HIV/AIDS Treatment

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12/2/10
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Overview of HIV

- **Human Immunodeficiency Virus (Retrovirus)**
  - Causes Acquired Immunodeficiency Syndrome
- **Disease causes immune system failure**
  - Targets T-Cells, Helper T Cells, CD4 T-Cells
  - Direct killing, apoptosis, CD8 lymphocytes
- Patients eventually die of other sicknesses
- In 2005 claimed 2.4-3.3 million lives
- WHO declares it a worldwide pandemic
HIV Retrovirus Lifecycle

- Capsid binds to T-Cell receptors (ex: CD4)
- Virus Capsid: RNA genome, reverse transcriptase, integrase, a few other enzymes
- DNA is transcribed, incorporated into host chromosome
- More virus and proteins are synthesized and sent out
Current Treatment

- Different drugs attack the replication at different steps
- HIV is adaptable so a “cocktail” of antivirals is prescribed at once
- HAART: Highly Active Anti Retroviral Therapy
- Drugs will target active infected cells
- Generally side effects are present but not immediately dangerous
HIV Antiviral Drug Classes

- **Nucleoside**
  - Fake nucleosides that break chain
  - May interfere with other body enzymes
  - Interfers with reverse transcriptase.

- **Non-Nucleoside**
  - The non-nukes bind directly to reverse transcriptase,
  - Metabolized in the liver
  - Rescriptor (delavirdine) Viramune (nevirapine) and Sustiva (efavirenz)
  - provide a choice for people who are intolerant of protease inhibitors
  - Fewer short-term side effects
Antivirals Continued

- Protease Inhibitors
  - Bind to the active site of protease, disrupt cleavage
  - Long-term side effects (hypercholesterolemia, fat redistribution, heart disease, diabetes)
  - Kaletra (opinavir/ritonavir), Crixivan (indinavir)
Antivirals Continued

- **Entry Fusion Inhibitors**
  - Works outside, changes binding site
  - Fuzeon (enfuvirtide) gp41 protein selzentry (maraviroc), CCR5 protein.
  - Good alternative for those resistant to other drugs

- **Integrase Inhibitors**
  - Prevents viral DNA from being inserted
  - Limited side effects
  - Relatively more expensive
HAART Shortcomings

- Latent HIV reservoirs
  - Dormant T-Cells
  - HAART only affects active
- Active replication feeds reservoirs
- Reservoir composed of mostly wild time, also drug-resistant and all other present strains (proportional)
- Virus reappears from combination of low-level replication and reservoir synthesis
Complimentary Drugs

- Need to induce HIV expression
- Adjuvants that stimulate
  - interleukin-2
  - valproic acid
  - toxicity or efficacy problems
- Phorbol-13-myrisitate-12-acetate (PMA),
  - tumor-promoting activity
Prostratin

- Prostratin (3, 12-deoxyphorbol-13-acetate) and DPP (4, 12-deoxyphorbol-13-phenylacetate) are safer alternatives
- In vitro, incudes HIV expression in latently infected cells
- Inhibis entry into target cells via CD4 and CXCR4 receptors
- Unclear; activation of protein kinase C (PKC) and nuclear factor κB (NF-κB) by prostratin have been proposed
Prostratin (2)

- Little observed side effects in limited tests
- Difficult to obtain
  - Pimelea prostrata euphorbia cornigera
- Used by Samoan healers
- In pre-clinical trials
- Great potential
Stanford Research

- Being done in Paul Wender’s lab
- Practical/affordable synthesis of prostratin
- Simple application of organic chemistry
- Novel method provides analogs
- Will allow further study of drug
- Solution is now significantly more viable
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