

HIV Gene Therapy

Michael Liu
Biochem 118
Douglas Brutlag
December 3, 2009

What is HIV?

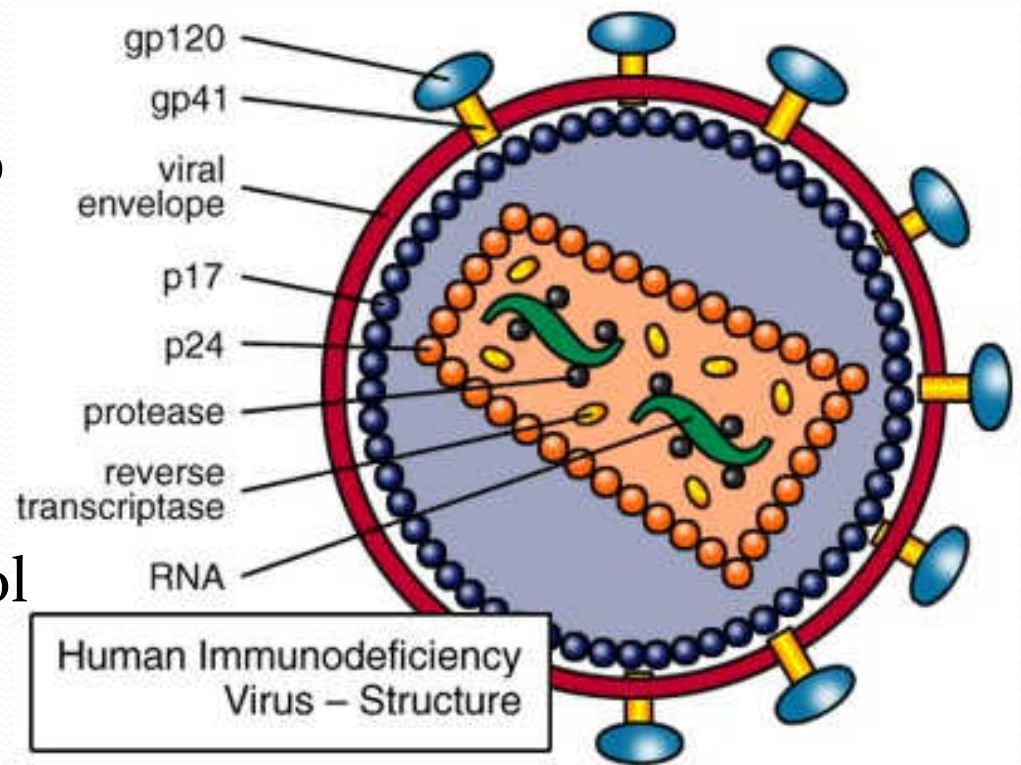
- Human immunodeficiency virus (HIV), causes acquired immune deficiency syndrome (AIDS)
- AIDS — AIDS defining illnesses, CD₄ count < 200.
- Retrovirus – RNA
- Killed more than 25 million people since 1981
- 1.1 million Americans among 33 million people with HIV
- 2.7 million new HIV infections and 2 million AIDS deaths in 2008
- More than half of those infected cannot get treatment

Background

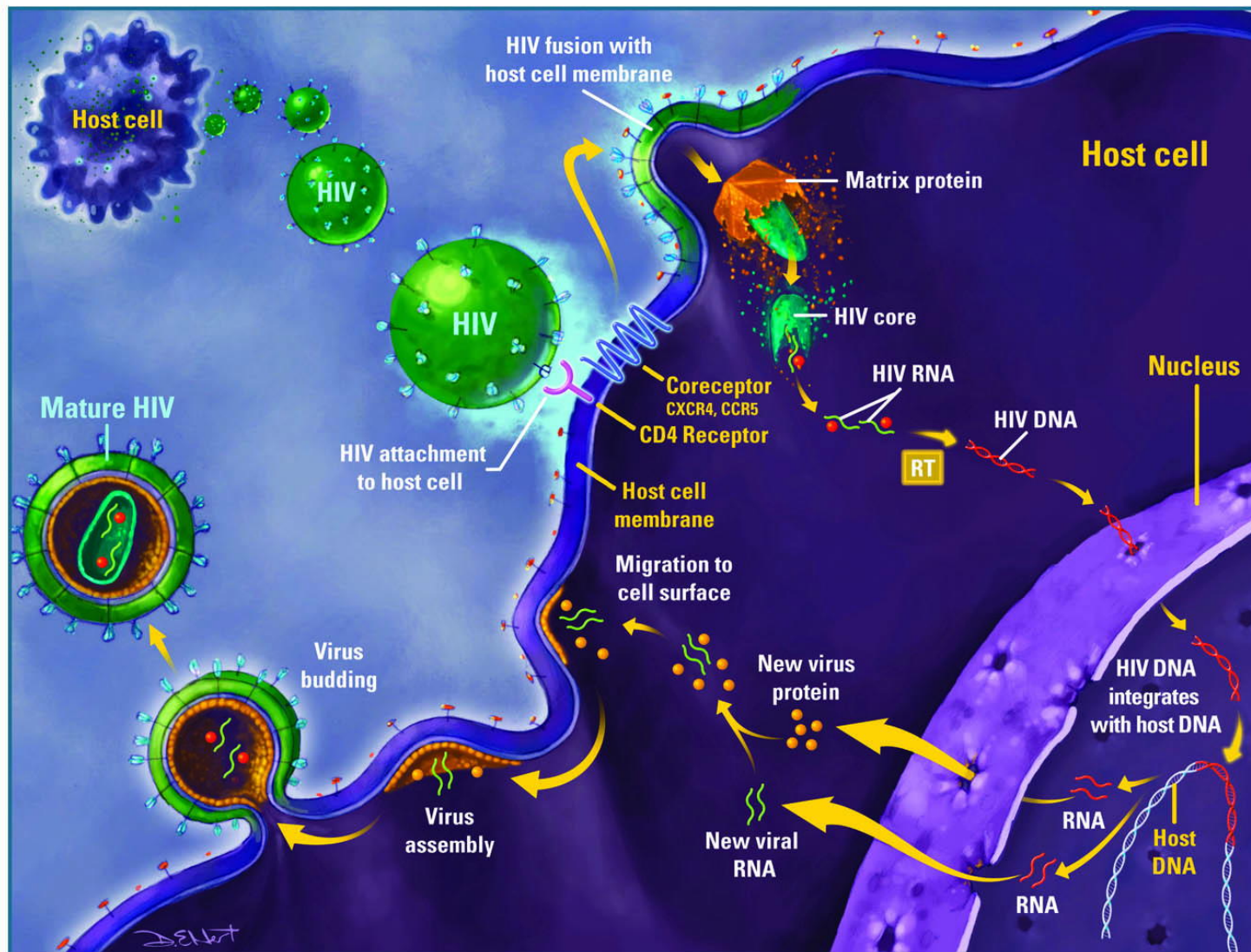
- 1900's – Monkeys to humans, West Central Africa
- 1981 – First HIV cases recognized, pneumocystosis, Kaposi's Sarcoma
- 1985 – First HIV test licensed
- 1991-2 – Leading C.O.D. in U.S. men aged 25-44.
- 1996-7 – HAART- highly active antiretroviral therapy
- 2001-2 – Leading C.O.D. worldwide, aged 15-59
- 2006-7 – Treatment extends life 24 years, \$618,900
 - Berlin man cured of HIV

HIV Structure

- Retrovirus – RNA
- 9 genes (500 genes in a bacteria, 20,000-25,000 in human).
 - Three - structural proteins for new virus particles.
 - Six - proteins to control the ability to infect & copy
- Viral envelope, viral core, 3 enzymes



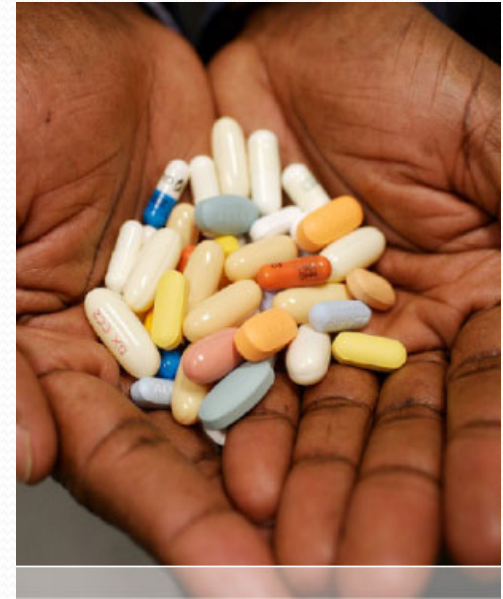
Mechanism of Infection



Copyright 2004, University of Washington. All rights reserved.

Current Treatment of HIV

- HAART - highly active antiretroviral therapy
 - Combination of inhibitors
 - Reduce mutation affects
- Fixed dose combinations
 - Increase adherence
- Mega-HAART / salvage therapy
- Drug Holidays



HAART side effects

- [Abdominal pain](#)
- [Alopecia](#)
- [Anemia](#)
- [Asthenia](#)
- [Diarrhea](#)
- [Dizziness](#) (Vertigo)
- [Fanconi syndrome](#)
- [Flatulence](#)
- [Headache](#)
- [Hepatitis](#)
- [Hyperbilirubinemia](#)
- [Hypercholesterolemia](#) (Dyslipidemia, Hyperlipidemia, high cholesterol)
- [Hyperpigmentation](#) (of nails, palms, or soles)
- [Ingrown nails](#)
- [Insomnia](#)
- [Jaundice](#)
- [Lipodystrophy](#)
- [Liver failure](#)
- [Malaise](#)
- [Mental confusion](#)
- [Migraines](#)
- [Mitochondrial toxicity](#)
- [Mood swings](#)
- [Myalgia](#)
- [Myalgic Encephalomyelitis](#) (chronic fatigue syndrome)
- [Myopathy](#)
- [Nausea](#)
- [Neutropenia](#) (low number of white blood cells)
- [Nightmares](#)
- [Oral ulcers](#)
- [Pancreatitis](#)
- [Paresthesia](#) (numbness)
- [Peripheral neuropathy](#)
- [Rash](#)
- [Renal failure](#) or insufficiency
- [Somnolence](#) (drowsiness)
- [Stevens-Johnson syndrome](#)
- Change in [taste](#) perception
- [Vomiting](#)
- [Xeroderma](#) (dry skin)
- [Xerostomia](#) (dry mouth)

Therapy

- Only one successful human case – Berlin man
- Focus usually placed on CD4 receptor and CCR5 coreceptor
- Types of therapy
 - Small-molecule approach to block CCR5
 - Maraviroc, mutations
 - Ribozymes
 - Blood stem cells infected with virus OZ1, trials successful
 - Zinc-finger nucleases
 - Disable CCR5 gene, currently researching / successful preliminary trials

Berlin Man

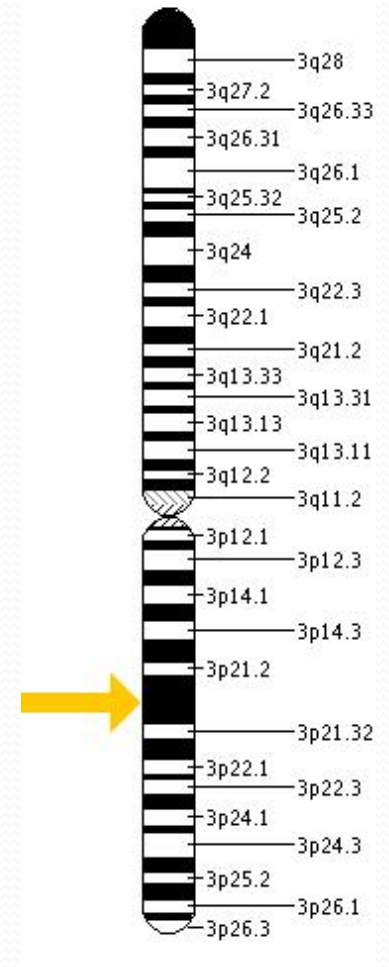
- Only successful human cured of HIV
- 42 y/o male American in Germany, HIV+, leukemia
- Successful HAART
- Stem cell transplant – blood
- Rare genetic mutation - delta32 CCR5
 - Deletion
- 13 million → 232 → 1

Berlin Man Treatment

- Leukemia – white blood cells
- Destroy all blood-forming cells (stem, bone marrow)
 - Radiation, 2 immunosuppressive drugs, drugs to kill all immune cells
- Replaced with sample 61
- Lurking HIV not a problem
- 2.5 years since off all antiviral drugs and transplant, no detectable virus, active or latent.
- Tests
 - Most sensitive, extensive biopsies
 - Antibody tests positive, decreasing

Mutations like delta32 CCR5

- [Multicenter AIDS Cohort Study \[MACS\]](#).
 - Followed many gay men in six U.S. centers
- Many mutations must exist
 - 5% - delta32 CCR5
 - 95% - under research



Obstacles to Similar Treatments in U.S.

- Rarity of matches
 - Two in U.S. identical to Berlin man
 - 13 million, placentas
- No money
 - No universal health care
 - Insurance pays for 10, maybe 20 calls to matches, number 61
 - Can't move to Germany
 - NIH, Academic study
- Only offered to those with leukemia, high mortality
- Real solution – changes in bone marrow registry
 - Current efforts on testing existing samples

Methods of Transmission

Significant risk

- Exchange of bodily fluids – blood, semen, vaginal fluid, breast milk
- Unprotected sex – vaginal and anal
- Mother to child
- Contaminated blood transfusions
- Needle sharing – intentional or accidental

Low risk / no risk

- Saliva, tears, sweat
- Insect bites
- Casual contact
- Airborne / environmental
- Kissing
- Tattoos / piercings



HIV prevention

- HIV vaccine
 - Envelope and protein coats
 - Only 1 success
- Post Exposure Prophylaxis
- Prevention
 - Condoms!
 - latex or polyurethane only
 - HIV testing



HIV – Still a Serious, Fatal Disease



References

- <http://www.thebody.com/content/art53624.html>
- <http://www.virology.ws/2009/02/24/anti-hiv-ribozyme-alternative-to-haart/>
- <http://www.webmd.com/hiv-aids/news/20090216/hiv-gene-therapy-major-advance>
- <http://www.cirm.ca.gov/content/zinc-finger-nuclease-based-stem-cell-therapy-aids-dr1-01490>
- <http://www.cdc.gov/hiv/resources/factsheets/transmission.htm>
- <http://ghr.nlm.nih.gov/gene=crtap>
- http://en.wikipedia.org/wiki/Antiretroviral_drug
- <http://www.avert.org/hiv-virus.htm>
- <http://genesdev.cshlp.org/content/14/21/2677.full>
- Perez, Elena. "Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases." *Nature Biotechnology* . 26.7 (2008): 808-16.