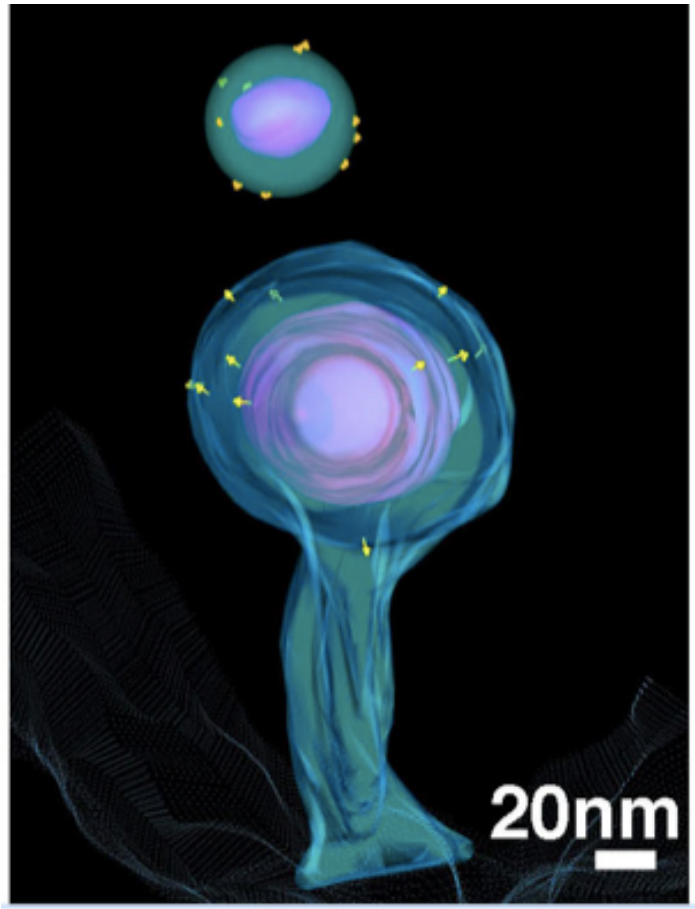
Still here after all these years: The continuing HIV/AIDS epidemic and new approaches to understand and cure a global killer

THE KIEFFER LAB



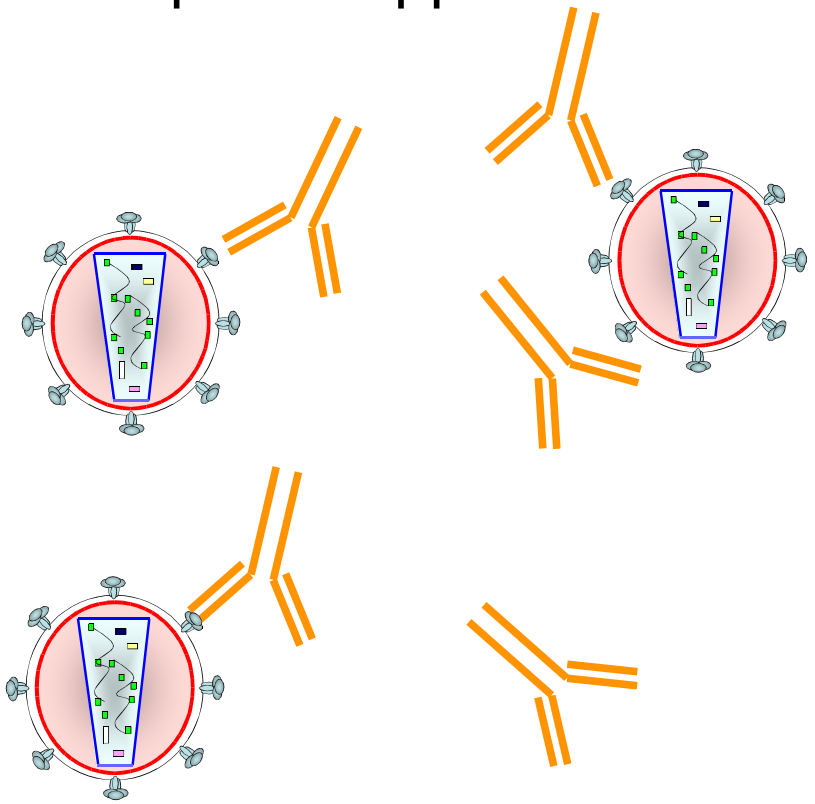
ILLINOIS

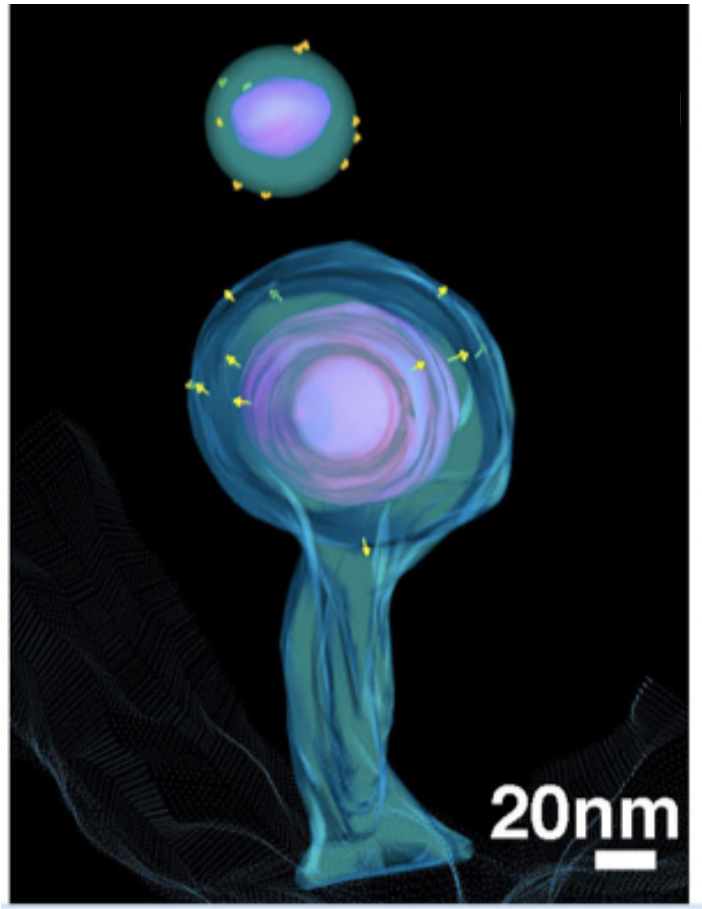
Collin Kieffer, PhD
Department of Microbiology
University of Illinois at Urbana-Champaign

Outline

I. Introduction to HIV epidemiology, virus pathogenesis, current treatments, and limitations.

II. New therapeutic approaches to eradicate HIV



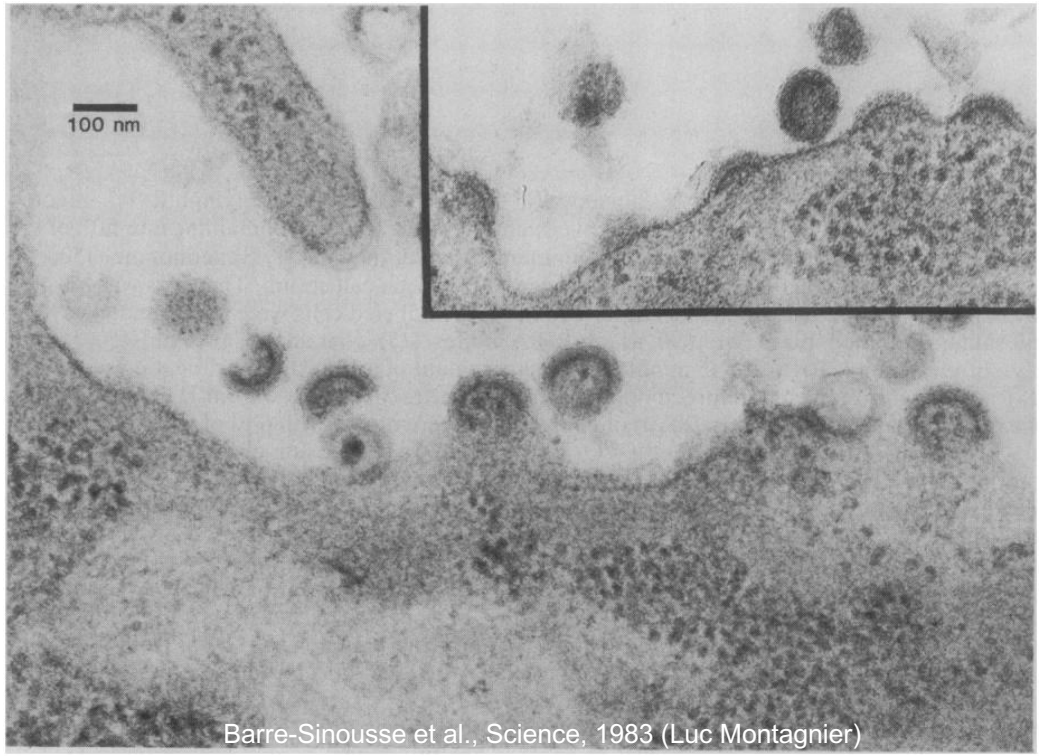


HIV (Human Immunodeficiency Virus) is the causative agent of AIDS (Acquired Immune Deficiency Syndrome)

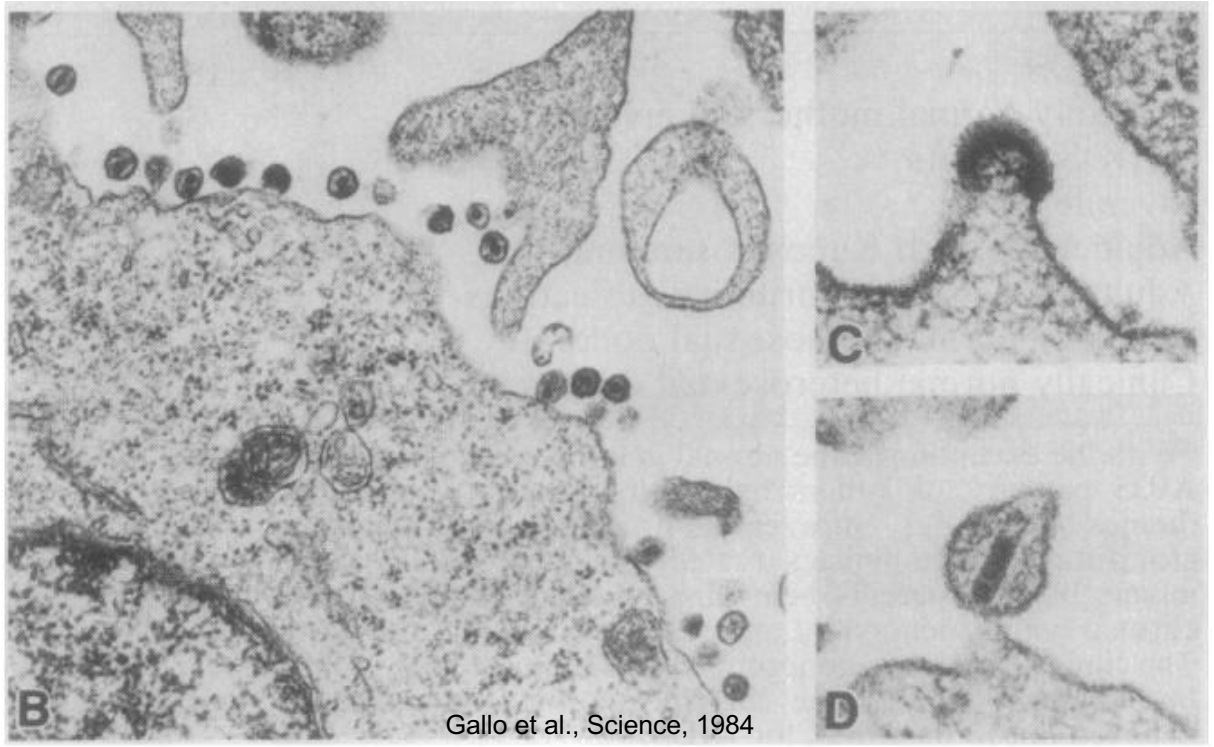
Similar to SARS-CoV-2 causing COVID 19 disease

During the late 1970's and early 1980's, populations of injection drug users and homosexual men in New York, San Francisco, and Los Angeles were presenting to doctors with unexplainable autoimmune like symptoms and opportunistic infections.

HIV was discovered to cause AIDS 35 years ago by the labs of Luc Montagnier and Bob Gallo.



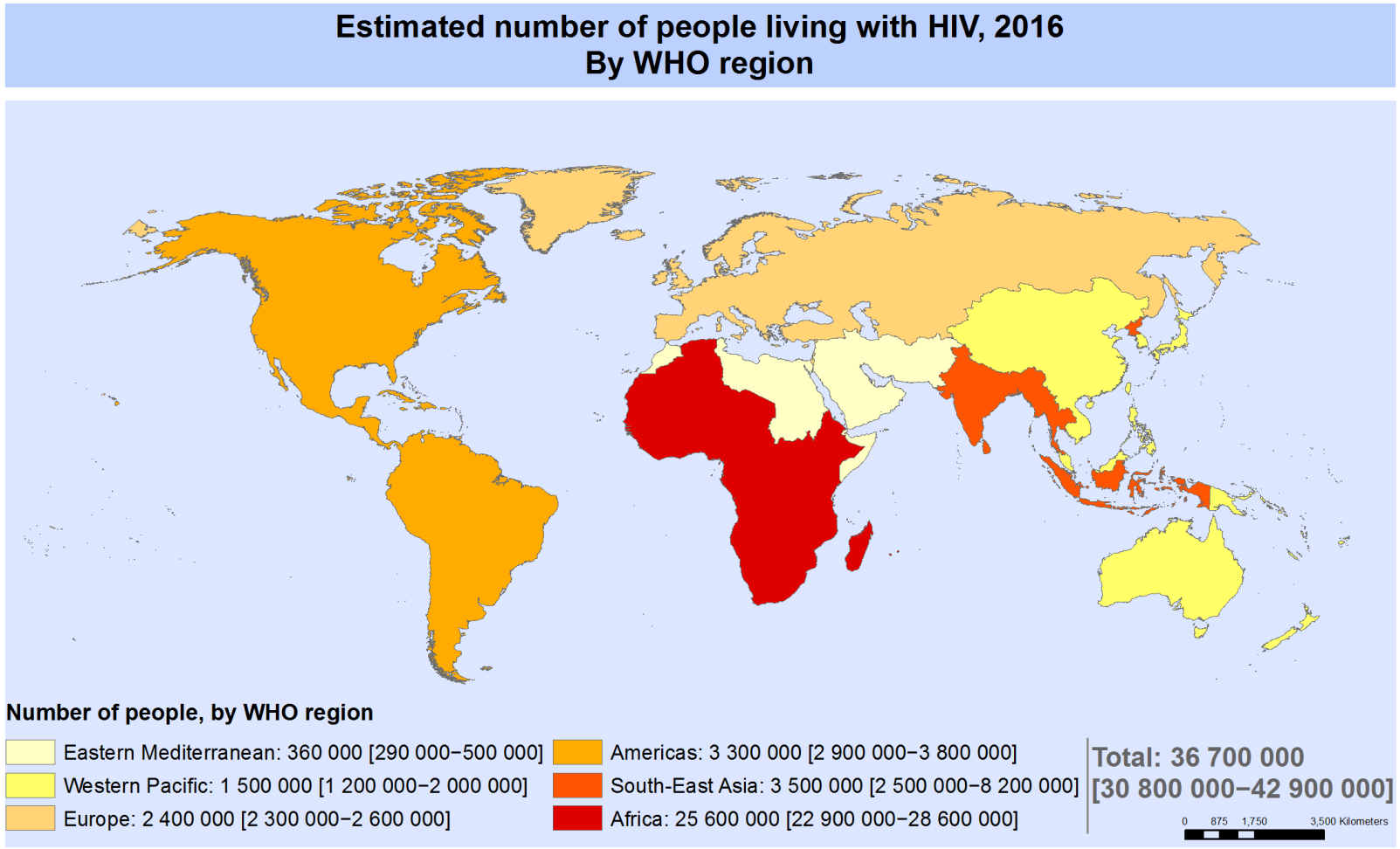
Cells from a biopsied lymph node co-cultured with cord blood lymphocytes



Cultured isolated T Lymphocytes from AIDS patient

Over 35 years later, HIV remains a huge global health concern

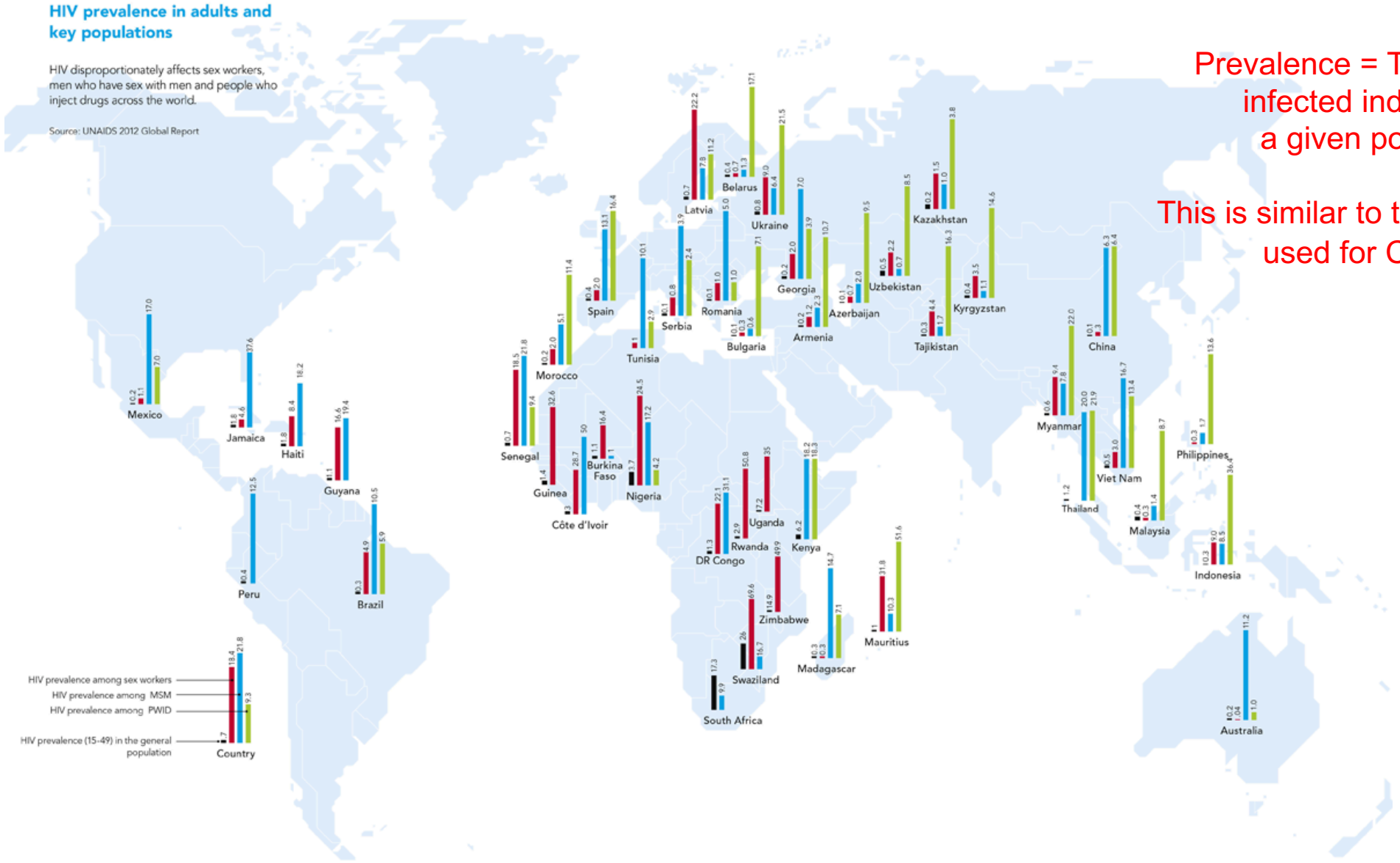
~38 million people currently living with HIV/AIDS, the majority concentrated in sub-sharan Africa.



~35 million people have died from HIV/AIDS and there is currently no effective cure.

Over 35 years later, HIV remains a huge global health concern

HIV disproportionately effects specific populations of individuals



Prevalence = The percent of infected individuals in a given population.

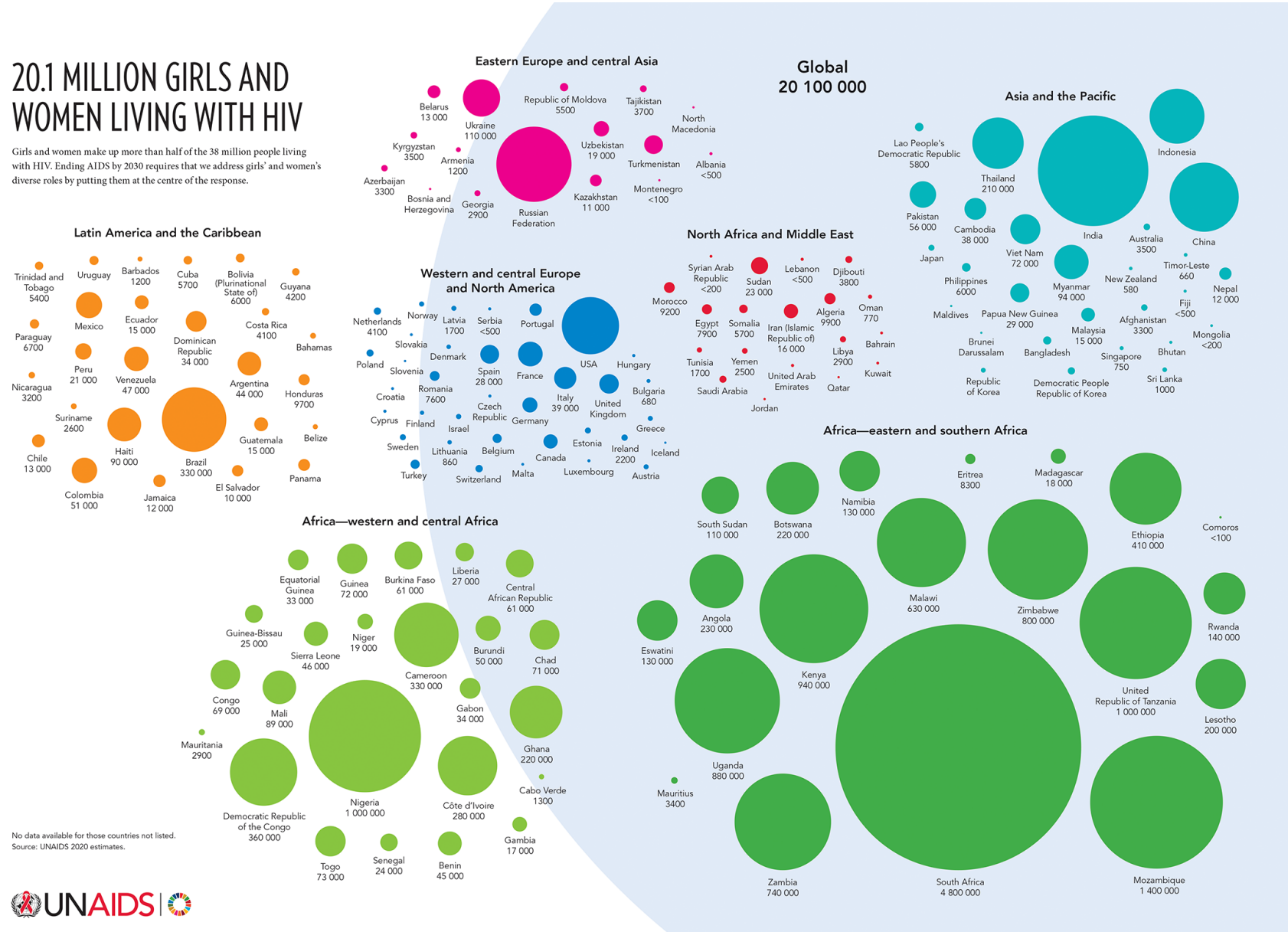
This is similar to the positivity rate used for COVID-19

UNAIDS

General Population Sex workers Men who have sex with men Drug Injecting

Over 35 years later, HIV remains a huge global health concern

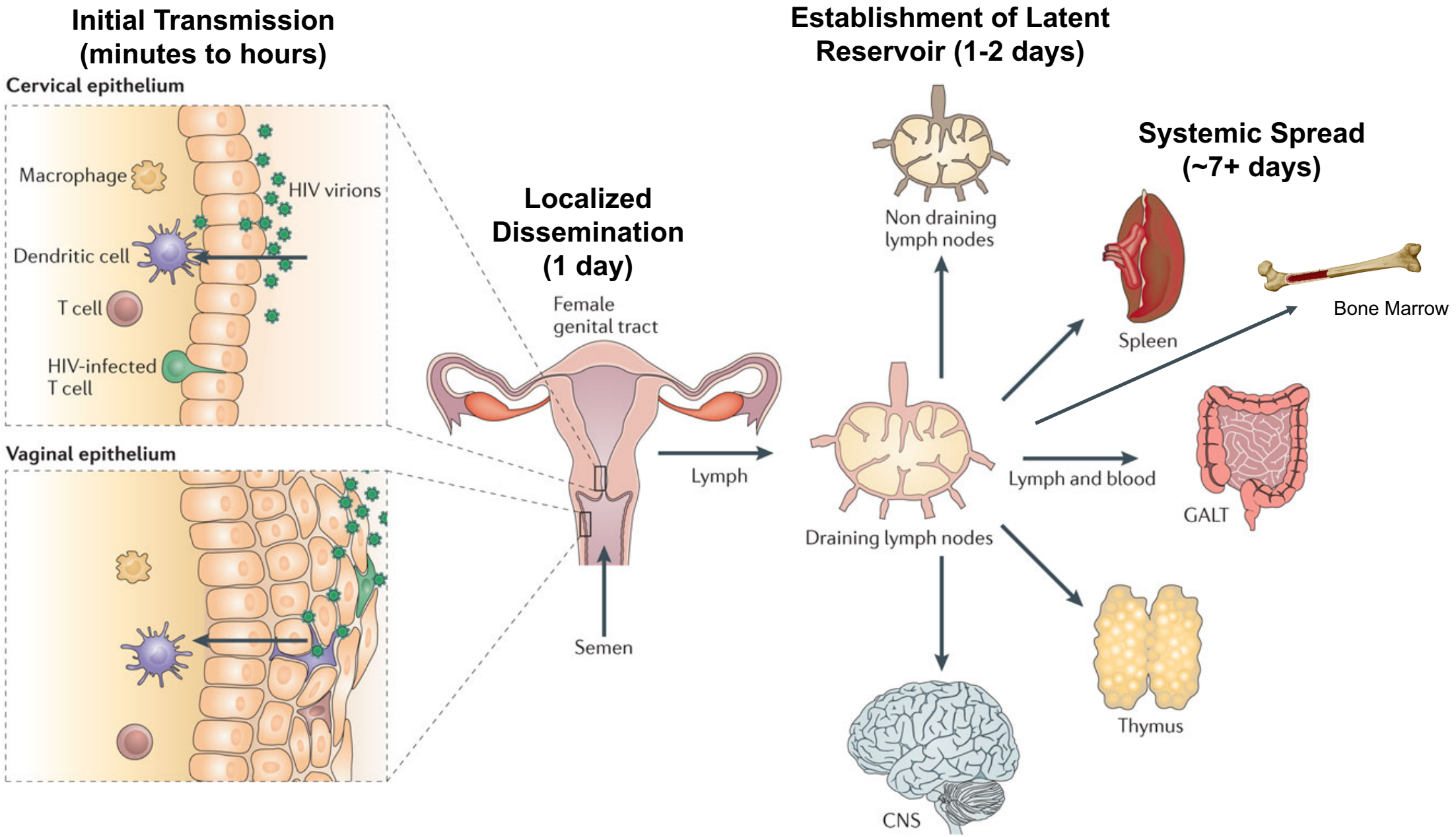
Women and girls make up the majority of all HIV-infected individuals worldwide



UNAIDS

HIV effects all populations, with the largest number of transmissions being heterosexual

How does HIV infection proceed during the acute stage?



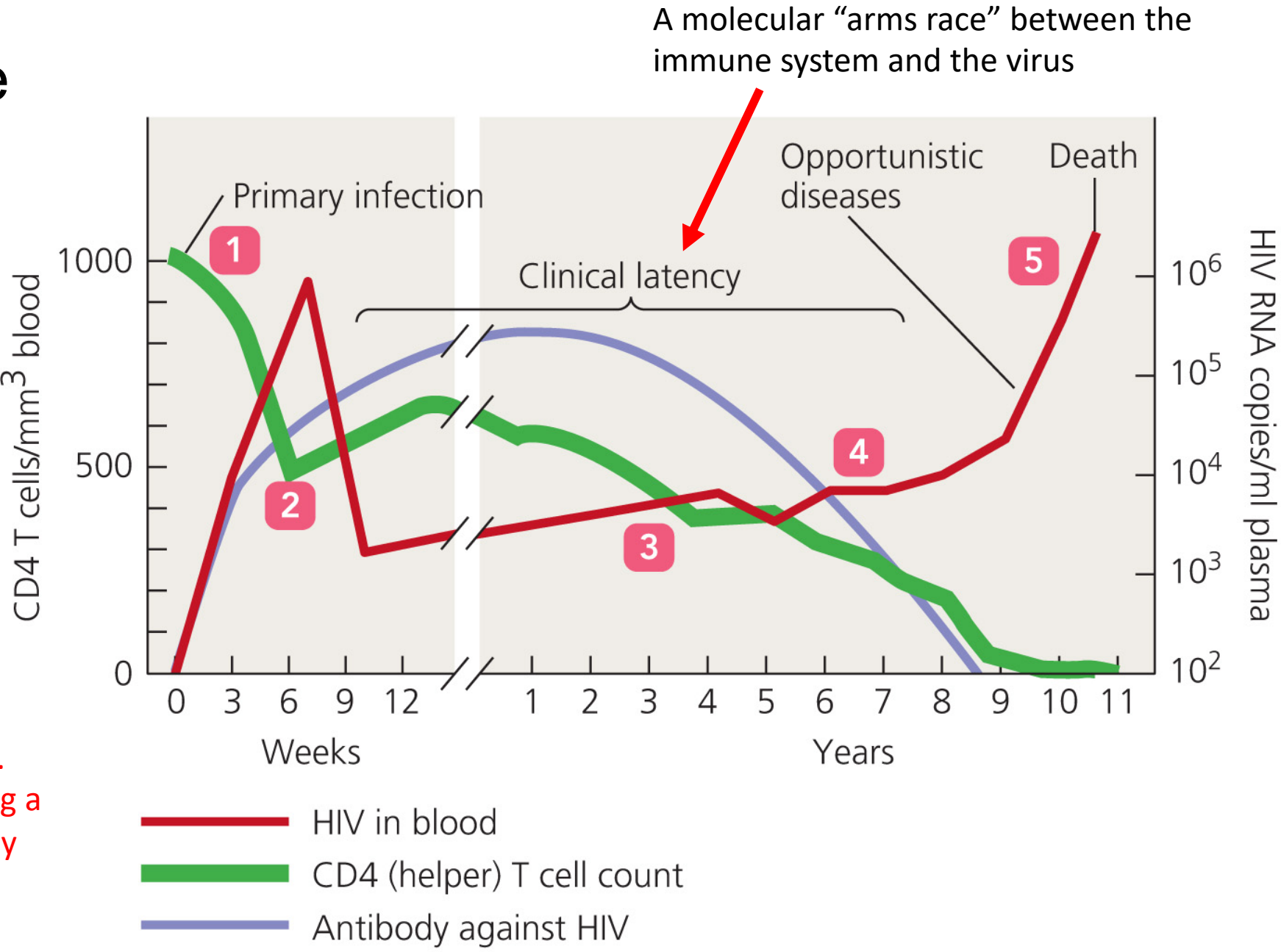
Fackler et al., Nat Rev Micro, 2014

Timeline of Disease for HIV/AIDS

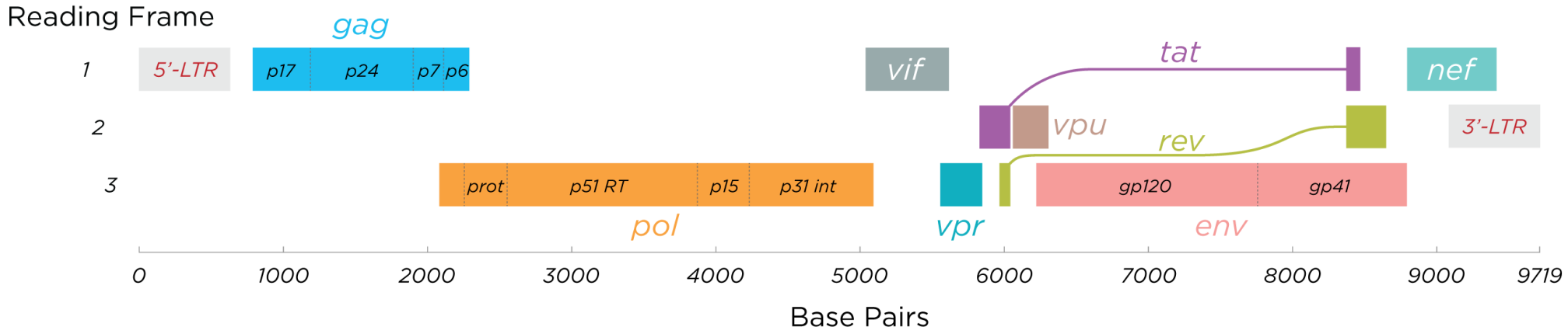
HIV Disease Course

1. Primary Infection
2. Acute Infection
3. Clinical Latency
4. Immune Dysfunction
5. AIDS (death due to being immunocompromised).

Having HIV does not mean having AIDS. AIDS is the resulting pathology of having a dysfunctional immune system caused by HIV infection.



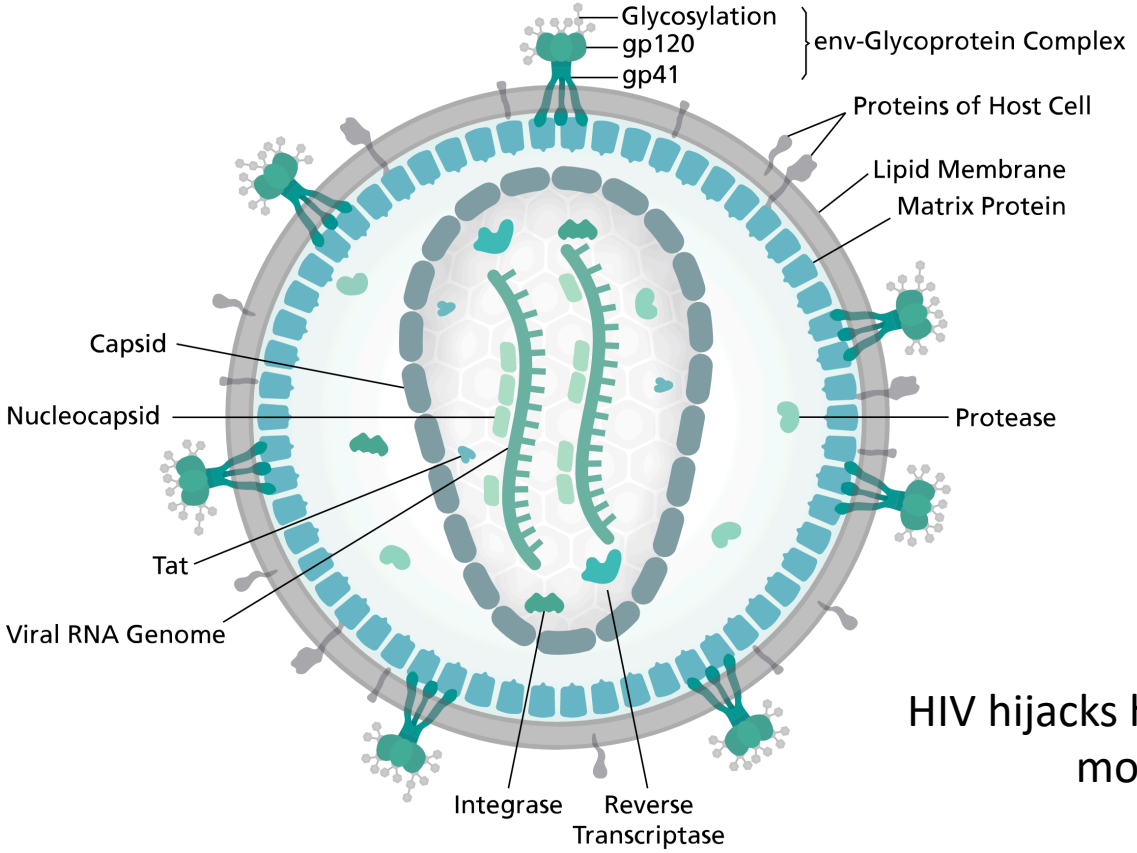
HIV is a retrovirus with a small RNA genome



**2 copies of a +ssRNA genome

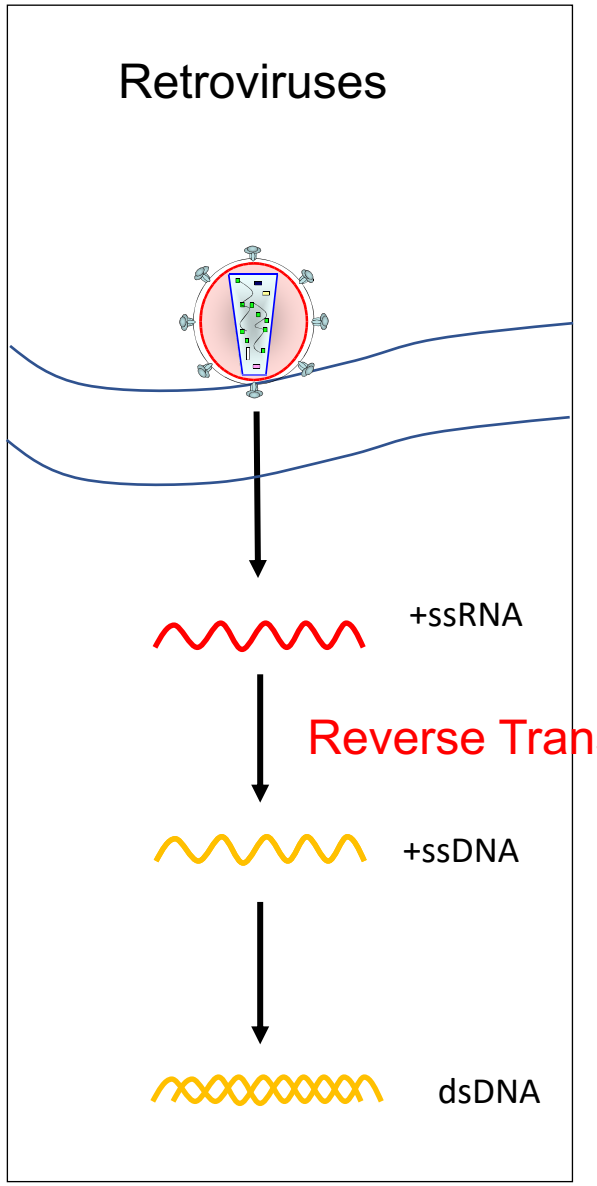
**~10,000 bp in length

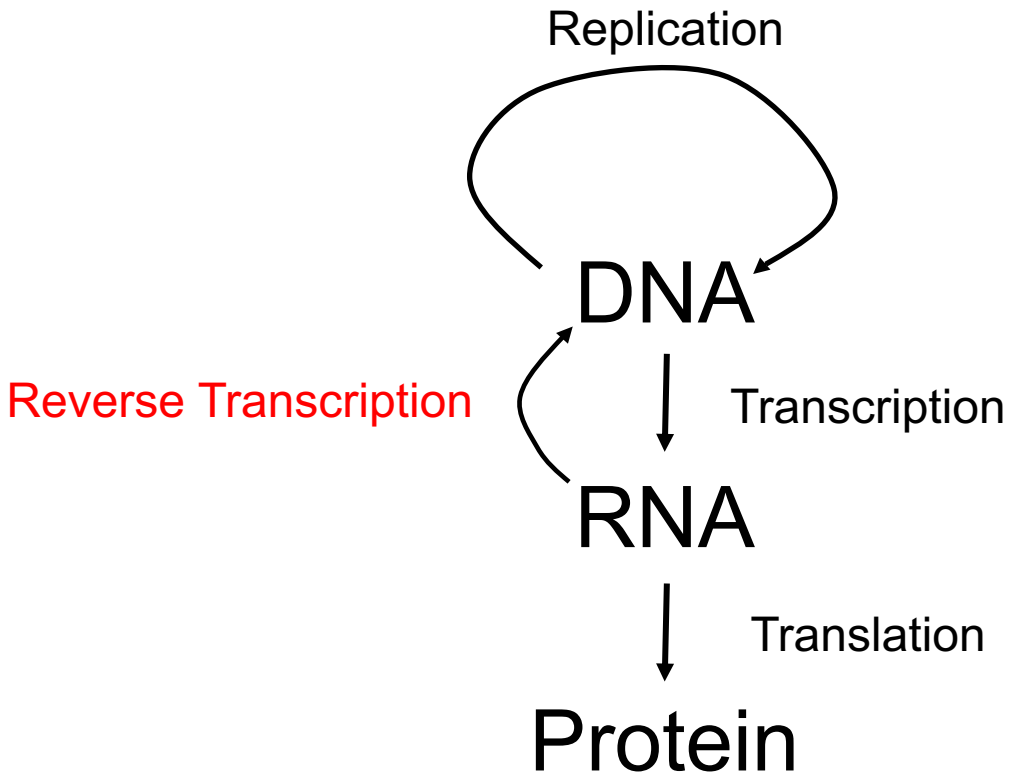
**9 genes, 15 proteins



HIV hijacks host-cell processes to accomplish most of its replication cycle

HIV goes against the central dogma of molecular biology





This discovery partially led to the 1975 Nobel prize for Howard Temin, David Baltimore, and Renato Dulbecco

The HIV life-cycle

1. Attachment
(binding of the virus to the host target cell).

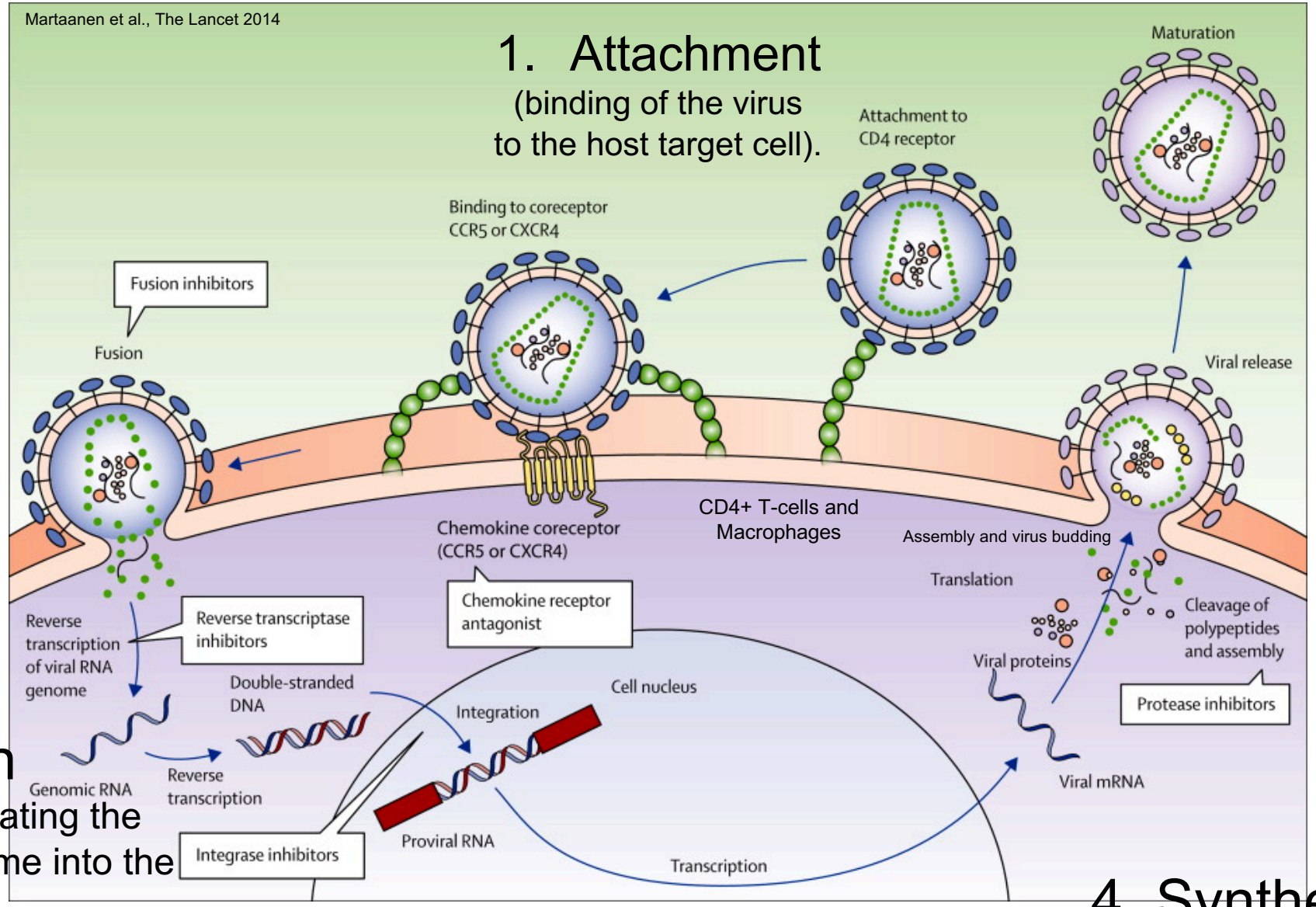
2. Entry
(transfer of the virus Genome into the host target cell).

3. Integration
(permanently integrating the DNA provirus genome into the host-cell genome).

4. Synthesis
(using the host machinery to make all of the parts of the virus).

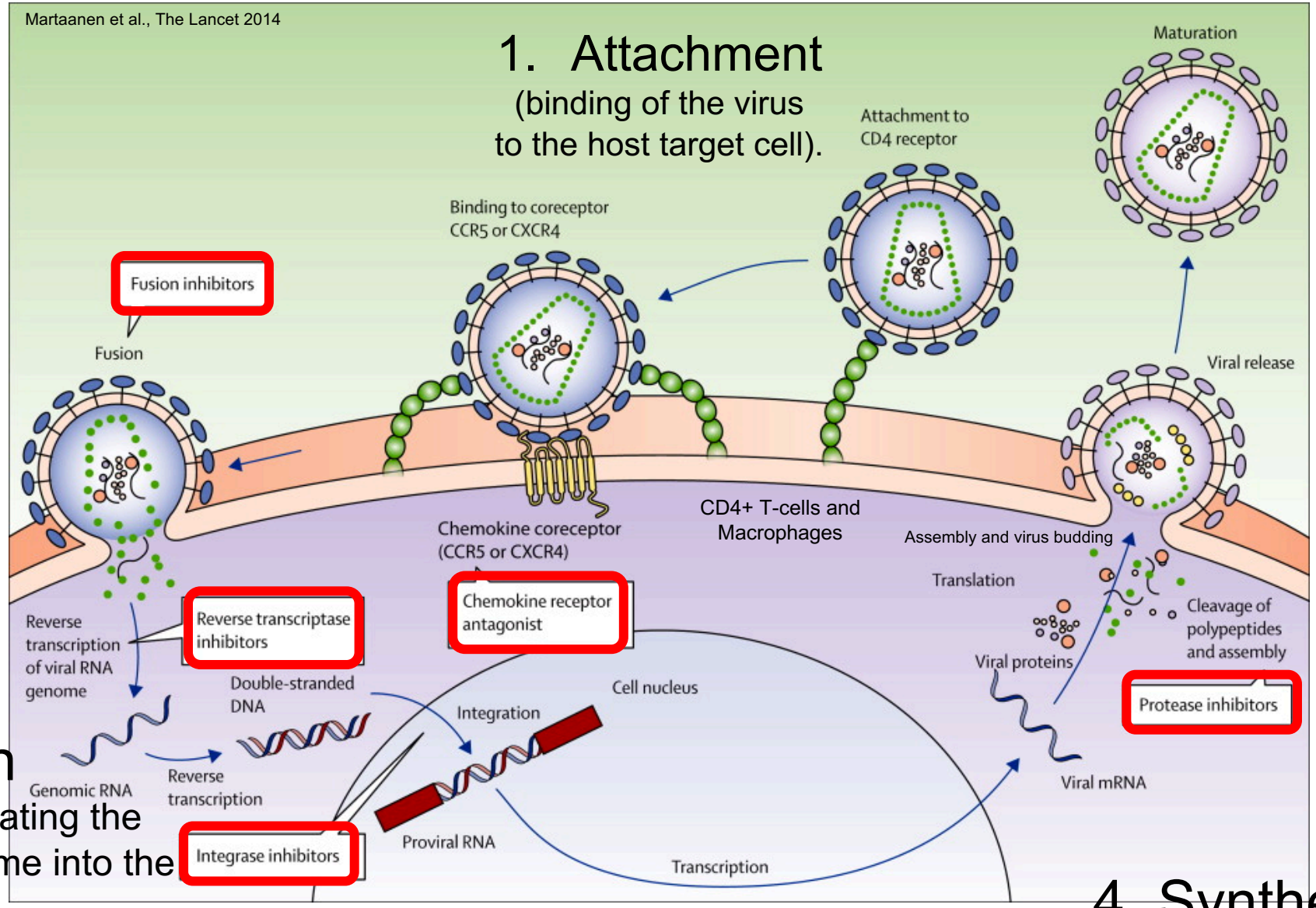
5. Assembly
(organization of all the virus parts to make new viruses).

6. Release
(delivery of newly made virus particles into the outside world so that the entire process can be repeated).



HIV specifically targets CD4+ T-cells (macrophages, and others).
It is essentially an infection of the immune system.

The HIV life-cycle



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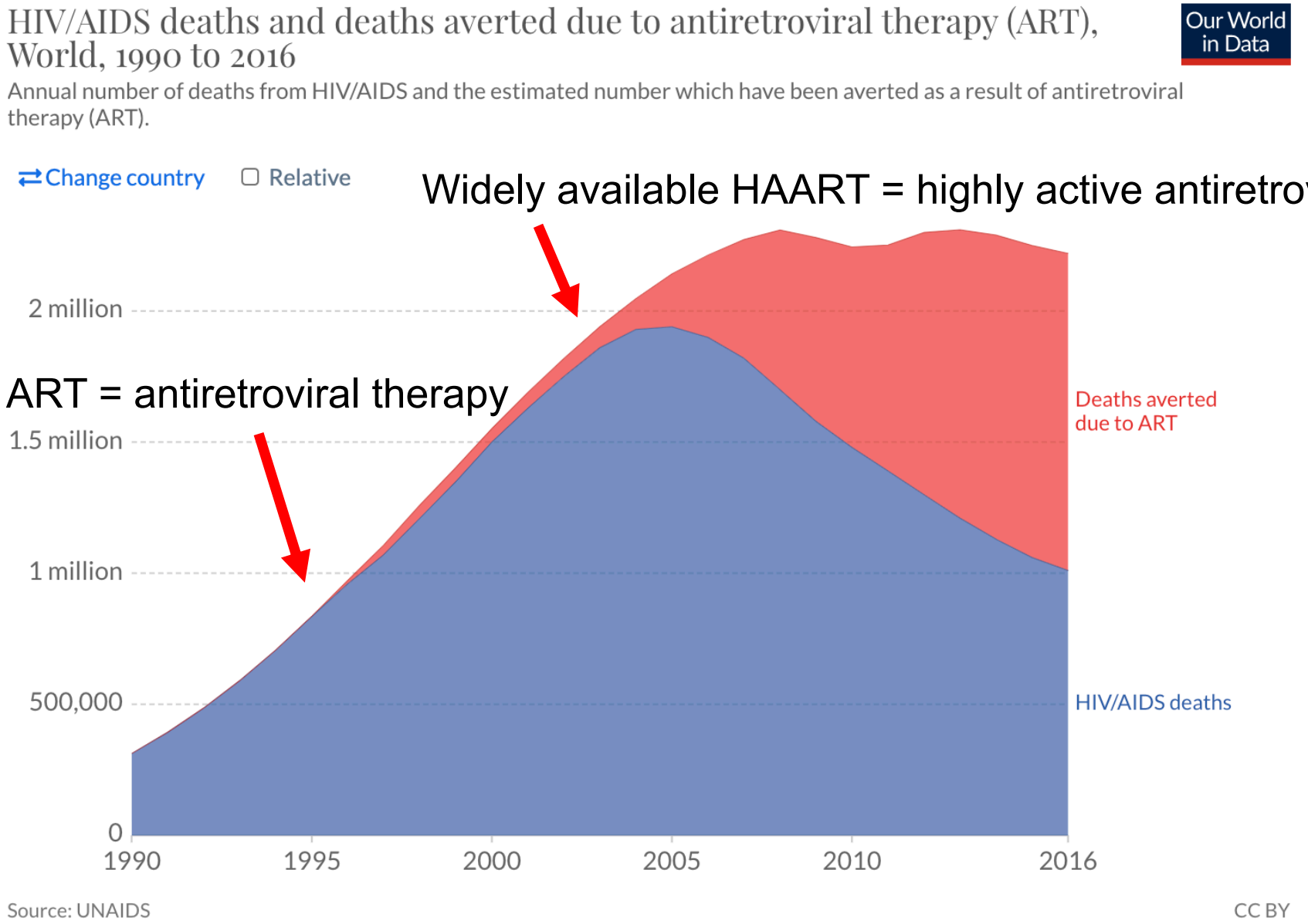
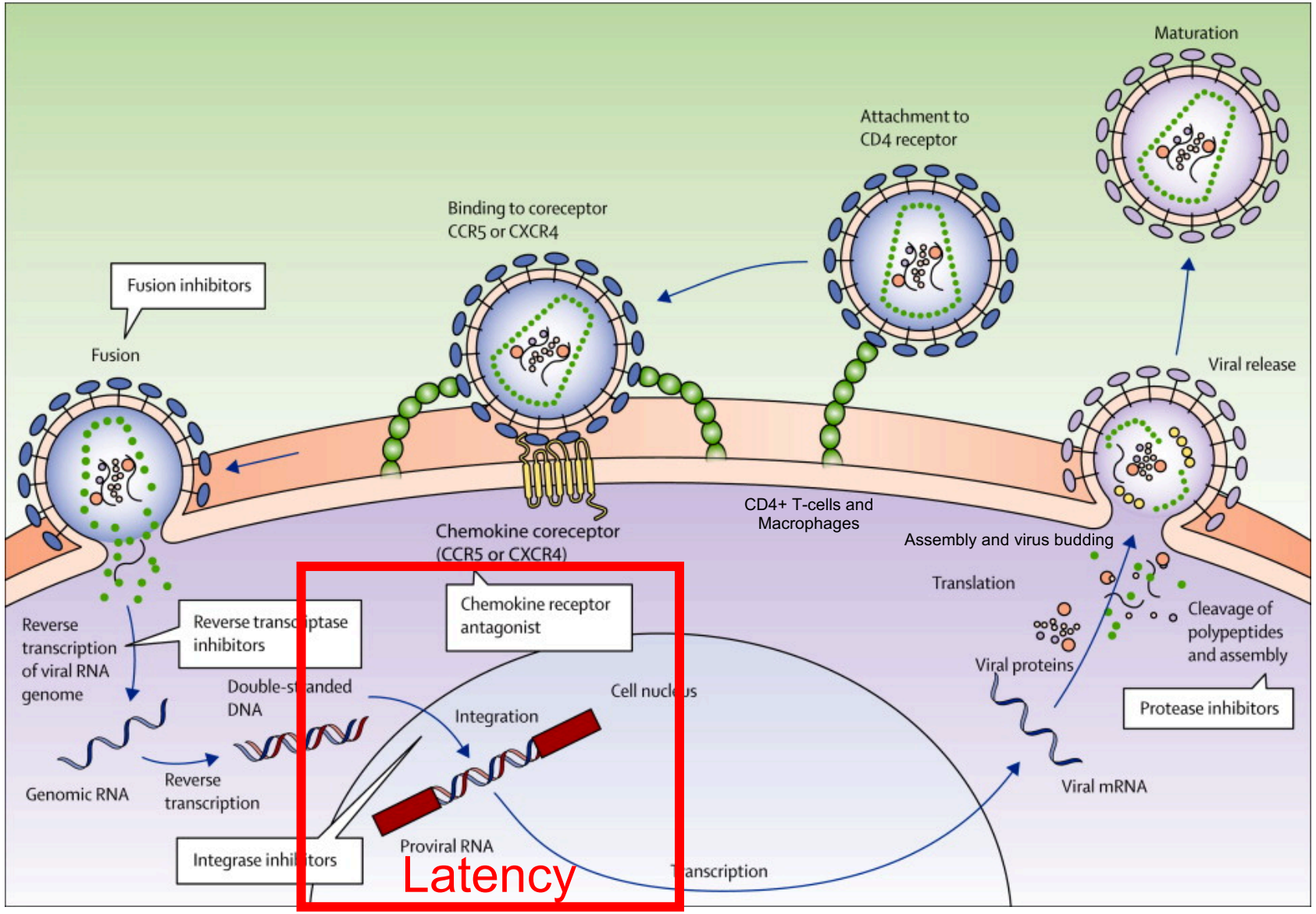
HIV specifically targets CD4+ T-cells (macrophages, and others).
It is essentially an infection of the immune system.

With the advent of ART, HIV is no longer a death sentence



Antiretroviral therapy allows HIV-infected individuals to live normal lives

Part II: There's a problem….Latency



Martaanen et al., The Lancet 2014

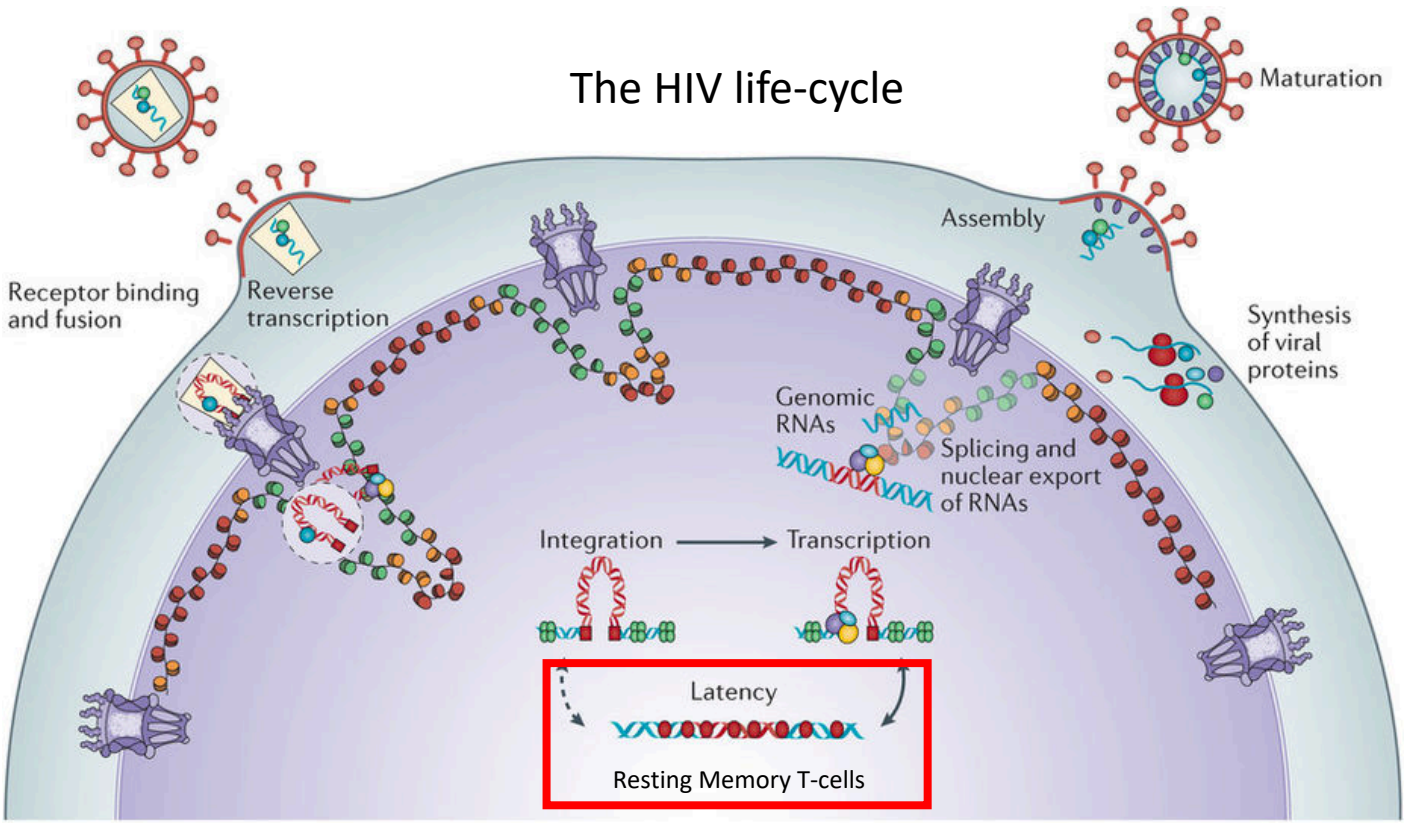
Antiretroviral therapy allows HIV-infected individuals to live normal lives, but they can't ever stop taking medication due to a reservoir of latently infected cells (infected, but not actively producing virus).

Why is HIV latency a problem?

HIV latency is one of the reasons there is no cure for HIV.

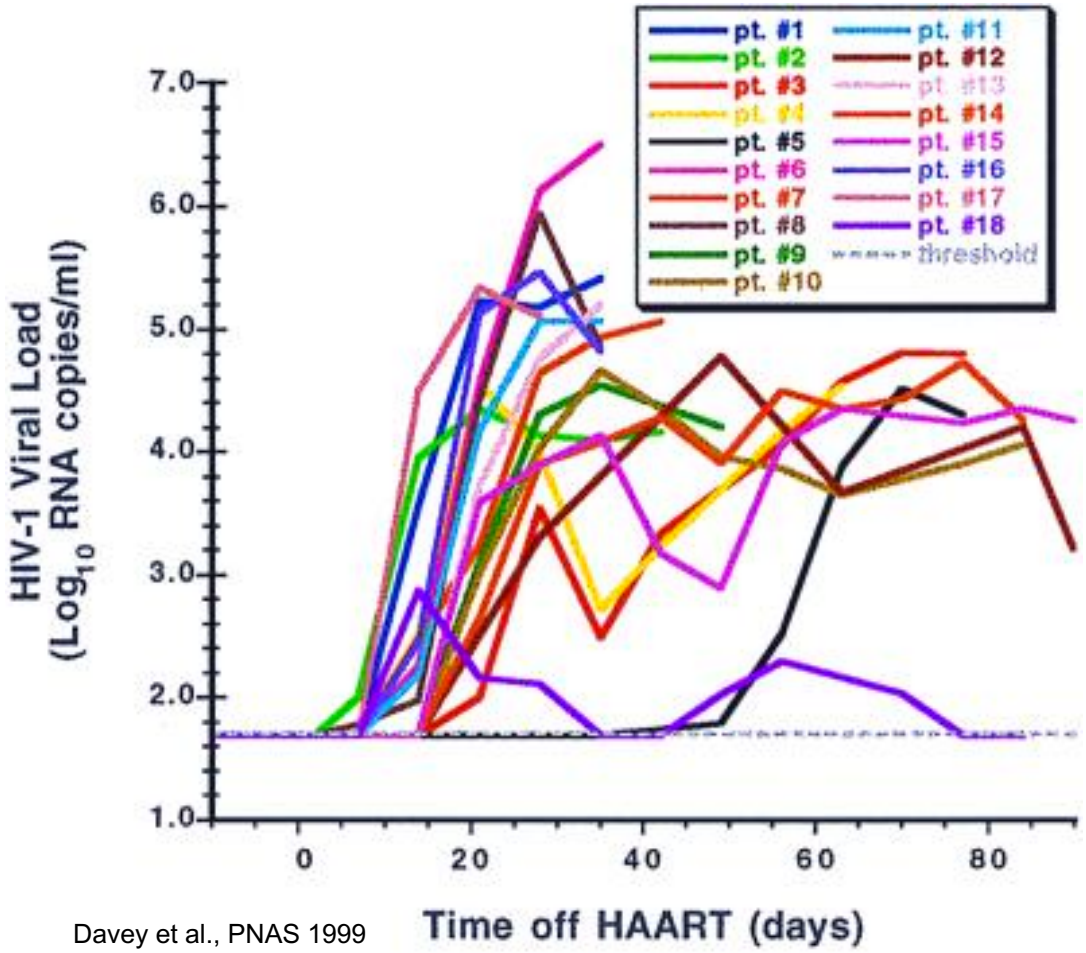
There is not a strong understanding of latent reservoirs *in vivo*.

Where are they, how do they respond to treatment,
what do they look like, which cells are responsible?



Lusic and Siliciano, Nat Rev Micro 2007

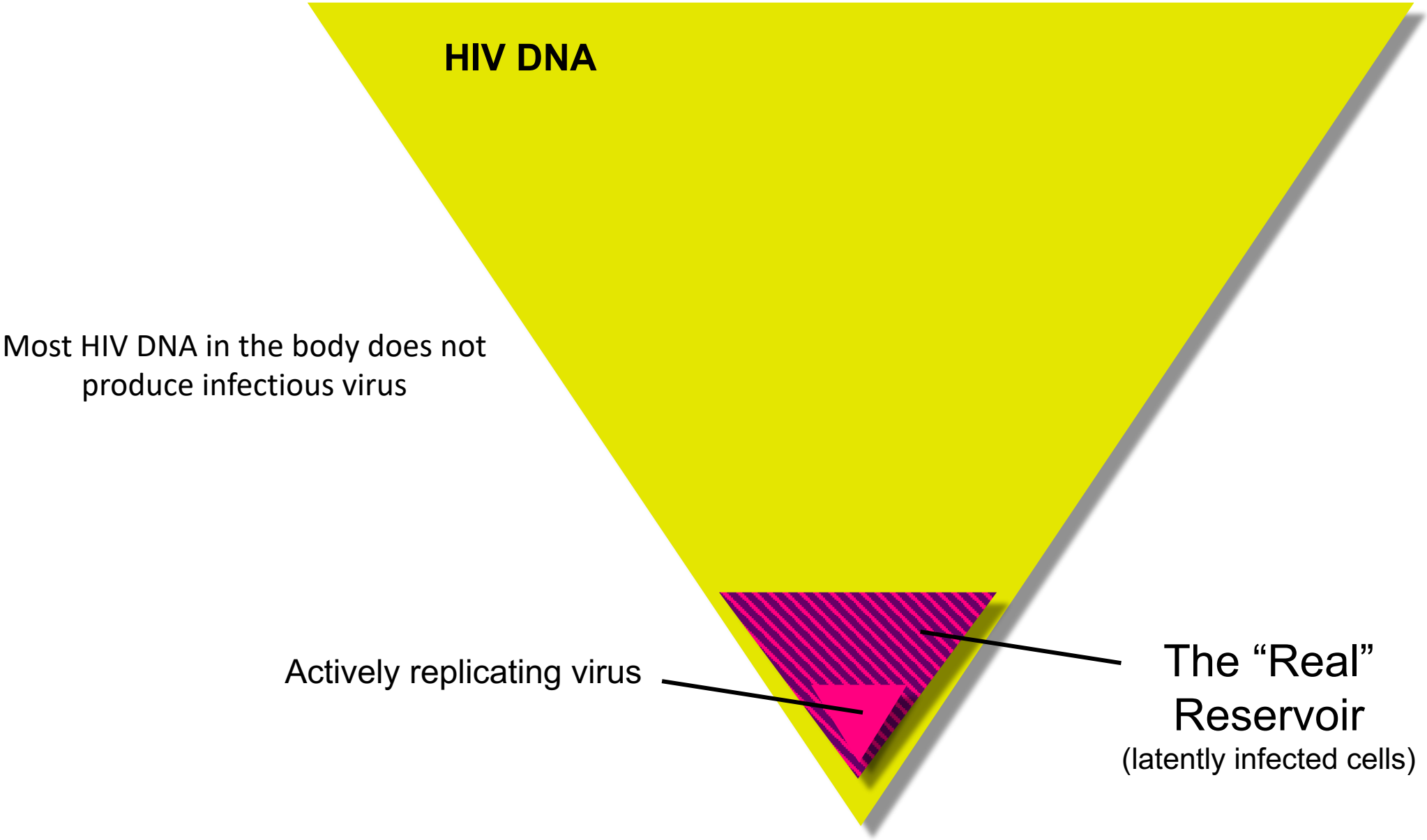
Nature Reviews | Microbiology



Davey et al., PNAS 1999

Latently infected cells are rare

The latent HIV reservoir is really small

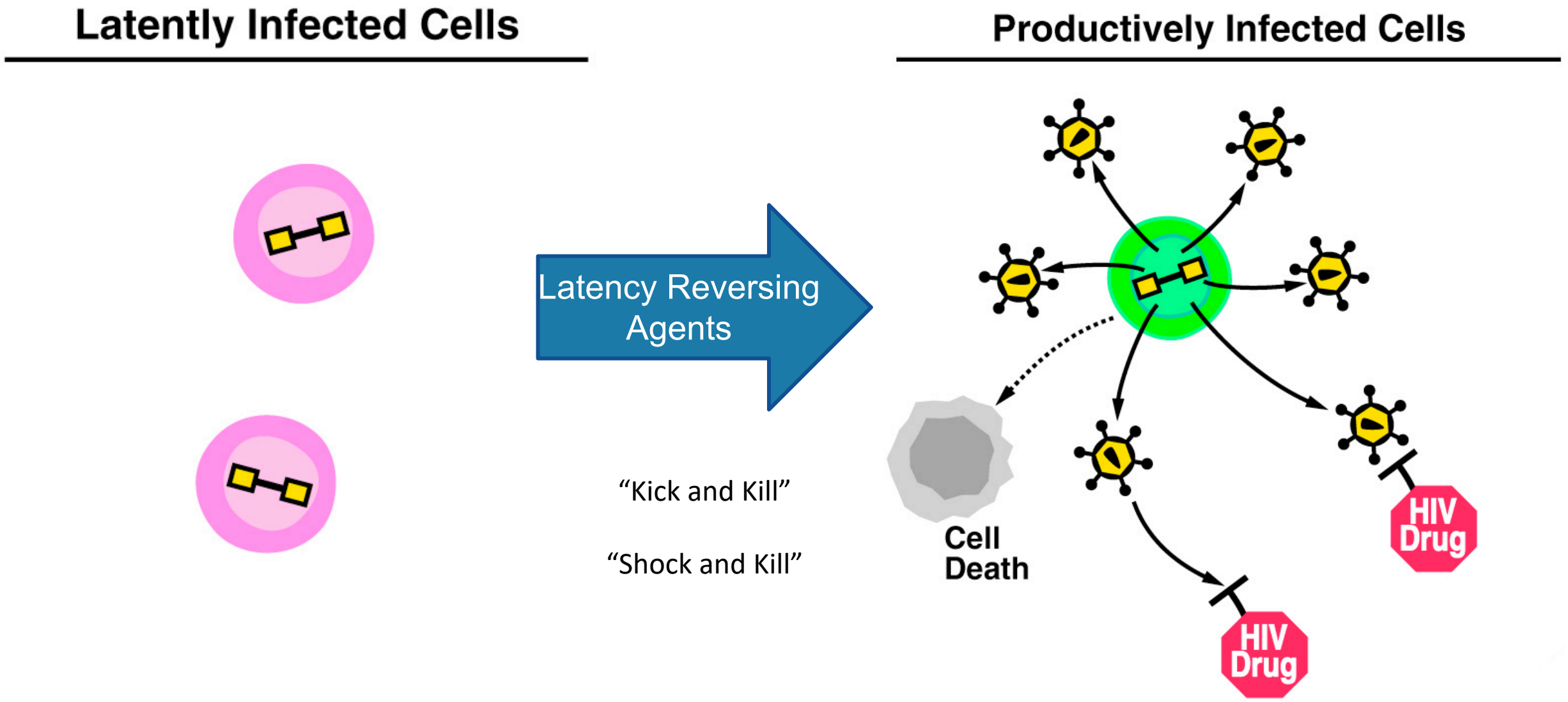


How are we going to generate a cure for HIV?

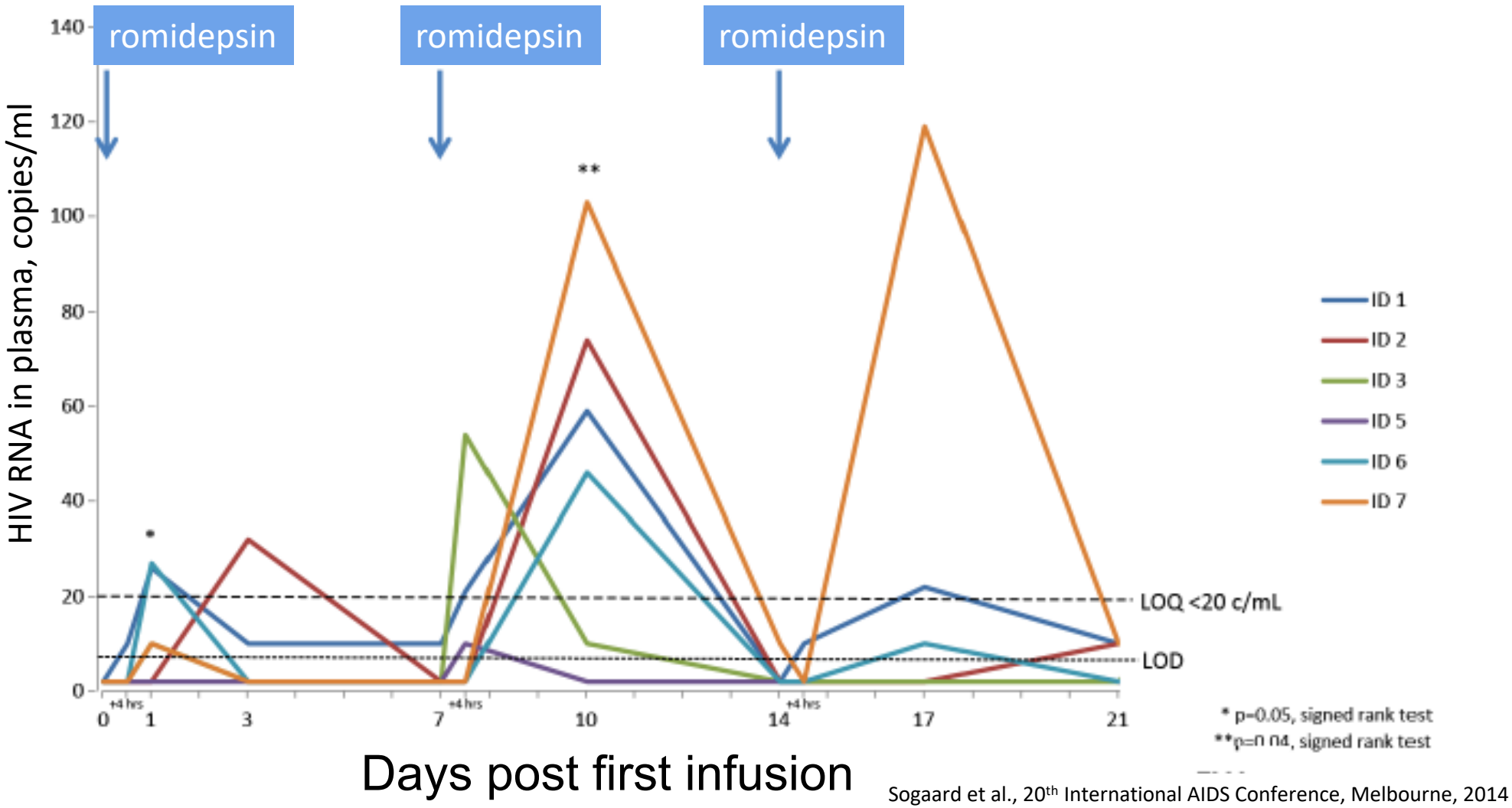
Latency Reversing Agents

Vaccines

Latency reversing agents should mobilize the latent reservoir



Do latency reversing agents work *in vivo*?



Sogaard et al., 20th International AIDS Conference, Melbourne, 2014

Kind of …

Are latency reversing agents the ultimate answer?

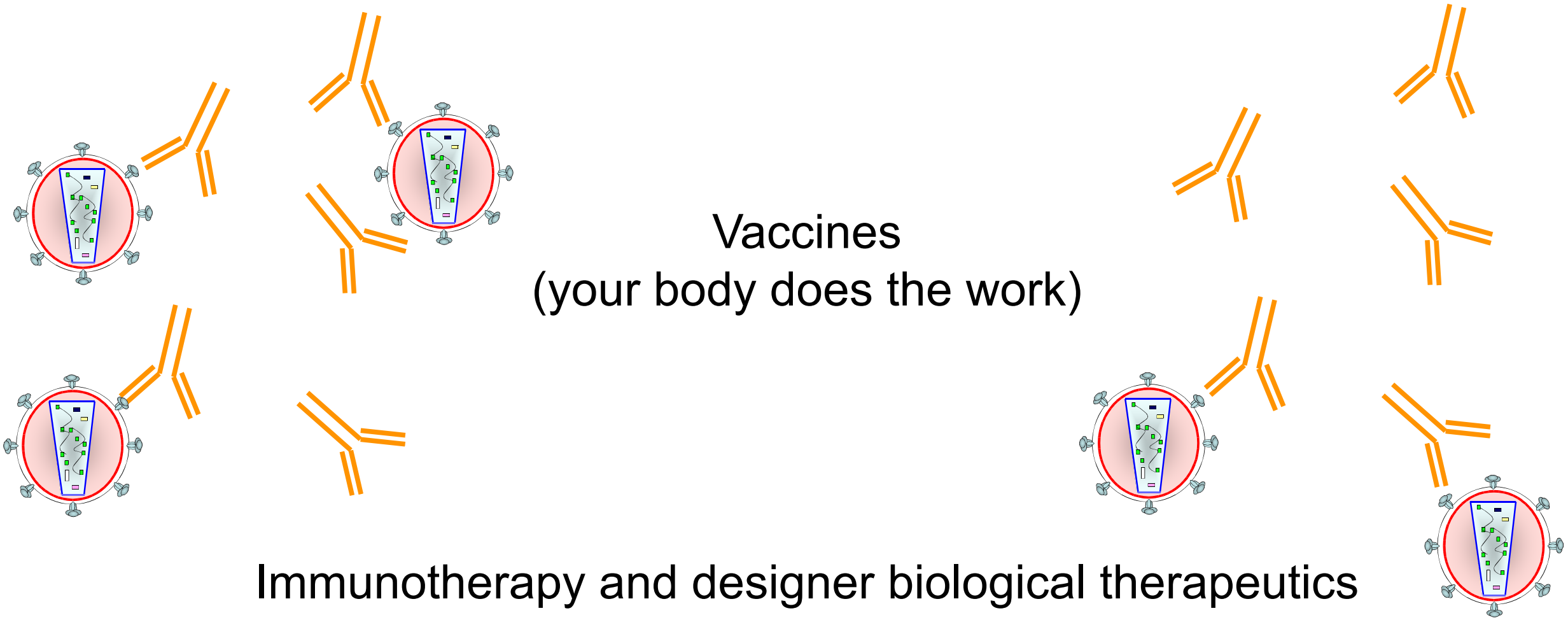
Probably not, although they will help.

- incomplete clearance of latently infected cells
- incomplete clearance of virions
- incomplete block of new infection

- Combinations of anti-latency compounds with different mechanisms of action may be more effective

- Latently infected cells that express HIV-1 RNA may not all die

Where do we go from here?



Vaccines
(your body does the work)

Immunotherapy and designer biological therapeutics
(can’t deploy to millions of individuals worldwide)

Unfortunately, HIV is not a good vaccine candidate

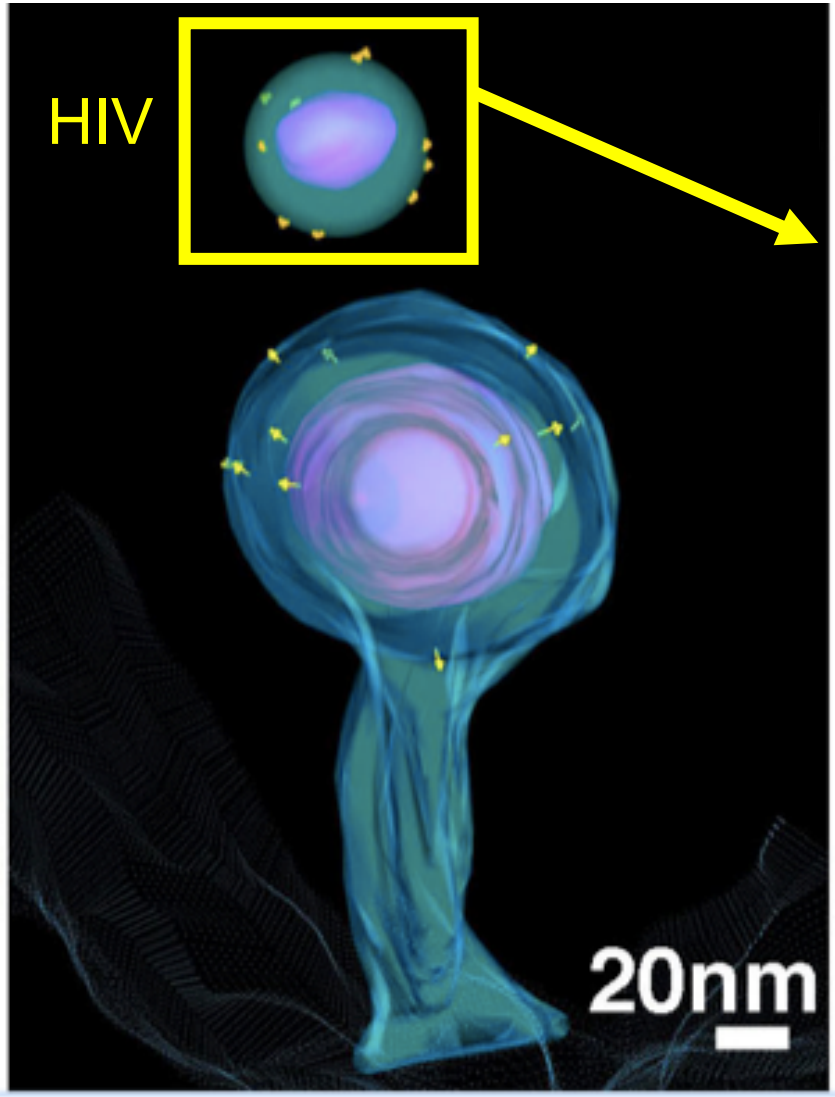
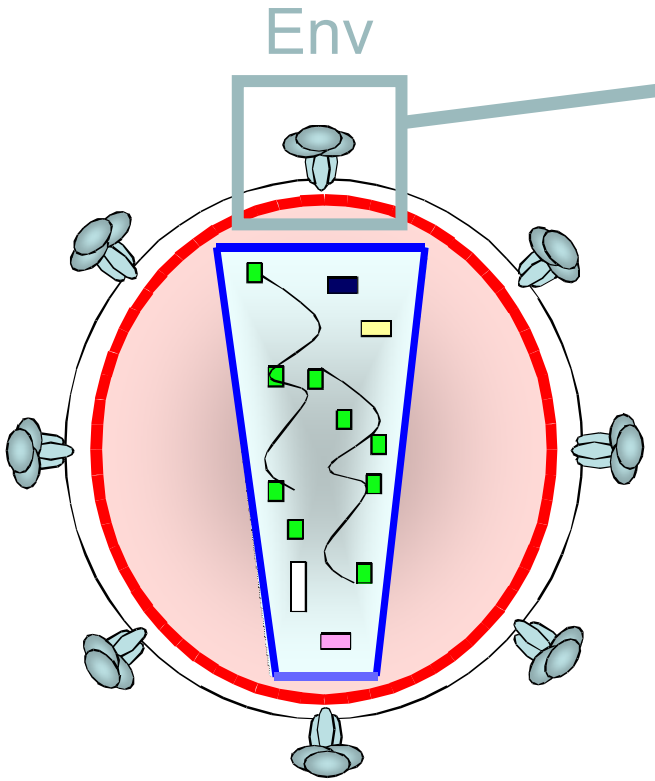
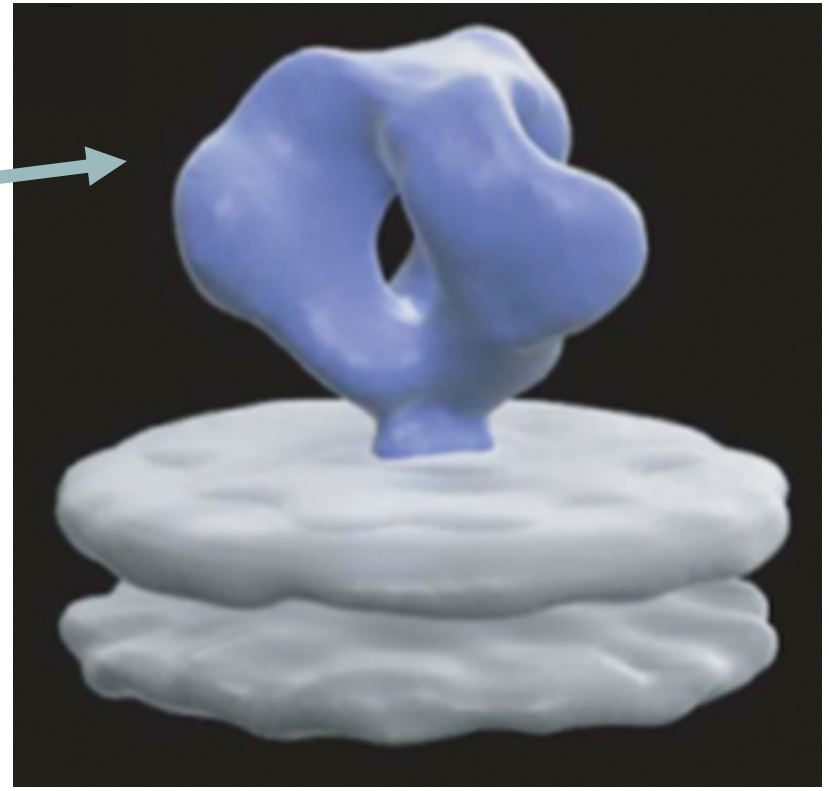


Image: Mark Ladinsky





Low-resolution (~20 Å)
of HIV Env on virions
Liu et al., 2008, *Nature*

Env is the major virus antigen the immune system encounters

Some Pathogens are difficult vaccine targets.

Pathogens can be intracellular, allowing the pathogen to persist in the presence of an immune response (HIV Latency).

Pathogens can often mutate rapidly (HIV).

Pathogens that look a lot like the host (eukaryotic pathogens and membrane enclosed viruses like HIV).

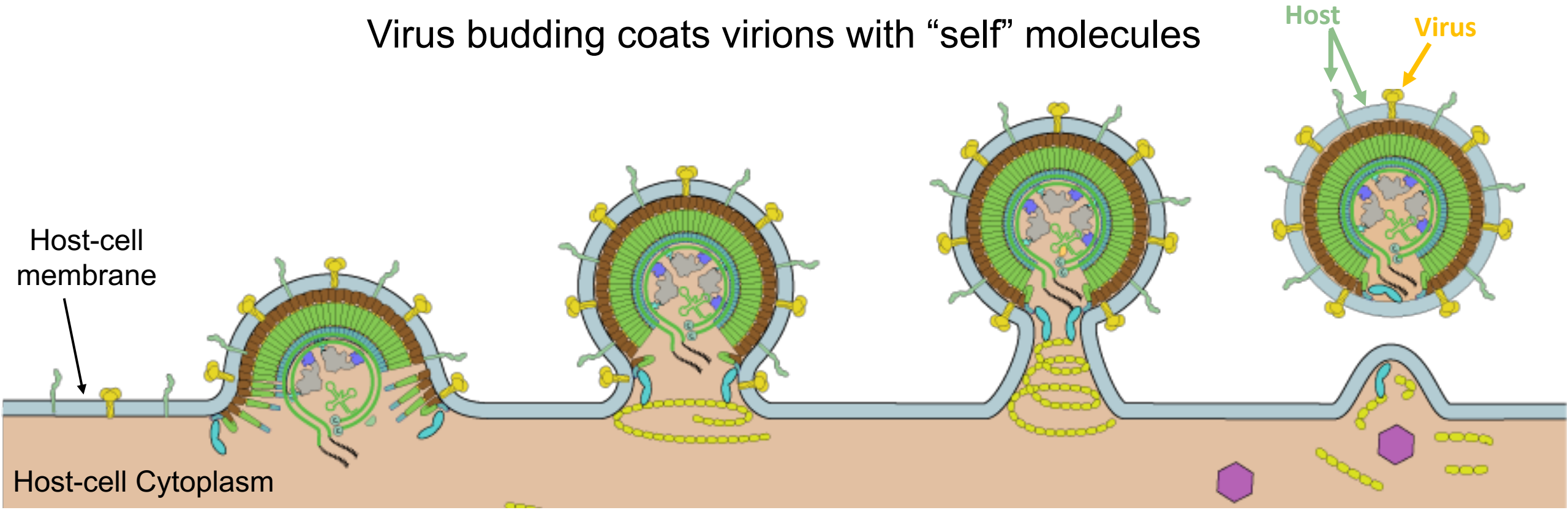
SARS CoV-2

Some pathogens do not have many antigens on them (HIV).

If you have difficulty mounting an effective immune response to a pathogen, it can be difficult to develop a good vaccine for that pathogen.

HIV is a difficult target for vaccination and antibody mediated immunity

Virus budding coats virions with “self” molecules

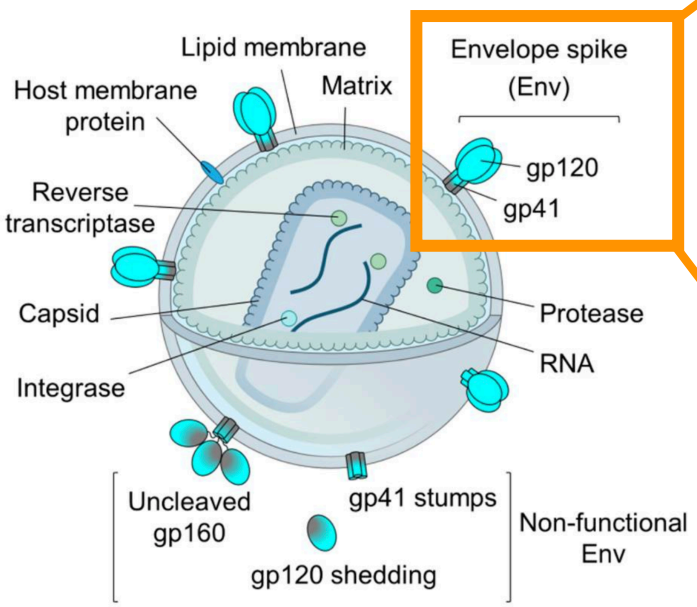


Mechanism of enveloped virus budding (HIV)

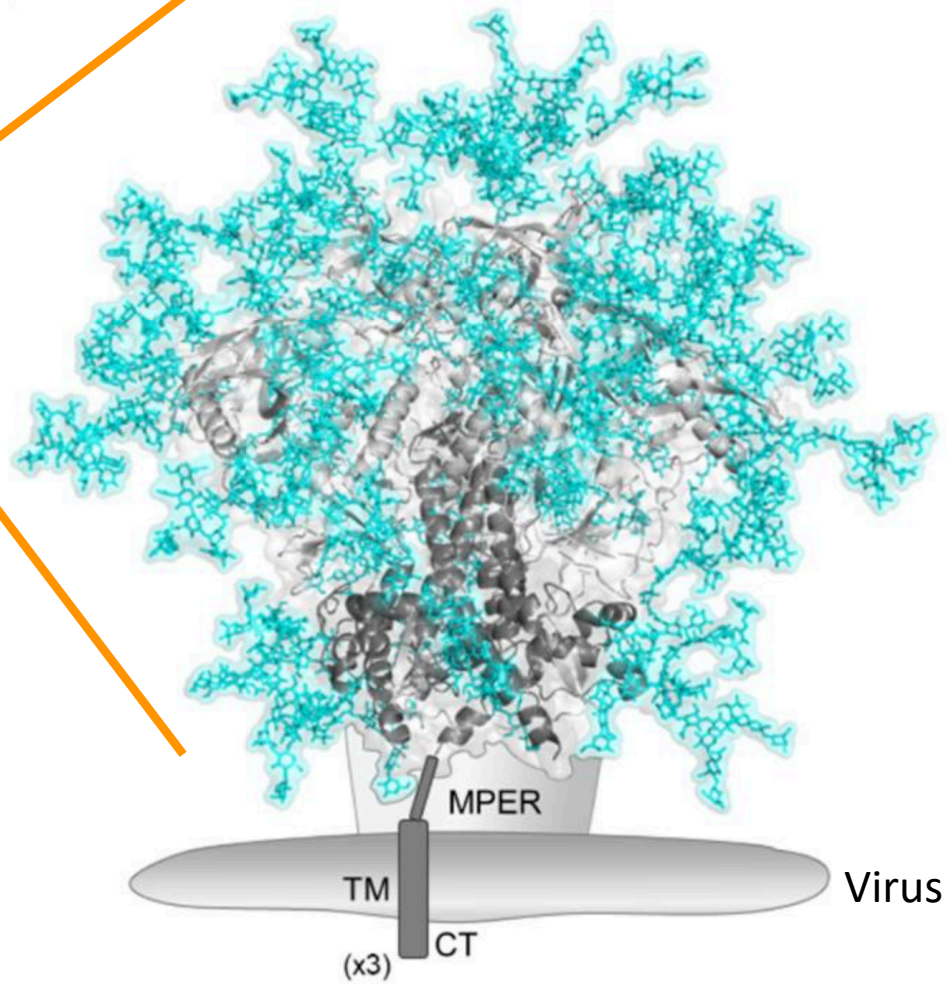
During release from the infected host-cell, many viruses become enveloped, meaning the virus capsid is coated with host cell membrane acquired during the virus budding process.

Antigens from viruses can be disguised by host molecules

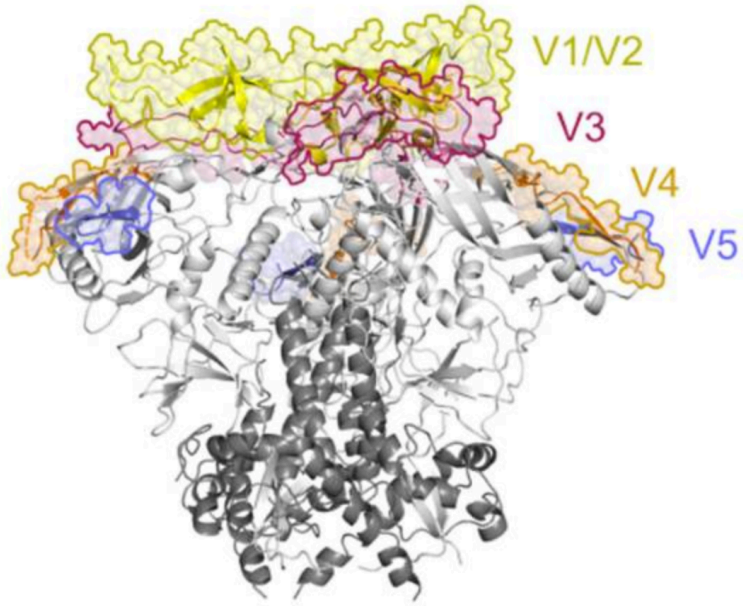
HIV Virion



Molecular Structure of HIV Envelope
covered in **host sugars**

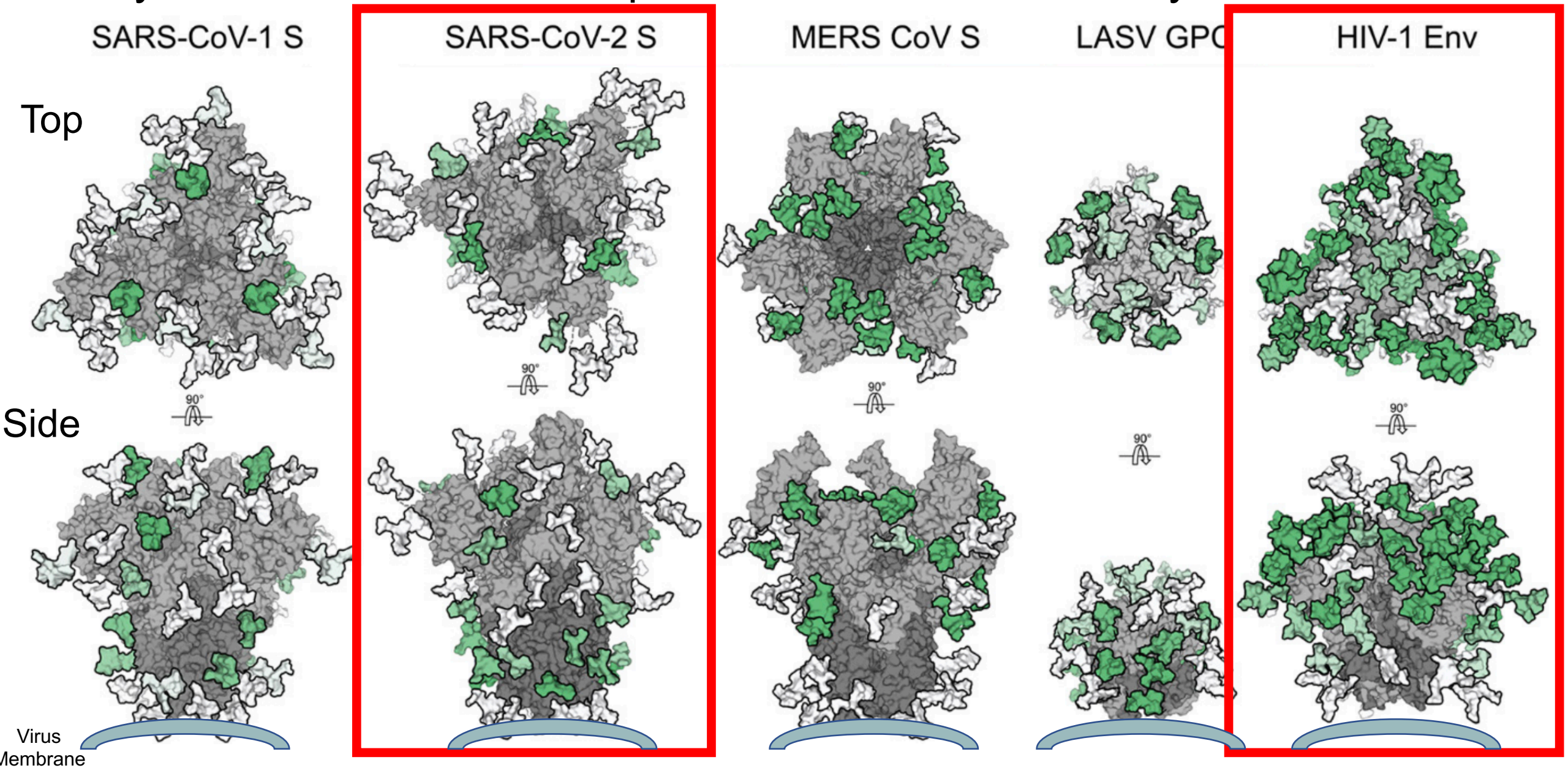


Molecular Structure of HIV Envelope
without host sugars



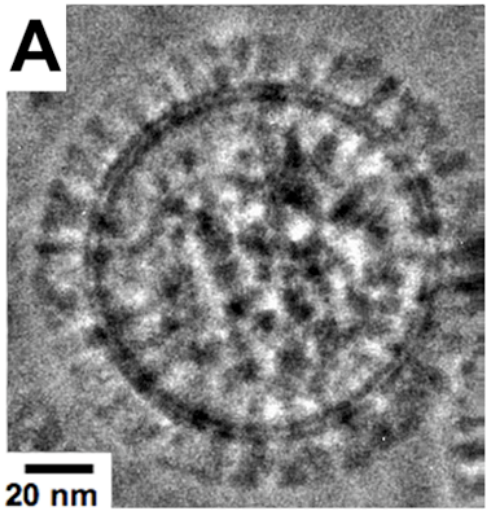
Coating antigens with “self” molecules helps avoid detection from the immune system

Many other virus membrane proteins are not shielded by host molecules

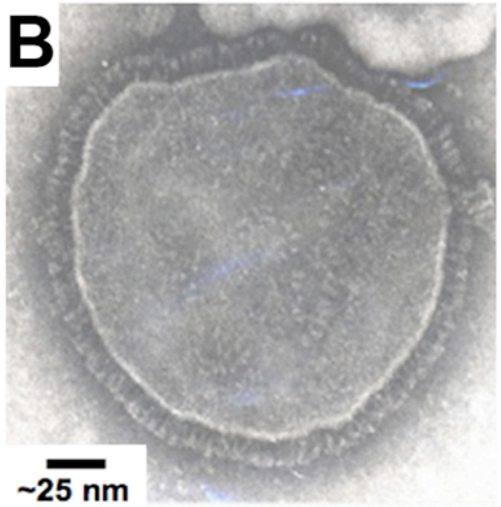


SARS-CoV-2 Should make a good vaccine candidate for eliciting a neutralizing antibody response

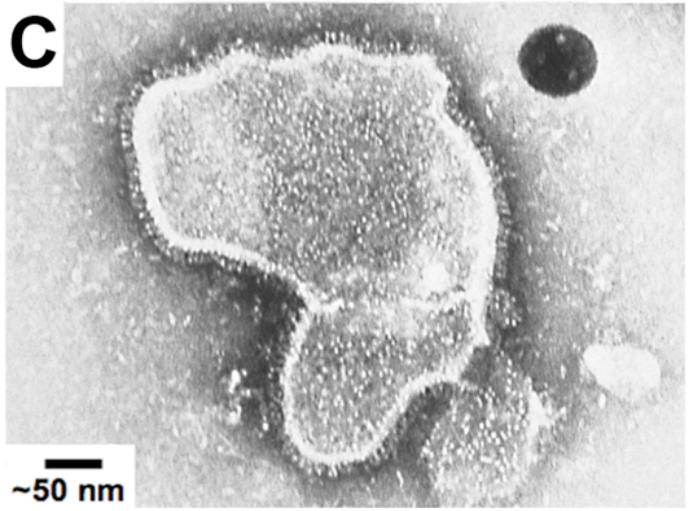
Numerous viruses have many surface antigens



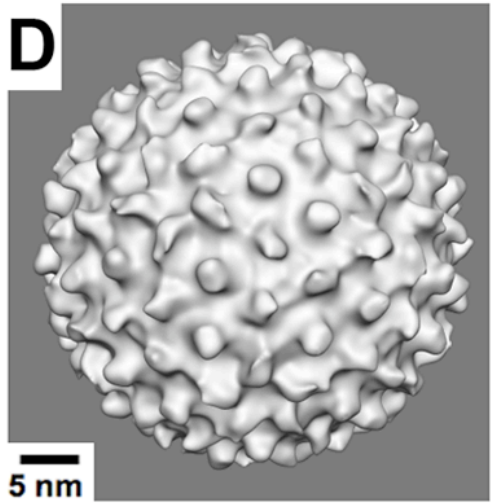
Influenza



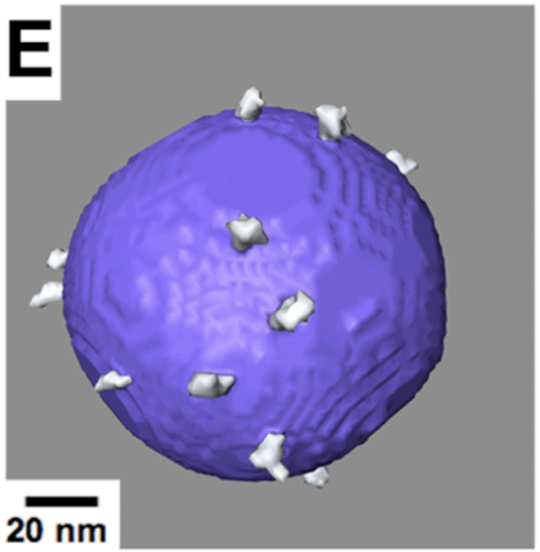
Measles



RSV



Hepatitis B



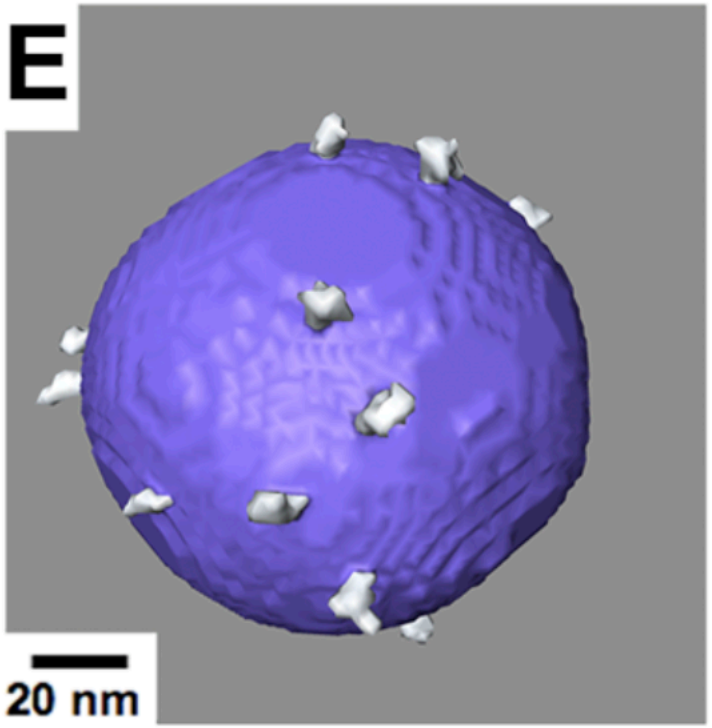
HIV

HIV does not

Klein and Bjorkman, PLoS Path, 2010

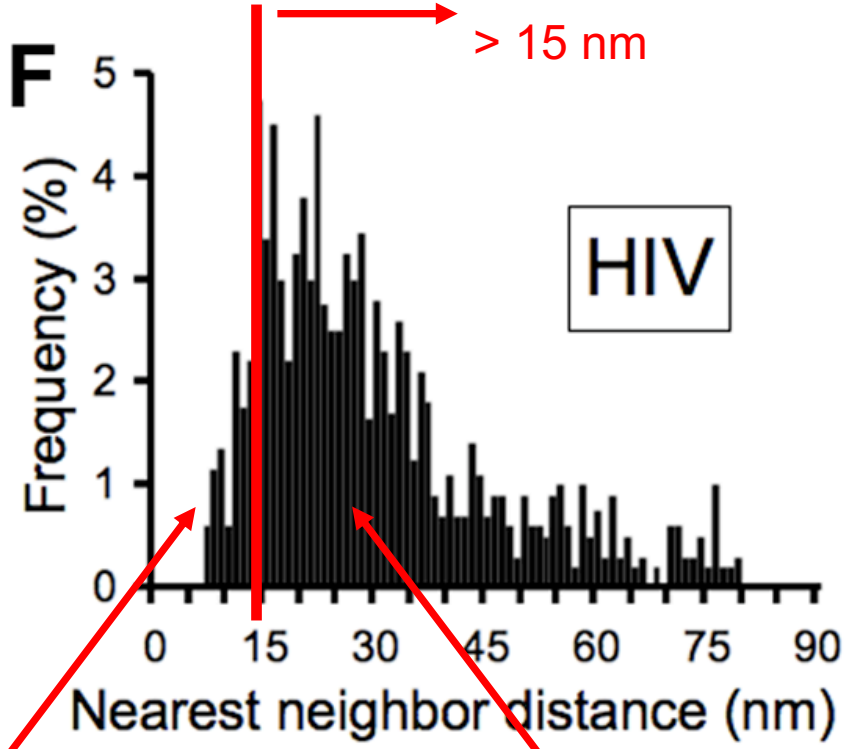
Some viruses have few surface antigens

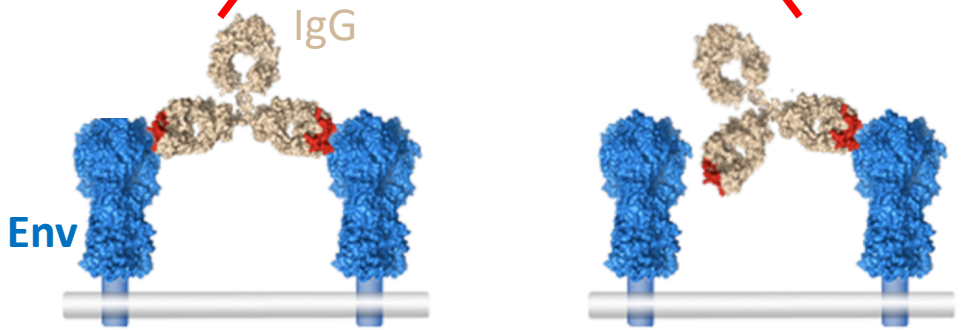
Reconstructed 3D EM Image of HIV



HIV

Most HIV Env spikes are far apart

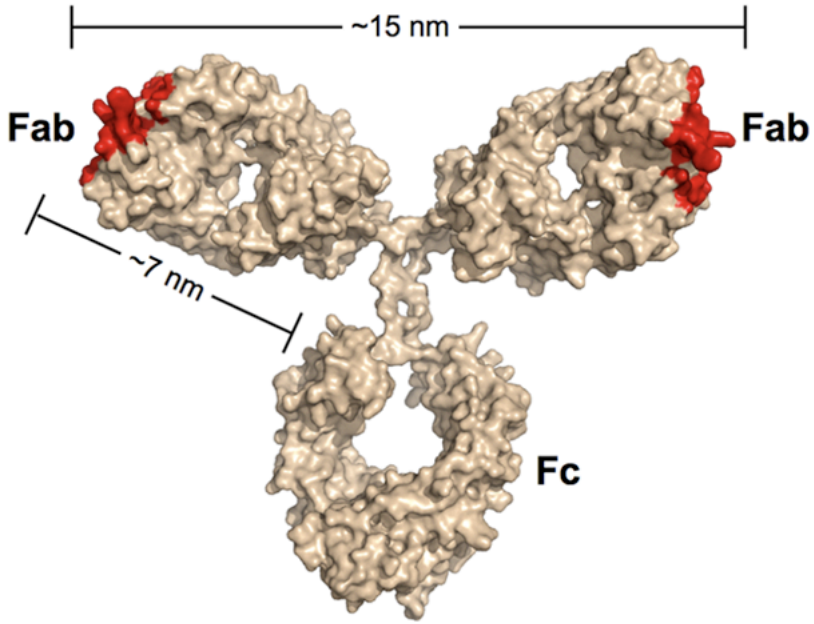




Tight binding with both arms
(strong immune recognition)

Weak binding with one arm
(weak immune recognition)

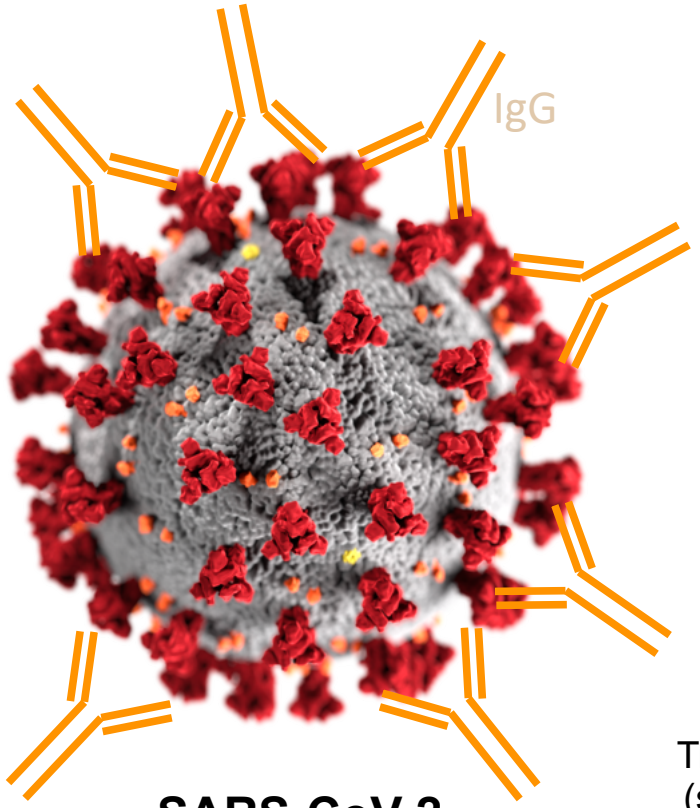
Molecular structure of IgG



Limiting the number of antigens on a virus can help limit recognition by the immune system

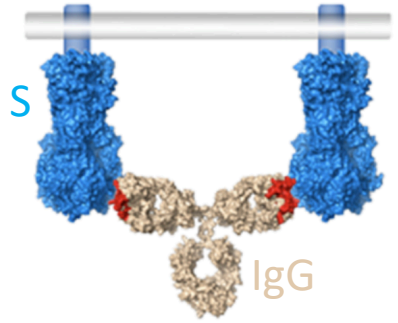
Klein and Bjorkman, PLoS Path, 2010

SARS-CoV-2 has many spikes on its surface which makes it a good vaccine candidate



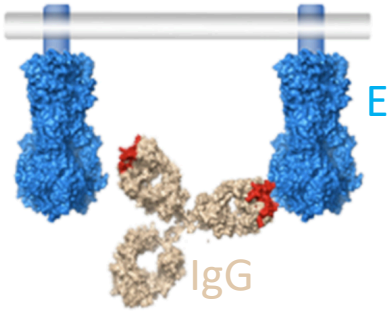
SARS-CoV-2

Coronavirus

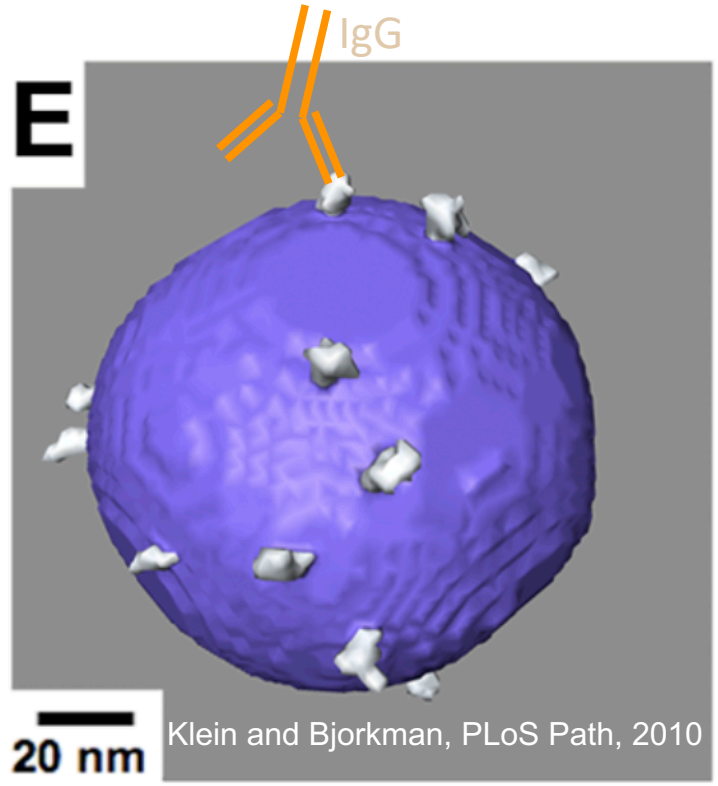


Tight binding with both arms
(strong immune recognition
= good vaccine candidate)

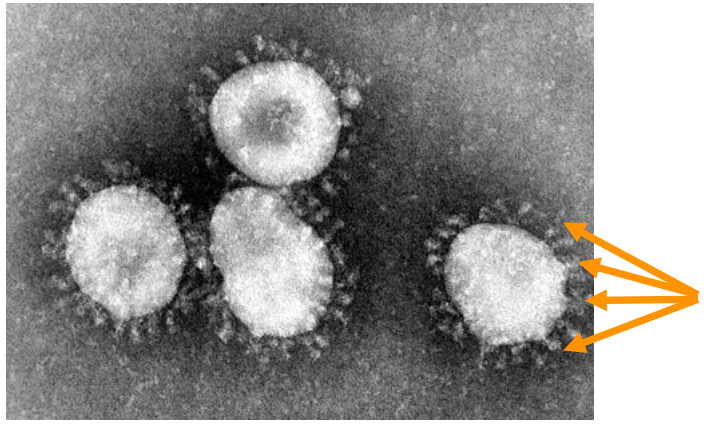
HIV



Weak binding with one arm
(weak immune recognition
= poor vaccine candidate)

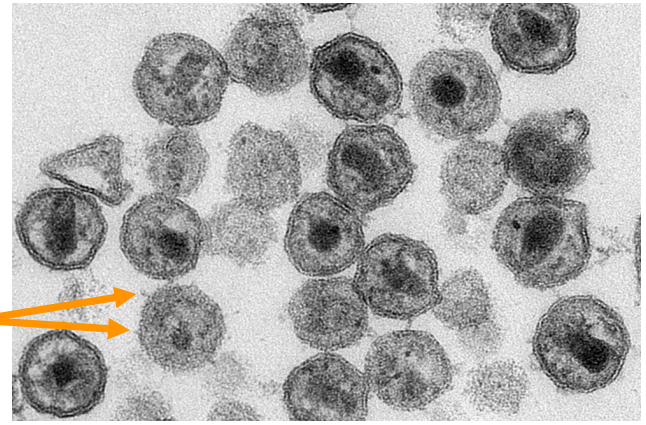


HIV



Many surface spikes

Few surface spikes

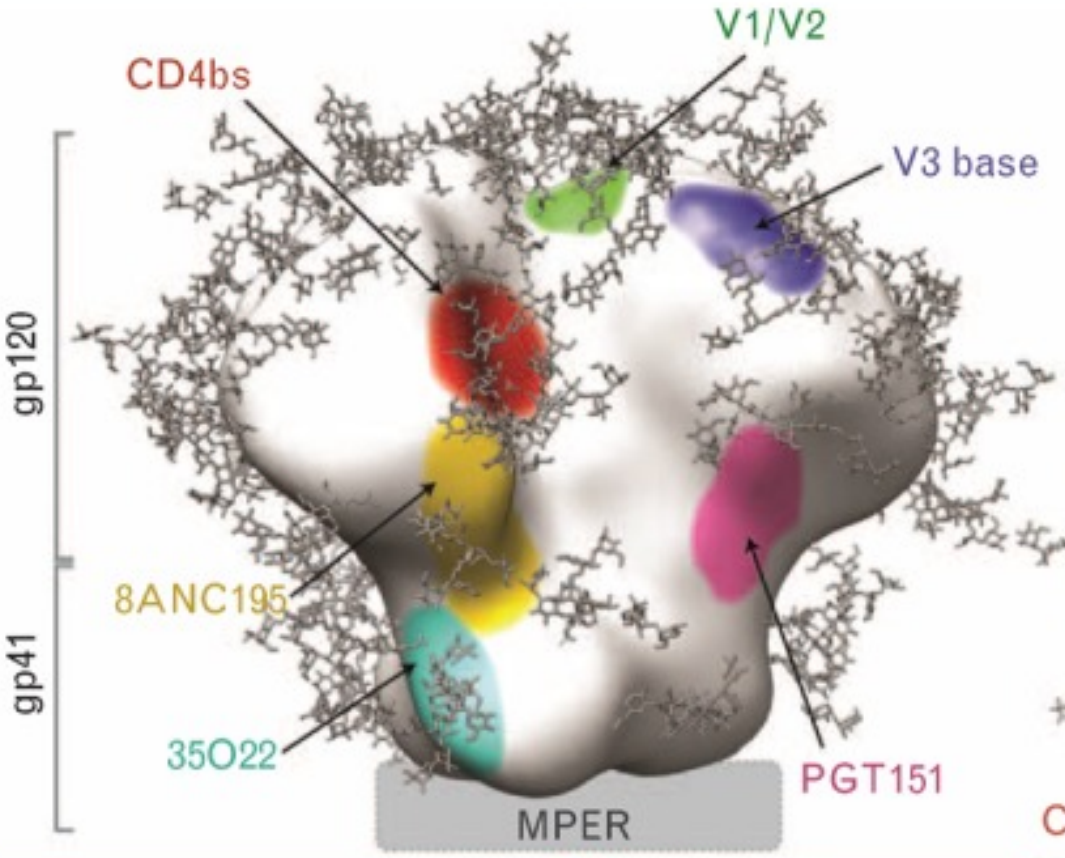


There is reason to be hopeful that an effective SARS-CoV-2 vaccine will be possible in a reasonable time frame.

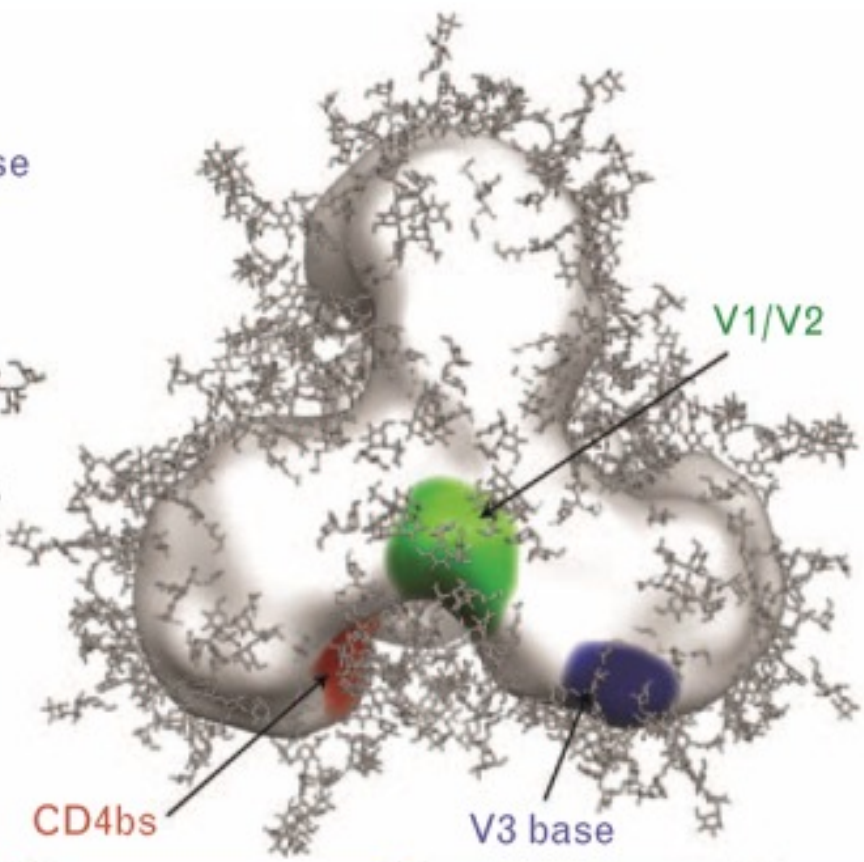
How are we going to trick the immune system to mount an effective immune response to HIV vaccines?

About 5-10% of HIV-infected individuals develop broadly neutralizing antibodies that protect from HIV challenge

Side



Top

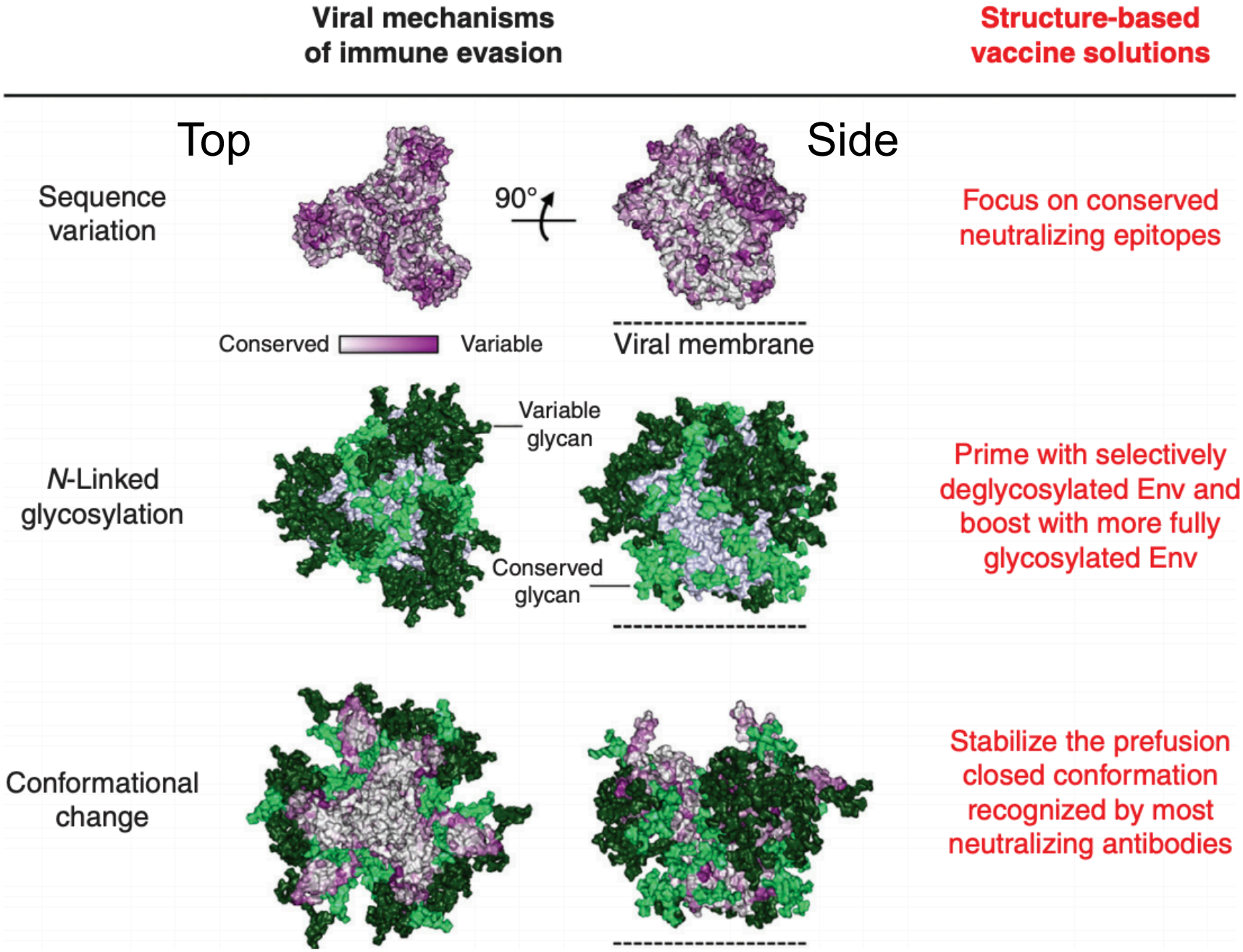


CD4-binding site	Asn160 glycan-V1/V2	Asn332 glycan-V3	gp120/gp41-interface	MPER
b12, VRC01, VRC07, NIH45–46, 12A12, 3BNC117, VRC-PGV04, VRC-CH31, 8ANC131, 1B2530, CH103, HJ16	PG9, PG16, CH01–04, PGT141–145	PGT121, 10–1074, PGT128, PGT135, 2G12	8ANC195, 35O22, PGT151	4E10, 2F5, 10E8, Z13, M66.6

Stuart Sievers, Louise Scharf, Anthony P. West Jr, Pamela J. Bjorkman (2015) Curr Opin HIV AIDS

Sites of vulnerability to "broadly neutralizing antibodies (bNAbs)"

How are we going to trick the immune system to mount an effective immune response to HIV vaccines?

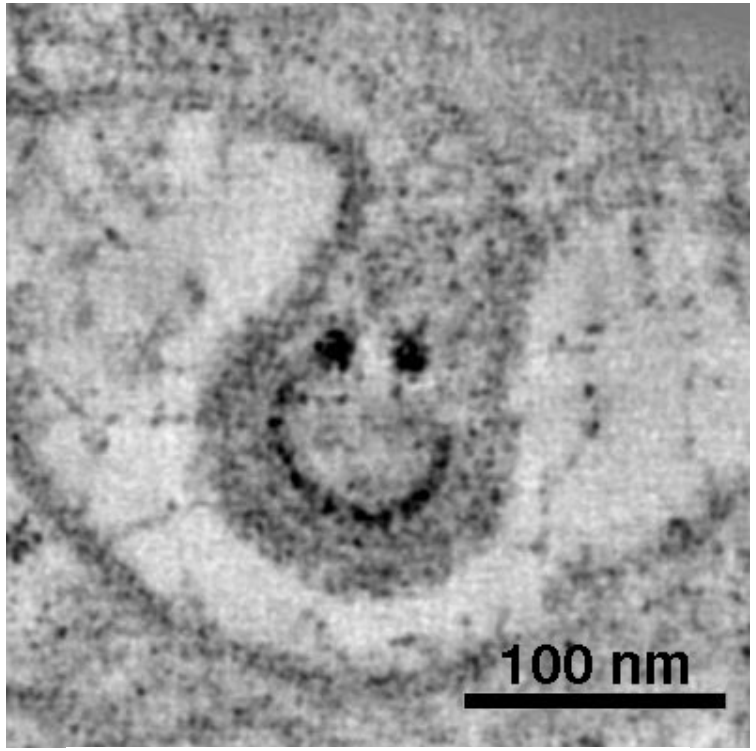


There is reason to be hopeful that an effective HIV vaccine is on the horizon

This was not the case 10-15 years ago.

By understanding the molecular structures of pathogens and how they interact with the immune system, we are gaining a clearer picture of how these fundamental processes work and this can allow directed approaches to design vaccines for worldwide pathogens.

Thanks!



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