Access to HIV, HBV, and HCV
Antiviral Agents Globally

John C. Martin, PhD
Gilead Sciences

William H. Prusoff HEP DART Lecture
Kona, Hawaii
December 4, 2017
Barcelona, 2004
Early HIV/AIDS Timeline

Rapid Development of AZT

- **1981** AIDS recognized, MMWR (CDC)
- **1983** HIV identified as cause of AIDS
- **1984** First method for testing potential drug candidates established
- **1985** AZT selective activity established
- **1986** First patient enrolled July 3, 1985
- **1987** Phase 2 study halted, September, 1986
- **1987** US FDA approved AZT, March, 1987

(a) Mitsuya et al., *Science*, 1984
(b) Mitsuya et al., *Proc. Natl. Acad. Sci. USA*, 1985
(c) Yarchoan et al., *Lancet*, 1986
(d) Fischl et al., *N. Engl. J. Med.*, 1987
HIV DART in San Diego, 2012
FDA Approval Dates, Dideoxynucleosides

- **AZT**
  - Zidovudine
  - March 19, 1987

- **ddI** (a)
  - Didanosine
  - October 9, 1991

- **ddC** (a)
  - Zalcitabine
  - June 19, 1992

- **d4T**
  - Stavudine
  - June 24, 1994

d4T, Stavudine Research


Synthesis of 2’,3’-dideoxynucleosides

- Didanosine (ddl, 1988)
- Stavudine (d4T, 1989)

References:
- Webb et al., *Nucleosides and Nucleotides*, 1988
Geometric Isomers of ddC, ddA, d4C and d4T

(b) Coates et al., *Antimicrob. Agents Chemother.*, 1992

L-ddC \(^{(a)}\) 3TC \(^{(b)}\) Lamivudine
Research on Nucleotide Analogues has Led to Major Advances in Antiviral Therapy
First Antiviral Isosteric Nucleotide Analogue

Ganciclovir

Ganciclovir Phosphate

Ganciclovir Phosphonate

Active against CMV

Martin et al., J. Med. Chem. 1983
Prisbe, Martin et al., J. Med. Chem., 1986
Nucleoside and Nucleotide Antivirals

- First step of activation requires viral kinase
- Short intracellular half-life

Nucleoside
Ganciclovir

Nucleotide
Tenofovir

- Bypasses first phosphorylation
- Extended intracellular retention
- Infrequent dosing

Martin et al., *J. Med. Chem.* 1983

De Clercq, Holý et al., *Nature*, 1986
NATO Conference in Italy, 1987
Selected Toxicities Associated with Mitochondrial Dysfunction*

- Peripheral neuritis/neuropathy
- Lipodystrophy
- Lactic acidosis

<table>
<thead>
<tr>
<th>Patients with Selected Toxicities</th>
<th>Week 48</th>
<th>Week 96</th>
<th>Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC + EFV</td>
<td>3%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>d4T + 3TC + EFV</td>
<td>10%</td>
<td>20%</td>
<td>28%</td>
</tr>
</tbody>
</table>

* Peripheral neuritis/neuropathy, lipodystrophy, lactic acidosis

† p < 0.001

Gallant et al., JAMA, 2004
Study 903 – TDF versus d4T

Change from Baseline in Body Weight

Gallant et al., *JAMA*, 2004
“Drug candidates are not high affinity ligands, they must have drug-like properties.”

Ron Borchardt, University of Kansas
### Prodrugs of Tenofovir

<table>
<thead>
<tr>
<th>Tenofovir</th>
<th>(parent nucleotide)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Tenofovir Structure" /></td>
<td><img src="image2" alt="Tenofovir Disoproxil Fumarate Structure" /></td>
</tr>
<tr>
<td><img src="image3" alt="Tenofovir Alafenamide Structure" /></td>
<td>Tenofovir Disoproxil Fumarate (prodrug) TDF, Viread®</td>
</tr>
<tr>
<td></td>
<td>Tenofovir Alafenamide (prodrug) TAF, Vemlidy®</td>
</tr>
</tbody>
</table>

Perspectives (2002) for Single Tablet Regimen - STR

• Need to treat more people for better health outcomes

• Improves compliance and reduces resistance development
  • Avoids partial regimens

• Treatment as a method of preventing transmission
L-Nucleoside Antiviral Drugs

- Higher affinity to HIV-RT
- More potent against HIV-1
- Longer intracellular half-life

HIV Regimen Simplification – Atripla®

1996

> 30 Pills a Day

2006

Approval of Atripla

1 Pill Once a Day

Single Tablet Regimen

STR

GILEAD


Bristol-Myers Squibb

Efavirenz (1998)

MERCK
## Tenofovir-Based HIV Antiretrovirals

<table>
<thead>
<tr>
<th>Product</th>
<th>Formula</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viread®</td>
<td>TDF</td>
<td>2001</td>
</tr>
<tr>
<td>Truvada®</td>
<td>FTC/TDF</td>
<td>2004</td>
</tr>
<tr>
<td>Atripla®</td>
<td>EFV/FTC/TDF</td>
<td>2006</td>
</tr>
<tr>
<td>Truvada®</td>
<td>FTC/TDF</td>
<td>2012</td>
</tr>
<tr>
<td>Stribild®</td>
<td>EVG/c/FTC/TDF</td>
<td>2012</td>
</tr>
<tr>
<td>Complera®</td>
<td>RPV/FTC/TDF</td>
<td>2012</td>
</tr>
<tr>
<td>Emtriva®</td>
<td>FTC</td>
<td>2003</td>
</tr>
<tr>
<td>Sustiva®</td>
<td>EFV</td>
<td>1998, BMS/Merck</td>
</tr>
<tr>
<td>Vitekta®</td>
<td>EVG</td>
<td>2014, JT</td>
</tr>
<tr>
<td>Tybost®</td>
<td>c</td>
<td>2014</td>
</tr>
<tr>
<td>Edurant®</td>
<td>RPV</td>
<td>2011, Tibotec/JNJ</td>
</tr>
</tbody>
</table>

### Additional Products

- **Genvoya®**: EVG/c/FTC/TAF 2015
- **Odefsey®**: RPV/FTC/TAF 2016
- **Descovy®**: FTC/TAF 2016
- **Bictegravir/FTC/TAF**: B/F/TAF Under Review

★ Single Tablet Regimen (STR) = One Pill Once Daily
### Progress in HIV Treatment - 1996

**HIV Patients in USA**

<table>
<thead>
<tr>
<th></th>
<th>1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>30-39</td>
</tr>
<tr>
<td>Male/Female</td>
<td>77% / 23%</td>
</tr>
<tr>
<td>Average Survival</td>
<td>19 years</td>
</tr>
<tr>
<td>Number of Pills/Day</td>
<td>25+</td>
</tr>
</tbody>
</table>

**1996**
Progress in HIV Treatment - 2016

<table>
<thead>
<tr>
<th>HIV Patients in USA</th>
<th>1996</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>30-39</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Male/Female</td>
<td>77% / 23%</td>
<td>76% / 24%</td>
</tr>
<tr>
<td>Average Survival</td>
<td>19 years</td>
<td>53 years</td>
</tr>
<tr>
<td>Number of Pills/Day</td>
<td>25+</td>
<td>1</td>
</tr>
</tbody>
</table>

Single Tablet Regimen (STR)
Early Treatment Initiation to Prevent Transmission and Preserve Health

- Prevention of HIV-1 Infection with early antiretroviral therapy
  - Study HPTN 052: 96% reduction in HIV transmission

- Reduction of risk of death or severe AIDS-related illness with early treatment
  - Study START and study TEMPRANO

- Better outcomes to patients and benefits society by reducing the number of new infections

• Truvada approved for reducing the risk of sexually acquired HIV infection (FDA, July 2012)

• PrEP using daily Truvada recommended by US PHS and CDC, WHO and UNAIDS
At the end of 2016, UNAIDS estimated:

- 36.7 million people globally were living with HIV
- 1.8 million people became newly infected with HIV
- 1.0 million people died from AIDS-related illnesses
- 19.5 million people were accessing antiretroviral therapy
> 90% of People Living with HIV Live in Developing Countries

Gilead Access and Emerging Countries Program

2003 ➔ 2006 ➔ 2011 ➔ 2017+

130+ Countries

- Country –by-country registration
- Branded products are offered at no-profit or discounted prices
- Manufacturer licensing partners offer generic products at further reduced prices
- Tier-pricing for middle-income countries

http://www.gilead.com/responsibility/developing-world-access
>11 million HIV patients receive Tenofovir-containing regimens worldwide

[Diagram showing the number of HIV patients receiving Tenofovir-containing regimens from 2006 to 2016, with a significant increase in 2016.]
Tenofovir Transformed the Care of HIV Patients

Nature paper on nucleotides

1986-1987
AZT

1994
d4T
Advent of HAART

1996

2001
TDF

2003
Atripla

2004
FTC

2006
Truvada

2012
STR as 1st Line (WHO)

2013
Truvada for PrEP

2015
Complera, Stribild

2016
Genvoya

2017
Odefsey

2018+
Descovy

> 11 million on tenofovir

B/F/TAF
HIV Stakeholders for the Developing World

**Procurement**
- The Global Fund
- FDA
- PEPFAR
- World Health Organization

**Clinical Studies**
- NIAID
- CDC (Centers for Disease Control and Prevention)
- Bill & Melinda Gates Foundation
- MRC (Medical Research Council)

**Improve Access**
- Médecins Sans Frontières (Doctors Without Borders)
- Medicines Patent Pool
- USAID

**Guidelines**
- World Health Organization
Nucleotide Antiretrovirals for HBV and HCV

HBV

- Hepsera®
  - ADV
  - 2002
- Viread®
  - TDF
  - 2008
- Vemlidy®
  - TAF
  - 2016

Sofobuvir
The First Nucleotide Prodrug for HCV

HCV
Sofosbuvir-Based Regimens

- Sovaldi®
  - SOF
  - 2013
- Harvoni®
  - LDV/SOF
  - 2014
- Epclusa®
  - SOF/VEL
  - 2016
- Vosevi®
  - SOF/VEL/VOX
  - 2017
HCV Products for 101 Developing Countries

- Gilead brand products are offered at discounted prices
- Gilead licensing partners offer generic products at further reduced prices
- Tier-pricing for middle-income countries

http://www.gilead.com/responsibility/developing-world-access
Licensing Partners Make Generic HCV Products

- Gilead partners received full technology transfer
- Required to manufacture to DCGI (India), WHO prequalification, EMA or FDA standards
- 11 manufacturers in India licensed to produce for 101 countries
- 3 manufacturers in Egypt and Pakistan licensed to produce only for in-country

http://www.gilead.com/responsibility/developing-world-access
Curing of HCV Infection Preserves Health

VA Cohort (n=62,354)
Started antivirals from 1999-2015 (IFN, IFA+DAA, or DAA)

- No evidence that DDA therapy increases HCC incidence
- Eradication of HCV associated with reduced risk of HCC, irrespective of regimen; 71% reduction by DAA
- HCC continue to occur in cirrhotic patients post SVR

Ioannou GN, et al. AASLD 2017, Washington DC. #73
Ioannou GN, et al. AASLD 2017, Washington DC. #142
### How Many Pills?

<table>
<thead>
<tr>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.5 million patients on treatment</td>
<td>71 million patients need treatment</td>
</tr>
<tr>
<td>1 pill/day</td>
<td>1 pill/day</td>
</tr>
<tr>
<td>365 pills/year for rest of life</td>
<td>84 pills for 12 weeks</td>
</tr>
<tr>
<td>7.1 billion pills in one year</td>
<td>6 billion pills</td>
</tr>
</tbody>
</table>
International Stakeholders for the Patients

**Product Procurement**
- Regulatory authorities
- Importers/Manufacturers
- Funders

**Strategic Plans for Treatment, Diagnosis and Prevention**
- National health ministries
- Public health organizations
- Reimbursement policy makers

**Patient Groups**

**Clinical and Implementation Studies**
- Academia
- Governmental health sciences institutes
- Public health organizations

**Treatment Guidelines**
- WHO
- Regional
- National
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