HIV and HIV chemotherapy

Adapté des exposés

• de la Chaire Franqui 2003
  "Antiviral drugs and Discoveries in Medicine"
  Prof. E. De Clercq, KU-Leuven
  http://www.md.ucl.ac.be/chaire-francqui/
• du Dr J. Nachega, Johns Hopkins University
donné à l’Ecole de Pharmacie en 2003
Adults and children estimated to be living with HIV/AIDS as of end 2002

- Western Europe & Central Asia: 570,000
- North Africa & Middle East: 550,000
- Sub-Saharan Africa: 29.4 million
- Eastern Europe & Central Asia: 1.2 million
- South & South-East Asia: 6 million
- East Asia & Pacific: 1.2 million
- Latin America: 1.5 million
- Caribbean: 440,000
- North America: 980,000
- Australia & New Zealand: 15,000
- 42 million
Estimated number of adults and children newly infected with HIV during 2002

- Western Europe & Central Asia: 250,000
- Eastern Asia & Pacific: 270,000
- East Asia & South-East Asia: 700,000
- Australia & New Zealand: 500
- North America & Caribbean: 105,000
- Latin America: 150,000
- Sub-Saharan Africa: 3,500,000
- North Africa & Middle East: 83,000
- North America: 45,000
- Caribbean: 60,000

Total: 5 million
Estimated adults and child deaths due to HIV/AIDS during 2002

- Western Europe & Central Asia: 8,000
- North Africa & Middle East: 37,000
- Sub-Saharan Africa: 2.4 million
- Eastern Europe & Central Asia: 25,000
- East Asia & Pacific: 45,000
- South & South-East Asia: 440,000
- Latin America: 60,000
- Caribbean: 42,000
- North America: 15,000
- Australia & New Zealand: <100
- South & South-East Asia: 440,000

Total: 3.1 million
Progress update on the global response to the AIDS epidemic, 2004

- AIDS epidemic continues to expand; vulnerable populations at greatest risk
- Sub-Saharan Africa is most heavily affected
- Diverse epidemics are under way in Eastern Europe and Central Asia. Injecting drug use is the main driving force behind epidemics across the region.
- In many high-income countries, sex between men plays an important role in the epidemic.
- Drug injecting accounted for more than 10% of all reported HIV infections in Western Europe

Source: UNAIDS
Progress update on the global response to the AIDS epidemic, 2004
## Leading causes of death in Africa, 2001

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV/AIDS</td>
<td>20.6</td>
</tr>
<tr>
<td>2</td>
<td>Acute lower respiratory infections</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>Malaria</td>
<td>9.1</td>
</tr>
<tr>
<td>4</td>
<td>Diarrhoeal diseases</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>Perinatal conditions</td>
<td>5.9</td>
</tr>
<tr>
<td>6</td>
<td>Measles</td>
<td>4.9</td>
</tr>
<tr>
<td>7</td>
<td>Tuberculosis</td>
<td>3.4</td>
</tr>
<tr>
<td>8</td>
<td>Cerebrovascular disease</td>
<td>3.2</td>
</tr>
<tr>
<td>9</td>
<td>Ischaemic heart disease</td>
<td>3.0</td>
</tr>
<tr>
<td>10</td>
<td>Maternal conditions</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Natural History of HIV disease
HIV-1 Life Cycle
HIV Receptors
Mucosal Entry HIV

A. Inhibition of Incoming Virus
- IgG
- Virus
- M cell

- Mucosal epithelium
- Lymphocyte

B. Limitation of Systemic Spread
- Lymphocyte
- M cell

- Mucosal epithelium
- Lymphatic system
- Blood vessel

HIV 19/03/2005
HIV Binding

Fusion domain
HIV Drug Targets

HIV

Entry inhibitor

Reverse-transcriptase inhibitor

Integrase inhibitor

Protease inhibitor

Mature HIV
HIV Therapeutic Possibilities

- Successful Therapy
- Salvage Therapy
- Unsuccessful Therapy

Plasma HIV RNA (copies/ml)

Week

0 4 8 12 16 20 24 28 32 36 40 44 48 52

HIV 19/03/2005
AIDS definition - CDC

- CD4 < 200 / mm3 or
- AIDS-defining illness
  - Candidiasis
  - Cervical cancer
  - Coccidiodomycosis
  - Cryptococcosis
  - Cryptosporidiosis
  - CMV
  - HSV > 1 month
  - Histoplasmosis
  - HIV-related dementia
  - HIV wasting
  - Isoporosis
  - Kaposi’s sarcoma
  - Burkitts Lymphoma
  - NH Lymphoma
  - MAI - disseminated
  - MTb
  - Nocardia
  - PCP
  - Bacterial PNA (>2 in 12 mos)
  - PML
  - Salmonella septicemia
  - Strongyloidosis
  - Toxoplasmosis
WHO Staging System

- **Clinical Stage I**
  - Asymptomatic
  - Persistent Generalized Lymphadenopathy
  - Performance scale - 1

- **Clinical Stage II**
  - Weight loss < 10% body wt
  - Minor skin manifestations
  - HSV
  - Recurrent URI
  - Performance scale - 2

- **Clinical Stage III**
  - Weight loss > 10% body wt
  - Chronic diarrhea
  - Fever
  - Thrush, OHL, Pulmonary TB
  - Severe bacterial infections
  - Performance scale - 3

- **Clinical Stage IV**
  - AIDS by CDC definition
  - HIV wasting syndrome
  - Disseminated mycosis
  - HIV encephalopathy
  - Performance scale - 4
Primary HIV Infection
Varicella-Zoster Infection
Oral Candidiasis (Thrush) vs. Oral Hairy Leukoplakia (OHL)
AIDS related Tuberculosis
Pneumocystis Carinii Pneumonia
Cerebral Toxoplasmosis: CAT-SCAN
Kaposi Sarcoma
Cerebral Toxoplasmosis: MRI
Prevention vs. Rx

To Fight AIDS, Use Both Treatment and Prevention
Prevalence among pregnant women, outside major urban areas, Uganda

HIV Prevalence (%)

Source: Uganda National AIDS Programme
HIV prevalence and reported consistent condom use among female sex workers, Abidjan, Côte d'Ivoire, 1992-1998

Source: Ghys PD et al. (2002) AIDS
Patent Rights vs. Patient Rights

Stop Drug Company Profiteering
Treat HIV/AIDS
‘Aids drugs made me well again’

LYNN ALTMANN and JO-ANNE SMITHERHAM

DOCTORS gave Matthew Damane just a few years to live after he was diagnosed with HIV, the virus that causes Aids, in 1997.

At that time, life-saving Aids medicines, widely available in the West, were too expensive for poor people in countries like South Africa.

The brand-name medicines, which cost R1 400 a month, even with discounts offered by drug companies, are still too expensive.

But Damane, 25, from Khayelitsha, has had access to less expensive generic versions, imported from Brazil, and he credits the drugs with restoring his health.

“I am now well,” he told a packed news conference in Johannesburg yesterday as he held up a plastic pill box. It has one pill compartment for each day of the week, helping him to take his Aids medicines on schedule.

Damane, a nervous smile showing under his blue base-

activist groups announced it had imported the medicines from Brazil in violation of drug company patent rights but with the full blessing of the Medicines Control Council (MCC).

Citing preliminary results from a pilot project in Khayelitsha, the activists said the Aids drugs had reduced the presence of the virus in people’s bloodstreams to undetectable levels after less than one year of treatment. They said patients were getting off their deathbeds and returning to productive work and family lives.

“We literally resuscitated people,” said Eric Goemaere, who heads the Aids clinic run by Medicins Sans Frontieres (MSF) in Khayelitsha.

The preliminary results of the Khayelitsha pilot study – which has reported findings for 86 patients taking the Aids medicines – are the first evidence from a township clinic in South Africa that the Aids drugs can be taken on a long-term basis and can have the same dramatic effect in improving health as they have had in industrialised countries.

The government did not comment on the activists’ calls. It said the MCC would check whether the Brazilian import was legal.

The drug companies that own the patent rights to the drugs do not have plans to sue the activists. Peter Moore, medical director at GlaxoSmithKline, said the company would wait for the MCC to act.

Boehringer-Ingelheim spokesman Kevin McKenna said he was not surprised at the developments.

“I don’t think we’re falling off our chairs at the moment.”
Pharmacists have assumed an increasingly important role in monitoring and fine-tuning HIV drug therapy for maximal effectiveness.

**Current Concepts in HIV/AIDS Pharmacotherapy**

Pharmacists have assumed an increasingly important role in monitoring and fine-tuning HIV drug therapy for maximal effectiveness.
HIV REPLICATIVE CYCLE

1. Virus adsorption
2. Virus-cell fusion
3. Virus uncoating
4. Reverse transcription
5. Proviral DNA integration
6. Proviral DNA replication
7. Proviral DNA transcription to viral mRNA
8. Viral mRNA translation to viral precursor proteins
9. Maturation (proteolysis/myristoylation/glycosylation)
10. Budding (Assembly/Release)
VIRUS ADSORPTION

Suramin
HIV REPLICATIVE CYCLE

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VIRUS-CELL FUSION

TAK-779

SCH-C
(SCH-351125)
Inhibiteur de fusion: l'enfuvirtide
Inhibiteur de fusion: l'enfuvirtide

The extracellular domain of gp41 contains a fusion peptide (FP) and 2 helical regions (HRs), HR1 and HR2. The FP region is made up of hydrophobic, glycine-rich residues essential for initiation of penetration into target cell membranes [1, 3, 4]. When fusion occurs, FP inserts into the target cell membrane, and HR1 and HR2 alter their conformation to form a 6-helix structure. The process results in the formation of a fusion pore through which the HIV capsid passes into the CD4+ cell.

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106
ENF is a synthetic peptide corresponding to the 36-aa sequence of the HR2 domain in gp41. ENF binds to the HR1 domain in the gp41 subunit of the viral envelope protein, which prevents the formation of the 6-helix structure and interferes with the conformational changes required for membrane fusion. ENF, in effect, binds to a structural intermediate of the fusion process, which impedes the transition of gp41 into a fusion-active state.

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106
Clinical uses of entifurvide

- must be used in combination with other antiretrovirals
- lack a bioavailable oral formulation (repeated subcutaneous injections are necessary)
- Therefore, use is restricted to patients with advanced disease who have few remaining antiretroviral treatment options (deep-salvage therapy)

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106
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Zidovudine

3’-Azido-2’,3’-dideoxythymidine

AZT
Didanosine (DDI)

2’,3’-Dideoxyinosine

2’,3’-Didehydro-2’,3’-dideoxythymidine (D4T)

Didanosine (DDI)
Lamivudine
2’,3’-Dideoxy-3’-thiacytidine
3TC

Zalcitabine
2’,3’-Dideoxycytidine
DDC

Abacavir
1592U89
Mechanism of action of 2’,3’-dideoxynucleoside analogues, as exemplified for AZT

AZT

AZT-MP

AZT-DP

AZT-TP

dThd kinase

dTMP kinase

NDP kinase

REVERSE TRANSCRIPTASE

DNA

RNA
Emtricitabine

2',3'-dideoxy-3'-thia-5-fluorocytidine

(±)2’-deoxy-3’-oxa-4’-thiacytidine (dOTC)

FdOTC
\[ R = H : \text{PMEA} \]
\[ R = H : \text{TFV-PMEA} \]

**adezovir**

**tenofovir**
Mechanism of action of adefovir (PMEA)

Similar mechanism of action applicable to tenofovir (PMPA)
bis(POC)-PMPA
Tenofovir disoproxil
Viread®
HIV Reverse Transcriptase

- Binding site for NRTIs and NtRTIs
- Thumb
- Fingers
- Palm
- RNase H
- p51
- Connection
U-90152S
Delavirdine

Nevirapine
BI-RG-587

Benzoxazinone
Efavirenz
Structures of classical NNRTI’s, ...
HIV RT genetic variability after drug pressure (N = 30,000)
HIV REPLICATIVE CYCLE

- Virus adsorption
- Virus-cell fusion
- Virus uncoating
- Reverse transcription
- Proviral DNA integration
- Proviral DNA replication
- Proviral DNA transcription to viral mRNA
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- Maturation (proteolysis/myristoylation/glycosylation)
- Budding (Assembly/Release)
Processing of peptide synthetized by the HIV genome

• Retrovirally encoded proteases are responsible for the maturation of immature viral particles yielding mature, infectious virus.
• This is done by self-activation of the protease (PR) from a larger viral gag-PR-(pol) protein (zymogen) precursor and subsequent processing of the viral reverse transcriptase (RT) and integrase (IN), and the gag protein precursor into mature gag proteins.
• Blocking this proteolytic process results in production of immature, non-infective virions.
• **All retroviral proteases are aspartic-type proteases and act on a Phe-Pro scissile bond of the gag/pol gene polyprotein product.**
Lien Phe-Pro et aspartate protease ...

![Chemical structures](image)
Mechanism of aspartate protease and typical inhibitor (pepstatin)

Pepstatine...
Ritonavir
HIV protease
HIV protease
HIV protease
HIV protease
MUTATIONS IN THE HIV PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS (PIs)

<table>
<thead>
<tr>
<th>Multi-Pl Resistance: Accumulation of Mutations</th>
<th>L</th>
<th>M</th>
<th>I</th>
<th>V</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>46</td>
<td>54</td>
<td>82</td>
<td>84</td>
<td>90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indinavir</th>
<th>10 20 24 32 36 46 54 71 73 77 82 84 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L K L V M M I A G V V I L</td>
</tr>
<tr>
<td>10</td>
<td>M R I I I L V V S I A V M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ritonavir</th>
<th>10 20 32 33 36 46 54 71 77 82 84 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L K V L M M I A V V I L</td>
</tr>
<tr>
<td>10</td>
<td>M R I F I L V V T I A V M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Saquinavir</th>
<th>10 48 54 71 73 77 82 84 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L G I A G V V I L</td>
</tr>
<tr>
<td>10</td>
<td>V V V V S I A V M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nelfinavir</th>
<th>10 30 36 46 71 77 82 84 88 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L D M M A V V I N L</td>
</tr>
<tr>
<td>10</td>
<td>F N I I I L V T I A V D M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amprenavir</th>
<th>10 32 46 47 50 54 73 84 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L V M I I I G I L</td>
</tr>
<tr>
<td>10</td>
<td>F I I V V V V S V M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lopinavir/ Ritonavir</th>
<th>10 20 24 32 33 46 47 50 53 54 63 71 73 82 84 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>L K L V L M I F I L A G V V I L</td>
</tr>
<tr>
<td>10</td>
<td>M R I F I L V V L V F V S A V M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atazanavir (expanded access)</th>
<th>32 46 50 54 71 82 84 88 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>V M I I A V V I N L</td>
</tr>
<tr>
<td>32</td>
<td>I I L L V A V S M</td>
</tr>
</tbody>
</table>
HIV protease gene diversity matrix
HIV protease genetic variability after PI drug pressure (N = 30,000)
Interférences médicamenteuses et inhibiteurs de protéase ...

- Cette protéase doit scinder un lien Phe-Pro
- Les inhibiteurs miment donc tous une Phe...
La plupart des médicaments (et autres substances) à noyau aromatique sont métabolisées en dérivés hydroxylés, ce qui est essentiel pour leur élimination.

- phénytoïne (antépileptique)
- phénobarvital (sédatif)
- propranololol (antihypertenseur)
- phénylbutazone (antiinflammatoire)
- éthinyloestradiol (hormone)
- dicoumarol (anticoagulant)
- ...

Par leur noyau aromatique (essentiel pour l'activité !!), les inhibiteurs de protéase entrent en compétition avec ces médicaments (et bien d'autres)

- il vont ralentir leur élimination, et, dès lors
- créer un risque d'intoxication par excès …
NRTIs
- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir

NNRTIs
- Nevirapine
- Delavirdine
- Efavirenz

PIs
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
NRTIs
Zidovudine
Didanosine
Zalcitabine
Stavudine
Lamivudine
Abacavir

NNRTIs
Nevirapine
Delavirdine
Efavirenz

PIs
Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprenavir
Lopinavir

NtRTIs
Tenofovir
Anti-retroviral Therapy (ART): When to initiate treatment - CDC Guidelines

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 count</th>
<th>HIV RNA VL</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic/AIDS</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic AIDS</td>
<td>&lt;200 /mm3</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-350 /mm3</td>
<td>Any value</td>
<td>Offer treatment; controversial</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt; 350 /mm3</td>
<td>&gt;55,000</td>
<td>Some would initiate or follow CD4/VL closely</td>
</tr>
<tr>
<td></td>
<td>&gt;350 /mm3</td>
<td>&lt;55,000</td>
<td>Many defer and observe as 3 yr risk AIDS &lt;15%</td>
</tr>
<tr>
<td>Acute HIV infection</td>
<td>Any value</td>
<td>Any value</td>
<td>Offer treatment</td>
</tr>
</tbody>
</table>
Anti-retroviral Therapy (ART): When to initiate treatment - WHO guidelines

- WHO stage IV (AIDS-defining diagnosis), regardless of CD4 count

- CD4 available: WHO stage I, II, III and CD4 < 200 cells/mm³

- CD4 not available: WHO stage II, III (symptomatic HIV) plus absolute lymphocyte count < 1200/mm³
Anti-retroviral Therapy (ART): Goals of Treatment

- Decrease viral load (0.5-0.75 log10) within 4 weeks or
- Decrease in viral load 1 log 10 in 8 weeks
- Undetectable VL (<50 or <20 copies) at 4-6 months
- Restoration or preservation of immune function
- Reduction of HIV related morbidity and mortality
## Anti-Retrovirals

### Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CDC Group</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Group A</td>
<td>300 mg bid</td>
<td>Hypersensitivity rxn, fever, rash, lactic acid</td>
</tr>
<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>Group B</td>
<td>200 mg tid, 300 mg bid</td>
<td>BM supp, anemia, GI, LA, HA, insomnia</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Group B</td>
<td>40 mg bid, 30 mg bid</td>
<td>Pancreatitis, LA w/ steatohep, neuropathy</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Group B</td>
<td>150 mg bid</td>
<td>LA w/ steatohepatitis</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Group B</td>
<td>200 mg bid, 400 mg qd</td>
<td>Pancreatitis, neuropathy, GI, LA w/ steatohepatitis</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>Group B</td>
<td>0.75 mg qd</td>
<td>Neuropathy, stomatitis, LA</td>
</tr>
</tbody>
</table>
## Anti-Retrovirals

### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>Combivir</td>
<td>1 tab bid</td>
<td>Same as AZT, 3TC</td>
</tr>
<tr>
<td>AZT + 3TC + ABC</td>
<td>Trizivir</td>
<td>1 tab bid</td>
<td>Same as AZT, 3TC, ABC</td>
</tr>
</tbody>
</table>

### Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

| Tenofovir (TDF)     | Group A | 300 mg qd | No renal toxicity; limited expanded access |
## Anti-Retrovirals

**Non-nucleotide Reverse Transcriptase Inhibitors (NNRTIs)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV)</td>
<td>Sustiva</td>
<td>600 mg qhs</td>
<td>Rash, CNS, hepatitis, induce, inhibits P450</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Viramune</td>
<td>200 mg bid</td>
<td>Rash, elevated LFTs, hepatitis, induce P450</td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>Rescriptor</td>
<td>400 mg tid</td>
<td>Rash, elevated LFTs, HA, inhibits P450</td>
</tr>
</tbody>
</table>
### Anti-Retrovirals

**Protease Inhibitors (PIs)**

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<th>Drug</th>
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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir (SQV)</td>
<td>Inivirase</td>
<td>400 mg bid w/ ritonavir</td>
<td>GI intolerance, N/D/HA</td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>Fortovase</td>
<td>1200 mg tid</td>
<td>Elevated LFTs, fat redistn, DM</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
<td>600 mg q12</td>
<td>GI, N/V/D, hepatitis, pancreatitis, incr lipids, DM, fat redistn, neuro</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
<td>1250 mg bid 750 mg tid</td>
<td>D/N, DM, Fat redistn, Lipids abnl</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>800 mg q8h</td>
<td>Nephrolithiasis, GI intol, N, HA, incr LFTs, DM, fat redistn, elevated LFTs</td>
</tr>
<tr>
<td>Lopinavir + Ritonavir</td>
<td>Kaletra</td>
<td>400 mg lop+ 100 mg rit bid</td>
<td>GI, N/V/D, DM, fat redistn, elevated LFTs</td>
</tr>
<tr>
<td>Amprenavir (APV)</td>
<td>Agenerase</td>
<td>1200 mg bid</td>
<td>GI, N/V/D, rash, DM, fat redistn, LFTs, Lipid</td>
</tr>
</tbody>
</table>
Anti-Retrovirals: Strongly Recommended Regimens

- **Group A**
  - Efavirenz
  - Indinavir
  - Nelfinavir
  - Ritonavir + Indinavir
  - Ritonavir + Lopinavir
  - Ritonavir + Saquinavir

- **Group B**
  - Didanosine + Lamuvidine
  - Stavudine + Didanosine
  - Stavudine + Lamuvidine
  - Zidovudine + Didanosine
  - Zidovudine + Lamivudine
Anti-Retrovirals

CDC Recommended Regimens

- Combine one from Group A and one from Group B
- No mono or dual therapies
- Class sparing regimens:
  - 2 NRTI + NNRTI
  - 3 NRTI
  - 2 NRTI + 1 or 2 PI
- If previous treatment, consider resistance testing prior to initiating treatment
### Anti-retroviral Therapy: WHO Guidelines for Resource Limited Settings

<table>
<thead>
<tr>
<th>NsRTIs</th>
<th>NtRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (ZDV, AZT)</td>
<td>Tenofovir (TDF)</td>
<td>Nevirapine (NVP)</td>
<td>Saquinavir (SQV)</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td></td>
<td>Efavirenz (EFV)</td>
<td>Ritonivir (RTV)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
<td>Indinavir (IDV)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td></td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td></td>
<td></td>
<td>Lopinavir/ritonavir (LPV/r)</td>
</tr>
</tbody>
</table>

**Notes:**
- NsRTIs: Nucleoside Reverse Transcriptase Inhibitors
- NtRTIs: Nucleotide Reverse Transcriptase Inhibitors
- NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors
- PIs: Protease Inhibitors
Anti-retroviral Therapy (ART): First Line agents in resource limited settings

- 2 nucleoside analogs + NNRT or PI
- Examples starting regimen:
  - Abacavir regimen: AZT/3TC/ABC
    - trizavir - one pill bid
  - NNRTI regimen: AZT/3TC/EFZ or AZT/3TC/ NVP (NVP in pregnancy)
  - PI regimen: AZT/3TC + one of IDV/RTV, SQV/RTV, or NFV
Prevention of Mother-to-Child Transmission: Resource Limited Settings

- Short course ARV regimens for prevention of MTCT can be associated with ARV resistance
  - Most often seen with Nevirapine and 3TC

- Suggested Regimens:
  - AZT or AZT/3TC - continued through delivery
  - Nevirapine - one dose to mother & child

- PIs do not cross placenta

- d4T/ddI *not* recommended during pregnancy due to side effects (lactic acidosis/steatohepatitis)
Antiretroviral Therapy
Adherence Support

- One-on-one support
  - Counselling
  - Treatment assistant (self-selected)
  - Home visits

- Peer support
  - Support groups composed of people on ART

- Adherence materials
  - Pill box (with customized packing instructions)
  - Daily schedule
  - Self-monitoring form
Antiretroviral Therapy
Adherence Support
## Opportunistic Infections & Complications by CD4 Count

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Infectious</th>
<th>Non-Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500/mm³</td>
<td>Acute HIV</td>
<td>PGL</td>
</tr>
<tr>
<td></td>
<td>Candidal vaginitis</td>
<td>GBS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myopathy</td>
</tr>
<tr>
<td>200-500/ mm³</td>
<td>Pneumococcal PNA</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td></td>
<td>Pulm Tb</td>
<td>CIN</td>
</tr>
<tr>
<td></td>
<td>Zoster</td>
<td>Cervical Cancer</td>
</tr>
<tr>
<td></td>
<td>Thrush</td>
<td>B-cell Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Crytosporidiosis</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>KS</td>
<td>Mononeuronal multiplex</td>
</tr>
<tr>
<td></td>
<td>OHL</td>
<td>ITP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hodkin’s Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIP</td>
</tr>
</tbody>
</table>
### Opportunistic Infections & Complications by CD4 Count

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Infectious</th>
<th>Non-Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200/mm³</td>
<td>P. carinii pneumonia, Disseminated mycoses, Miliary /extrapulm Tb, PML</td>
<td>Wasting, Peripheral neuropathy, HIV dementia, Cardiomyopathy, Vacuolar myelopathy, Polyradiculopathy, NH Lymphoma</td>
</tr>
<tr>
<td>&lt; 100/mm³</td>
<td>Disseminated HSV, Toxoplasmosis, Cryptococcosis, Cryptosporidiosis, Microsporidiosis, Candidal esophagitis</td>
<td></td>
</tr>
<tr>
<td>&lt; 50/mm³</td>
<td>Disseminated CMV, Disseminated MAI</td>
<td>CNS lymphoma</td>
</tr>
</tbody>
</table>
# Primary Prophylaxis of Opportunistic Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>First agent</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneum. Cyst. C.</td>
<td>CD4&lt;200</td>
<td>Cotrimox.1 DSqd or 1 SS qd</td>
<td>Dapsone 100 qd Dapsone 50 + pyrimethamine + leuco Atovaquone 1500/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTb</td>
<td>PPD &gt; 5 mm Exposure</td>
<td>INH 300 + B6 x 9 m</td>
<td>Rifampin 600 qd x 4 m</td>
</tr>
<tr>
<td>MTb (INH resistant)</td>
<td>PPD &gt; 5 mm</td>
<td>Rifampin 600 qd</td>
<td>Pyrazinamide + rifampin or rifabutin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifabutin 300 qd</td>
<td></td>
</tr>
<tr>
<td>Toxo</td>
<td>IgG Ab + &amp; CD4&lt;100</td>
<td>Cotrimox.1 DSqd</td>
<td>Bactrim 1 SS qd, Dapsone+ pyrimethamine+ leuvovorin Rifabutin, azithro + rifabutin</td>
</tr>
<tr>
<td>MAI</td>
<td>CD4&lt;50</td>
<td>Azithromycin 1200 qw Clarithromycin 500 bid</td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td>Exposure</td>
<td>VZIG –5 vials within 96 hours</td>
<td>-</td>
</tr>
</tbody>
</table>
## Primary & Secondary Prophylaxis of Opportunistic Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>First agent</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep PNA</td>
<td>CD4&lt;200</td>
<td>Pneumovax</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>HbsAb neg</td>
<td>HBV vaccine x 3</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Oct-dec</td>
<td>Flu vaccine</td>
<td>Anti-virals</td>
</tr>
<tr>
<td>HAV</td>
<td>HAV negative + risk</td>
<td>HAV vaccine x 2</td>
<td></td>
</tr>
<tr>
<td>Crypto</td>
<td></td>
<td>Fluconazole 200 qd</td>
<td>Itraconazole 200 bid</td>
</tr>
<tr>
<td>Histo</td>
<td></td>
<td>Intraconazole 200 qd</td>
<td></td>
</tr>
<tr>
<td>Coccidio</td>
<td></td>
<td>Fluconazole 400 qd</td>
<td>Itraconazole 200 bid</td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>Consult expert</td>
<td></td>
</tr>
</tbody>
</table>
OI Prophylaxis in Resource Limited Settings

- **Pneumocystis Carinii** Pneumonia & Toxoplasma
  - Cotrimoxazole 1 DS or 1 SS qd

- Recurrent Bacterial PNA and Infections
  - Cotrimoxazole 1 DS or 1 SS qd

- Mycoses (ie Cryptococcus) when CD4<100
  - Fluconazole 200 mg qd

- Esophageal Candidiasis
  - Fluconazole 200 mg qd

- *Mycobacterium Tb*
  - PPD, Chest X-ray
  - INH 300 mg po qd + B6 x 9 months or short regimens
Web Resources

- WHO - Expanded Access to HIV/AIDS treatment
  - http://www.who.int/hiv/topics/arv/en/
  - http://www.who.int/hiv/en/

- STI treatment

- JHU Medical Management of HIV
  - http://www.hopkins-aids.edu/

- CDC/USPHS Guidelines
  - http://www.hivatis.com
References

- WHO/UNAIDS. Scaling up Antiretroviral Therapy in Resource-Limited Settings. December 2002
- CDC/USPHS. Guidelines for Using Antiretroviral Agents Among HIV Infected Adults and Adolescents. May 2002