The Genetics of HIV and Humans

'Had the AIDS epidemic started 20 years earlier, ….we would have had little knowledge of retroviruses, of the function of lymphocytes, or had much of a technology to allow such rapid advances in treatment and care'. Gazzard 2013

Cloning DNA 1972

Sanger Sequencing 1977

PCR 1983

CFTR gene discovered 1989

Human genome project 1990

Automated sequencers 1992

Sanger Centre 1993

Pilot human genome seq begins 1996

E coli genome 1997

Draft human genome 2000

Finished human genome 2003

NGS 2006

1000G 2008

UK10K 2010

GEL 100K 2013

Rous discovery of retroviruses 1911

CDC defines AIDS 1982

Terrence Higgins dies 1982

LAV/ HTLVIII 1983

CD4 receptor 1984

ELISA 1985

HIV named 1986

AZT 1987

AZT resistance 1989

HIV Viral load assay 1994

HAART 1995

CXCR4/CCR5 co-receptors 1996

FDA approved resistance profiles 2001

AIDSVAX trail 2003

RV144 trial 2009

bNAbs 2009

Treatment reduces transmission 2011

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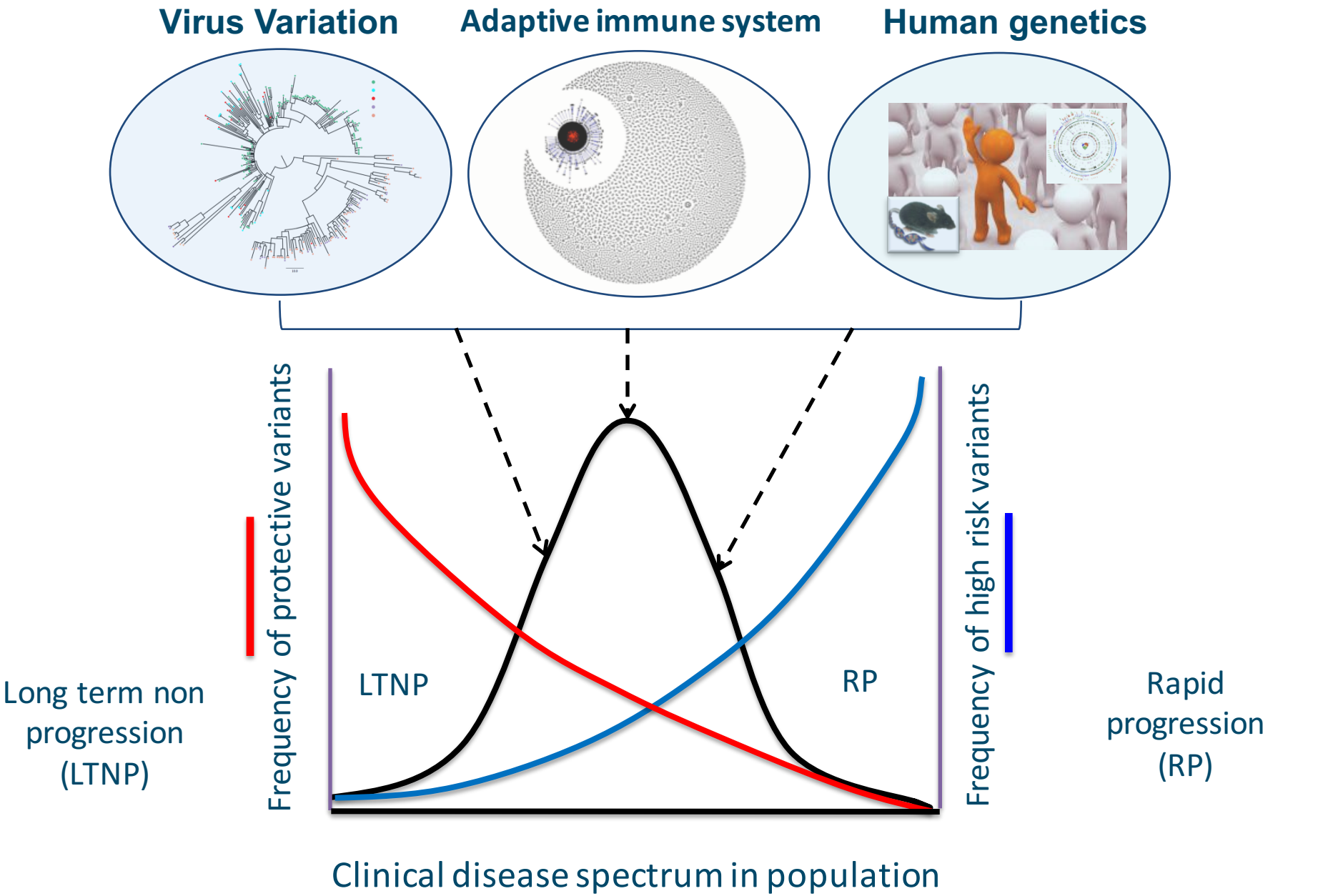
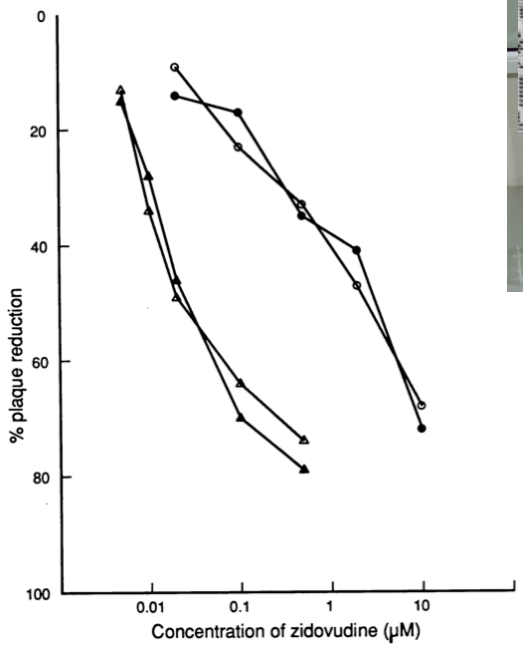
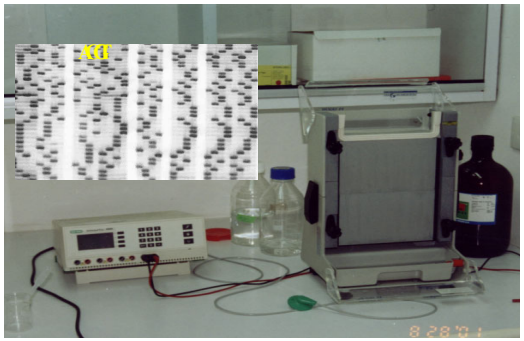
Virus pathogenesis and genetics

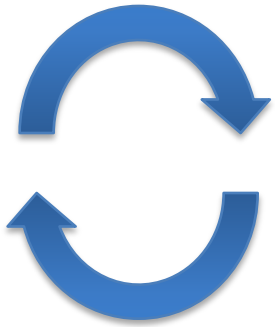


Virtuous circle of early virus genetics (~1990s)

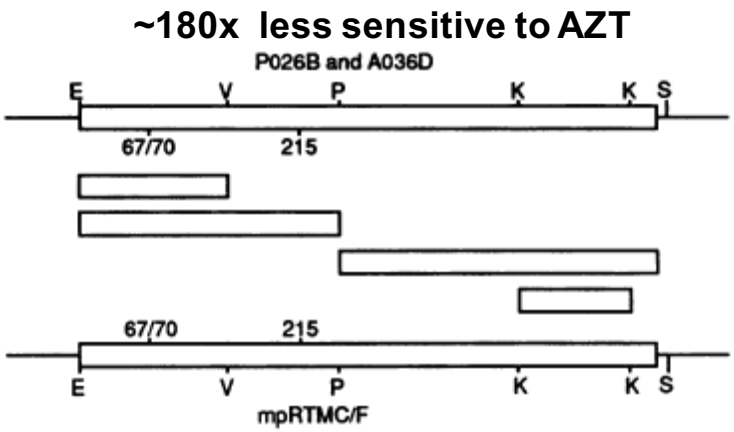
Phenotype







Association



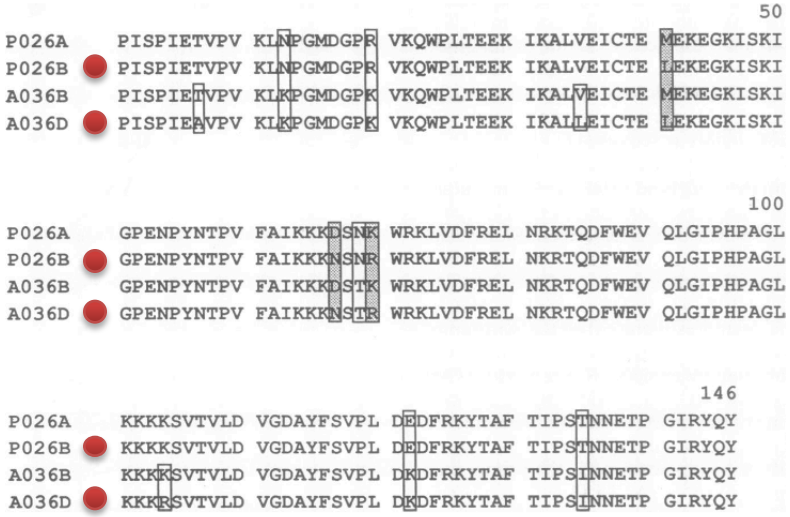


Table 2. Zidovudine sensitivity of HIV variants with defined mutation

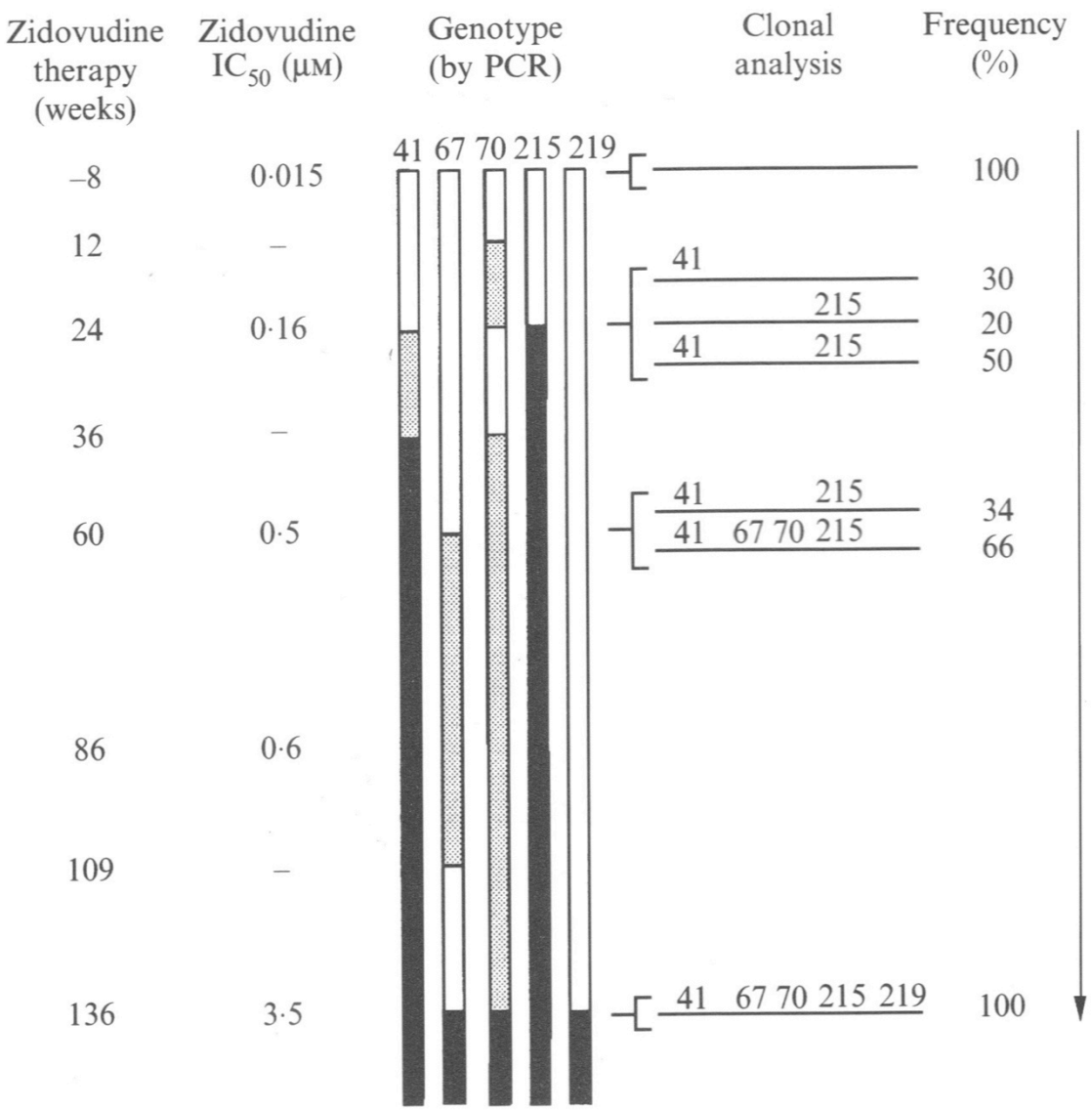
HIV variant	Mutations introduced	Zidovudine IC_{50}, μM	Fold increase
HXB2-D		0.01	1
HXB 41L	L-41	0.04	4
HIVRTMF	Y-215	0.16	16
HXB 41L/215Y	L-41, Y-215	0.60	60
HIVRTMC/F	N-67, R-70, Y-215	0.31	31
RTMC/F 41L	L-41, N-67, R-70, Y-215	1.79	179
HIVRTMCY	N-67, R-70, Y-215, Q-219	1.21	121
HIVRTMC	N-67, R-70, F-215, Q-219	1.47	147

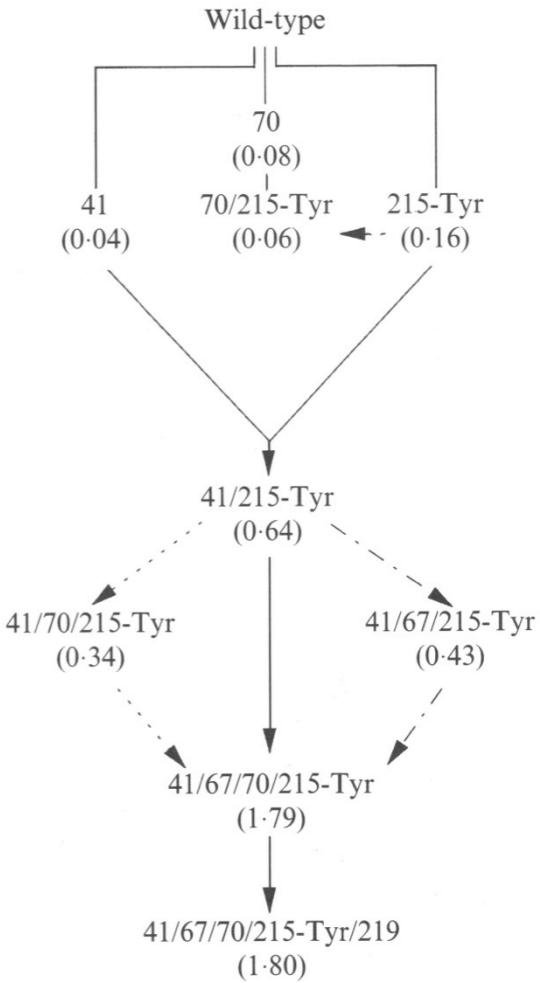
Proof

Genotype

Kellam et al PNAS (1992); 89, 1934-1938

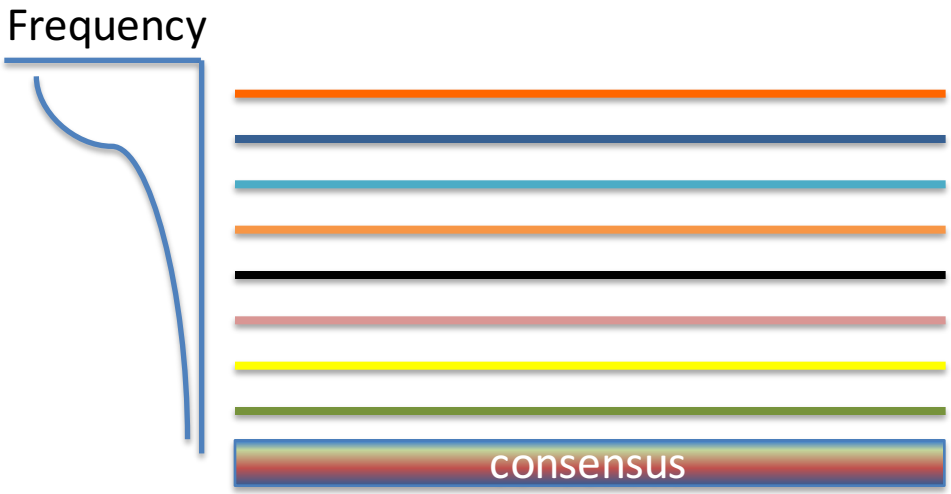
Evolution of drug resistance drug therapy





Kellam P, et al **J. Gen. Virol** 1994
Kellam P, and Larder B.A. **J. Virol.** 1995
Kemp S, **Kellam P** & Larder B.A **Nature.** 1993

HIV genome sequencing 2015

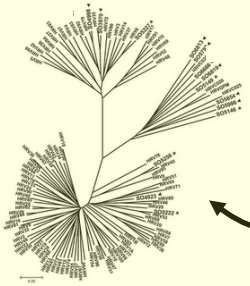


1. Samples & phenotype

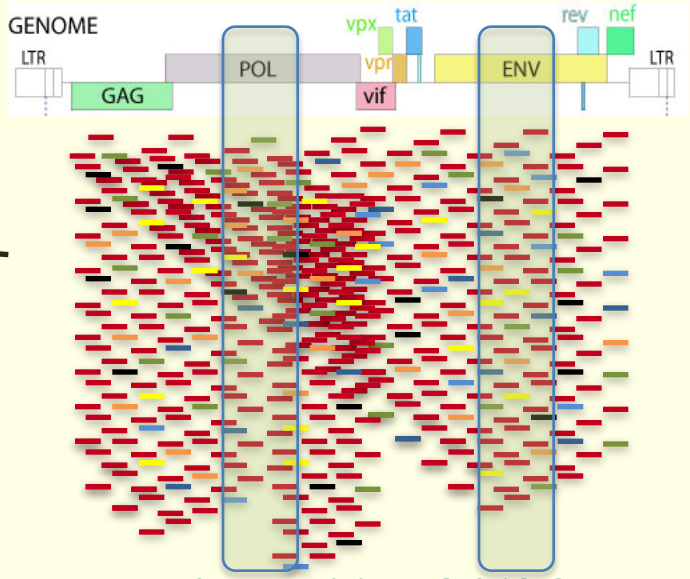
4 MiSeq

4. Illumina

4. 454



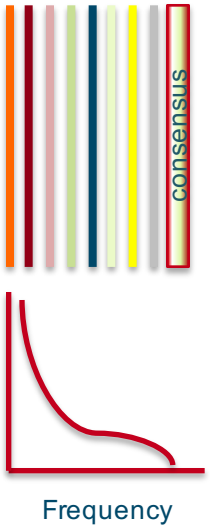
6. Analysis

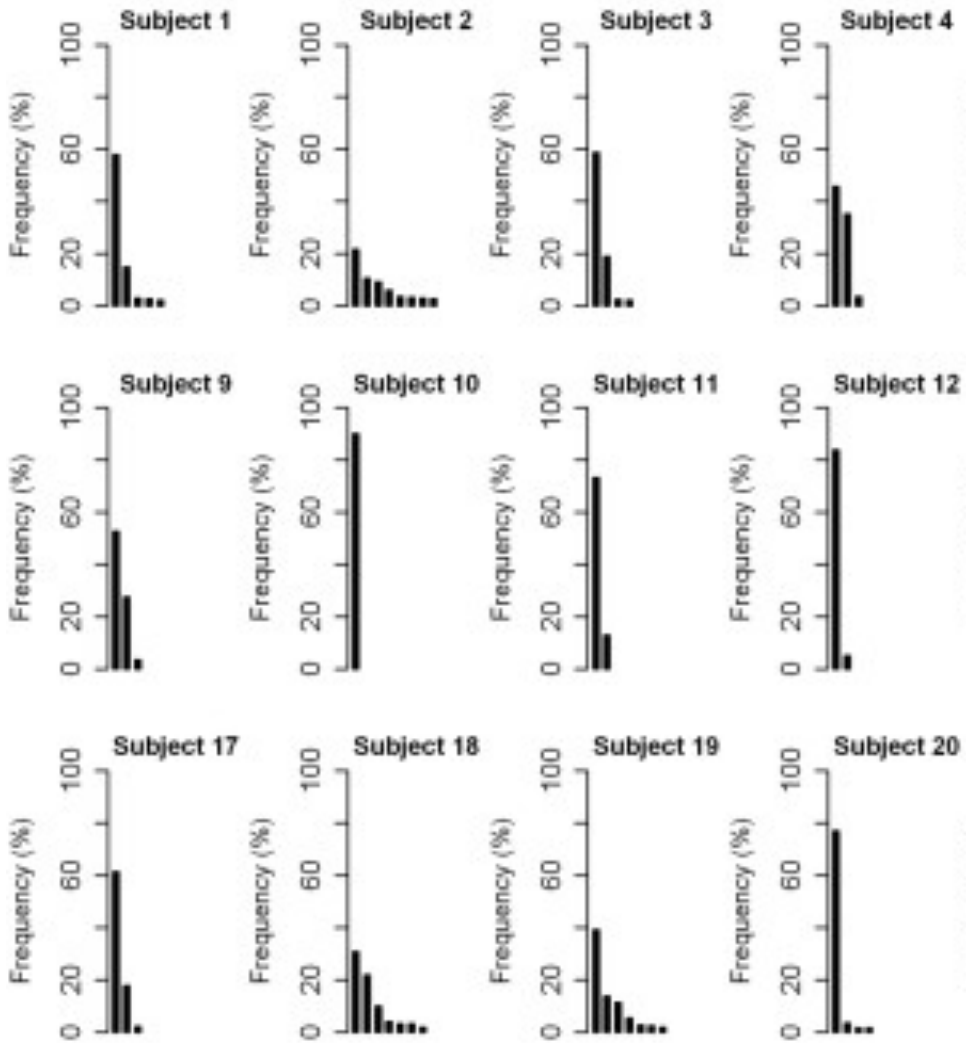


5. Assembly + QA/QC

Restriction of V3 region sequence divergence in the HIV-1 envelope gene during antiretroviral treatment in a cohort of recent seroconverters

Astrid Gall[1], Steve Kaye[2], Stéphane Hué[3], David Bonsall[2], Richard Rance[1], Gregory J Baillie[1], Sarah J Fidler[2], Jonathan N Weber[2], Myra O McClure[2], Paul Kellam[1,3*] and the SPARTAC Trial Investigators





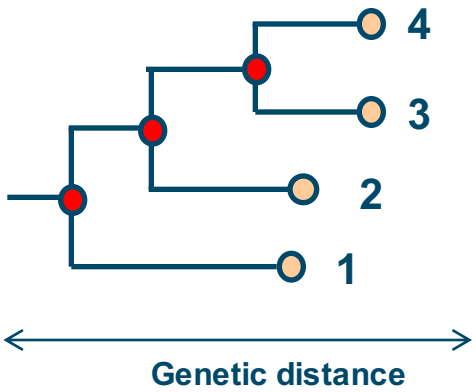
Gall et al **Retrovirology** 2013, 10(1), 8

Phylogenetics

Viral gene sequences

1 AAAGTTCTCAGACT…
2 AAAGTTCTCACACT…
3 AATGTTCTCAGACT…
4 AATGTTCTCAGACT…

Genetic ancestry



Phylogenetics

Model of molecular evolution

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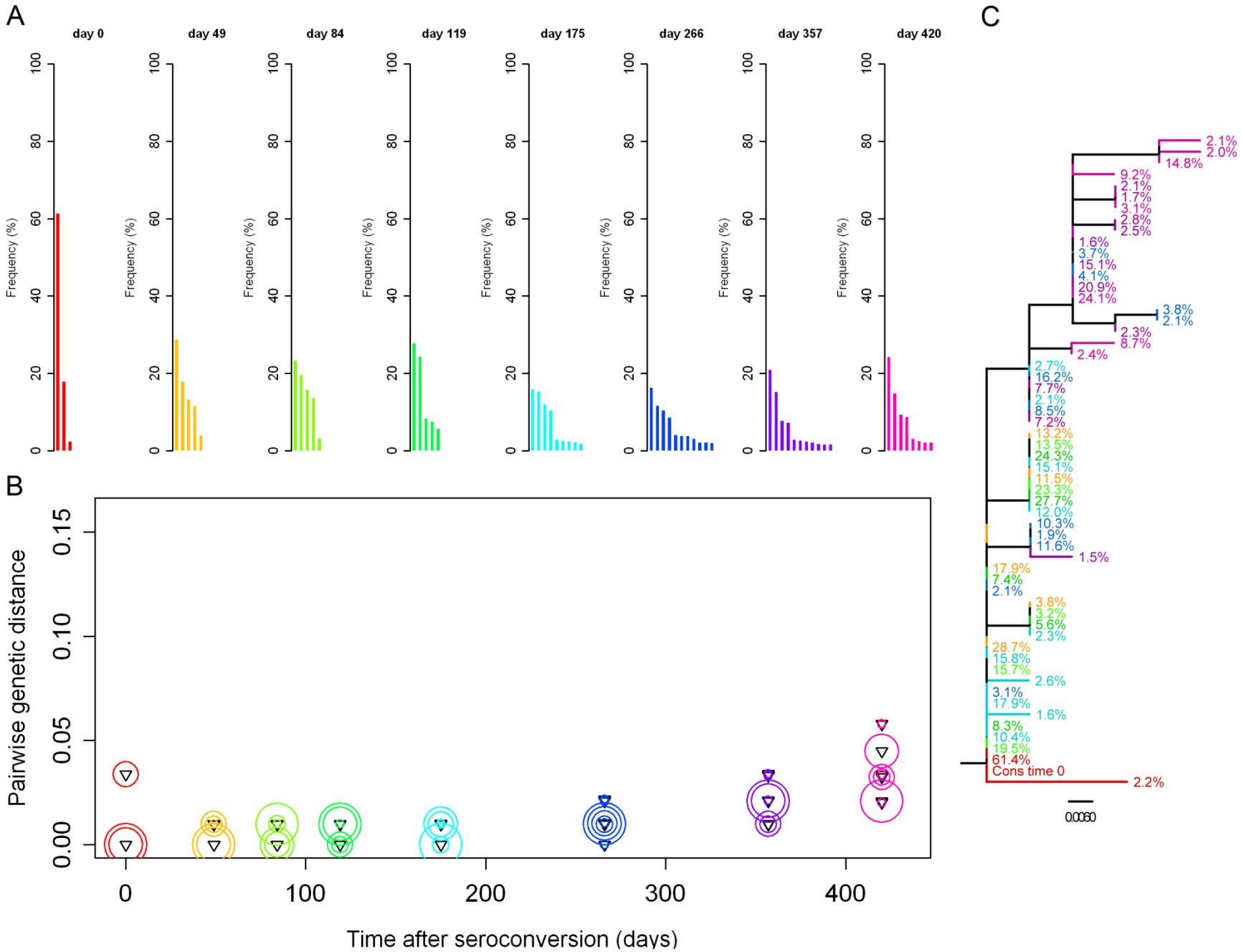
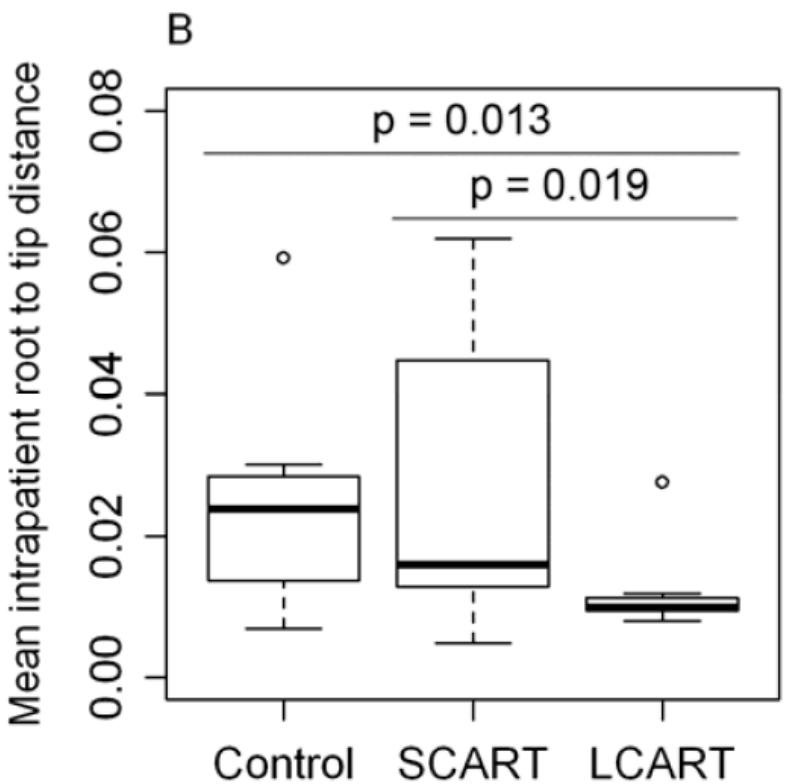
Thanks to Stephane Hue

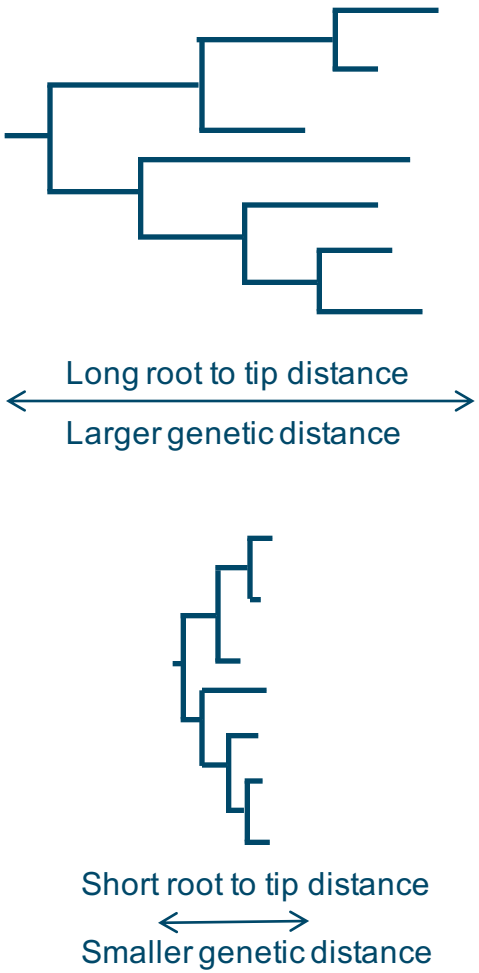


Gall et al **Retrovirology** 2013, 10(1), 8

ART supresses HIV genetic variation

- Evidence for complete virus replication suppression?





SCART: Short course ART (12 Weeks)
LCART: Long course ART (48 Weeks)

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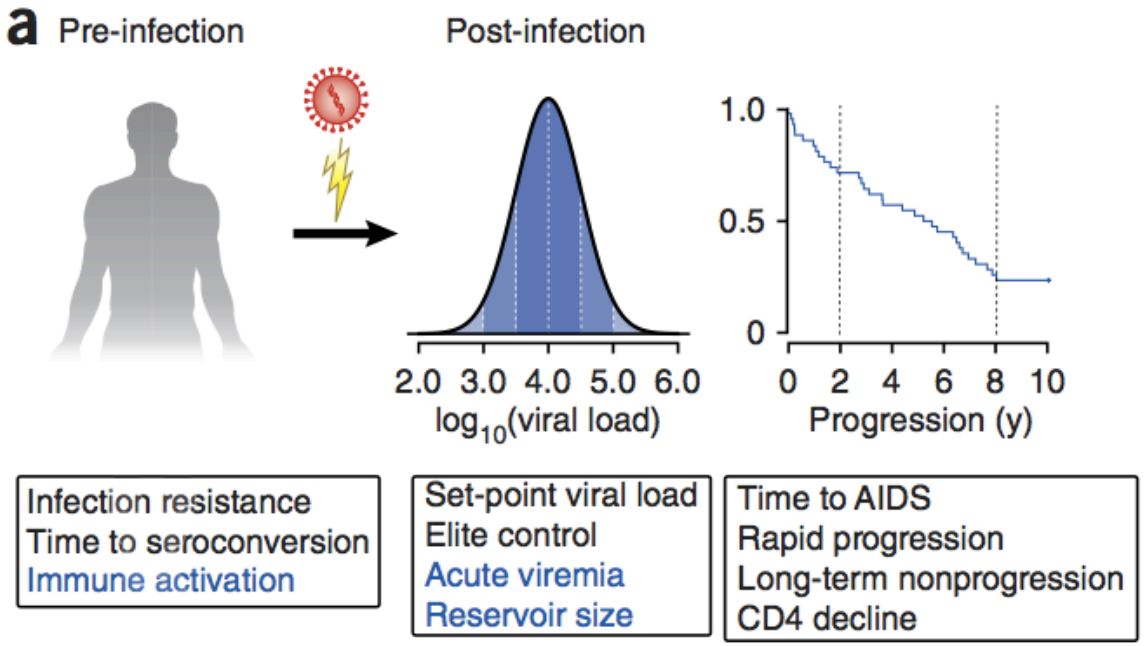
Gall et al **Retrovirology** 2013, 10(1), 8

Genetic diversity & HIV infection phenotypes - large scale studies



Every place in an HIV genome (~9000 bp) and a human genome (3 billion bp) represents a significance test for genetic variation associated with the phenotypic trait.

- Large multiple testing problem – corrected p-values
- Different frequencies of variants (common >5%, rare < 5%)
- **Therefore need large sample sizes and/or large effect sizes**

McLaren & Carrington, Nature Immunology 2015, 16(6), 577-583

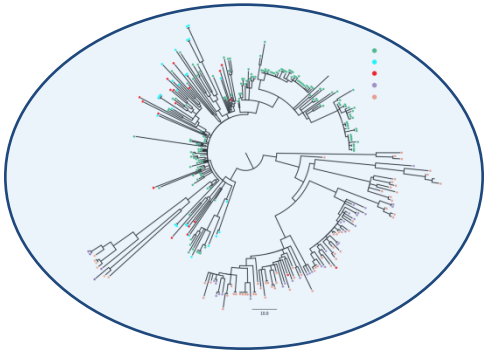
Genetics and HIV infection phenotypes

Heritability is proportion of variance in phenotype explained by variation in genotype

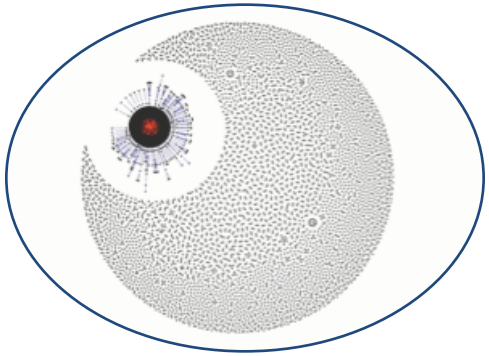
Heritability can be measured by:

- Comparing parents and offspring
- Genome-wide association studies

Virus Variation



Adaptive immune system



Host genetics

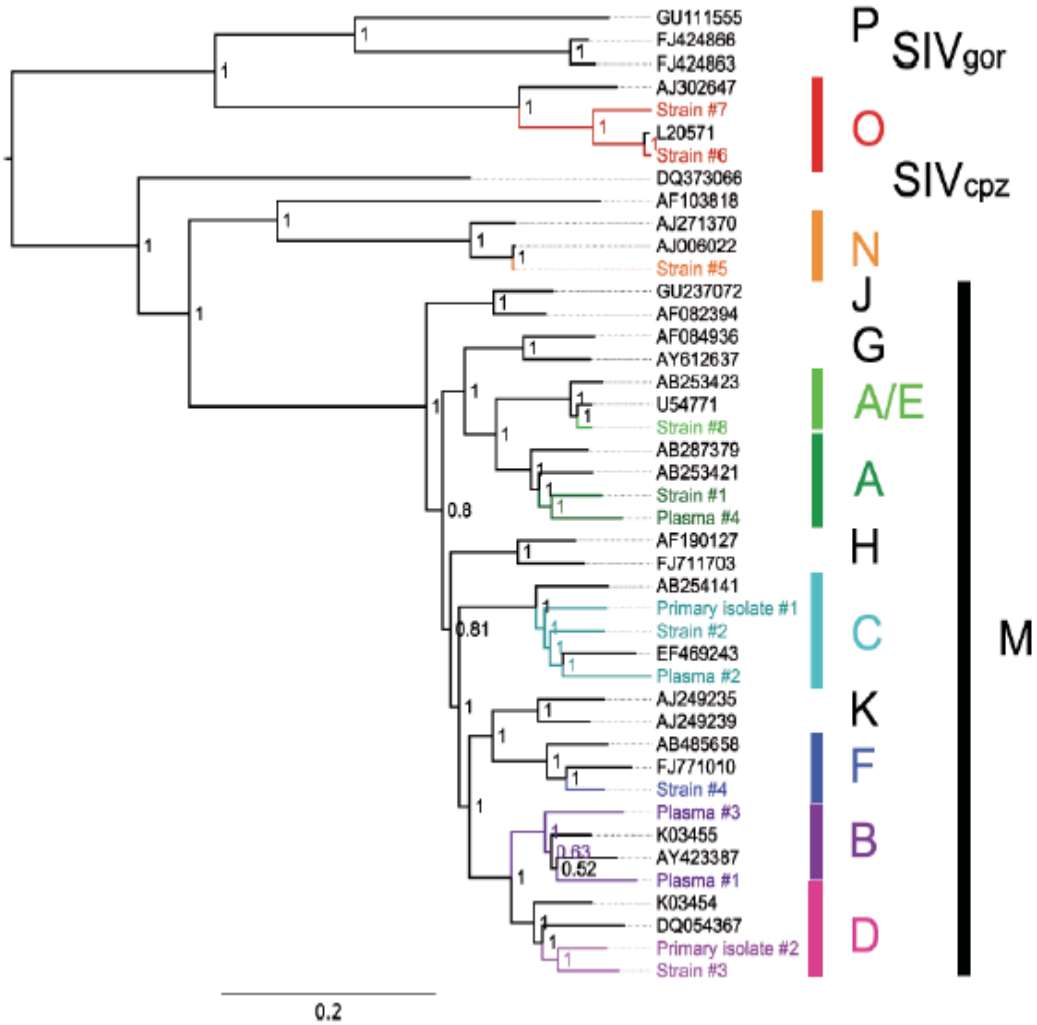
Estimates from clinical data on VL
33% (20-46%)
Recent small studies on VL
23% (0-50%)

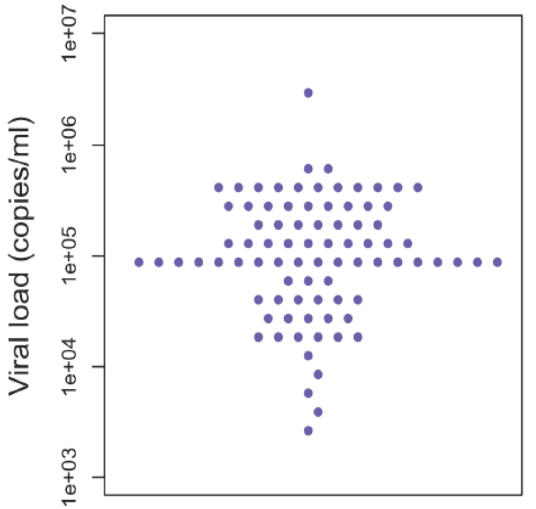
?

GWAS on VL set-point
13%

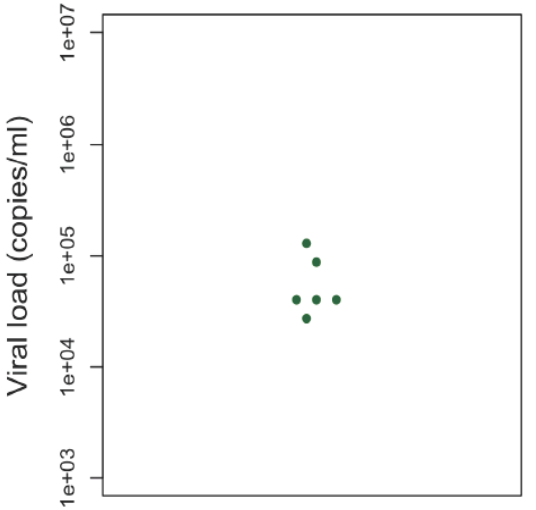
Full HIV genome sequencing, Group M & O

2015 HIV Sequence compendium has 5834 near full HIV-1 genomes





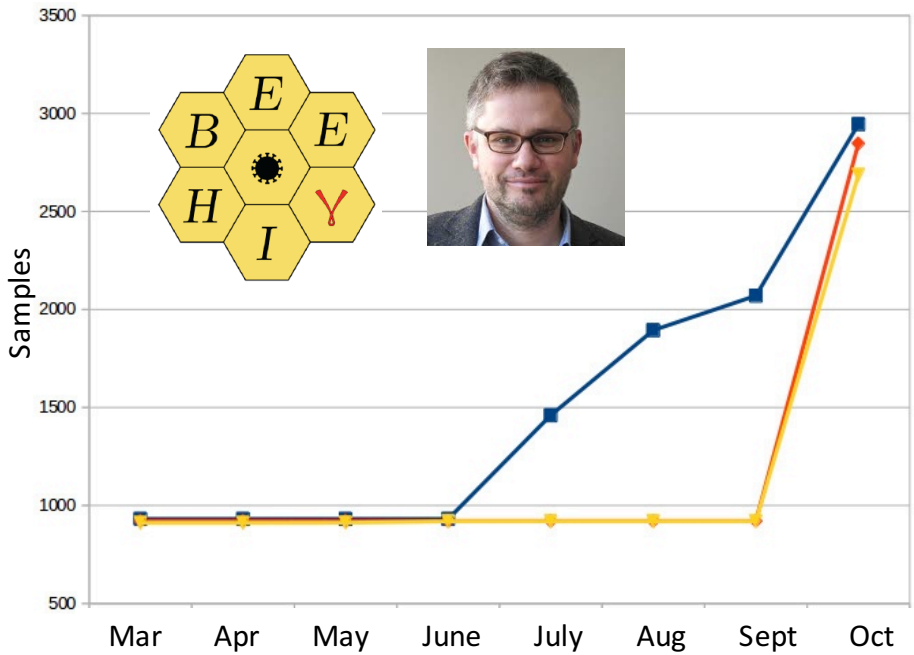
4/4 amplicons successfully amplified

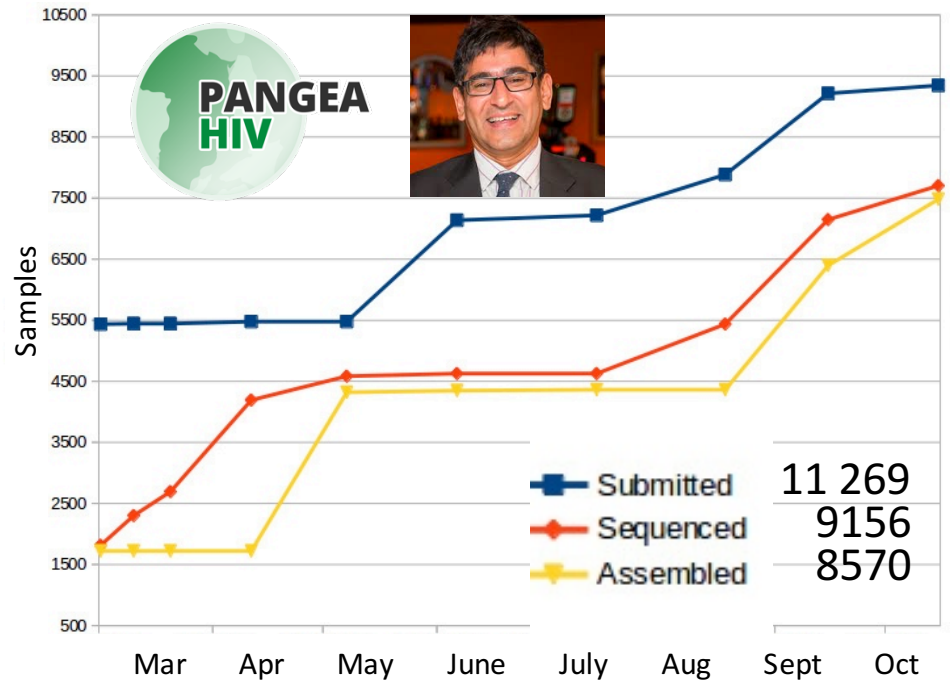


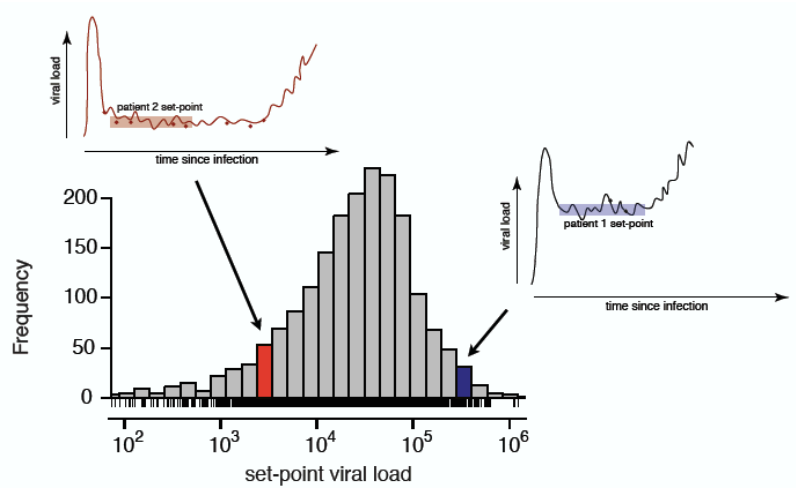
3/4 amplicons successfully amplified

Gall A, et al.. J Clin Microbiol. **2012**, 50(12), 3828-3844

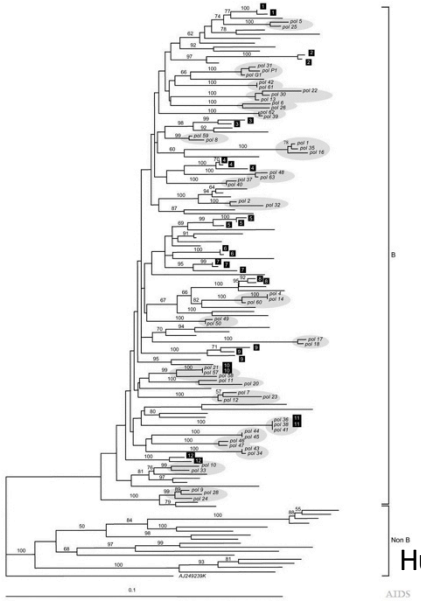
Get to 20K HIV genomes







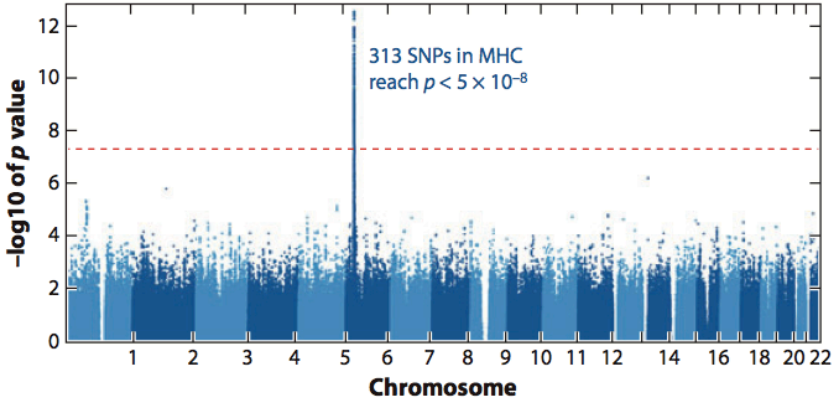
Hypothesis: HIV has evolved to maximise its transmission potential during untreated infections



Hypothesis: HIV 'full' genomes accurately define transmission chains for TasP in Africa

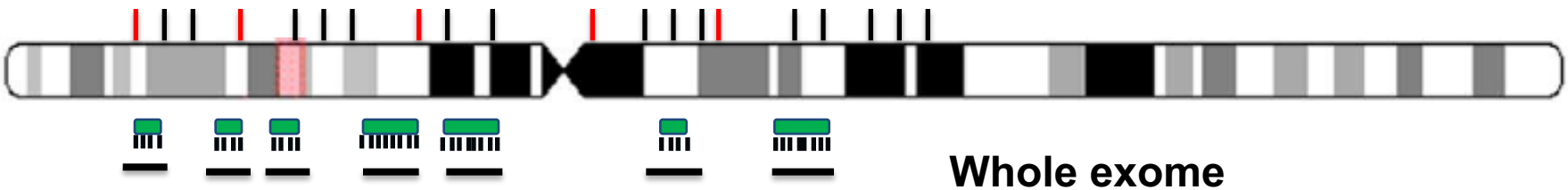
Hue et al. AIDS 2004, 18:719–728

Human genome variation – so far not that successful when applied to HIV disease phenotypes



Manhattan plot of data derived from 974 HIV controllers and 2,648 progressors. Shown are p-values for 1,384,048 data points

GWAS – 5% MAF (Minor allele frequency)

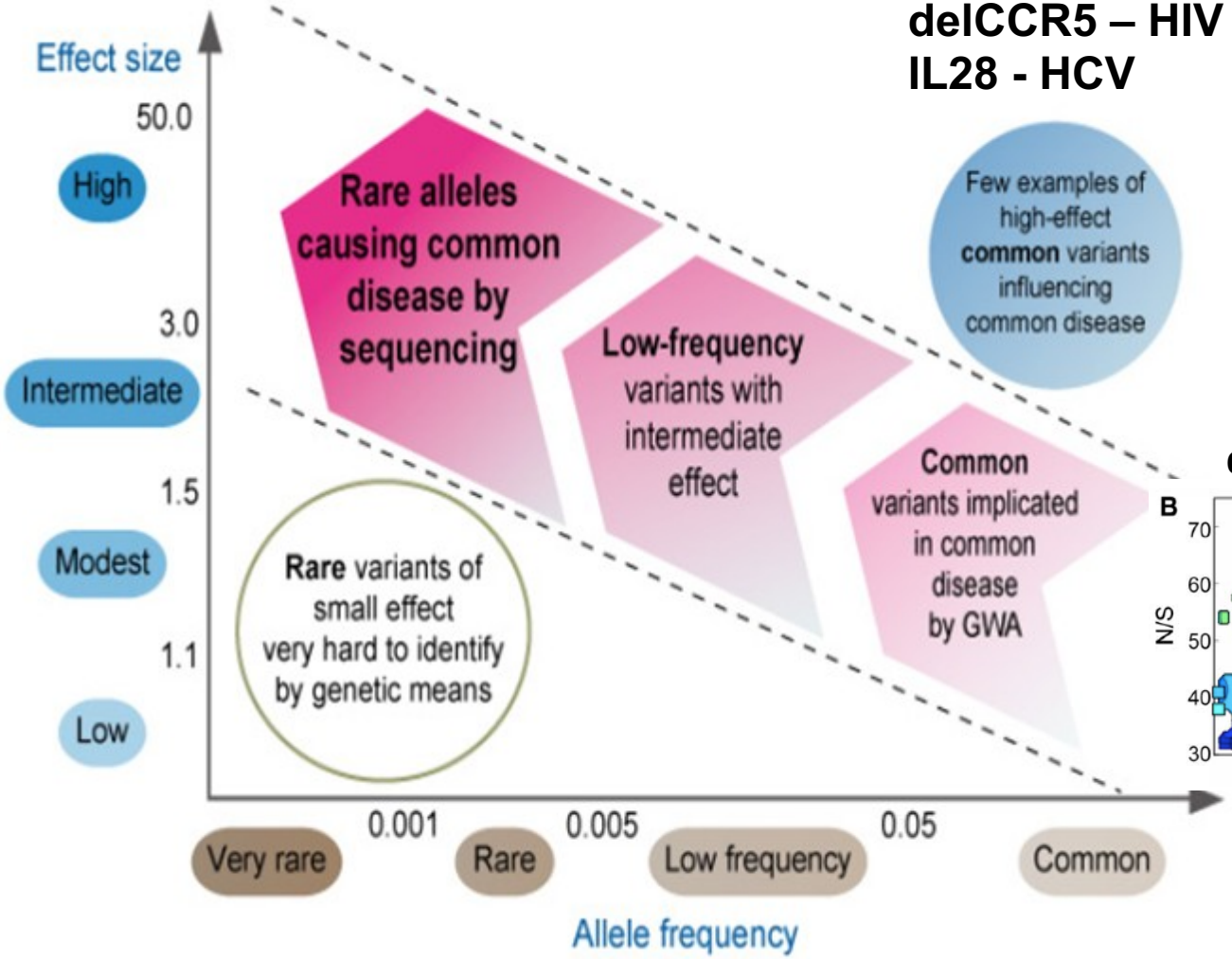


Whole exome

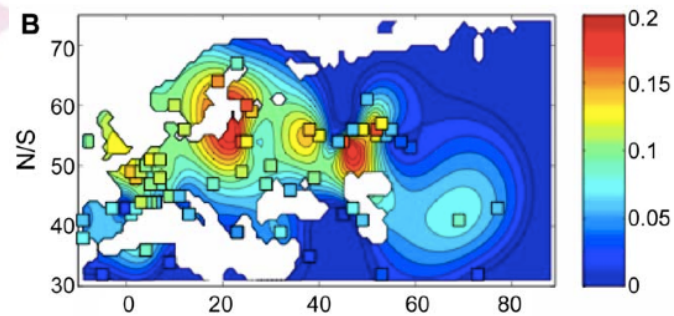
Whole genome 30-40x coverage

Host Genetics of infection – genome wide association studies (GWAS)

IFITM3 - Influenza
delCCR5 – HIV
IL28 - HCV

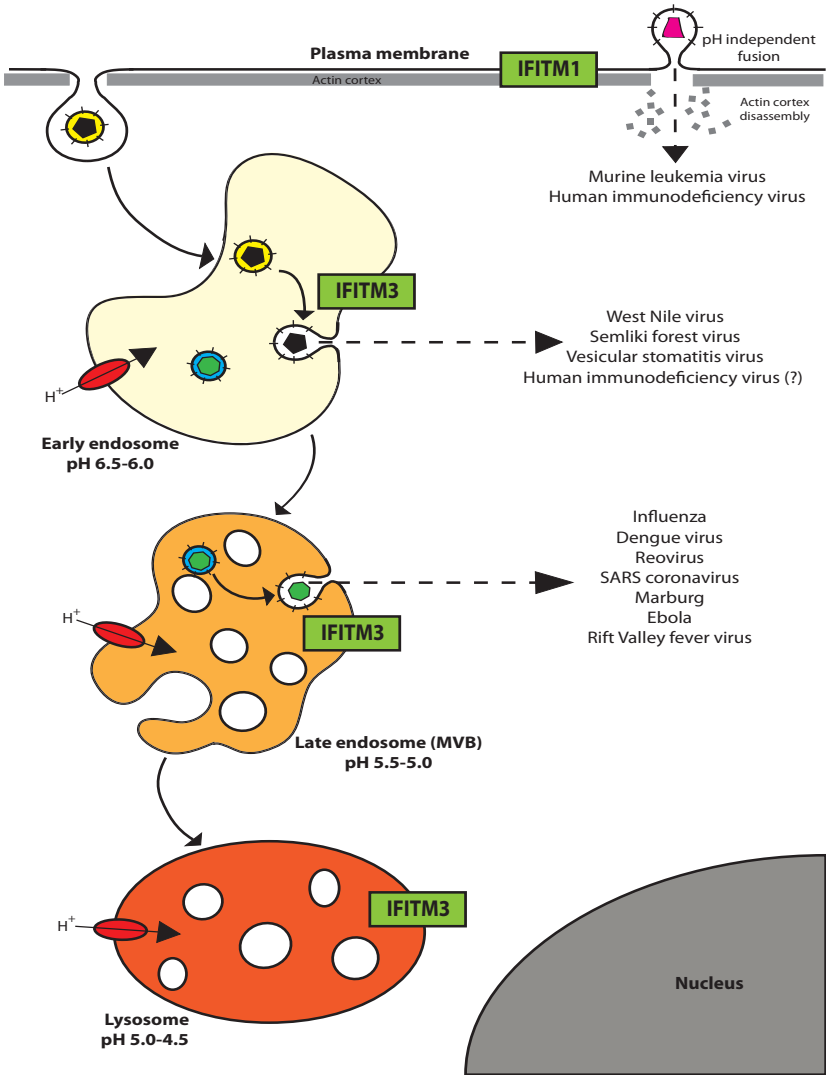


delCCR5 allele frequencies



Galvani & Novembre, Microbes and Infection, 2005; 7, 302–309

Host Genetics of HIV infection – things GWAS misses



Smith et al. 2014, Current opinion in virology 4, 71-77

LETTER

doi:10.1038/nature10921

IFITM3 restricts the morbidity and mortality associated with influenza

Aaron R. Everitt[1], Simon Clare[1], Thomas Pertel[2], Sinu P. John[2], Rachael S. Wash[1], Sarah E. Smith[1], Christopher R. Chin[2], Eric M. Feeley[2], Jennifer S. Sims[2], David J. Adams[1], Helen M. Wise[3], Leanne Kane[1], David Goulding[1], Paul Digard[3], Verneri Anttila[1], J. Kenneth Baillie[4,5], Tim S. Walsh[5], David A. Hume[4], Aarno Palotie[1], Yali Xue[1], Vincenza Colonna[1,6], Chris Tyler-Smith[1], Jake Dunning[7], Stephen B. Gordon[8], The GenISIS Investigators*, The MOSAIC Investigators*, Rosalind L. Smyth[9], Peter J. Openshaw[7], Gordon Dougan[1], Abraham L. Brass[2,10] & Paul Kellam[1,11]

Cell Reports
Article
ACCESS
CellPress

IFITM Proteins Restrict HIV-1 Infection by Antagonizing the Envelope Glycoprotein

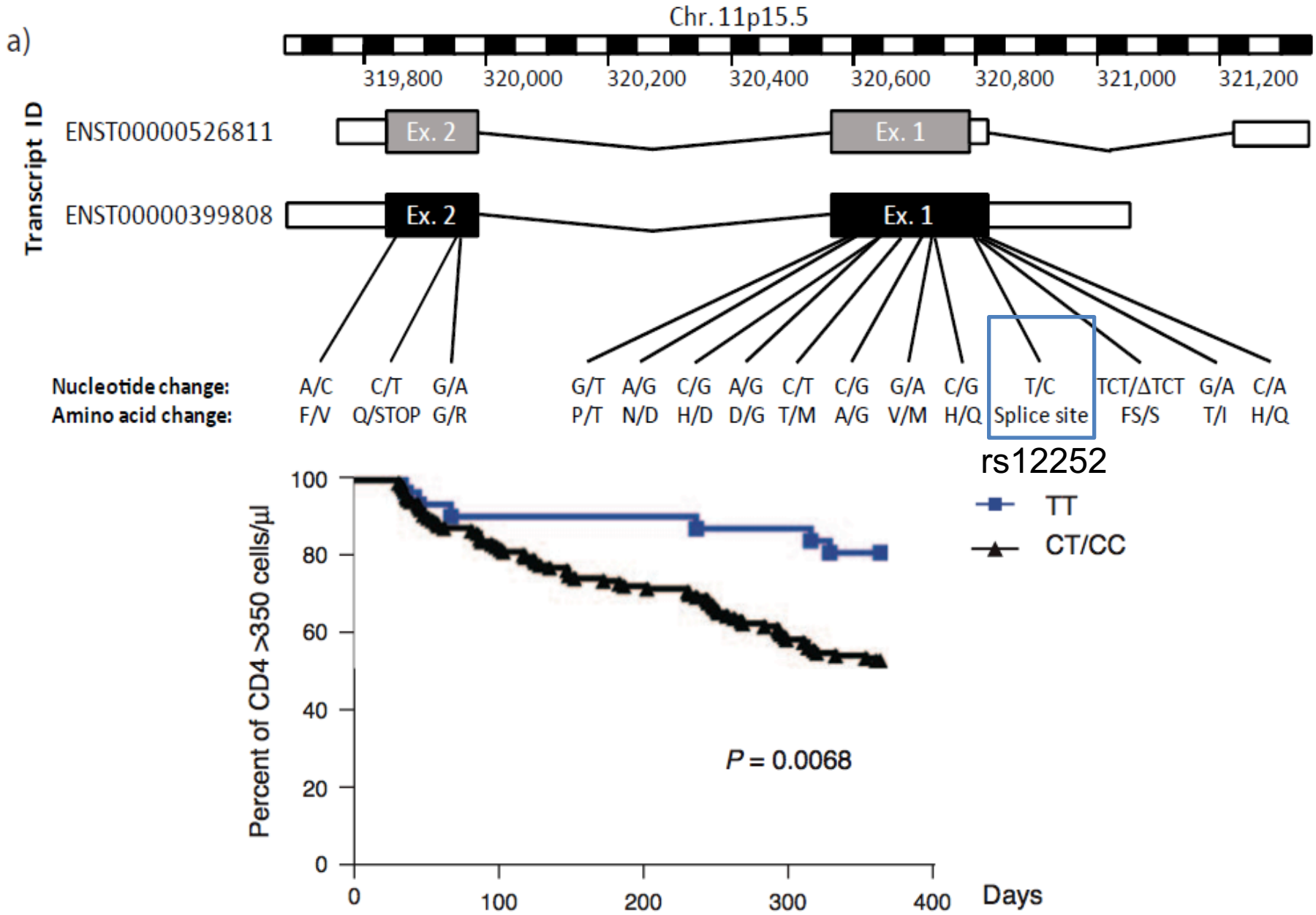
Jingyou Yu,[1,6] Minghua Li,[1,6] Jordan Wilkins,[1] Shilei Ding,[3,4] Talia H. Swartz,[2] Anthony M. Esposito,[2] Yi-Min Zheng,[1] Eric O. Freed,[5] Chen Liang,[3,4] Benjamin K. Chen,[2] and Shan-Lu Liu[1,*]
[1]Department of Molecular Microbiology and Immunology, Bond Life Sciences Center, University of Missouri, Columbia, MO 65211, USA
[2]Division of Infectious Diseases, Department of Medicine, Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
[3]McGill AIDS Centre, Lady Davis Institute, Montreal, QC H3T 1E2, Canada
[4]Department of Microbiology and Immunology, McGill University, Montreal, QC H3A 2B4, Canada
[5]Virus-Cell Interaction Section, HIV Dynamics and Replication Program, National Cancer Institute-Frederick, Frederick, MD 21702, USA
[6]Co-first author
*Correspondence: liushan@missouri.edu
http://dx.doi.org/10.1016/j.celrep.2015.08.055

Cell Host & Microbe
Article
CellPress

IFITM Proteins Incorporated into HIV-1 Virions Impair Viral Fusion and Spread

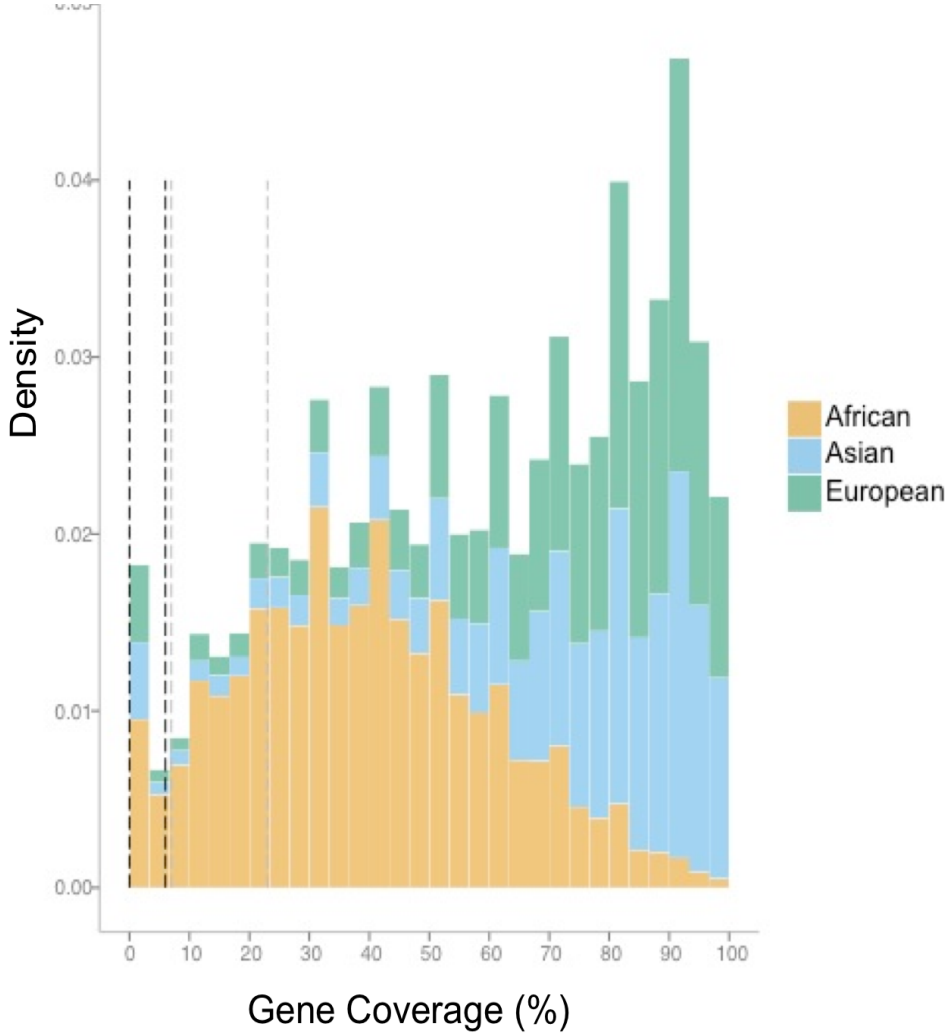
Alex A. Compton,[1,2,*] Timothée Bruel,[1,2] Françoise Porrot,[1,2] Adeline Mallet,[3] Martin Sachse,[3] Marine Euvrard,[1,4] Chen Liang,[5] Nicoletta Casartelli,[1,2] and Olivier Schwartz[1,2,6,*]
[1]Institut Pasteur, Department of Virology, Virus & Immunity Unit, Paris 75015, France
[2]CNRS URA 3015, Paris 75015, France
[3]Institut Pasteur, Imagopole, Ultrastructural Microscopy Platform, Paris 75015, France
[4]École Normale Supérieure, Department of Biology, Cachan 94230, France
[5]Lady Davis Institute, McGill AIDS Centre, Montreal, QC H3T 1E2, Canada
[6]Vaccine Research Institute, Creteil 94010, France
*Correspondence: alex.compton@pasteur.fr (A.A.C.), schwartz@pasteur.fr (O.S.)
http://dx.doi.org/10.1016/j.chom.2014.11.001

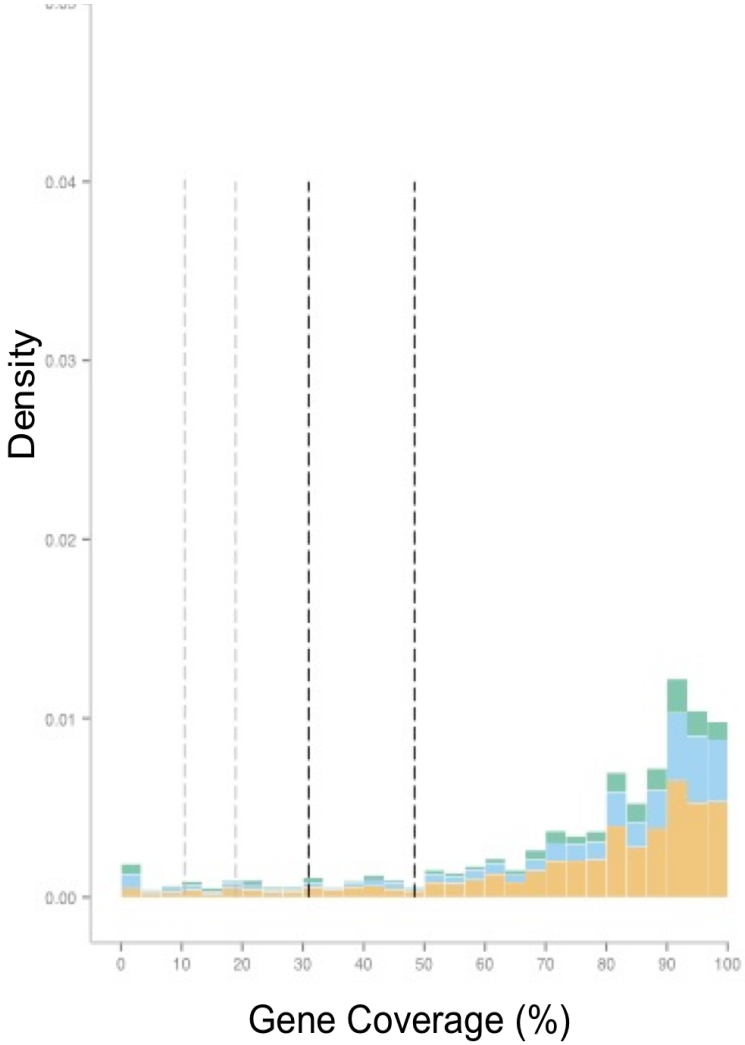
rs12252-C is associated with rapid progression of acute HIV-1 infection



Zhang et al. AIDS, 2015, 29(8), 889-894

If IFITM genes are so important, why have they never showed up in any GWAS of HIV diseases?





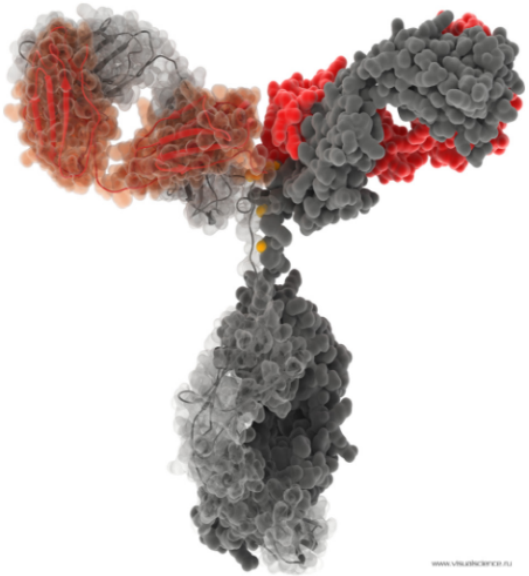
IFITM locus is not interrogated by previous GWAS SNP arrays

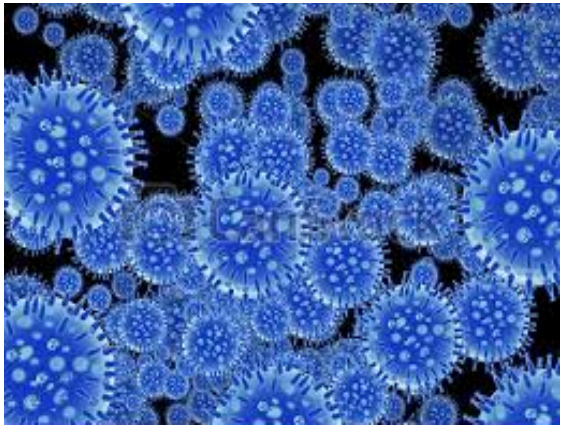
Large scale Whole Human Genome Sequencing is next

B cell receptor repertoires – the last genetic frontier

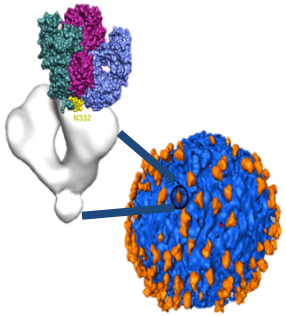
~3x10^9 different antigen binding CDR3s in a human

~0.5x10^9 new HIV viruses per day (untreated)



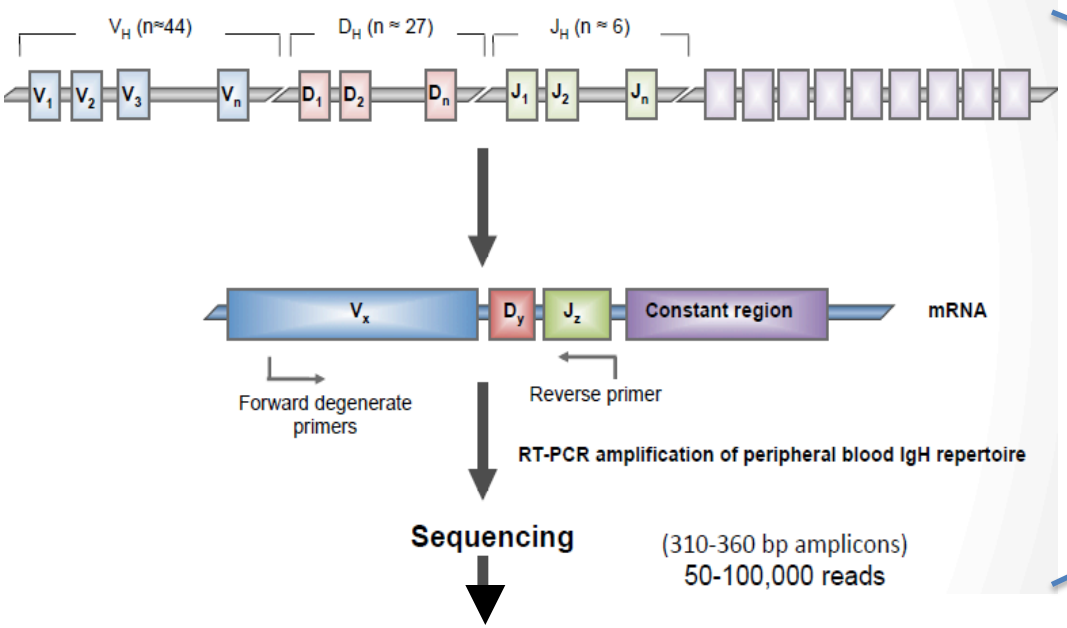


Can an individuals antibody diversity, history of infection and potential for heterotypic response be defined digitally using BCR sequencing.

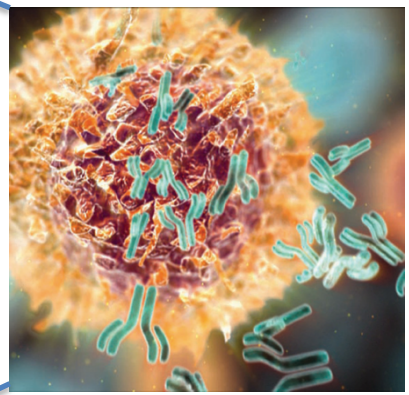


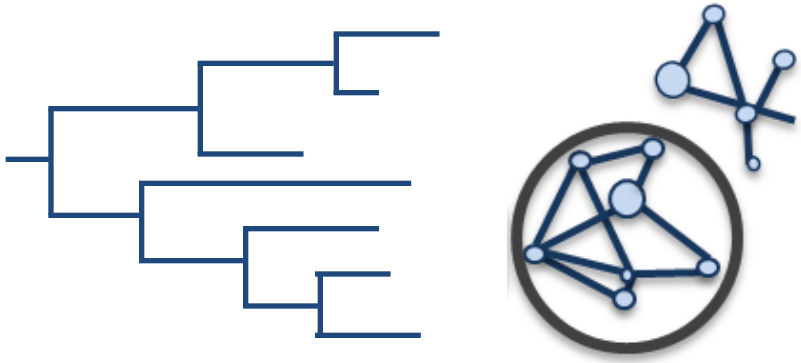
Can an deeper understanding of virus population genetics inform vaccine studies and efficacy in small scale studies

Network structures within B cell receptor sequence space



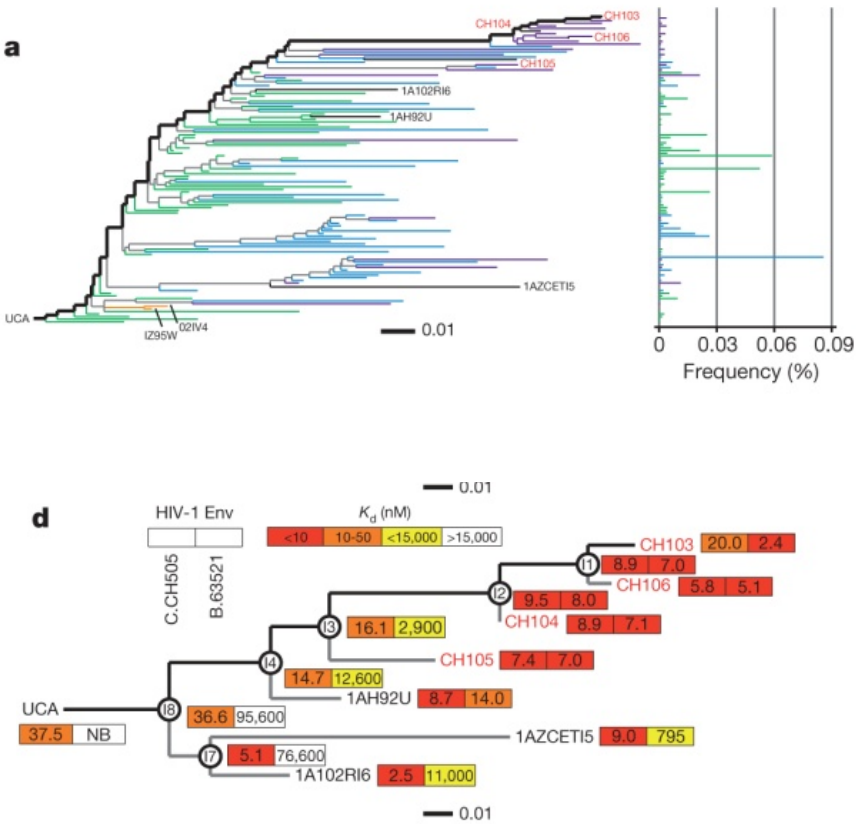
Antibody secreting cells

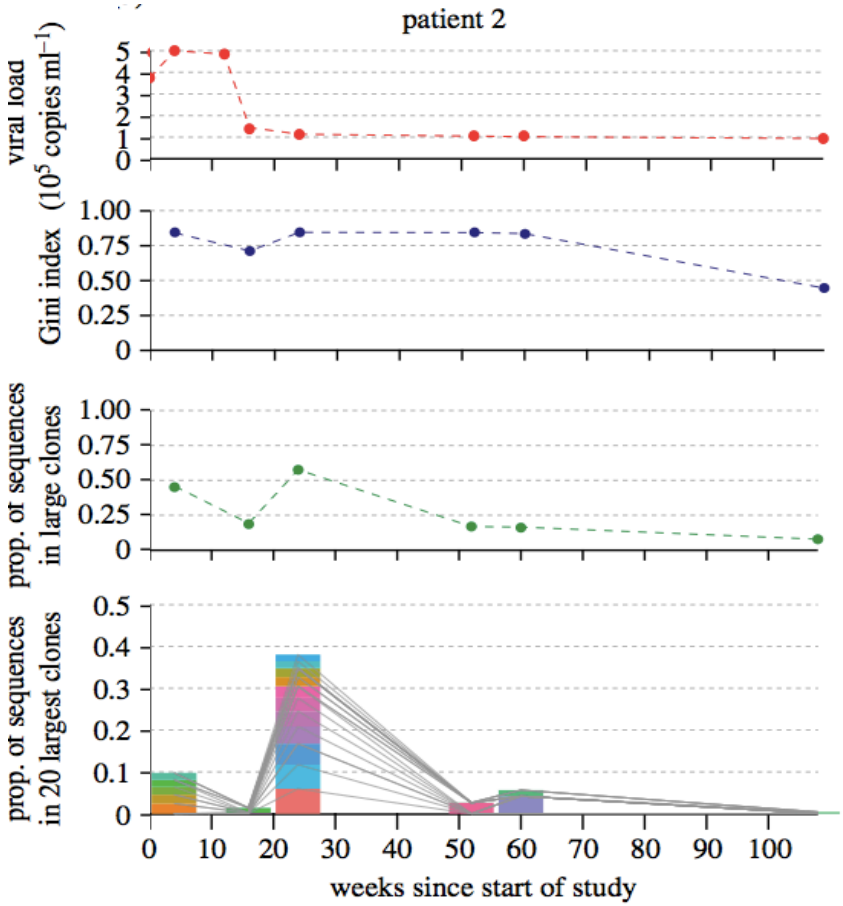




Bashford Rogers et al, BMC Immunology 2014, **15(29)**,
Bashford Rogers et al, Genome Research 2013, **23(11)**, 1874-1884

Can functional B cell repertoire sequence guide vaccination strategies



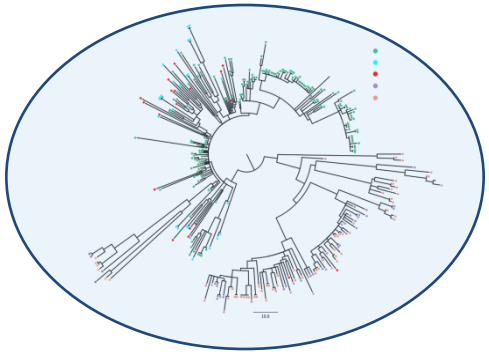


H-X Liao *et al. Nature* 2013; 496; 469-475

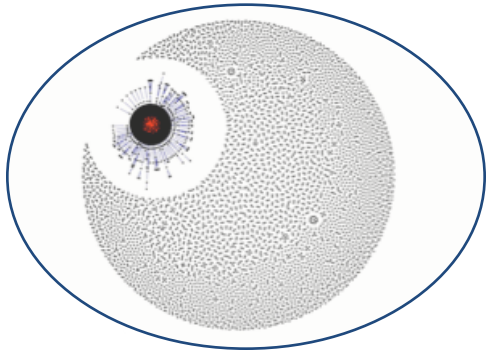
Hoehn K et al. Phil Trans R Soc B. 2015; 370(1676); 20140241-11

Conclusions

Virus Variation



Adaptive immune system



Human genetics

- Understanding HIV genetics in the 1990s contributed greatly to drug development and treatment strategies.
- Large scale genetics of virus and human are affordable, ongoing and should finally reveal the heritability of HIV infection phenotypes.
- Insights gained will help towards HIV cures, therapies and preventions.

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