Exceptional HIV Elite Controllers

Session: Let's talk about HIV Cure

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Conflict of interest disclosure

AIDS 2022

Affiliated Independent Event

Towards an HIV Cure

IAS

I have no relevant financial relationships with ineligible companies to disclose in the context of this presentation topic

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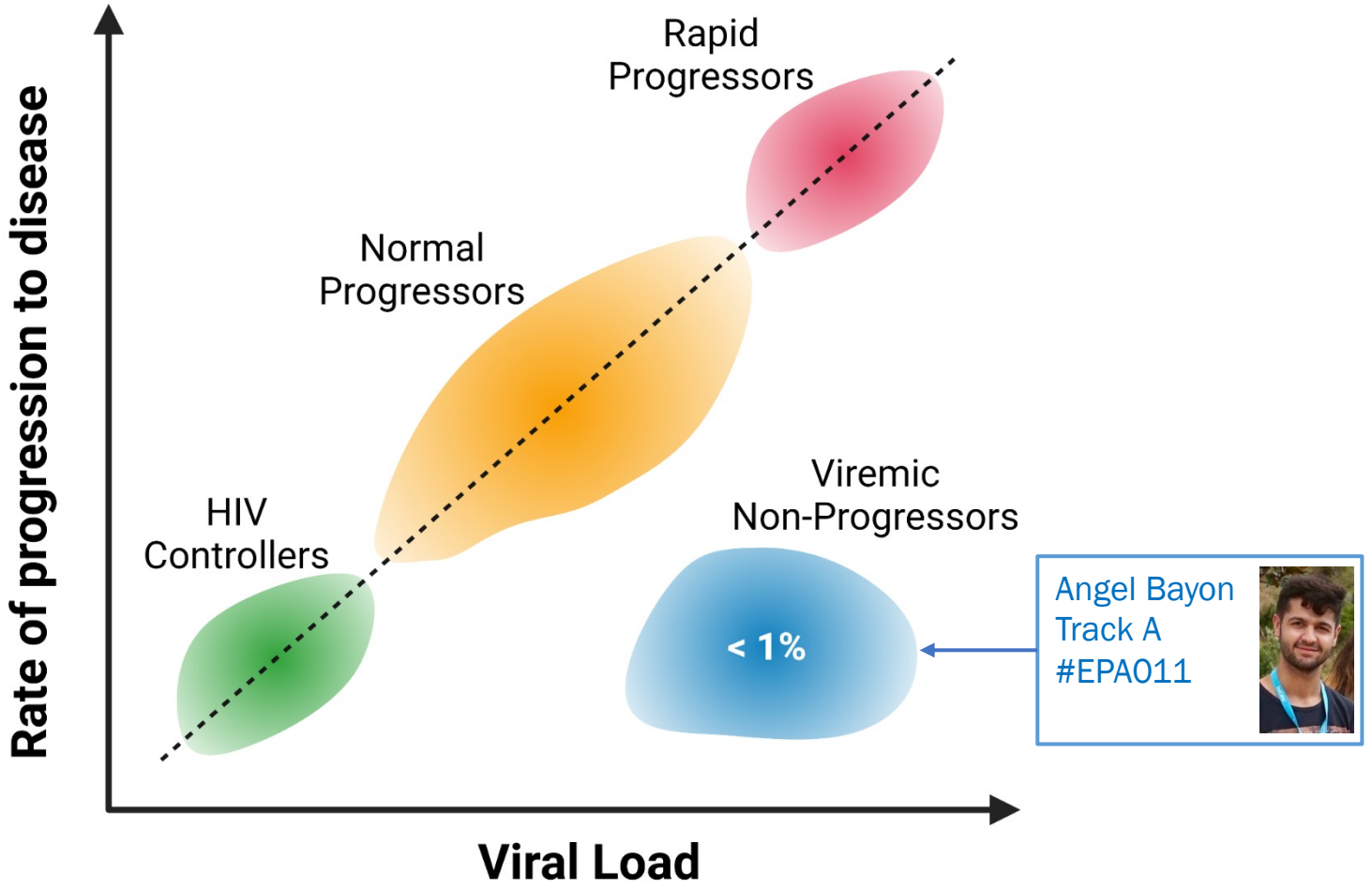
Extrem Cases of HIV-1 Disease Progression



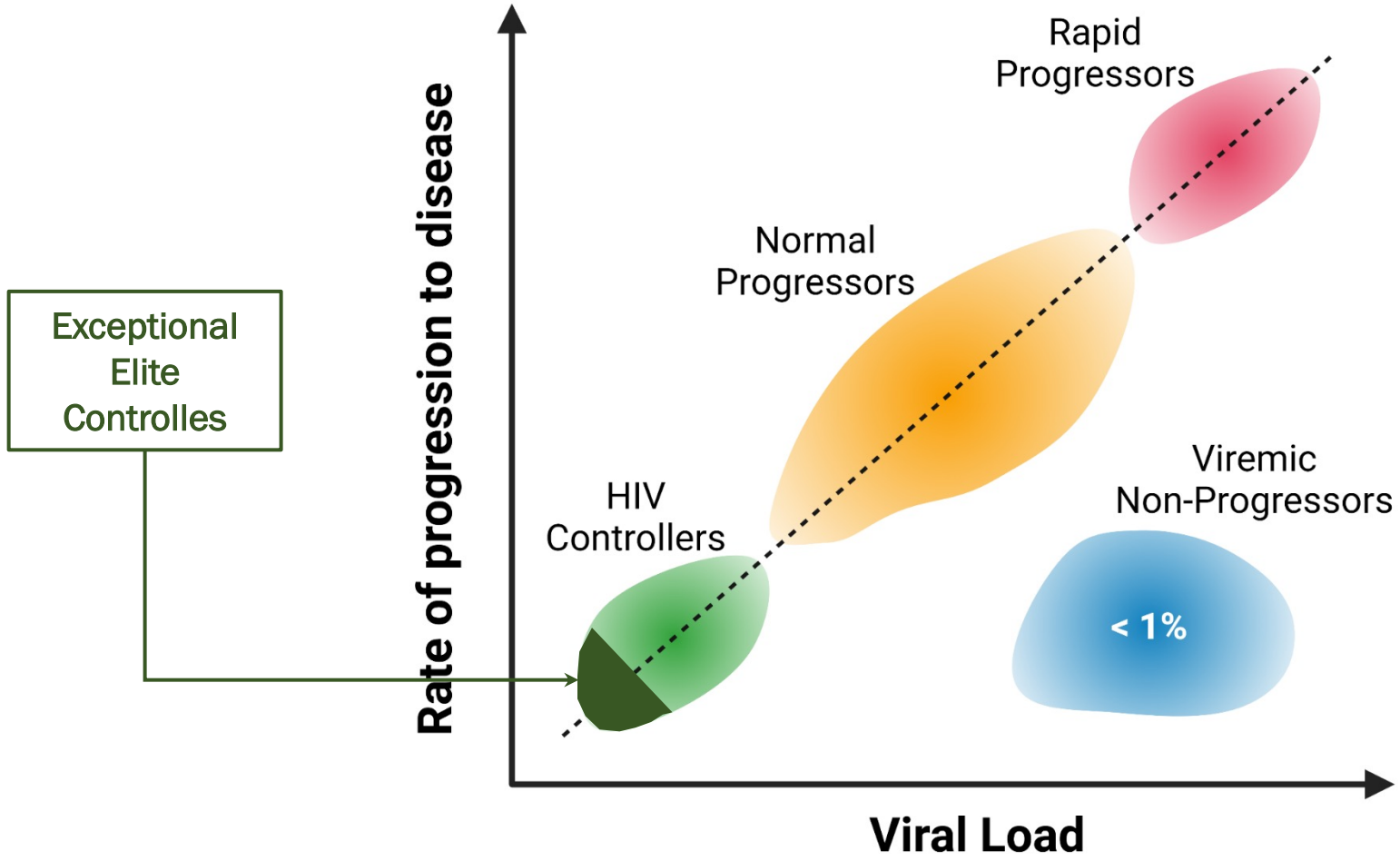
Angel Bayon
Track A
#EPA011

Are elite controllers a model for a functional cure?

- Is it the virus?
  - Resevoirs, evolution, virus intactness?
- Is it the host?
  - Genetics, immunology, immuno-genetics?
- But elite controllers are heterogeneous in terms of long-term clinical, virological and immunological progression
- Are SOME elite controllers a model for a functional cure?
  - Undetectable plasma viremia and normal CD4 T-cell counts for >10 years appear to represent a very promising model

Autran *et al.* 2011. Curr Opin HIV AIDS; Canoui *et al.* 2017. Open forum Infect Dis

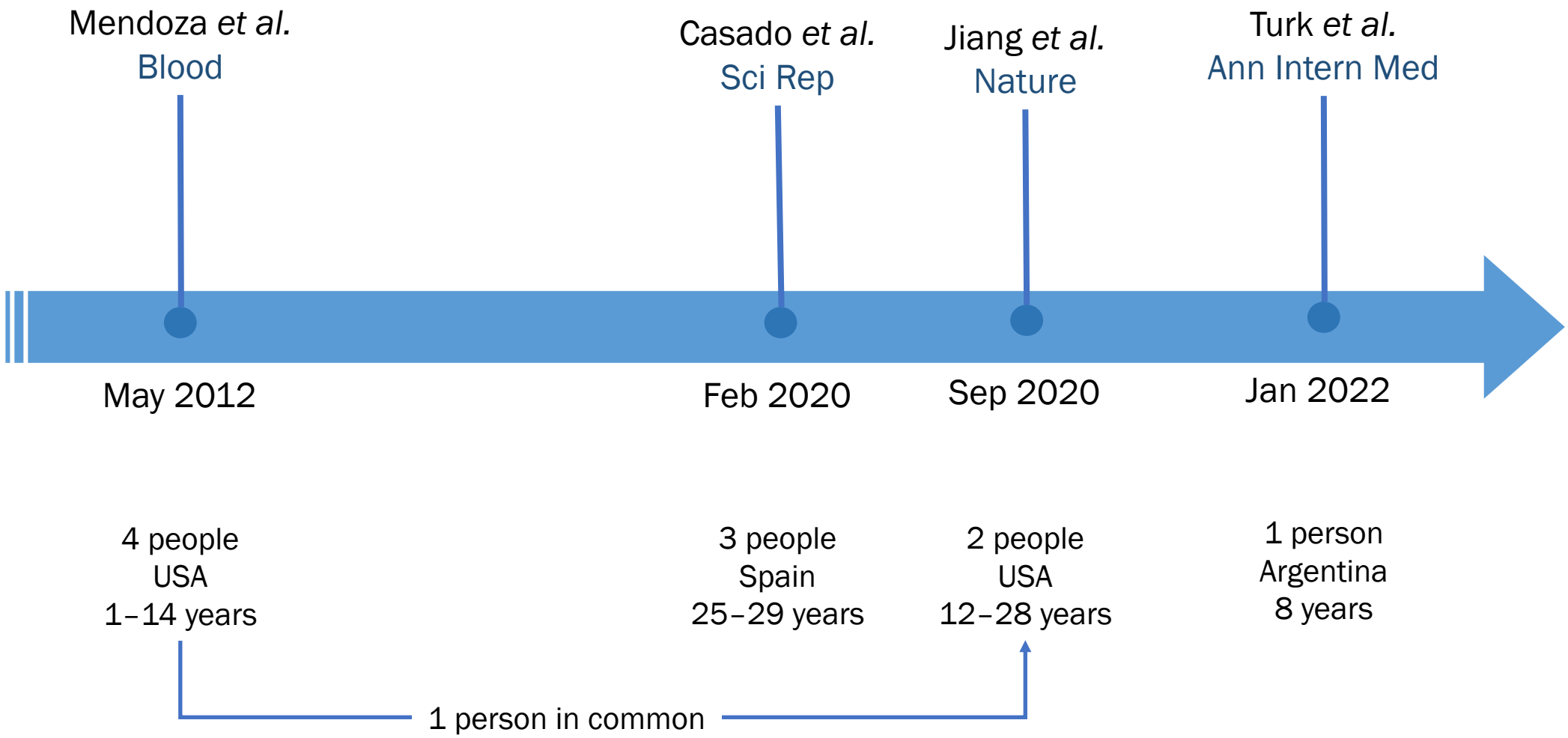
Extrem Cases of HIV-1 Disease Progression



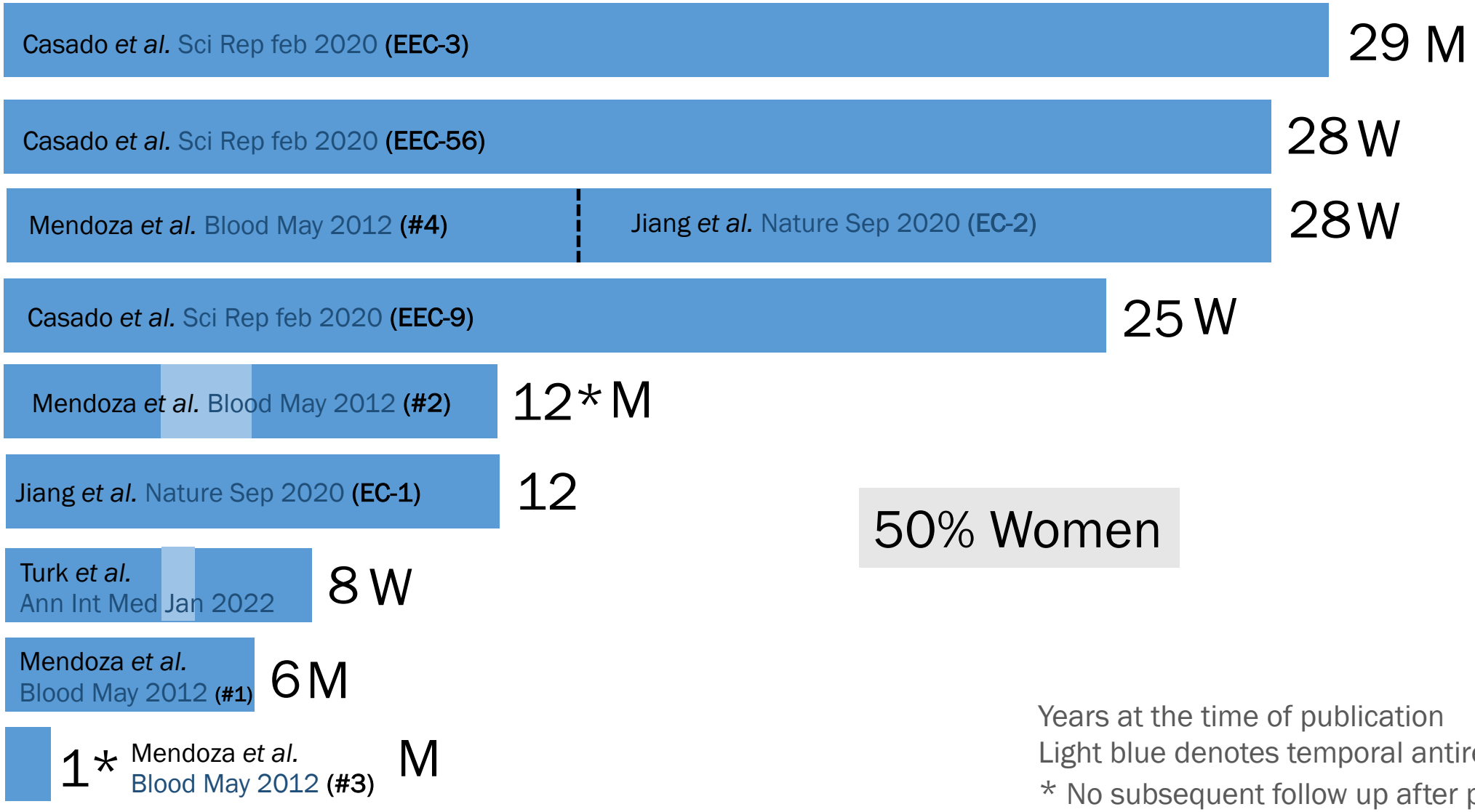
“Exceptional” HIV Elite Controllers (EEC)
the limitation of definitions …

- People with HIV that spontaneously control viral replication in absence of immune dysfunction
- No disease progression in absence of antiretroviral therapy
- Extraordinarily low HIV burdens
- Comparatively weak immune response
- Long-term control: >10-25 years
- Partially reactive for HIV-specific antibodies

Reports on Exceptional HIV Elite Controllers



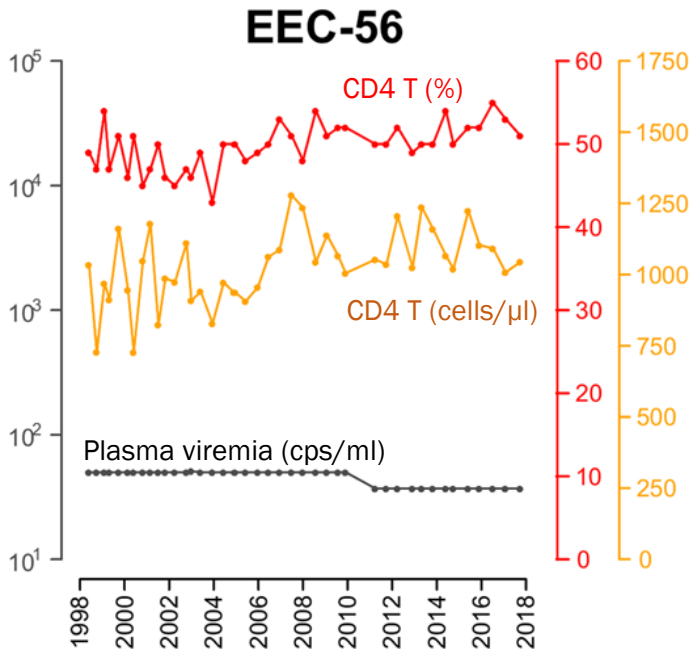
Years after HIV diagnose



Years at the time of publication
Light blue denotes temporal antiretroviral therapy
* No subsequent follow up after publication

Mendoza *et al.* 2012; Casado *et al.* 2020; Jiang *et al.* 2020; Turk *et al.* 2022

Clinical evolution



- Median of 24 (range 6–64) plasma viral load tests
  - Always below the limit of detection of contemporary assays
  - Except for ≤2 non-consecutive blips below 400 cps/ml
- Ultrasensitive plasma viremia / SCA below 0.4 cps/ml
  - Except for 1 sample of 2 cps/ml
- Median absolute CD4+ T cells in last determination of 921 (range 529-1488)
- Ratio CD4/CD8 always >1
  - Except for the Esperanza's case in whom is variable

Mendoza *et al.* 2012; Casado *et al.* 2020; Jiang *et al.* 2020; Turk *et al.* 2022

Host Genetic Determinants

	#1	#2	#3	#4/SFO	EEC-3	EEC-9	EEC-56	Esperanza
CCR5	WT/Δ32	WT/WT	WT/WT	WT/WT	WT/WT	WT/WT	WT/WT	WT/WT
HLA class I A loci	24, 31			02, 30	02, 02	02, 31	01, 02	02, 31
HLA class I B loci	40, **44**	**15**, 57	**44**, **51**	**13**, 57	27, **58**	**39**, 57	**14**, 57	**15**, **44**
CCR2 V64I rs1799864					WT/WT	WT/WT	WT/WT	
HLA C rs9264942					-35 TT→CC	-35 TT→CC	-35 TT→CC	

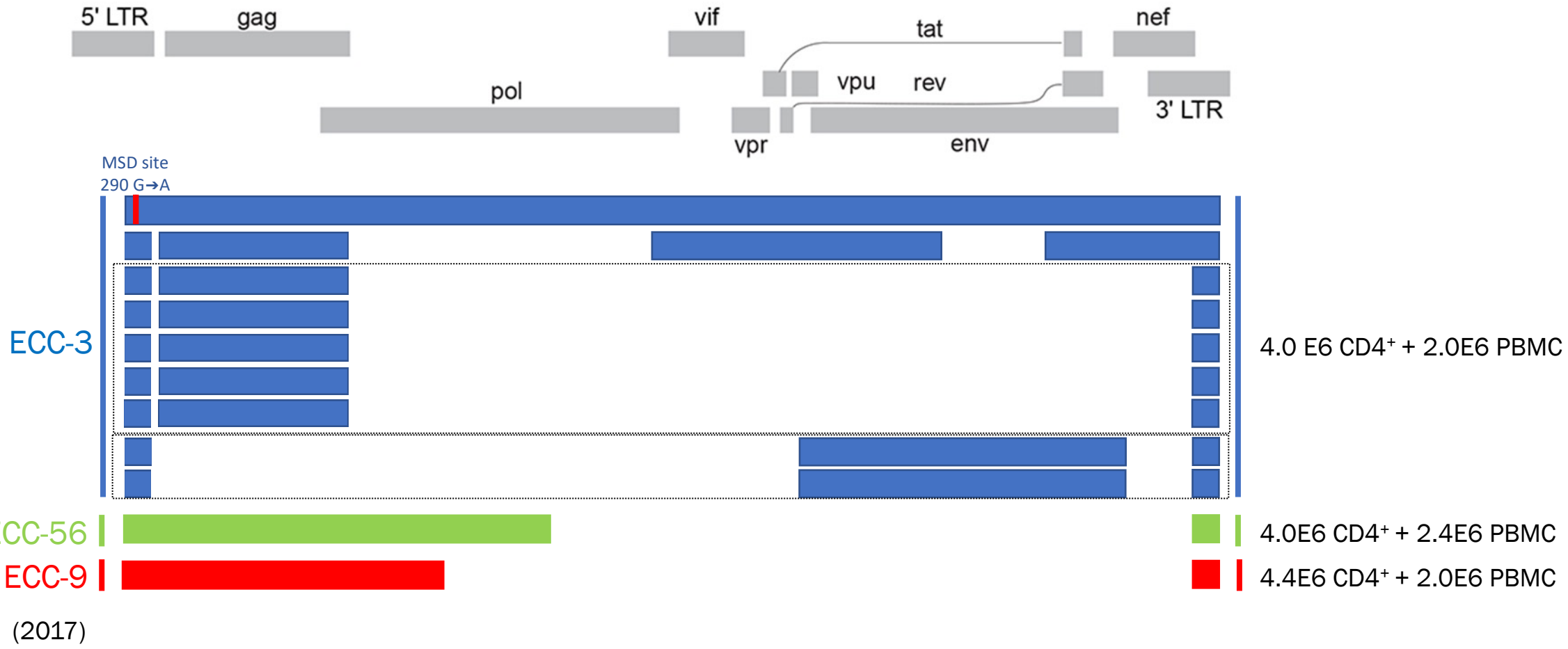
Migueles *et al.* 2000; Kiepiela *et al.* 2004; Lambotte *et al.* 2005; Bailey *et al.* 2006; Fellay *et al.* 2006; McLaren *et al.* 2012; Mendoza *et al.* 2012; Casado *et al.* 2020; Jiang *et al.* 2020; Turk *et al.* 2022

Proviral DNA and qVOA

	#1	#2	#3	#4/SFO	EEC-3	EEC-9	EEC-56	Esperanza
Proviral DNA copies/E6 cells	6.56 PBMC	25.2 PBMC	n.a.	IPDA^{-} 14E6 rCD4^{+}	27.09 4E6 tCD4^{+}	8.75 2.6E6 tCD4^{+}	10.05 3.2E6 tCD4^{+}	n.a.
qVOA copies/E6 cells	<0.004	<0.002	0.046	<0.004 41E6 tCD4^{+} 340E6 rCD4^{+}	<0.025 28E6 tCD4^{+}	<0.018 38E6 tCD4^{+}	<0.018 63E6 tCD4^{+}	<LOD 150E6 rCD4^{+}
Tissues copies/E6 cells	n.a.	colon 2.8cp E6/CD4	colon 1.9cp E6/CD4	HIV DNA^{-} in 4E6 CD45^{+} from rectum & ileum*	n.a.	n.a.	n.a.	placenta (neg)

qVOA: quantitative Viral Ourgrowth Assay; rCD4+: resting CD4^{+}; tCD4^{+}: total CD4^{+}; n.a.: no available
*, a previous sample from 2012 : <2.6 copies/10^{6}cells in colon, and 42.4 copies/10^{6}cells in ileum
Mendoza *et al.* 2012; Casado *et al.* 2020; Jiang *et al.* 2020; Turk *et al.* 2022

Near-full length virus sequencing

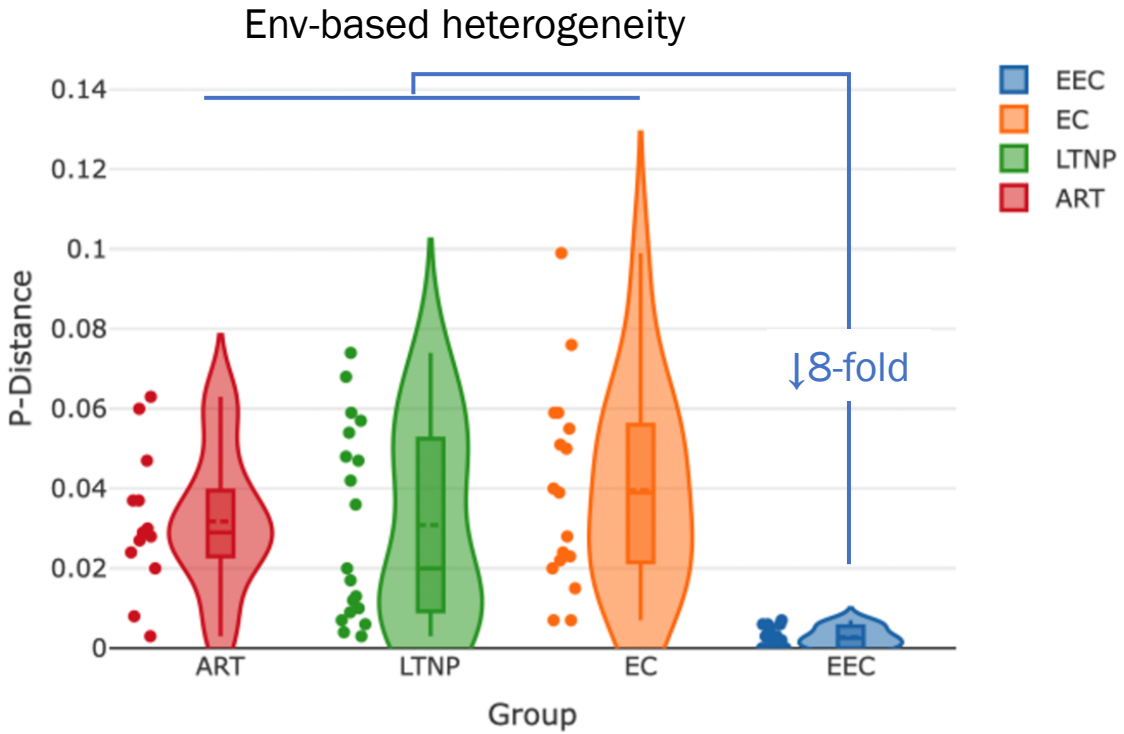


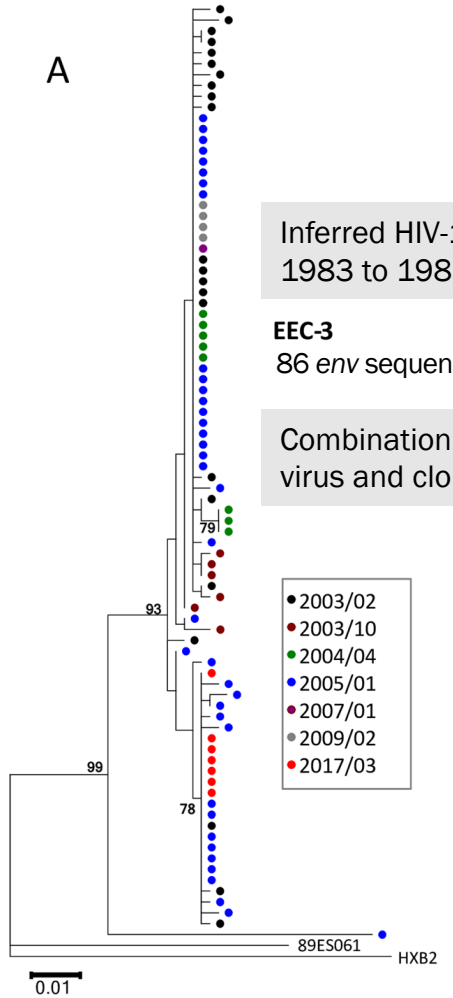
(2017)

337 amplification attempts with 12.4E6 CD4⁺ and 6.4E6 PBMCs
Casado *et al.* 2020

Viral Evolution and Genetic Variability

- Very restricted genetic diversity: 0.010 ± 0.003 s/n
- Almost null viral genetic evolution





Inferred HIV-1 infection time: 1983 to 1986

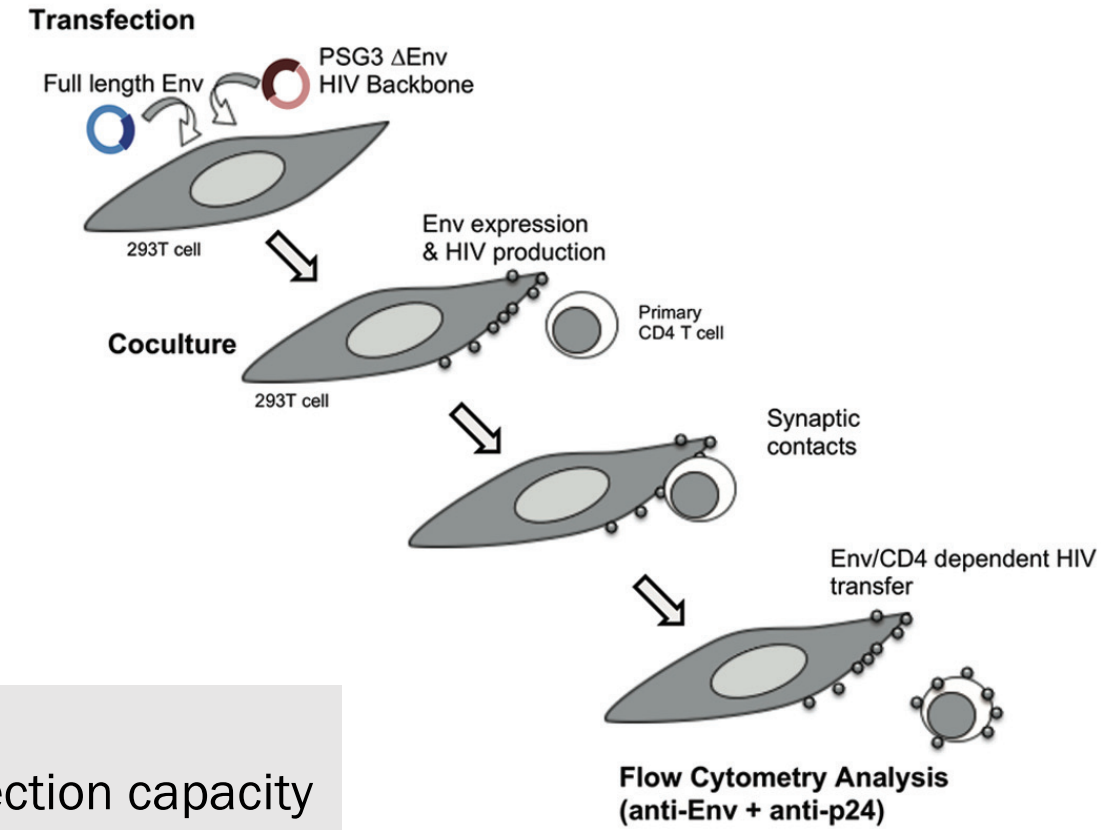
EEC-3
86 *env* sequences (all R5-tropic)

Combination of low evolving virus and clonal expansion

Casado *et al.* 2020

Envelope Functionality

- Cloned Envs from EEC allowed functional characterization of the initial events of the viral infection:
  - Ineffective binding to CD4 and the subsequent signaling activity to modify actin/tubulin cytoskeletons

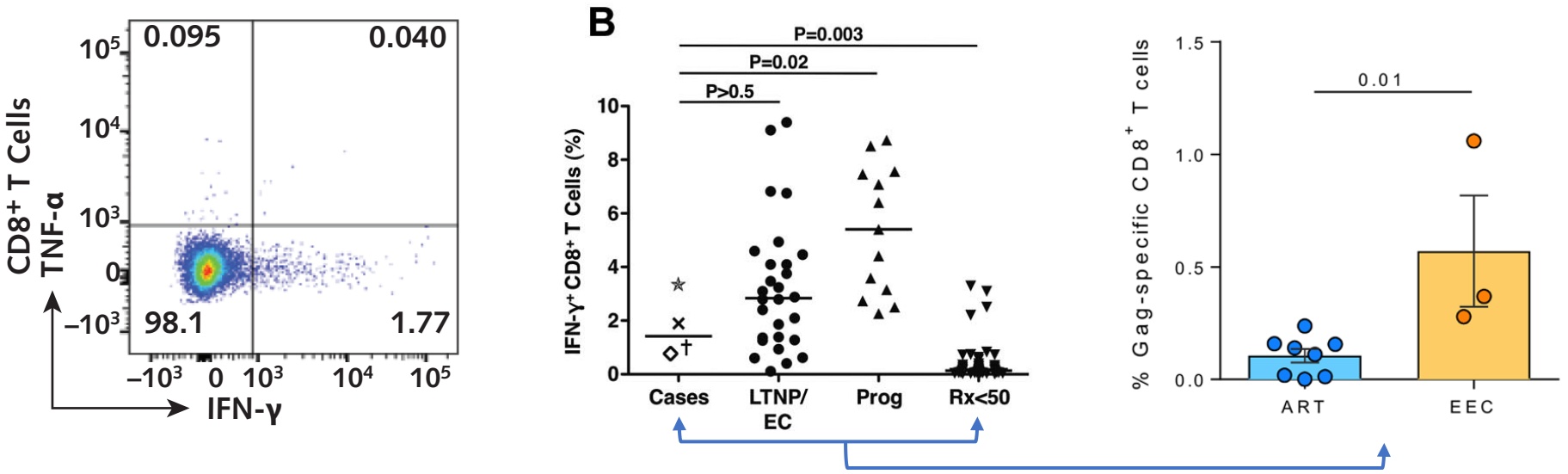


- Low fusion
- Deficient entry and infection capacity

Casado *et al.* 2017 mBio

Cellular Immune Responses

- HIV-specific T-cell responses were present
  - Comparatively higher and greater polyfunctionality than those from PWH on ART
  - Similar to other LTNP/EC

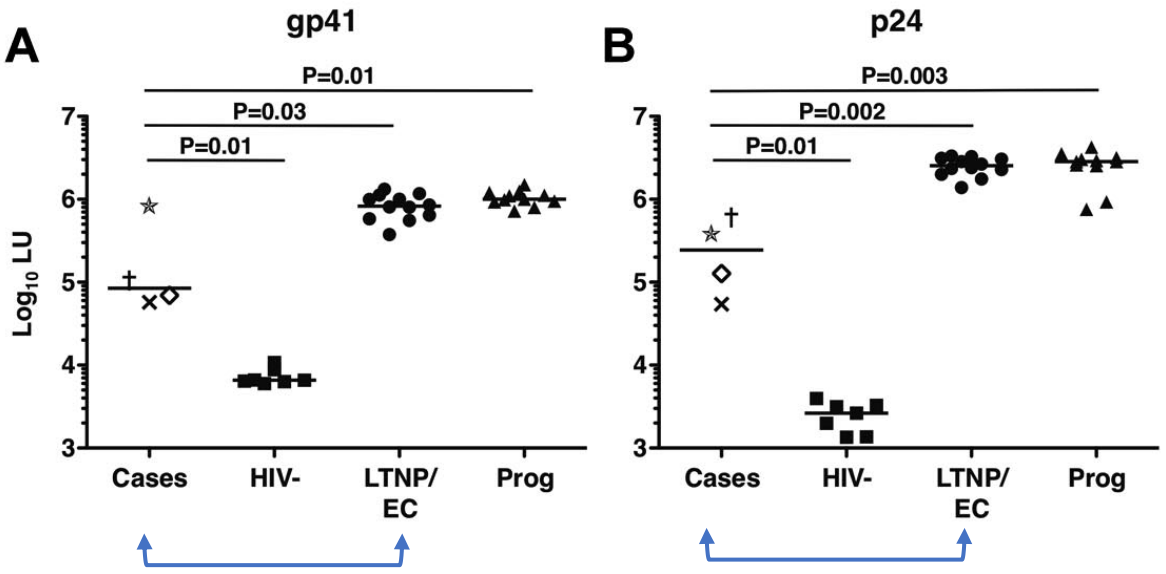


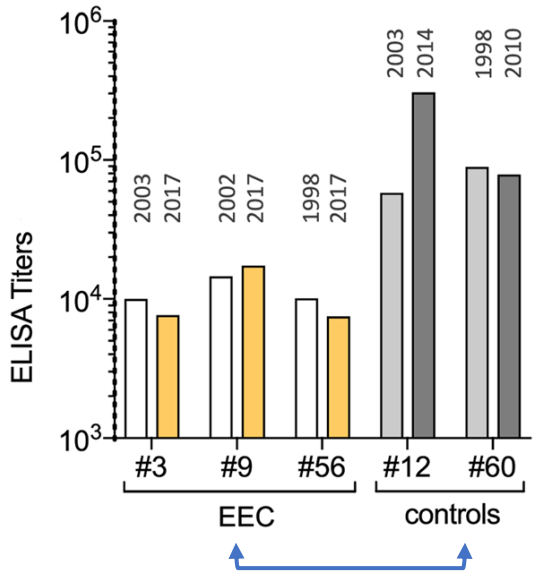
- Host CD4+ T cells are susceptible to infection with R5 or X4-tropic HIV
- Host CD8+ T cells are effective in suppressing viral viral replication *ex vivo*

Mendoza *et al.* 2012; Casado *et al.* 2020

Humoral Immune Responses

- All weakly reactive, either Western Blot or ELISA
  - But superior to 2 cases of stem-cell transplant with CCR5Δ32/Δ32 donor cells (*IciStem cohort*)
  - Viral antigens and/or truncated viral proteins could be generated from defective genomes

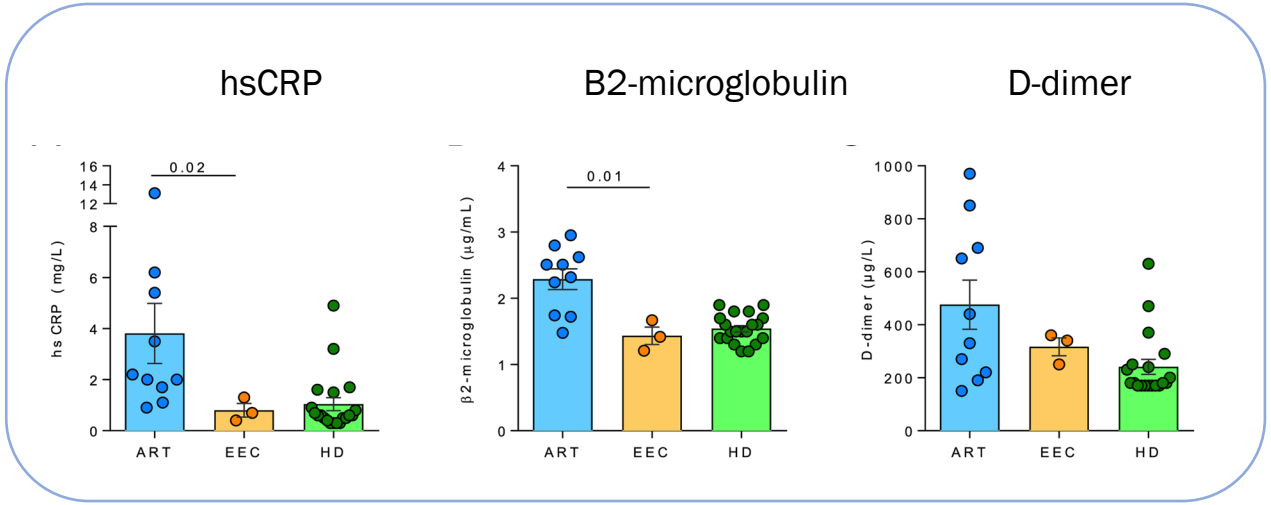


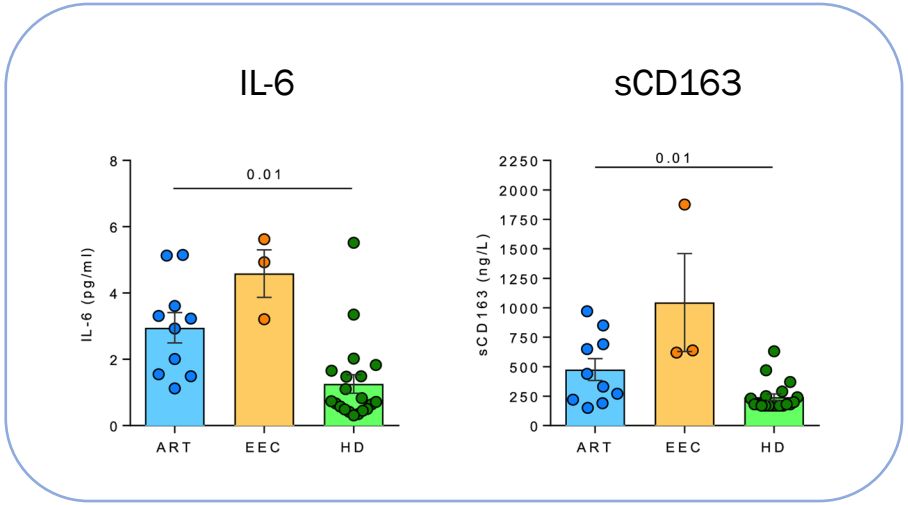


Mendoza *et al.* 2012; Casado *et al.* 2020

Inflammation Biomarkers

- Similar to those in the blood of healthy donors
  - Innate immune responses seem to be relatively normalized





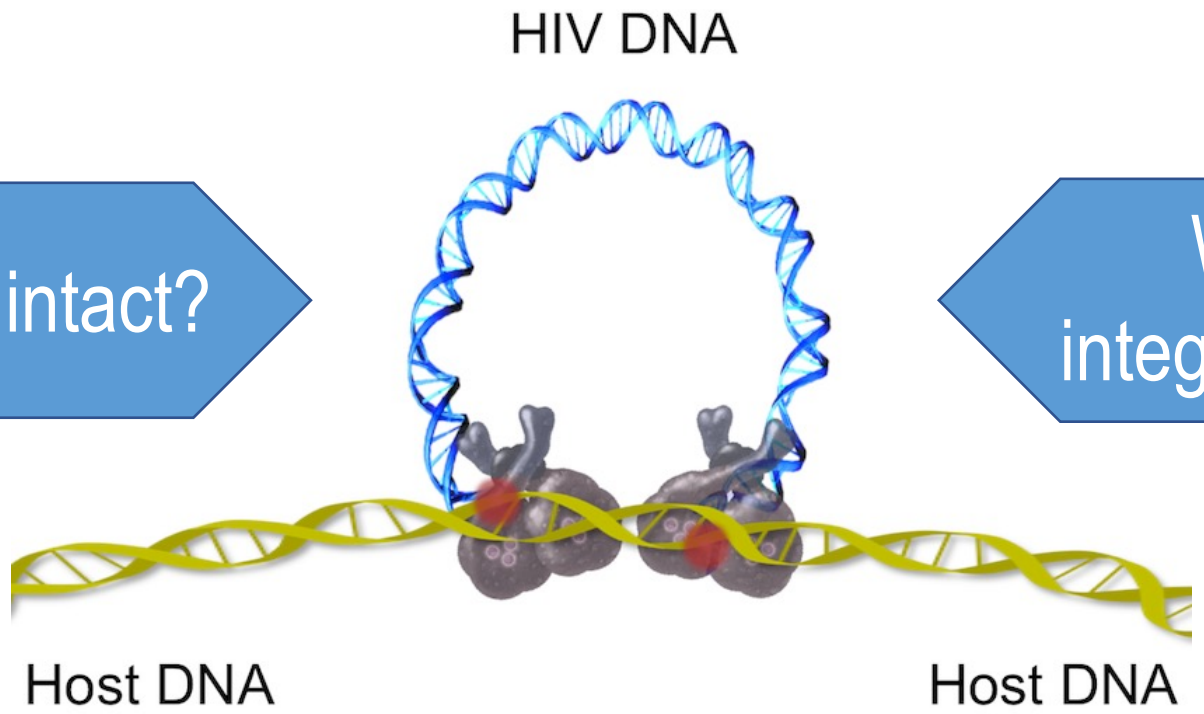
- Analyses in greater number of subjects is required

Casado *et al.* 2020

Proviral HIV intactness and chromosomal location

distinct proviral reservoir configurations in natural viral control

Is the HIV provirus intact?

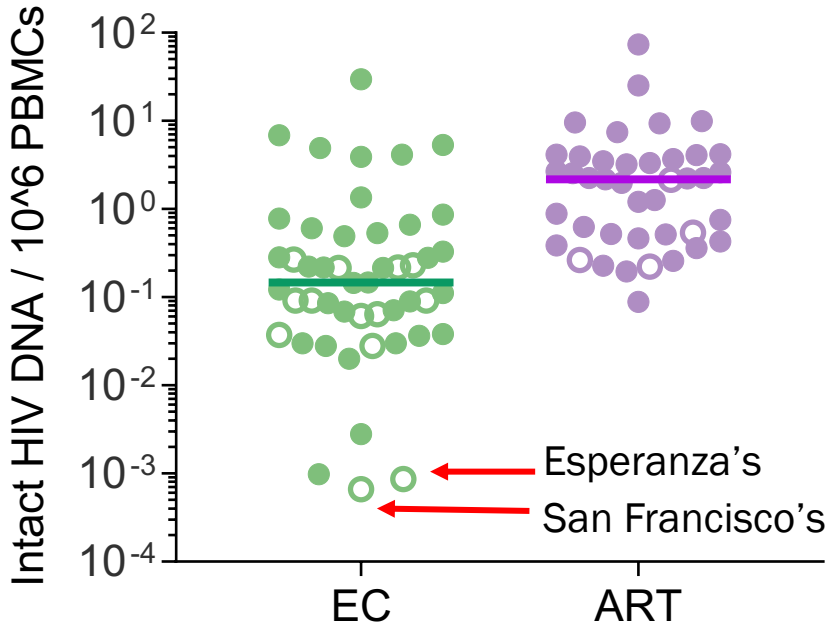


Where does HIV integrate in the genome?

Jiang C *et al.* 2020 Nature 2020; Turk *et al.* 2021. Ann Intern Med

Breakthroughs on the SFO and Esperanza cases

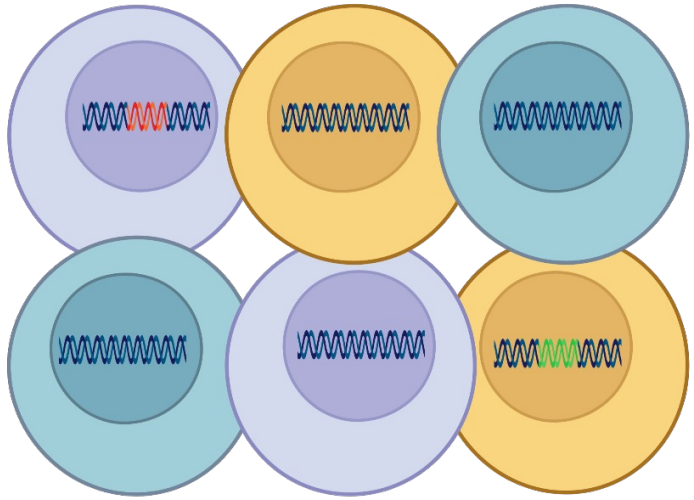
Descriptive data on EEC → Mechanistic data on EEC



Bruce Walker, Steven Deeks, Janet Siliciano, Robert Siliciano

Jiang C *et al.* 2020 Nature 2020; Turk *et al.* 2021. Ann Intern Med

Near-full length virus sequencing



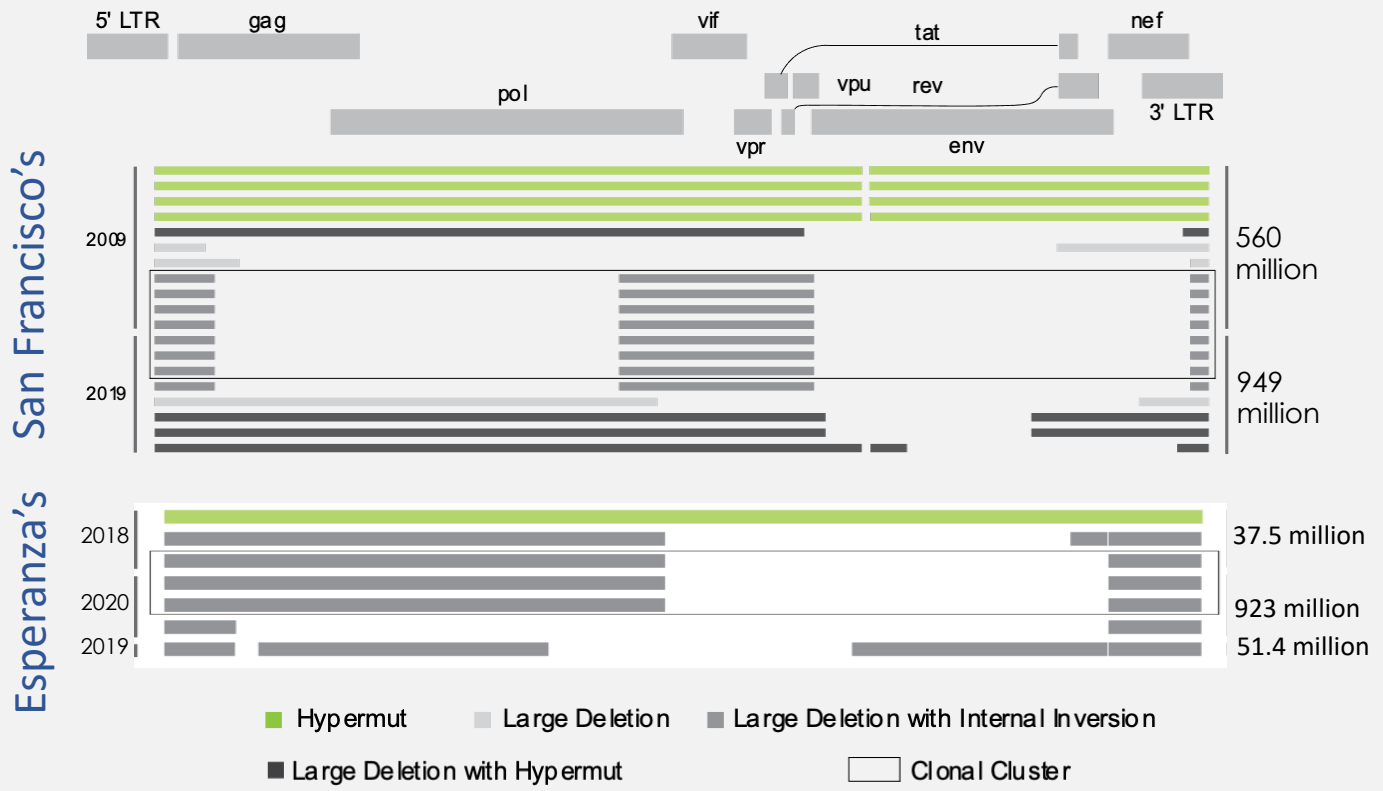
Genomic DNA

Intact Provirus

Defective Provirus

- Full-Genome Individual Proviral Seq
- IPDA
- Viral outgrowth assay

Essentially … Defective Proviruses



Jiang C *et al.* 2020 Nature 2020; Turk *et al.* 2021. Ann Intern Med

Conclusions

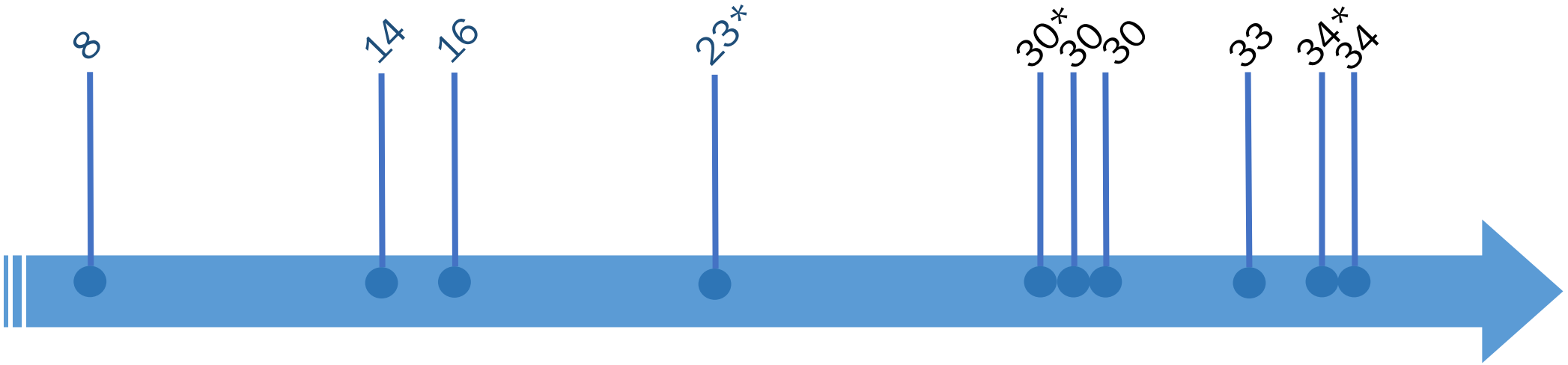
- Consistently low, and apparently defective, viral DNA reservoir
- Practically null viral genetic evolution and extremely low complexity of the viral populations ⟶ absence of viral replication for >25 years
- Low population size and viral diversity are associated with low replication and viral fitness
- Contribution of host genetic factors and cellular-adaptive immune responses

- Hypotheses:
  - Primary infection might have occurred with a low fitness viral founder strain
  - Initial innate immune responses might have shaped the selection of an unfit virus

- Is it possible to induce a permanent control of HIV-1 pathogenesis?

Future directions

- Current cases on follow up (years)



Argentina, Belgium, Spain, United States

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*, unpublished cases

Future directions

Hematological Stem Cell Transplant

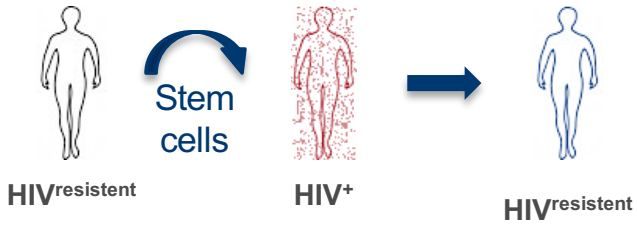
Adam Castillejo
London Patient
4.5 years

Düsseldorf Patient
3.5 years

Non-CCR5Δ32 donors
on ART

ICISTEM

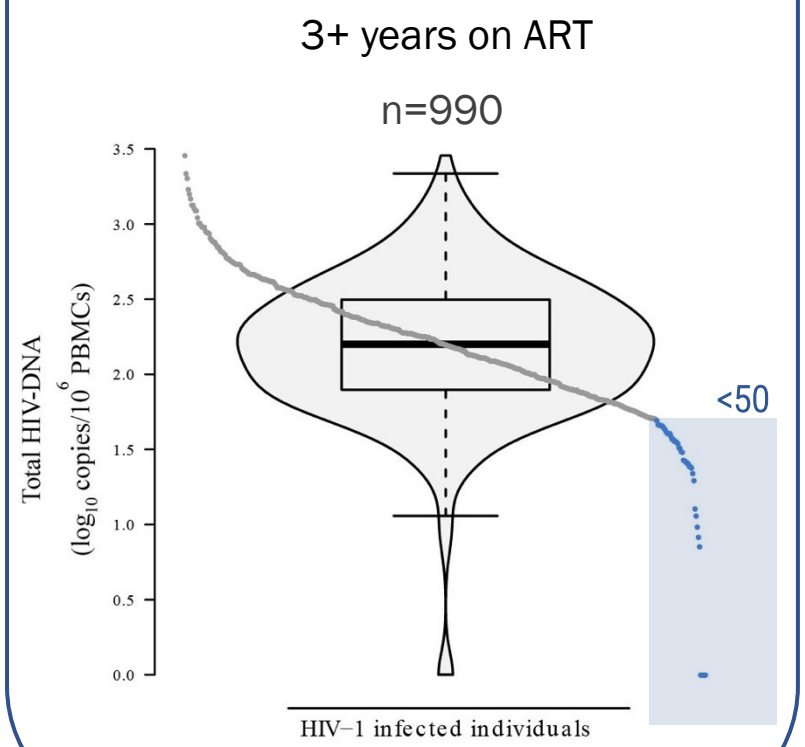
Δ32 Donor → **HIV patient** → **cured HIV patient**



Hütter *et al.* 2009 NEJM; Gupta *et al.* 2019 Nature;
Jensen *et al.* CROI 2019; Hsu *et al*. CROI 2022

Exceptional Elite Controllers

Extremely low viral reservoir (LoViReT)



Gálvez *et al.* 2020. EBioMedicine; Gálvez *et al.* 2022. J Int Med

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