HIV and HIV chemotherapy

Estimated number of adults and children newly infected with HIV during 2002

North America
45,000

Caribbean
60,000

Latin America
150,000

Western Europe
30,000

North Africa & Middle East
83,000

Eastern Europe & Central Asia
250,000

South & South-East Asia
700,000

East Asia & Pacific
270,000

Australia & New Zealand
500

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

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

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

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

<table>
<thead>
<tr>
<th>Clinical Stage I</th>
<th>Clinical Stage II</th>
<th>Clinical Stage III</th>
<th>Clinical Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aysmptomatic</td>
<td>Weight loss &lt; 10% body wt</td>
<td>Weight loss &gt; 10% body wt</td>
<td>AIDS by CDC definition</td>
</tr>
<tr>
<td>Persistent Generalized Lymphadenopathy</td>
<td>Minor skin manifestations</td>
<td>Chronic diarrhea</td>
<td>HIV wasting syndrome</td>
</tr>
<tr>
<td>Performance scale - 1</td>
<td>HSV</td>
<td>Fever</td>
<td>Disseminated mycosis</td>
</tr>
<tr>
<td></td>
<td>recurrent URI</td>
<td></td>
<td>HIV encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Performance scale- 2</td>
<td></td>
<td>Performance scale - 4</td>
</tr>
</tbody>
</table>

### Primary HIV Infection

- [Image of a person's face]
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

Newsday
April 10, 2001

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

HIV prevalence

Reported consistent condom use

Source: Ghys PD et al. (2002) AIDS
‘Aids drugs made me well again’

LINDA AHERNE, 31, YOUGHAL, CORK

‘I was in bed for six months. I was weak, I was.

The government did not have much of a say in the matter. We were just a group of people who were suffering. We were just a group of people who were suffering.

The diagram shows the HIV-1 Life Cycle. The steps include attachment, penetration, reverse transcription, integration, transcription, translation, and assembly. Each step is crucial for the virus to replicate and infect new host cells.

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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)

Suramin

![Chemical structure of Suramin](image)

Broder et al., Lancet ii, 627-630 (1985)
HIV REPLICATIVE CYCLE

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VIRUS-CELL FUSION

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

Inhibiteur de fusion: l'enfuvirtide

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

HIV REPLICATIVE CYCLE

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HIV Reverse Transcriptase

- Binding site for NRTIs and NtRTIs
- Binding site for NNRTIs
**Zidovudine**

3'-Azido-2',3'-dideoxythymidine

AZT

**Didanosine**

2',3'-Dideoxyinosine

DDI
Mechanism of action of 2',3'-dideoxynucleoside analogues, as exemplified for AZT

![Diagram showing the mechanism of action of AZT](image-url)
Emtricitabine

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

(±)FTC

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

FdOTC

adefovir

R = H : PMEA

tenofovir

R = H : (R)-PMPA
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

Binding site for NNRTIs

p66

p51

Thump

Connection

RNase H

Fingers

Palm

U-90152S

Delavirdine

Nevirapine

BI-RG-587

Benoxazinone

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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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 ...

Mechanism of aspartate protease and typical inhibitor (pepstatin)
HIV protease

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

http://www.iasusa.org/resistance_mutations/index.html
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...

Métabolisme des substances à noyau aromatique...

- 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)
- propranolol (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 ...


HIV/AIDS Pharmacotherapy

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

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>Asymptomatic</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):
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</td>
<td>BM supp, anemia, GI, LA, HA, insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg bid</td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Group B</td>
<td>40 mg bid</td>
<td>Pancreatitis, LA w/ steatohep, neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg bid</td>
<td></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></td>
<td></td>
<td>125 mg bid, 250 mg qd</td>
<td></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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TDF)</td>
<td>Group A</td>
<td>300 mg qd</td>
<td>No renal toxicity; limited expanded access</td>
</tr>
</tbody>
</table>

## 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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dose</th>
<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 DM, fat redistn, DM, fat redistn, neuro</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
<td>1250 mg bid</td>
<td>Elevated LFTs, fat redistn, DM</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>750 mg tid</td>
<td>Liver enzymes abnormal, D/N, DM, Fat redistn, Lipids abnl</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 NRTIs + NNRTI
  - 3 NRTIs
  - 2 NRTIs + 1 or 2 PIs
- If previous treatment, consider resistance testing prior to initiating treatment

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, Candidal vaginitis</td>
<td>PGL, GBS, Myopathy, Aseptic meningitis</td>
</tr>
<tr>
<td>200-500/mm³</td>
<td>Pneumococcal PNA, Pulm Tb, Zoster, Thrush, Cryptosporidiosis, KS, OHL</td>
<td>CIN, Cervical Cancer, B-cell Lymphoma, Anemia, Mononeuronal multiplex, ITP, Hodkin’s Lymphoma, LIP</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.</td>
<td>CD4&lt;200</td>
<td>Cotrimox.1 DSqd or Dapsone 100 qd</td>
<td></td>
</tr>
<tr>
<td>Cyst. C</td>
<td></td>
<td>1 SS qd</td>
<td>Dapsone 50 + pyrimethamine + leucovorin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atovaquone 1500/day</td>
</tr>
<tr>
<td>MTb</td>
<td>PPD &gt; 5 mm</td>
<td>INH 300 + B6 x 9 m</td>
<td>Rifampin 600 qd x 4 m</td>
</tr>
<tr>
<td></td>
<td>Exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTb (INH resistant)</td>
<td>PPD &gt; 5 mm</td>
<td>Rifampin 600 qd</td>
<td>Pyrazinamide +</td>
</tr>
<tr>
<td></td>
<td>rifampin or rifabutin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxo</td>
<td>IgG Ab + &amp;</td>
<td>Cotrimox.1 DSqd</td>
<td>Bactrim 1 SS qd,</td>
</tr>
<tr>
<td></td>
<td>CD4&lt;100</td>
<td></td>
<td>Dapsone+ pyrimethamine+ leuvovorin</td>
</tr>
<tr>
<td>MAI</td>
<td>CD4&lt;50</td>
<td>Azithromycin 1200 qw</td>
<td>Rifabutin, azithro +</td>
</tr>
<tr>
<td></td>
<td>bid</td>
<td>Clarithromycin 500 qd</td>
<td>rifabutin</td>
</tr>
<tr>
<td>Zoster</td>
<td>Exposure</td>
<td>VZIG –5 vials within</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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>Anti-virals</td>
</tr>
<tr>
<td>Influenza</td>
<td>Oct-dec</td>
<td>Flu vaccine</td>
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<tr>
<td>HAV</td>
<td>HAV negative + risk</td>
<td>HAV vaccine x 2</td>
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<td>Crypto</td>
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<td>Itraconazole 200 bid</td>
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<td>Histo</td>
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<td>CMV</td>
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<tr>
<td></td>
<td>Consult expert</td>
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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