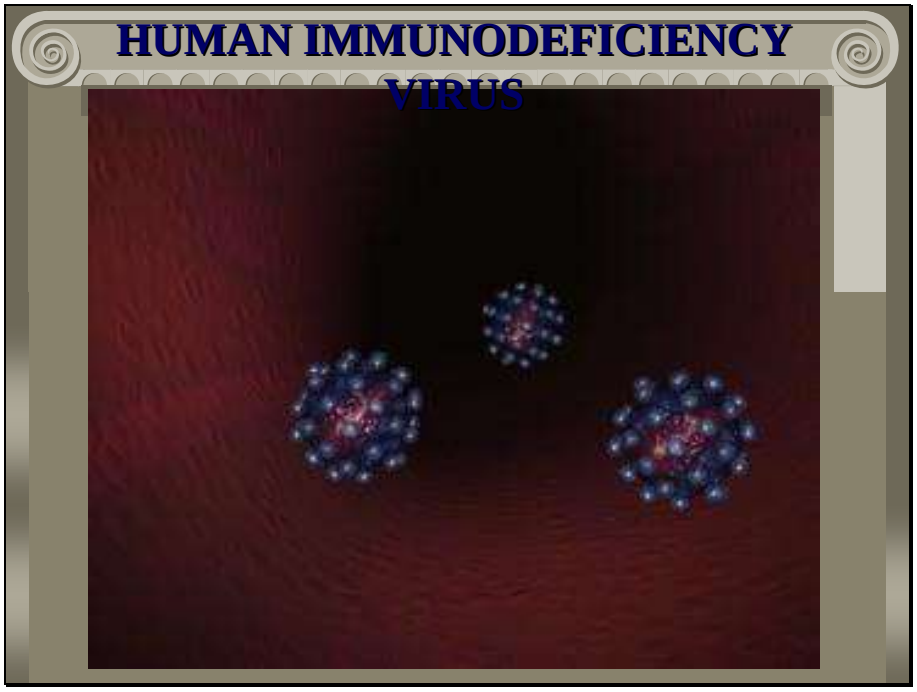
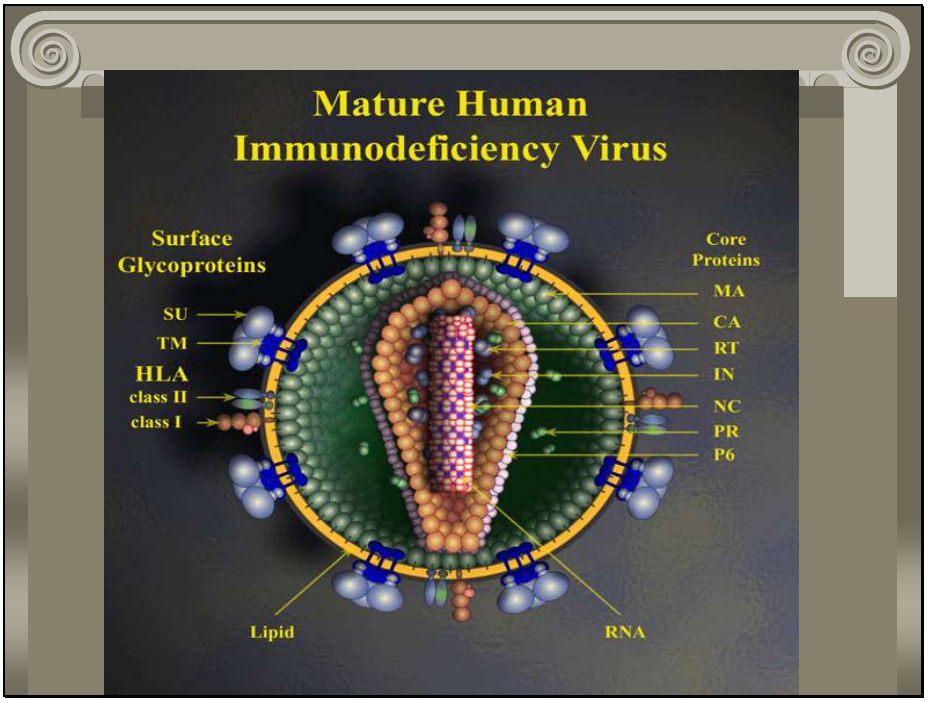
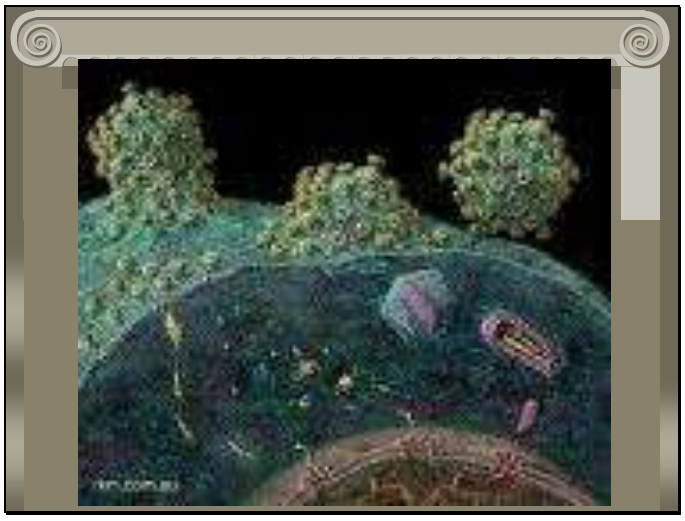
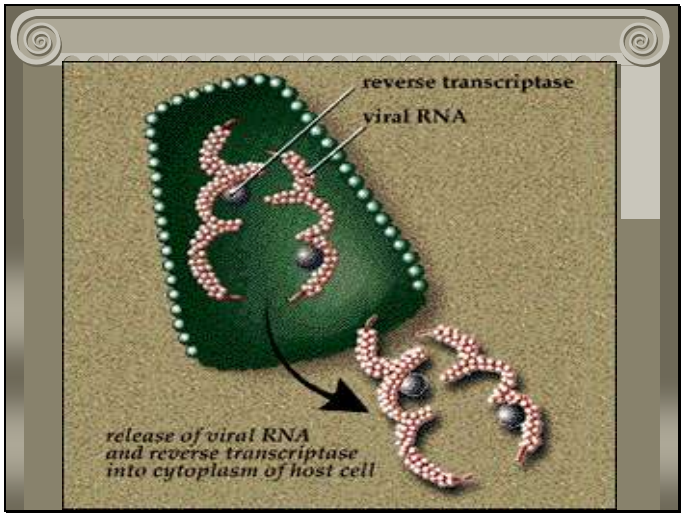
Futuro promisorio de la terapia antirretroviral: Nuevos blancos terapéuticos.

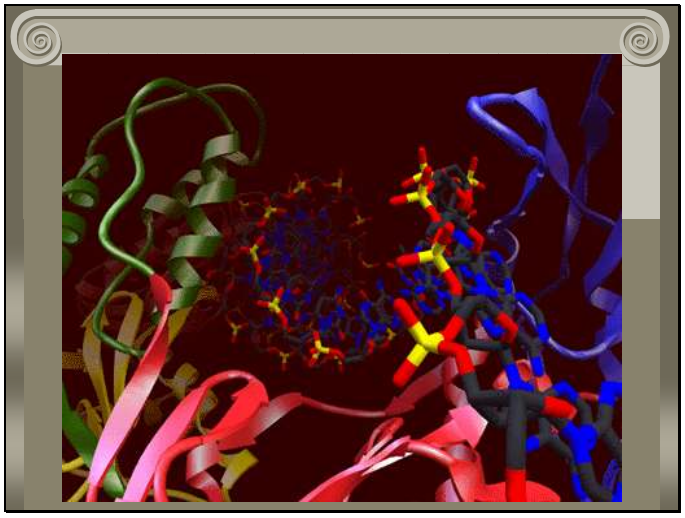
María José Míguez, M.D., PhD., Universidad de Miami, EE.UU.

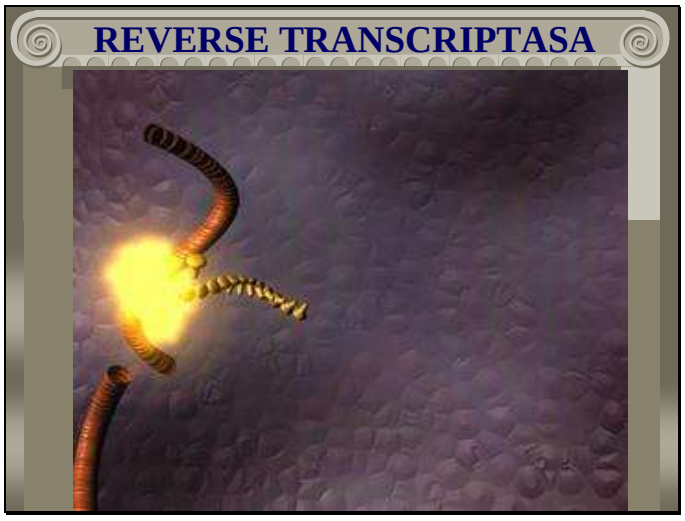


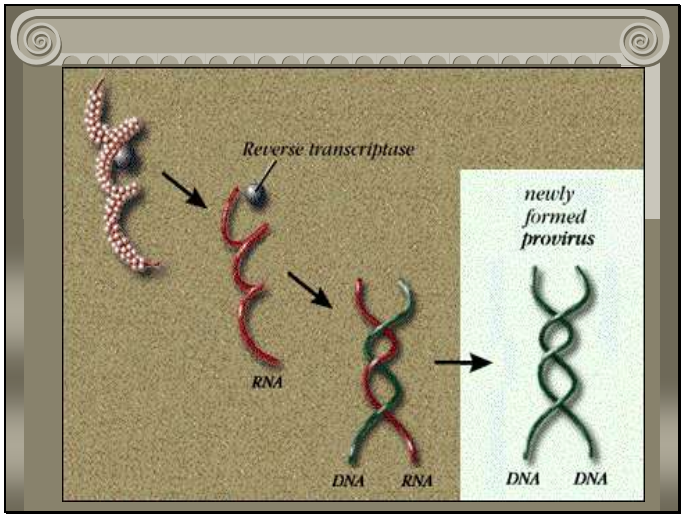


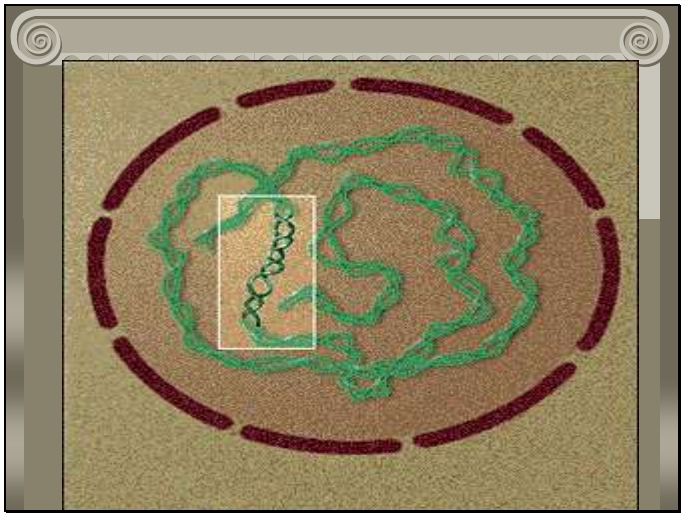



reverse transcriptase
viral RNA
release of viral RNA
and reverse transcriptase
into cytoplasm of host cell




REVERSE TRANSCRIPTASA

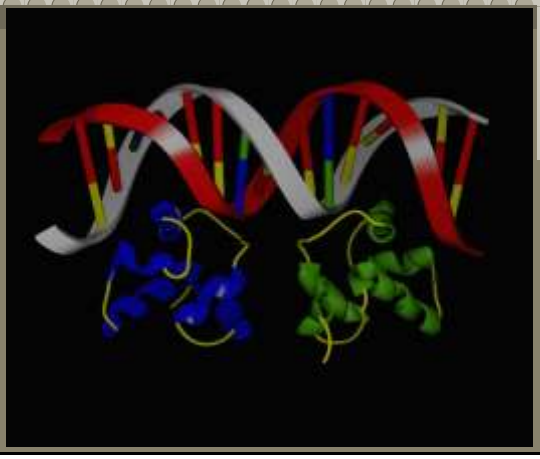

Reverse transcriptase
RNA
DNA
RNA
newly
formed
provirus
DNA
DNA



REPLICATION

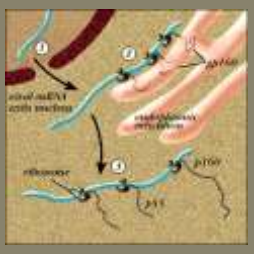
The protective shell and the helper and anchor proteins.

TRANCRIPTION



The proteins are cut into usable pieces and packaged with the RNA.

synthesis of three polyproteins:

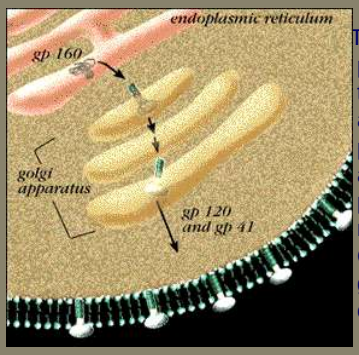


oENV gp 160 - containing gp 120 and gp 41

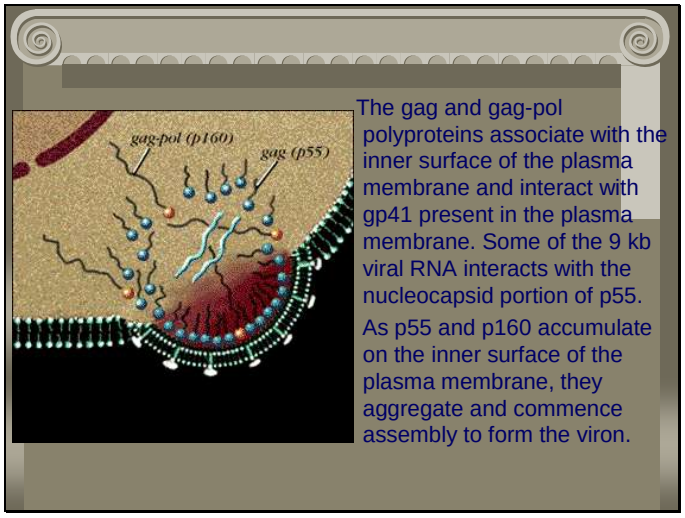
oGAG p55 - containing MA (matrix), CA (capsid), and NC (nucleocapsid protein)

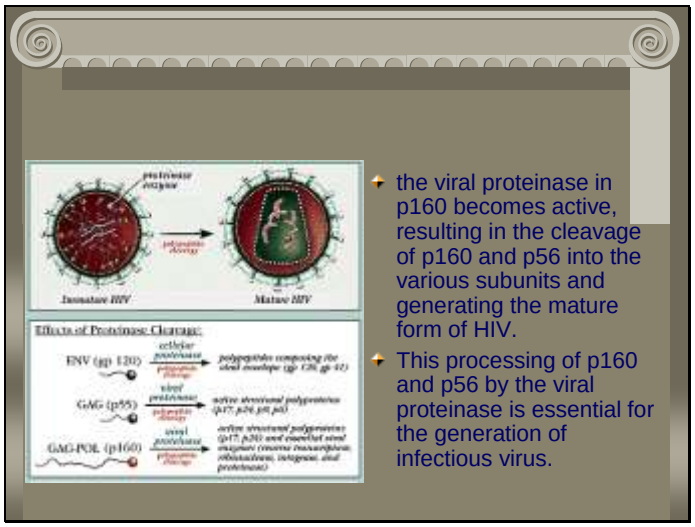
oGAG-POL p 160 - containing MA (matrix), CA (capsid), PR (proteinase), (RT) reverse transcriptase, and INT (integrase)

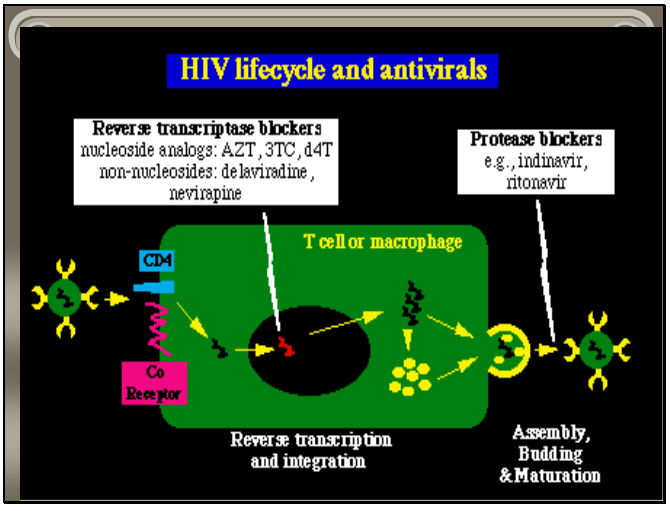
op55 and p160 are generated from the same mRNA strand by the process of ribosome frame shifting.

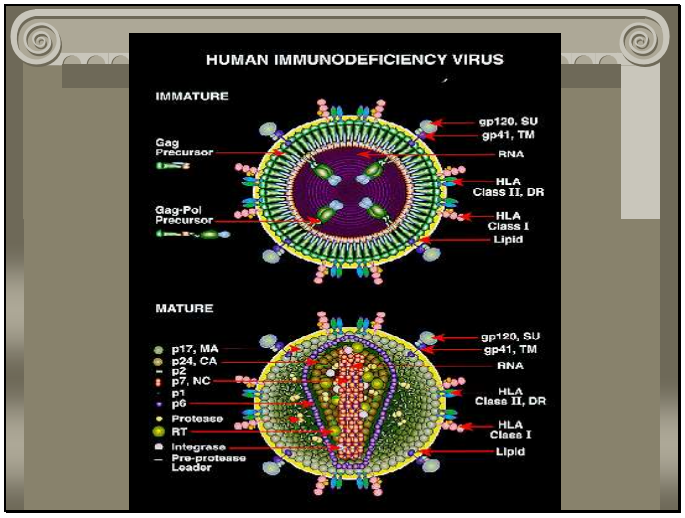


The env (gp160) proteins pass through the E.R. and Golgi apparatus to be processed into gp120 and gp41 HIV envelope proteins. During movement through the Golgi apparatus, glycosylation of gp120 occurs.


gag-pol (p160)
gag (p55)
The gag and gag-pol polyproteins associate with the inner surface of the plasma membrane and interact with gp41 present in the plasma membrane. Some of the 9 kb viral RNA interacts with the nucleocapsid portion of p55.
As p55 and p160 accumulate on the inner surface of the plasma membrane, they aggregate and commence assembly to form the viron.


Immature HIV
Mature HIV
Effects of Proteinase Cleavage:
ENV (gp 120)
GAG (p55)
GAG-POL (p160)
the viral proteinase in p160 becomes active, resulting in the cleavage of p160 and p56 into the various subunits and generating the mature form of HIV.
This processing of p160 and p56 by the viral proteinase is essential for the generation of infectious virus.

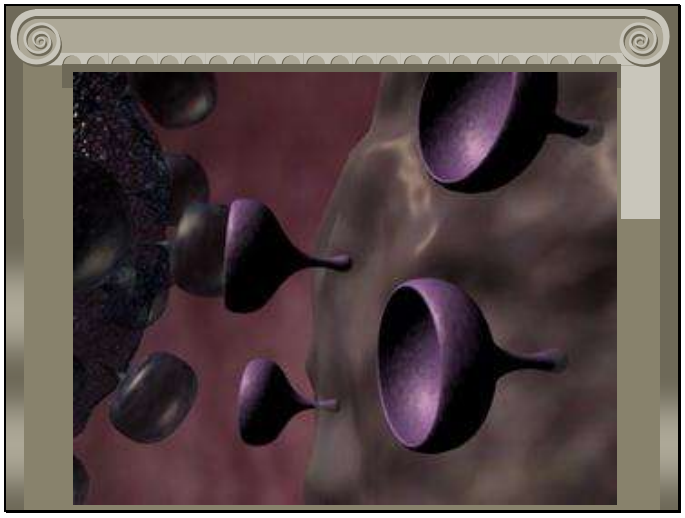

HIV lifecycle and antivirals
Reverse transcriptase blockers
nucleoside analogs: AZT, 3TC, d4T
non-nucleosides: delaviradine, nevirapine
Protease blockers
e.g., indinavir, ritonavir
T cell or macrophage
CD4
Co Receptor
Reverse transcription and integration
Assembly, Budding &Maturation

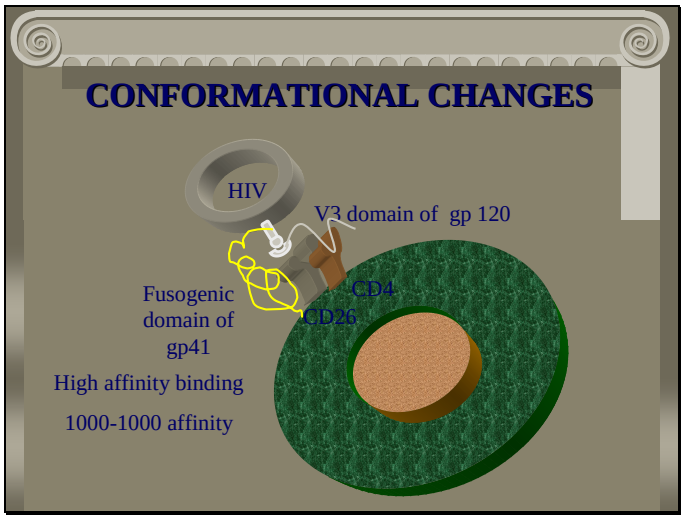


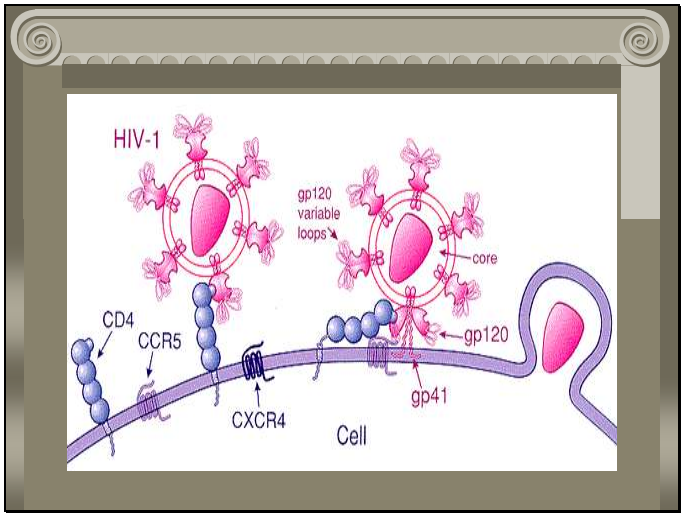
- **Cellular Receptors**
- **Immunoglobulin Superfamily**
- CD4
- **Chemokine (Seven-transmembrane) Receptor Superfamily**
- CXCR4 (also known as Fusin; LESTR; NPY3R)
- CCR5 (also known as CKR-5; CMKRB5)
- CCR3 (also known as CC-CKR-3; CKR-3; CMKBR3)

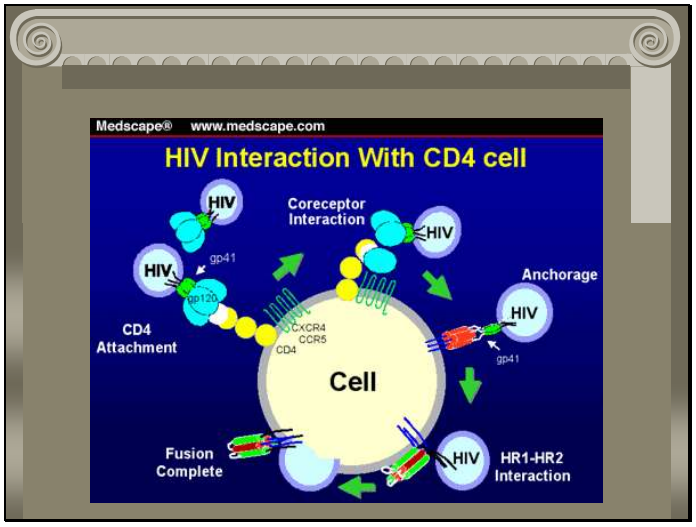
Intracellular Targets

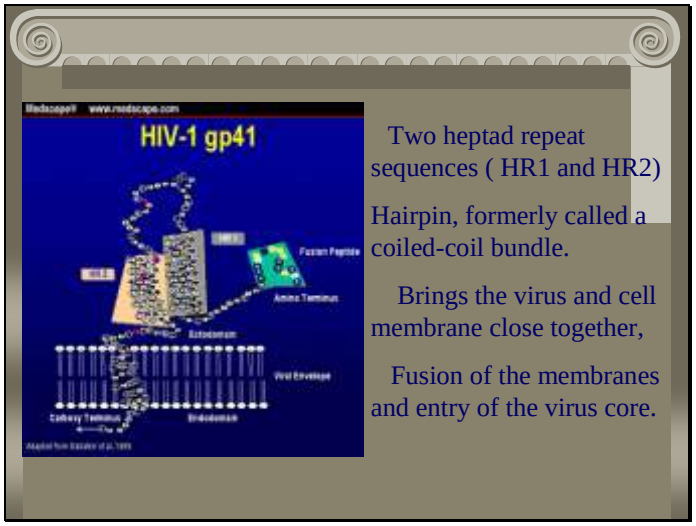
- **Cellular Enzymes**
- N-myristoyltransferase
- Glycosylation Enzymes
- gp-160 Processing Enzymes
- Ribonucleotide Reductase
- Polyamine Biosynthesis
- **Cellular Transcription Factors**
- Sp1
- NF-kB




CONFORMATIONAL CHANGES
HIV
V3 domain of gp 120
CD4
CD26
Fusogenic
domain of
gp41
High affinity binding
1000-1000 affinity


HIV-1
gp120
variable
loops
core
CD4
CCR5
gp120
gp41
CXCR4
Cell



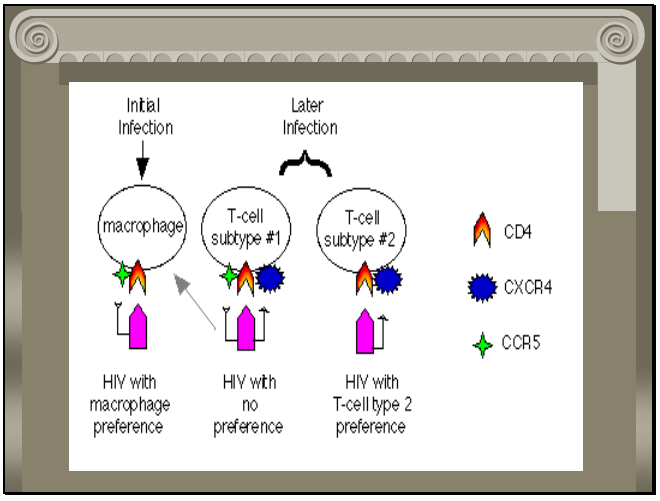


Two heptad repeat sequences (HR1 and HR2)

Hairpin, formerly called a coiled-coil bundle.

Brings the virus and cell membrane close together,

Fusion of the membranes and entry of the virus core.



CD4 BINDING

ADVANTAGES

1. The soluble form of CD4, rsCD4 block viral binding in vitro
2. Had minimal toxicity

DISADVANTAGES

1. But had no demonstrated antiviral effect in vivo.[11]
2. Most primary virus strains are relatively resistant to rsCD4 inhibition [12,13]

CD4 BINDING

HOPE

A tetravalent form of CD4 linked to IgG appears to neutralize a broad range of primary HIV strains 90% inhibition of HIV infection in vitro.[14]

CXCR4 INHIBITORS AMD3100

ADVANTAGES

1. Phase 2 trials, oral formulation.
2. Outstanding CXCR4 inhibition properties.

CXCR4 INHIBITORS AMD3100

DISADVANTAGES

1. Cardiac arrhythmias
2. Adequate efficacy was not demonstrated

CXCR4 INHIBITION

1. **CONCERNS ABOUT CLASS OF INHIBITION**
   1. CXCR4 is important for vascularization and organogenesis.[18]
   2. Blocking chemokine receptor pathways.

INHIBITION OF CCR5 SCH-C

BENEFITS

1. Inhibit chemotaxis induced by MIP-1 beta.
2. Block the calcium flux induced by chemokines.
3. In vitro inhibit of HIV isolates that use CCR5.

INHIBITION OF CCR5 SCH-C

DISADVANTAGES

1. It does not block infection through CXCR4.
2. Some HIV strains exhibit high-level resistance.

INHIBITION OF CCR5

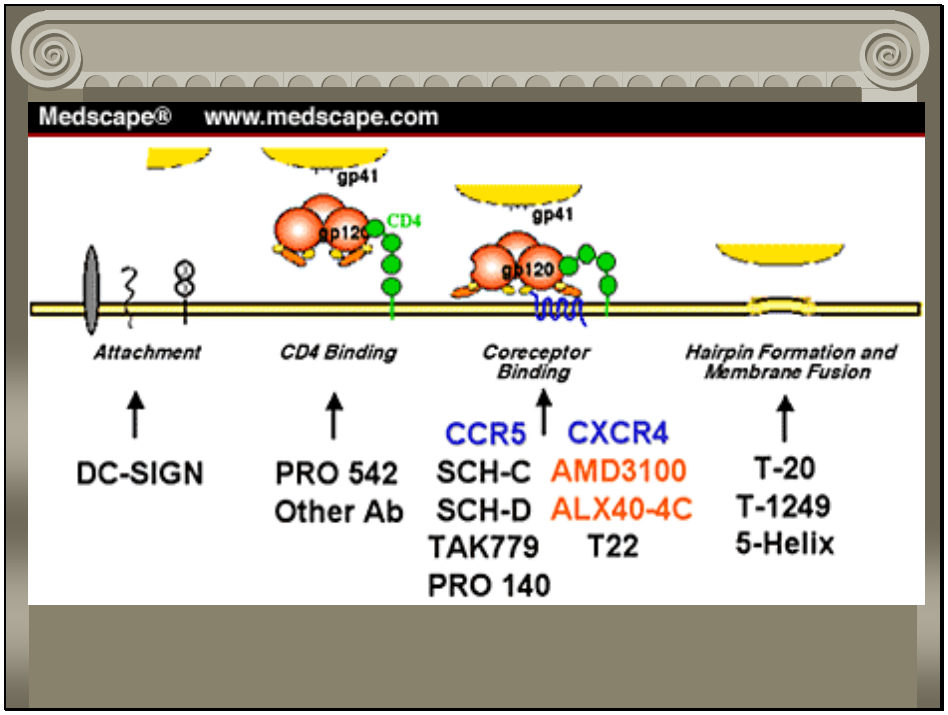
SCH-C clinical trials

Heart conduction abnormalities (prolonged QTc intervals).

Virus population may shift to one that uses CXCR4

Syncytium-inducing (SI)

more rapid CD4+ cell count depletion and clinical progression.


Medscape® www.medscape.com
gp41
gp120
CD4
gp41
gp120
Attachment
CD4 Binding
Coreceptor Binding
Hairpin Formation and Membrane Fusion
DC-SIGN
PRO 542
Other Ab
CCR5
CXCR4
SCH-C
AMD3100
SCH-D
ALX40-4C
TAK779
T22
PRO 140
T-20
T-1249
5-Helix