Introduction to the Biology of HIV-1

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Disclosures

Dr. Spach does not have any disclosures.
Introduction to the Biology of HIV-1: Outline

Structure
Introduction to the Biology of HIV-1: Outline

Genome

HIV-1 Genomic RNA

gag

vif

pol

vpr

env

vpu

tat

rev

nef

Introduction to the Biology of HIV-1: Outline

Structural Proteins

- Envelope
- Matrix
- Capsid
- Nucleocapsid
- p6
Introduction to the Biology of HIV-1: Outline

Enzymes

Protease
Reverse Transcriptase
Integrase
Accessory and Regulatory Proteins
Introduction to the Biology of HIV-1: Outline

- Structure
- Genome
- Structural Proteins
- Enzymes
- Accessory and Regulatory Proteins
HIV Structure
HIV = Human Immunodeficiency Virus
HIV Envelope

Envelope glycoprotein

Lipid Membrane
HIV Matrix Shell

Matrix proteins

100-150 nm

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Core (Capsid)

Core (capsid)

Capsid proteins

100-150 nm

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Nucleocapsid Complex

Illustration: Cognition Studio, Inc. and David H. Spach, MD

Nucleocapsid complex

100-150 nm
HIV Genome
HIV-1 Genome

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV-1 RNA Genome

Positive-sense, single strand RNA, ≈ 9,750 base pairs

LTR = long terminal repeat; U = unique; R = Repeat
HIV-1 Genome: 9 Genes

Illustration: David H. Spach, MD
HIV-1 Genome Contains 9 Genes that Encode 15 Viral Proteins

Illustration: David H. Spach, MD
HIV Proteins
HIV-1 Proteins (n = 15)

- Structural (6)
- Enzymes (3)
- Accessory (4)
- Regulatory (2)
<table>
<thead>
<tr>
<th>Structural (6)</th>
<th>Enzymes (3)</th>
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<tbody>
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Enzymes

Structural (6)
- gp120
- gp41
- Matrix (p17)
- Capsid (p24)
- Nucleocapsid (p7)
- p6

Enzymes (3)
- Protease
- Reverse Transcriptase
- Integrase

Accessory (4)

Regulatory (2)
## Accessory Proteins

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<tr>
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### Regulatory Proteins

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HIV-1 Proteins (n =15)

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HIV-1 Proteins by Relative Size (aa = amino acid)

- **Reverse Transcriptase**: 1,000 aa
- **Env (gp120/gp41)**: 835 aa
- **Integrase**: 288 aa
- **Capsid**: 231 aa
- **Nef**: 206 aa
- **Protease**: 198 aa
- **Vif**: 192 aa
- **Matrix**: 132 aa
- **Rev**: 116 aa
- **Vpr**: 96 aa
- **Tat**: 86-101 aa
- **Vpu**: 81 aa
- **Nucleocapsid**: 55 aa
- **P6**: 52 aa
HIV Structural Proteins
HIV Structural Proteins

Envelope (gp120/gp41)
Matrix (p17)
Capsid (p24)
Nucleocapsid (p7)
p6
HIV Envelope Glycoprotein
HIV Envelope Glycoprotein

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Envelope Glycoproteins: gp120 and gp41 Subunits

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Envelope Glycoprotein: Trimer Structure

Envelope Trimer

gp120 (surface)

HIV Membrane

gp41 (transmembrane)
HIV Envelope Glycoprotein: Trimer Structure

Trimer

gp120-gp41 pair

Noncovalent bond

gp120

gp41

Envelope Trimer

gp120 (surface)

HIV Membrane

gp41 (transmembrane)
HIV Envelope Glycoprotein: Regions Involved in Cell Entry

- CD4 Binding Region
- V3 Region
- gp120 (surface)
- gp41
- HIV Membrane
HIV Envelope Glycoprotein: Glycan Shield

Glycan Shield

gp120 (surface)

HIV Membrane

gp41 (transmembrane)
HIV Matrix (p17)
HIV Matrix

HIV Matrix (p17)

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Matrix: Monomer Structure

HIV Matrix Monomer

- N-terminal domain (NTD)
- C-terminal domain (CTD)

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Matrix: Basic Region

N-terminal domain (NTD)

Basic Region

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Matrix: Myristyl Group

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Matrix: Myristyl Group Sequestered Conformation

Sequestered Conformation

Myristyl Group

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HIV Matrix: Myristyl Group Exposed Conformation

Exosed Conformation

Myristyl Group
HIV Matrix: Membrane Bound Trimers

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HIV Matrix: Trimers Forming Matrix Shell

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HIV Matrix: Role Late in Viral Assembly

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HIV Matrix: Role Anchoring HIV Gag and Gag-Pol

Host Cell Membrane

Host Cell

HIV Gag

HIV Gag-Pol

Matrix

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Capsid (p24)
HIV Capsid and HIV Core
HIV Capsid: Monomer Structure

HIV Capsid Monomer

N-terminal domain (NTD)
Flexible Linker
C-terminal domain (CTD)
HIV Capsid: Hexamers and Pentamers

Illustration: Cognition Studio, Inc. and David H. Spach, MD

Capsid Hexamer

Capsid Pentamer
HIV Capsid: Hexamers and Pentamers

Illustration: Cognition Studio, Inc. and David H. Spach, MD

Capsid Hexamer

Capsid Pentamer

Capsid Hexamer

Capsid Pentamer
HIV Capsid: Cone-Shaped Structure of HIV Core

HIV Core (capsid)

Capsid Hexamer

Capsid Pentamer
HIV Core: Structural Barrier

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HIV Core: Role in Migration to Host Cell Nucleus
HIV Nucleocapsid (p7)
HIV Nucleocapsid (p7)

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Nucleocapsid (p7): HIV RNA Coating

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Nucleocapsid: Structure

HIV Nucleocapsid Monomer

N-terminal region

C-terminal region
HIV Nucleocapsid: Zinc-Binding Domains

HIV Nucleocapsid Monomer

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HIV Nucleocapsid: Complexed with HIV RNA
HIV Ribonucleoprotein Complex

HIV Genomic RNA + Nucleocapsid Proteins = Ribonucleoprotein Complex

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Ribonucleoprotein Complex with Integrase

HIV Genomic RNA + Nucleocapsid Proteins + Integrase = Ribonucleoprotein Complex

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Ribonucleoprotein Complex

Illustration: Cognition Studio, Inc. and David H. Spach, MD

(-) Integrase

(+) Integrase
HIV Nucleocapsid Protein: Role in Reverse Transcription

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HIV p6
HIV p6
HIV p6: Structure

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV p6: Role

Gag Polyproteins

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV p6: Role in HIV Budding
HIV p6: Role as Docking Site for Vpr

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HIV p6: Facilitates Incorporation of Vpr
HIV Enzymes
HIV Enzymes

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HIV Protease

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Homodimer Structure

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Structural Domains

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Active Site

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Conformations

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Polypeptide Cleavage

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Protease: Polypeptide Cleavage

HIV Gag

HIV Gag-PI

HIV Maturation

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HIV Reverse Transcriptase

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Reverse Transcriptase: Subunits

p66 subunit

p51 subunit
HIV Reverse Transcriptase: Enzymatic Domains

- Polymerase Domain
- Ribonuclease H (RNase H) Domain

p66 subunit

p51 subunit
HIV Reverse Transcriptase: Enzyme Active Sites

- Polymerase Active Site
- Ribonuclease H (RNase) Active Site
- p66 subunit
HIV Reverse Transcriptase: p66 Subunit Right Hand Structure

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Reverse Transcriptase: Reverse Transcription

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase
HIV Integrase: Component of Ribonucleoprotein Complex

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase: Complexes

Monomer ↔ Dimer ↔ Tetramer
HIV Integrase: Dimer Structure

C-terminal domain (CTD)

N-terminal domain (NTD)

Catalytic core domain (CCD)
HIV Integrase: Catalytic Core Domain

Catalytic triad (DDE)

Catalytic core domain (CCD)
HIV Integrase: Active Enzymatic Region

Active Enzymatic Region

Catalytic core domain (CCD)

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase: 3' Processing of HIV DNA

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase: 3′ Processing of HIV DNA

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Integrase: Strand Transfer

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Accessory and Regulatory Proteins
HIV Accessory Proteins

Vif  Vpr  Vpu  Nef
Viral Infectivity Factor (Vif)

Illustration: Cognition Studio, Inc. and David H. Spach, MD

Accessory Protein
Vif and Host Restriction Factor APOBEC3G

Accessory Protein

Vif

Host Restriction Factor

APOBEC3G

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APBOPEC3G Conversion of Cytosine to Uracil

Illustration: Cognition Studio, Inc. and David H. Spach, MD
APBOPEC3G-Induced Altered Base Pairing

Illustration: Cognition Studio, Inc. and David H. Spach, MD
APBOPEC3G-Induced “G to A” Hypermutation

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Vif: Clustering at Host Cell Membrane

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vif: Binding to APOBEC3G at Host Cell Membrane
Vif: Neutralizing Action of APOBEC3G

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Viral Protein R (Vpr)

Vpr

Accessory Protein
Vpr: Component of HIV Core

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpr: Role in HIV Reverse Transcription

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpr: Role in Nuclear Import

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Viral Protein U (Vpu)
Vpu and Host Restriction Factor Tetherin

Accessory Protein

Vpu

Host Restriction Factor

Tetherin (BST-2)

dimer

Notes: Vpu 81 aa; Tetherin 160 aa (dimer 320)
Tetherin: Prevention of Budding

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Tetherin: Synthesis in Endoplasmic Reticulum and Golgi

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Tetherin: Bound to Endoplasmic Reticulum Membrane

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Accumulation at Endoplasmic Reticulum Membrane

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Binding to Tetherin

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Destruction of Tetherin

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Blocked Recycling of Tetherin

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Neutralizing Action of Tetherin

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Vpu: Downregulation of Host Cell CD4 Receptor

CD4 Receptors

Cell Membrane

Cytosol

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Vpu and CD4 Interaction

CD4

Cytosol

Endoplasmic Reticulum

Vpu

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Interaction with Host CD4 Receptor

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Destruction of CD4 Molecule

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CD4 Trapping of HIV Envelope in Endoplasmic Reticulum

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Vpu: Production Correlates with Amount of CD4
Vpu Production: Reduces Amount of CD4

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Vpu: Augments HIV Envelope Migration to Cell Surface
Negative Regulatory Factor (Nef)
Nef: Myristyl Group

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Nef: Downregulation of Cellular Receptors

Illustration: Cognition Studio, Inc. and David H. Spach, MD

CD4 Receptor

CD8 Receptor

Cell Membrane
Cytosol
Nef: Binding to Host Cell Receptors

CD4 Receptor

CD8 Receptor

Cell Membrane

Cytosol

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Nef: Destruction of Host Cell Receptors

Illustration: Cognition Studio, Inc. and David H. Spach, MD
HIV Regulatory Proteins

HIV Transcription

Tat

HIV Translation

Rev
Transactivator of Transcription (Tat)
Latent Proviral HIV DNA

Host Cell Nucleus

HIV Proviral DNA

Host DNA

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Activation of Transcription

Host Cell Nucleus

- Host DNA
- Host cell RNA polymerase
- HIV Proviral DNA
- HIV genomic RNA
- HIV mRNA

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Tat: Activation of Transcription

Host Cell Nucleus

- Host cell RNA polymerase
- HIV Proviral DNA
- HIV Tat
- HIV genomic RNA
- HIV mRNA
- Host DNA

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Regulator of Expression of Virion Proteins (Rev)

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Rev: Early Synthesis

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Rev: Migration into Nucleus

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Rev: Enhanced Shuttling of mRNA to Cytoplasm

- Unspliced mRNA transcripts
- Partially-spliced mRNA transcripts

Illustration: Cognition Studio, Inc. and David H. Spach, MD
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