Disclosures

Learning Objectives:

• At the conclusion of this presentation, you will be able to:
  – Explain the 6 mechanistic classes of antiretroviral drugs to your patients.
  – Select the optimal number of antiretroviral drugs for an effective HIV treatment regimen for your patients.

Off-Label Disclosure

• I intend to discuss investigational antiretroviral agents in this presentation.
Goal of Antiretroviral Therapy

• To suppress HIV RNA (viral load level) as low as possible, for as long as possible

• To preserve or enhance immune function

• To delay clinical progression of HIV disease and prolong healthy survival
Estimated Numbers of AIDS Cases, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas

Note. Data have been adjusted for reporting delays.
Antiretroviral Drug Approval: 1987 - 2010

Number of approved drugs

AZT, ddI, ddC, d4T, 3TC, SQV, RTV, IDV, NFV, NVP, 3TC, SQV, EFV, ABC, LPV/r, TDF, ENF, ATV, FTC, FPV, DRV, TPV, RAL, MVC, ETR
Life Cycle of HIV

- Reverse transcriptase inhibitors
- Integrase inhibitors
- Protease inhibitors
- Fusion inhibitors
- Chemokine receptor inhibitors
- HIV entry inhibitors
- Nucleosides
- Non-nucleosides
Antiretroviral Drugs: 2010

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

NNRTIs
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)

protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 ant)

integrase inhibitors (IIs)
- raltegravir (RAL)
zidovudine (3’-azido-2’,3’-dideoxythymidine, AZT)
Reverse Transcriptase Mechanism (2)

Yarchoan NEJM 1987;316:557
adenosine

didanosine (ddl)

didanosine (ddI)

zalcitabine (ddC)
zalcitabine (ddC)

abacavir (ABC)

zidovudine (AZT)

thymidine

stavudine (d4T)

thymidine

tenofovir (TDF)
tenofovir (TDF)

emtricitabine (FTC)

guanine

didanosine (ddl)

zalcitabine (ddC)

abacavir (ABC)

zidovudine (AZT)

thymidine

tenofovir (TDF)

emtricitabine (FTC)
## Combination Therapy: 2 vs 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Avg CD&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Regimens</th>
<th>Results (2-3 yrs f/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 175</td>
<td>352</td>
<td>AZT, ddl, AZT/ddI, AZT/ddC</td>
<td>ddl, combos clinical benefit</td>
</tr>
<tr>
<td>(N=2467)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hammer, NEJM 1996</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta 1 &amp; 2</td>
<td>210</td>
<td>AZT, AZT/ddI, AZT/ddC</td>
<td>combos clinical benefit</td>
</tr>
<tr>
<td>(N=3308)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Delta Coord. Committee, Lancet, 1996</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPCRA 007</td>
<td>92</td>
<td>AZT, AZT/ddI, AZT/ddC</td>
<td>no difference</td>
</tr>
<tr>
<td>(N=1113)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Saravolatz, NEJM 1996</em></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
## Choice of Dual NRTIs

<table>
<thead>
<tr>
<th>Combo</th>
<th>DHHS</th>
<th>Dosing</th>
<th>Toxicities</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>preferred</td>
<td>1 tab qd</td>
<td>renal (rare)</td>
<td>TDF/FTC/EFV available</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>alternate</td>
<td>1 tab qd</td>
<td>HSR (5-8%)</td>
<td>B5701 testing; ↑MI</td>
</tr>
<tr>
<td>ddI + (FTC or 3TC)</td>
<td>alternate</td>
<td>2 tab qd</td>
<td>PN, pancreatitis</td>
<td>least clinical experience; ↑MI</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>alternate</td>
<td>1 tab bid</td>
<td>GI, anemia</td>
<td>longest clinical experience</td>
</tr>
<tr>
<td>d4T + 3TC</td>
<td>inferior to above</td>
<td>3 tab/bid</td>
<td>PN, pancreatitis, lipoatrophy</td>
<td>toxicity</td>
</tr>
</tbody>
</table>
Structures of NNRTI

- nevirapine (NVP)
- efavirenz (EFV)
- delavirdine (DLV)
- etravirine (ETR)
Reverse Transcriptase Enzyme

Reverse Transcriptase

Active Site

NNRTI binding site
Initial ART

**NNRTI-based regimens:**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>NVP</td>
</tr>
</tbody>
</table>

DHHS Guidelines, 12/1/09
Life Cycle of HIV: Later Steps

Immature Virion

HIV Protease Activity

Mature HIV Virion

CD4 Lymphocyte
HIV Aspartyl Protease Enzyme
<table>
<thead>
<tr>
<th>HIV Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saquinavir</strong></td>
</tr>
<tr>
<td><img src="#" alt="Saquinavir Structure" /></td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
</tr>
<tr>
<td><img src="#" alt="Ritonavir Structure" /></td>
</tr>
<tr>
<td><strong>Indinavir</strong></td>
</tr>
<tr>
<td><img src="#" alt="Indinavir Structure" /></td>
</tr>
<tr>
<td><strong>Nelfinavir</strong></td>
</tr>
<tr>
<td><img src="#" alt="Nelfinavir Structure" /></td>
</tr>
</tbody>
</table>
HIV Protease Inhibitors (2)

amprenavir (APV)

lopinavir (LPV)

atazanavir (ATV)

fosamprenavir (FPV)
HIV Protease Inhibitors (3)

tipranavir (TPV)  darunavir (DRV)
## Combination Therapy: 3 vs. 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens</th>
<th>Results (1 yr f/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRK 035</td>
<td>AZT/3TC vs. IDV AZT/3TC/IDV</td>
<td>3-drugs: ~80% HIV RNA &lt;500 cps/ml (compared to 30-45%)</td>
</tr>
<tr>
<td>(N=97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Gulick, NEJM 1997</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTG 320</td>
<td>AZT/3TC vs. AZT/3TC/IDV</td>
<td>3-drugs reduced AIDS/death by ~50%</td>
</tr>
<tr>
<td>(N=1156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hammer, NEJM 1997</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 511</td>
<td>AZT/3TC vs. AZT/3TC/NFV</td>
<td>3-drugs: ~75% HIV RNA &lt;400 cps/ml (compared to 37%)</td>
</tr>
<tr>
<td>(N=297)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Saag, AIDS 2001</em></td>
<td></td>
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</tbody>
</table>
### Initial ART

**PI-based regimens:**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRV/r</td>
</tr>
<tr>
<td>Alternative</td>
<td>FPV/r</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td>SQV/r</td>
</tr>
<tr>
<td>Acceptable</td>
<td>ATV</td>
</tr>
</tbody>
</table>

DHHS Guidelines, 12/1/09
Antiretroviral Activity: 1987-1997

1987: AZT monotherapy

1994: 2-drug ART

1997: 3-drug ART

HIV RNA change (log₁₀ c/mL)

6 month responses

Fischl NEJM 1987

Eron NEJM 1995

Hammer NEJM 1996

Gulick NEJM 1997

Montaner JAMA 1998
Study 903E: TDF+3TC+EFV

81%

Durability of ART: 7 years

Figure 3. Proportion with HIV-1 RNA < 50 c/mL Through 7 Years (M=F)

Figure 4. Mean Change from Baseline in CD4 Through 7 Years

Cassetti
HIV Clin Trials
2007;8:164-72;
IAS 2008 abstract
#TuPE0057
3-Drug Combination ART: 2006

TDF/FTC/EFV
ART Response: Clinical Cohorts

ART Cohort collaboration
May, AIDS 2007;21:1185
12 HIV clinical cohort studies in Europe and North America
16167 individuals starting ≥3 drug ART
76% had HIV RNA <500 cps/ml at 6 months

Antiretrovirals in Lower Income Countries (ART-LINC)
Braitstein, Lancet 2006;367:817
18 ART programs in Africa, Asia, South America
4810 individuals starting ≥3 drug ART
76% had HIV RNA <500 cps/ml at 6 months
Antiretroviral Drug Approval:
1987 - 2010

Number of approved drugs
HIV Entry Mechanism

1. CD4 Attachment

2. Co-receptor interaction

3a. Anchorage

3b. coil-coil interaction

3c. Fusion Complete

CCR5 or CXCR4

Cell

Chemokine Receptor Inhibitors

Fusion Inhibitors

HIV

gp41

gp120

CD4

CXCR4

CCR5

HIV

HIV

HIV

HIV

HIV

HIV

HIV
**R5 viruses**
- a.k.a. M-tropic, **NSI**
- Transmitted variants
- Prevalent in early disease

**X4 viruses**
- a.k.a. T-tropic, **SI**
- Can emerge in late disease
- Associated with rapid CD4+ decline and progression

Dual-tropic viruses use **CCR5** or **CXCR4** (in vitro)
Virus uses CCR5 co-receptors to enter the CD4+ cell.

Activity of CCR5 antagonist anticipated?

- YES
- NO
HIV Integrase Mechanism

1. Assembly on Viral DNA in a Nucleoprotein Complex

2. In-Dependent Processing of 3'Ends

Viral DNA Synthesis

Nuclear Entry

Nuclear Membrane

Gap Repair

Mature Provirus

3a. Target DNA Binding

3b. Concerted Target DNA Cleavage and Joining

Strand Transfer Inhibitors
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETR exp. access</strong></td>
<td>206 treatment-experienced pts.</td>
<td>HIV RNA &lt;75 in 132/206 (64%) 48 weeks</td>
</tr>
<tr>
<td>Towner JAIDS 2010;53:614</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spain cohort</strong></td>
<td>32 treatment-experienced pts., no prior DRV/r</td>
<td>HIV RNA &lt;50 in 30/32 (94%) 24 weeks</td>
</tr>
<tr>
<td>Imaz JAIDS 2009;52:382</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRIO (ANRS 139)</strong></td>
<td>103 pts with NNRTI + PI resistance, no prior DRV/r, ETR, RAL; could use NRTI or ENF</td>
<td>HIV RNA &lt;50 in 93/103 (90%) 24 weeks; 89/103 (86%) 48 weeks</td>
</tr>
<tr>
<td>Yazdanpanah CID 2009;49:1441</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Survival: CASCADE Cohort
23 cohorts from Australia, Europe and Canada

Figure. Reduction in All-Cause Mortality pre-1996 to 2006 and Comparison With That of the General Population, by Age Group

Bhaskaran, JAMA 2008; 300: 51-59
ART 2010: Conclusions

• ART suppresses HIV RNA, improves immune function, decreases disease progression and prolongs survival.
• There are 25 approved antiretroviral drugs in 6 mechanistic classes.
• A majority of patients achieve durable suppression of HIV RNA, increased CD4, decreased clinical progression, and prolonged survival.
• Further research is needed.
Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Medical College of Cornell University
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!