Precision Medicine: Focus on Age-independent Immunosenescence

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Disclaimer

- The views expressed are those of the presenter and do not reflect the official views or policy of the Department of Defense or its Components

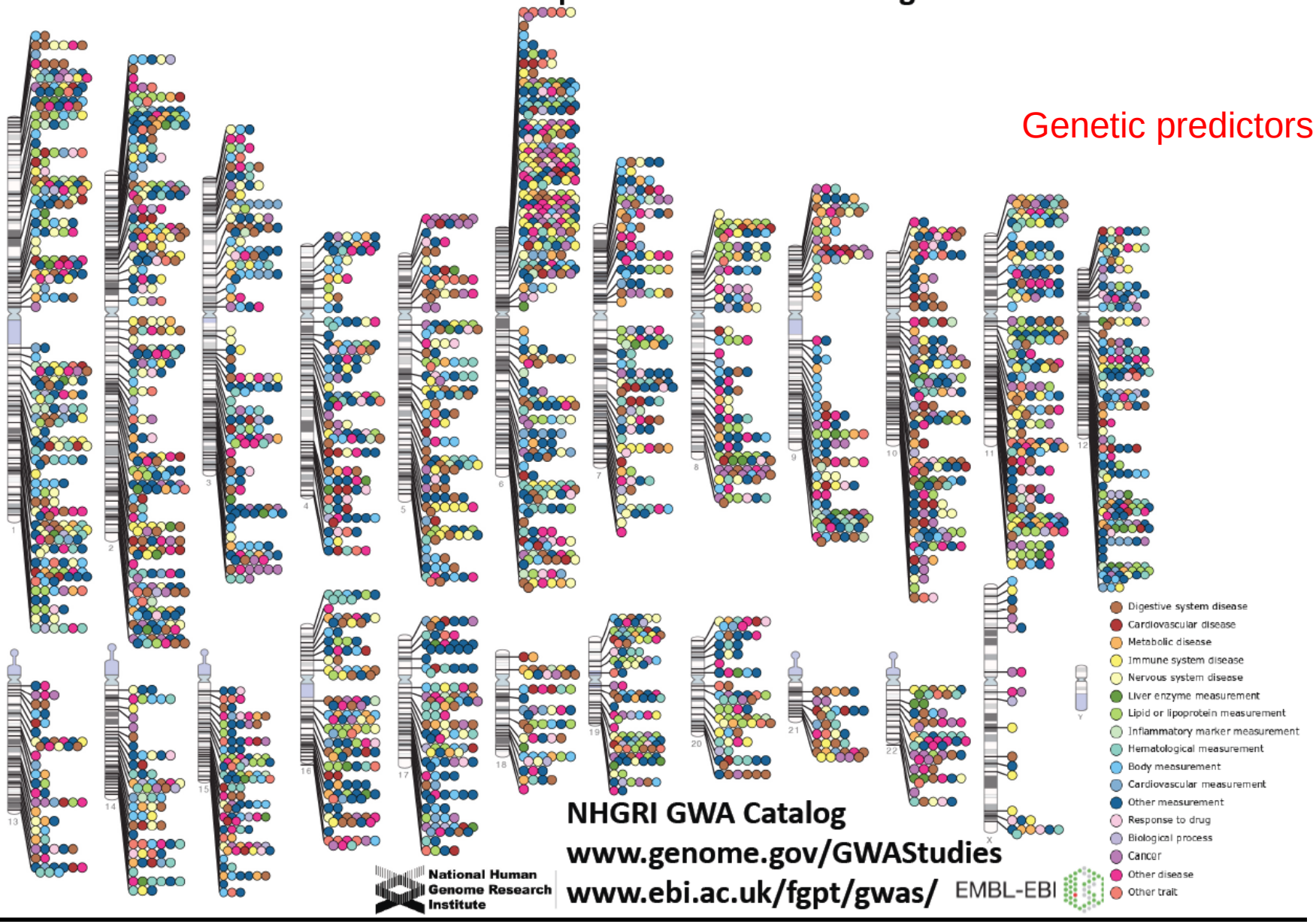
The New Era of Predictive, Preventive, Personalized, & Participatory (P4) Medicine

Age-independent immunosenescence (AIIS): a disease-predicting, sexually dimorphic immunologic program activated in response to antigenic challenges

Published Genome-Wide Associations

Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories

Genetic predictors



NHGRI GWA Catalog

www.genome.gov/GWAStudies

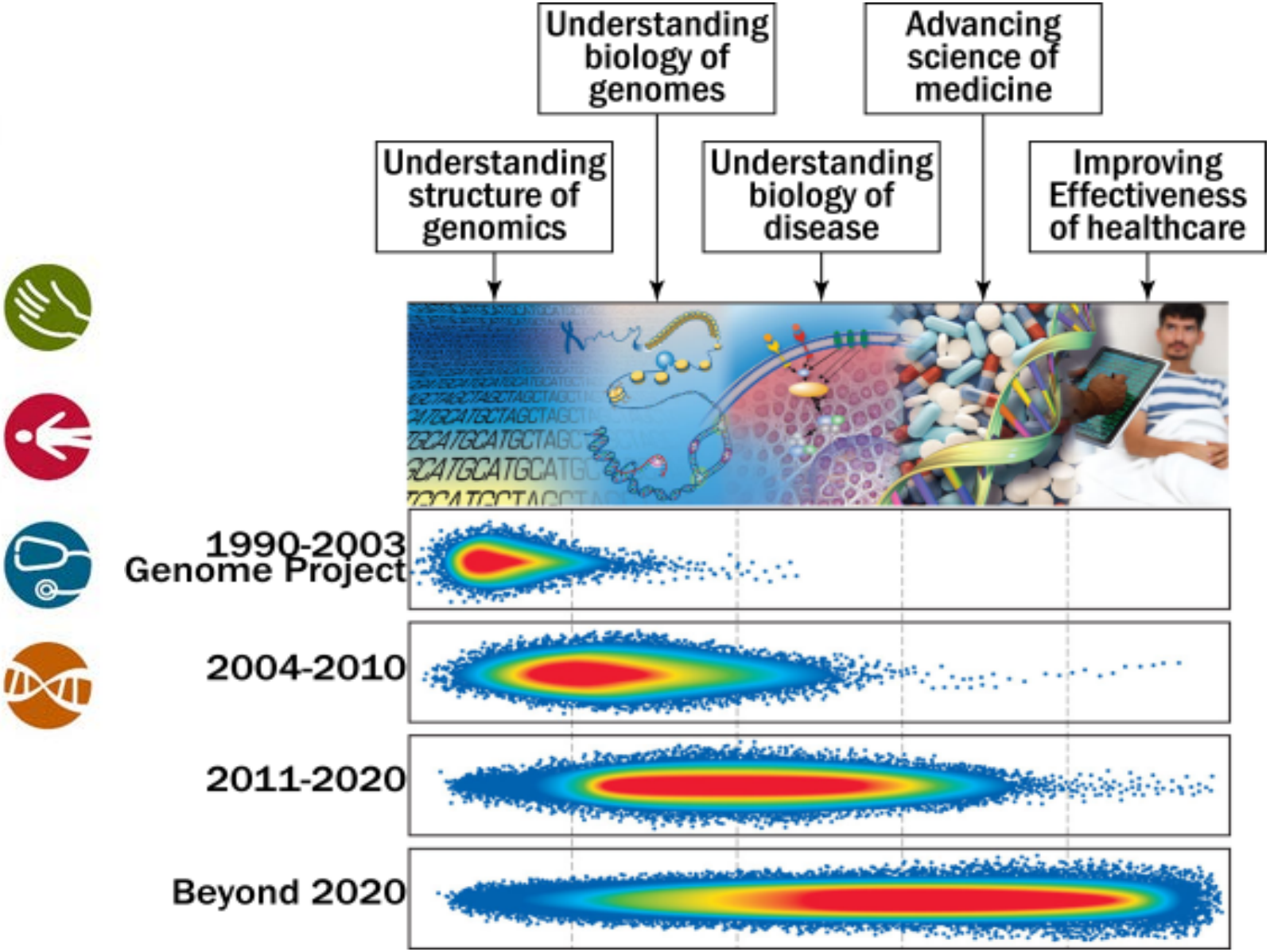
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

P4 Medicine

PREDICT • PREVENT • PERSONALIZE • PARTICIPATE



Age-independent immunosenescence (AIIS)

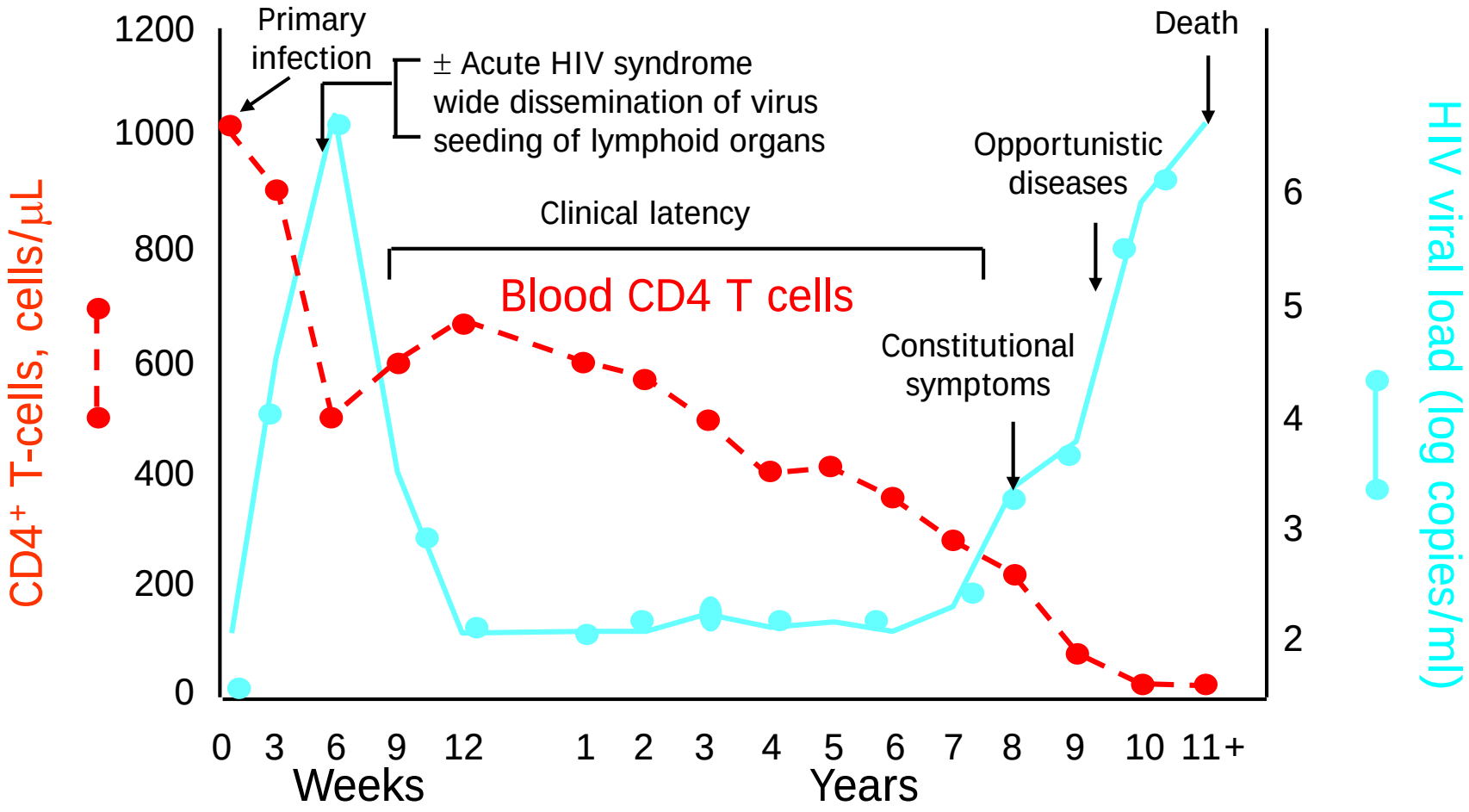
Can occur at any age & is a sign of immunologic frailty

The past informed the present

Past – NEJM (2013)
JAMA-Internal Medicine (2015)

Present – May, 2019
70,000 person study (~6000 HIV-)
232 non-human primates
Influenza vaccine challenge study
Mice models of infection

Natural History of Untreated HIV-1 Disease

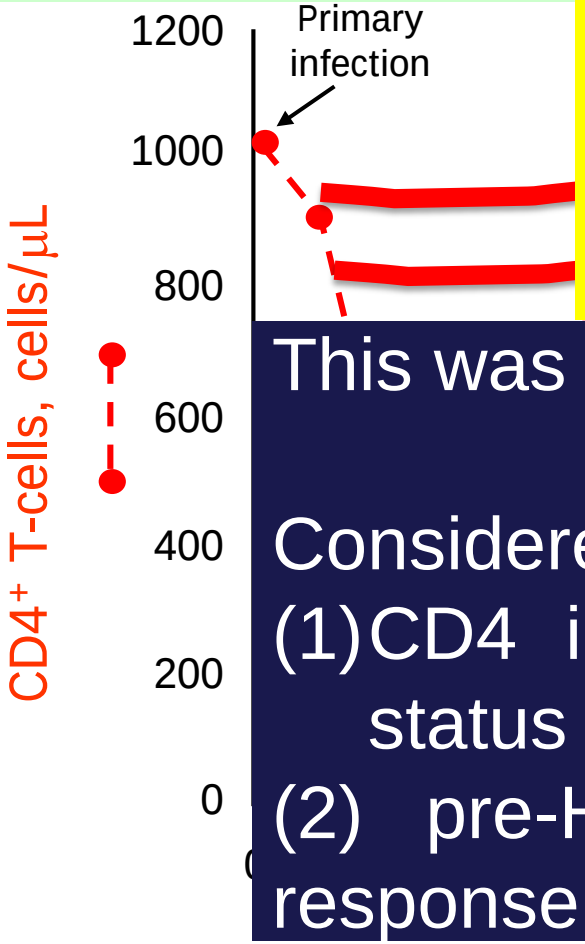


Modified from Fauci et al, Ann Int Med 1996

Hypothesis: Suppress VL with Early ART + ‘Normalize’ CD4+ = ‘normalize’ immune health

Established median CD4+ in ~16000 HIV- = 900, lower IQR = 800

greatly increased likelihood of CD4+ normalization



- Not all people achieved this CD4+ threshold despite early ART
- Much lower but *persistent* AIDS risk & immune deficits

This was dismaying & paradoxical ---

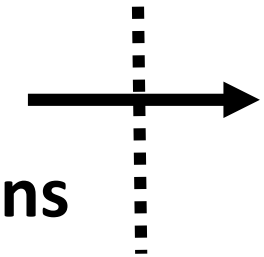
Considered 2 missing pieces--

(1) CD4 imperfect metric to gauge immune status &

(2) pre-HIV immune status predicts ART response

Prediction

Risk factors induce poor immunologic health; because of its non-HIV origins it is not responsive to ART



Conundrum

Post-HIV poor immunologic health despite early ART

Persons with a 'better immune system'

- **Resist acquiring HIV**
- **Have better outcomes pre- & post-ART**

2 distinct forms of immunosenescence

Age-independent immunosenescence (AIIS)

Age-dependent immunosenescence (ADIS)

Conflation of these 2 forms of immunosenescence

➡

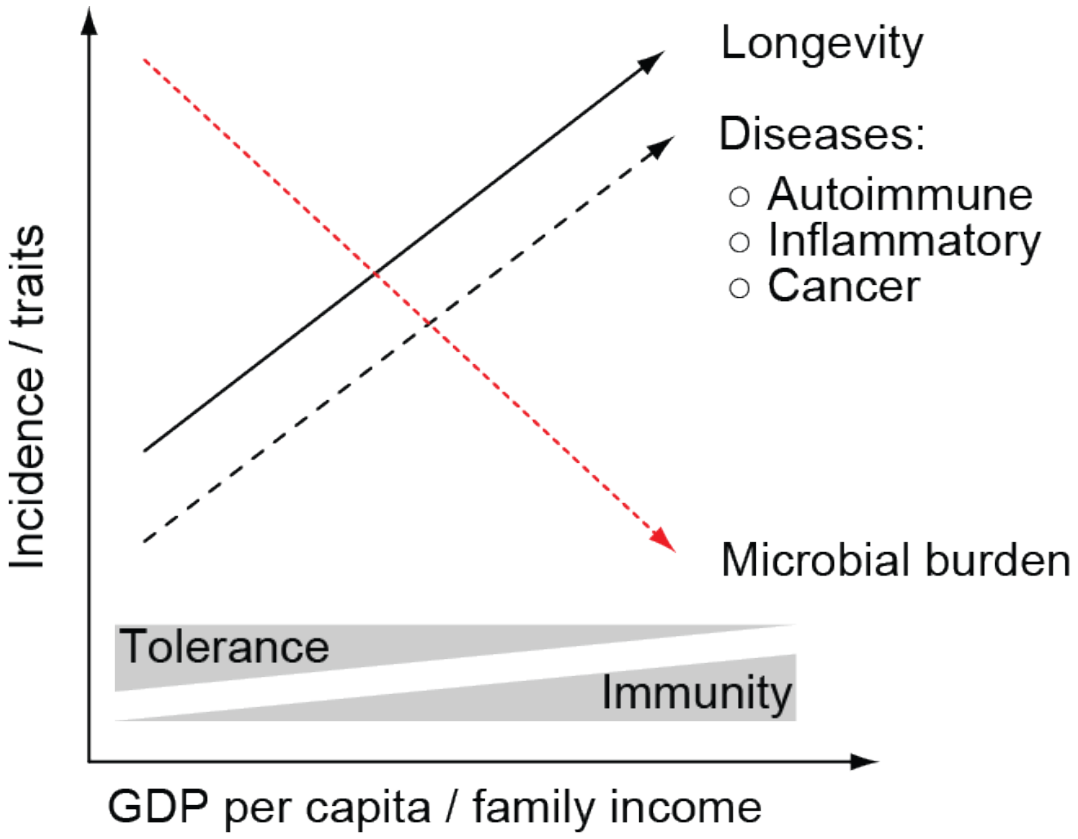
confounding in aging/immunity/vaccine research

HIV as a cause of "accelerated aging, premature aging or inflamma-aging"

Is a flawed concept

Arising from failure to distinguish between AIIS vs. age-dependent immunosenescence

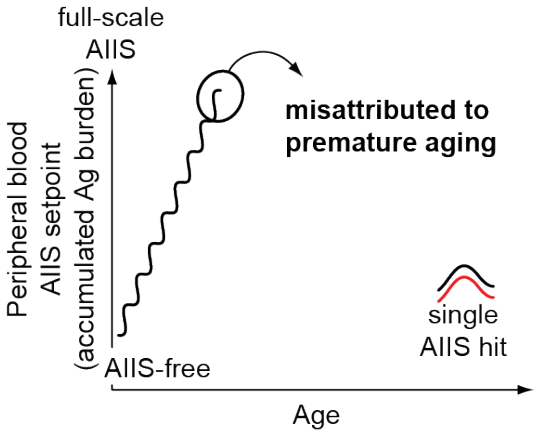
Trade-offs

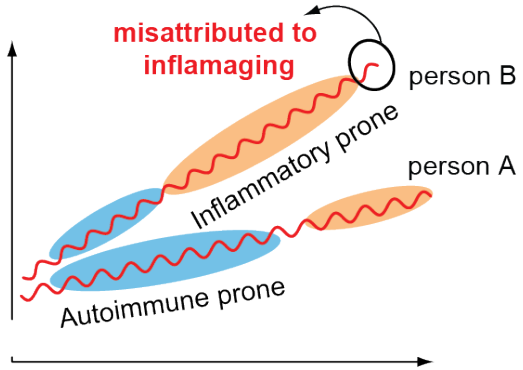

Longevity
Diseases:
Autoimmune
Inflammatory
Cancer
Microbial burden
Tolerance
Immunity
Incidence / traits
GDP per capita / family income

Trade-offs and AIIS setpoint

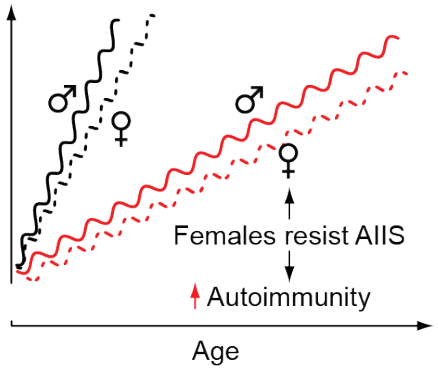
	Trade-offs of GDP per capita/family income	
	lower	higher
Microbial burden	higher	lower
Onset of higher AIIS setpoint	younger	older
Lifespan	shorter	longer
Autoimmune diseases	less	more
Inflammatory diseases	less	more

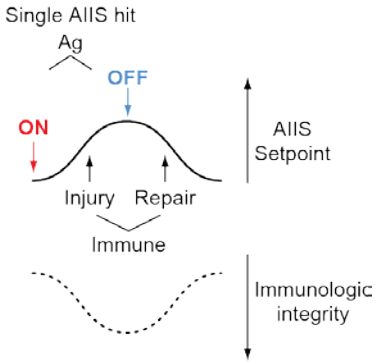
	Sexually dimorphic trade-offs	
	♂	♀
Setpoint	higher	lower
Immunocompetence	lower	higher
Lifespan	shorter	longer
Autoimmune diseases	less	more
Inflammatory diseases	more	less





(Age: imperfect proxy of Ag experience)





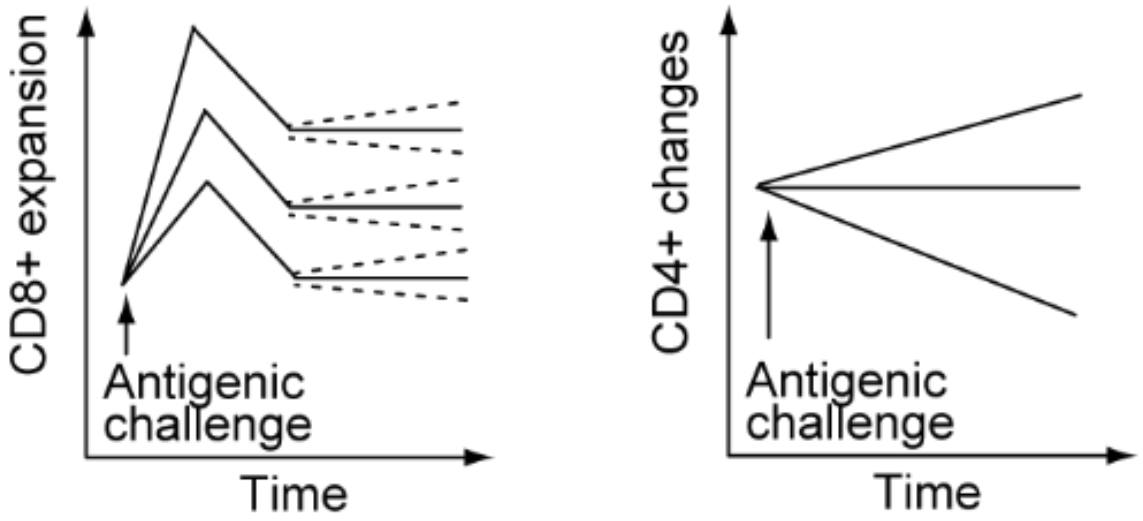
Approach

Laboratory indicators of AIIS

IHG	Ratio ≥ 1.0	CD4+ ≥ 800	CD8+ expansion	CD4+ levels	CD8-CD4	Status
I	+	+	lower	higher	Equilibrium	AIIS-free
II	+	–	lower	lower		
III	–	+	higher	higher	Disequilibrium	**Full-scale AIIS**
IV	–	–	higher	lower		

1. Derived five genomic signatures that are proxies for epidemiologic and immunologic hallmarks of AIIS
2. Probed 23,162 publicly available gene expression datasets
3. Applied Bradford Hill criteria to determine causal link between AIIS setpoint and trade-offs
4. Identified molecular and cellular mechanisms
5. Distinguished AIIS from ADCS

CD8 and CD4 changes upon antigenic challenge



A novel way to summate this response

Immunologic health grades

Grade	Ratio ≥ 1.0	CD4+ ≥ 800
I	+	+
II	+	–
III	–	+
IV	–	–

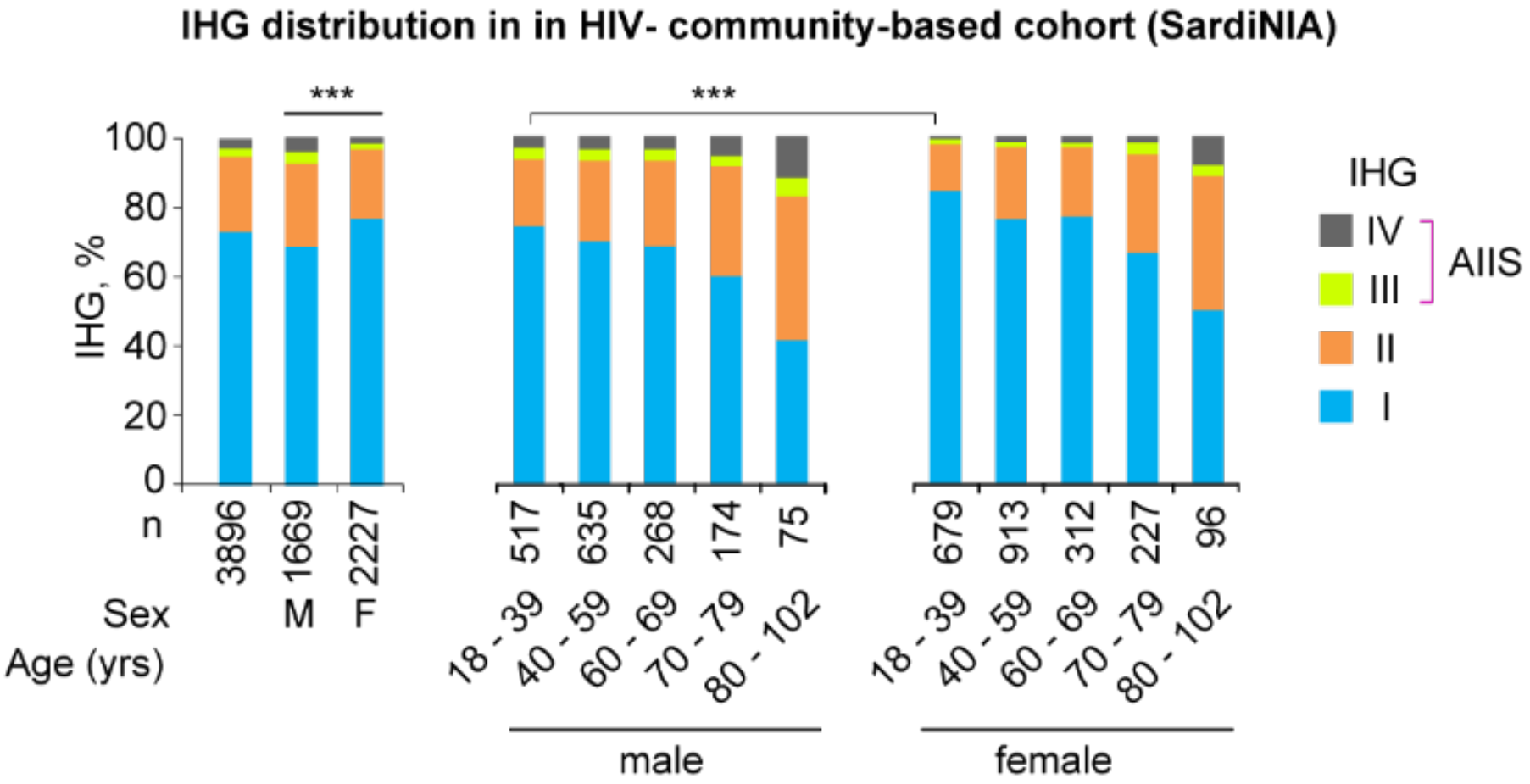
Immune Health Grades (IHG)

IHG-I and III - similarly higher CD4+ but divergent CD8+
IHG-II and IV – similarly lower CD4+ but divergent CD8+

IHG	n (%)	CD8+	CD4+	Ratio	CD8+ expansion	CD8+	CD4+	CD8-CD4	AIIS Status
I	2852 (73.2)	525 (392-689)	1154 (980-1393)	2.26 (1.75-2.97)	Restrained	Lower	Higher	equilibrium	AIIS-free
II	840 (21.6)	354 (267-447)	675 (592-746)	1.90 (1.44-2.38)	Restrained	Lowest	Lower		
III	95 (2.4)	1195 (1033-1463)	988 (870-1197)	0.87 (0.76-0.93)	Unrestrained	Highest	Higher	disequilibrium	AIIS
IV	109 (2.8)	781 (646-932)	616 (517-712)	0.82 (0.66-0.93)	Unrestrained	High	Lower		

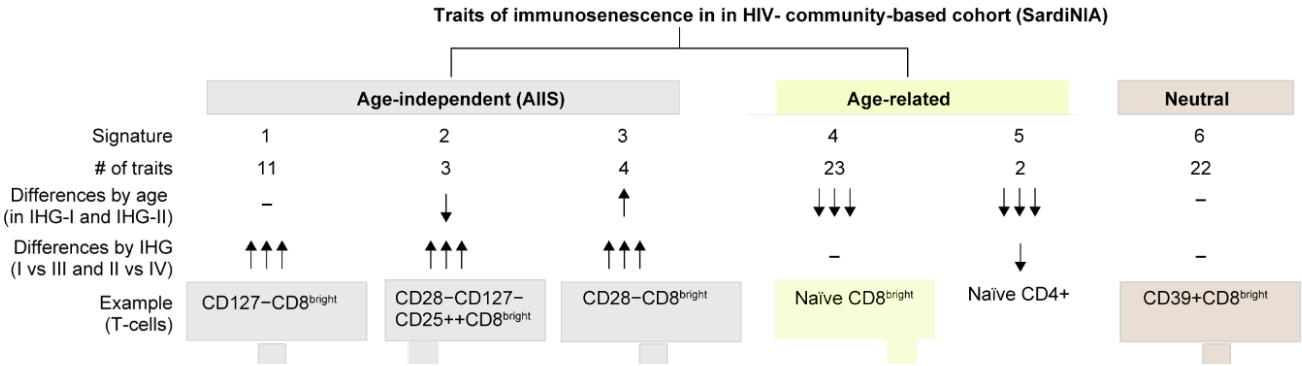
Analysis of immune traits by chronologic age or CD4+ counts is a conflated/confounded analysis

AIIS (IHG-III and IHG-IV) increases with age; M>F



AIIS vs. Age-dependent immunosenescence immune traits

AIIS is marked by expansion of senescent, activated and regulatory-like CD8+ T-cells & NK T-cells



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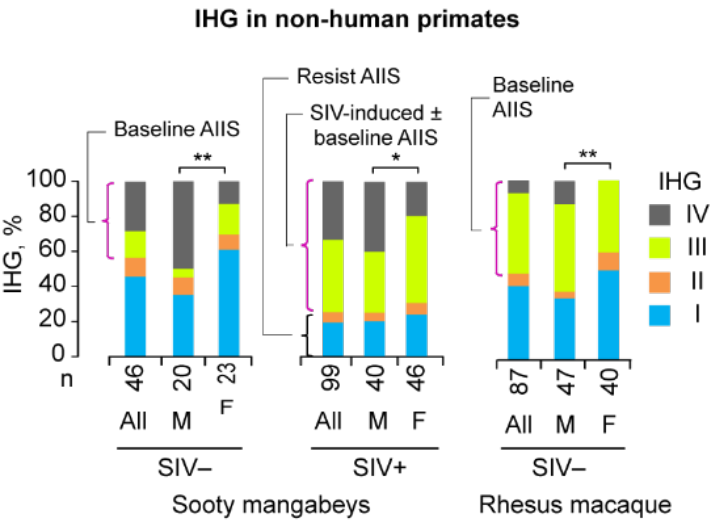
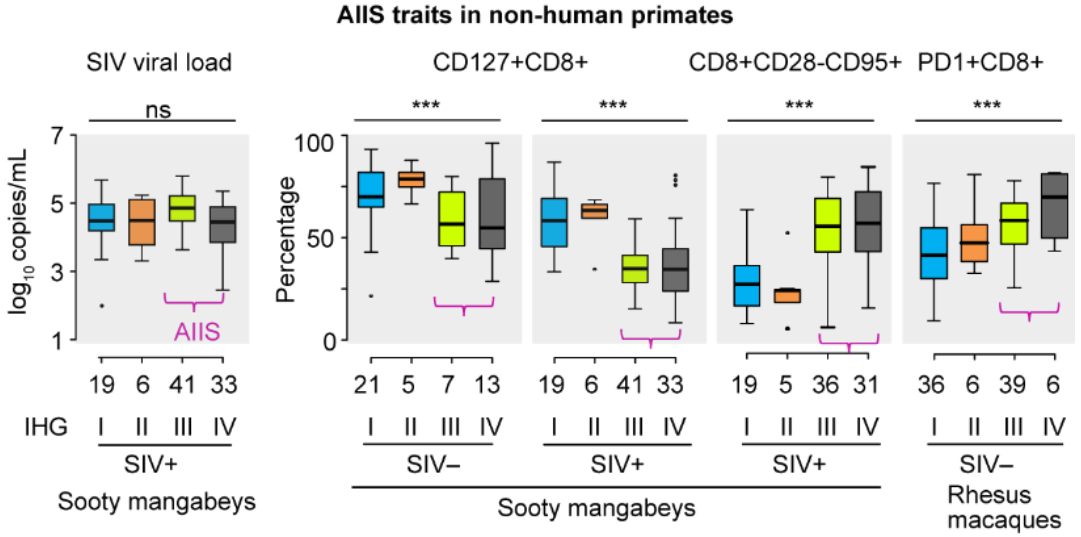
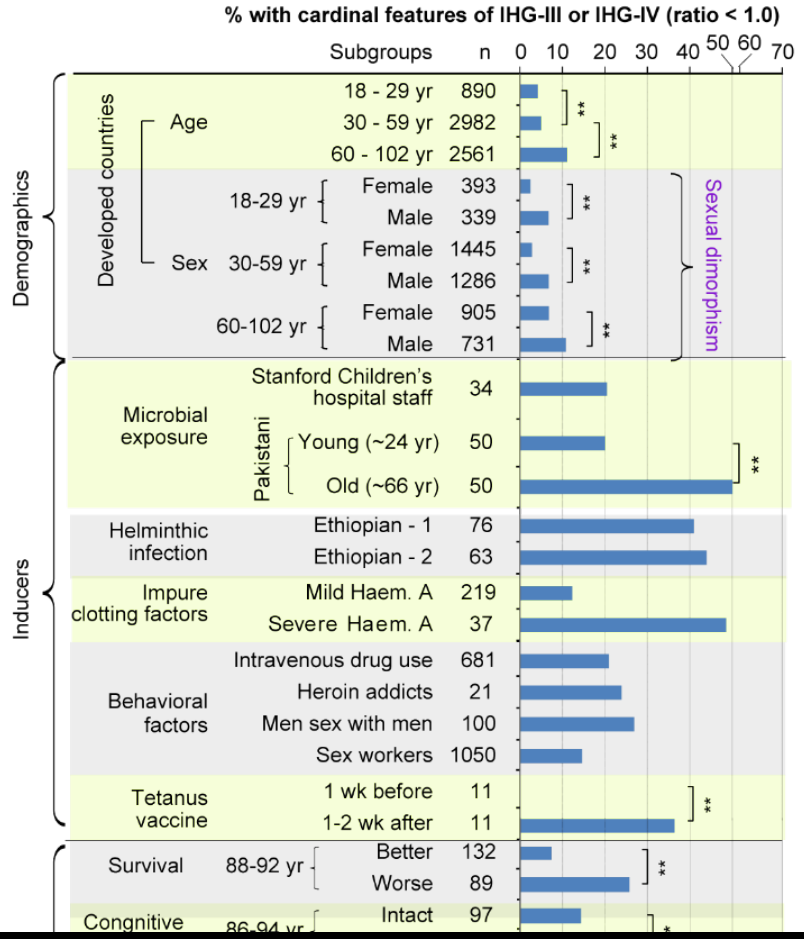
Evolutionary conservation of IHGs: stratification in 3 categories





Features of AIIS

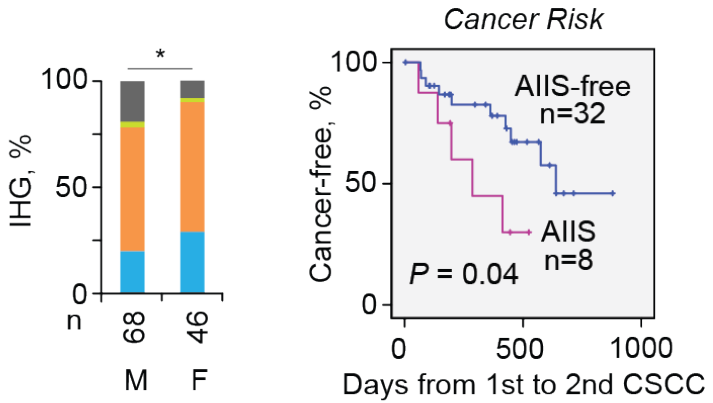
- Sexual dimorphism
- More acquire CMV
- Age is proxy for antigenic load
- Sensitive to antigenic load
- Adverse outcomes

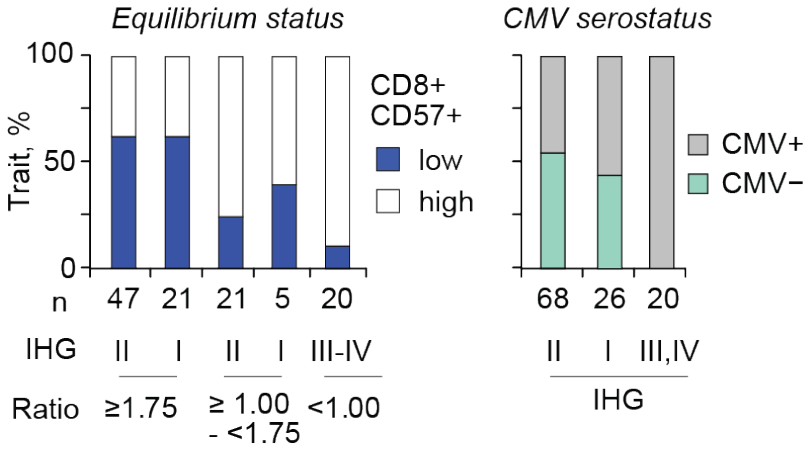


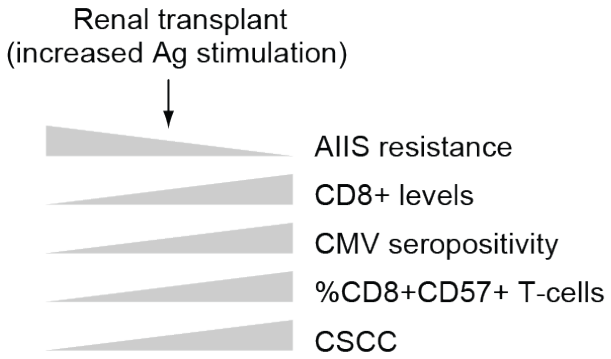
Prediction:

Younger persons with AIIS are at higher risk for vaccine failures and 'age-associated disorders' (e.g., atherosclerosis, cancer)

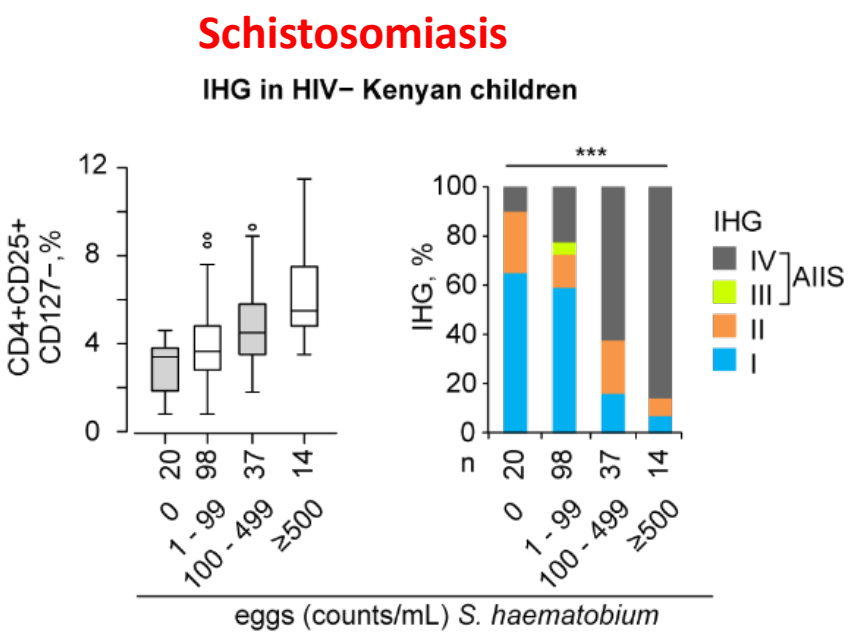
Pre-existing AIIS correlates with cancer

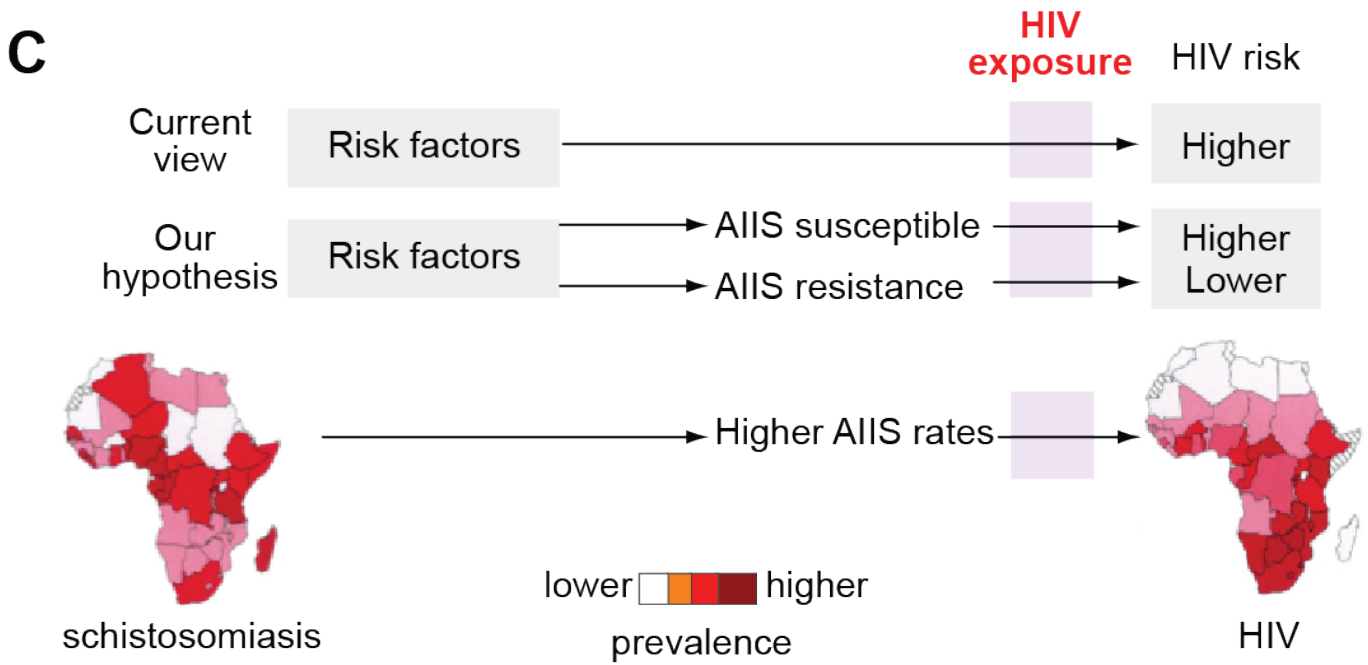




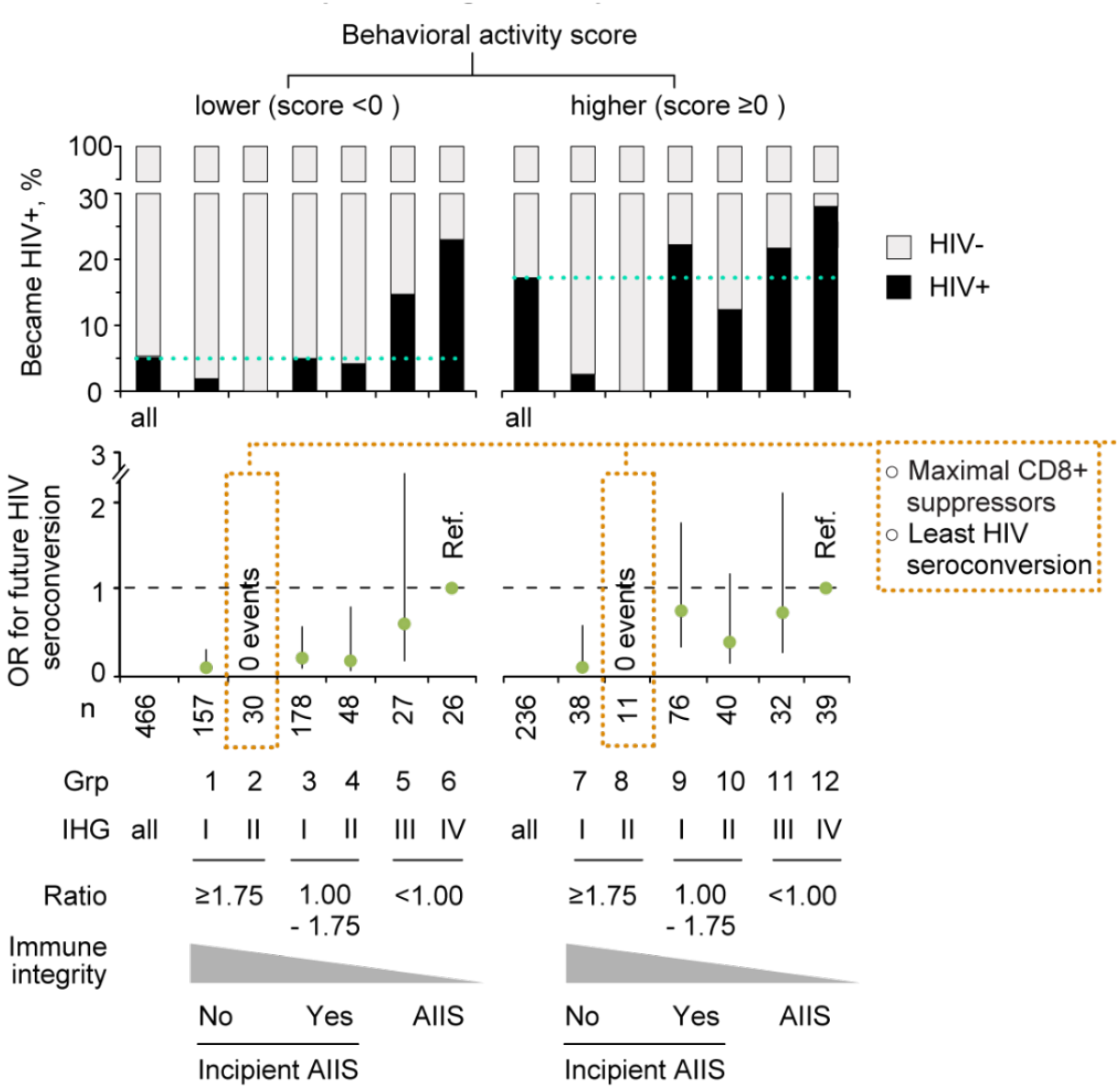


Pre-existing AIIS and HIV acquisition





Correlation vs. causality: increased sensitivity to AIIS; risk for HIV



- Immunologic integrity predicts HIV
- HIV seroconversion has a proxy function

Prediction: Vaccine studies (HIV/TB etc) – confounded unless placebo vs. trial arms are balanced for AIIS

Laboratory → genomic markers of AIIS

Laboratory indicators of AIIS

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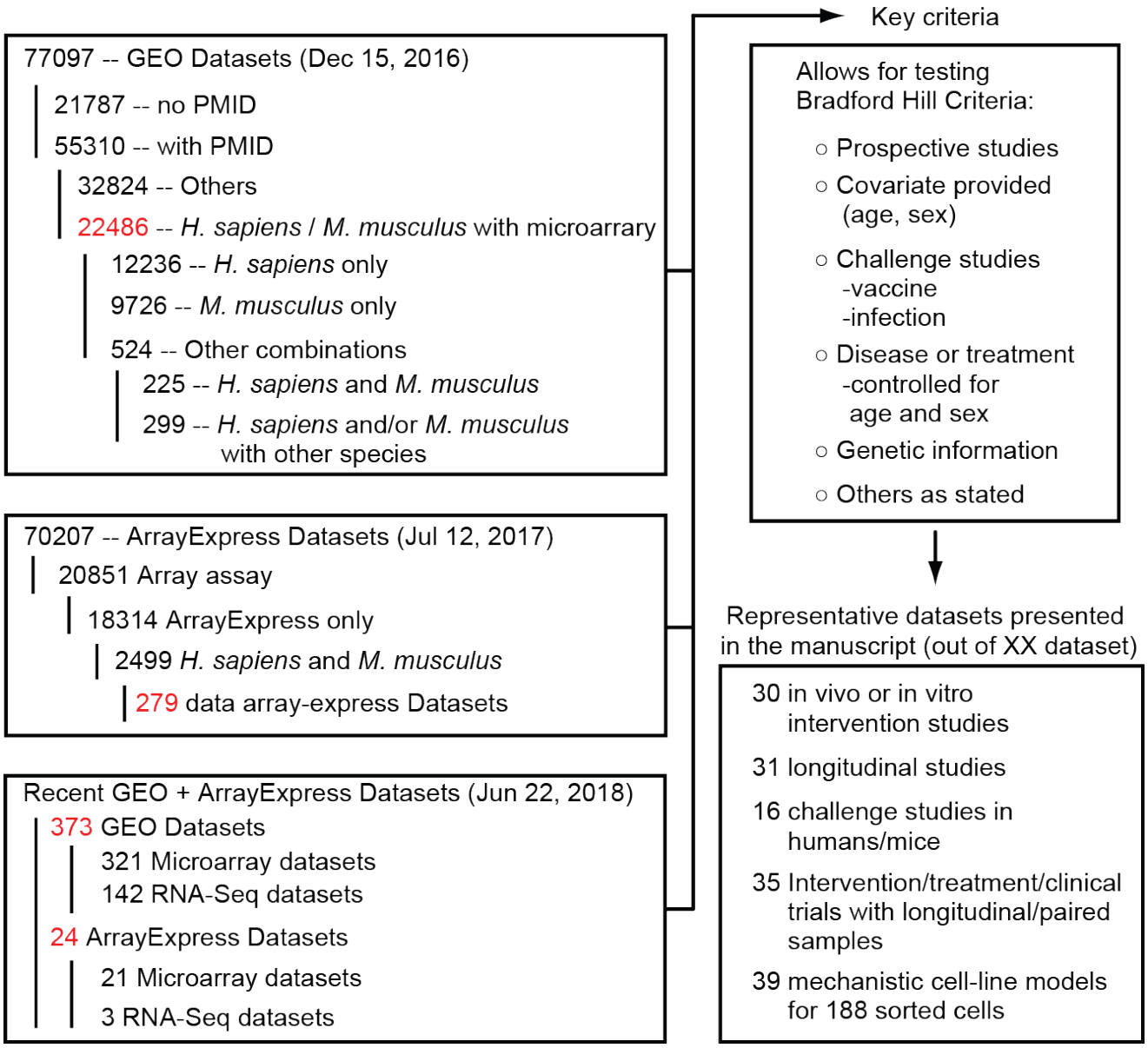
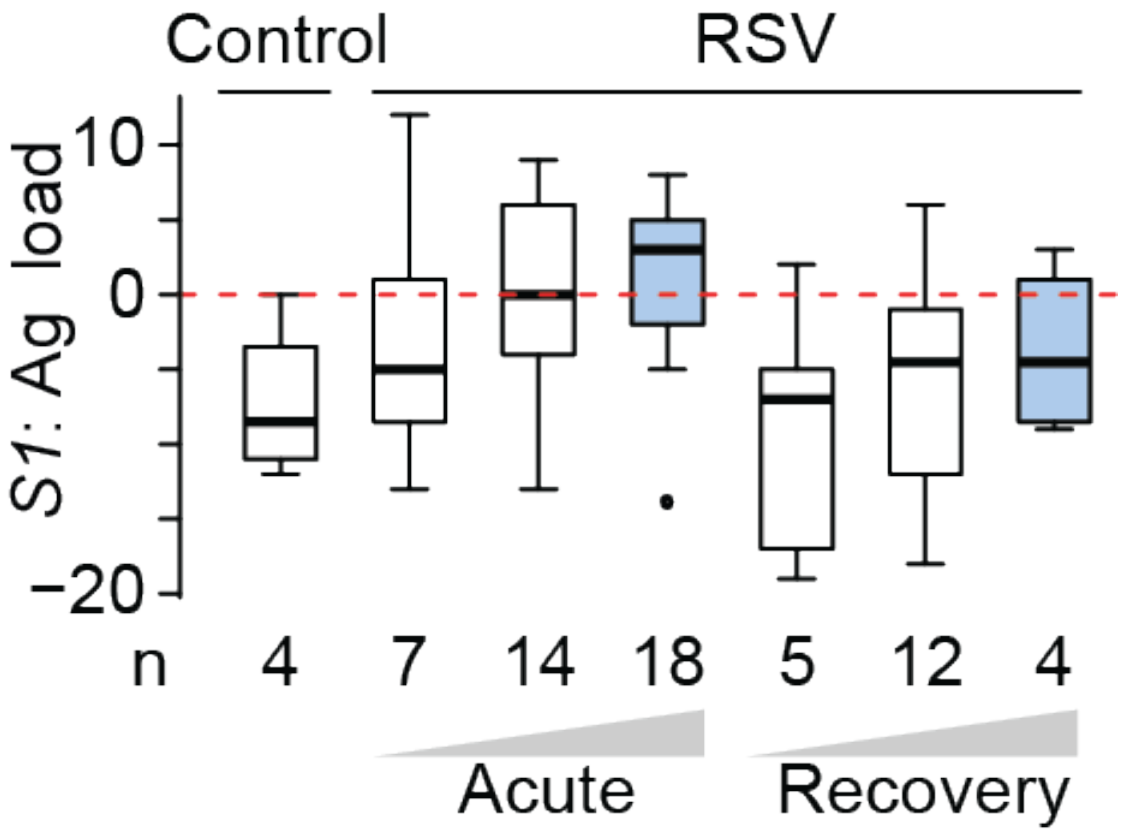
Gene signatures that correlate with AIIS vs. non-AIIS programs

AIIS immunologic program		*Score range*	*Higher scores correlate with*
S1	Antigenic (Ag) load	–26 to 25	Increased host Ag load
S2	AIIS triad	–6 to 6	Three hallmarks of full-scale AIIS
S3	Immunologic Integrity	–21 to 32	↑ T-cell responsiveness ↓ T-cell dysfunction
S4	Effector-Naïve	–6 to 6	↑ Effector T-cells ↓ Naïve T-cells
S5	CD8+ T-cell health (CXCR5+TIM3-PD1+CD8+)	–26 to 33	↑ Stem-cell like self-renewing memory precursor T-cells ↓ Effector-like exhausted T-cells
Non-AIIS immunologic program			
S6	Th1-Th2	–8 to 8	↑ T-helper (Th) 2 cells ↓ Th1 cells
S7	Immune checkpoint	–14 to 10	↑ Co-stimulatory T-cells signals ↓ Co-inhibitory T-cells signals
S8	Type 1 regulatory T-cells (Tr1)	–5 to 12	↑ Tr1-associated cells ↓ T_H0-associated cells
S9	IFN related	0 to 38	↑ IFN-related signaling
Cellular Senescence (CS) program			
S10	Core CS signature	–23 to 32	↑ Conventional CS

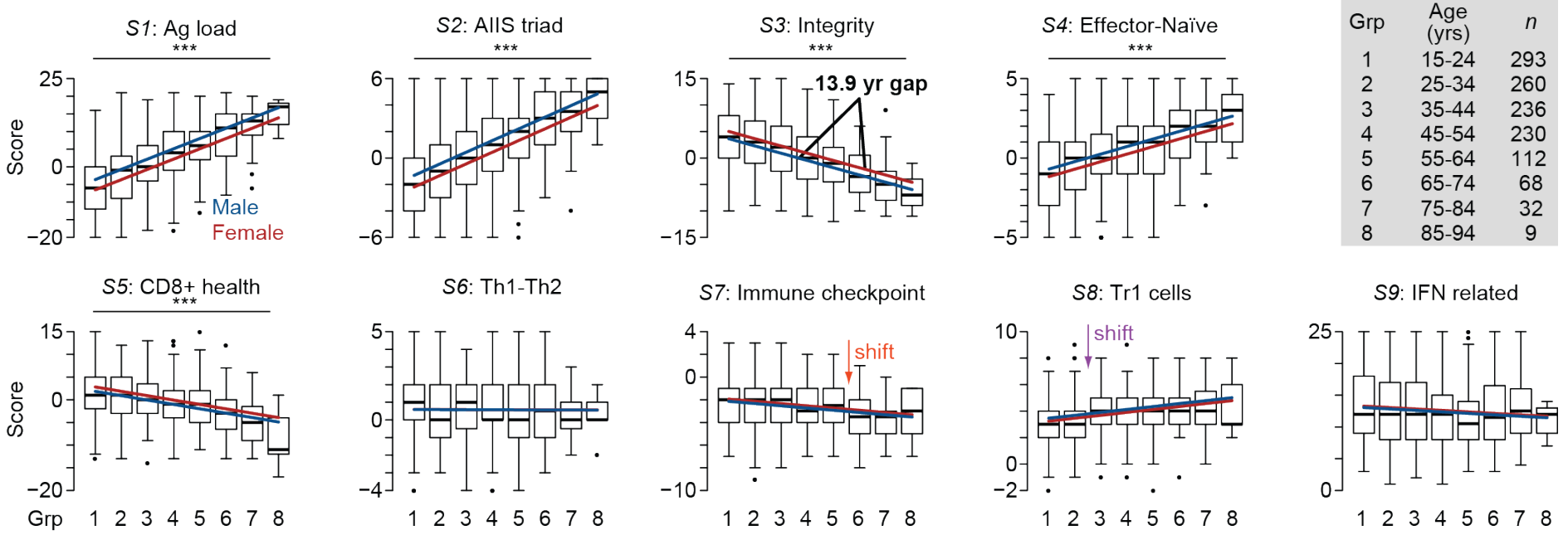
Evaluated >140,000 publicly available gene expression arrays



AIIS setpoint correlates with RSV disease severity in neonates



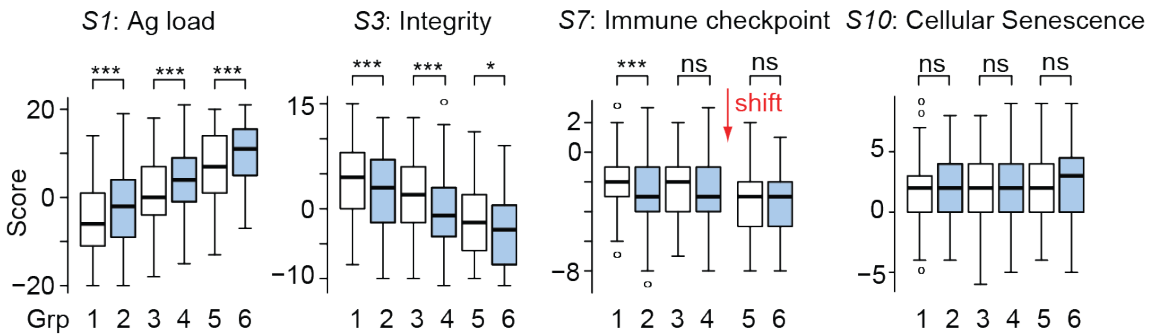
Effects of repetitive AIIS hits over a lifetime: AIIS setpoint increases with age (M>F)



Grp	Age (yrs)	*n*
1	15-24	293
2	25-34	260
3	35-44	236
4	45-54	230
5	55-64	112
6	65-74	68
7	75-84	32
8	85-94	9

A

Grp	Age (yrs)	Sex	*n*
1	15-34	F	310
2	15-34	M	243
3	35-54	F	290
4	35-54	M	176
5	55-94	F	134
6	55-94	M	87



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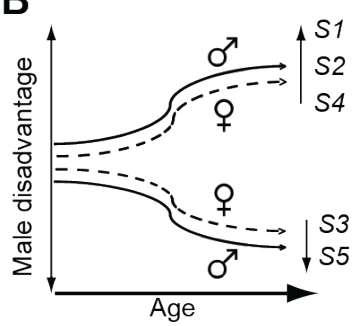
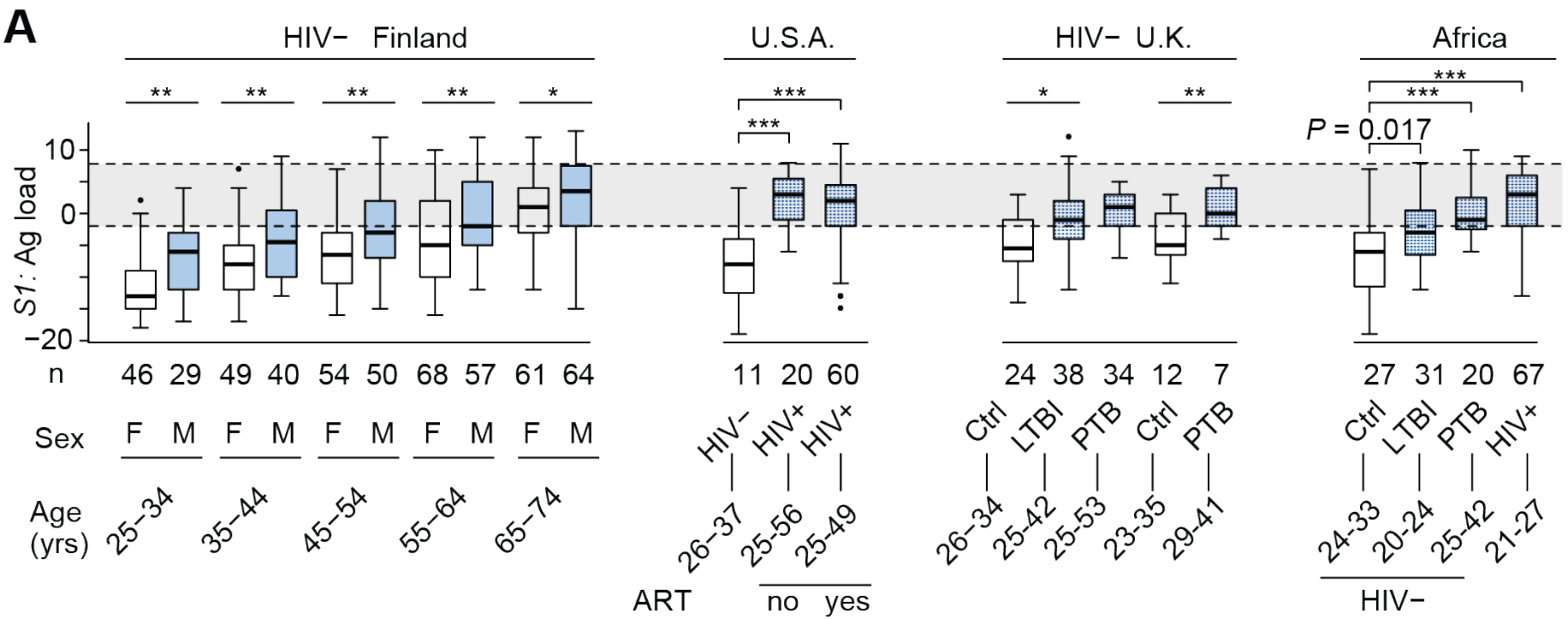
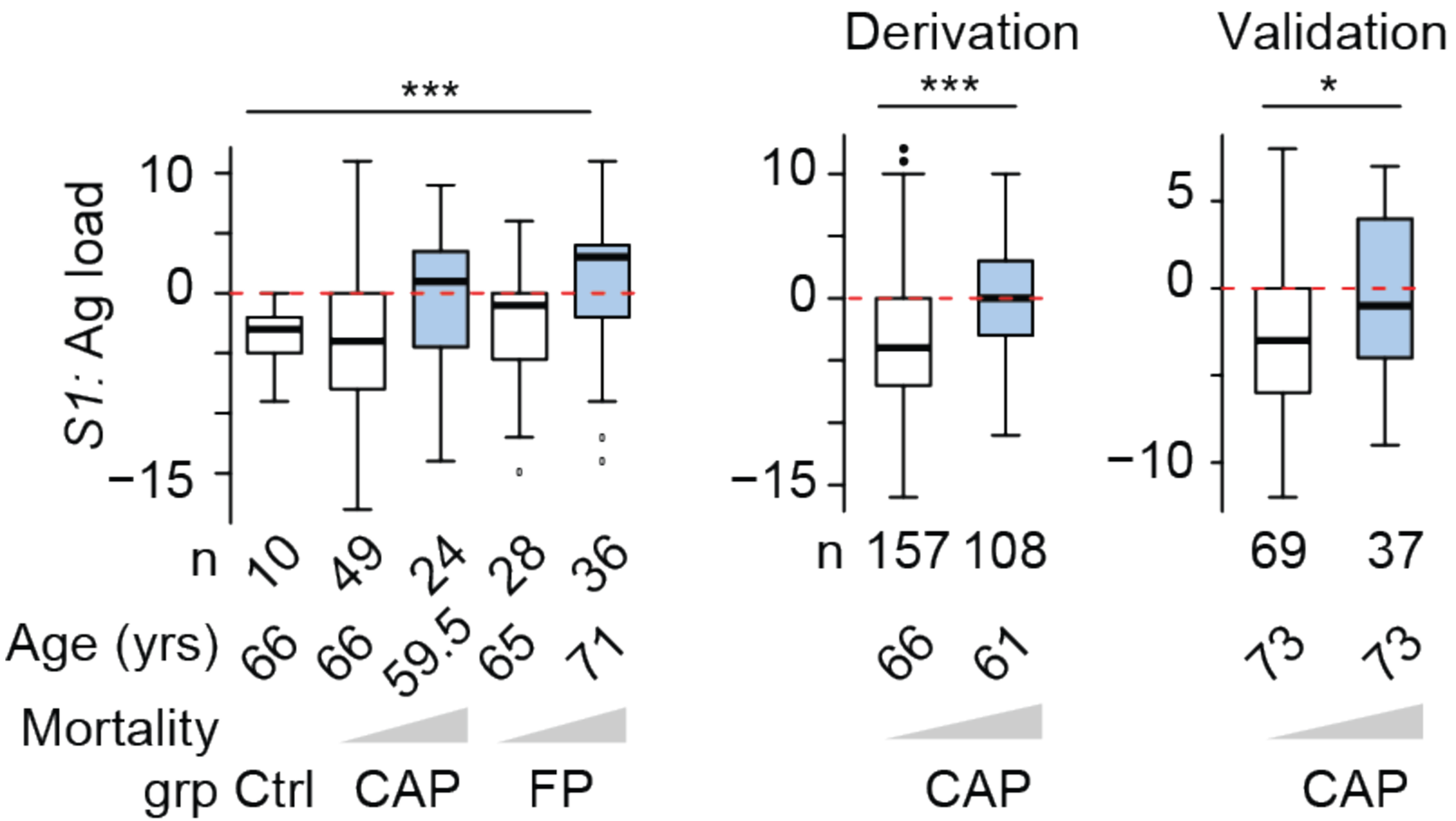


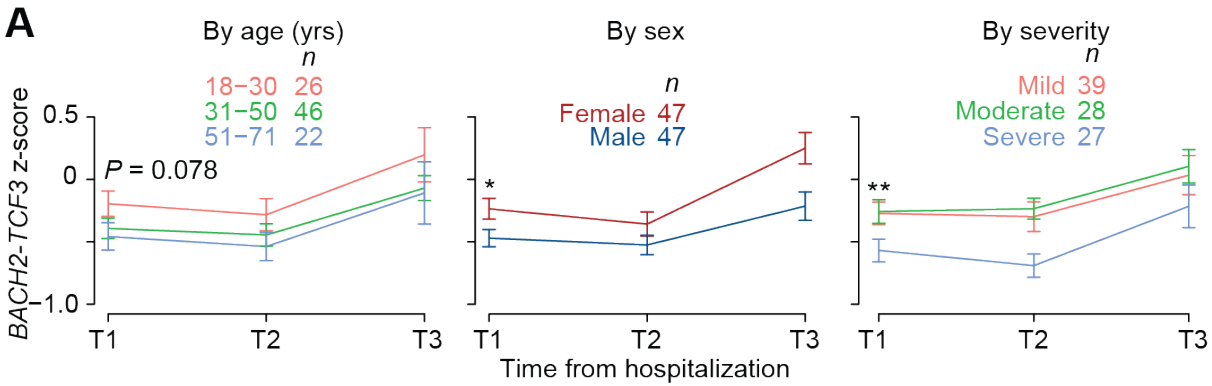
AIIS setpoint of older HIV- individuals = younger individuals with increased Ag stimulation

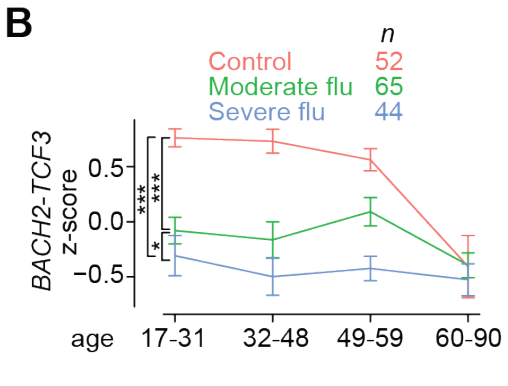


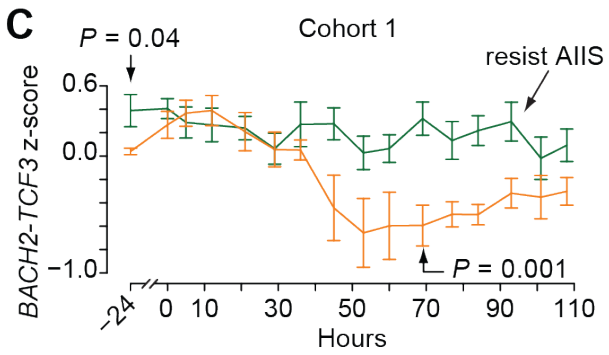
Higher AIIS setpoint at baseline predicts mortality in severely ill individuals



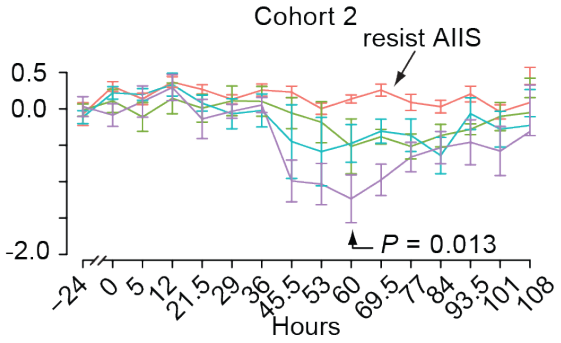
Higher AIIS setpoint correlates with influenza susceptibility, severity and vaccine responsiveness







	sex (%F)	Age (yrs)	n
Asymptomatic	38	28	8
Symptomatic	56	27	9



Grp	TSS	sex (%F)	Age (yrs)	n
1	0-10	32	24	25
2	11-20	29	25	7
3	21-30	75	26	4
4	>30	40	25	5

Disease model