HIV/AIDS

Alice Long
Literature Talk
May 30th, 2023
HIV/AIDS

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What is HIV/AIDS?

HIV = human immunodeficiency virus, which is the virus that causes HIV infection.

AIDS = acquired immunodeficiency syndrome. AIDS is the most advanced stage of HIV infection.
Actue HIV Infection
early symptoms 2-4 weeks after first exposure

What is HIV/AIDS?
What is HIV/AIDS?

AIDS
CD4 levels decrease below 200 cells per cubic millimeter of blood

- Persistent High Fever Over 100 °F
- Night Sweats
- Mouth Ulcers
- Sore Throat
- Swollen Lymph Nodes
- Muscle Aches
- Rash
- Chills
- Fatigue
- Pneumonia
HIV vs AIDS

Acute phase:
- Primary infection
- Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs

Chronic phase:
- Clinical latency
- Constitutional symptoms
- Setpoint viral load

AIDS:
- Opportunistic diseases
- Death

CD4+ T lymphocyte count (cells/mm³) vs Weeks
HIV RNA copies per ml plasma vs Years
What is HIV/AIDS?

Estimated Number of AIDS-related deaths worldwide

<table>
<thead>
<tr>
<th>Year</th>
<th>1990</th>
<th>2000</th>
<th>2010</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>2,000,000</td>
<td>1,500,000</td>
<td>1,000,000</td>
<td>500,000</td>
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</tbody>
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HIV in 1980s
Lifespan upon exposure: 10-13 years

HIV in 2023
Lifespan upon exposure with proper treatment: normal lifespan

How did we get to this point?
1981
AIDS Gets Its Name
The CDC called the new disease acquired immune deficiency syndrome, or AIDS

1982
First Cases Recognized
CDC publishes a report from Los Angeles of five young homosexual men with fatal or life-threatening PCP pneumonia. Many had Kaposi’s sarcoma (KS)

1983
Scientists Discover HIV
Luc Montagnier and Francoise Barre-Sinoussi isolate a virus from the swollen lymph gland of someone with AIDS.

1985
Testing Begins
The FDA approves ELISA, the first commercial blood test for HIV. Blood banks began to screen donations.

1996
A Breakthrough?
U.S. AIDS deaths drop by more than 40%.

2001-2003
The Global Problem Grows
AIDS becomes the leading cause of death worldwide for people ages 15 to 59.

2006-2007
Treatment Works?
Researchers say HIV treatment is shown to extend life by 24 years — cost of $618,900.

2001-2003
President Bush announces the $15 billion President’s Emergency Plan for AIDS Relief.

2017
CDC announces that people living with HIV who are on treatment and have undetectable viral loads have effectively no risk of transmitting the virus to sexual partners.

U=Undetectable
History of HIV Drug Development

1987

Zidovudine (NRTI)

Didanosine (NRTI)

1991

Stavudine (NRTI)

Zalcitabine (NRTI)

1992-1994

Lamivudine (NRTI)

1995-1999

Saquinavir (PI)

1997

Stavudine (NRTI)

2013

Didanosine (NRTI)

7 HIV drug classes

Saquinavir (PI)

Dolutegravir (INSTI)

58 types of HIV medication
Treatment of HIV

1. Binding

2. Fusion

3. Reverse transcription

4. Integration

5. Transcription

6. Translation

7. Assembly

8. Budding

9. Release & Maturation

CCR5/CXCR4 Inhibitors

HIV

CD4

CCR5

Viral RNA

Viral DNA

Cytoplasm

Nucleus

Virus core structure
Mechanism of Action - Entry Inhibitors

1. The binding of HIV surface protein gp120 to the CD4 receptor
2. A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41
3. The binding of gp120 to a co-receptor CCR5

Maraviroc
CCR5 antagonist
(post attachment inhibitor)
Mechanism of Action - Entry Inhibitors

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**Diagram:**
- Attachment
- Hemi-fusion

**Key:***
- Attachment: gp41, CCR5, Cytoplasm, HIV
- Hemi-fusion: gp41, Host Cell, Cytoplasm
Mechanism of Action - Entry Inhibitors

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Mechanism of Action - Entry Inhibitors

**Attachment**

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**Hemi-fusion**

What drug would you develop to halt this process?
Mechanism of Action - Entry Inhibitors

1. The binding of HIV surface protein gp120 to the CD4 receptor

2. A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41

3. The binding of gp120 to a co-receptor CCR5

Attachment

Hemi-fusion

Enfuvirtide (36 Amino Acids)
Mechanism of Action - Entry Inhibitors

Attachment

1. The binding of HIV surface protein gp120 to the CD4 receptor
2. A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41
3. The binding of gp120 to a co-receptor CCR5

Hemi-fusion

Enfuvirtide (36 Amino Acids)
MW: 4492 g/mol
Entry Inhibitors - Drugs on the Market

Aplaviroc (GlaxoSmithKline)
Allosteric Modulator, $t_{1/2} = 100$ h
**Entry Inhibitors - Drugs on the Market**

**Aplaviroc (GlaxoSmithKline)**
Allosteric Modulator, $t_\frac{1}{2} = 100$ h
**Entry Inhibitors - Drugs on the Market**

Aplaviroc (GlaxoSmithKline)
- Allosteric Modulator, $t_{1/2} = 100$ h
- Failed early clinical trials
  - (Severe liver toxicity)

Vicriviroc (Schering-Plough)
- Failed Phase II clinical trials

Evaluated over 500,000 compounds
Assayed on the inhibition of MIP-1B binding to CCR5 receptor

Maraviroc (Pfizer)
- $IC_{50} = 0.2$ nM
- Antiviral $IC_{90} = 2$ nM
**Entry Inhibitors - Drugs on the Market**

Evaluated over 500,000 compounds

Assayed on the inhibition of MIP-1B binding to CCR5 receptor

Maraviroc (Pfizer)

$IC_{50} = 0.2 \text{ nM, } t_{1/2} = 14-18 \text{ h}$

Antiviral $IC_{90} = 2 \text{ nM}$
Treatment of HIV

1. Binding
2. Fusion
3. Reverse transcription
4. Integration
5. Transcription
6. Translation
7. Assembly
8. Budding
9. Release & Maturation

HIV
CD4
CCR5
CCR5/CXCR4 Inhibitors
NRTIs NNRTIs
Viral RNA
Viral DNA
Cytoplasm
Nucleus
Virus core structure
Mechanism of Action - NRTIs

- Viral RNA
- Proviral DNA
- Viral reverse transcriptase
Mechanism of Action - NRTIs

polymerization occurs from the free hydroxyl
Mechanism of Action - NRTIs

viral RNA

proviral DNA

viral reverse transcriptase

'spirational'

\[
\text{HO-} \text{N} \text{NH}_2
\]

\[
\text{NH}_2
\]
**Mechanism of Action - NRTIs**

- **Zidovudine**
  - 1987 FDA Approved

- **Didanosine**
  - 1991 FDA Approved

- **Stavudine**
  - 1994 FDA Approved

- **Lamivudine**
  - 1995 FDA Approved

- **Abacavir**
  - 1998 FDA Approved

- **Emtricitabine**
  - 2006 FDA Approved

- **Tenofovir**
  - 2001 FDA Approved

- **Zalcitabine**
  - Discontinued in 2006
Mechanism of Action - NRTIs

Lamivudine
1995 FDA Approved

Emtricitabine
2006 FDA Approved

Prof. Dennis C. Liotta
Emory University
Mechanism of Action - NRTIs

Lamivudine
1995 FDA Approved

Emtricitabine
2006 FDA Approved

18 life-saving FDA-approved drugs

How did this invention come to life?
Mechanism of Action - NRTIs

Prof. Dennis C. Liotta
Emory University

Lamivudine
1995 FDA Approved

Initial Hit: racemic
3’-thia-2’,3’-dideoxycytidine

Silylated Base
Lewis Acid
no facial selectivity

Prof. Dennis C. Liotta
Emory University
Mechanism of Action - NRTIs

Lamivudine
1995 FDA Approved

Initial Hit: racemic
3′-thia-2′,3′-dideoxycytidine

Syn
Anti

1:1 mixture of diastereomers

Prof. Dennis C. Liotta
Emory University
Lamivudine
1995 FDA Approved

Initial Hit: racemic 3′-thia-2′,3′-dideoxycytidine

Synthetic Route:
1) DIBAL-H
2) Ac₂O

1) (TMS)₂-cytosine SnCl₄
2) TBAF

β:α > 300:1

Prof. Dennis C. Liotta
Emory University
Mechanism of Action - NNRTIs

Reverse transcriptase

Allosteric inhibition of viral reverse transcriptase

Hydrophobic region

proviral DNA

viral RNA

viral reverse transcriptase

p66

p51
Despite chemical diversity, they all bind at the same site in the reverse transcriptase.

Each non-nucleoside reverse transcriptase inhibitor interacts with different amino acid residues.
**Mechanism of Action - NNRTIs**

Nevirapine

'butttterfly-like'

- 'Body': Hydrophilic center
- 'Wing 1': heteroaromatic
- 'Wing 2': phenyl or allyl substituent

Over 38 amino acid interactions
HIV Integrase

288 amino-acid protein

C-terminal domain

N-terminal domain

Catalytic core domain

Catalytic triad

divalent metal ions (Mg$^{2+}$ or Mn$^{2+}$)
HIV Integrase

288 amino-acid protein

C-terminal domain
N-terminal domain
Catalytic core domain

Mg$^{2+}$

E152  D64  D116
HIV Integrase

288 amino-acid protein

C-terminal domain

N-terminal domain

Catalytic core domain

Mg$^{2+}$

E152  D64  D116

Cytoplasm

Nucleus

Intasome formation

3' processing

Disassembly of strand transfer complex

Gap repair and integration into cellular genome
INTSIs

288 amino-acid protein

C-terminal domain
N-terminal domain
Catalytic core domain
Catalytic triad

Triad of coplanar oxygen atoms

Halogenated phenyl ring

1. Raltegravir
2. Dolutegravir
3. Bictegravir

E152  D64  D116

Mg$^{2+}$  Mg$^{2+}$
What is HIV/AIDS?

- **Estimated Number of AIDS-related deaths worldwide/US**

- **HIV in 1980s**
  - Lifespan upon exposure: 10-13 years

- **HIV in 2023**
  - Lifespan upon exposure with proper treatment: normal lifespan

- **How did we get to this point?**

**Introduction of highly active antiretroviral therapy**

- 1990
- 2000
- 2010
- 2020
HIV Assembly, Budding, and Maturation
Protease Inhibitors

Telaprevir
Back box warning

Darunavir
FDA 2006
Darunavir interacts with Asp25 and Asp25’

Simeprevir
FDA 2013

$K_d = 4.5 \times 10^{-12} \text{ M}$
Protease Inhibitors

Telaprevir
Back box warning

Darunavir
FDA 2006

Simeprevir
FDA 2013

> 12
FDA approved
Pis
Outlook

Modern Day

Daily dose of oral medication

Perpetual need to refill medication

Barriers to medical access

Daily pills

Hypothetical

One pill to cure
Is there a cure?

The New York Patient

Stem cell donors all carried two copies of CCR5 Δ32 which confers resistance to HIV.
5th person confirmed to be cured of HIV

The Dusseldorf patient is latest to be rid of HIV with no signs of return.

By Dr. Kaviya Sathyakumar

February 20, 2023, 11:01 AM

Is there a cure?

Do we need a cure?
Is there a cure?

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The Dusseldorf patient is latest to be rid of HIV with no signs of return.

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Do we need a cure?