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Key Inforbits

What is HIV/AIDS? --- Prevention --- Approach to Treatment --- New Medications --- Drugs in Development

What is HIV/AIDS?

Overview¹

Originating in primates, human immunodeficiency virus (HIV) is first believed to have crossed over to human species in central Africa circa 1900 and subsequently spread across the globe. HIV is a single stranded RNA retrovirus that attacks the body's immune system and decreases its ability to fight off infection. More specifically, CD4⁺ T-cells are the primary target of viral replication which takes place in three general phases: acute, chronic, and terminal. A person who is in the terminal phase of infection is characterized by depletion of CD4⁺ cells and ultimate destruction of the immune system. This results in autoimmune deficiency syndrome (AIDS) which leaves the patient vulnerable to a multitude of opportunistic infections that can be fatal.

Clinical Presentation/Detection¹

For most patients who are infected with HIV, the symptoms resemble that of a mononucleosis-like illness which typically persist for ~ 2 weeks:

- Fever, sore throat, fatigue
- Maculopapular rash of the trunk
- Nausea, vomiting, diarrhea
- Swollen lymph nodes, night sweats

Diagnosis of HIV is made by performing a repeated enzyme-linked immunosorbent assay (ELISA), which detects the presence of antibodies against HIV. If one or both ELISA tests are positive, then a confirmatory test is performed to establish diagnosis. Viral load and CD4⁺ cell count are used as surrogate markers to monitor the disease and direct treatment. AIDS occurs when CD4⁺ cell counts drop to < 200 cells/mm³ or the development of an AIDS indicating condition.

Transmission Patterns^{1,2}

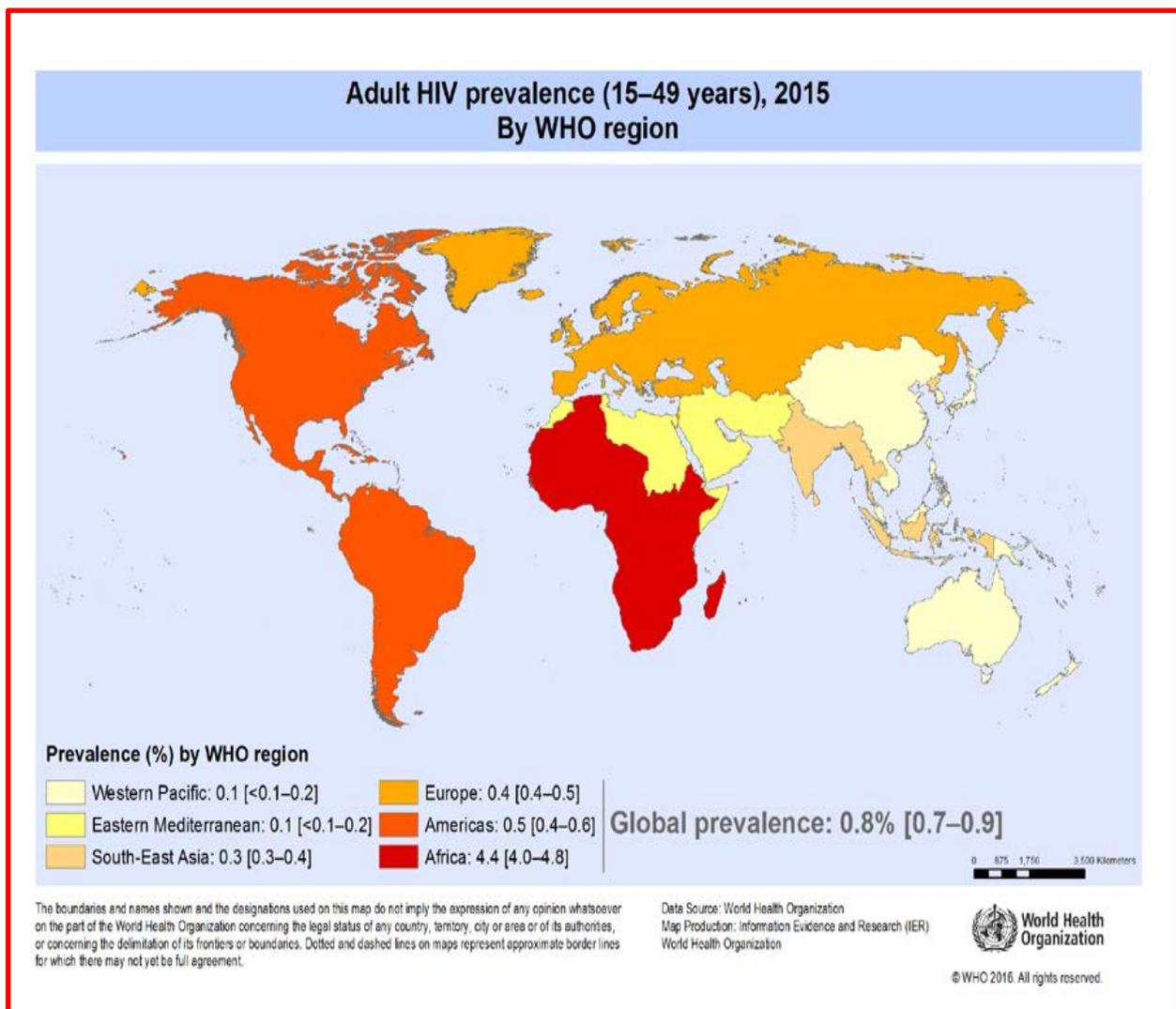
HIV is spread through the transmission of bodily fluids from one person to another including blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk that must come in direct contact with a mucous membrane, damaged tissue, or direct injection into the bloodstream. Specific patterns of transmission are largely dependent upon geography, cultural practices, route of infection, and government resources.

In the United States transmission most commonly occurs via one of the following:

- Anal intercourse (receiving poses the greater risk)
- Vaginal intercourse
- Sharing of needles used to inject

Less common modes of transmission:

- Mother-to-child transmission
- Accidental needle-stick



Global Health Observatory (GHO) data, HIV/AIDS [map]. [Washington, D.C.]: World Health Organization; c2015. Available from: <http://www.who.int/gho/hiv/en/>

Rare modes of transmission

- Oral sex
- Blood transfusions
- Being bitten by an infected person
- Deep kissing with open mouth sores

Statistics²

- ~36.7 million people living with HIV worldwide
- ~1.1 million people died worldwide of AIDS-related illness in 2015
- ~ 2.1 million new HIV cases worldwide in 2015 with Sub-Saharan Africa making up 65% of all new cases
- In the U.S. in 2014, ~ 44,000 people were diagnosed with HIV with a total of ~ 1.2 million people living with the infection as of 2012 with nearly 7,000 deaths from HIV/AIDS in 2013



Lifestyle⁵



Available from: <https://wrapitupph.wordpress.com/tag/safe-sex/>

- **Know your partner's HIV status and get tested yourself.** Talk to your partner about HIV testing and get tested before having sex.
- **Have less risky sex.** The most risky type of sex for HIV transmission is anal sex. Other forms might reduce risk of transmission.
- **Use condoms.** Using a condom correctly can reduce your risk of transmission.
- **Limit number of sexual partners.** The more partners you have, the more likely you are to have a partner with HIV.
- **Get tested and treated for STDs.** Insist that partners get tested and treated. Having an STD has shown to increase your risk of becoming infected with HIV or spreading it to others.
- **Pre-exposure prophylaxis (PrEP).** An HIV prevention option for people who don't have HIV but who are at high risk of infection.
- **Don't inject drugs.** But if you or your partner does, use only sterile drug injection equipment and never share equipment with others.

Pharmacological (Vaccination)⁶



Available from: http://www.zazzle.com/dove_of_hope_red_ribbon_aids_hiv_postcard-239008560659064919

There is currently no FDA approved vaccine that will prevent HIV infection or treat those who have it.

However, the National Institution of Health has recently funded a new HIV vaccine efficacy study in South Africa called HVTN 702. The Phase 2b/3 study is the largest and most advanced HIV vaccine clinical trial to take place in South Africa and the only current HIV vaccine efficacy trial worldwide in the past seven years. HVTN 702 is actually a combination of two vaccines that have been in development for the HIV subtype C including a canarypox vector-based vaccine called ALVAC-HIV and a two-component gp120 protein subunit vaccine with an adjuvant to enhance the body's immune response to the vaccine.

The two vaccines do not contain HIV themselves thus do not pose any harm to the participants in the trial. The first participant was enrolled on Oct. 26, 2016 with expected follow up time of three year thus results are not to be expected until late 2020.

Approach to Treatment³

Formerly a disease with a poor prognosis, HIV/AIDS has become a manageable condition with the utilization of appropriate antiretroviral therapy (ART). While current ART does not allow for the complete eradication for the disease, it does dramatically improve patient outcomes. The main goals of ART use are to reduce morbidity and mortality, maximize suppression of circulating HIV RNA, restore and preserve a functional immune system, improve quality of life, and prevent further transmission of HIV.

As a result of the benefits it provides, ART is recommended for all patients who have contracted HIV and should be initiated as soon as possible following diagnosis. The availability of a variety of medication classes such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), CCR5 receptor antagonist, and pharmacokinetic (PK) enhancers provides each patient with a multitude of treatment regimen options. Generally, treatment should consist of two NRTI medications in addition to one of NNRTI, INSTI, or PI + PK enhancer for a total of 3 antiretroviral agents for the treatment naive patients. Since most of the recommended regimens have similar efficacy, patient specific considerations should be made when choosing a regimen that addresses pill burden, the potential for medication interactions, side effects, comorbidities, co-infection with HBV/HCV/TB, patient preference, and cost. No matter which ART regimen is chosen, it is of utmost importance to ensure patient adherence in order to maximize therapeutic efficacy and to prevent the development of resistance to the medications.

Summary Table of ART Medication Classes and Agents¹						
NRTIs	NNRTIs	INSTIs	PIs	FIs	CCR5 Antagonist	PK Enhancers
abacavir didanosine emtricitabine lamivudine stavudine tenofovir zidovudine	delavirdine efavirenz etravirine nevirapine rilpivirine	elvitegravir raltegravir	fosamprenavir atazanavir darunavir indinavir lopinavir nelfinavir ritonavir saquinavir tipranavir	enfuvirtide	maraviroc	ritonavir cobicistat

New Medications⁵

Recently three new HIV medication combinations have been approved by the FDA produced by the Gilead biopharmaceutical company. Descovy (emtricitabine, tenofovir alafenamide), Odefsey (rilpivirine, emtricitabine, tenofovir alafenamide) and Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) all contain tenofovir alafenamide which has reduced side effects in these regimens. Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir with a similar high antiviral efficacy and at a dose less than one-tenth that of Gilead's Viread[®]

(tenofovir disoproxil fumarate [TDF]). An advantage of TAF is that it can be given at a much lower dose due to its improved ability to enter HIV-infected cells. Additionally, when combined with other antiretroviral agents, TAF has demonstrated a reduction in renal and bone adverse effects when compared to TDF in clinical trials.

Drugs in Development

Biopharmaceutical companies are continually working on new ways to treat and prevent HIV. Recent drugs in development are focused on attachment inhibitors; gene modification and inducing T cell responses.

- Attachment inhibitors prevent the virus from attaching to new cells and breaking through cell membranes. An example of this is BMS-663068, which attaches to the virus on gp120 to prevent it from being able to enter the cell by blocking the interaction between gp120 and cell receptors.
- Gene modifiers recently are focused on CCR5, which is a co-receptor on the surface of the cell that allows the virus to enter and infect T cells. Without CCR5 it is more difficult for HIV to attach and infect the cells. New drugs in development are designed to modify the DNA sequence in patient's own cells with the intent of making the cells resistant to infection by HIV. This therapy would give the patient a group of cells that can fight HIV as well as opportunistic infections.
- T cell response inducers are designed to induce CD4+ T cell responses in HIV infected patients. CD4+ play an important role in immune protection against viral reactivation and opportunistic infections. By inducing these cells hopefully the patient will be better protected and have a better chance of survival especially when paired with other therapies.

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The Last Dose

"We live in a completely interdependent world, which simply means we cannot escape each other. How we respond to AIDS depends, in part, on whether we understand this interdependence. It is not someone else's problem. This is everybody's problem."

- William Jefferson "Bill" Clinton (42nd President of the United States)



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