INTRODUCTION TO HIV PATHOPHYSIOLOGY

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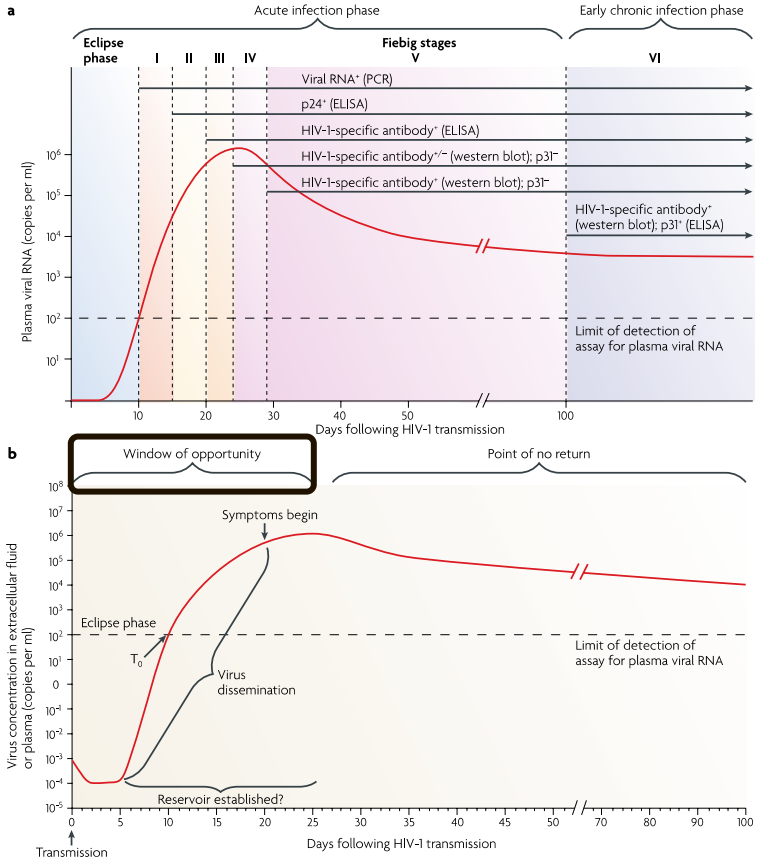
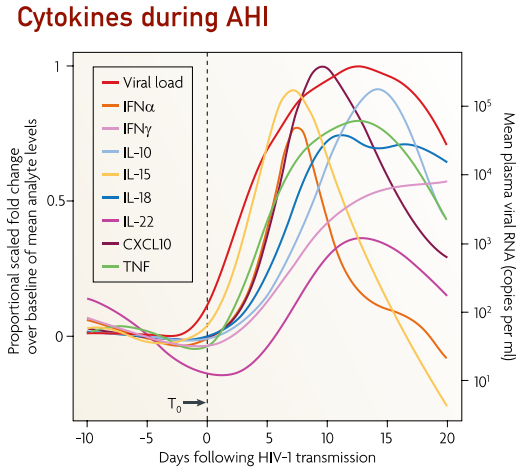
DISCLOSURES

- 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

ACUTE HIV-1 INFECTION





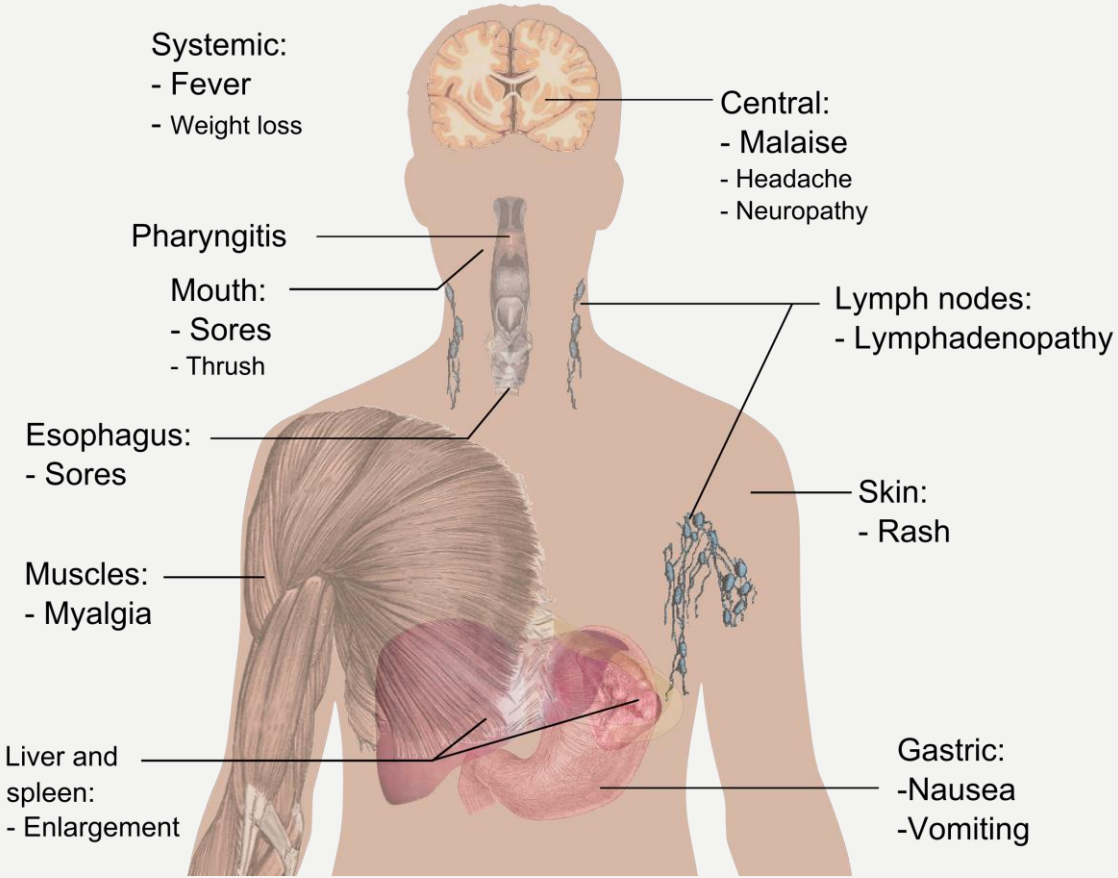
Acute: 0 - 100 days

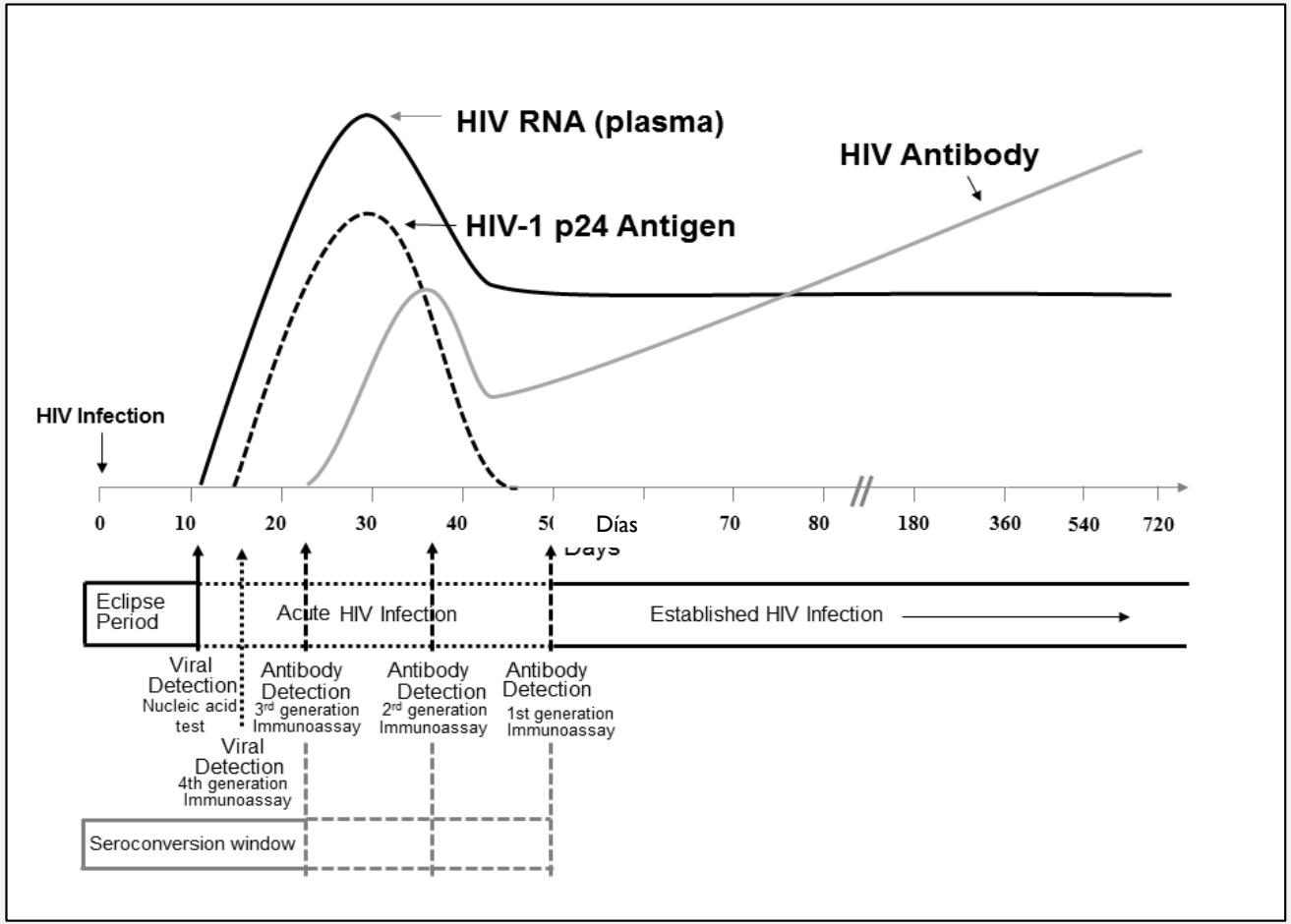
Recent: 0 - 6 months

McMichael A, et al. 2010, Nat Rev Immunol

Main symptoms of

Acute HIV infection

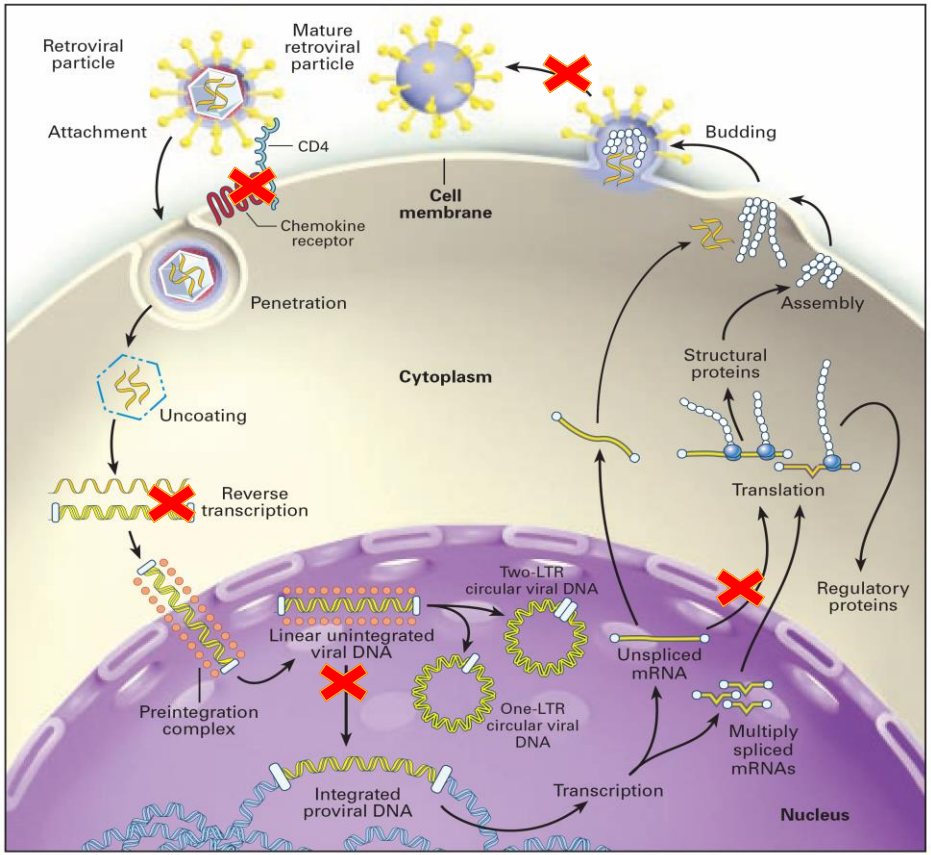



HIV RNA (plasma)
HIV Antibody
HIV-1 p24 Antigen
HIV Infection
0
10
20
30
40
50
Días
70
80
180
360
540
720
Eclipse Period
Acute HIV Infection
Established HIV Infection
Viral Detection
Nucleic acid test
Antibody Detection
3rd generation Immunoassay
Antibody Detection
2nd generation Immunoassay
Antibody 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 LIFE CYCLE AND ART

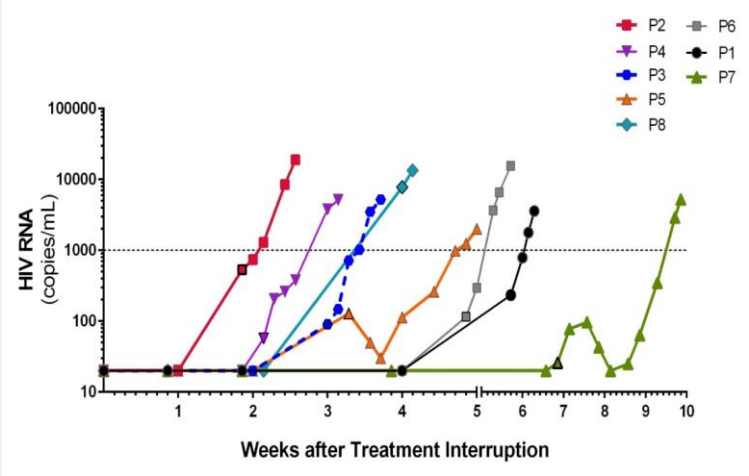


VIRAL LOAD FOLLOWING TREATMENT INTERRUPTION

- 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.

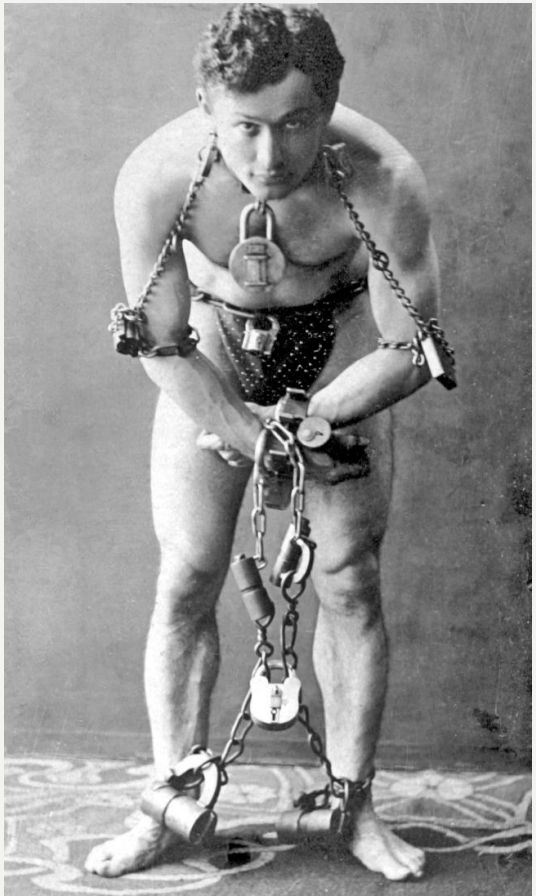
- At least 30% of individuals will have delayed time to VL rebound (VL<50 at 24 w).
- Proceed to stage 2 if ≥ 1 person has VL <50 c/ml at week 12.



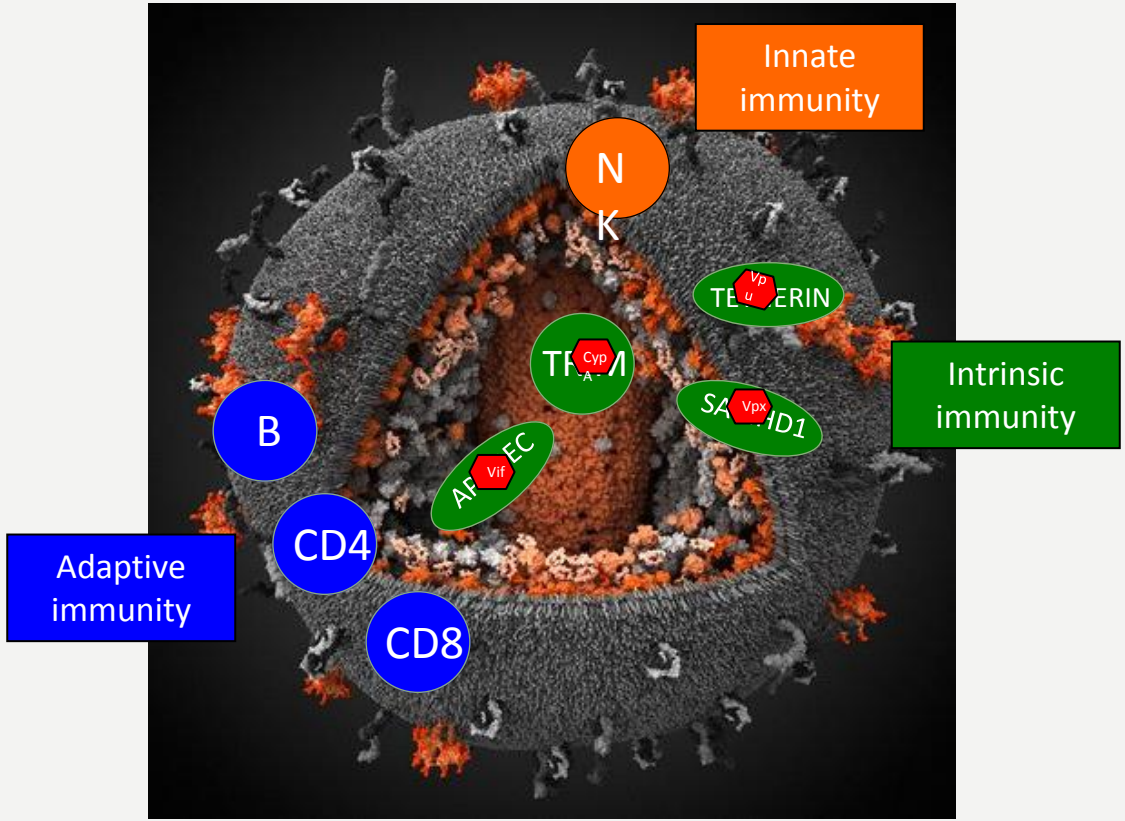
Median time to viral rebound: 26 days (range 13-48)
Highest VL at rebound (median): 5169 (2005 – 13462)

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

HIV is the greatest escapist

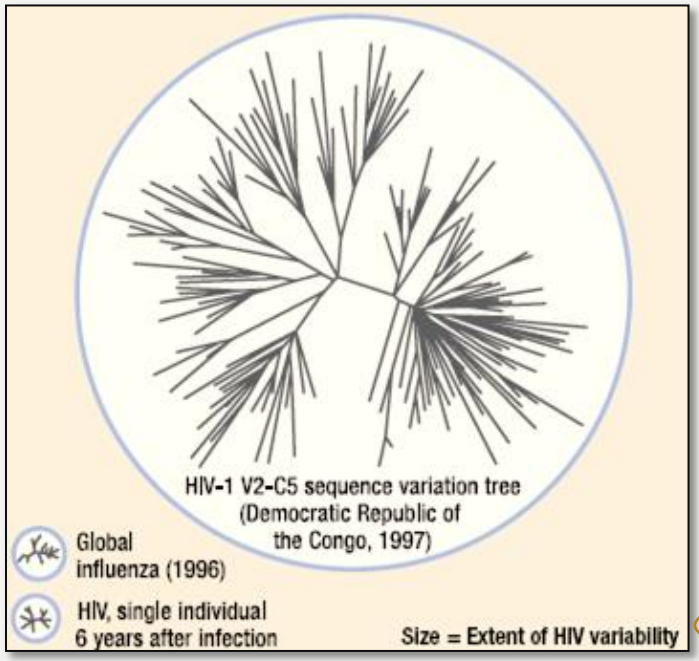


HIV-1 Strategies to counteract host immunity

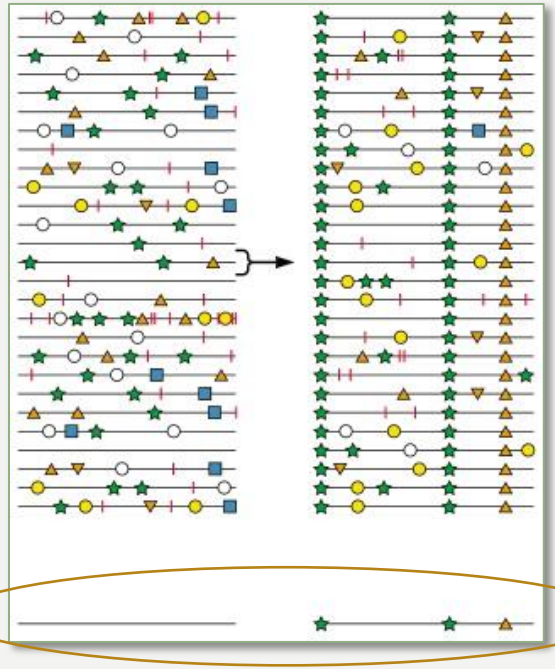


HUGE GENETIC DIVERSITY

Population level



Individual level

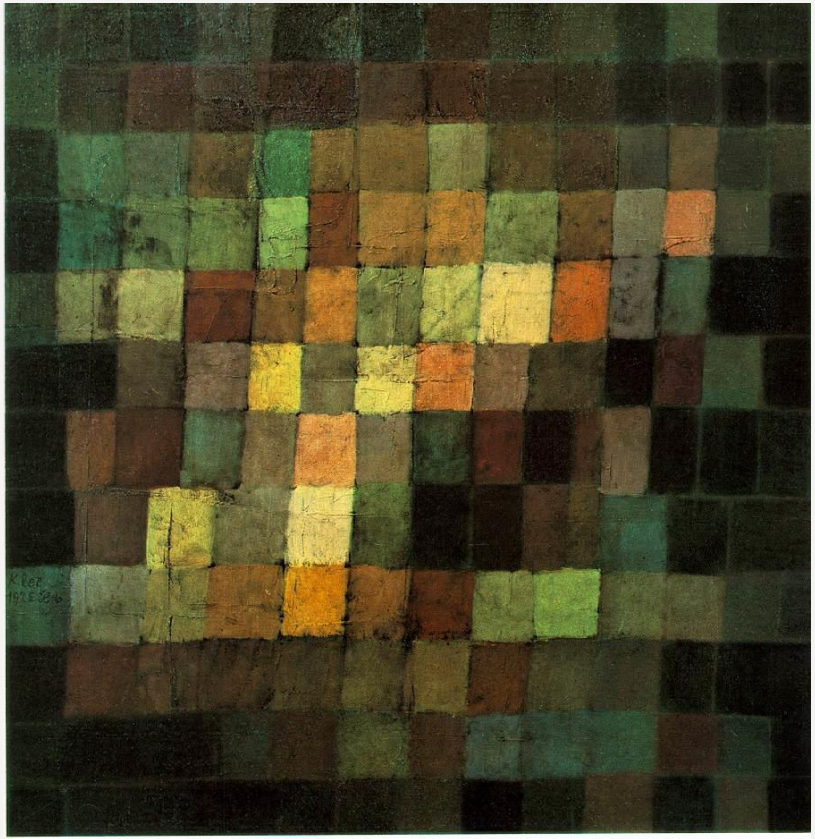


Deep sequencing

Sanger sequencing

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

1. High replication rate: 10^{9-12} 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

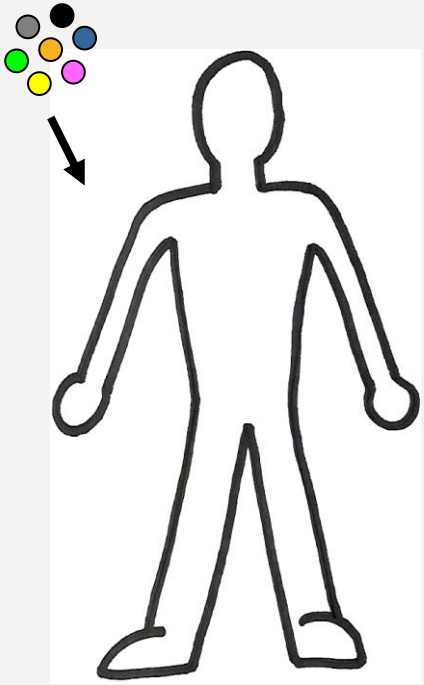


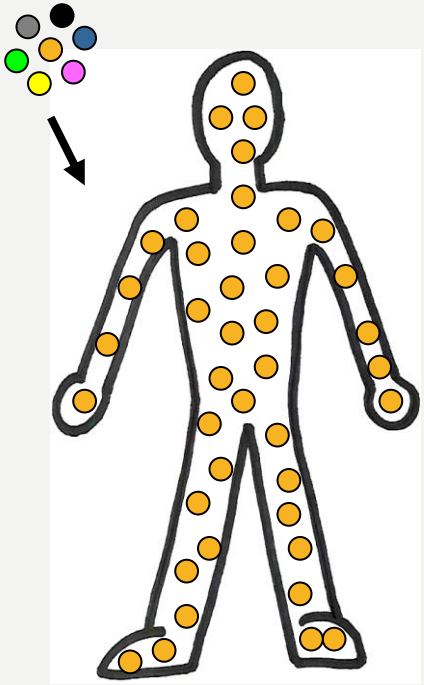
QUASISPECIES

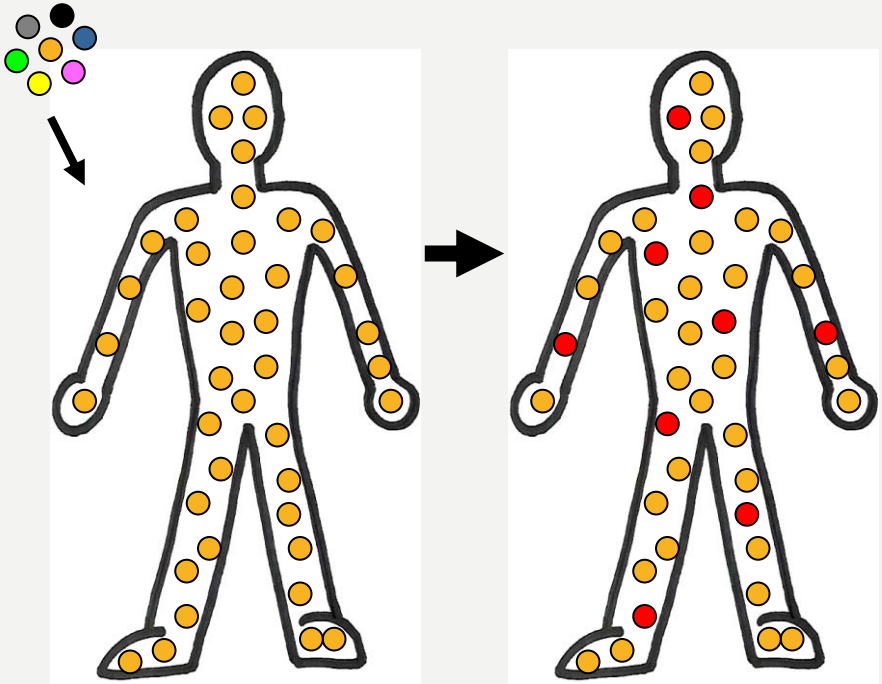
"A population of viruses that share a common origin but which have distinct genomic sequences as a result from mutation, drift and the impact of selection"

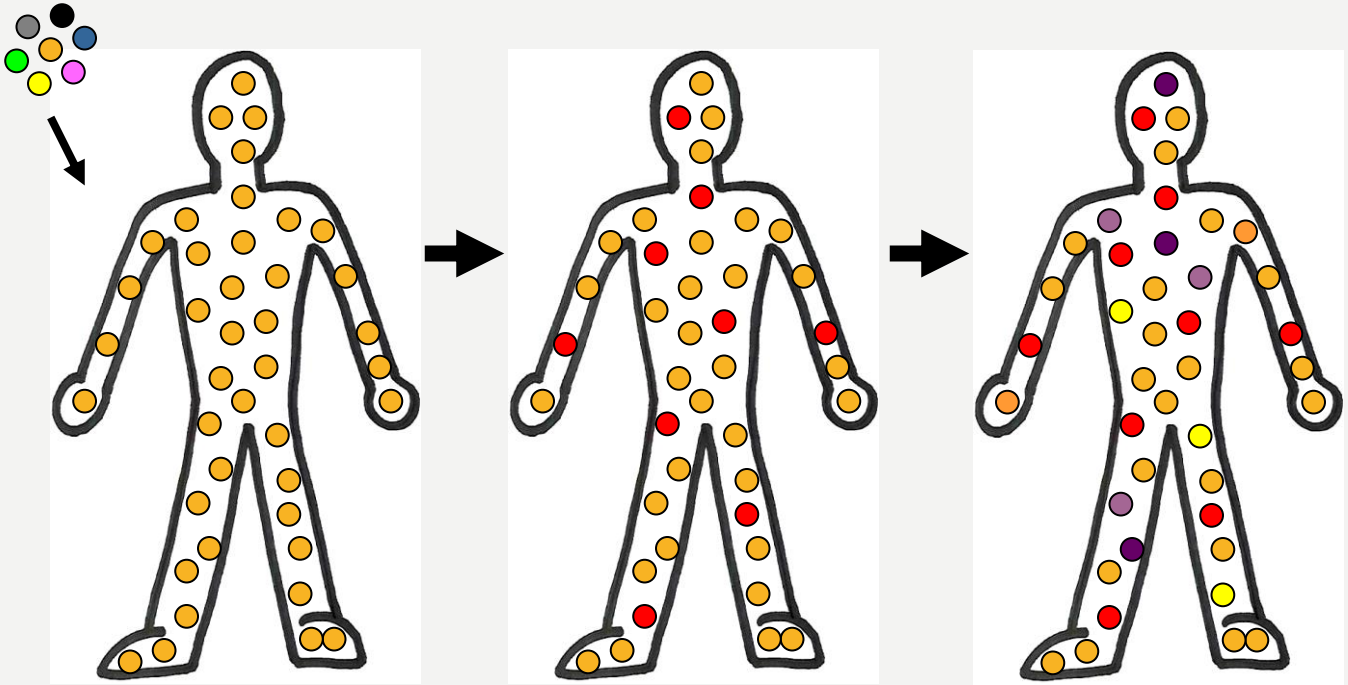
In ARV-naïve subjects chronically infected with a "wild-type" HIV-1

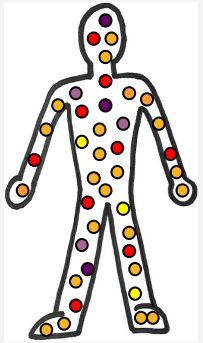
- All non-deletereous single mutants likely preexist
- Few double mutants preexist
- Almost no triple mutants are expected

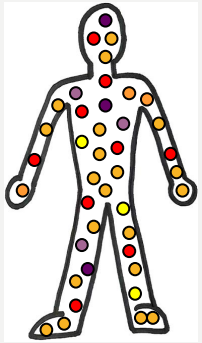




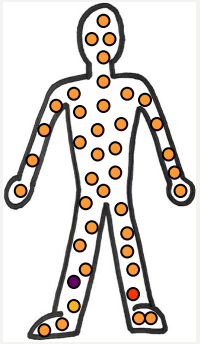


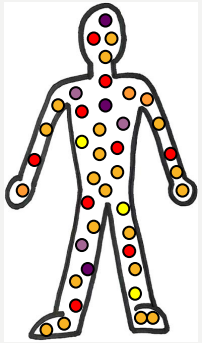




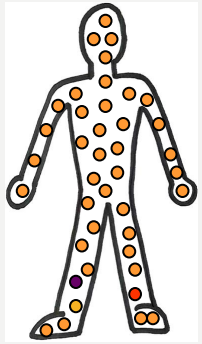


Pressure ↑

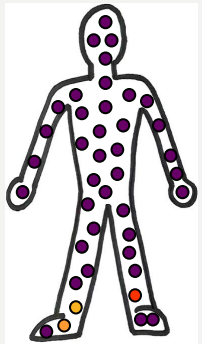


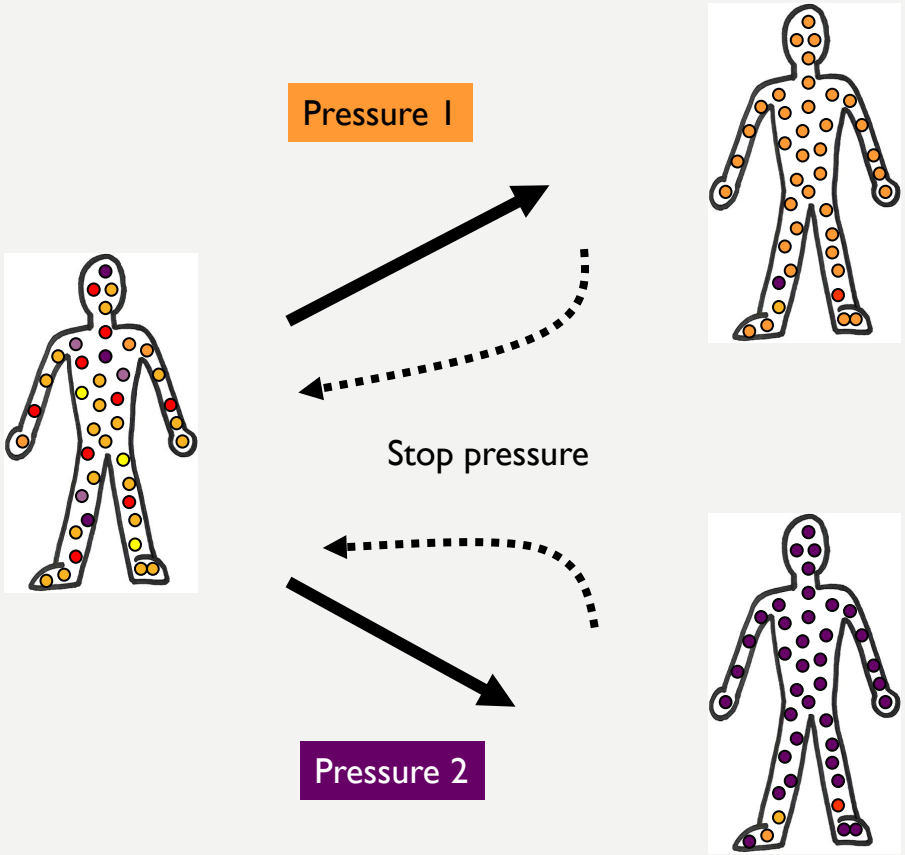


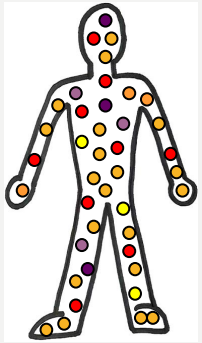
Pressure 1



Pressure 2

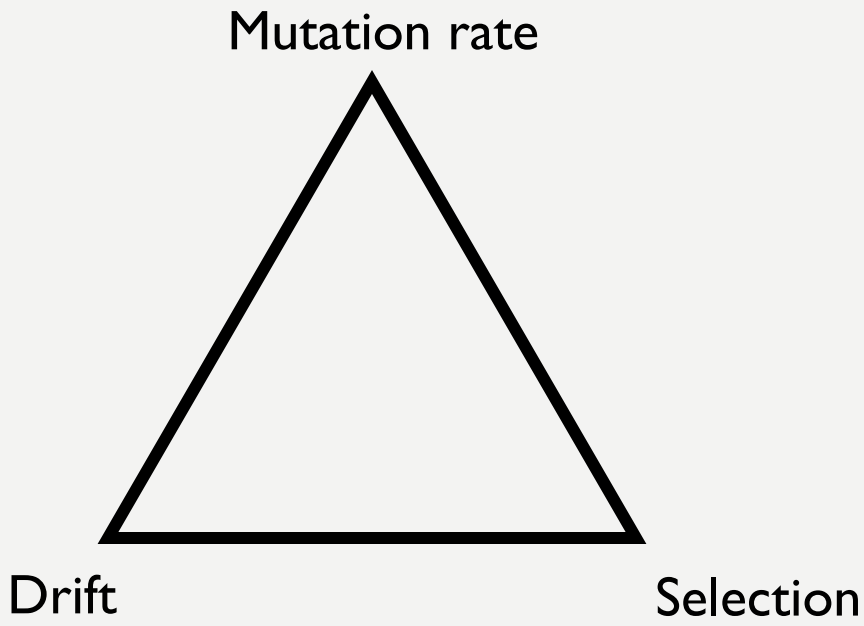



Pressure 1
Stop pressure
Pressure 2

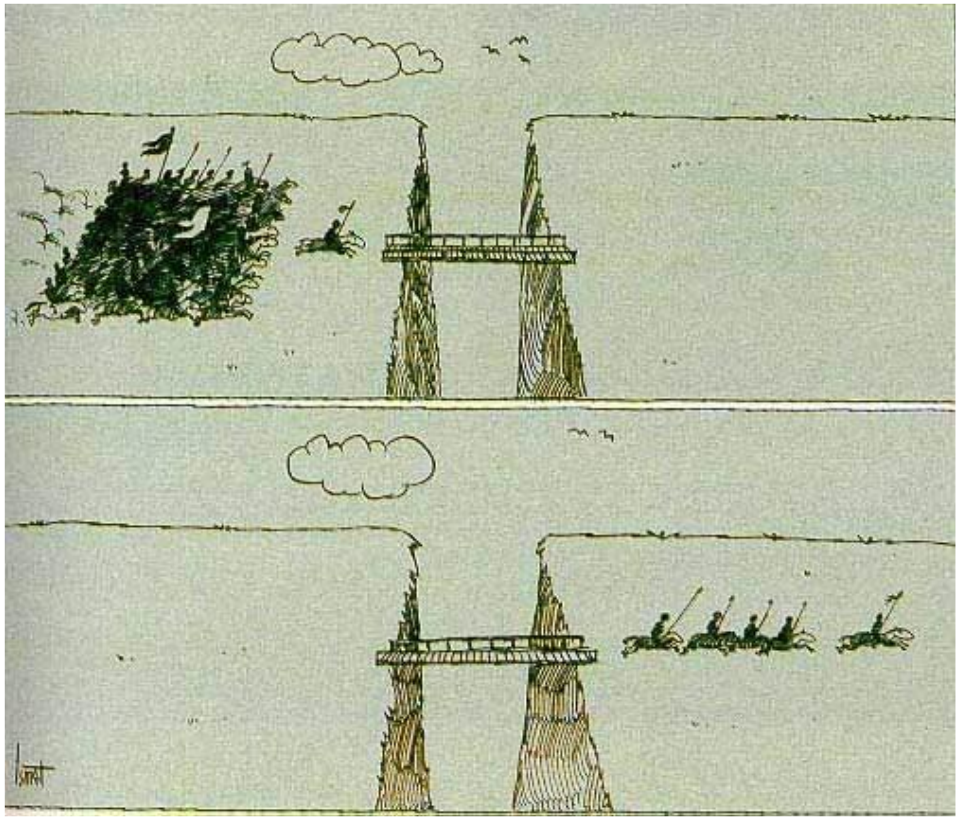


Stop pressure

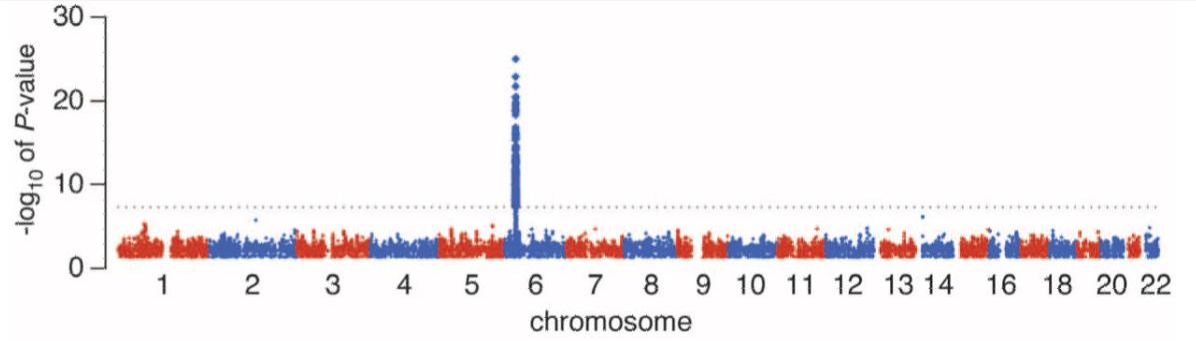
DIVERSITY



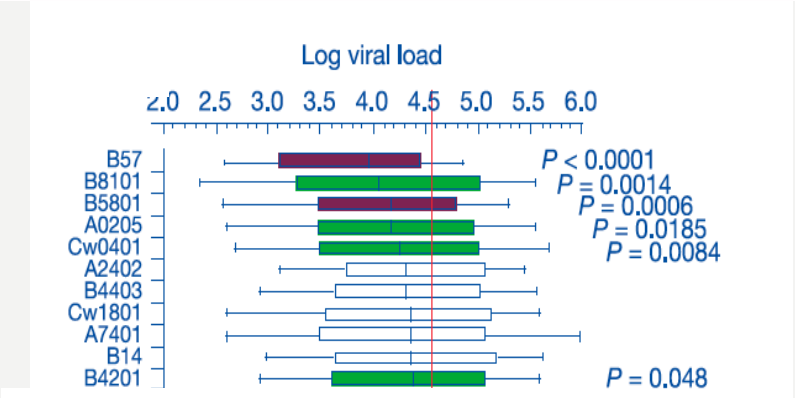
Drift



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

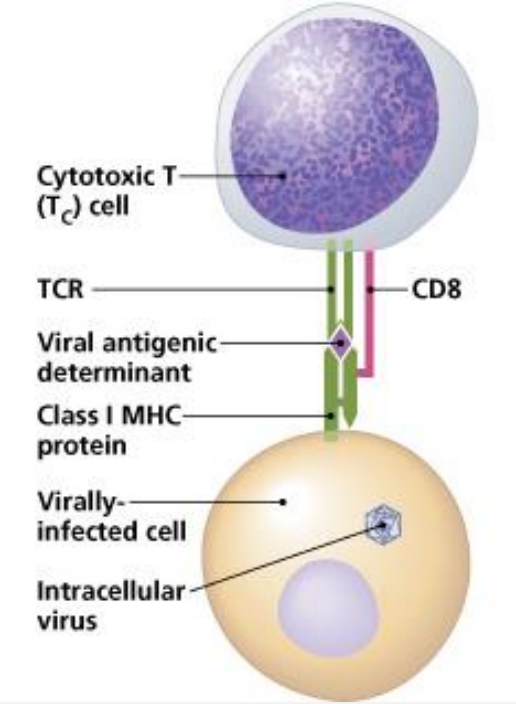


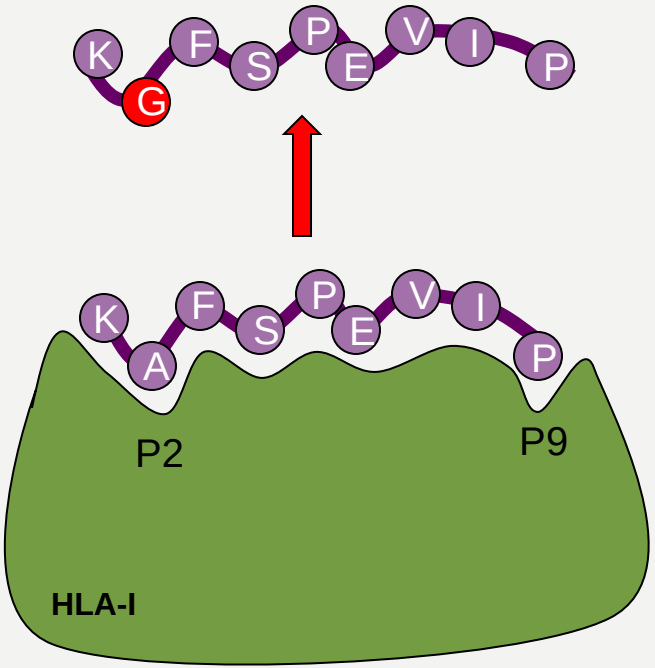
Pereyra et al, Science 2010



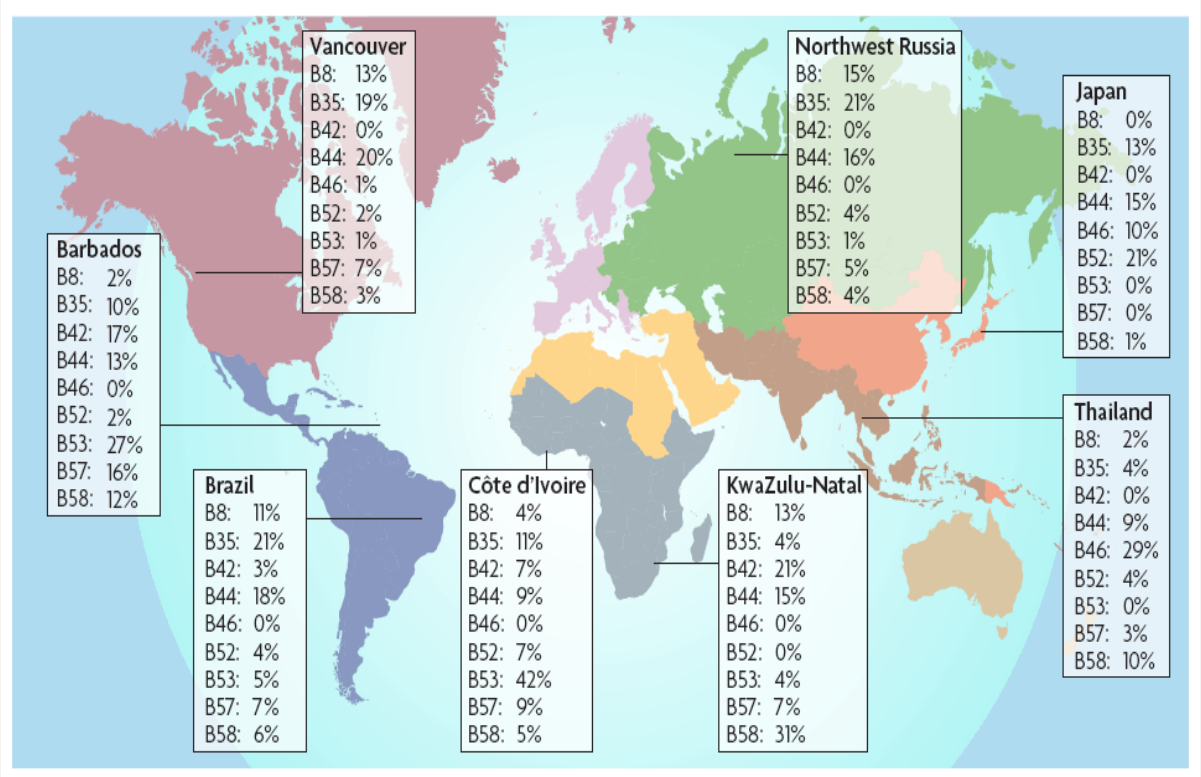
Kiepiela et al, Nature 2004

CD8+ T-cell responses and HIV-1 escape





HLA class I alleles are also highly diverse



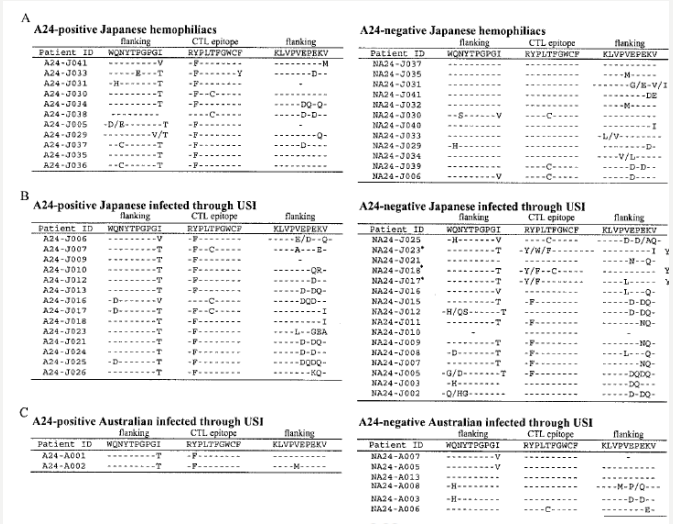
Host HLA genetics and HIV diversity: frequent transmission of escaped epitopes and epitope loss over time

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	CTL epitope	flanking
A24-J041	---------V	-F---------	---------M
A24-J033	-----E---T	-P-------Y	-------D--
A24-J031	-H------T-	-F-------	-
A24-J030	---------T	-P--C-----	----------
A24-J024	---------T	-P---------	-----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	CTL epitope	flanking
NA24-J037	----------	----------	----------
NA24-J035	----------	----------	----M-----
NA24-J031	----------	-F-------	-------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	CTL epitope	flanking
A24-J006	---------V	-F---------	-----E/D--Q-
A24-J007	---------T	-P--C-----	-----A---E-
A24-J009	---------T	-F---------	-
A24-J010	---------T	-F---------	-------QR-
A24-J012	---------T	-P---------	-------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	CTL epitope	flanking
NA24-J025	-H-------V	----C-----	-----D-D/AQ-
NA24-J023*	---------T	-Y/H/F-----	---------I Y
NA24-J021	----------	----------	-----M--Q-
NA24-J018*	---------T	-Y/F--C-----	---------- Y
NA24-J017*	---------T	-Y/F-------	-----I----- Y
NA24-J016	---------V	----------	-----I---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/HQ-------	----------	-----D-DQ-

C

A24-positive Australian infected through USI

Patient ID	flanking	CTL epitope	flanking
A24-A001	---------T	-F---------	----------
A24-A002	---------T	-P---------	----M-----

A24-negative Australian infected through USI

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

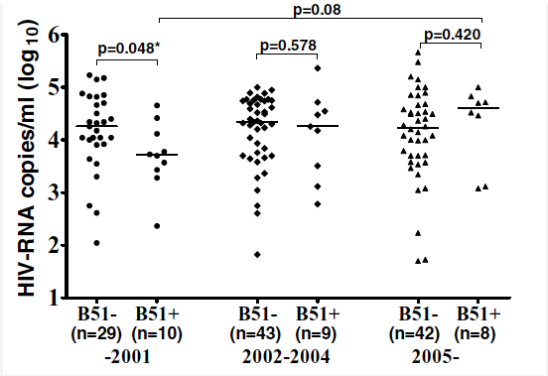
Microbiol Immunol 2010; 54: 196–205
doi:10.1111/j.1348-0421.2010.00206.x

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]

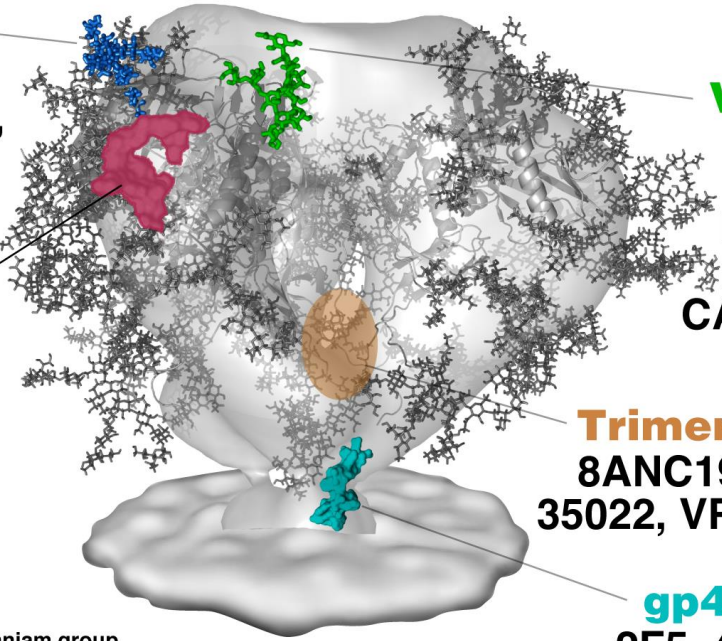
[1]Division of Infectious Disease, Advanced Clinical Research Center, [3]Department of Infectious Diseases and Applied Immunology, Research Hospital, [4]Department of Infectious Disease Control, International Research Center for Infectious Diseases, [5]Department of infectious Disease and Applied Immunology, 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

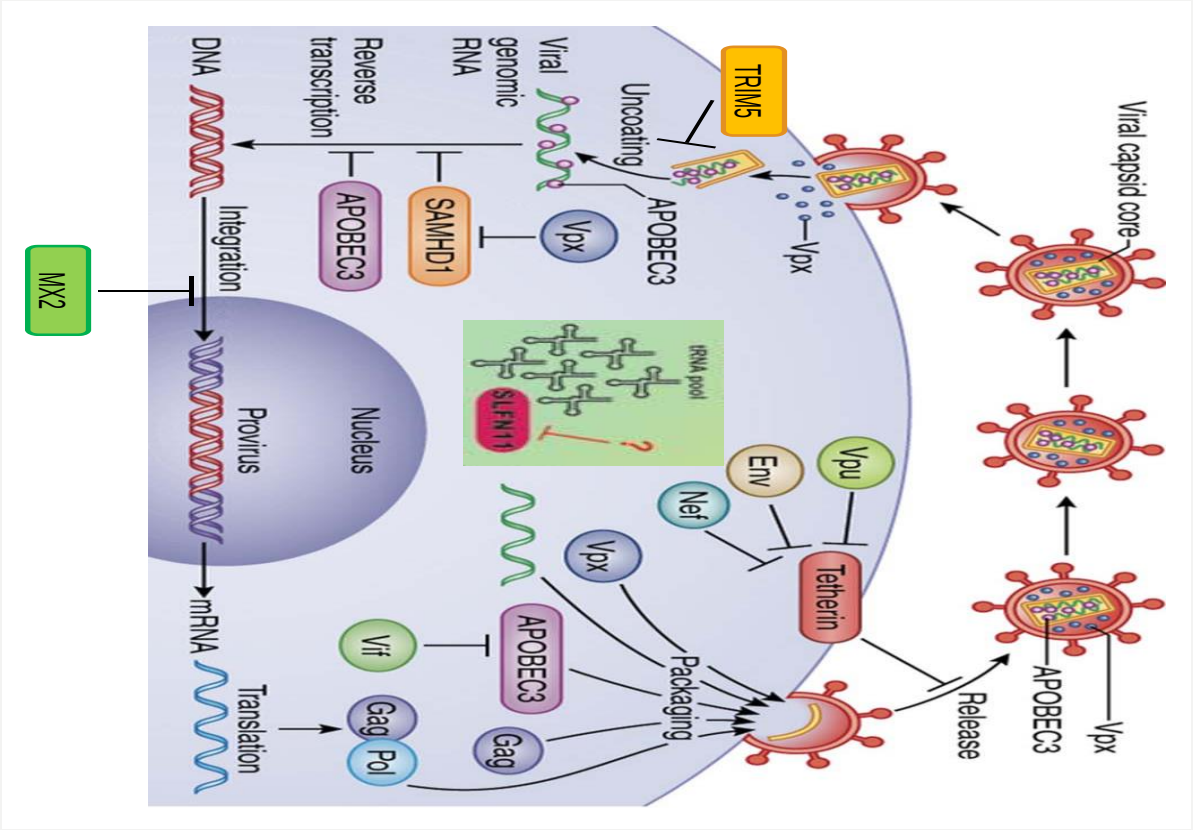
gp41 MPER
2F5, 4E10, 10E8

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

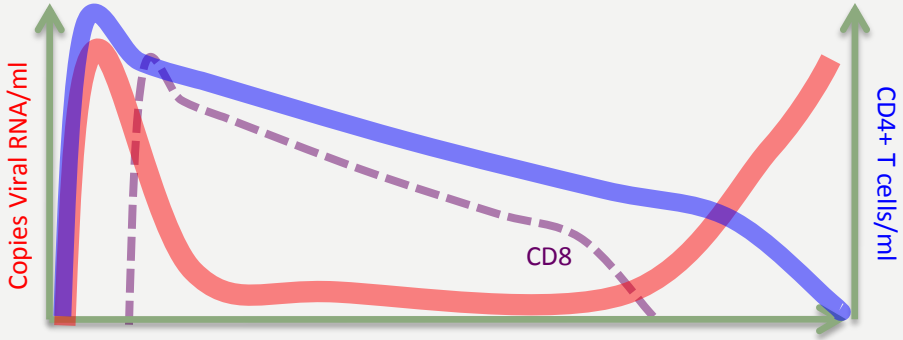
Courtesy of John Mascola

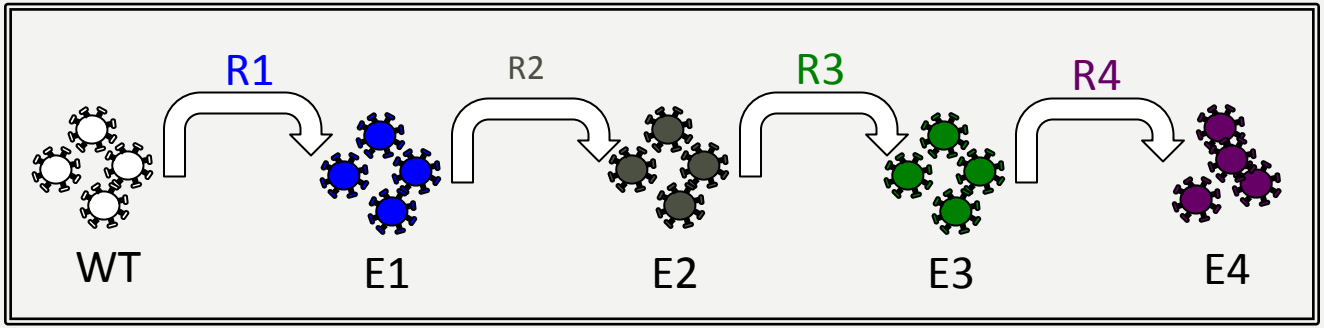
GP160 FROM THE OUTSIDE

RESTRICTION FACTORS

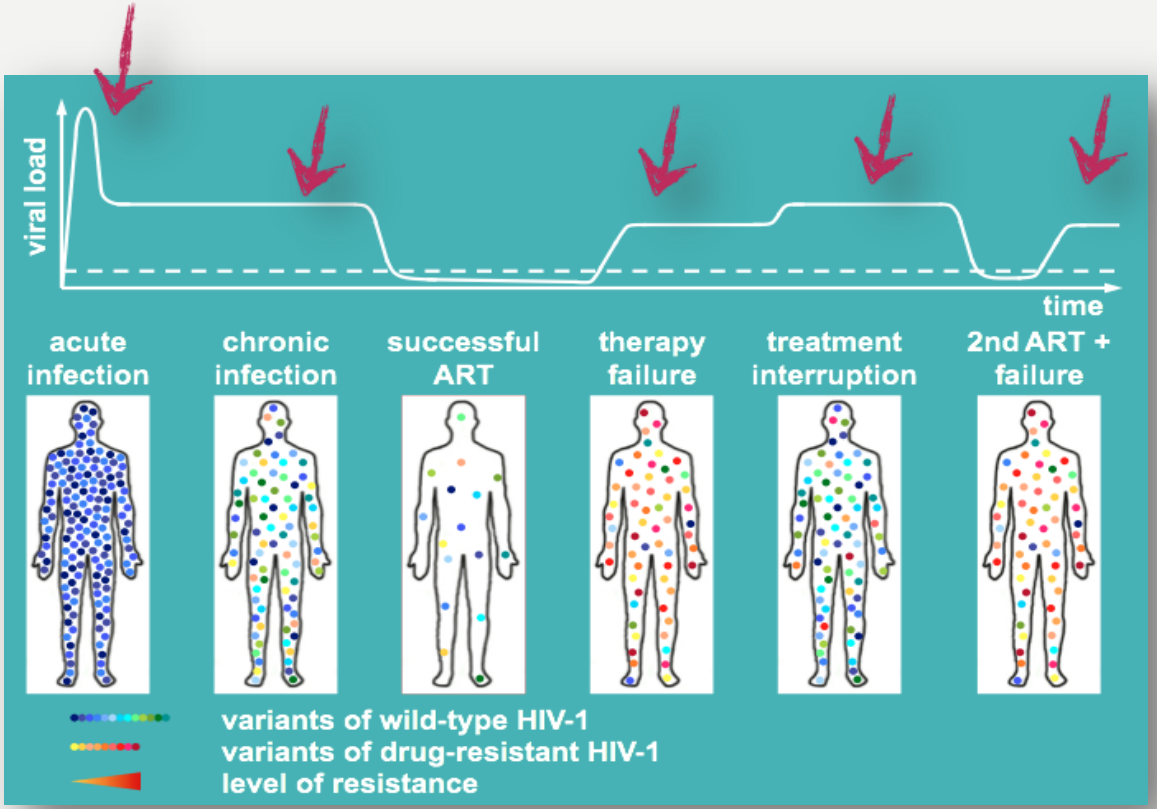


HOST RACE HIV EVOLUTION



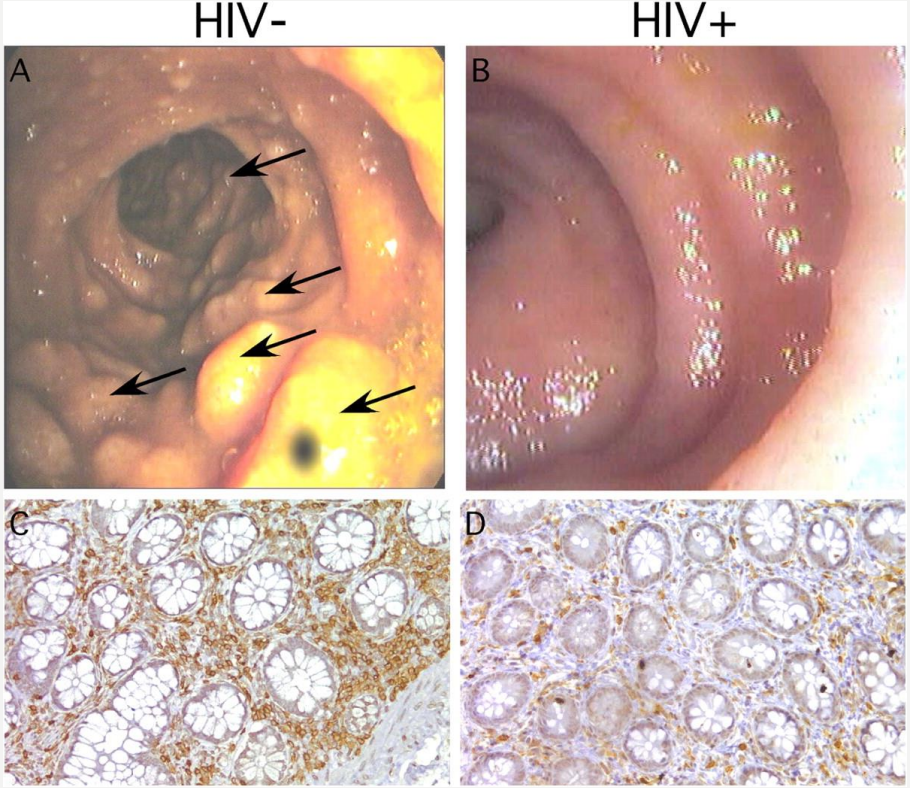


QUASISPECIES AS A SURVIVAL STRATEGY

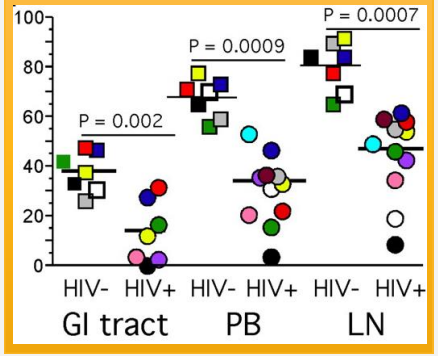


Metzner K, Paredes R, CHAIN Training slides

HIV INFECTION DAMAGES THE GALT

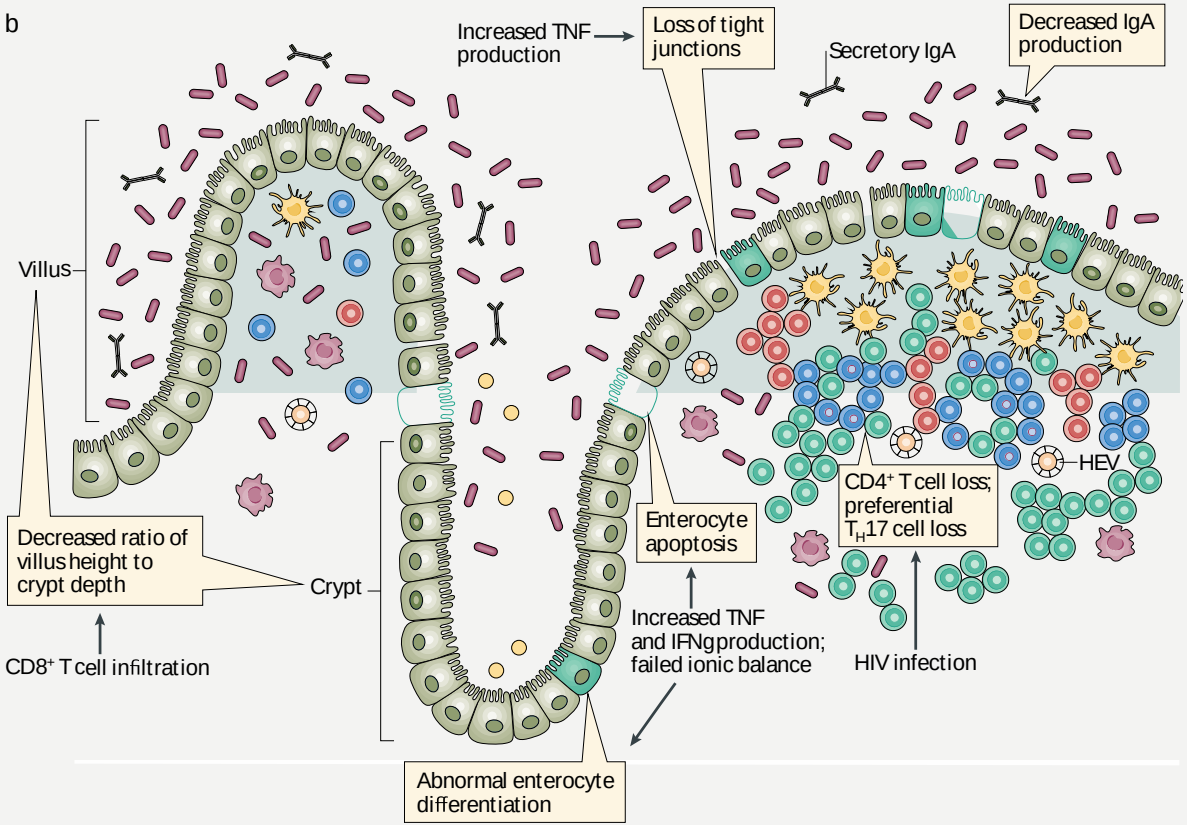


% CD4+ T-cells

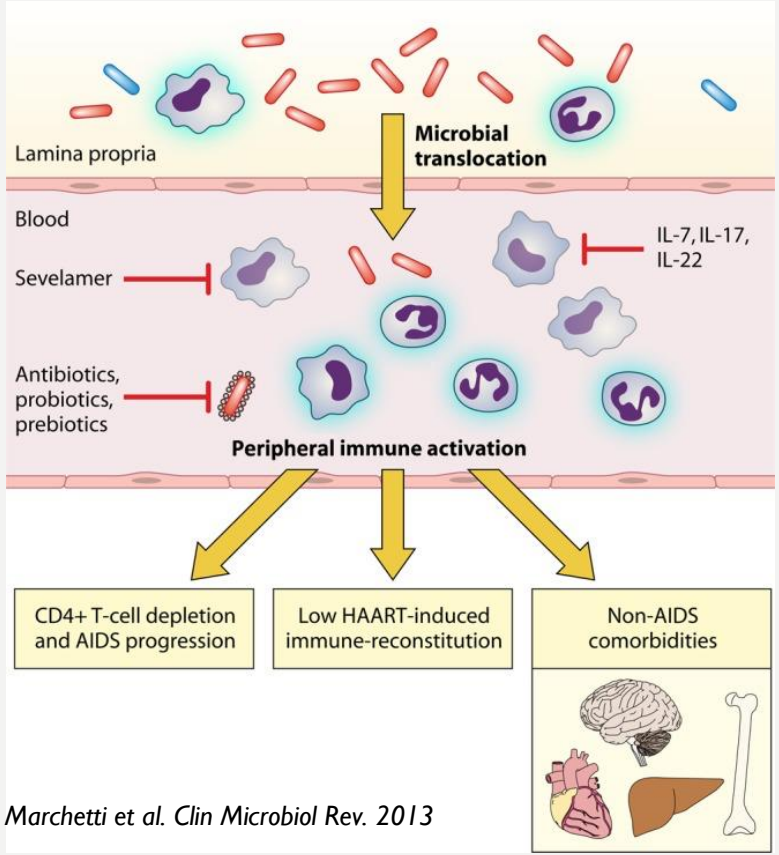


Brenchley J M et al. J Exp Med 2004;200:749-759

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.

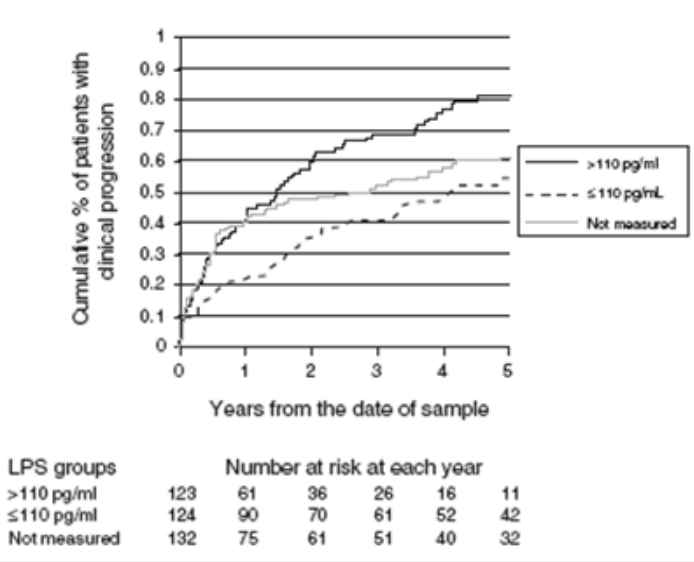
Marchetti G, Cozzi-Lepri A, Merlini E, Bellistrì GM, Castagna A, Galli M, Verucchi G, Antinori A, Costantini A, Giacometti A, di Caro A, D'arminio Monforte A; ICONA Foundation Study Group.

ICONA Cohort

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

- Plasma sample stored while ART-naive

N=379.

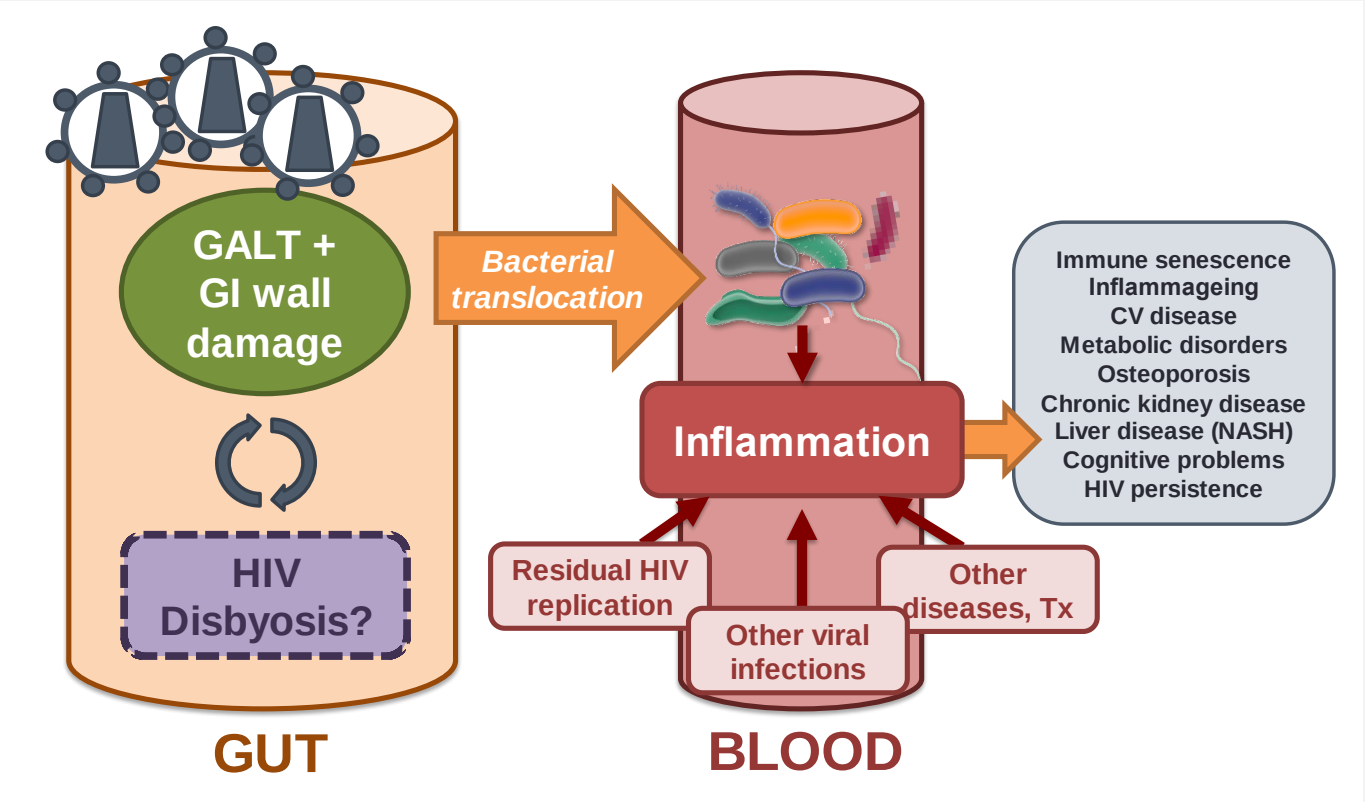


LPS groups	Number at risk at each year					
>110 pg/ml	123	61	36	26	16	11
≤110 pg/ml	124	90	70	61	52	42
Not measured	132	75	61	51	40	32

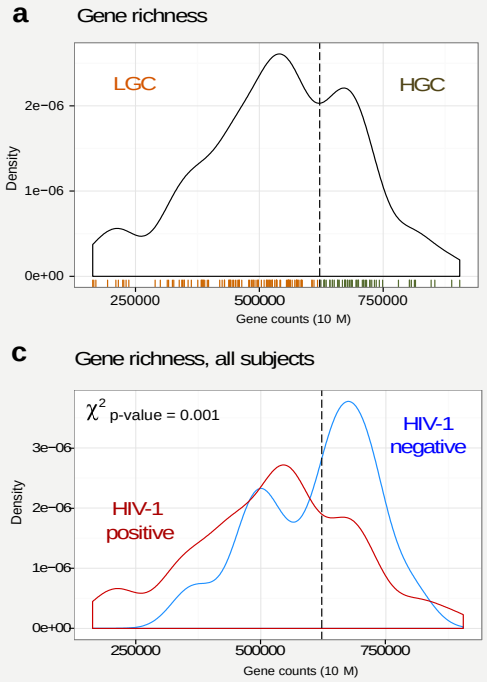
Circulating LPS in the first year of infection is a good predictor of progression

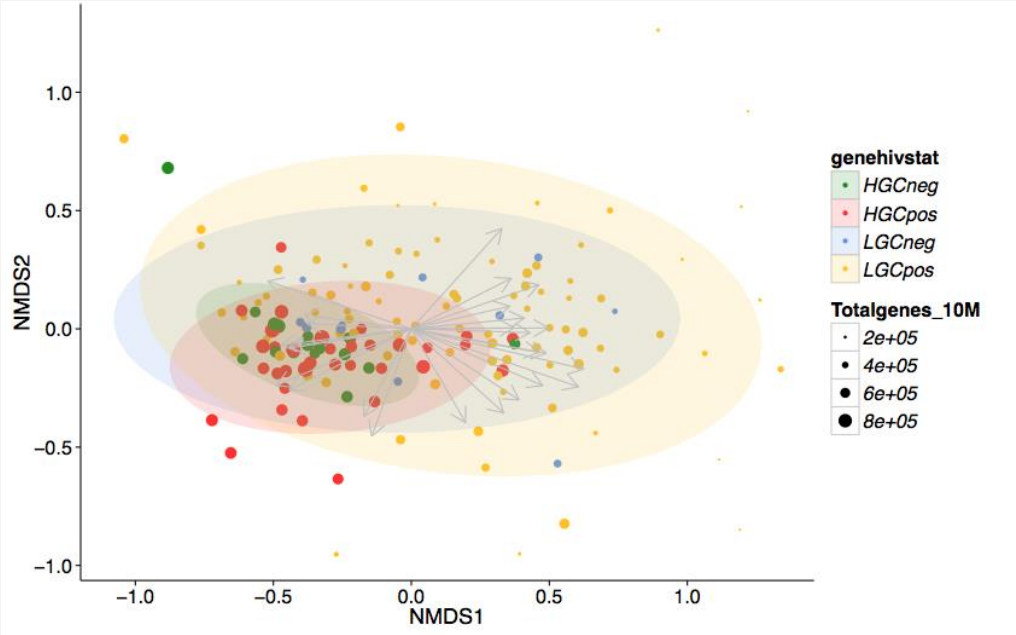
Marchetti G, et al. AIDS 2011;25(11):1385-94.

INFLAMMAEGING



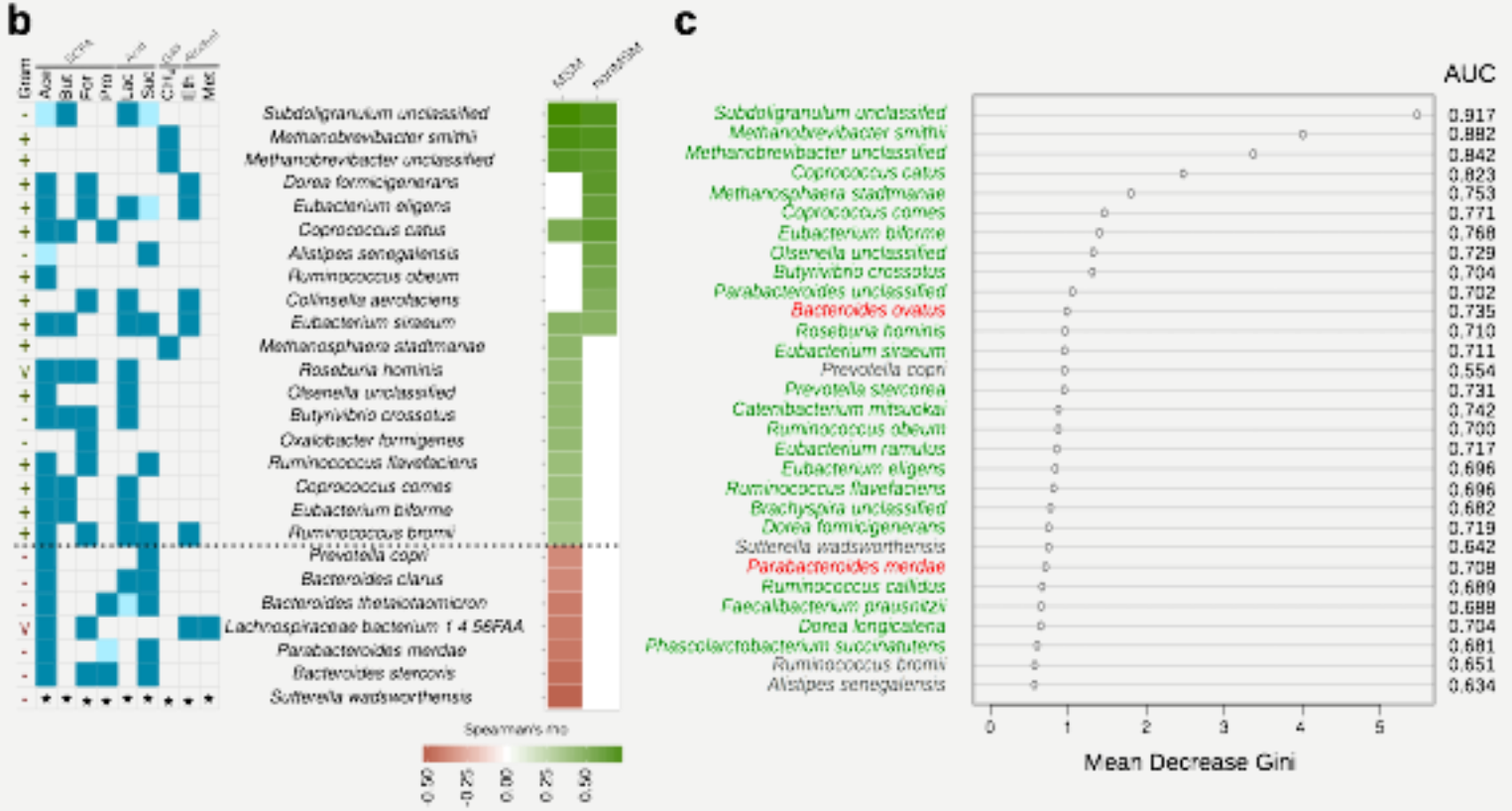
MICROBIOME IN HIV





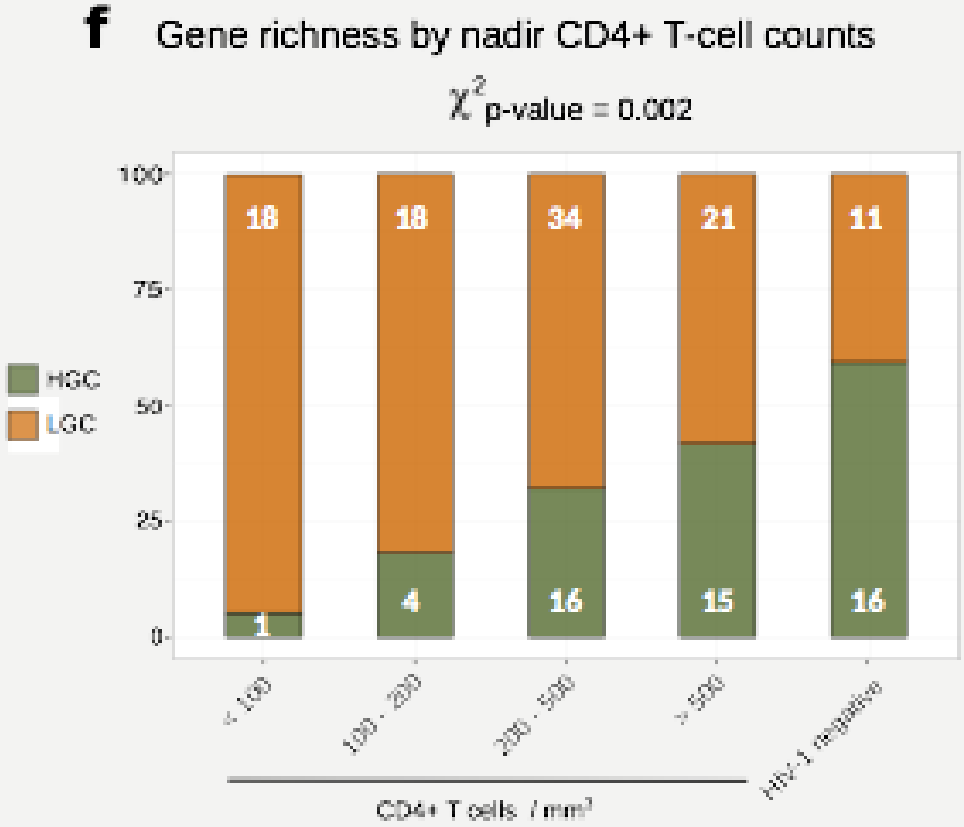
Guillén et al. Mucosal Immunology 2018

DYSBIOSIS BY GENE RICHNESS



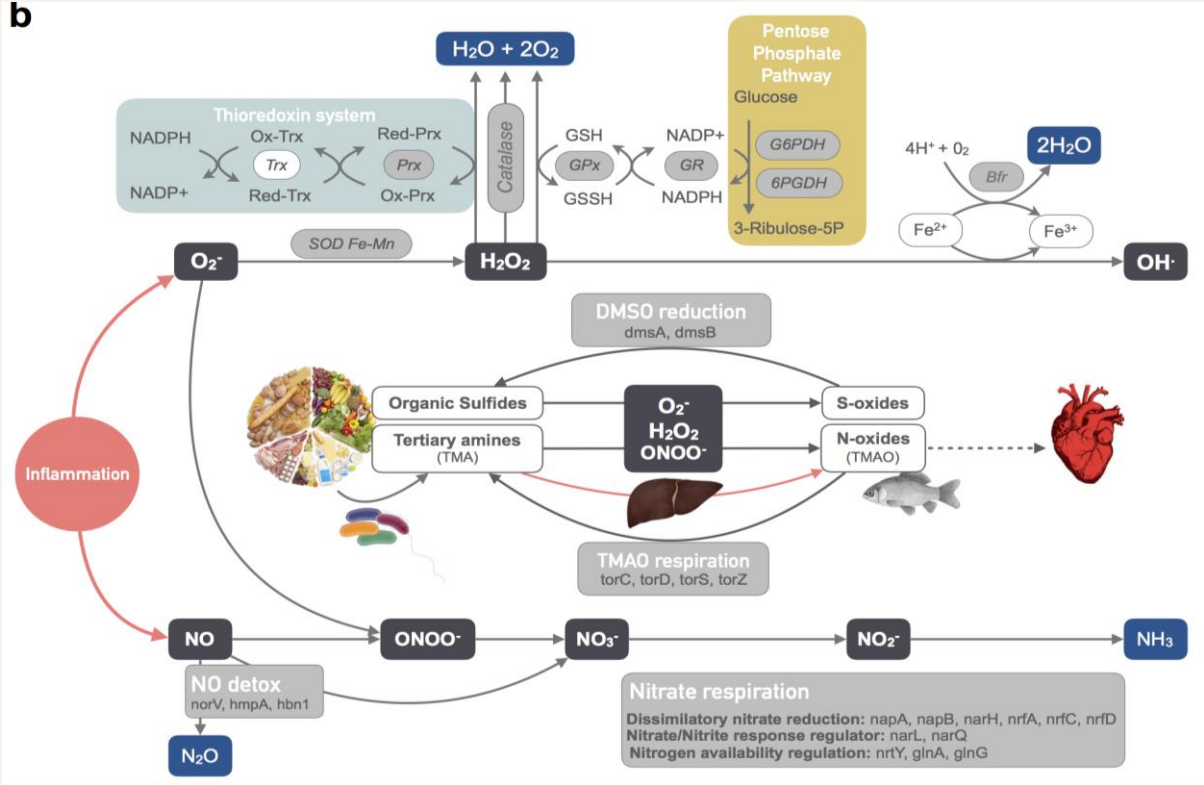
Guillén et al. Mucosal Immunology 2018

LOW MICROBIAL GENE RICHNESS LINKED TO NADIR CD4



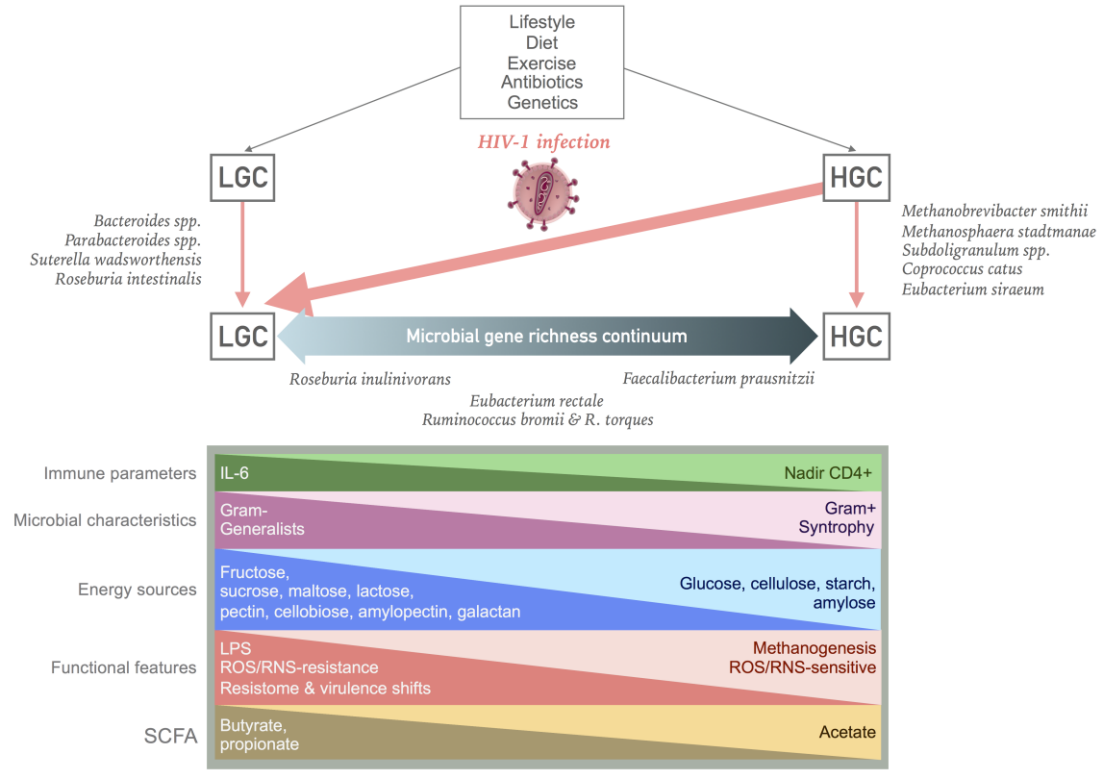
Guillén et al. Mucosal Immunology 2018

MICROBIOME IN HIV



Guillén et al. Mucosal Immunology 2018

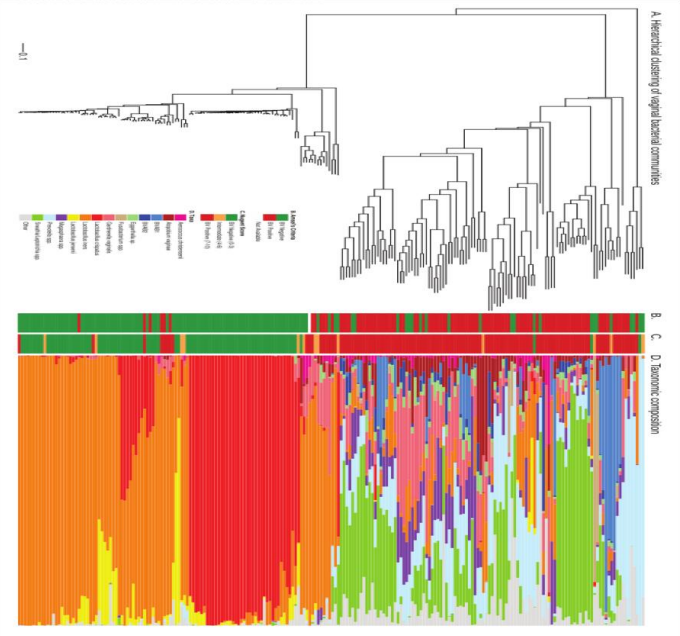
MICROBIOME IN HIV



Guillén et al. Mucosal Immunology 2018

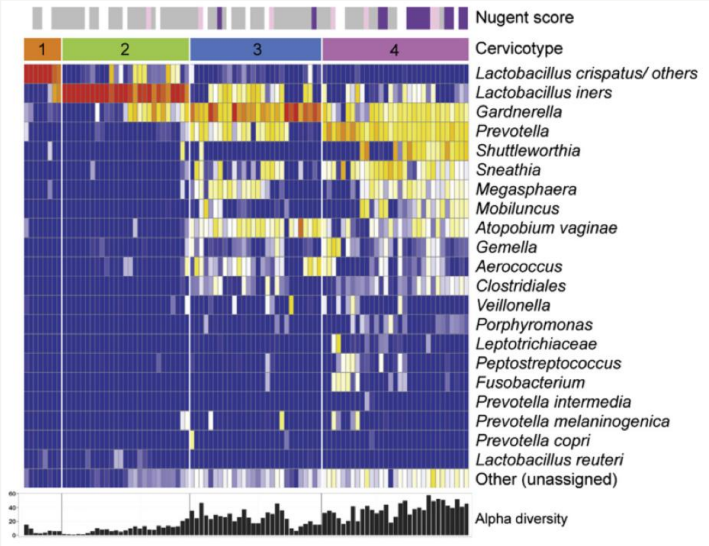
VAGINAL DYSBIOSIS RECOGNIZABLE AS COMMUNITY-TYPES

Srinivasan et al. 2012

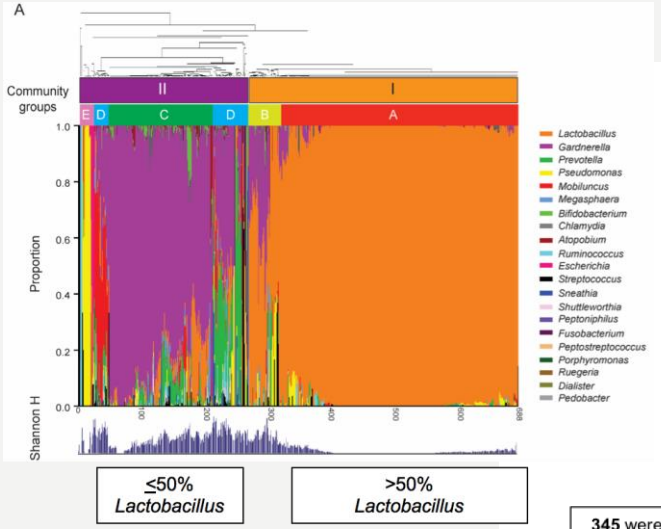


Anahtar et al., Immunity, 2015

Young women in SA have high vaginal microbial diversity

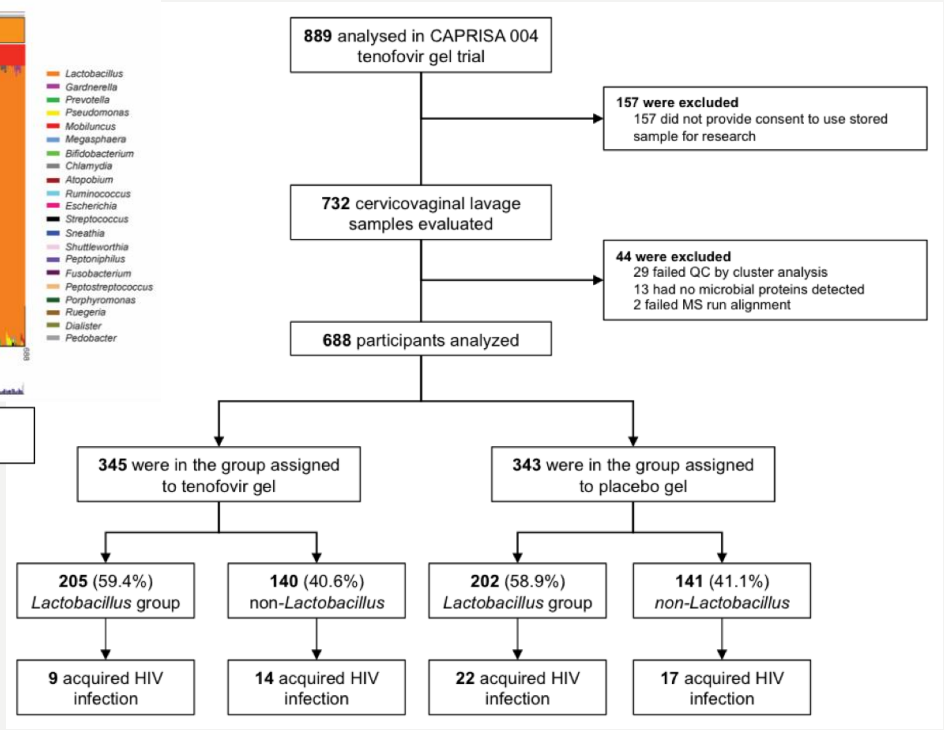


CAPRISA-004



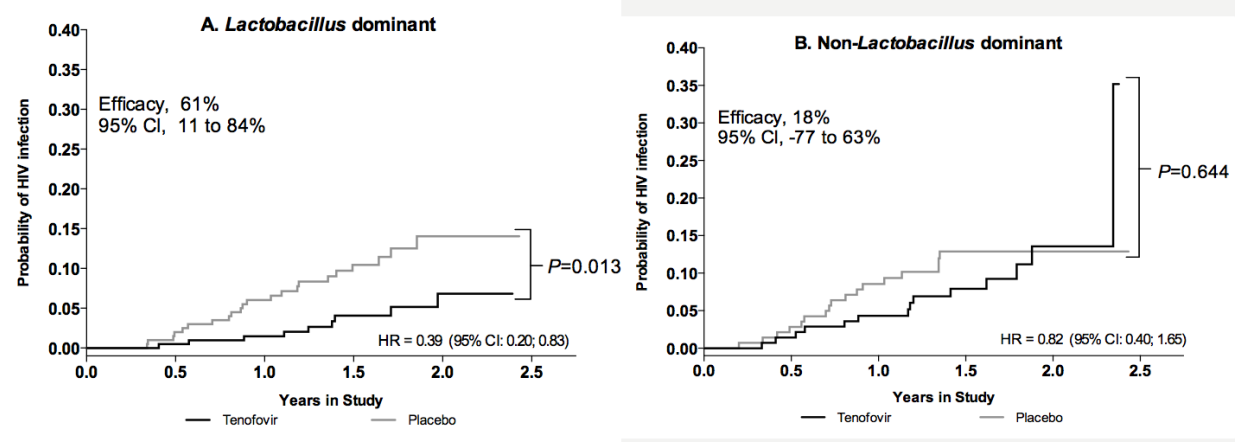
≤50% *Lactobacillus*

>50% *Lactobacillus*



Klatt et al., Science 2017

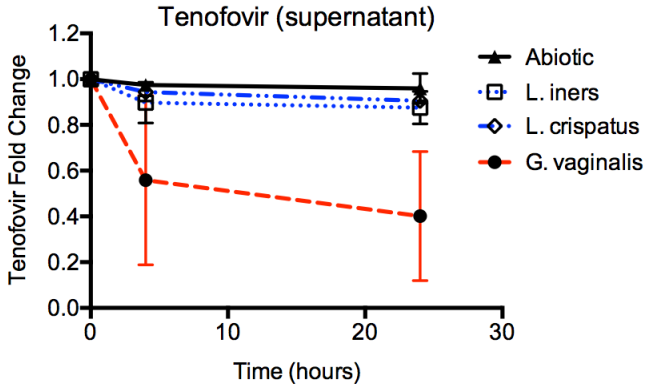
CAPRISA-004



	Lactobacillus dominant		non- *Lactobacillus* dominant	
	Tenofovir	Placebo	Tenofovir	Placebo
# HIV-1 infections	9	22	14	17
HIV-1 incidence per 100 person-years	2.7	6.9	6.4	7.8
HIV-1 protection effectiveness 95% CI, *P*-value	**61%** (11, 84), *p*=0.013		**18%** (-77, 63), *p*=0.644	

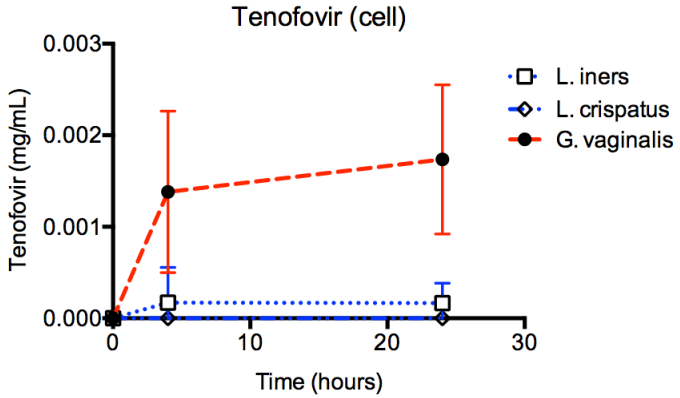
Klatt et al., Science 2017

TDF DEPLETED BY GARDENERELLA BUT NOT LACTOBACILLUS



4 hours:
G. vag vs Abiotic: *P*<0.0001
G. vag vs. L. iners: *P*=0.0037
G. vag vs. L. crisp: *P*=0.0019
L. iners vs L. crisp: *P*=ns

24 hours:
G. vag vs Abiotic: *P*<0.0001
G. vag vs. L. iners: *P*<0.0001
G. vag vs. L. crisp: *P*<0.0001
L. iners vs. L. crisp: *P*=ns

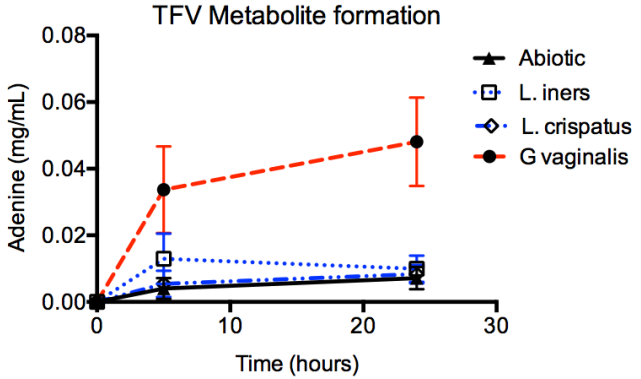


4 hours:
G. vag vs. L. iners: *P*<0.0001
G. vag vs. L. crispatus: *P*<0.0001
L. iners vs. L. crispaturs: *P*=ns

24 hours:
G. vag vs. L. iners: *P*<0.0001
G. vag vs. L. crispatus: *P*<0.0001
L. iners vs. L. crispaturs: *P*=ns

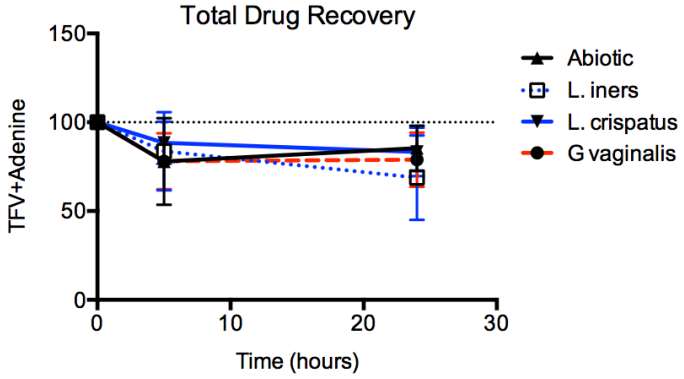
Klatt et al., Science 2017

TDF METABOLISED TO ADENINE



4 hours:
G. vag vs Abiotic: *P*<0.0001
G. vag vs. L. iners: *P*<0.0001
G. vag vs. L. crispatus: *P*<0.0001
L. iners vs. L. crispatus: *P*=0.02

24 hours:
G. vag vs Abiotic: *P*<0.0001
G. vag vs. L. iners: *P*<0.0001
G. vag vs. L. crispatus: *P*<0.0001
L. iners vs. L. crispatus: *P*=ns

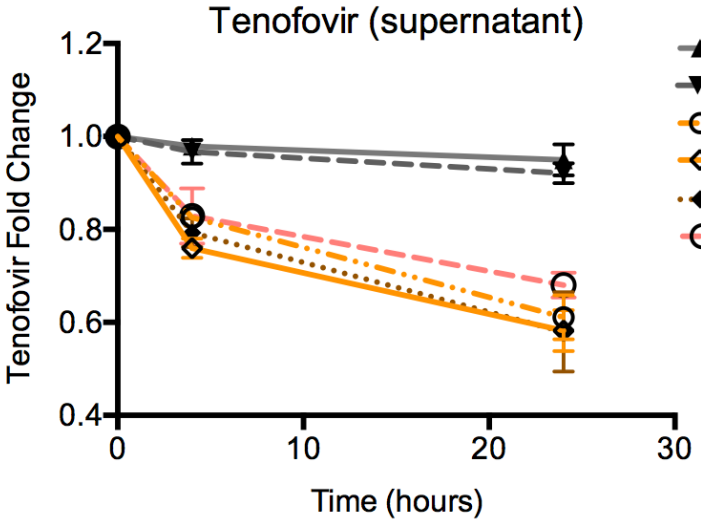


4 hours:
G. vag vs Abiotic: *P*=ns
G. vag vs. L. iners: *P*=ns
G. vag vs. L. crispatus: *P*=ns
L. iners vs. L. crispatus: *P*=ns

24 hours:
G. vag vs Abiotic: *P*=ns
G. vag vs. L. iners: *P*=ns
G. vag vs. L. crispatus: *P*=ns
L. iners vs. L. crispatus: *P*=ns

Klatt et al., Science 2017

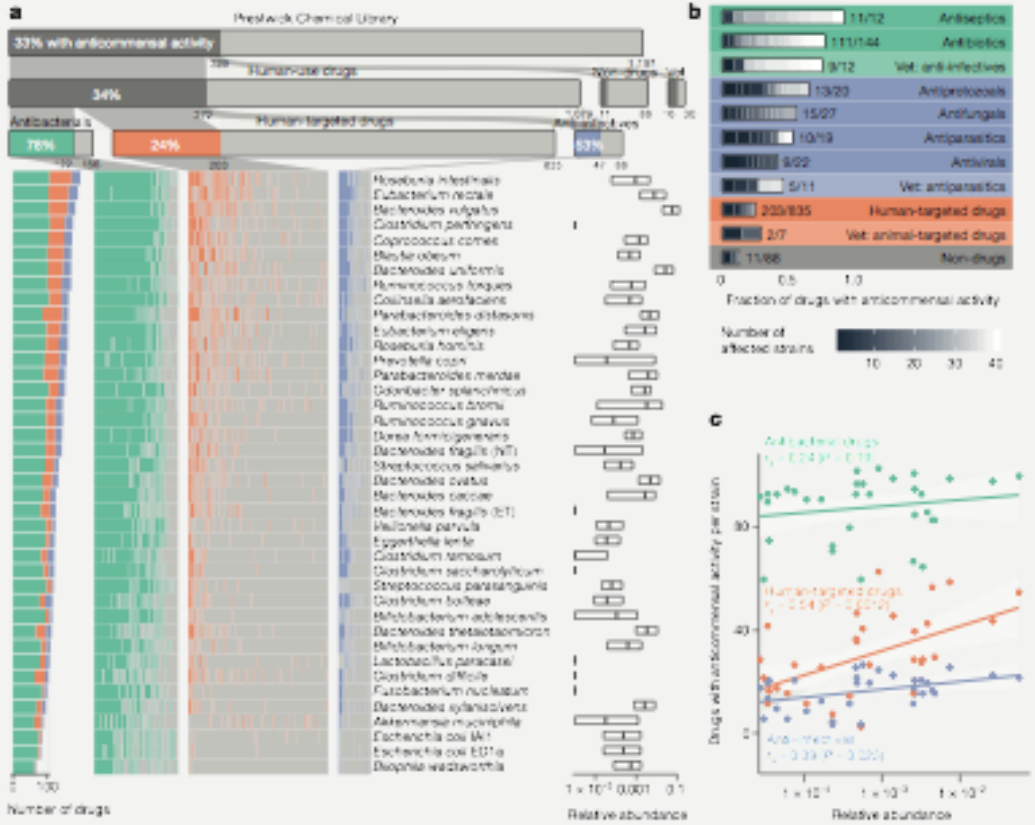
MULTIPLE BV BACTERIA (BUT NOT LACTOBACILLUS) CAN METABOLIZE TENOFOVIR



24 hours:
P. amnii vs Abiotic (NYCIII): *P*=0.0007
P. bivia vs Abiotic (NYCIII): *P*=0.0007
M. mulierus vs Abiotic (NYCIII): *P*=0.0007
E. coli vs Abiotic (TS): *P*=0.1000

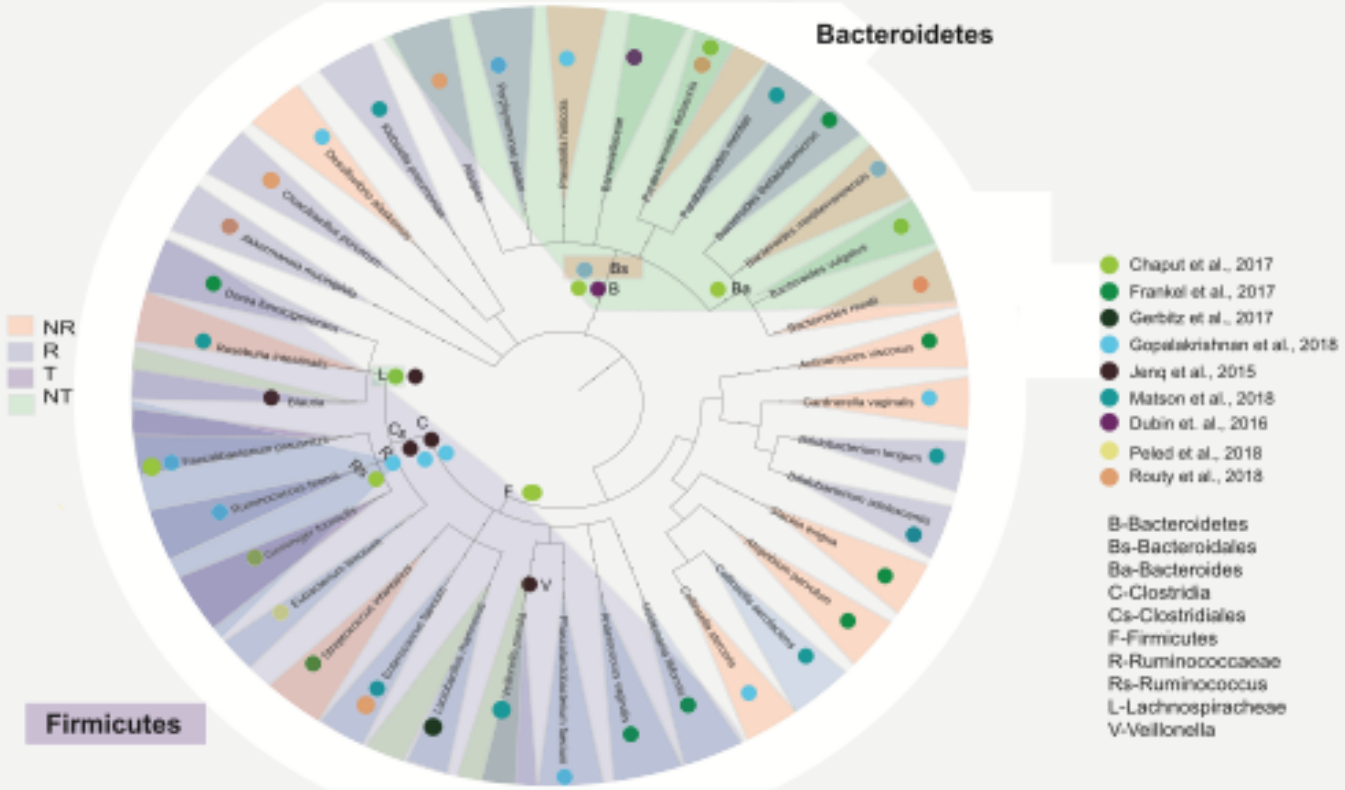
Klatt et al., Science 2017

EXTENSIVE IMPACT OF NON-ANTIBIOTIC DRUGS ON HUMAN GUT BACTERIA



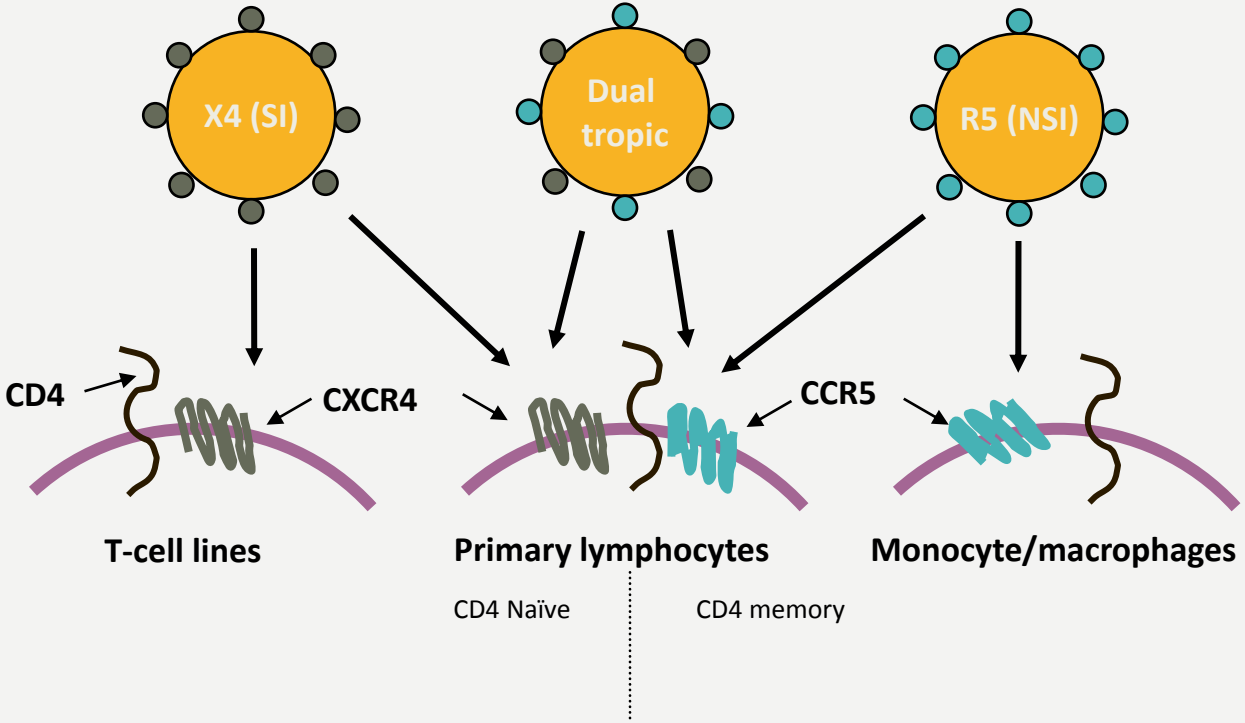
Maier Nature 2018

MICROBIOME IN CANCER

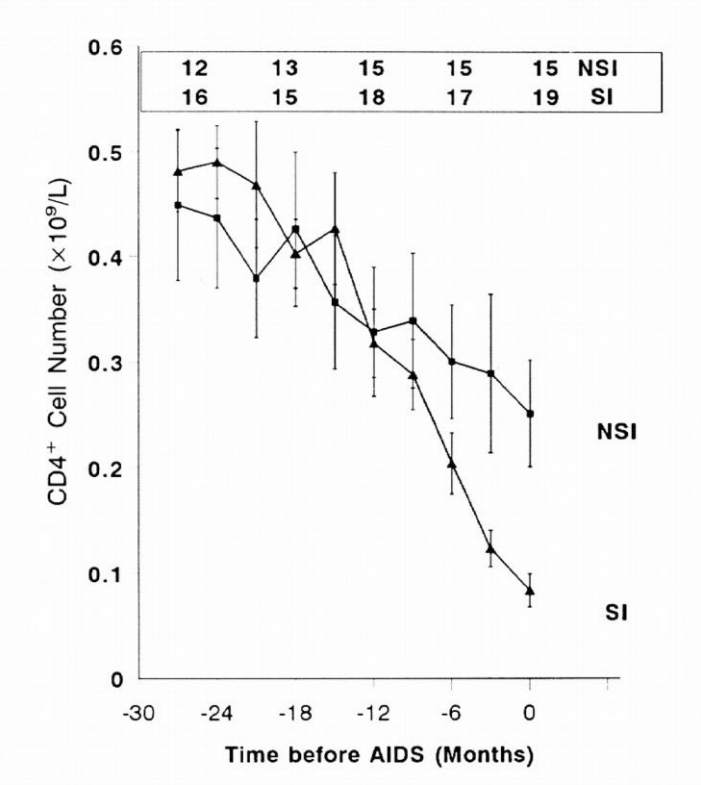


Gopalakrishnan et al, Cancer Cell 2018

TROPISM PREDICTION

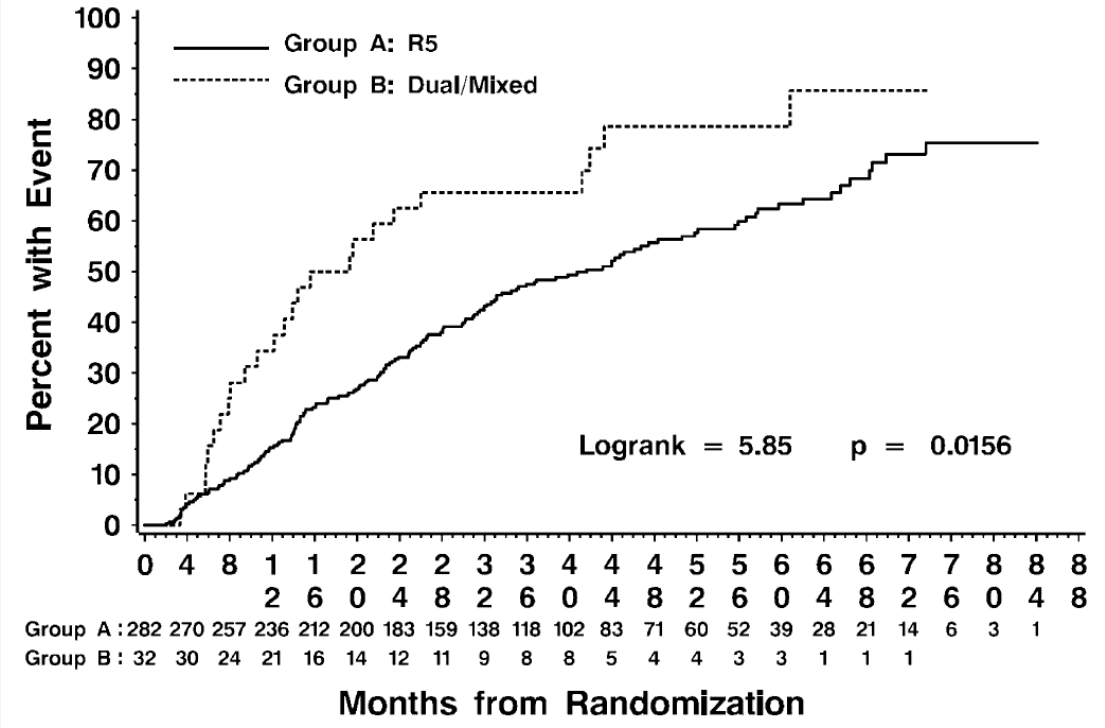


TROPISM



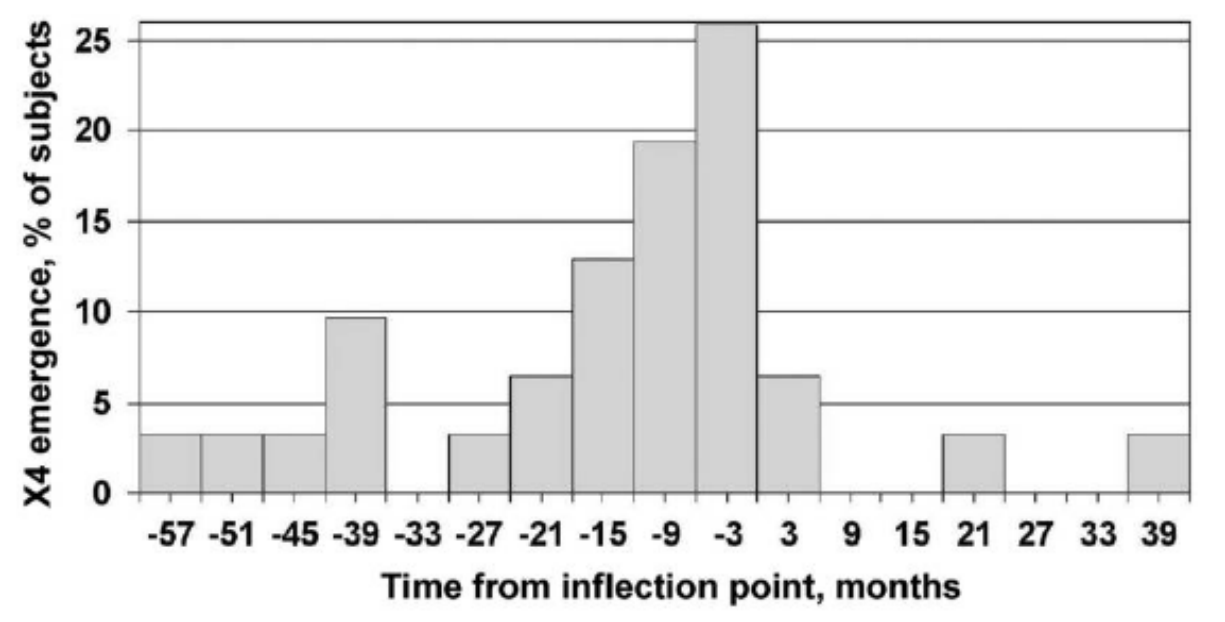
Koot M, et al: Prognostic Value of HIV-1 Syncytium-Inducing Phenotype for Rate of CD4+ Cell Depletion and Progression to AIDS. Annals Int Med 1993

RATE OF PROGRESSION TO CD4+<350, INITIATION OF ART OR DEATH



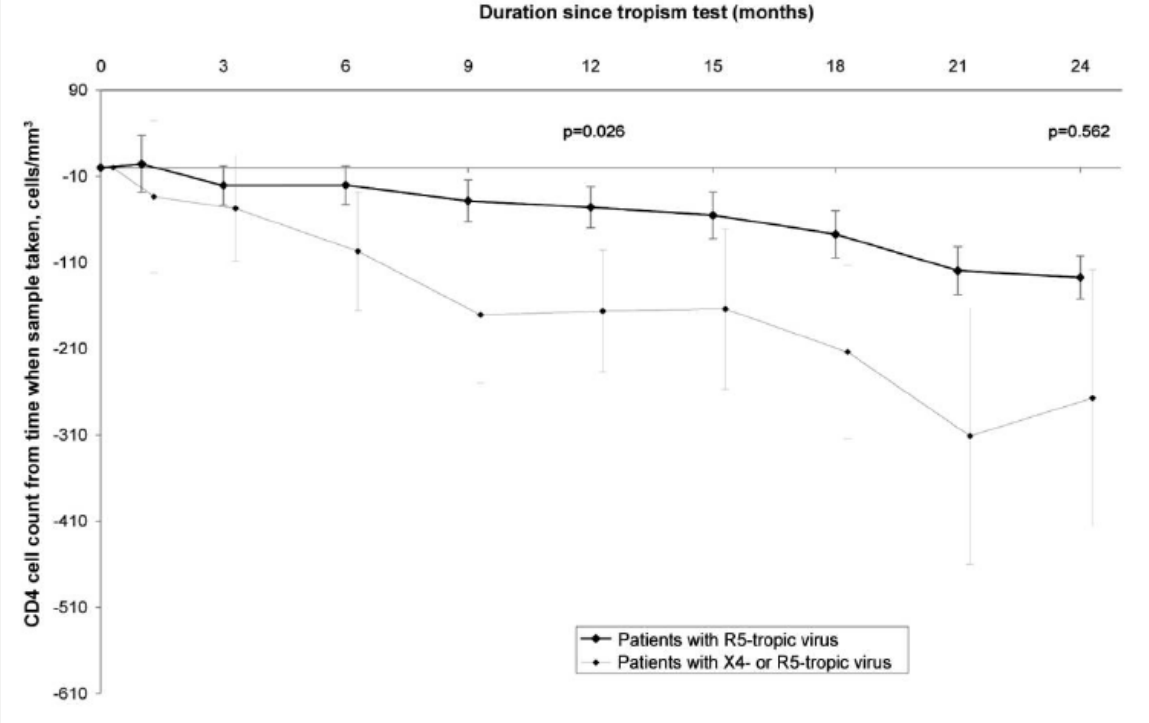
Goetz. JAIDS 2009

TIME OF X4 VIRUS EMERGENCE IN RELATION TO CD4 INFLECTION POINT



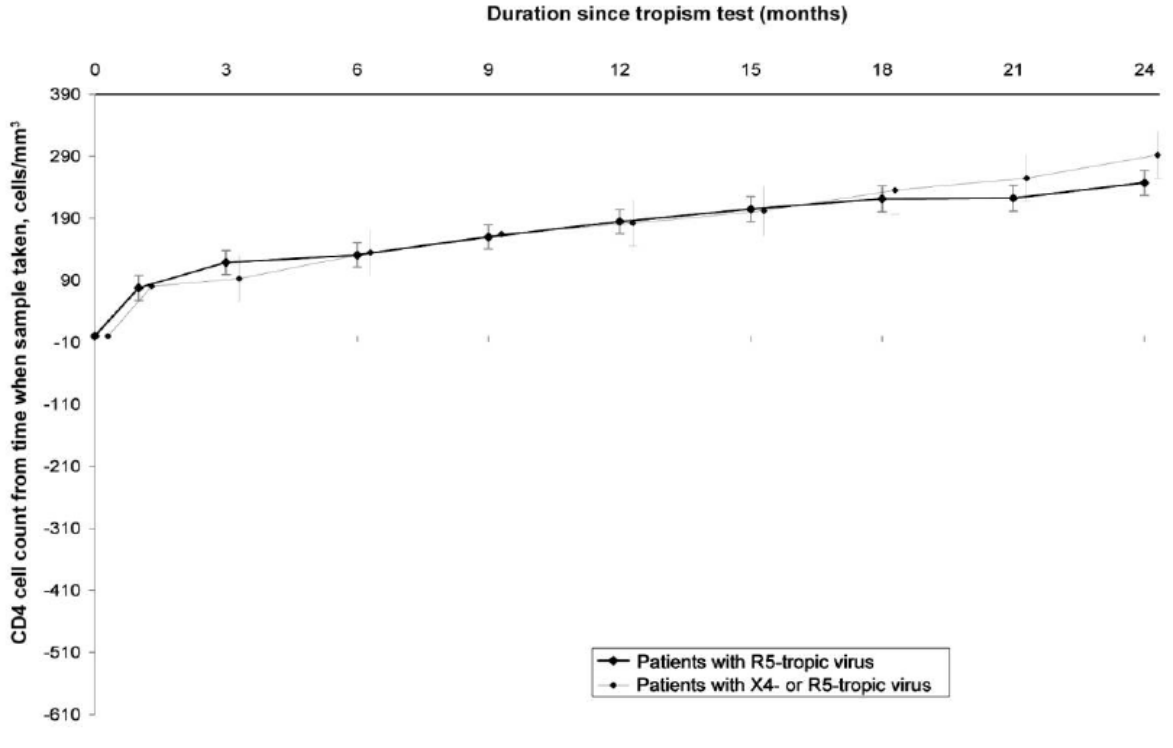
Shepherd. MACS cohort, JID 2008

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

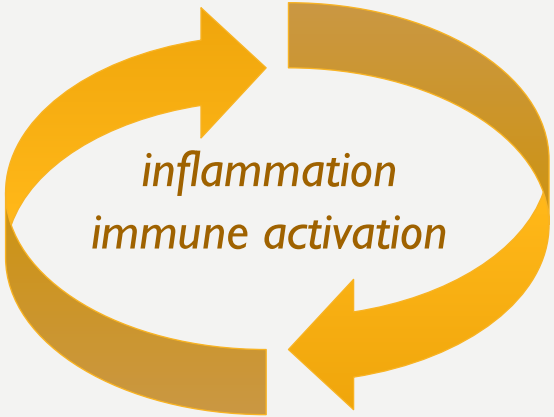
22 billion USD

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

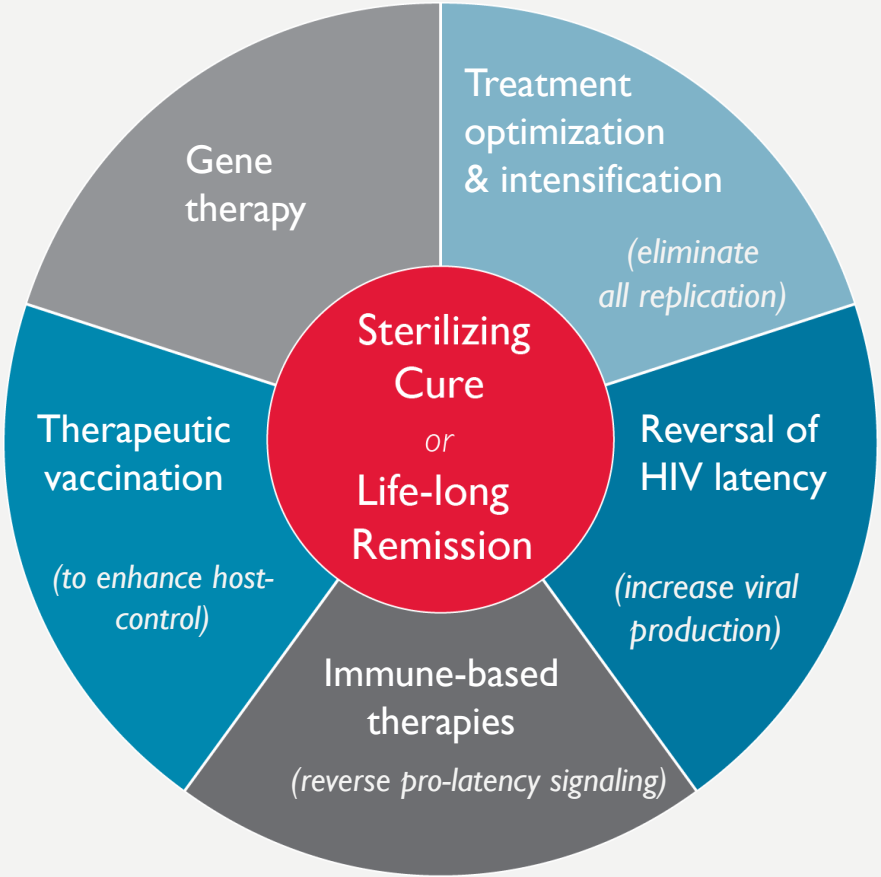
J.Martinez-Picado

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

CONCLUSIONS

- HIV is the great scapist
  - Diversity
    - HIV
    - HLA
  - Integrated DNA
  - Env glycosylation
  - GALT damage
  - Inflammaging

Gràcies!

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RETIC-RIS

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