



Human Immunodeficiency Virus

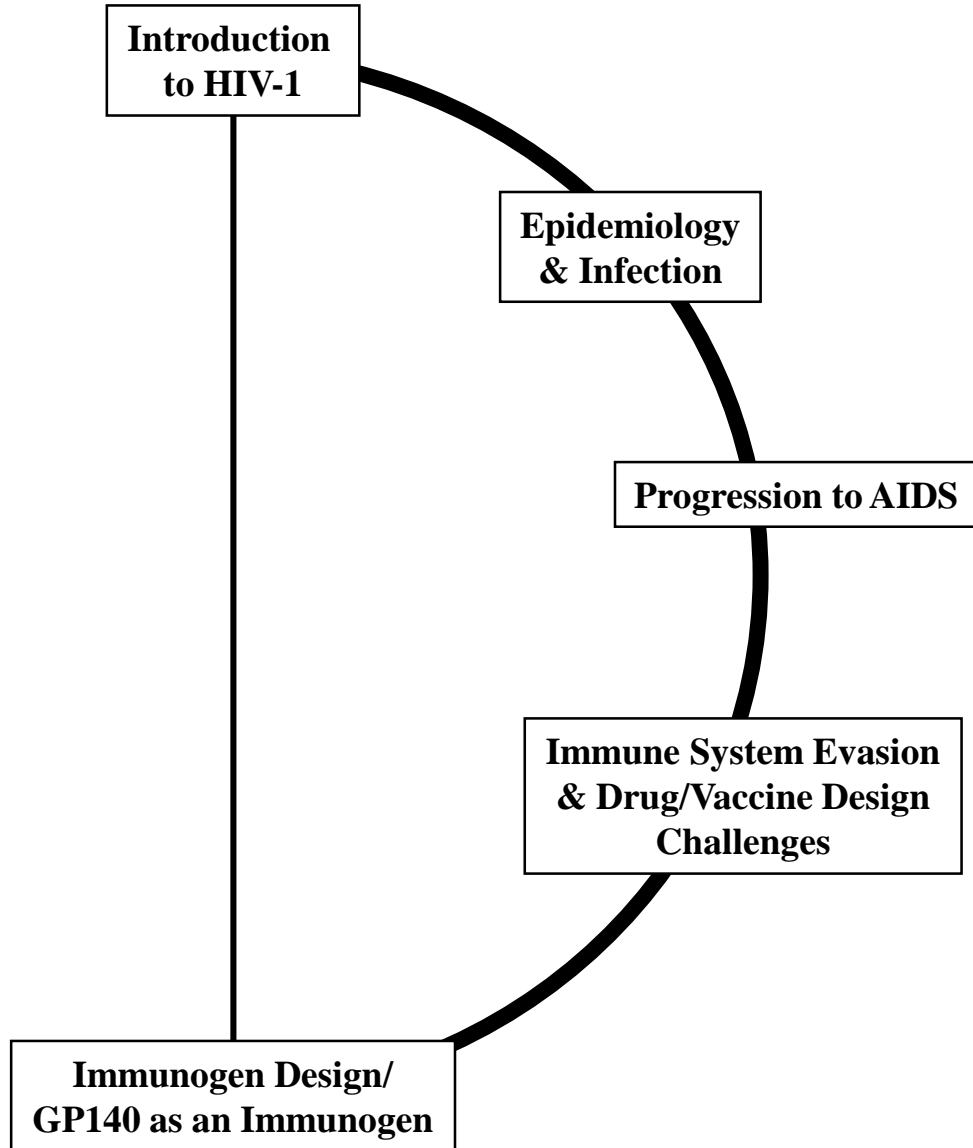
An Evolutionary Masterpiece



Presenter: Mo Baikoghli
University of California, Davis
Cheng Laboratory
8.14.14

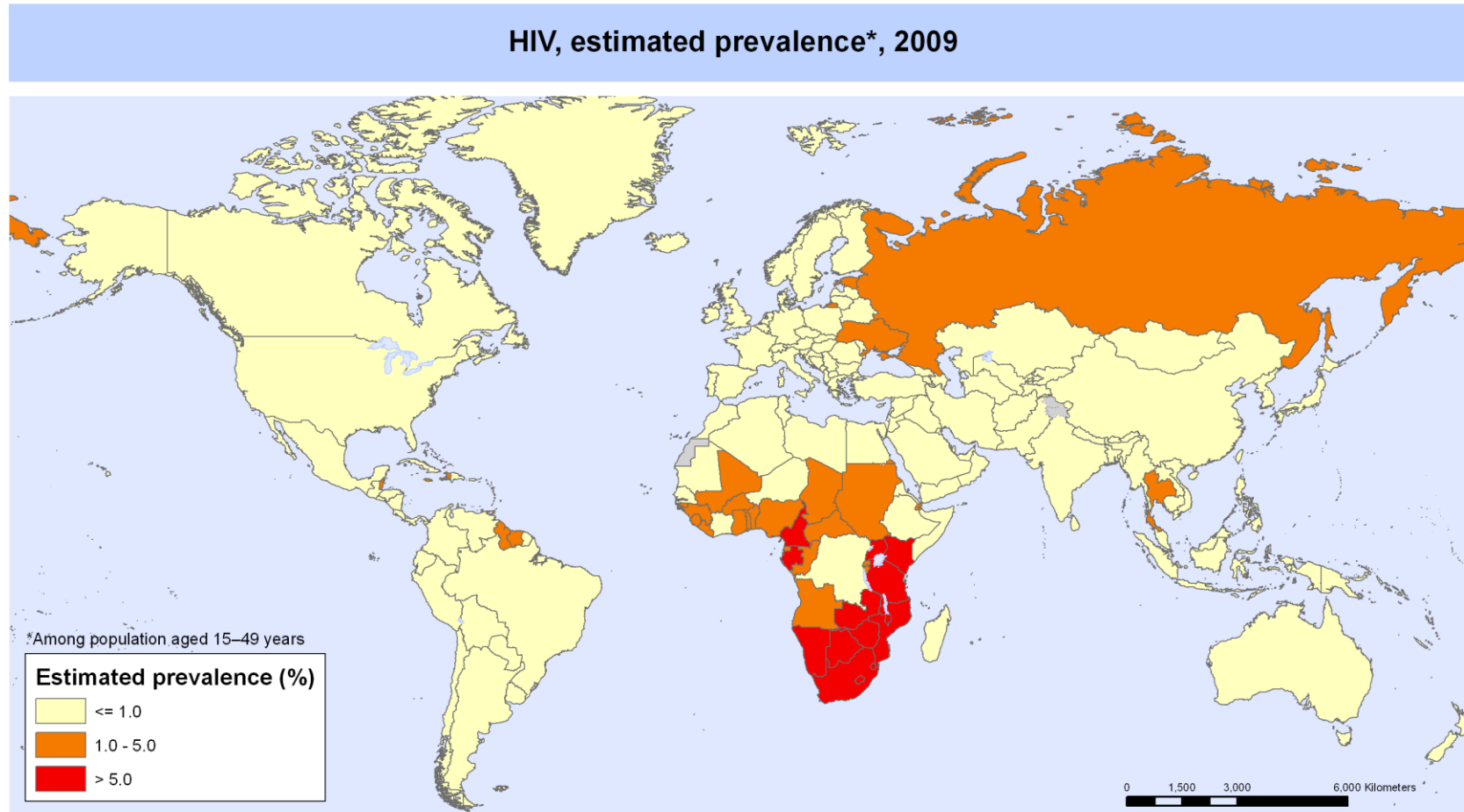


Today's Talk



HIV/AIDS Global Impact / Epidemiology

Rapid Spread



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO/UNAIDS
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



World Health
Organization

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$\sim 3.3 \times 10^7$ people living with HIV

HIV/AIDS Global Impact / Epidemiology

Death Estim.



- Rapid spread
- High death rates
- No cure from HIV infection
- No vaccination / intravenous prevention

People living with HIV/AIDS

35.3 million

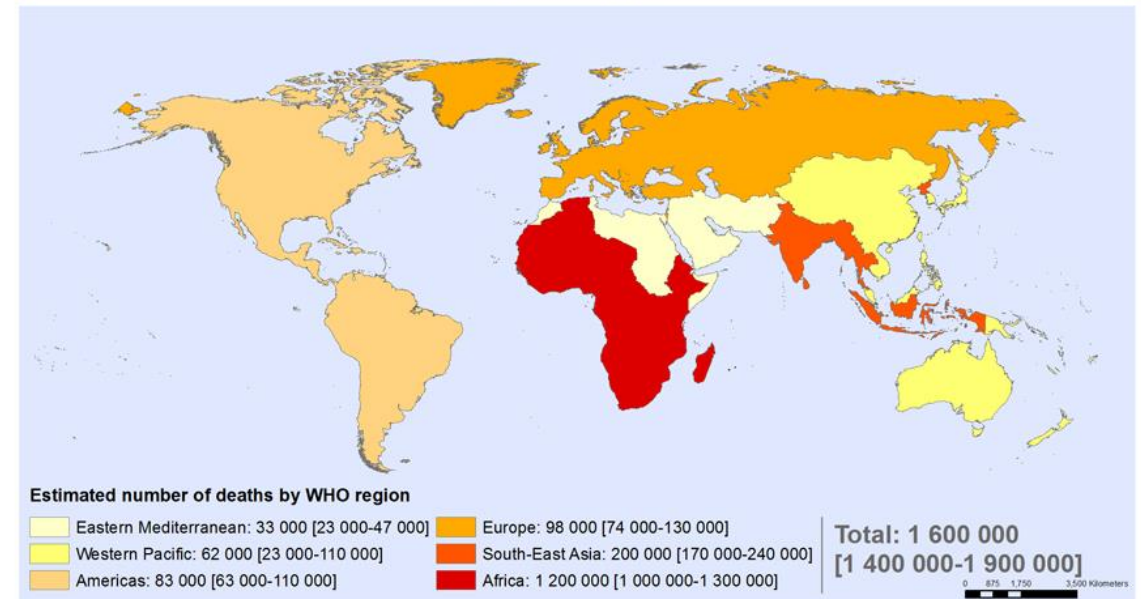
people living with HIV/AIDS worldwide in 2012

Mortality

1.6 million

people died of AIDS-related illnesses worldwide in 2012

Estimated adult and child deaths from AIDS, 2012
By WHO region

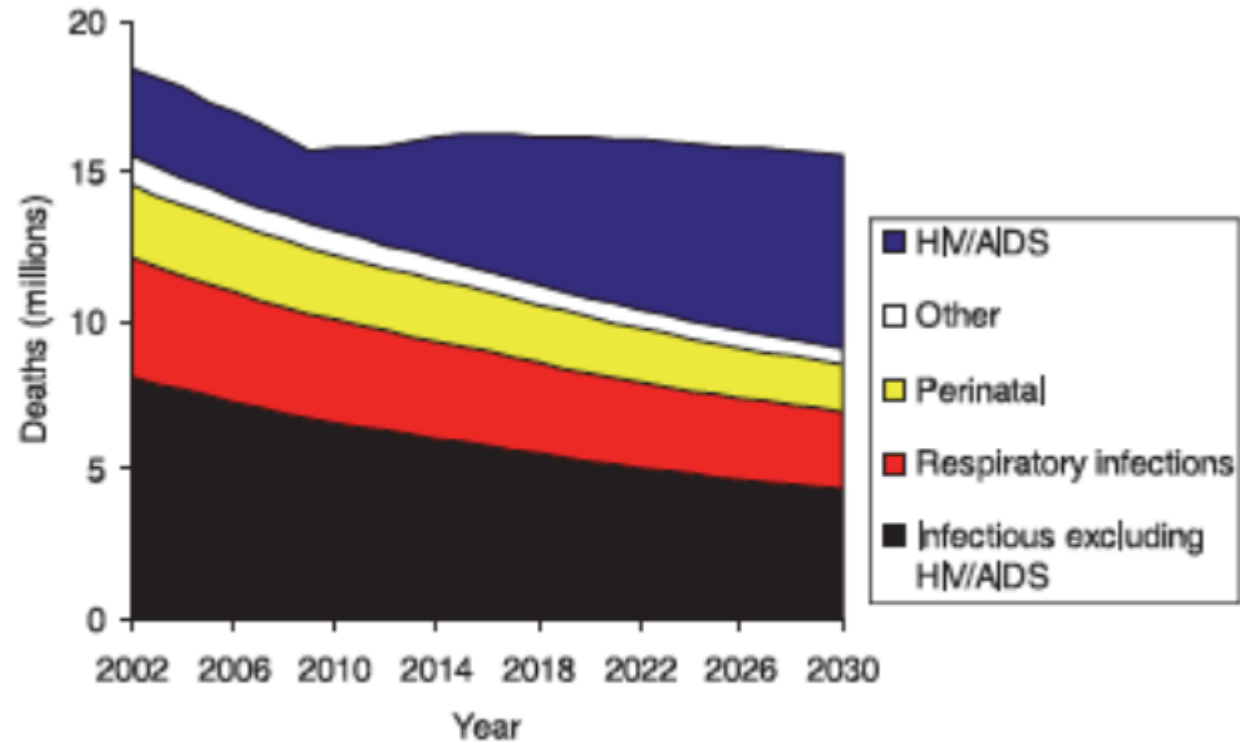


The boundaries and names shown on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization
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$\sim 3.9 \times 10^7$ people living with HIV



Source: Mathers, C.D. and D. Loncar. Projections of Global Mortality and Burden of Disease from 2002 to 2030. Figure 3, PLoS Medicine, November 2006 3(11): e442. www.plosmedicine.org

HIV/AIDS Global Impact / Epidemiology

Transmission

HIV → AIDS

1980s

Among all the cool technology 1980s....
There was a new epidemic!

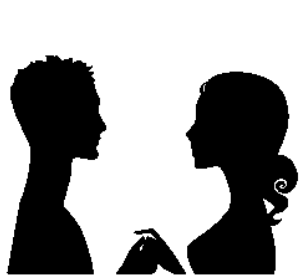


Early Recognition

- Late 1970s and early 1980s
- Diminished count of CD4+ T-Lymphocytes
- Reduction of mitogen-induced proliferative capacity of lymphocytes
- A group of homosexual men were noted to be dying of normally benign opportunistic infections.
- Gallo et al. and Montagnier et al. reported the isolation of HIV-1 from patients with lymphadenopathy and AIDS in 1983 – later, a variant of HIV-1, HIV-2 was isolated in West Africa.

Modes of Transmission

- 1) Unsafe sex with infected partner
- 2) Vertical transmission
- 3) Injection paraphernalia



Unprotected sexual
intercourse with
an infected partner



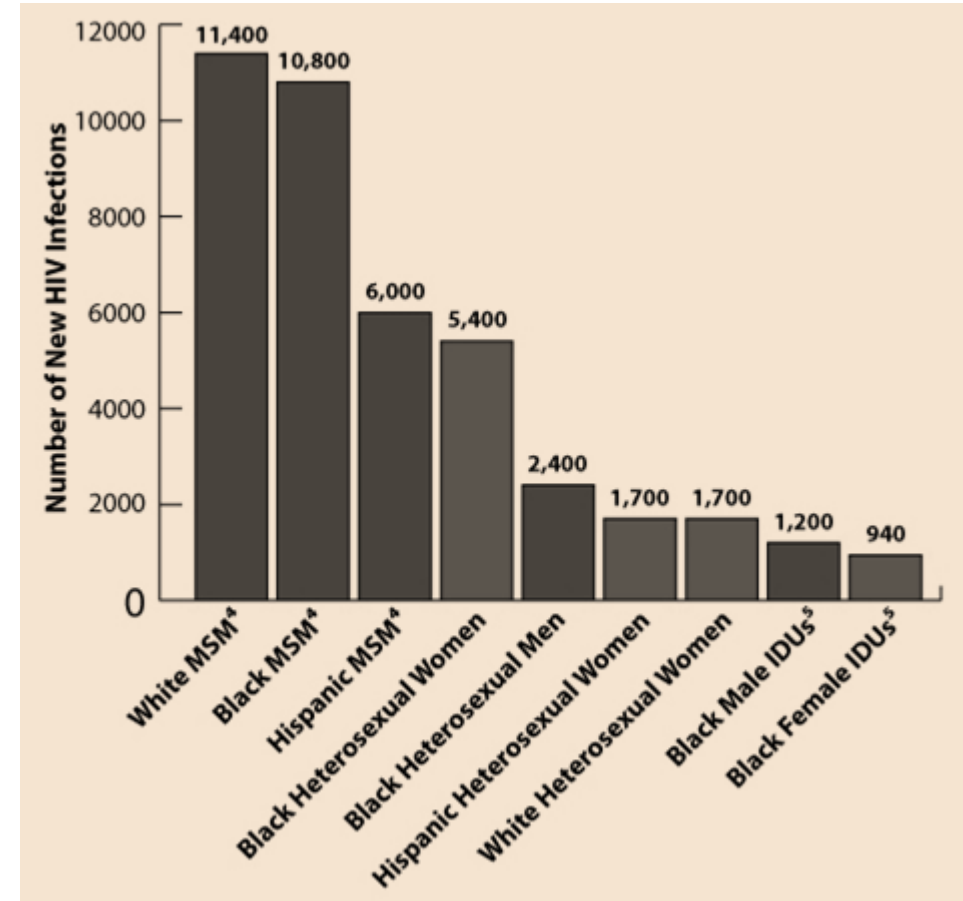
Vertical transmission
(from mother to child)

- in utero
- during delivery
- breastmilk



Injection drug use
(rare: infected
blood/blood products)

HIV infection



Rare Cases!

Transmission via saliva, through open wounds or mucosa.

Via Insect bite! (very rare)

A rare case of infection was reported for a new born, whose mother pre-chewed the food for her! One in a trillion chance! But it could happen. (Gaur et al. 2008)

The higher the viral load, the higher chances of contracting HIV



Table 1. Potentially Infectious Body Fluids

Potentially Infectious	Not Considered Infectious ^a
Blood	Feces
Tissue	Nasal secretions
Semen	Saliva
Vaginal secretions	Sputum
Visibly bloody body fluids	Sweat
Cerebrospinal fluid	Tears
Synovial fluid	Urine
Pleural fluid	Vomit
Peritoneal fluid	
Pericardial fluid	
Amniotic fluid	

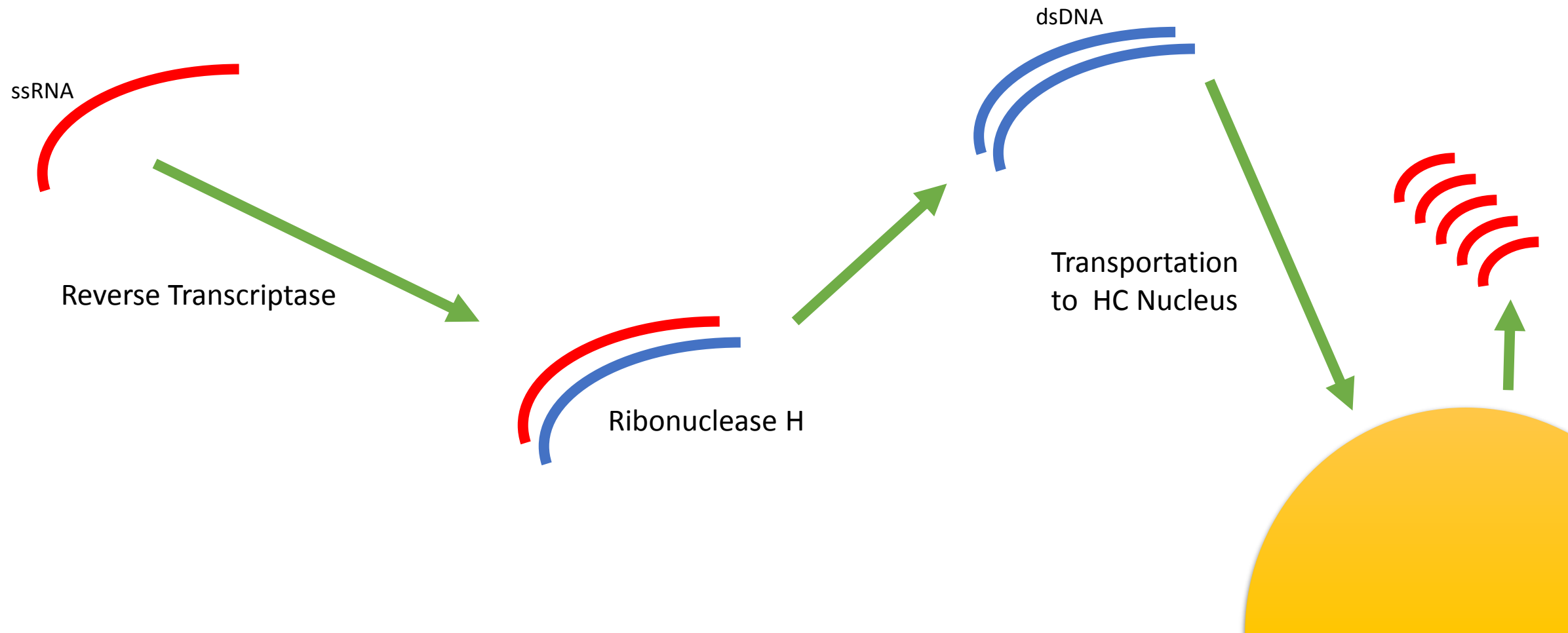
^a Unless visibly bloody. Source: References 3, 7.

Causative Agent of AIDS – Central Dogma?

Target inf.

Retroviruses – HIV

DNA → RNA → Protein!

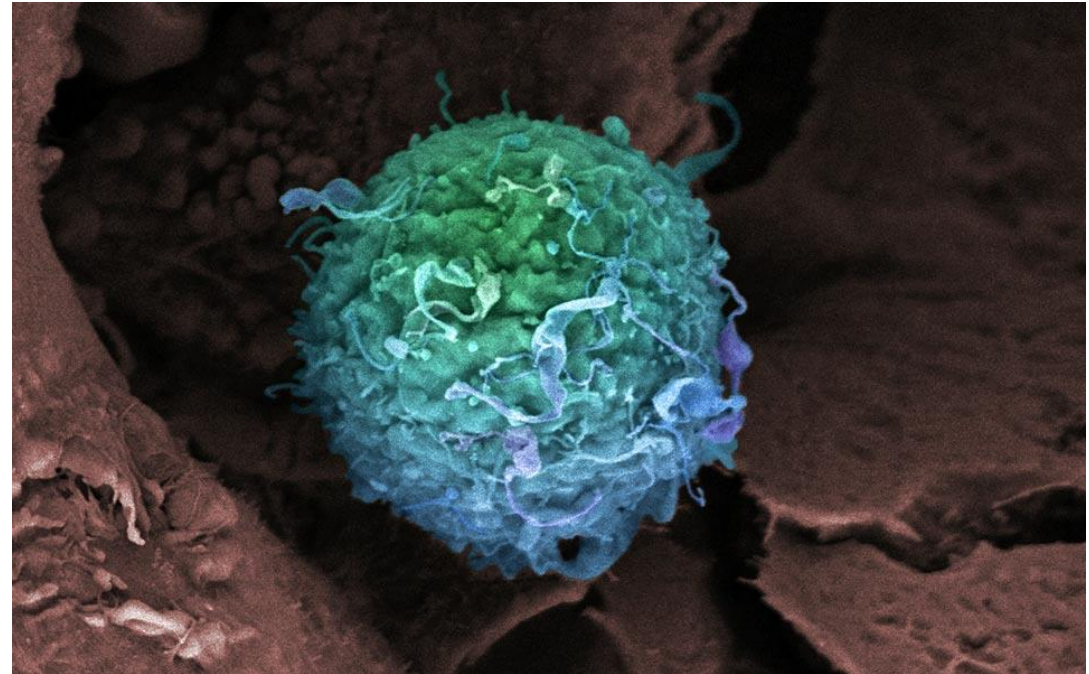
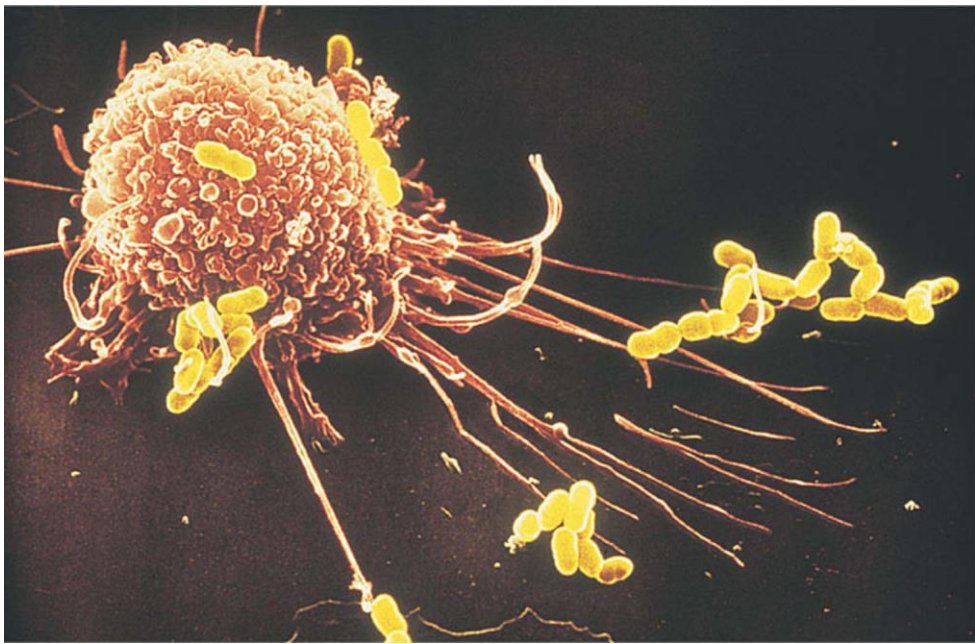


HIV/AIDS Global Impact / Infection

Importance
T Cell

Virus Target

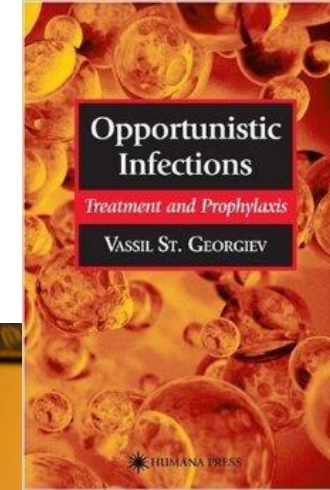
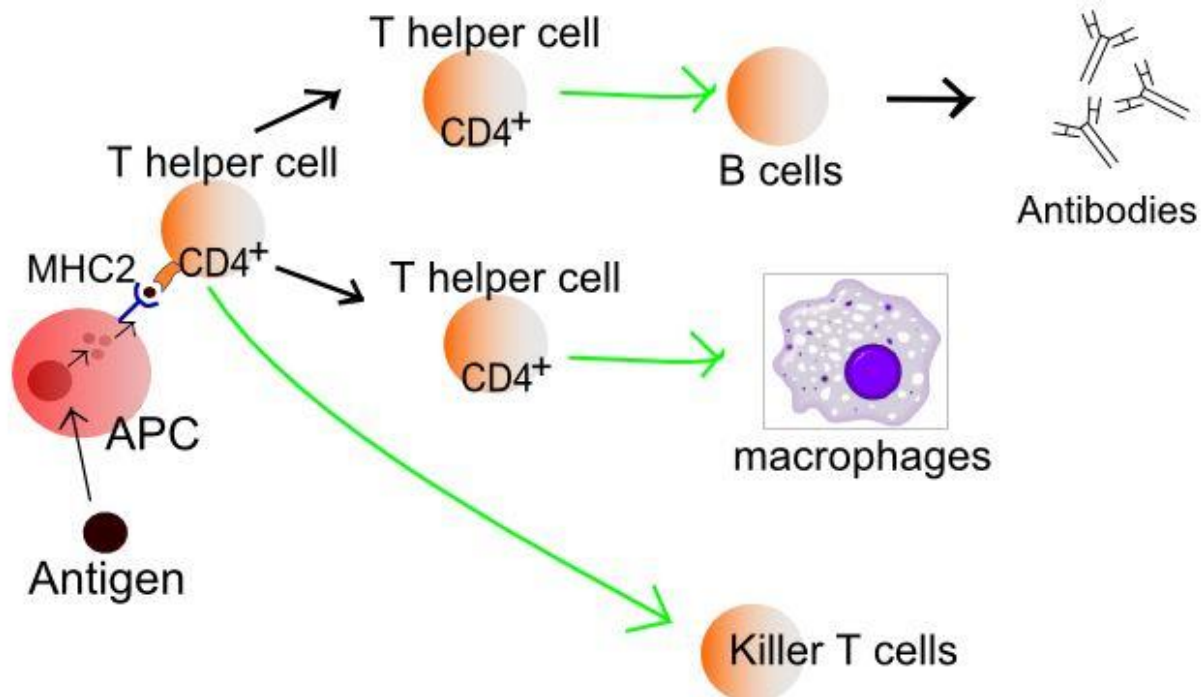
CD4 + T Cells and Macrophages/Monocytes



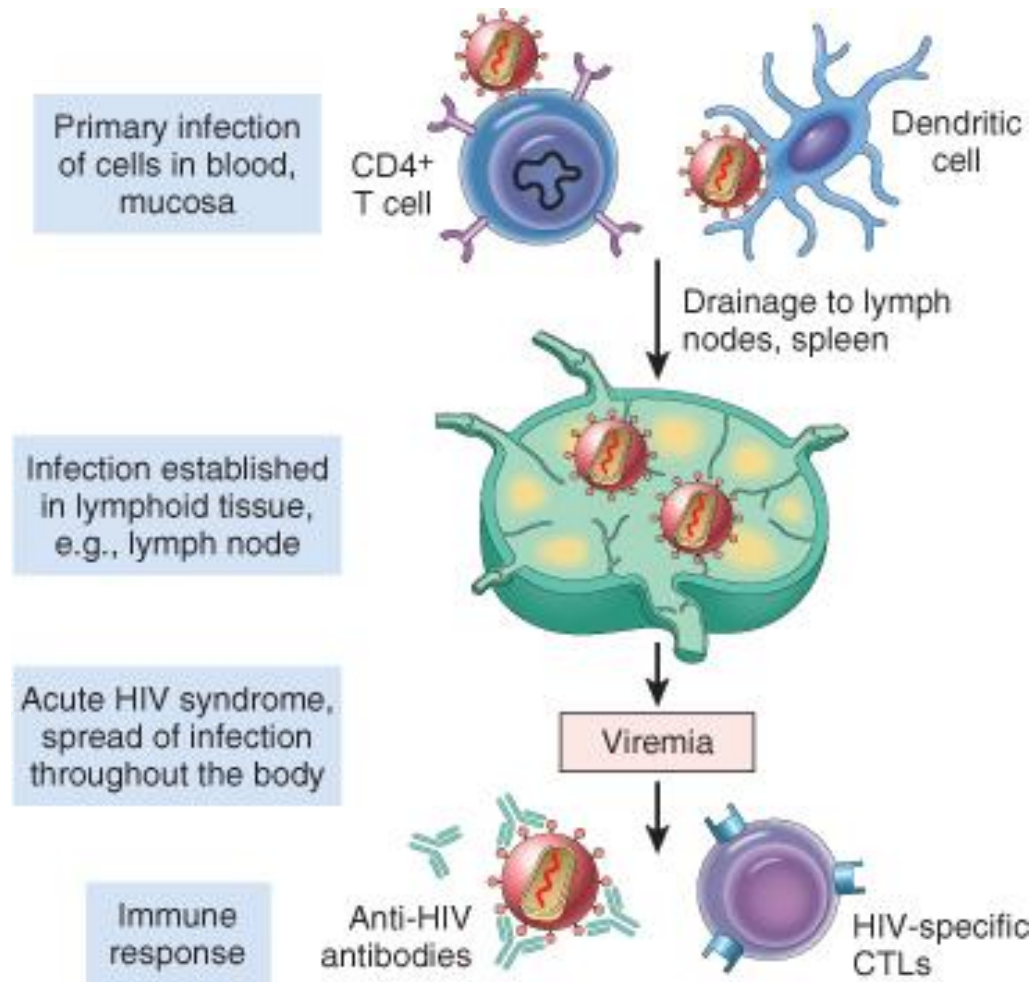
HIV/AIDS Global Impact / Impaired Immunity

Dissemination

Role of CD4+ T Cells & Monocytes/Macrophages:



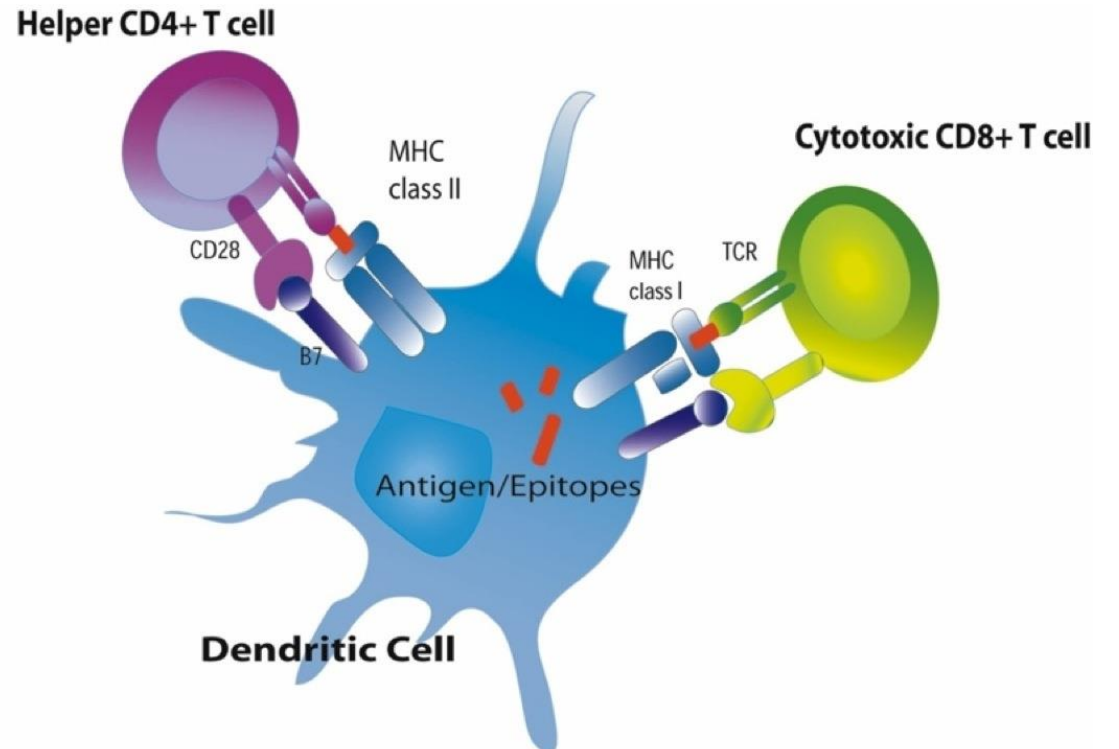
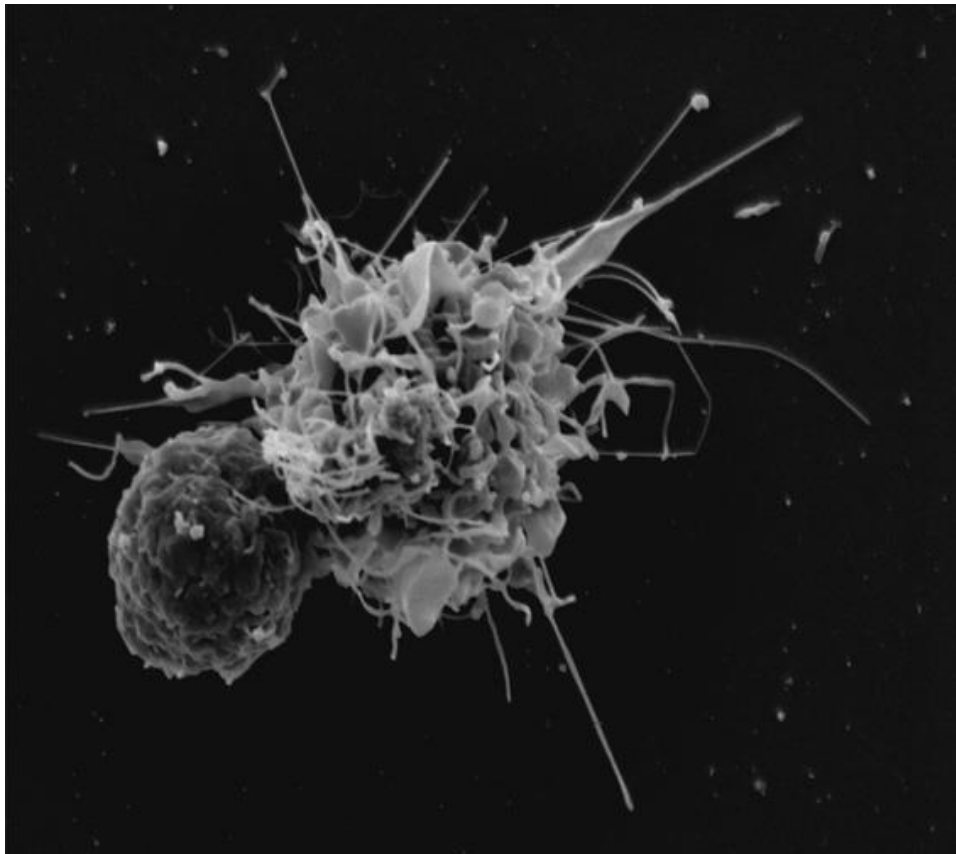
Viral Dissemination



DC Mediated HIV-1 Transmission

DC

Dissemination

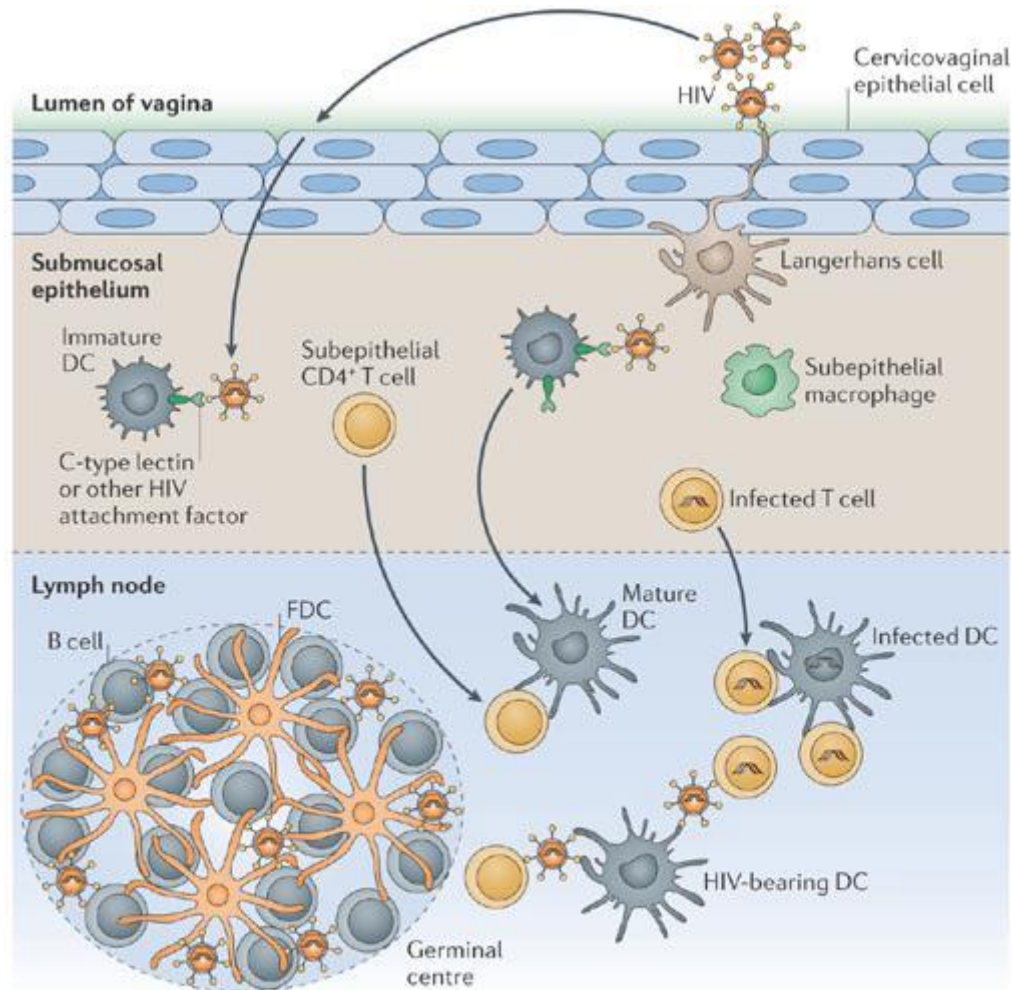


HIV/AIDS Global Impact / Infection

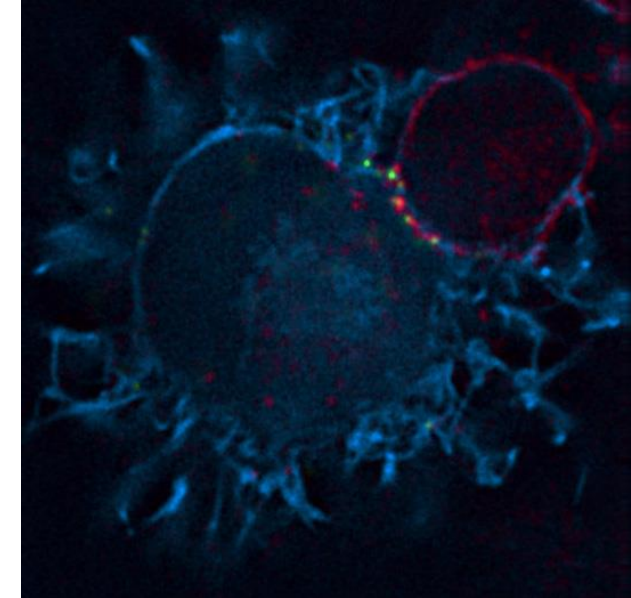
structure

DC Mediated HIV-1 Transmission

DC
Dissemination



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Causative Agent of AIDS - HIV

Human Immunodeficiency Virus or HIV is a Retrovirus

Retrovirus

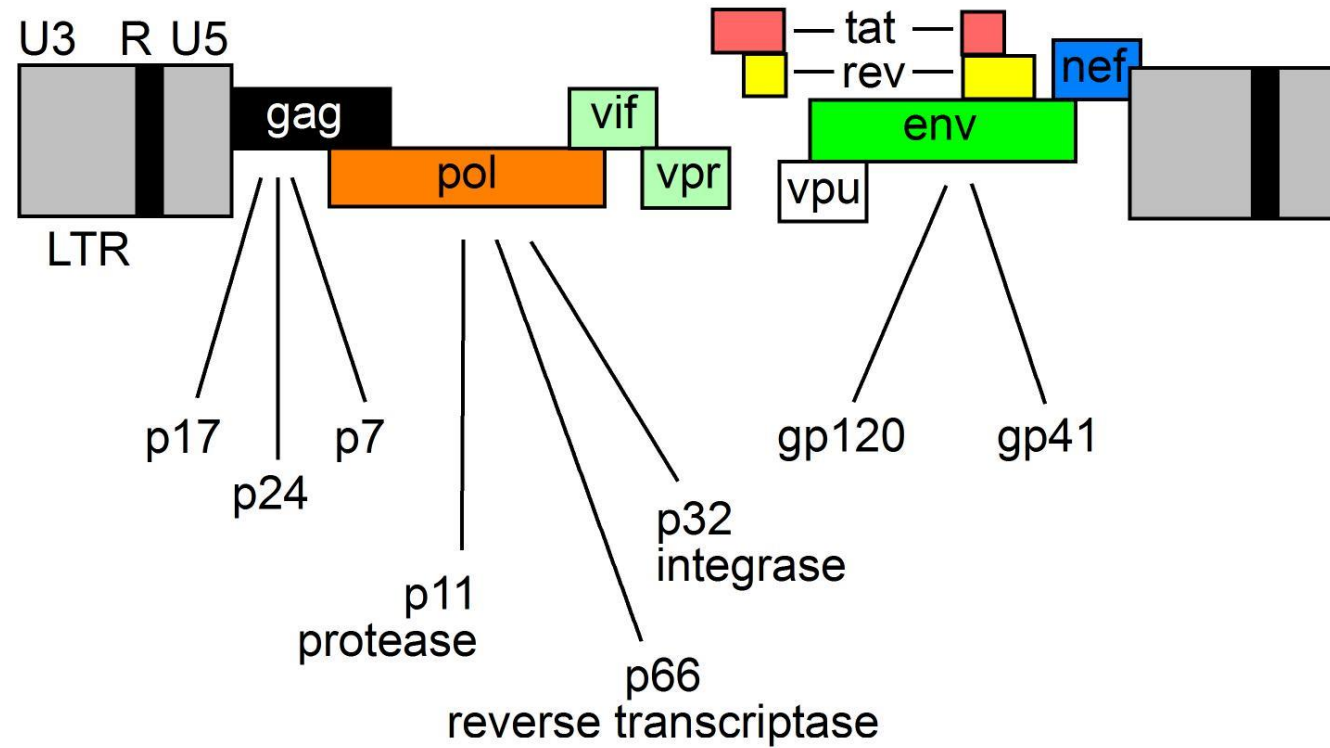
- Unique Genome
- Host Dependent
- Encode for their own Enzymes
- Utilize Host Cell's Replication Machinery
- Genome consists of three major genes
 - GAG
 - group-specific antigen, capsid, matrix, and nucleic acid-binding proteins
 - POL
 - Polymerase, protease, and integrase
 - ENV
 - Envelope glycoproteins
- At both ends of the genome are “long-terminal repeat (LTR) sequences.”
 - Contain promoters, enhancers, and other gene sequences used for binding different cellular transcription factors.



Causative Agent of AIDS - HIV

HIV Genome

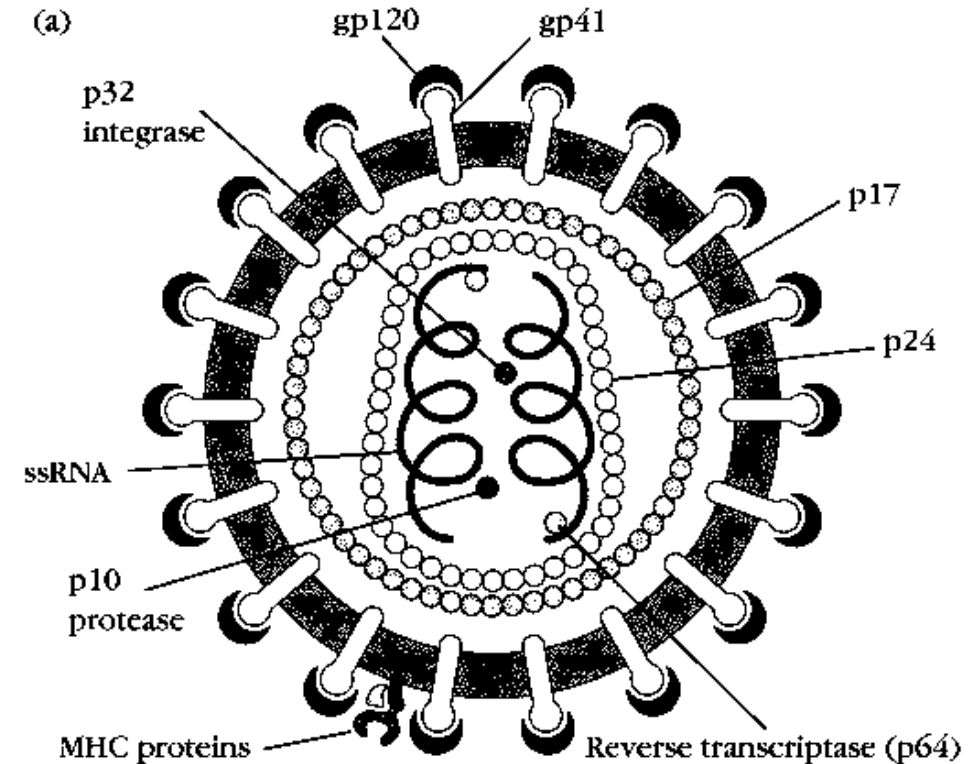
Accessory Proteins



Causative Agent of AIDS - HIV

HIV

- Diameter ~100 nm
- Enveloped – Host cell derived lipid bilayer
- The envelope contains viral glycoproteins
- Capsid (CA-p24)
 - Truncated Cone Shaped
 - Two copies of +RNA genome
 - Not directly infectious
 - Two copies of cellular transfer RNA (tRNA)
 - Genome codes of viral enzymes:
 - Reverse Transcriptase (RT)
 - Integrase (IN)
 - Protease (PT)

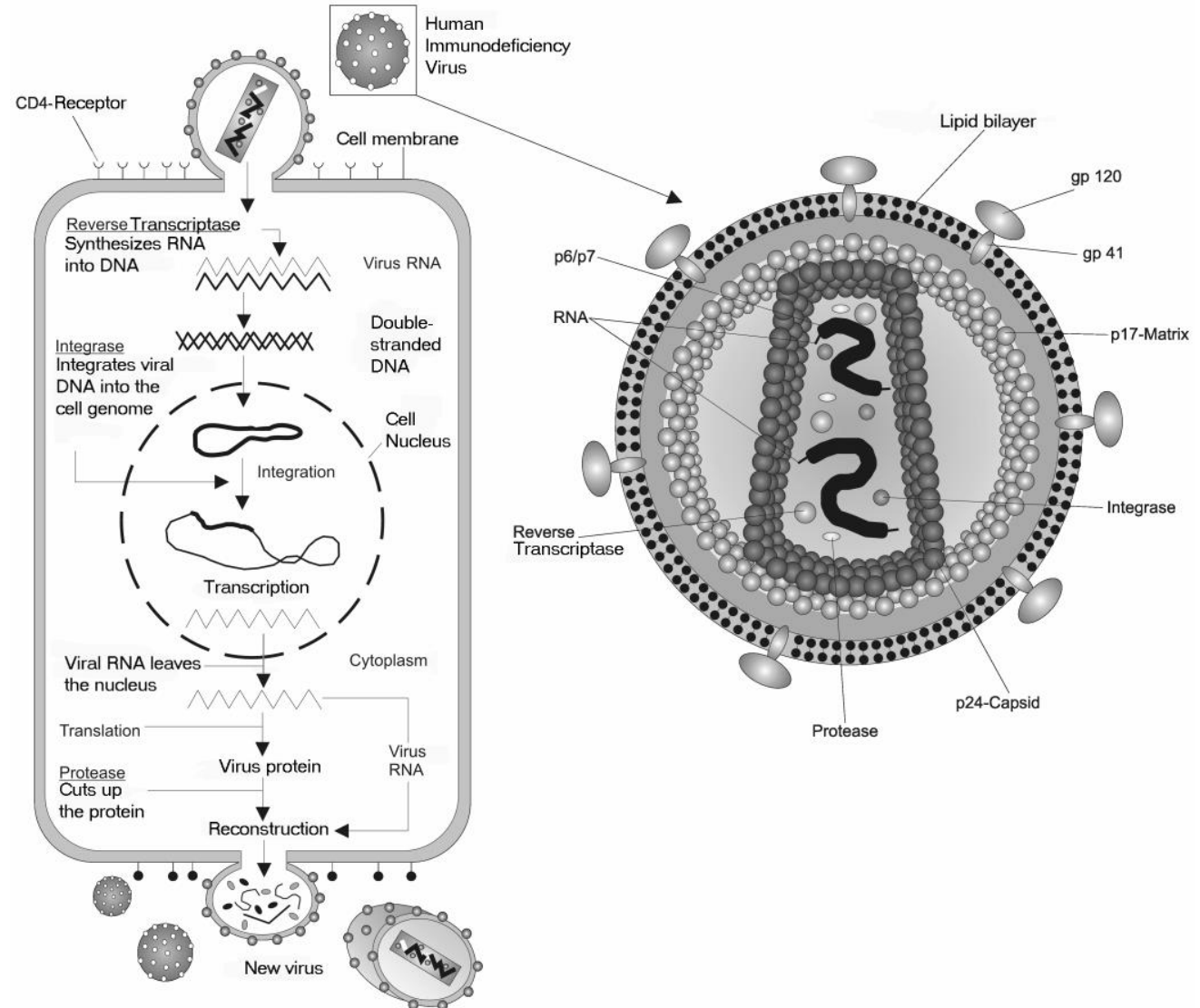


HIV – Life Cycle

v. load

HIV-1 Surface Proteins

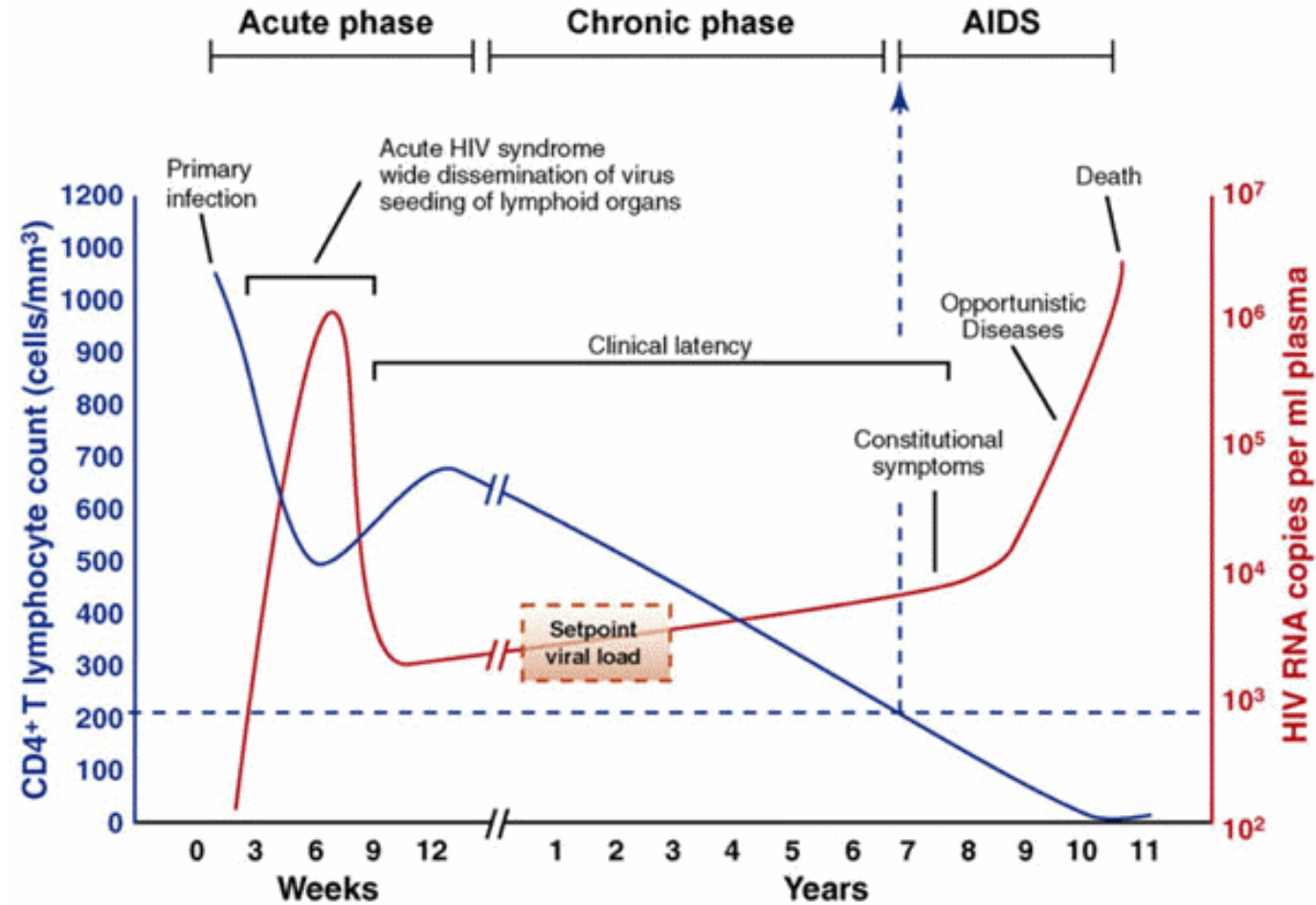
- 1) HIV Infection
- 2) Virology



HIV/AIDS Progression

Why Cant...

Viral Load



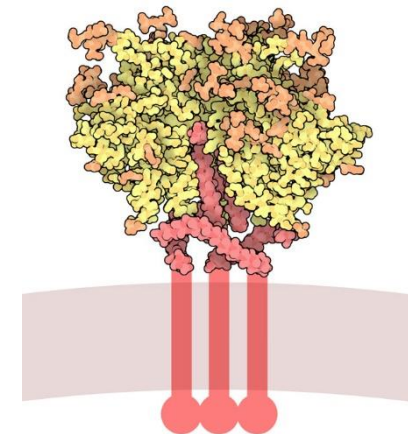
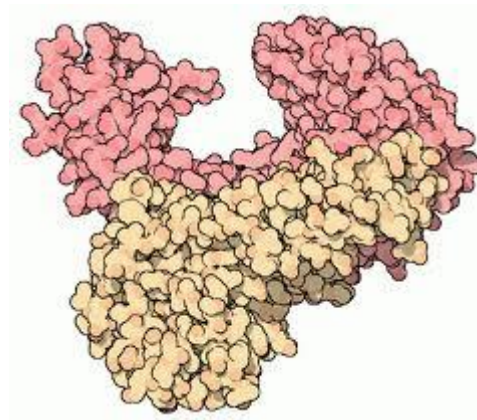
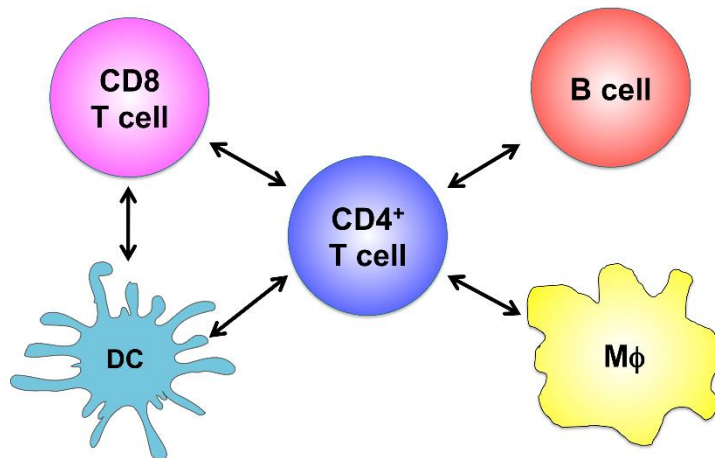
WHY CAN'T WE CURE AIDS?

- **HIV is able to evade the human immune system**
 - HIV belongs to the Retroviruses group and to the Lentiviruses sub-group
 - Lentiviruses are known to have “latency” period – HIV can hide in the host cell’s genome for a long time
- HIV possesses an enzyme called Reverse Transcriptase, which does not have proof-reading capabilities
 - **GP120 Genetic Drift**
 - Therefore, every time it replicates the genome, it makes mistakes – variations
 - These variations are seen more in some parts of GP120 than others
 - For instance, the Variable Loops of GP120, are highly “dynamic” and unstable in terms of structural/biochemical consistency
- **Glycosylation**
- Limited Host Range of HIV-1 – Lack of model
- One can get infected with multiple strains of HIV at once!

Variation due to Error-Prone Reverse Transcriptase

Evading the Human Immune System

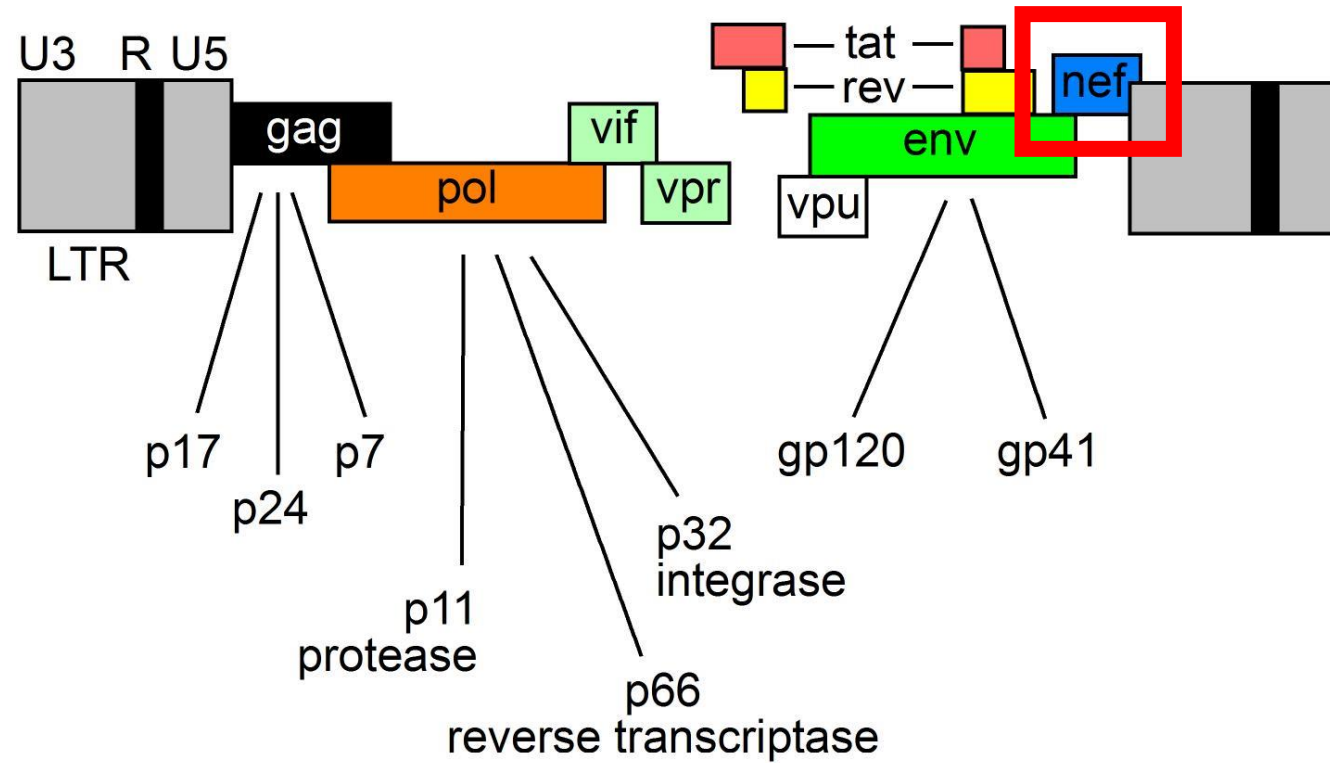
Characteristic	Function
Infection of Lymphocytes and Macrophages	Inactivation of key element of immune defense
Inactivation of CD4 helper cells	Loss of activator of the immune system and delayed-type hypersensitivity
Antigenic drift of gp120	Evasion of antibody detection
Heavy glycosylation of gp120	Evasion of antibody detection



Causative Agent of AIDS - HIV

HIV Genome

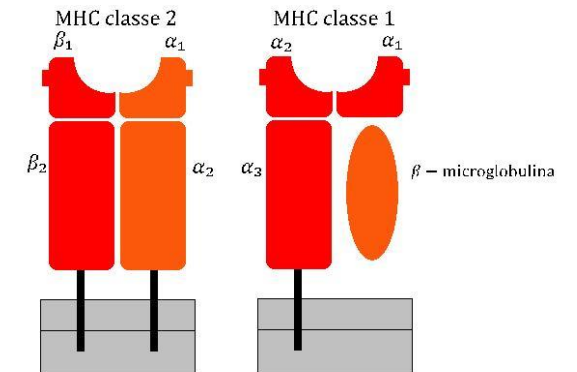
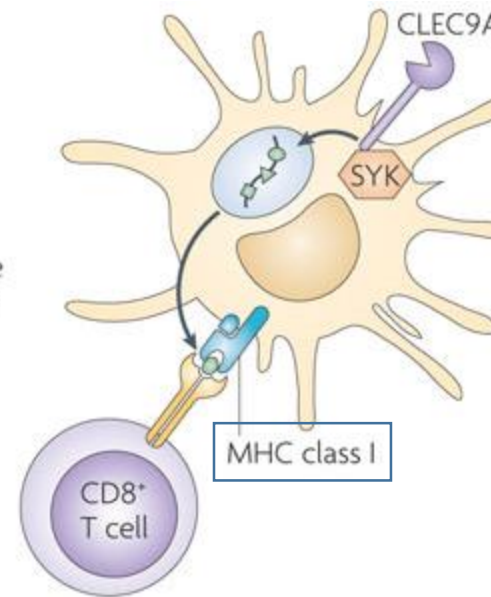
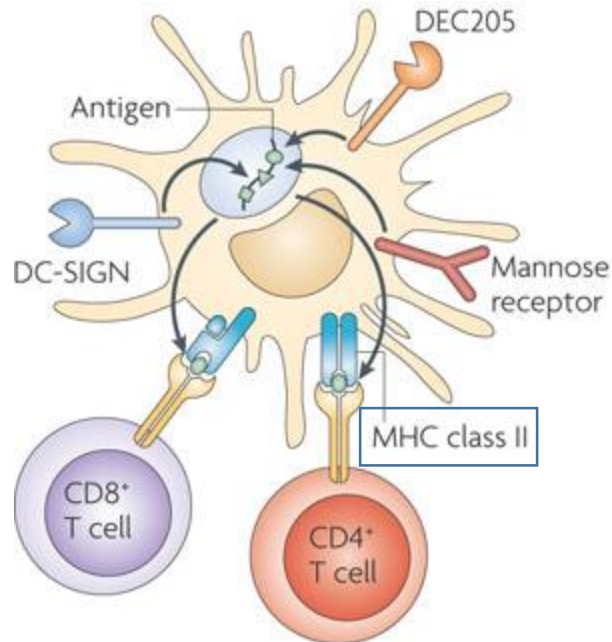
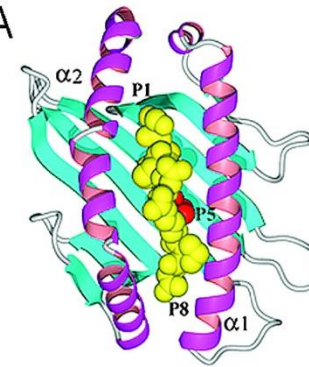
Accessory Proteins



Limited host

Reduction of cell surface CD4 and MHC I

A



Causative Agent of AIDS – Vaccination/Drug

Lack Of Suitable Infection Model

Viruses related to HIV-1:

- Variants of Simian Immunodeficiency Virus, SIV – Cause no disease to normal host
- Example:
 - **SIV_{agm}** – Carried by a high percentage of healthy African Green Monkeys
 - When injected into Macaques, causes severe immunodeficiency – often lethal.
- Other animal retroviruses such as Feline and Bovine Immunodeficiency Virus, as well as the Mouse Leukemia virus only yield information concerning the general nature of retroviruses.
- Only our closest relatives, chimpanzees support HIV-1 infection! (vaccination/drug?)
 - However they rarely develop AIDS



You have SIV_{agm}!

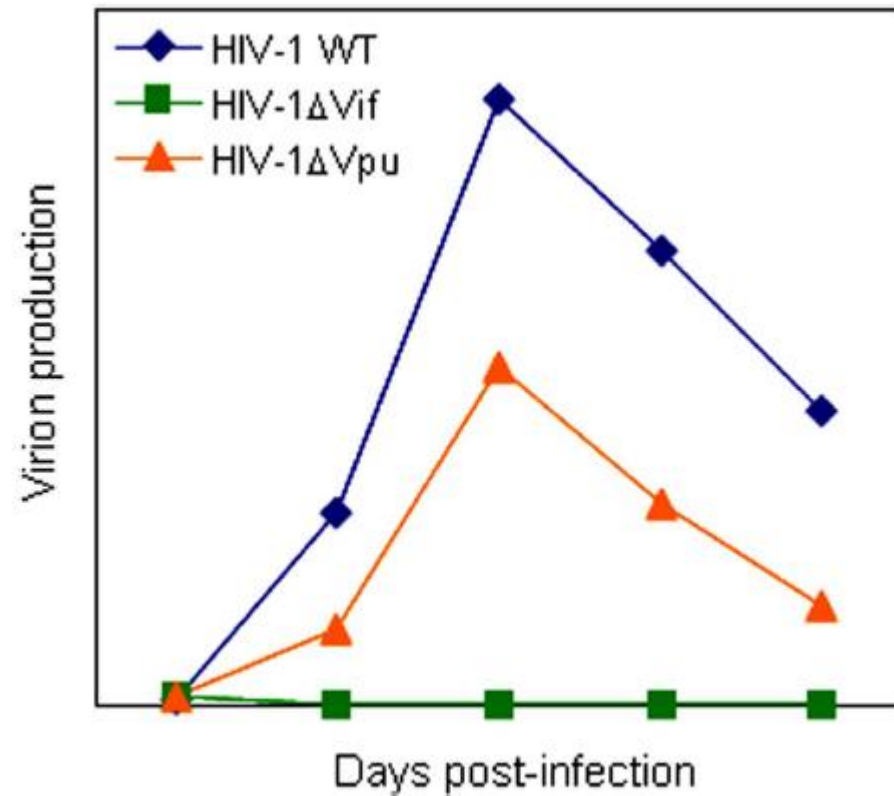


Reasons For Limited Host Range?

Causative Agent of AIDS – Limited Host Range

Lack Of Suitable Infection Model

- Virion coded genomic proteins such as vif and vpu, and their interactions with host (humans) cell proteins are key!



Causative Agent of AIDS – Limited Host Range

Lack Of Suitable Infection Model

- Variation in host genes and cellular factors.
 - Human Tetherin and HIV-1 VPU

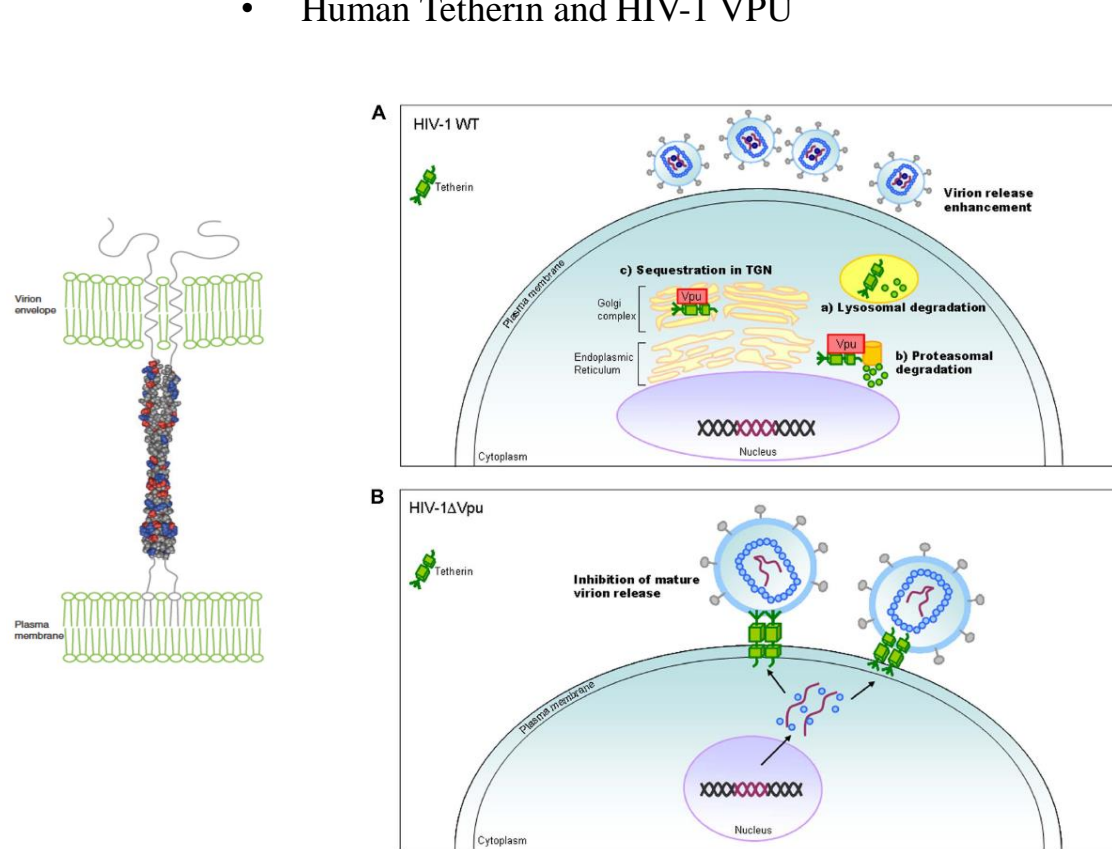
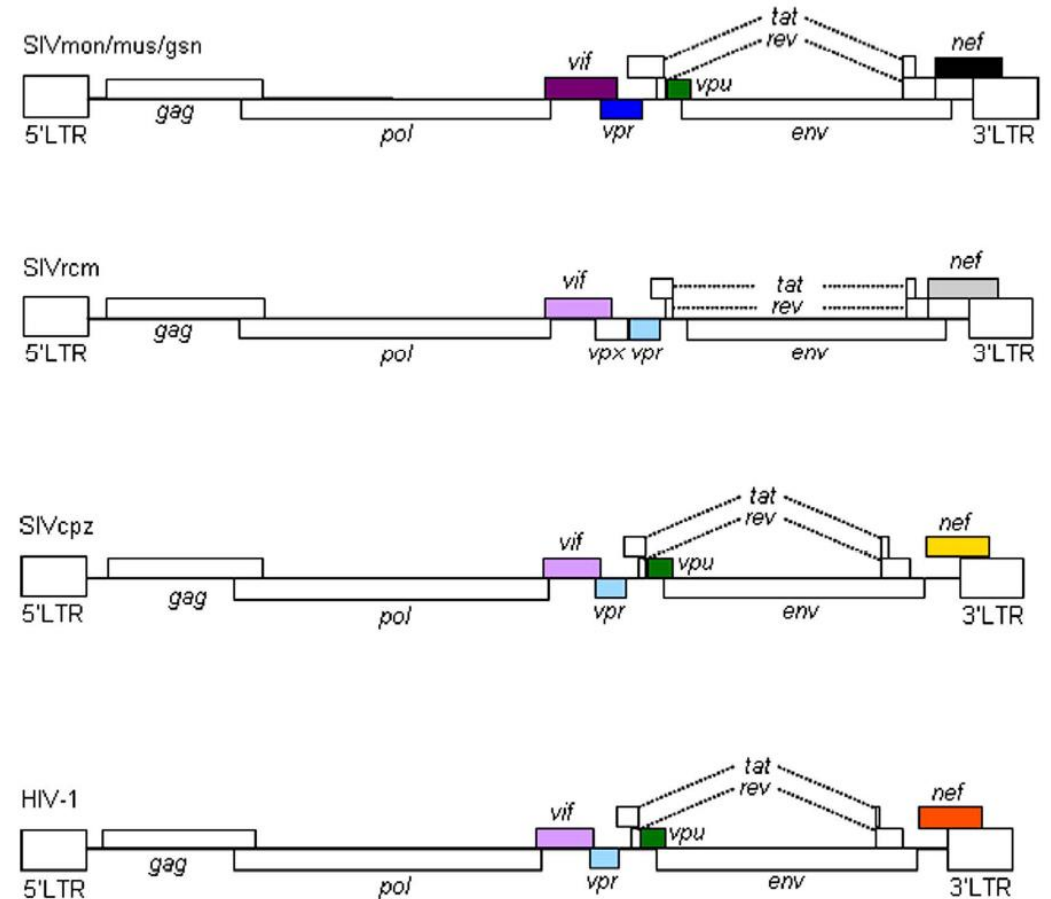


FIGURE 4 | HIV-1 replication and Tetherin. On the basis of results reported so far, the action mechanism of Vpu is depicted. Replication process for wild-type (WT) and ΔVpu mutant viruses are schematically

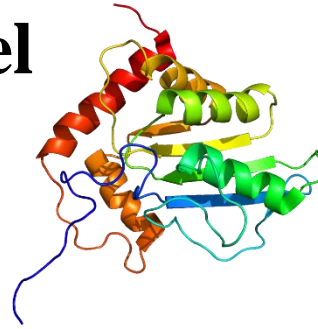
shown on the basis of previously reported review articles (Tokarev et al., 2009; Douglas et al., 2010; Evans et al., 2010). TGN, trans-Golgi network.



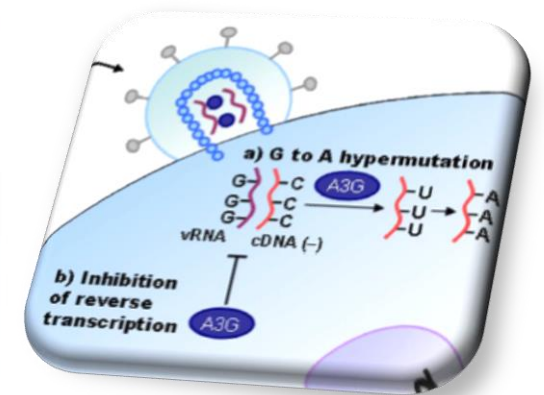
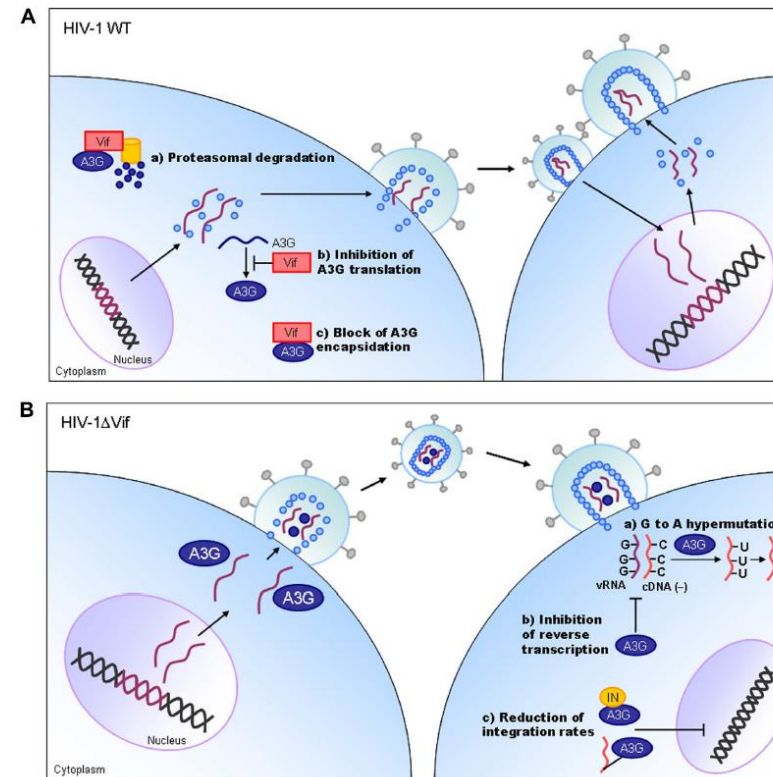
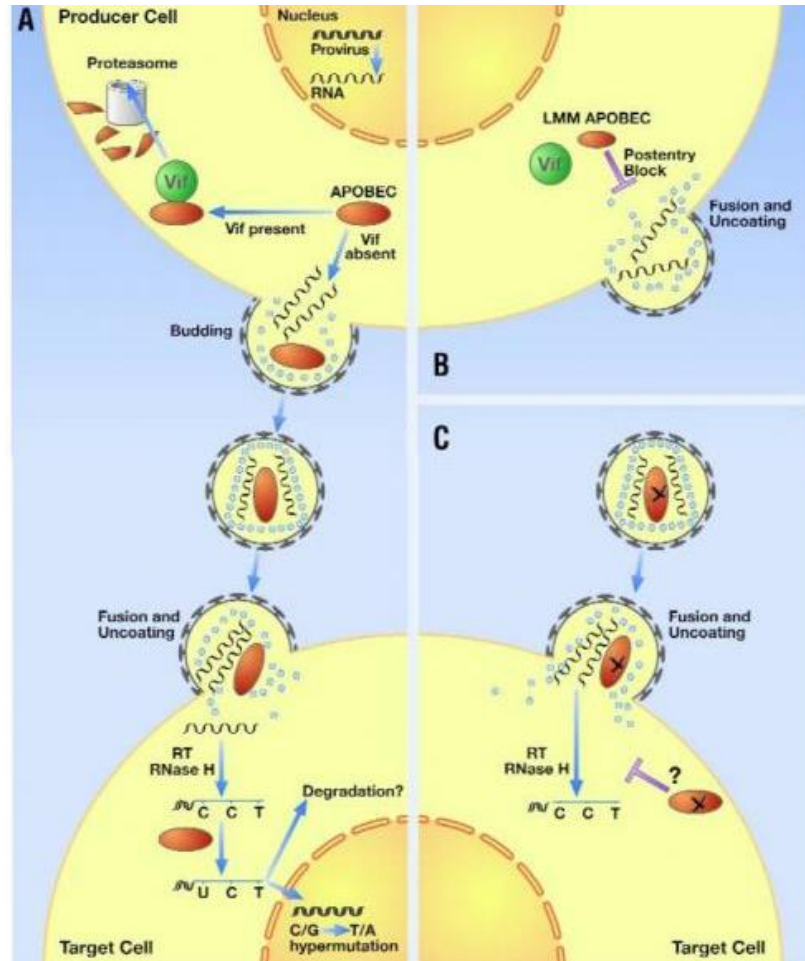
Causative Agent of AIDS – Limited Host Range

Lack Of Suitable Infection Model

- Variation in host genes and cellular factors.
 - Human APOBEC3G (A3G) and HIV-1 Vif



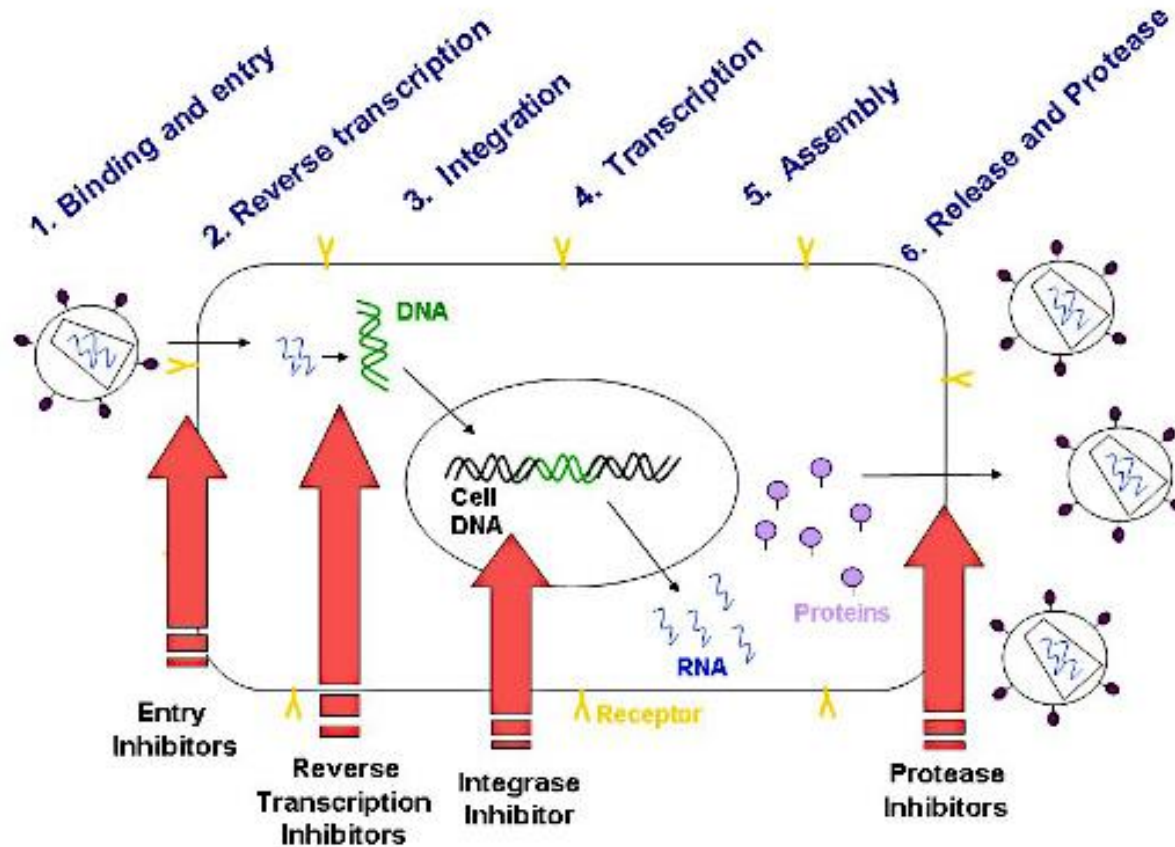
Blocks viral replication in natural target cells
Causes a G → A hypermutation



Causative Agent of AIDS – Lentiviruses

Human Immunodeficiency Virus or HIV

Drug Targets



Many classes of drugs have been developed to attack HIV at different stages of its life cycle. Some examples (drug name is followed by its three-letter code and *trade name*):

Entry Inhibitors (EIs)

TNX 355	CD4 binding blocker
Maraviroc	chemokine receptor binding blocker
Enfuvirtide (ENF, Fuzeon)	gp41 zipping inhibitor

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

Tenofovir (TDF, Viread)	adenosine monophosphate (A) analog
-------------------------	------------------------------------

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine (AZT, Retrovir)	thymidine (T) analog
Lamivudine (3TC, Epivir)	cytidine (C) analog
Emtricitabine (FTC, Emtriva)	cytidine (C) analog
Abacavir (ABC, Zigen)	guanine (G) analog
Didanosine (ddI, Videx)	adenosine (A) analog

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz (EFV, Sustiva)
Nevirapine (NVP, Viramune)

Integrase Inhibitors

Raltegravir (RGV, Isentress)
Elvitegravir

Protease Inhibitors (PIs)

Lopinavir (LPV)	given with ritonavir as Kaletra
Ritonavir (RTV, Norvir)	
Fosamprenavir (908, Lexiva)	
Atazanavir (ATV, Reyataz)	

Reduction of Disease Severity and Progression

Anti-retrovirus Drugs

- Complications:
 - Resistance
 - Toxicity
 - Side Effects
 - Financial Aspect

Natural Selection!
HIV = evolutionary masterpiece

High replication rate!
Higher mutation rate!
Resistance build up to antiviral drugs have been linked to the error prone RT enzyme encoded by viral genome

Overall, 80% of participants had at least one major resistance mutation to at least one drug from the three major classes of antiretrovirals – nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Specifically, two-thirds carried resistance to an NRTI, 50% to an NNRTI and 33% to a protease inhibitor.

De Luca A et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis*, online edition, 2013.

Accumulation of chemicals in patient's body

Toxic Buildup From ART – Killed by what’s saving you...

Mitochondrial Toxicity

Pancreatitis

Peripheral Neuropathy

Lactic Acidosis

Metabolic Complications such as:

Dyslipidemia or Dysglycemia

Bone Metabolism and Lipodystrophy

Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

Must be used with at least two other drugs

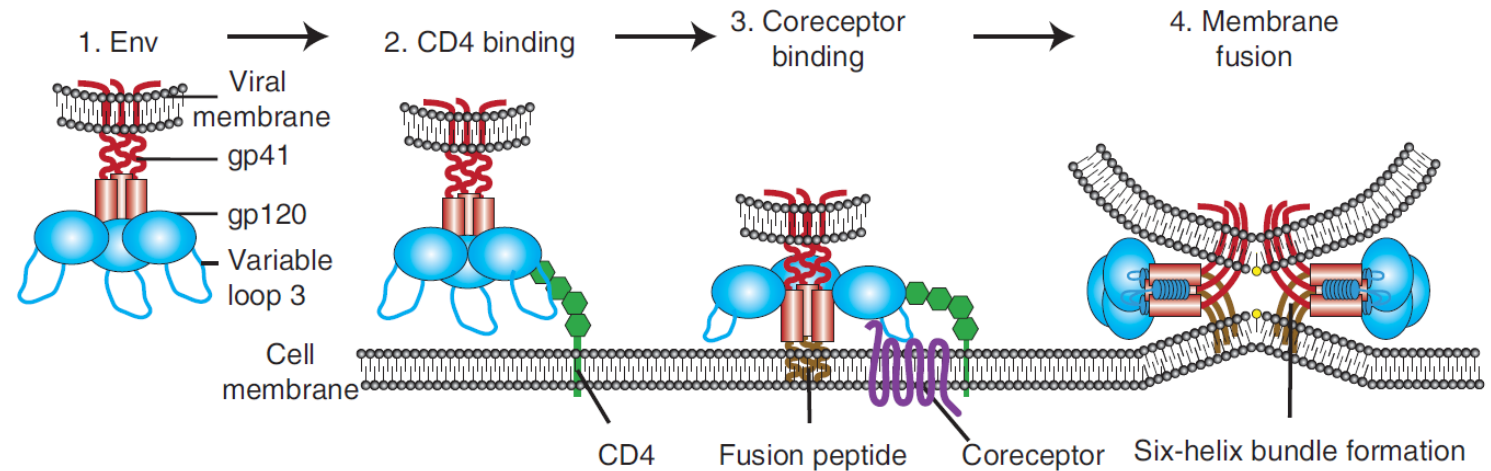
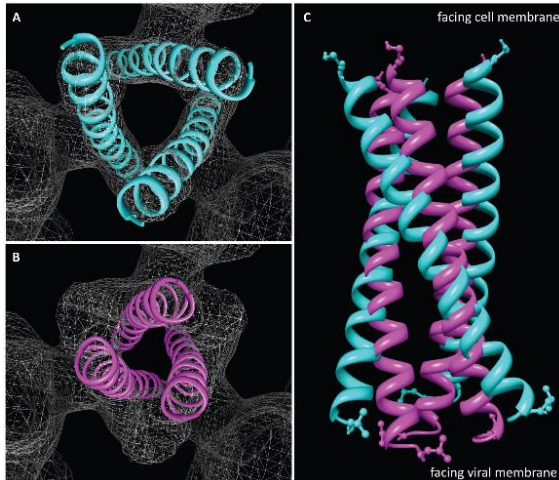
Appetite loss, malaise, diarrhea, nausea, vomiting

Code	Unit name (in English)	Unit name (in Russian)	Unit name (in Russian)
010000	General studies	Общие дисциплины	General studies and culture
010001	English language	Английский язык	English language and culture
010002	Mathematics	Математика	Mathematics
010003	Physics	Физика	Physics
010004	Chemistry	Химия	Chemistry
010005	Biology	Биология	Biology
010006	Geography	География	Geography
010007	History	История	History
010008	Philosophy	Философия	Philosophy
010009	Psychology	Психология	Psychology
010010	Sociology	Социология	Sociology
010011	Political Science	Политология	Political Science
010012	Law	Право	Law
010013	Economics	Экономика	Economics
010014	Management	Управление	Management
010015	Information Systems	Информационные системы	Information Systems
010016	Computer Science	Компьютерные науки	Computer Science
010017	Engineering	Инженерия	Engineering
010018	Architecture	Архитектура	Architecture
010019	Design	Дизайн	Design
010020	Art	Искусство	Art
010021	Music	Музыка	Music
010022	Sports	Спорт	Sports
010023	Health Sciences	Научные дисциплины	Health Sciences
010024	Medicine	Медицина	Medicine
010025	Nursing	Сестринское дело	Nursing
010026	Pharmacy	Фармация	Pharmacy
010027	Veterinary Medicine	Ветеринария	Veterinary Medicine
010028	Agriculture	Сельское хозяйство	Agriculture
010029	Forestry	Лесное хозяйство	Forestry
010030	Fishing	Рыбное хозяйство	Fishing
010031	Marine Biology	Морская биология	Marine Biology
010032	Environmental Science	Экология	Environmental Science
010033	Geology	Геология	Geology
010034	Mineralogy	Минералогия	Mineralogy
010035	Metallurgy	Металлургия	Metallurgy
010036	Chemical Engineering	Химическое машиностроение	Chemical Engineering
010037	Food Science	Пищевая промышленность	Food Science
010038	Textile Engineering	Текстильная промышленность	Textile Engineering
010039	Leather Engineering	Кожевенная промышленность	Leather Engineering
010040	Paper Engineering	Бумажная промышленность	Paper Engineering
010041	Printing	Печать	Printing
010042	Bookbinding	Книгосвязь	Bookbinding
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010097	Sports	Спорт	Sports
010098	Health Sciences	Научные дисциплины	Health Sciences
010099	Medicine	Медицина	Medicine
010100	Nursing	Сестринское дело	Nursing

Anti-HIV-1 Drug T20

T20 Blocks Viral Entry

- GP41
 - Extra cellular domain contains Fusion Peptide (FP) and 2 helical regions –
 - FP is highly hydrophobic and glycine rich
 - Post FP activity – HR1 and HR2 undergo conformational → 6-helix bundle → membrane fusion

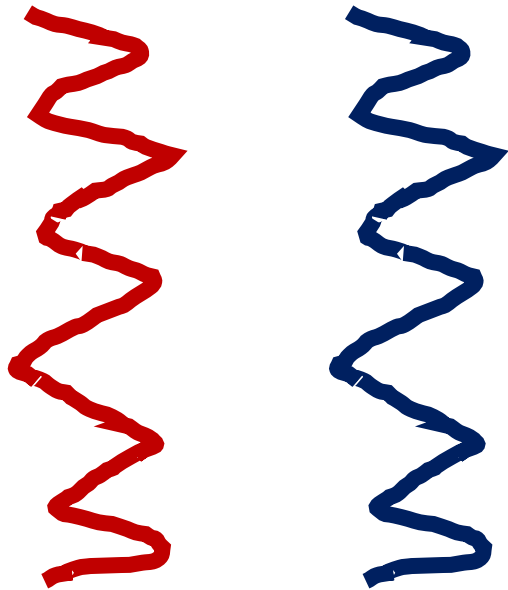


Overview of viral entry mechanism

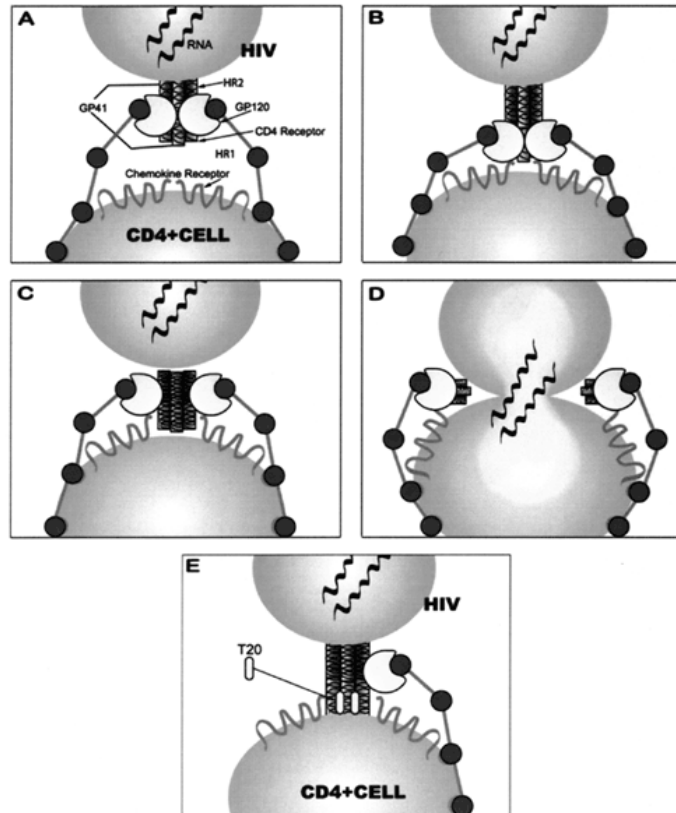
Anti-HIV-1 Drug T20

T20 Blocks Viral Entry

- T20 or ENF
 - 36 AA Seq. corresponding HR2 domain in GP41
 - Furthermore, T20 binds the HR1 domain of GP41 to prevent the formation of 6-helix bundle – impeding the translation of GP41 into a fusion active state.



Blocking Fusion
By blocking the formation
of 6-helix bundle



Have we eradicated the virus from the human body? No more AIDS?

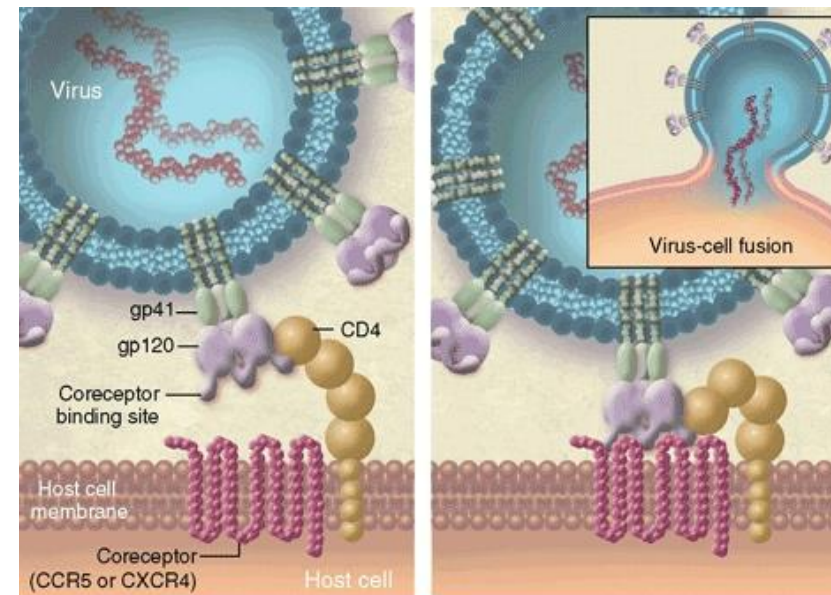
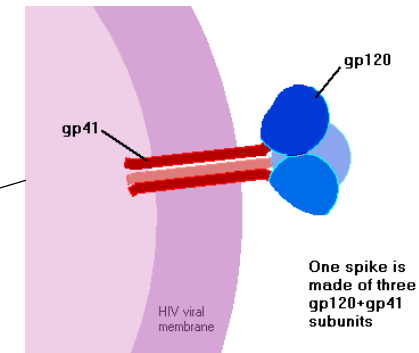
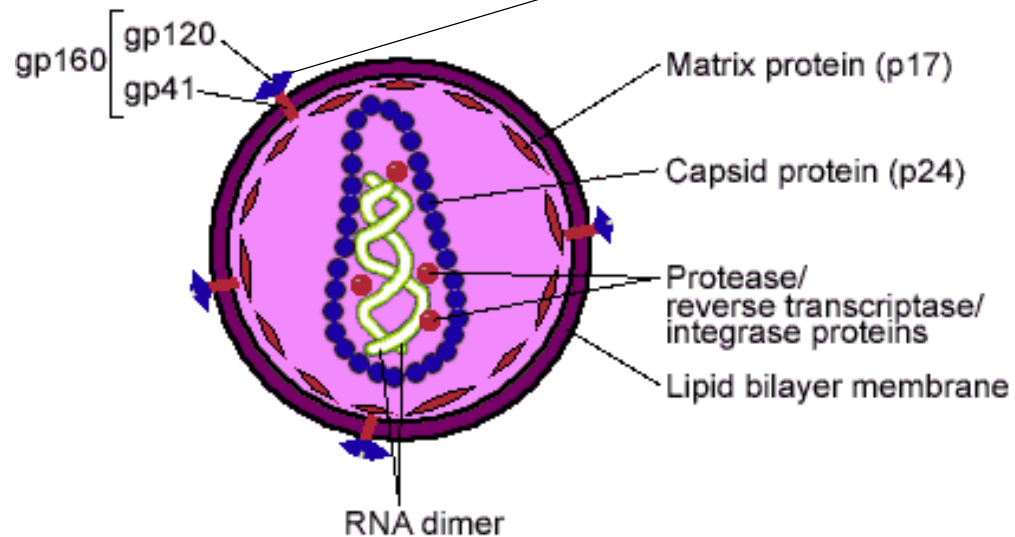
■ Causative Agent of AIDS – Immunogen Design

The Focus On HIV-1 Env
Revealing Structural Details
Crucial For Drug/Vaccine Design

Bio-Medical Image Analysis – Background

HIV-1 Surface Proteins

- 1) HIV Env – Viral Entry
- 2) Structural Variability
- 3) Vaccine Development

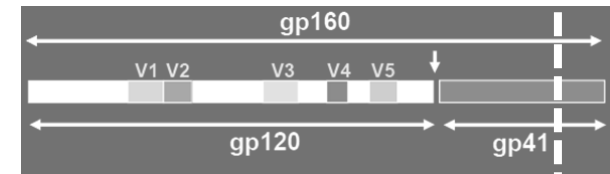
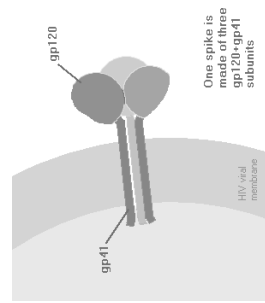


Host CD4+ T-Lymphocytes

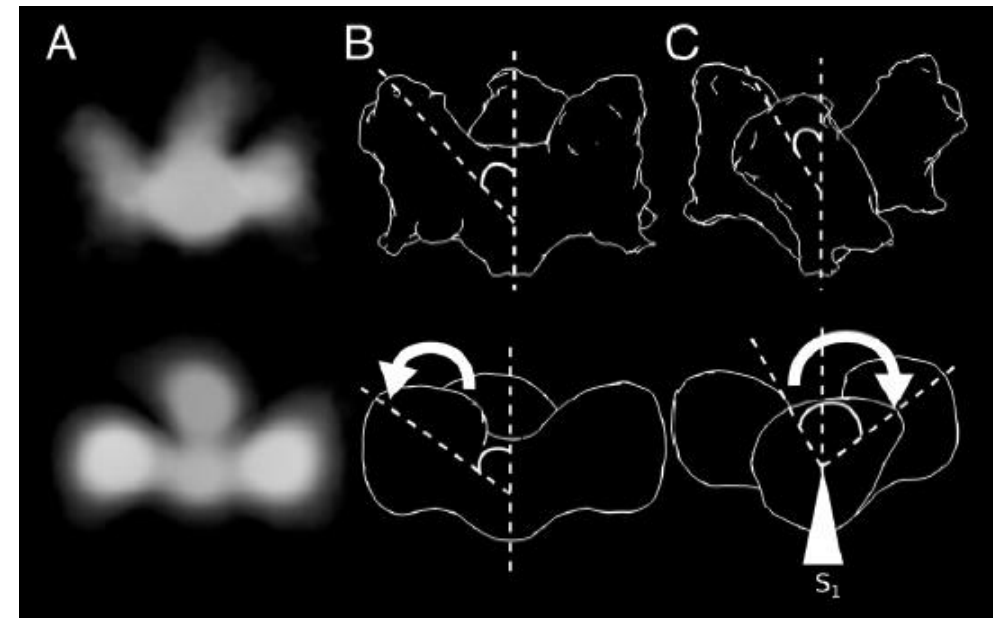
Characterization of Env – GP140 as an Immunogen!

HIV-1 Surface Proteins

- 1) HIV Env – Viral Entry
- 2) Structural Variability
- 3) Vaccine Development



GP140 a soluble form of GP160, with truncated trans-membrane domain



Moscoso et al. 2010

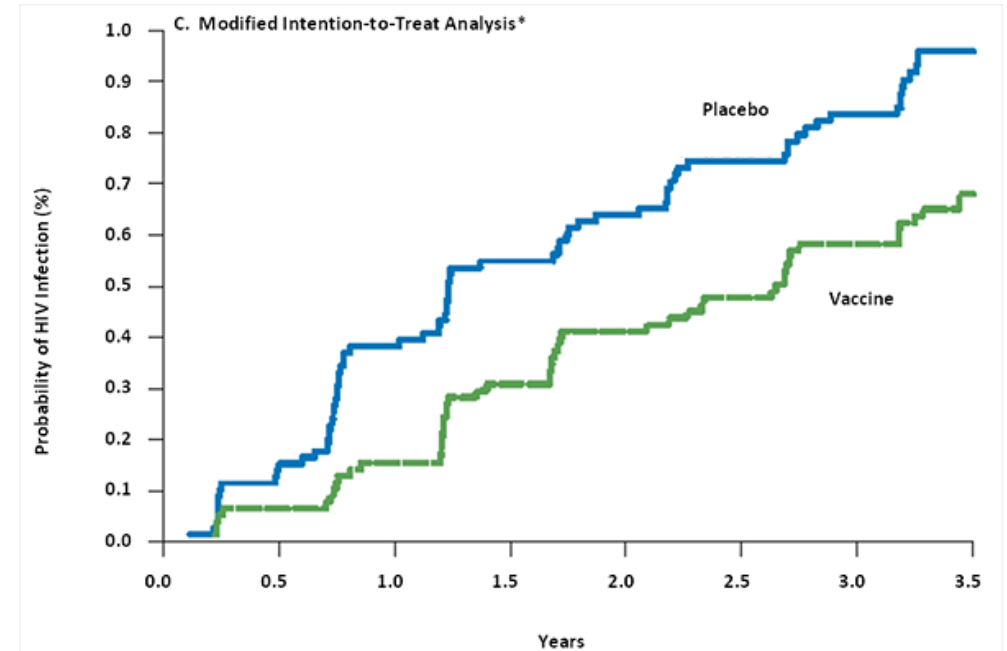
Immunogen Design – GP120

Env Derived Immunogen

- GP120 – Monomeric – Vaccine Candidate RV144
 - With efficacy of 31%
 - Failure to induce bNAbs

Failure?

- GP140 – trimeric Immunogen
 - Induces bNAbs
 - Debate on cleavage site presence between gp41 and gp120 subunits.
 - Controversial deletion of V2



N=16,395

51 vaccine, 74 placebo HIV infected

Est. VE = 31% 95% CI 1-51% (p=0.04)

Rerks-Ngarm et al. (2009, *NEJM*)

Immunogen Design – Immune System Evasion

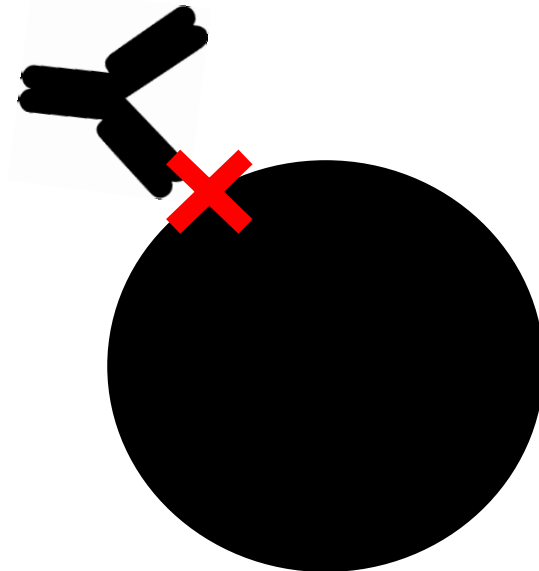
Formidable Barrier to Ab Efficacy

Major Consideration - Env Derived Immunogen

Enforcing Nano-imaging & Structural Studies

Abrogation of the impact of bNAbs

- **AA Seq. Variation**
 - V1,V2,V3
 - Error-prone RT
- **Glycosylation**
 - The “Fence” – “Viral Defense”!?
- **Steric Exclusion**
 - CD4BS
 - Example: Common Cold Picornavirus
 - CRBS
 - MPER
- **Metastability and Adaptation**
 - Native, CD4B, CRB, and Intermediate
 - Example: Dissociation of GP120
- **Heterologation of B-cells**
 - Leading to the dearth of high avidity antibody production



Immunogen Design

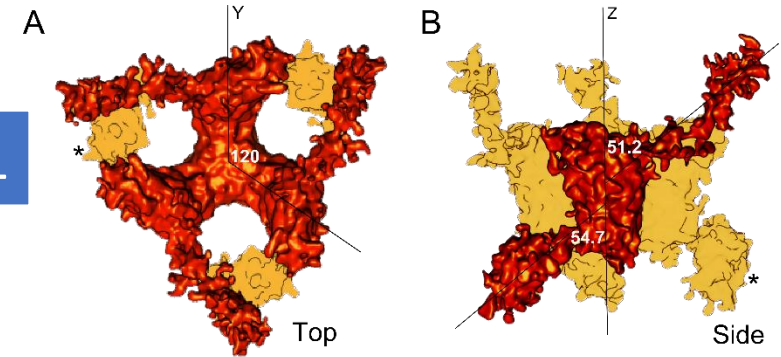
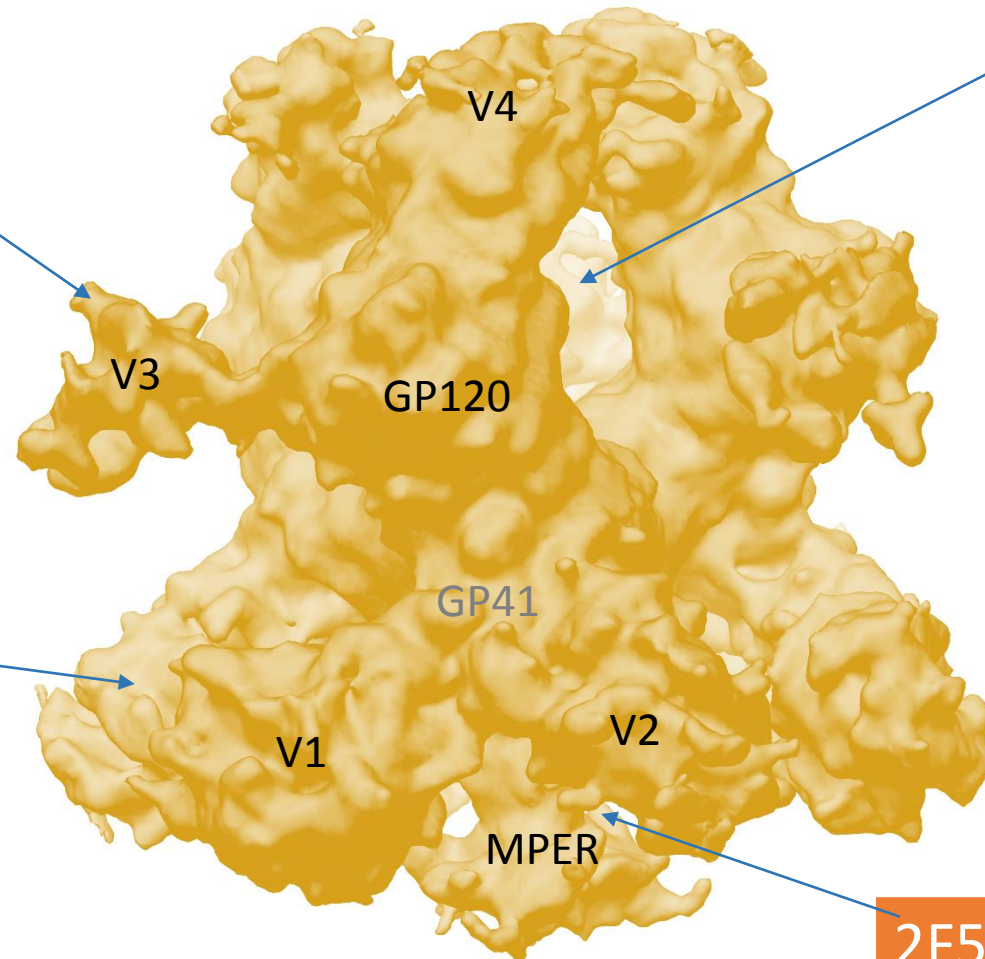
Closer look at some bNAbs

PGT121

VRC01

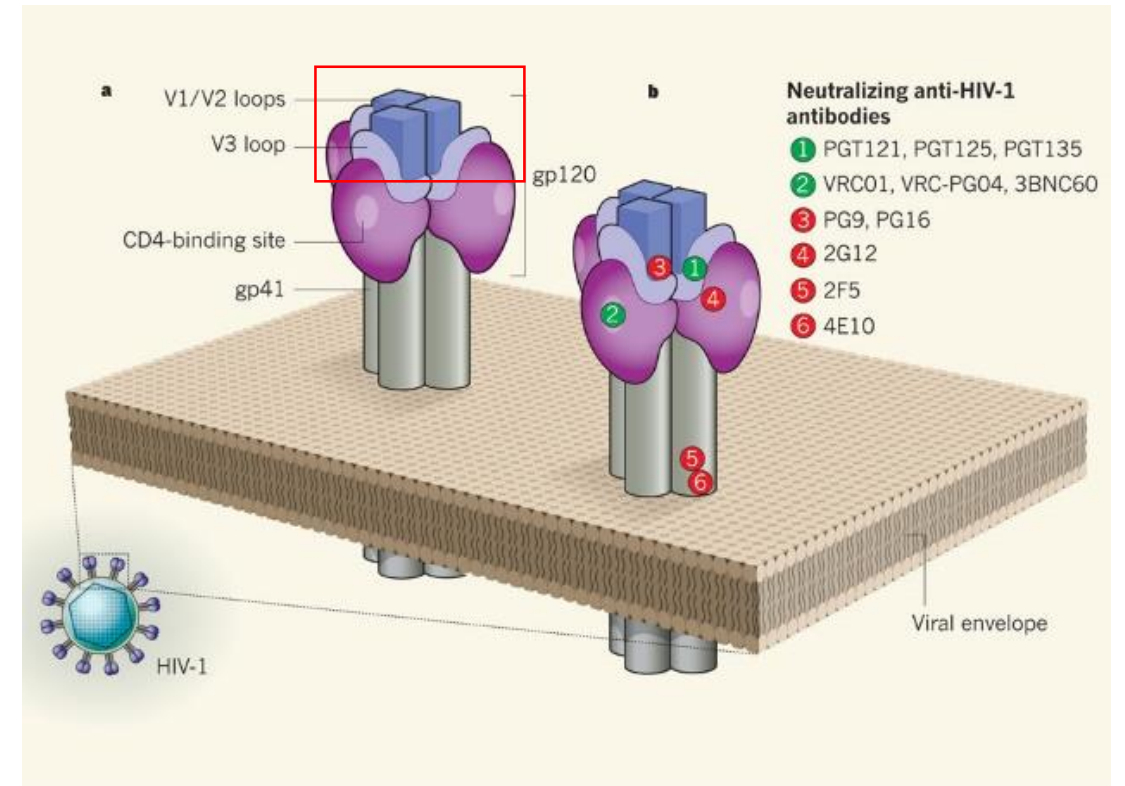
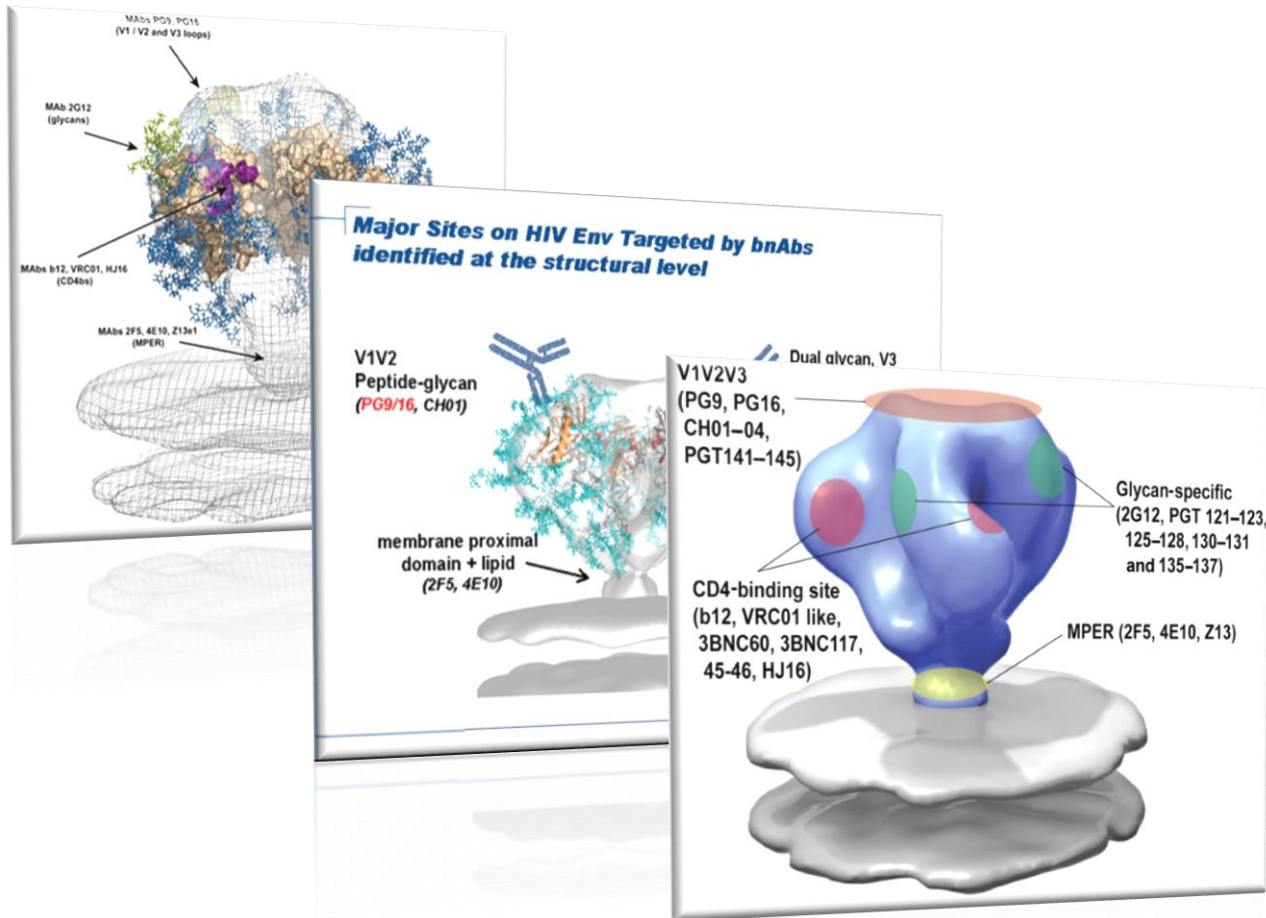
2G12

2F5,4E10



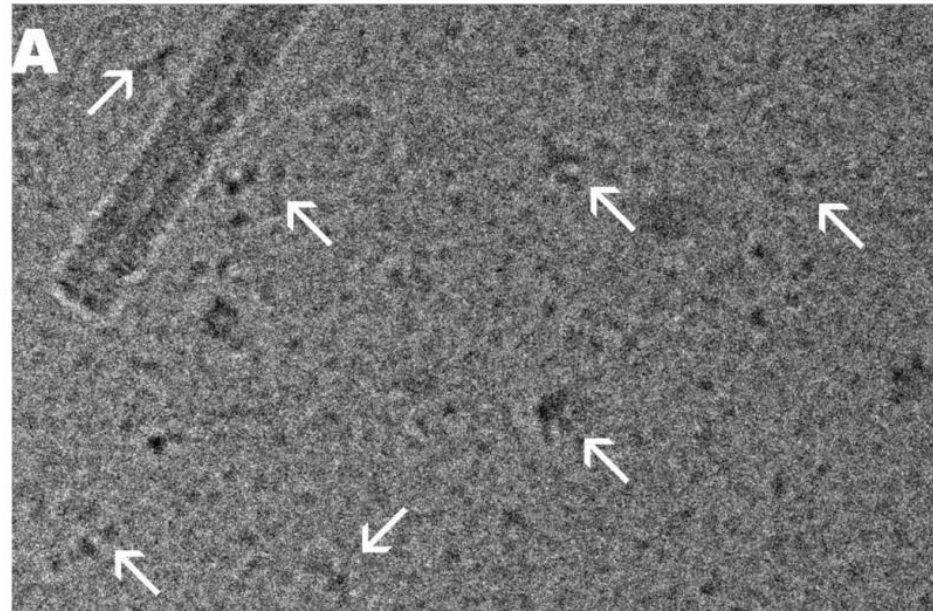
Immunogen Design

Locations Of Variable Loops!



Immunogen Design / Structural Biology

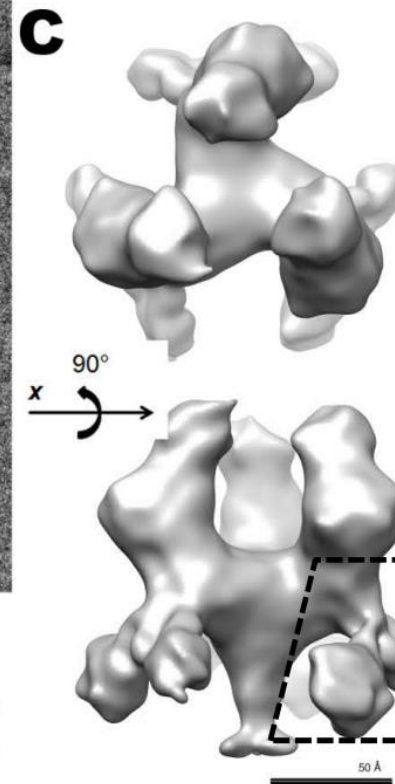
4° location of variable loop 2



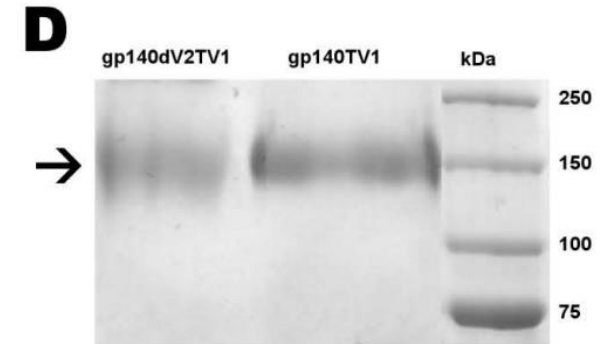
B

gp140TV1 Full length
120 CVTLHCTNLKNATNTKSSNWKEMDRGEIKNCSFKVttsirnmqkeyalfyldvvpidndntsyKLINCNTSVITQAC 199
gp140dV2TV1
120 CVTLHCTNLKNATNTKSSNWKEMDRGEIKNCSFKVgag-----KLINCNTSVITQAC 199

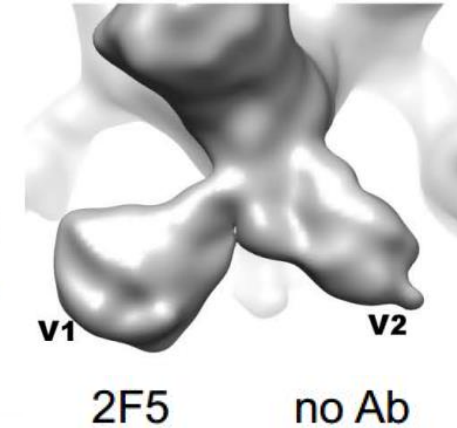
C



D

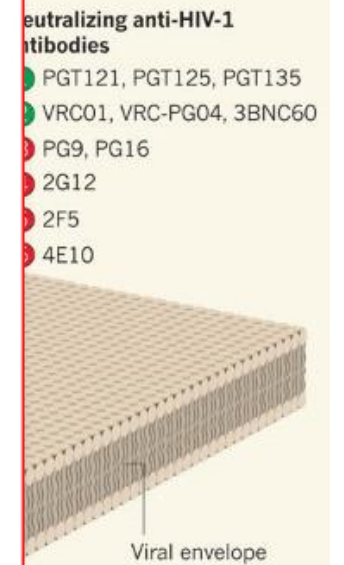
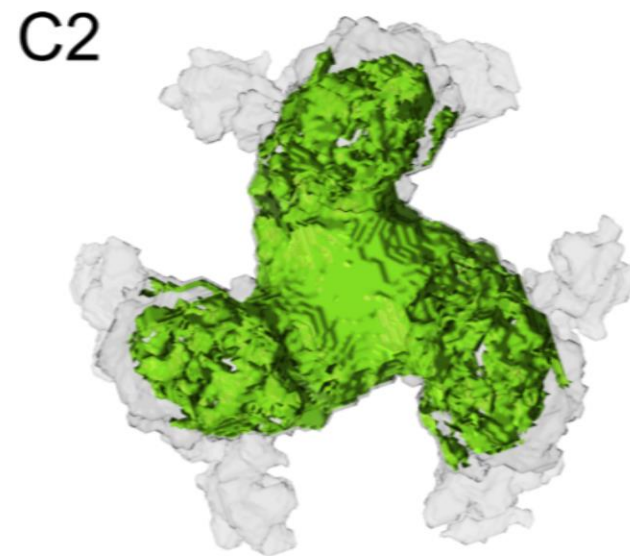
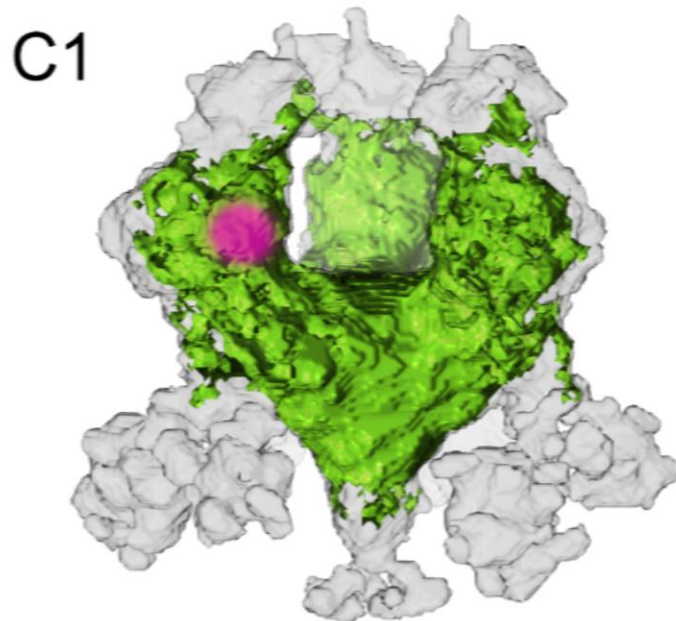
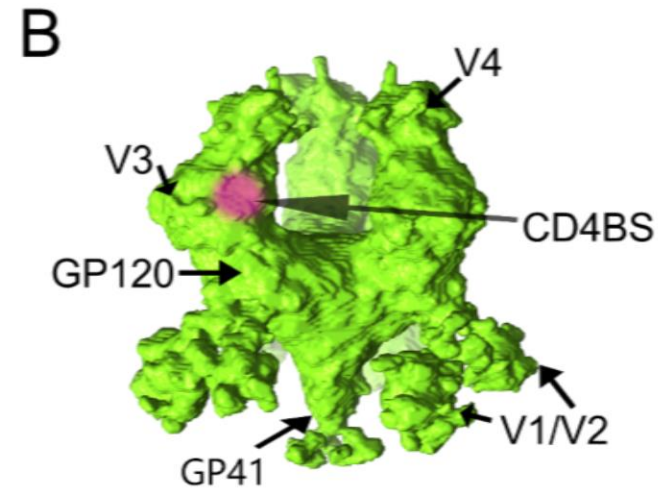
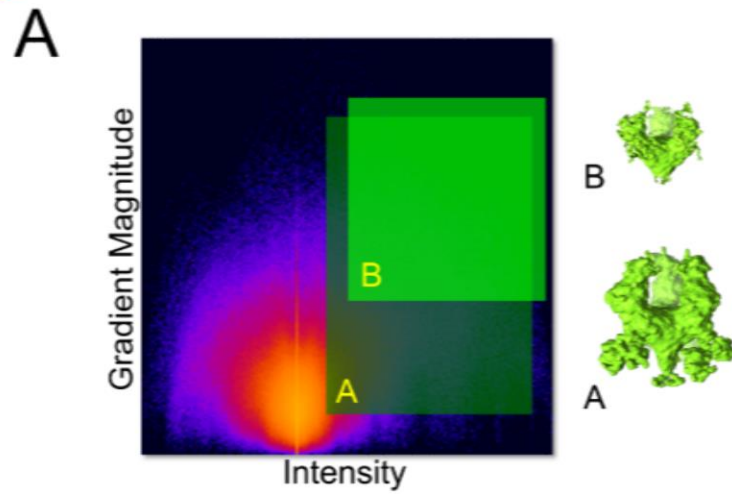


E

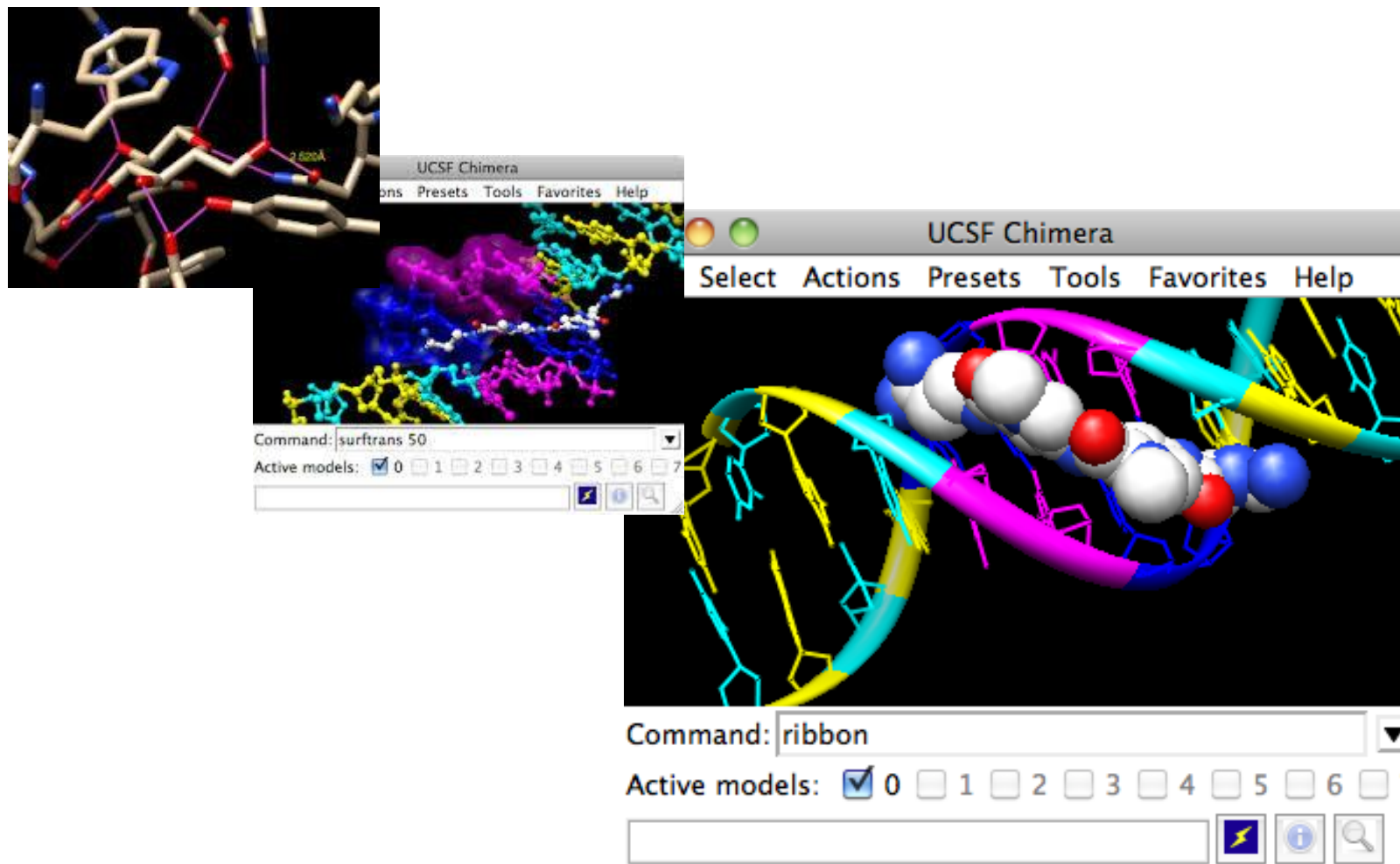


Immunogen Design

Local



Quick demonstration of Chimera



- Structure-based studies enable us to further investigate possible routes towards effective, highly potent, and high Ab (or bNAbs) avidity vaccine development.
- In discussion of “NanoMedicine”, multiple approaches, whether biochemical, structural, or computational, can be combined to generate effective results, and draw more accurate conclusion.
- Furthermore, 3D analysis of reconstructed structures will enhance our understanding of the inter and intra molecular interaction, as well as structural elements, which will ultimately help us facilitate drug delivery and drug design.

Thanks to:

University of California, Davis

Dr. Holland Cheng
Dr. Li Xing

Carlos Moscoso
Lassi Paavolainen
C.C. Chen
Tingwei Ou
Everyone else ...

Onur Yenigun
Shawyon Malek
Amrit Randwaha
Ben Lorton
Marie Stark
Mike Stout

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