HIV/AIDS Treatment

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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

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QuickTime⁷ and a decompressor are needed to see this picture.

Current Treatment

- Different drugs attack the replication at different steps
- HIV is adaptable so a "cocktail" of antivirals is perscribed 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

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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

Wender Lab Proposed Synthesis

QuickTime[‡] and a decompressor are needed to see this picture.

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Works Cited

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