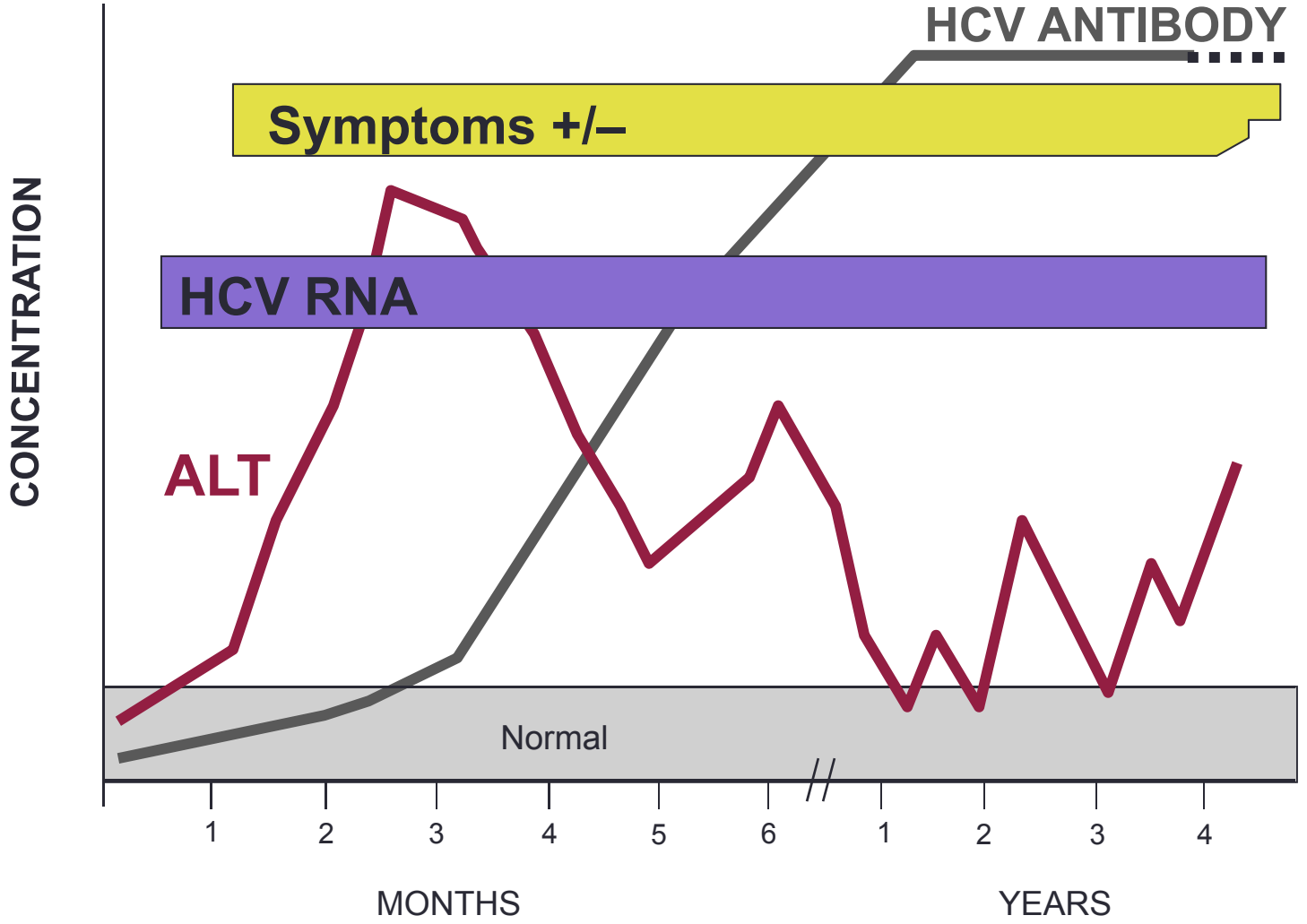


Pattern of Acute HCV Infection with Clearance



MA Martinez

Pattern of Acute Hepatitis C with Progression to Chronic Infection

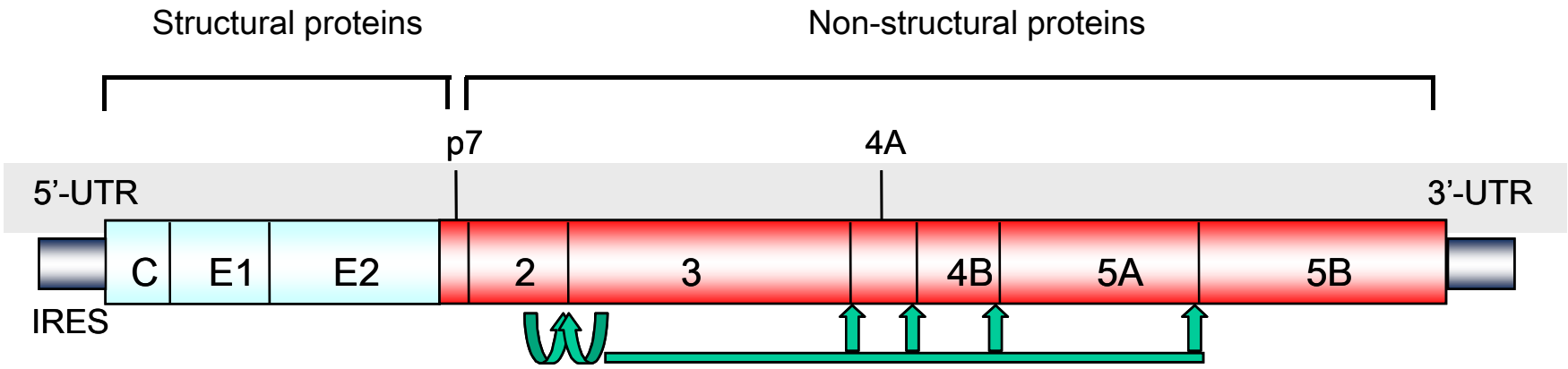


MA Martinez

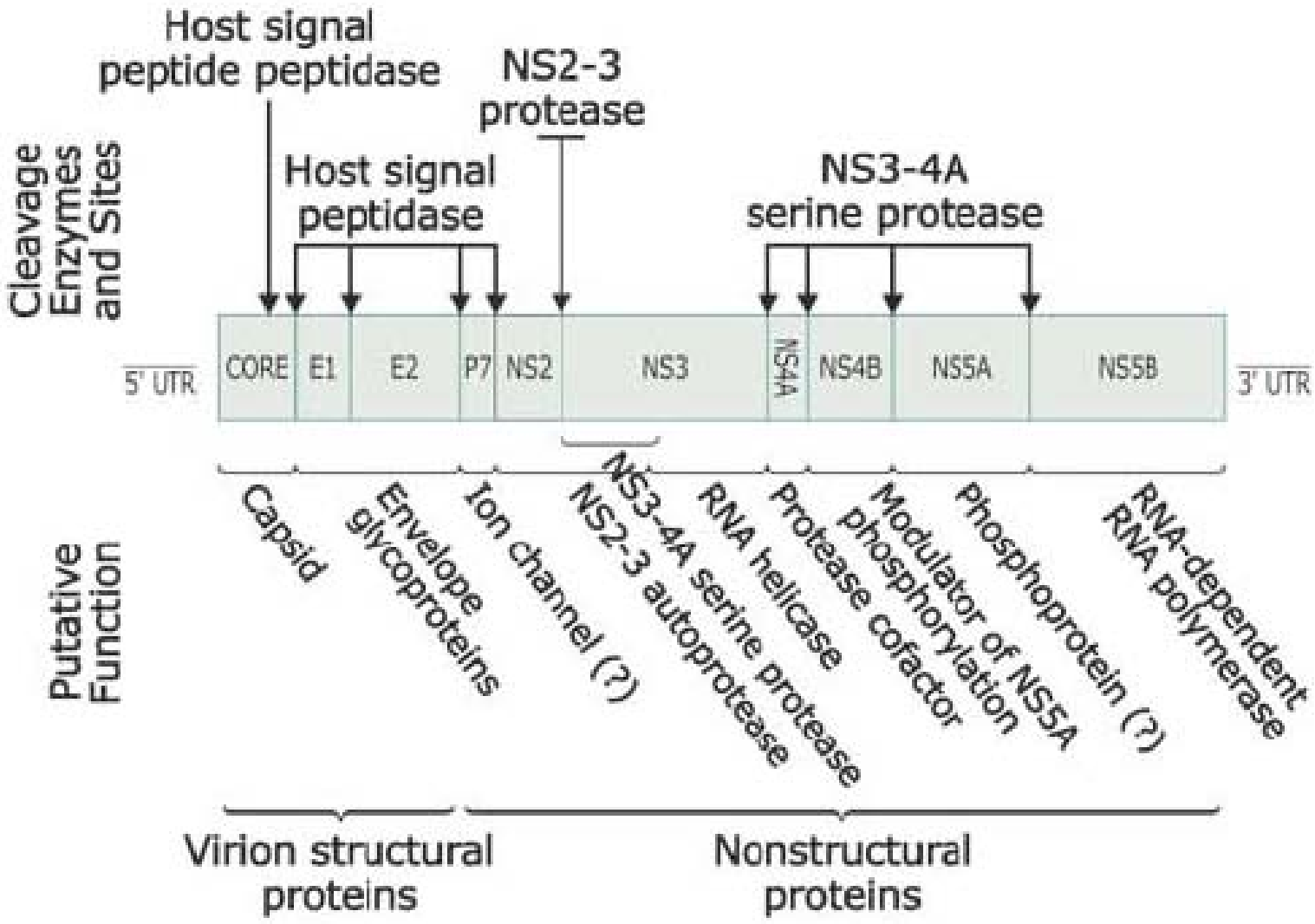
Genomic organization of HCV

Hepacivirus, member of the *Flaviviridae family*:

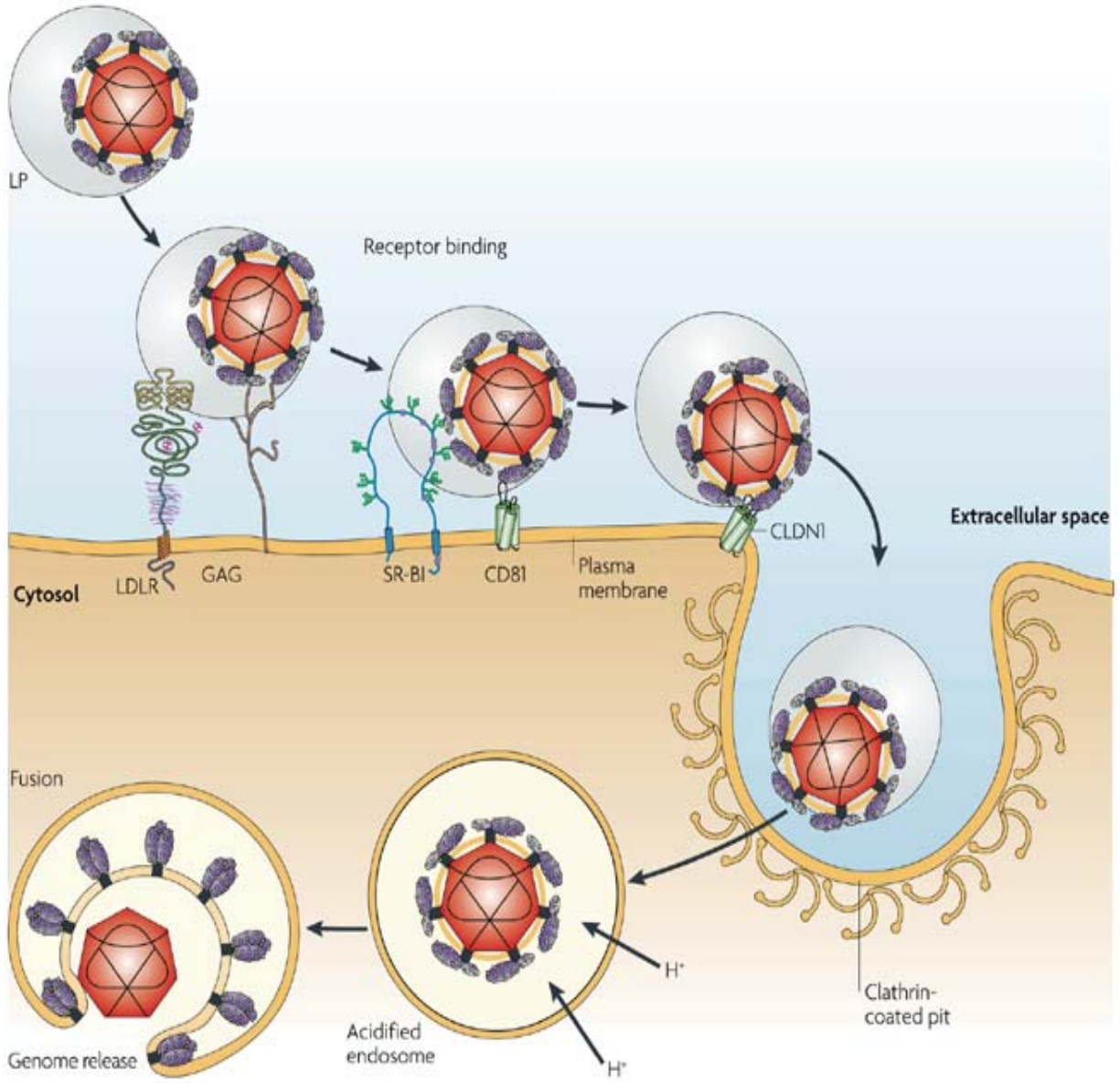
- single stranded RNA of positive polarity and 9,6 Kb in lengh
- Codify for one polyprotein that is proteolytically processed in:
  - 3 structural proteins: Core, E1 y E2.
  - 6 non-structural proteins: NS2, NS3, NS4A y NS4B, NS5A and NS5B.



Known Functions of the HCV Proteins



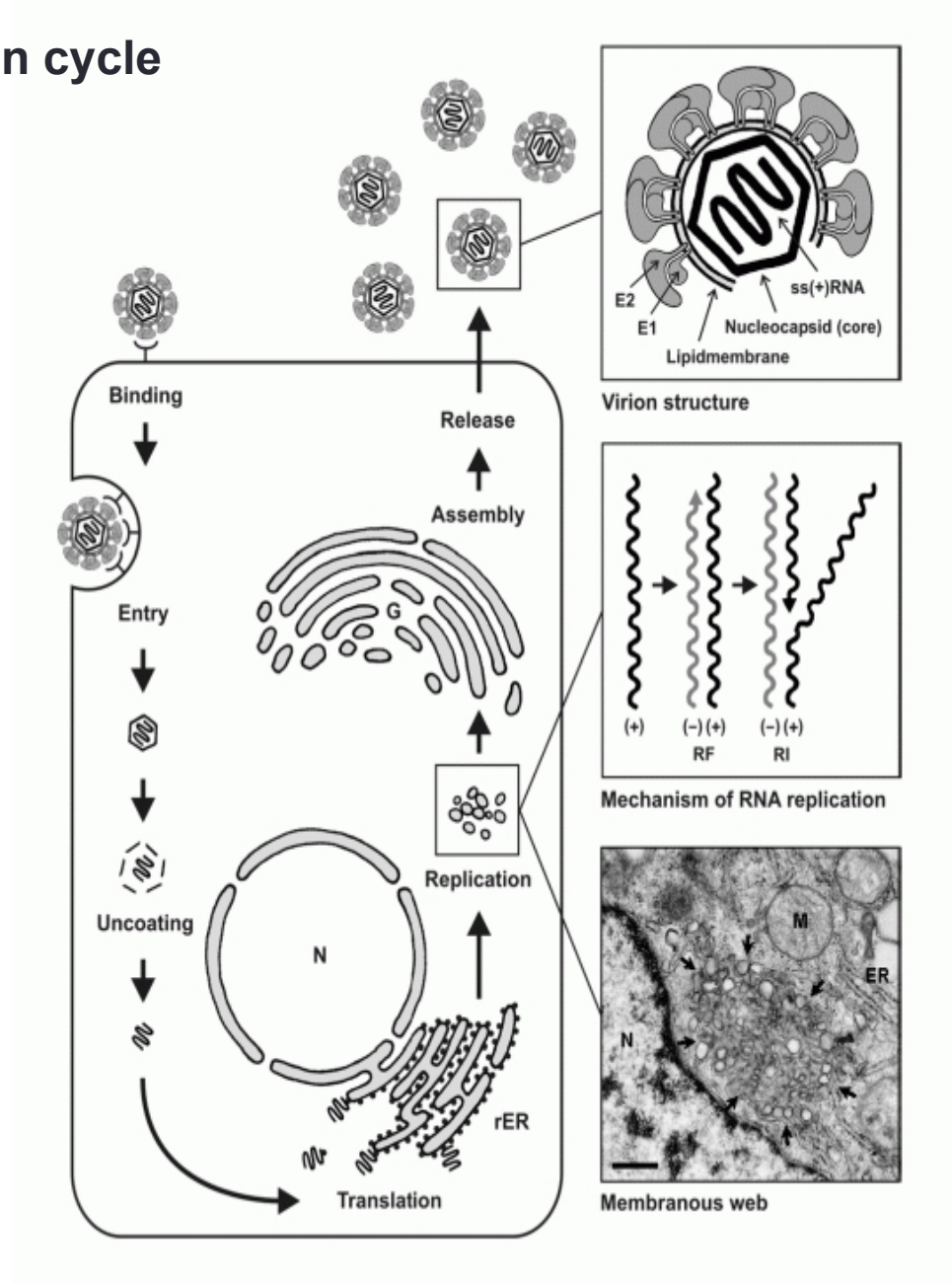
Courtesy of Dr. Charles Rice



Nature Reviews | Microbiology

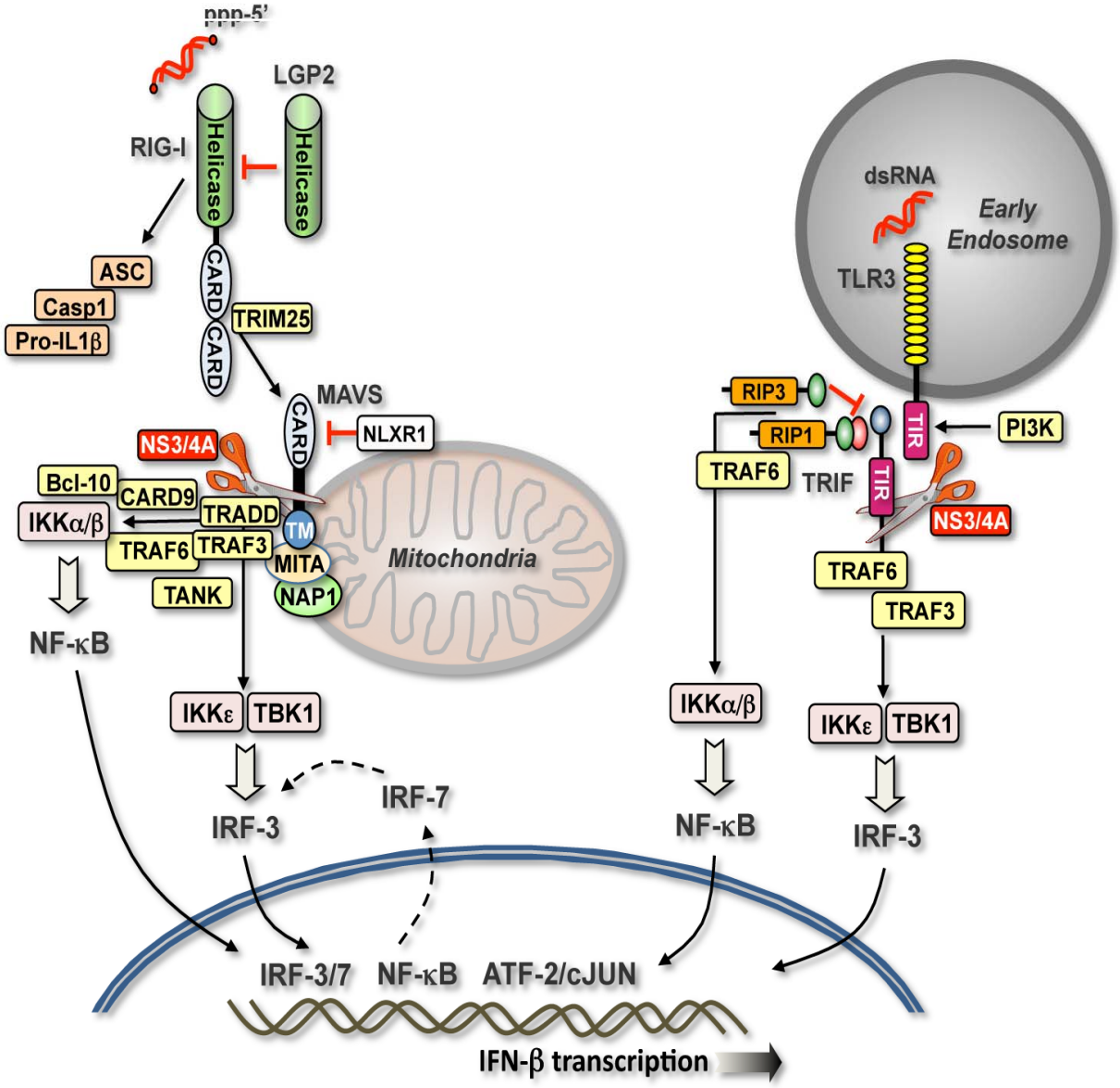
MA Martinez

HCV replication cycle

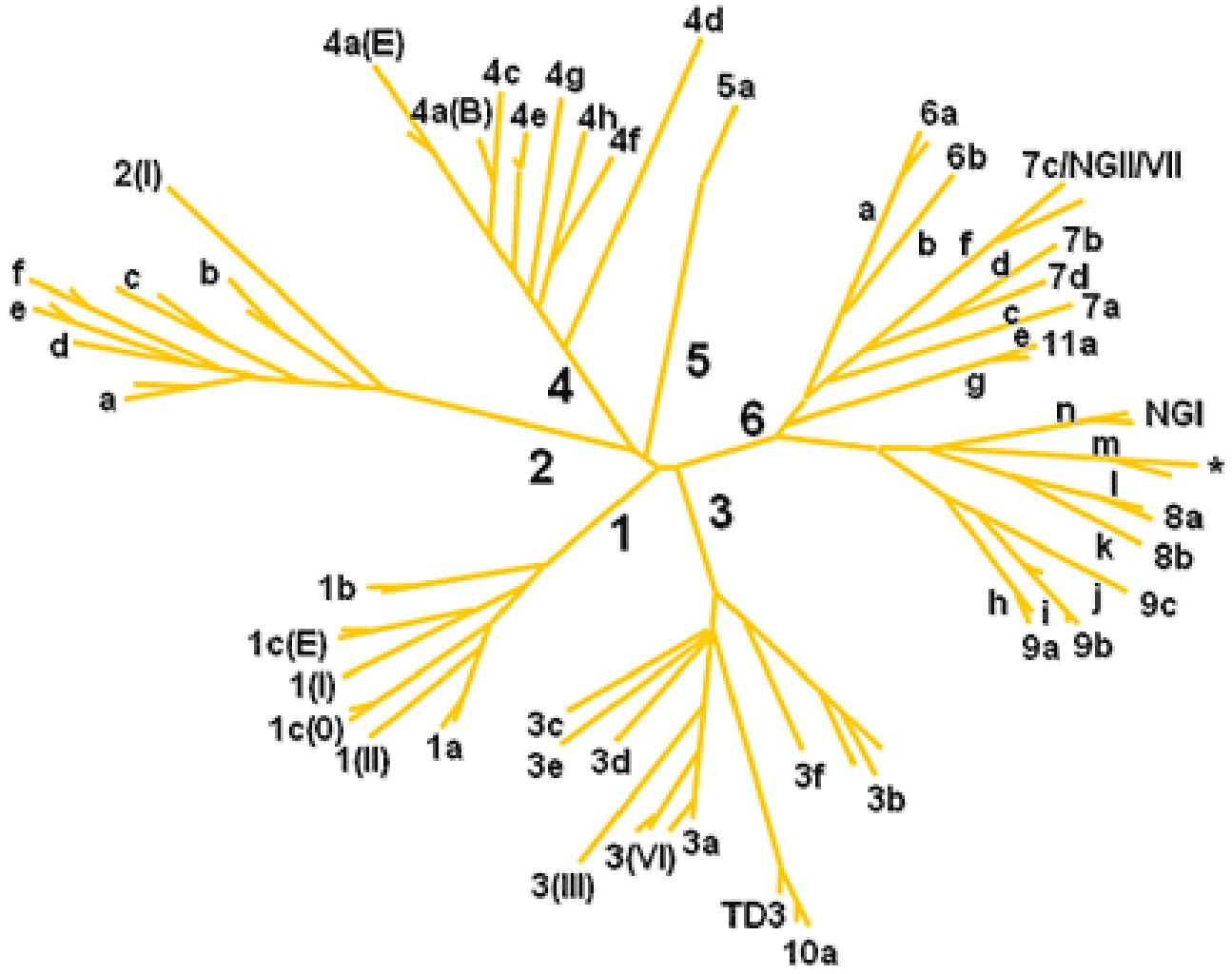


MA Martinez

HCV inhibits cellular IFN synthesis



HCV Genotypes and Subtypes



Genotype

≥ 30% nucleotide difference

25-30% Amino acid difference

Well-established diversity

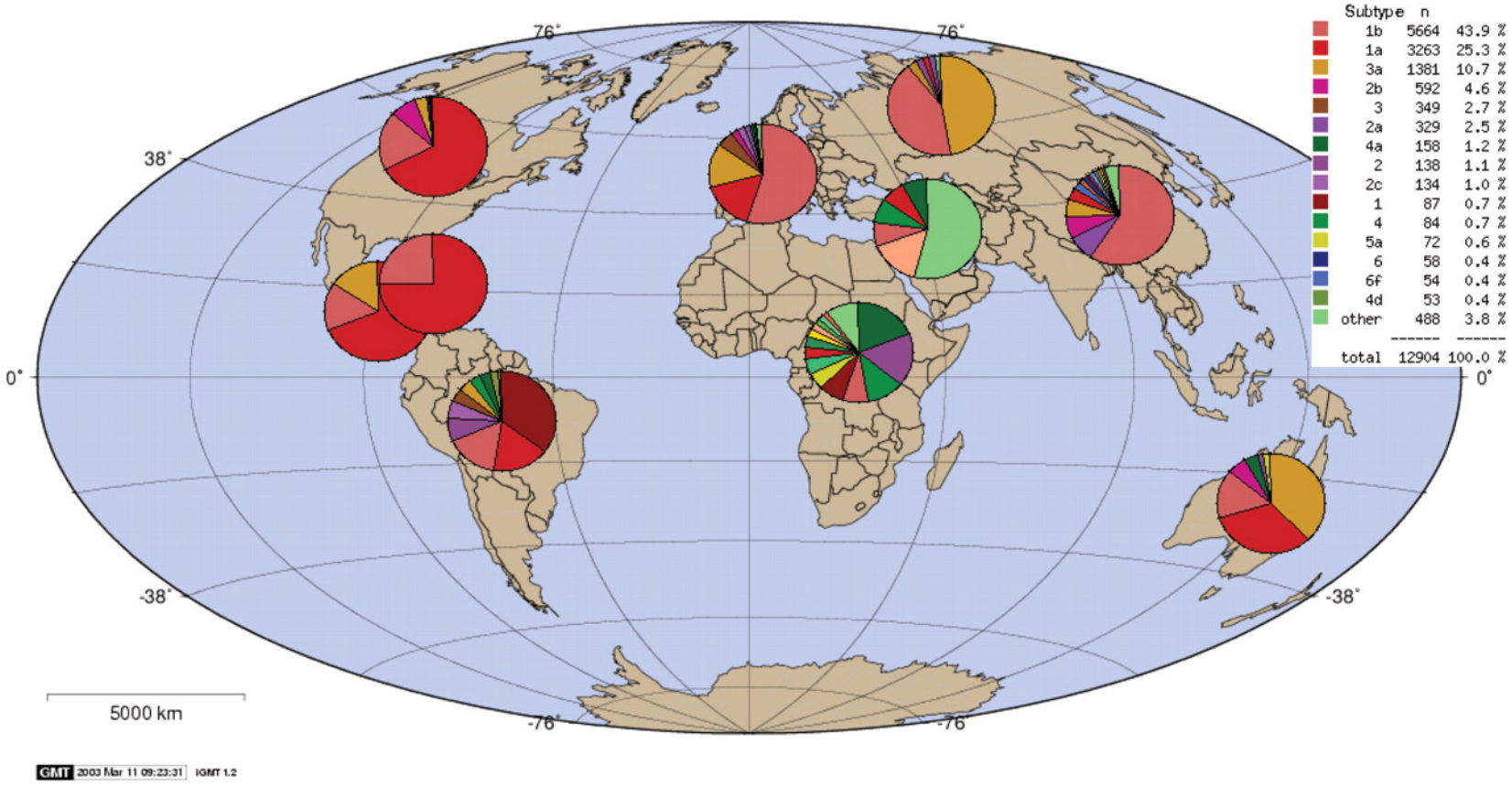
Subtype

~20% nucleotide difference

Quasispecies (individual)
1-5% nucleotide difference

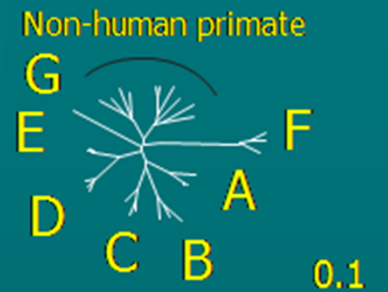
MA Martinez

Global distribution of HCV subtypes

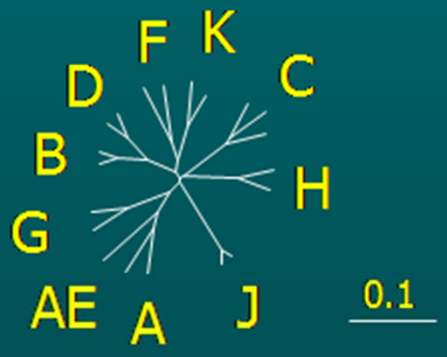


Kuiken C et al. Nucl. Acids Res. 2008;36:D512-D516

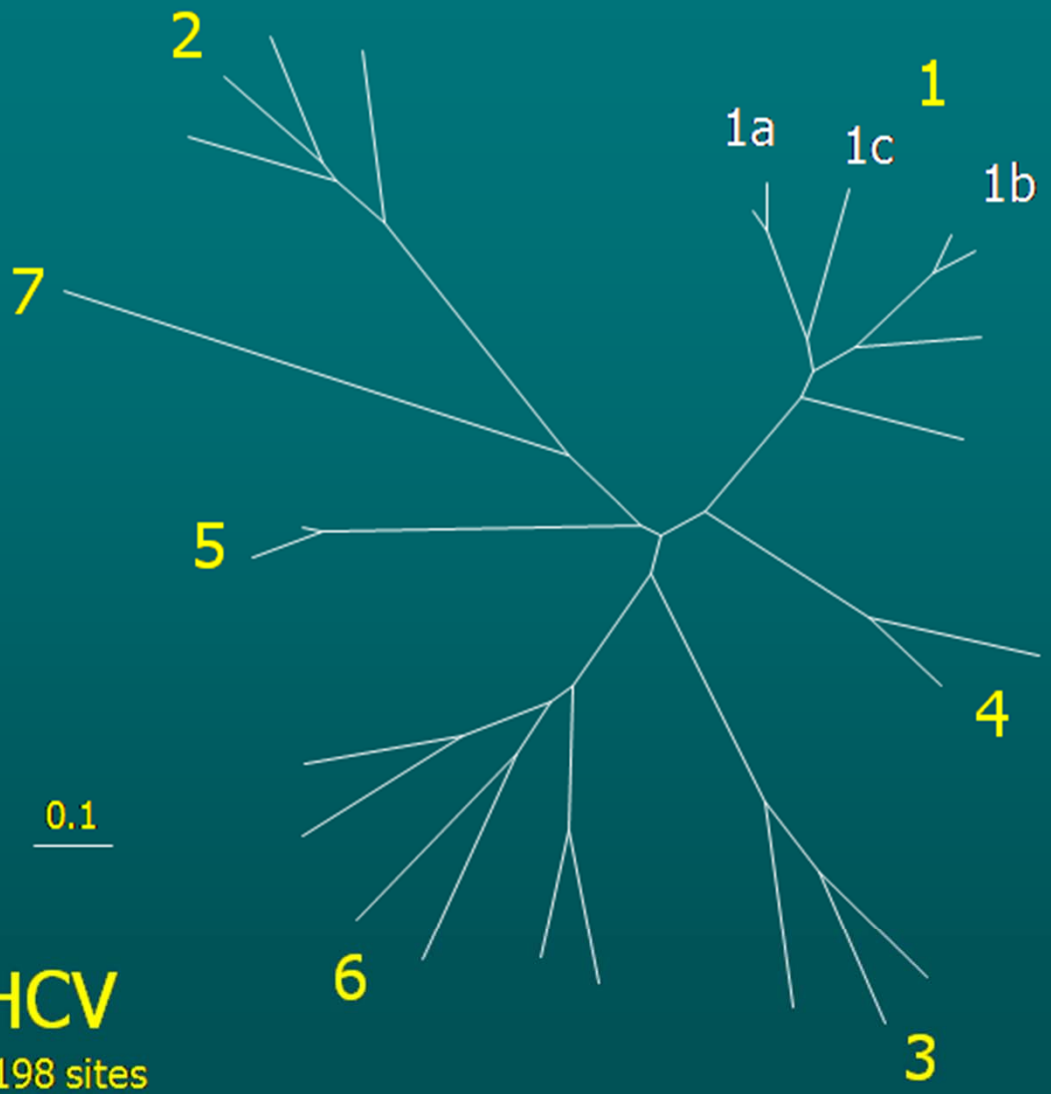
HCV sequences are more genetically diverse than HBV or HIV



HBV
3181 sites



HIV
8316 sites



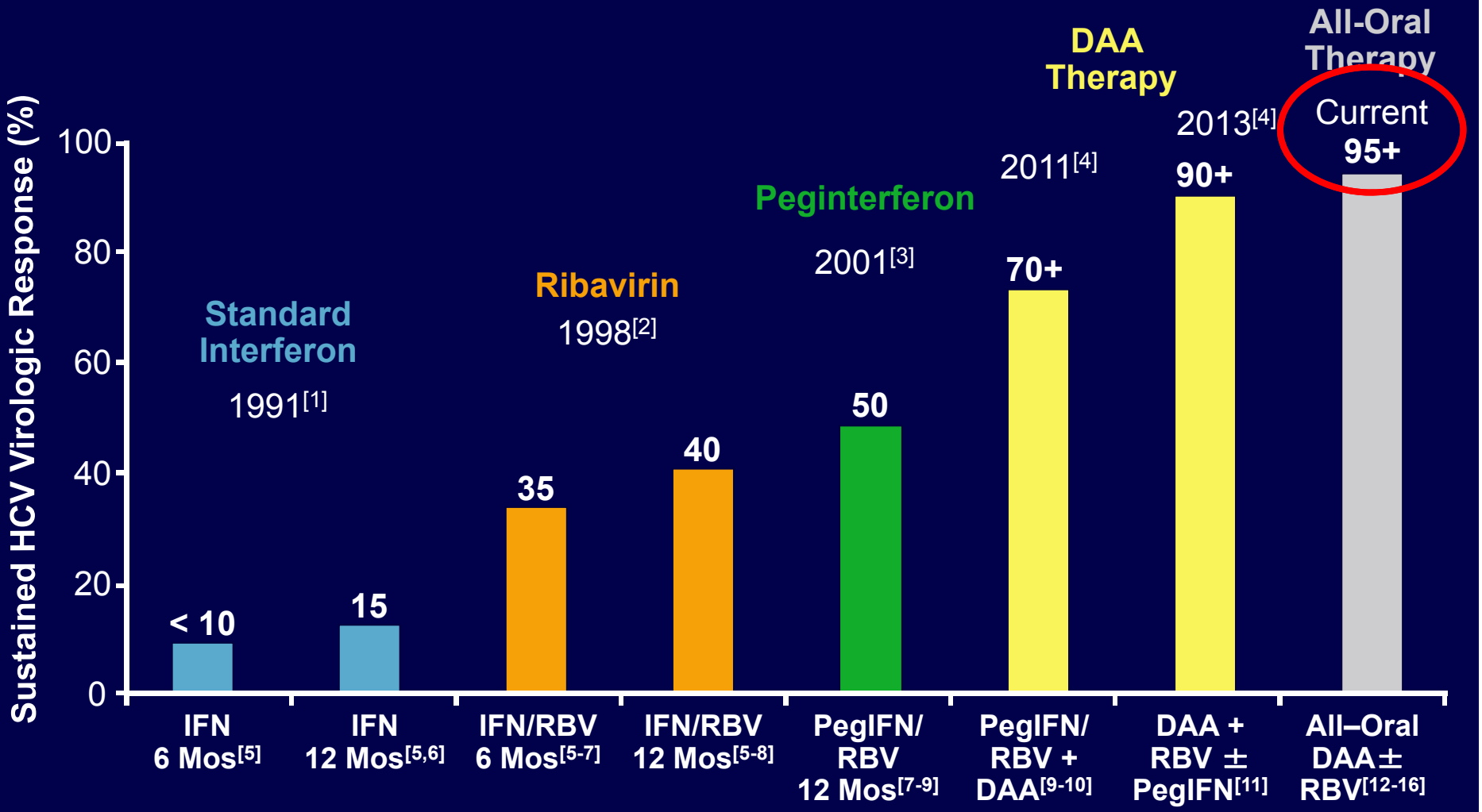
HCV
9198 sites

Ray SC and Thomas DL. *PPID7th* ed. 2009, Figure 154-4

HIV-1 and HCV mutation rate and turnover

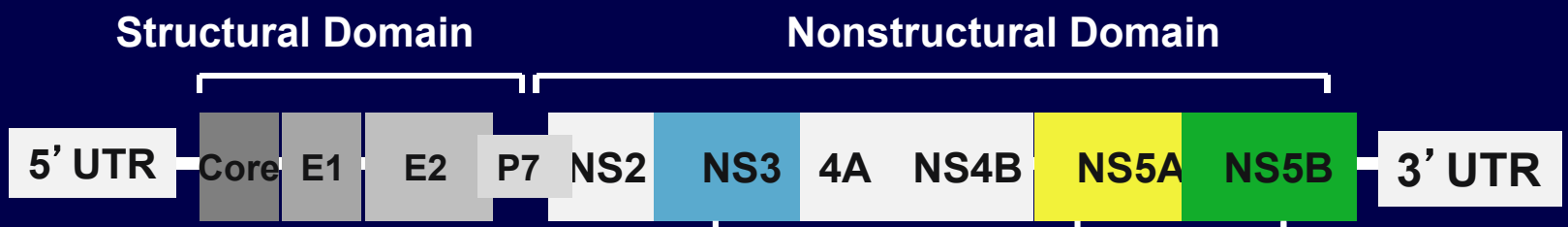
	HIV	HCV
mutations per site per cycle	3.4×10^{-5} (*ex vivo*) (Mansky and Temin J Virol 1995)	2.5×10^{-5} (Ribeiro et al. PLoS Pathogens 2012)
virions per day viral in infected patients	1.0×10^{11} (Ho et al. Nature 1995)	1.3×10^{12} (Neumann et al. Science 1998)

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



References in slidenotes.

Approved DAAs From Multiple Classes: Basis of 2017 Combination HCV Regimens



Protease

Polymerase

Ribavirin (RBV)

NS3 Protease Inhibitors

Grazoprevir (GZR)
Paritaprevir/Ritonavir (PTV/RTV)
Simeprevir (SMV)
*Voxilaprevir (VOX)**
*Glecaprevir (GLE)**

NS5A Replication Complex Inhibitors

Daclatasvir (DCV)
Elbasvir (EBR)
Ledipasvir (LDV)
Ombitasvir (OBV)
Velpatasvir (VEL)
*Pibrentasvir (PIB)**
*Ruzasvir (RZR)**

NS5B NUC Inhibitors

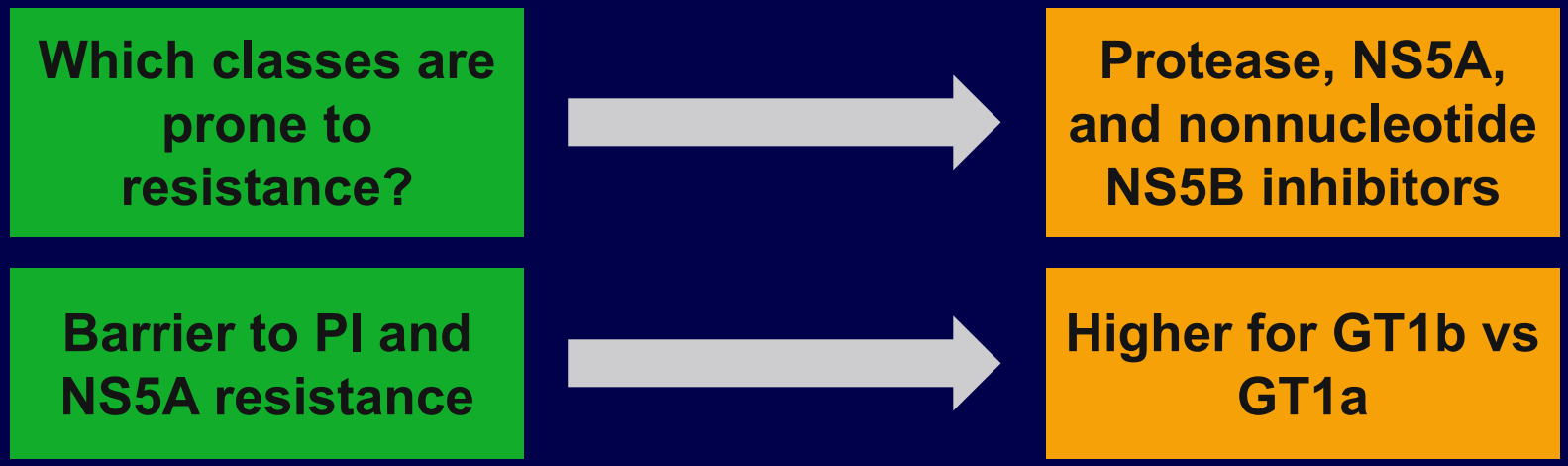
Sofosbuvir (SOF)
*Uprifosbuvir (UPR)**

NS5B Non-NUC Inhibitors

Dasabuvir (DSV)
Radalbuvir (GS-9669)

*Approval in 2017/2018.

Resistance Considerations

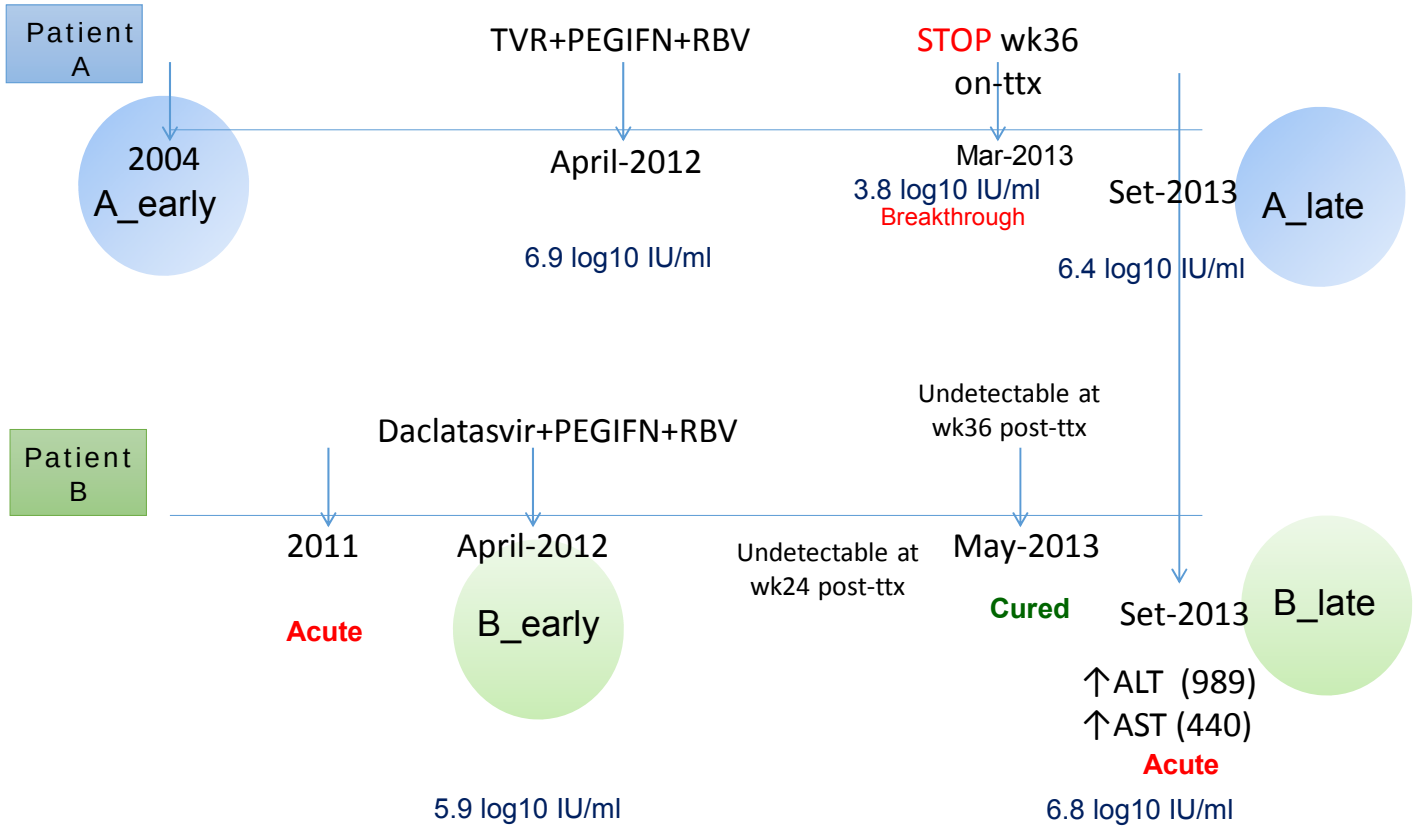


- Most pts with failure of current DAAs have emergent resistance-associated substitutions (RASs)
  - NS5A RASs persist much longer than PI RASs
- 15% of pts have baseline NS5A RASs with variable effects on GT1a response
- Second-generation drugs designed to cover RASs

Slide credit: clinicaloptions.

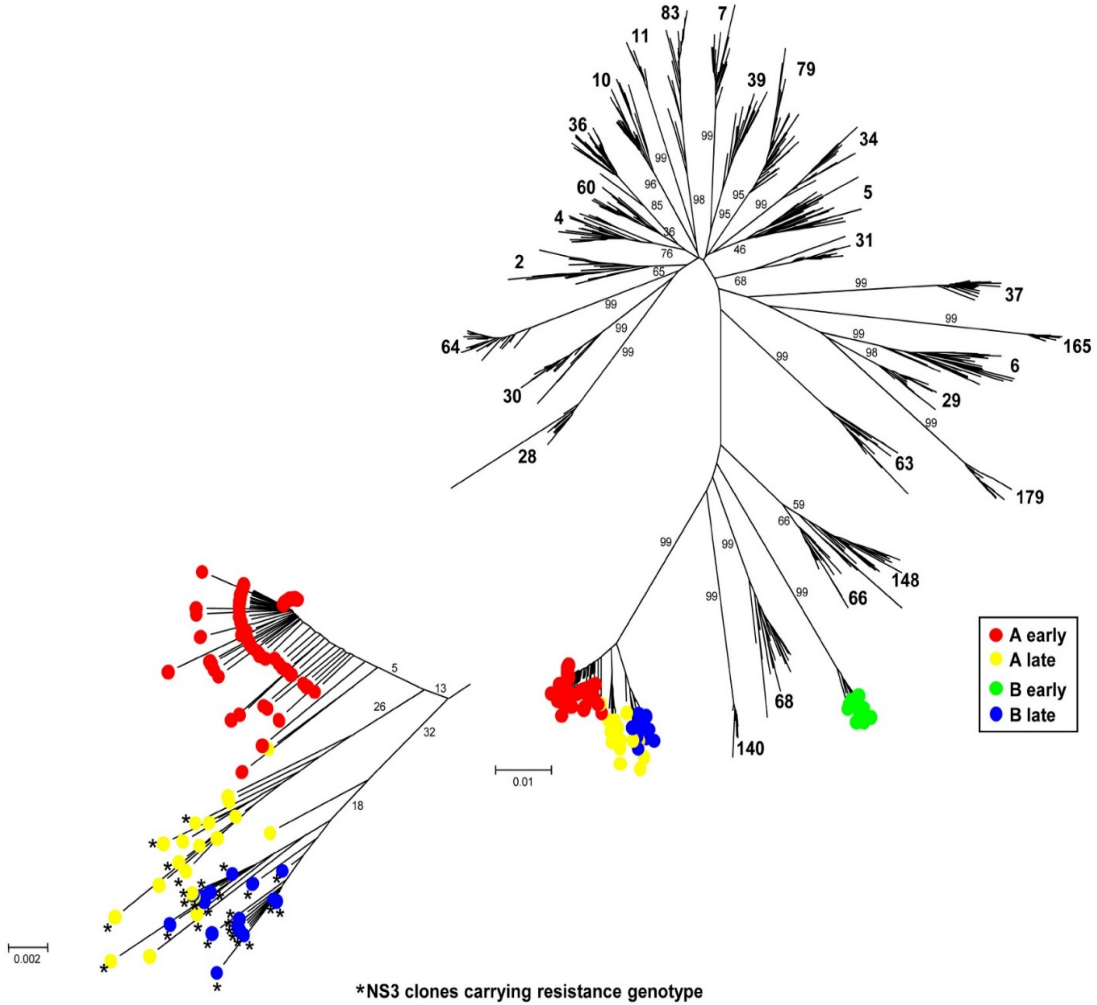
Transmission of DAA resistance

Case report: We documented the first transmission of a DAA resistant variant of HCV from a patient (A) who was treated with Telaprevir to his sexual partner (B)



Franco et al. Gastroenterology (2014)

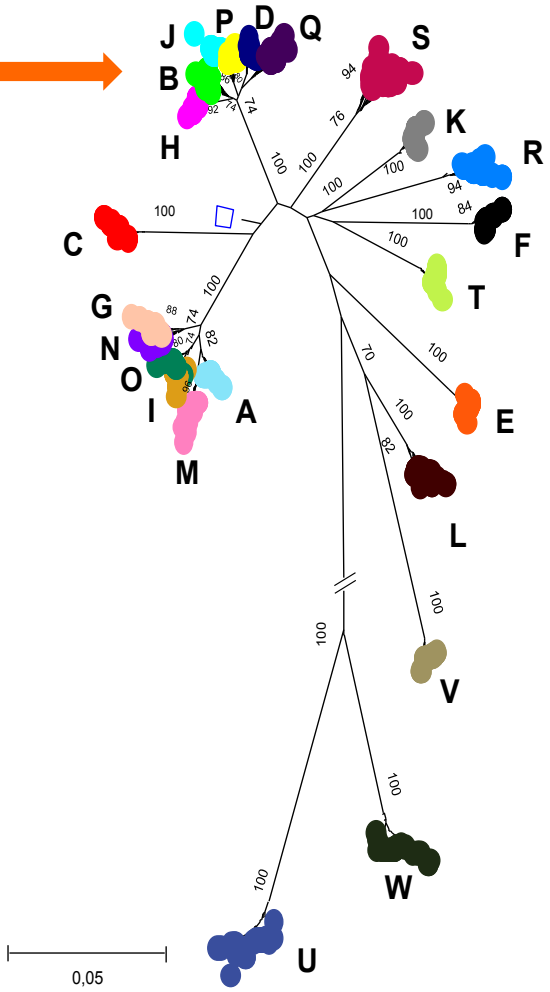
Phylogenetic relationship of HCV NS3 protease sequences obtained from patients A and B



Franco et al. Gastroenterology (2014)

Identified epidemiologic networks of HCV transmission among HIV-1 positive MSM

The transmitted HCV DAA resistant variant belongs to this network

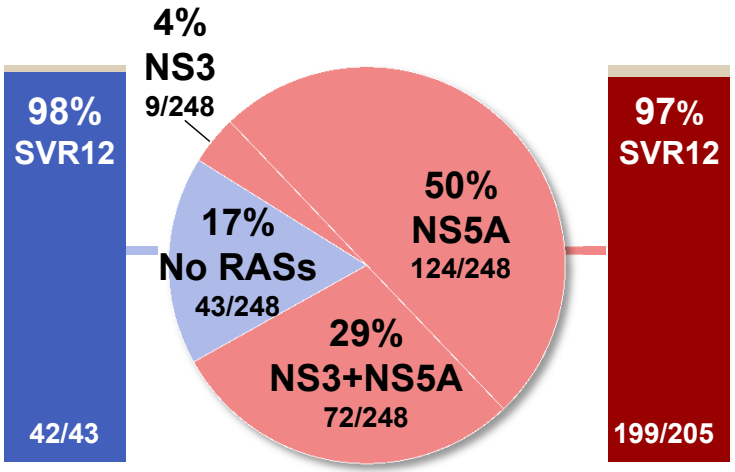


Nevot et al. JVH 2014

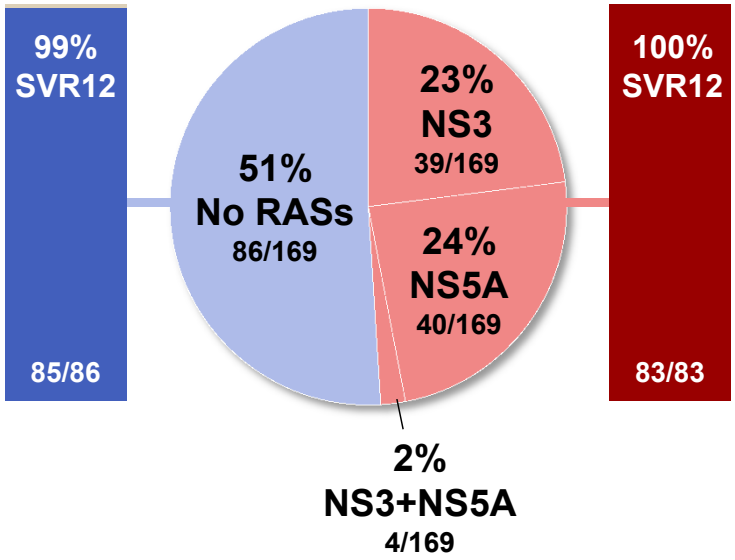
‡

Resistance Analysis of SOF/VEL/VOX for 12 Weeks in DAA-Experienced Patients

POLARIS-1:
DAA-experienced patients who had previously received NS5A inhibitor



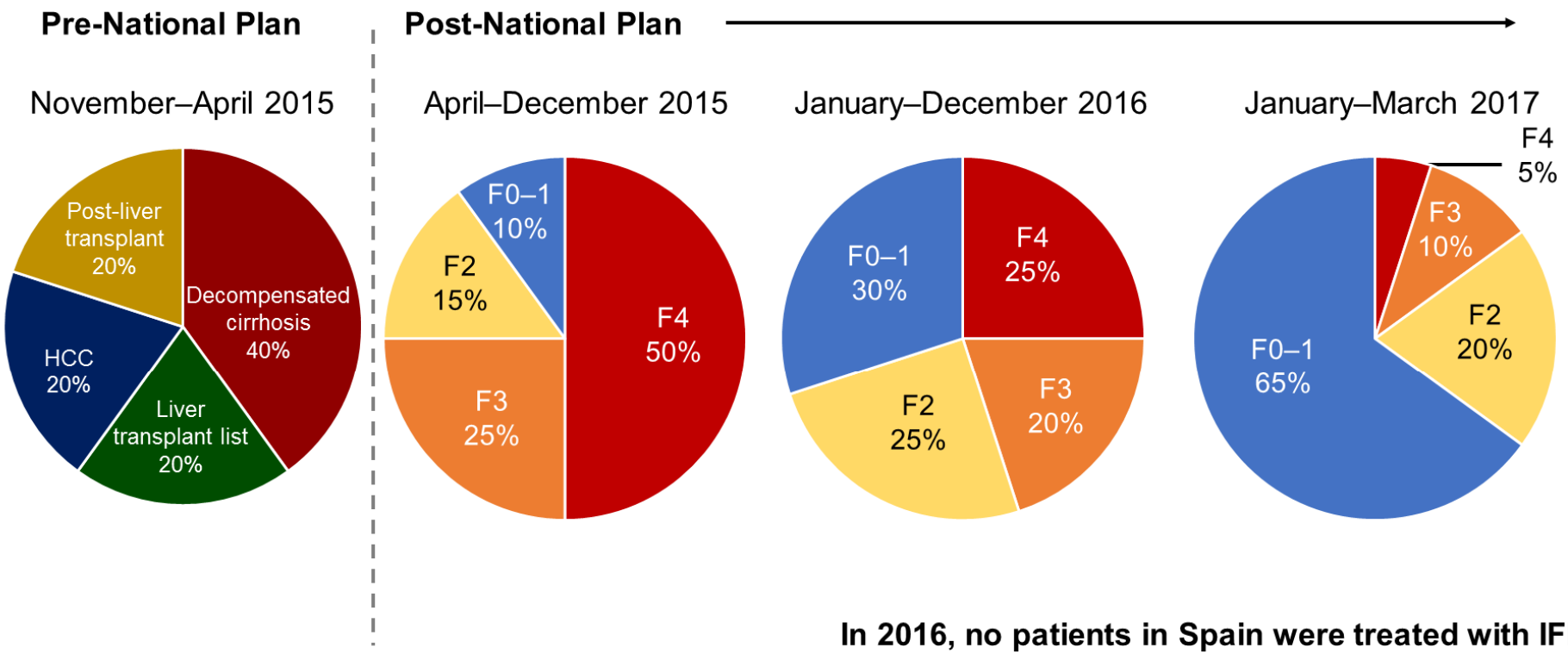
POLARIS-4:
DAA-experienced patients who had not received NS5A inhibitor



High SVR12 rates regardless of presence of baseline RASs in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks

Sarrazin, EASL 2017, THU-248

Change in the epidemilogical profile
Madrid: Impact of the Spanish National Plan



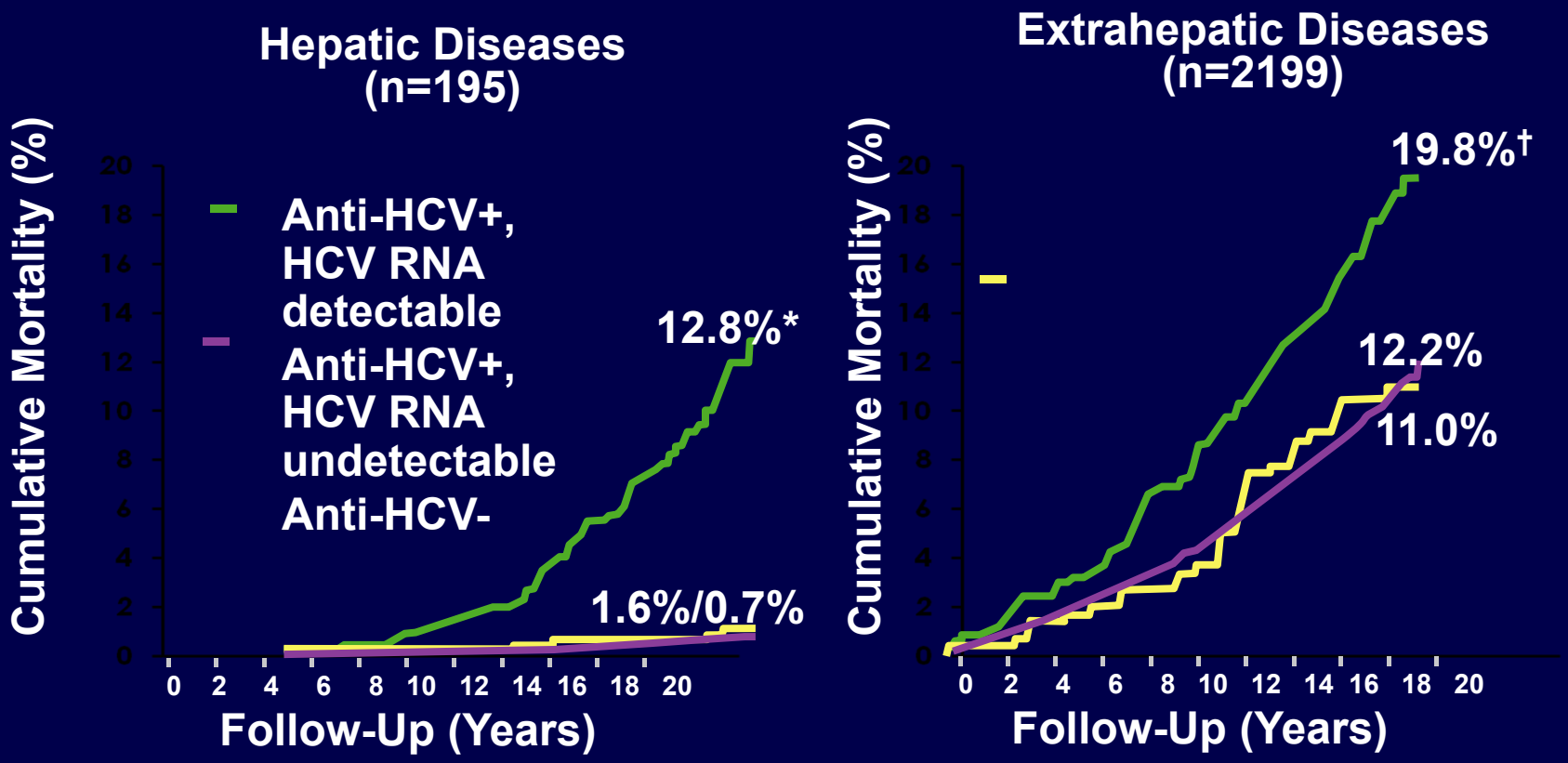
In 2016, no patients in Spain were treated with IFN

SaludMadrid. Available at: http://www.madrid.org/cs/Satellite?pagename=PortalSalud/Page/PTSA_home (accessed April 2017); Data courtesy of Calleja J-L

June 21, 2017: HCV treatment approved* for all HCV-infected subjects in Spain

* Approved but not funded yet in all Autonomous Communities

REVEAL-HCV Study Mortality: Hepatic Diseases and Extrahepatic Diseases



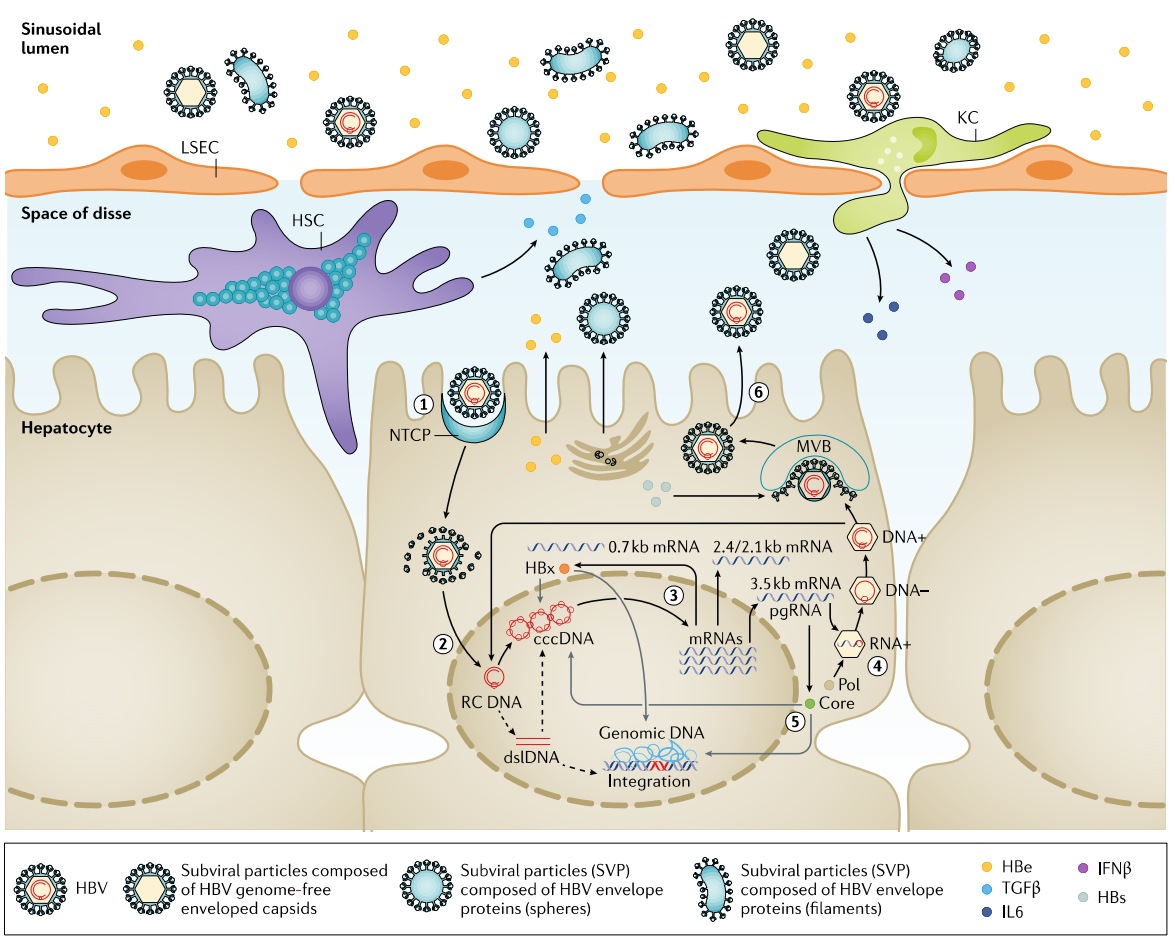
*P<0.001 for comparison among all 3 groups and P<0.001 for HCV RNA detectable versus undetectable.

†P<0.001 for comparison among all 3 groups and P=0.002 for HCV RNA detectable versus undetectable.

Lee M-H, et al. *J Infect Dis*. 2012; 206:469-477.

HBV eradication

Drug class	Actions
HBV entry inhibitors	Lipopeptides mimicking pre-S1 domain competing with Dane particle for binding to NTCP
Targeting cccDNA	Damage and destruction of cccDNA via cytokines or cccDNA- sequence-specific nucleases. Functional silencing via modulation of host cellular epigenetic-modifying enzymes by cytokines or inhibition of viral protein function.
HBV mRNAs	Small-interfering RNA approaches or antisense oligonucleotides to block viral replication and viral protein expression.
HBV polymerase inhibitors	Reverse transcriptase inhibitors of the nucleos(t)ide analogue family are part of the standard of care. RNAseH inhibitors are in preclinical evaluation .
Core modulators	Nucleocapsid assembly and pgRNA packaging. Capsid assembly modulators can affect nucleocapsid assembly, pgRNA encapsidation, and the nuclear functions of HBc (cccDNA regulation and interferon stimulated gene expression
Egress inhibitors	Phosphorothioate oligonucleotides inhibiting HBsAg release and monoclonal antibodies to decrease circulating HBsAg load are under evaluation



Revill, Testoni, Locarnini and Zoulim. Nat Rev Gastroenterol 2016

HBV eradication

Box 1 | **Unanswered questions in HBV virology**

- What are the other possible additional receptors or co-receptors required for viral entry?
- What are the host and virological factors that regulate HBV replication? Identifying factors involved in cccDNA synthesis, stability and transcriptional regulation across HBV genotypes and host ethnicities is crucial. The discovery that tyrosyl-DNA phosphodiesterase 2 is one of the cellular enzymes involved in the first step of cccDNA formation from incoming relaxed circular DNA by removing the phosphodiester bond between the viral polymerase and viral minus strand DNA should pave the way for future studies of the biology of cccDNA[30].
- Does cccDNA need to be eliminated, or will rendering it transcriptionally inactive be sufficient for effective cure? For example, since the HBx protein regulates transcription from the cccDNA minichromosome[39,106], would inactivation of HBx through the development of specific anti-HBx compounds be sufficient to prevent transcription[52]?
- Would the elimination of a replication competent virus be sufficient to result in the resolution or reversal of established liver disease?
- Can a functional cure be promoted in the setting of potent antiviral therapy? This question points to the use of potent antiviral therapy to deplete the pool of cccDNA and earlier treatment intervention before the establishment of precancerous molecular damage in infected hepatocytes, that is, treating at the stage of so-called immunotolerance[42,107,108].

cccDNA, covelantly closed circular DNA; HBx, hepatitis B x protein.

Conclusions

- 3 important diseases with overlapping epidemiology
- HIV is the great scapist
  - Diversity
    - HIV
    - HLA
  - Integrated DNA
  - Env glycosylation
  - GALT damage
  - Inflammaging
- No reservoir in HCV → cure (global eradication?) ongoing
- HBV has a reservoir → promising pipeline

Gràcies!

Fundació Glòria Soler

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Ministerio de Economía y Competitividad

Instituto de Salud Carlos III

RETIC-RIS

Thanks for the slides to :

Christian Brander
Javier Martínez Picado
Miguel Ángel Martínez
Júlia Garcia-Prado
Ester Ballana
Josep Maria Llibre