Optometric Education Consultants

HIV and AIDS: What Every Optometrist Needs to Know

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CENTER FOR SIGHT US EYE

Disclosures

- Alcon Novartis, B&L, Zeiss, Allergan, Ocular Therapeutix, Aerie, Sun Pharma
- Co-owner of Optometric Education Consultants www.optometricedu.com
- Nothing pertinent to this lecture

Stages of Our Understanding

AIDS in the Dark Ages

Holland GN et al. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. Am J Ophthalmol. 1982 Apr;93(4):393-402

Among the prominent features of a newly described acquired cellular immunodeficiency syndrome that affects previously healthy male homosexuals are multiple opportunistic infections and Kaposi's sarcoma.

"Immunosuppression induced by cytomegalovirus infection may play a major role in the pathogenesis of this disorder"

AIDS as the Ebola Virus

AIDS as Diabetes

- Chronic disease
- Medications and lifestyle alterations increase longevity
- Some ocular complications
- Can live a normal lifespan
- May contribute to death

Acquired Immune Deficiency Syndrome (AIDS)

- Not a specific disease; rather, a complex assortment of secondary disorders
- Results from infection by the human immunodeficiency virus (HIV)
- Virus selectively attacks T-helper (CD4-T) lymphocytes and ultimately destroys the cell
- Transmitted via contaminated bodily secretions

Global HIV Statistics

- 28.2 million people were accessing antiretroviral therapy as of 30 June 2021.
- 37.7 million people globally were living with HIV in 2020.
- 1.5 million people became newly infected with HIV in 2020.
- 680 000 people died from AIDS-related illnesses in 2020.
- 79.3 million people have become infected with HIV since the start of the epidemic.
- 36.3 million people have died from AIDS-related illnesses since the start of the epidemic.

People living with HIV

- In 2020, there were 37.7 million people living with HIV.
  - 36.0 million adults.
  - 1.7 million children (0–14 years).
  - 53% of all people living with HIV were women and girls.
- 84% of all people living with HIV knew their HIV status in 2020.
- About 6.1 million people did not know that they were living with HIV in 2020.

People living with HIV accessing antiretroviral therapy

- As of 30 June 2021, 28.2 million people were accessing antiretroviral therapy, up from 7.8 million in 2010.
- In 2020, 73% of all people living with HIV were accessing treatment.
  - 74% of adults aged 15 years and older living with HIV had access to treatment, as did 54% of children aged 0–14 years.
  - 79% of female adults aged 15 years and older had access to treatment; however, just 68% of male adults aged 15 years and older had access.
- 85% of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their child in 2020.

New HIV Infections

- New HIV infections have been reduced by 52% since the peak in 1997.
  - In 2020, around 1.5 million people were newly infected with HIV, compared to 3.0 million people in 1997.
  - Women and girls accounted for 50% of all new infections in 2020.
- Since 2010, new HIV infections have declined by 31%, from 2.1 million to 1.5 million in 2020.
  - Since 2010, new HIV infections among children have declined by 53%, from 320 000 in 2010 to 150 000 in 2020.

AIDS related deaths

- AIDS-related deaths have been reduced by 64% since the peak in 2004 and by 47% since 2010.
  - In 2020, around 680 000 people died from AIDS-related illnesses worldwide, compared to 1.9 million people in 2004 and 1.3 million people in 2010.
- AIDS-related mortality has declined by 53% among women and girls and by 41% among men and boys since 2010.

COVID-19 and HIV

- People living with HIV experience more severe outcomes and have higher comorbidities from COVID-19 than people not living with HIV.
- Studies from England and South Africa have found that the risk of dying from COVID-19 among people with HIV was double that of the general population.
- COVID-19 lockdowns and other restrictions disrupted HIV testing and in many countries led to steep drops in diagnoses and referrals to HIV treatment.

Key populations

- In 2020, key populations (sex workers and their clients, gay men and other men who have sex with men, people who inject drugs, transgender people) and their sexual partners accounted for 65% of HIV infections globally:
- The risk of acquiring HIV is:
  - 35 times higher among people who inject drugs.
  - 34 times higher for transgender women.
  - 26 times higher for sex workers.
  - 25 times higher among gay men and other men who have sex with men.

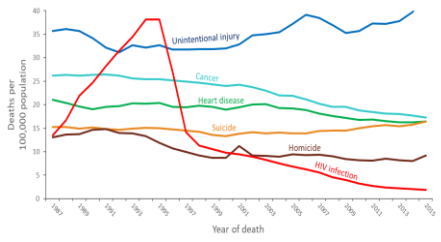
Florida ranks #5 in US

- Areas with the highest rates of persons living with diagnosed HIV infection at the end of 2016 were:
  1. The District of Columbia (2,459.9)
  2. New York (759.7)
  3. Maryland (642.8)
  4. The U.S. Virgin Islands (625.0)
  5. **Florida (610.8)**.

HIV in Florida

- In 2019, Florida identified 4,584 new HIV diagnoses.
- The HIV diagnosis rate per 100,000 population decreased from 22.7 in 2018 to 21.6 in 2019.
- The diagnosis rate per 100,000 among Black persons decreased from 57.8 in 2018 to 53.2 in 2019.
- The diagnosis rate per 100,000 among Hispanic/Latino individuals decreased from 29.7 in 2018 to 29.2 in 2019.

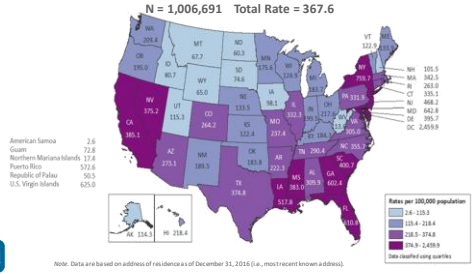
Trends in Annual Rates of Death due to the 6 Leading Causes among Persons 25–44 Years Old, 1987–2015—United States



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

Rates of Adults and Adolescents Living with Diagnosed HIV Infection Year-end 2016—United States and 6 Dependent Areas

N = 1,006,691 Total Rate = 367.6



Note: Data are based on address of residence as of December 31, 2016 (i.e., most recent known address).

Conclusions

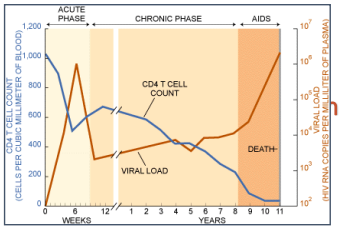
- After rapidly increasing since the 1980s, the annual rate of death due to HIV infection peaked in 1994 or 1995 (depending on the demographic group), decreased rapidly through 1997, and continued to decrease much more slowly thereafter.
- Persons dying of HIV infection increasingly consist of:
  - women (26% in 2015)
  - blacks/African Americans (52% in 2015)
  - residents of the South (53% in 2015)
  - persons 45 years of age or older (74% in 2015)
- HIV infection continues to remain among the 10 leading causes of death among persons 25 to 44 years old, particularly among blacks/African Americans.

HIV & AIDS -- What's It All About?

- The Human Immunodeficiency Virus (HIV)
  - Lentiviridae family of retroviruses (slow viruses)
  - Binds to host cells including T helper cells (CD 4 cells), macrophages, monocytes

Life Cycle of HIV

- Acquire HIV ➔ seroconversion ➔ viral replication ➔ no antibodies yet ➔ becomes symptomatic (~14 days) ➔ patient develops immunity with profuse viral accumulation ➔ immune system suppresses and partially clears virus ➔ asymptomatic stage (10 years) ➔ immune system wears out ➔ onset of further replication ➔ CD 4 cell count drops ➔ patient become symptomatic ➔ AIDS

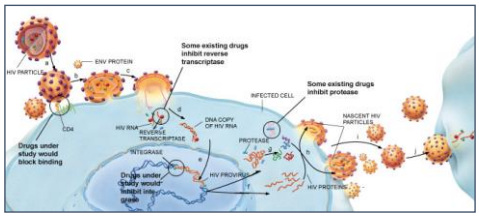


Natural Course of HIV Infection

- Virus is never 'dormant' – virus replicates at 'set point' controlled by immune system
- Replication of HIV causes immune system damage

Pathogenesis of HIV Infection

- HIV binds and fuses with host cell (CD 4 cell) ➔ HIV releases viral RNA into nucleus of host cell ➔ viral RNA infects T lymphocytes (as well as glial cells and monocytes) ➔ viral RNA incorporated into cell ➔ enzyme reverse transcriptase forms viral DNA from viral RNA in reverse fashion ➔ enzyme integrase integrates new DNA into host cell's genetic material ➔ viral genetic material packaged into new viral particles with new viral RNA (requires enzyme protease) ➔ released from cell to infect new cells



HIV Life Cycle

- HIV replicates 10 billion particles/day
  - Want viral load to be below 10,000 copies
  - Best to be undetectable (< 200 copies)
  - Undetectable viral load may still have virus in semen and *may* cause infection**
- 2017: medical authorities are now agreeing that those with undetectable viral loads cannot transmit the virus.
  - 9/27/17: CDC releases statement that those taking daily medication and maintain an undetectable viral level "have effectively no risk of sexually transmitting the virus to an HIV-negative partner".
- U=U: Undetectable = Untransmittable

HIV Life Cycle

- Primary HIV infection:
  - Highest viral titers during primary stage (1st 14 days)
  - Most likely to transmit virus
  - Patient unaware of infection
- Acute retroviral syndrome:
  - Fever, fatigue, sore throat, muscle pain, nausea
  - Symptoms equate to viral load and progression to AIDS

Acquired Immune Deficiency Syndrome (AIDS)

- Emphasizes CD4 count in categorization of HIV-related problems
- Expanded AIDS case definition
- Progression from infection to AIDS: 8 mos. to 18 years
- Long-term non-progressors: viral load stays down and T cells stay up.
- Rapid progressors: viral load is high and T cells are low

Acquired Immune Deficiency Syndrome (AIDS)

- Study of blood frozen early in disease (mid 1980's)
  - Those with initial viral load < 3,000: only 10% developed AIDS at this point
  - Those with initial viral load > 110,000: 75% developed AIDS
- High initial viral load most predictive of AIDS development
- High viral load 6 months after infection predicts rapid progression
  - These patients can be converted to non-progressors

Systemic Manifestations of HIV & AIDS

- Initial infection causes mild, self-limited condition:
  - upper respiratory infection; 1-2 weeks duration
  - generally asymptomatic course (months to years) until immune system becomes depressed
- AIDS defined by:
  - CD4+ T-lymphocyte count below 200/L, AND/OR
  - development of other recognized secondary infections or conditions

AIDS and the Eye

- If CD4 count < 200:
  - 1st year: 33% incidence of opportunistic infection
  - 2nd year: 58% incidence of opportunistic infection
- If CD4 count < 100
  - 1st year: 25% incidence of CMV retinitis

AIDS and the Eye

- Follow up for patients with no retinal pathology:
  - CD4 > 600: Annually
  - CD4 599-300: 6 months
  - CD4 299-100: 3-4 months
  - CD4 < 100: 2-3 months
  - Systemic CMV: 2-3 months

Transmission, Prevention, Testing, Reporting, and Management

Modes of Transmission

- HIV can be isolated from the following body fluids:
  - Blood
  - Semen and vaginal secretions
  - CSF, synovial fluids, pleural fluid, pericardial fluid, amniotic fluid, tears
  - Transmission occurs via *"exposure of mucous membranes to visible blood or body fluids…"*
    - Sexual contact
    - Sharing of needles by IV drug users
    - Blood transfusion

Modes of Transmission

- **Negligible risk** of HIV transmission by exposure of:
  Vagina, rectum, eye, mouth or other mucous membrane, intact or non-intact skin, or percutaneous contact
  WITH
  Urine, nasal secretions, saliva, sweat or **TEARS,**
  if not physically contaminated with blood

Source: Morbidity Mortality Weekly Report January 21, 2005

Modes of Transmission

- Accidental exposure to contaminated vectors by medical personnel
  - Most common is needle stick
  - 51 cases of transmission and conversion in health care workers
  - Can be contracted through broken skin or open lesions
  - Universal precautions should be used when dealing with known HIV-infected samples

Prevention

- Hand Washing
  - With soap and water after EACH patient
  - Dry with FRESH towel
- Gloves
  - Used if open wound, weeping lesions, dermatitis or exposure to tears or mucous membranes
  - Discard after EACH patient
  - Double glove if risk of needle stick
  - Double glove removes innoculum from needle
- Gowns & Masks
  - Unnecessary for routine exam
  - Used only if splashing of blood or blood products anticipated (ER)

Disinfecting Equipment

- Goldmann tonometer
  - 70% alcohol, wiped vigorously, washed with water, air dry OR
  - Soak in fresh 3% hydrogen peroxide for 5 minutes OR
  - Soak in fresh 1:10 dilution of bleach for 5 minutes
- Gonio prisms (& other instruments)
  - Wiped clean, then
  - Disinfected with above regimen
- Trial contact lenses
  - Any commercially available Peroxide system OR
  - Heat disinfection: 80 degrees X 10 minutes (may warp RGPs)

Florida Statutes Pursuant to HIV Infection

- Sections 381.004 and 384.25
  - 381.004 refers to testing for HIV
- The state must facilitate informed, voluntary, and confidential use of HIV testing
- Florida DOH has established a network of voluntary HIV testing programs in every county.
  - Also provides for counseling
  - Program is anonymous and confidential

Florida Statutes Pursuant to HIV Infection

- Results of these tests may not be used to:
  - Determine eligibility for disability, health, or life insurance
  - Screen or determine suitability for, or discharge a person from, employment
- HIV testing must be preceded by informed consent; must inform patient that:
  - All test results are treated as confidential information
  - Positive results are reported to county health department
  - Centers are available for anonymous testing should the patient desire

Florida Statutes Pursuant to HIV Infection

- The individual ordering the HIV test is obligated to inform the patient of the test results as well as:
  - Availability of treatment and support services
  - Importance of notifying partners who may have been exposed
  - Methods of preventing transmission of HIV
- HIV test results may be released only to the individual patient or the patient's LEGALLY AUTHORIZED REPRESENTATIVE

Case History Questions

- When were you first diagnosed?
- Have you had or been treated for any opportunistic infections?
- What medications are you taking?
  - Are you compliant with your medications?
- When was your last blood work done?
- What is your T-Cell or CD4 count?
- What was is the viral load?

Clinical Management of HIV Infection

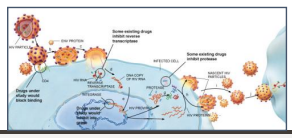
- Treatment Goals:
  - Maintain viral load as low as possible
    - may never get viral load to undetectable level, esp if load high
  - Maintain CD4 count as high as possible
  - Manage opportunistic infections

Established Medical Therapies

- **Nucleoside reverse transcriptase inhibitors (NRTIs)**- prevents infection of new cells: incorporated into viral DNA and prevents further synthesis
  - Zidovudine- **AZT, ZDV** (Retrovir): 300 mg PO BID
  - Zalcitabine- **ddC**, (Hivid)
  - Didanosine- **ddI**, (Videx) also enteric coated ddI EC
  - Lamivudine- **3TC**, (Epivir): reverses AZT resistance
  - Lamivudine + Zidovudine – **CBV** (Combivir)
  - Acabavir – **ABV, ABC** (Ziagen)
  - Stavudine – **d4T** (Zerit) also available as extended release Zerit XR
  - Emitricitabine – **FTC** (Emtriva)
  - Tenofovir – **TNV, TDF** (Viread)
  - Lamivudine+Acabavir+Zidovudine – **TZV** (Trizivir) 3TC+ABV+AZT

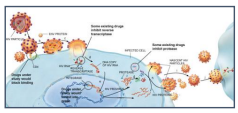
Established Medical Therapies

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**: directly inhibits reverse transcriptase
  - Nevirapine – **NVP** (Viramune): rapid resistance; not indicated for monotherapy
  - Delavirdine- **DLV** (Rescriptor)
  - Efavirenz- **EFV** (Sustiva)



Established Medical Therapies

- **Protease inhibitors**- prevents assembly of new virus cells- leads to a dramatic reduction in viral load
  - Saquinavir – **SQV** (Invirase Hard gel cap) (Fortovase Soft gel cap)
  - Ritonavir – **RTV** (Norvir**)**
  - Indinavir- **IDV** (Crixivan**)**
  - Nelfinavir- **NFV** (Viracept)
  - Amprenavir – **APV** (Agenerase)
  - Atazanavir – **ATV** (Reyataz)
  - Fosamprenavir – **FPV, 908** (Lexiva)
  - Lopinavir + Ritonavir – **LPV** (Kaletra)



Treatment Guidelines

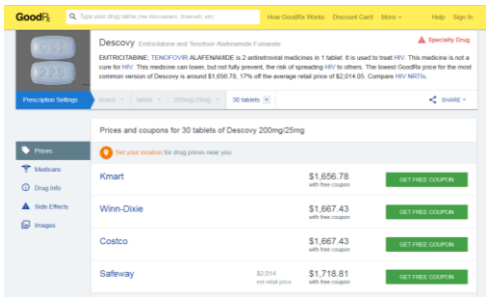
- Combination therapy is patient's best option- Highly Active Anti-Retroviral Therapy (HAART) :
  - synergistic effects can improve effectiveness of each med
  - lower dosages may be possible
  - decrease in resistance
  - better penetration of all body compartments
- Convergent (drugs within same family) and divergent therapy (drugs in different families)

Treatment Guidelines

- CAN NOT MISS DOSAGES. THIS <u>WILL</u> LEAD TO RESISTANCE
  - Up to 1 million mutations occur daily
  - Signs of drug failure:
    - development of opportunistic infection
    - decreasing T cells
    - increasing viral load
- When doing combination therapy, do not stop individual drugs due to resistance. Stop all 3 and start 3 new drugs.
- All pregnant patients get AZT at least ➔ reduces vertical transmission to infant
  - Decreases perinatal transmission by 90% to < 100 cases annually

Descovy

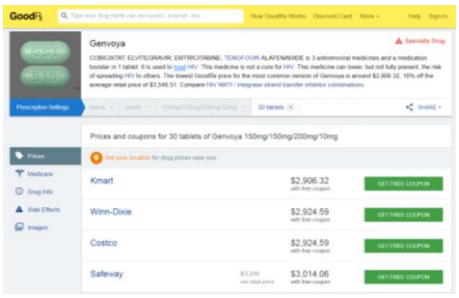
- Unique design which allows it to enter the patient's cells in a more efficent manner than prior drugs, and leaves significantly less tenofovir in the patient's body.
- Descovy is a prodrug which lowers the amount of HIV in a user's blood more efficently than older antiretrovirals. In clinical trials, Descovy was able to lower the HIV in someone's body as well as Viread, but by using one-tenth the size dosage.

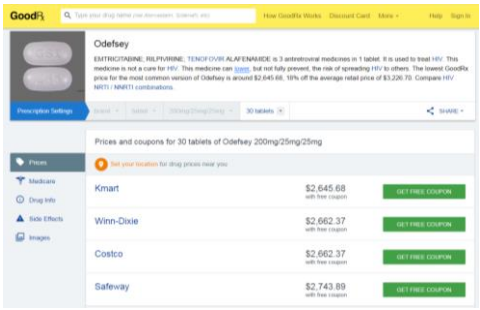


Genvoya and Odefsey

- Genvoya: Elvitegravir + tenofovir alafenamide + emtricitabine + cobicistat
- Odefsey: Rilpivirine + emtricitabine + tenofovir alafenamide (one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs).
- Once-a-day dosing

- GENVOYA® is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years and older who have no antiretroviral (ARV) treatment history or to replace the current ARV regimen in patients who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for ≥6 months with no history of treatment failure and no known resistance to any component of GENVOYA



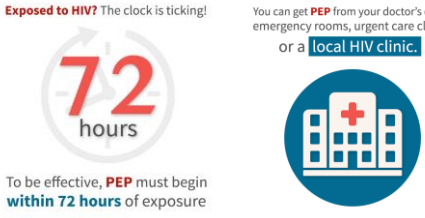


HIV Post Exposure Prophylaxis (HIV PEP)

- AIDS can be prevented in a substantial number of cases
- Needle stick is second highest exposure risk (after HIV blood transfusion- 90% conversion rate)
- 0.3% convert (1/300)
  - Conversion dictated by amount of innoculum and patient's viral load
  - As of 2010, 57 documented transmissions and 143 possible transmissions had been reported in the United States.
  - HIV virus not hearty; killed by most antiseptics

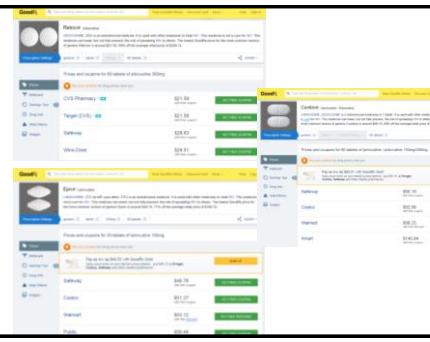
HIV Post Exposure Prophylaxis (HIV PEP)

- Soak affected part in Betadine, alcohol, peroxide immediately after exposure
- HIV PEP is highly recommended
  - Triple therapy of AZT (200 mg PO Q8H on empty stomach), 3TC (150 mg PO BID), and Crixivan (800 mg PO Q8H on empty stomach)
  - **Must begin within 72 hours after exposure (sooner better)**
  - Should be continued for four weeks
  - Reduces the conversion rate by approximately 80%
- Can not test patients' blood for HIV without consent after needlestick



PEP Regimen

- Basic Regimen
  - **Truvada** or **Descovy**
    - **Viread** tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with **Emtriva** emtricitabine (200 mg) once daily
    - ***Plus***
  - **Isentress** raltegravir (RAL) 400 mg twice daily or **Tivicay** dolutegravir (DTG) 50 mg daily.
    - *Preferred dosing*
- All persons offered PEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen



HIV Pre Exposure Prophylaxis (HIV PrEP)

- Medical or public health procedure used before exposure to the disease causing agent
  - Purpose is to prevent, rather than treat or cure a disease
    - E.g. malaria
- Theoretically, if HIV replication can be inhibited from the very first moment the virus enters the body, it may not be able to establish a permanent infection.
- Antiretrovirals to HIV-infected women reduces the risk of mother-to-child transmission by about 50 percent.

HIV Pre Exposure Prophylaxis (HIV PrEP)

- CDC-sponsored trials safety and efficacy studies
- Tenofovir (Viread®) or tenofovir plus emtricitabine (Truvada®) PO QD
  - Three populations at high risk for infection:
    - heterosexuals in Botswana, injection drug users in Thailand, men who have sex with men (MSM) in the United States
      - Efficacy 62%; poor compliance
- Additional study in Uganda - Partners PrEP Study
  - Examining the safety and efficacy of PrEP among heterosexual couples in which one partner is infected and the other is not
  - Study stopped in 2011 due to clear efficacy

HIV Pre Exposure Prophylaxis (HIV PrEP)

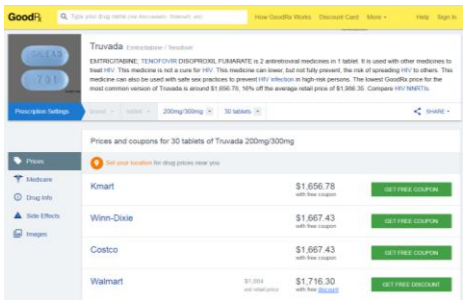
- All trials assess effects of taking a daily pill on:
  - HIV risk behaviors
  - Adherence to and acceptability of the regimen
  - Resistance characteristics of the acquired virus in cases where participants become HIV-infected.

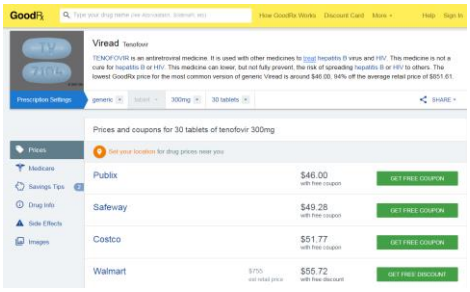
HIV Pre Exposure Prophylaxis (HIV PrEP)

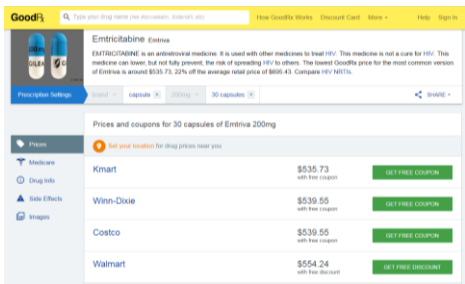
- In November, 2010, the *New England Journal of Medicine* published the results of a three-year clinical trial, funded by the National Institutes of Health, announcing the arrival of a treatment that could reduce the risk of contracting HIV by more than ninety per cent.
- Seen as replacement for condoms
- Has led to risky behavior

Truvada

- Truvada® is approved for daily use as PrEP to help prevent an HIV-negative person from getting HIV from a sexual or injection-drug-using partner who's positive. Tenofovir/ emtricitabine
- FDA has approved Truvada® for PrEP for HIV-negative adults and adolescents weighing at least 35 kg (approximately 77 lbs.)
- Studies have shown that PrEP is highly effective for preventing HIV if it is used as prescribed.
- PrEP is much less effective when it is not taken consistently.







Eradicating HIV and Curing AIDS

- 50-500 billion viral particles are produced per day in untreated patients
- Free viral particles have half life of minutes
- Actively infected CD4 T cells have half life of 1 day (17 days in non-infected cell)
- HIV infected macrophages have half life of 14 days
- In regards to these cells, HIV is curable

Eradicating HIV and Curing AIDS

- Memory CD4 T cells are reservoir for HIV virus to hide – half life 40-50 months – allows for viral latency
- It would take 60 years of treatment (assuming average half life of 43.9 months for memory T cells) in order to completely eradicate virus due to viral latency in memory T cell reservoirs
- Patients treated for years with HAART therapy and undetectable viral loads all break through with cessation of therapy

The Future of Treatment

- CCR5 antagonists
  - Chemokyne receptors – CCR5 targeted by HIV
  - All transmissions involve CCR5 receptors on CD4 T cells
- Experiment of nature
  - 2-5% of Caucasians (mostly Northern European descent) have CCR5 mutation
  - Individuals who are homozygous for this mutation have healthy immune systems and are very resistant to HIV infection
  - Binding site not available for HIV

Eradicating HIV

- In 2008, one man, Timothy Ray Brown, also known as the "Berlin patient," was considered cured of his infection after receiving two bone-marrow transplants to treat a separate disease he had been diagnosed with a few years earlier: acute myeloid leukemia.
- The bone marrow he received came from a donor whose genes carried a rare mutation that made them resistant to HIV, known as CCR5-delta 32, which was transferred on to Brown.
- Traces of the virus were seen in his blood a few years later, but remained undetectable despite him not being on antiretroviral treatment, meaning he was still clinically cured of his infection, according to his clinicians.

Eradicating HIV

- Timothy Ray Brown was given very harsh chemotherapy, had intense complications, and nearly died.
  - Was put into medically induced coma
  - Received massive destruction to immune system
- Now there is "The London Patient"- who remains anonymous
- London Patient had Hodgkin's lymphoma and underwent bone marrow transplant from a CCR5 mutation donor
- Also received much less aggressive immunosuppression

Eradicating HIV

- London Patient stopped anti-retroviral drugs in 9/17
  - Remains undetectable levels
- Transplant destroyed cancer cells
- Transplanted immune cells now are resistant to HIV
- Indicates that patients don't have to 'nearly die' to be cured.

Eradicating HIV

- 2016- new set of HIV positive patients whose reservoirs of HIV have fallen to very low levels after receiving a range of stem cell transplants similar to Brown's.
- The study is part of the EPISTEM project (now iciStem), a European project to investigate the potential for an HIV cure using stem cell transplantation
- Everyone included in the project is in need of stem cell transplantation to cure severe blood disorders, in addition to being infected with HIV.

Eradicating HIV

- iciStem maintains database of 22,000 donors with CCR5 HIV-resistant mutation (called delta 32).
- Tracking 38 HIV-infected patients who have received bone-marrow transplants
  - 6 are from donors without the mutation
- London Patient is #36 on list
- "Dusseldorf Patient" is #19 on list and has been off anti-virals for several months
  - Considered #3 patient cured of HIV (3/19)

Eradicating HIV

- All HIV-infected patients that received a stem cell transplantation had a significant reduction of the viral reservoir in their body.
  - This has not been demonstrated with other cure strategies
- The minute levels of the virus that have been seen to date were not considered competent enough to replicate

2021-2022 successes

- A woman became the third person ever to be cured of HIV, the virus that causes AIDS, after she received a stem-cell transplant that used cells from umbilical cord blood
- In addition to being HIV-positive, the woman had acute myeloid leukemia
  - She had received the umbilical cord blood as both a treatment for the cancer and for her HIV, as her doctors identified a donor with the HIV-blocking genetic mutation
- 2 women have eradicated the deadly virus from her body without the help of drugs or a bone marrow transplant