AU InforMed

Volume 8 Number 10 (Issue 234) *Friday, December 3, 2010*

Guest editors: Megan Hardin, Whitney Mitchell, and Ami Pearson, Pharm.D. Candidates, Wesley Lindsey, Pharm.D.

Key Inforbits

World AIDS Day:

Since its inception in 1988 World AIDS (Acquired Immune Deficiency Syndrome) day has been raising awareness and money for research, improving education, and reducing prejudice. It is currently estimated that 33.3 million people world-wide are living with HIV (Human Immunodeficiency Virus), and nearly 2 million people die from AIDS related illnesses annually.[1,2]

HIV Timeline:[2]

- 1884-1924: HIV is transferred to humans from primates in Africa
- Around 1965: HIV reaches Haiti
- During the 1970s: HIV reaches the US
- 1981: AIDS is discovered in IV drug abusers and gay men in New York and California
- 1982: The term AIDS is coined and hemophiliacs, Haitians living in the US, and citizens of several European countries are diagnosed with AIDS
- 1983: AIDS is detected in women and children
- 1984: HIV is found to be the cause of AIDS
- 1985: AIDS has been found in all regions of the world
- 1987: AZT becomes the first drug approved for treatment
- 1993: Resistance to AZT has begun in the early stages of HIV
- 1996: Beginning of combination antiviral therapy
- 2003: The first AIDS vaccine is developed, but ineffective

1. AIDS & HIV information from AVERT.org [Internet]. West Sussex, UK: AVERT; AVERTing HIV and AIDS; 2010 [cited 2010 Nov 30]. Available from: www.avert.org
2. UNAIDS. Report on the global AIDS epidemic [Internet]. United Nations Program on AIDS;2010 [cited 2010 Nov 30]. Available from: http://www.unaids.org/en/splash.html

Mechanism of the Disease:

The HIV infection process can be broken down into 7 steps:

ATTACHMENT: Once HIV enters the body, a glycoprotein found on the virus' surface targets CD4 receptors and uses one of its protein subunits to attach. CD4 receptors are found on T-helper lymphocytes, monocytes, macrophages, dendritic cells and brain microglia. To ensure binding, additional attachment to chemokine receptors help to anchor the virus.

FUSION/INTERNALIZATION: When HIV is securely attached, a different glycoprotein subunit promotes membrane fusion with internalization of the virus and its enzymes so they can prepare for replication.

REVERSE TRANSCRIPTION: Once inside the cell, the viral capsid "protein shell" uncoats exposing HIV's nucleic acid. In uninfected cells, DNA produces RNA, but HIV starts with a single stranded RNA and by RNA-dependent DNA polymerase, transcribes double stranded DNA. Since the order of transcription is reversed, HIV is called a retrovirus. This process is not flawless, and the mistakes made can allow for mutations that create many drug resistant strains of the virus.

INTEGRATION: Once the new DNA strand is created, it migrates into the nucleus using integrase (specific HIV enzyme) and incorporates itself into the host's cell chromosomes. Chromosome integration is difficult and the virus can hide in the memory T lymphocytes causing a persistent, latent infection. Once integrated, replication can begin in activated cells.

REPLICATION: Activation is through antigens, cytokines or other factors that stimulate production of nuclear factor kappa B, an enhancer binding protein. The virus produces different proteins to enhance replication and inhibit innate immunity. Under the host cell's lipid bilayer, step-wise assembly of virion particles and the merging of HIV proteins occur. They produce a nucleocapsid that carries in it a single strand of infected RNA.

BUDDING: The newly created virion buds through the plasma membrane acquiring the characteristics of the host bilayer. After budding, the virus can mature.

MATURATION: Inside the virion, protease (enzyme unique to HIV), cleaves a polypeptide into functional proteins necessary to produce a completed virus. Without protease, the virion stays immature and cannot infect other cells.

Diagnosis and Monitoring:

The most common diagnosing method is ELISA – enzyme linked immunosorbent assay. This method is used to detect antibodies against HIV. It is highly sensitive and specific. The time to develop antibodies can vary, but the minimum is 3-4 weeks from initial exposure. If results are positive for ELISA, a repeat test followed by a confirmatory test is performed for diagnosis.

Once HIV is diagnosed, the disease is monitored by two markers, viral load and CD4 cells.

- Viral load tells the degree of viremia by measuring the number of copies of viral RNA in the plasma, and it is the major prognostic factor for monitoring progression and effect of treatment.
- CD4 Cell count is also a marker for progression due to HIV destroying cells with the CD4 receptor.
    - Normal human CD4 cell count is 500-1600 cells/mm^3.
    - HIV infection causes a drop in CD4 count and an AIDS diagnosis is made when the CD4 count falls below 200 cells or after an AIDS indicator condition is diagnosed.

Clinical presentation of HIV can vary but most patients have an Acute Retroviral Syndrome, a mononucleosis-like illness with symptoms lasting about 2 weeks, and possible hospitalization.

- Symptoms include fever, sore throat, fatigue, weight loss, and myalgias.
    - About 40-80% of patients have a morbiliform or maculopapular rash involving the trunk of the body.
    - Other symptoms include diarrhea, nausea, vomiting, lymphadenopathy and night sweats.
    - Aseptic meningitis (fever, headache, photophobia, stiff neck) can be seen in about ¼ of cases.
- Primary infection is associated with a high viral load >10^6copies/mL and a precipitous drop in CD4 cells. The virus disseminates to and is replicated in the lymph tissues. After several weeks, an immune response is mounted and the HIV RNA amount falls greatly and symptoms resolve gradually.
- This latent period is not virologically latent (HIV replication is continuous-10 billion viruses a day) and the immune system has ongoing destruction.
- The persistent CD4 decrease is the best way to measure the immune system deterioration.
- The viral load will appear to have stabilized at a "set point"

The "set point" coincides directly with the time to AIDS and morbidity. The higher the viral set point, the poorer the prognosis, and the faster to onset of AIDS and death.

1. Anderson PL, Fletcher CV, and Kakuda TN. Human Immunodeficiency Virus Infection. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiolgic Approach 7th ed. New York: McGraw Hill; 2008. p 2065-2070.
2. Dumond JB and Kashuba A. Chapter 69: Pharmacotherapy of Human Immunodeficiency Virus Infection. In: Koda-Kimble MA, Young LY, Alldredge BK, Corelli RL, Guglielmo BJ, Kradjan WA, Williams BR, editors. Applied Therapeutics: The Clinical Use of Drugs. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2009. p. 69-1 to 69-13.

Bottoms Up: Combating HIV/AIDS with "Cocktails"

While there is no cure for HIV/AIDS, treatment has vastly improved. Combination highly active antiretroviral therapy (HAART), or better known as "cocktail regimen", is the cornerstone of HIV management. HAART is the combination of at least three antiretroviral drugs that attack different parts of HIV or stop the virus from entering blood cells. This multi-modal attack has proven effective at slowing down the disease progression and has helped achieve the primary goals of therapy:

- Reduce HIV-related morbidity and mortality
- Improve Quality of Life
- Restore and preserve immunologic function
- Maximally suppress viral load

Who Gets Treated?

- All patients with history of an AIDS-defining illness or severe symptoms of HIV infections, regardless of CD4+ T cells/µL
- Asymptomatic patients with <350 CD4+ T cells/µL. Most physicians defer therapy if >350 CD4+ T cells/µL and plasma HIV RNA level >100,000 copies/mL
- Fusion/Entry Inhibitors: Work during attachment and internalization phase
- Reverse Transcriptase Inhibitors (NRTIs): incorporate into elongating strand of DNA to cause chain termination
- Non-Nucleoside reverse transcriptase inhibitors (NNRTIs): bind noncompetitively to the reverse transcriptase
- Integrase inhibitors: Work during integrase phase
- Protease inhibitors (PIs): Work during the maturation phase

Complications of ART:

- Lipodystrophy syndrome: alteration in body fat distribution in which excess fat develops in different areas of the body, most notably around the liver, stomach, and other abdominal organs (visceral body fat).
- Hyperlipidemia: especially hypertriglyceridemia, is mainly associated with PIs and can be treated with statins or triglyceride lowering agents
- Lactic Acidosis with liver steatosis is rare but fatal and is mostly associated with NRTI therapy

1. Anderson PL, Fletcher CV, and Kakuda TN. Human Immunodeficiency Virus Infection. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiolgic Approach 7th ed. New York: McGraw Hill; 2008. p 2065-2070.
2. Dumond JB and Kashuba A. Chapter 69: Pharmacotherapy of Human Immunodeficiency Virus Infection. In: Koda-Kimble MA, Young LY, Alldredge BK, Corelli RL, Guglielmo BJ, Kradjan WA, Williams BR, editors. Applied Therapeutics: The Clinical Use of Drugs. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2009. p. 69-1 to 69-13.
3. Nurutdinova D, Overton ET. Human Immunodeficiency virus infection and acquired Immunodeficiency syndrome. In: Cooper DH, Krainik AJ, Lubner SJ, Reno HE. The Washington Manual of Medical Therapeutics. 32nd Ed. Lippincott Williams and Wilkins. Philadelphia, PA; 2009: 408-428

From the Medical Literature

Approval of Egrifta® (tesamorelin) to treat lipodystrophy

On November 10, 2010, the Food and Drug Administration approved tesamorelin, a synthetic growth hormone releasing factor (GRF) drug that is administered in a once-daily injection, to treat HIV patients with lipodystrophy. Egrifta® was approved to induce and maintain a reduction of excess visceral abdominal fat in HIV-infected patients with lipodystrophy.

Egrifta® was developed by Montreal-based Theratechnologies Inc. and marketed in the U.S. by Rockland, Massachusetts-based EMD Serono. Egrifta® approval was based on data from 2 multicenter, randomized, double-blind, placebo-controlled phase 3 studies of 816 HIV-infected adult men and women with lipodystrophy and excess abdominal fat. Of these, 543 patients received Egrifta® during a 26-week, placebo-controlled period. In both studies, patients treated with Egrifta® experienced greater reductions in abdominal fat (15 - 17%) as measured by CT scan, compared with patients receiving another injectable

solution (placebo). Some patients reported improvements in their self image. The decreases in visceral abdominal fat and waist circumference were sustained in patients who received extended therapy with tesamorelin for 52 weeks.

The recommended dose of tesamorelin is 2 mg injected subcutaneously once daily in the abdomen. Adverse events most commonly reported in tesamorelin-treated study patients included arthralgia (13% vs placebo, 11%), pain in extremity (6.1% vs 4.6%), myalgia (5.5% vs 1.9%), injection-site erythema (8.5% vs 2.7%), injection-site pruritus (7.6% vs 0.%), and peripheral edema (6.1% vs 2.3%).Worsening blood sugar control occurred more often in patients treated with Egrifta® than with placebo.

1. Falutz J, Allas S, Mamputu JC, Potvin D, Kotler D, Somero M, Berger D, Brown S, Richmond G, Fessel J, Turner R, Grinspoon S. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. AIDS. 2008; 22 (14): 171-28.
2. Jefferson E. FDA approves Egrifta to treat lipodystrophy in HIV patients. FDA News Release. Updated 10 November 2010 [cited 18 November 2010]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm233516.htm
3. Lowry F. FDA panel gives thumbs up for Egrifta. Medscape Medical News. Copyright 2010 [cited 18 November 2010]. Available from: http://www.medscape.com/viewarticle/722647

Prophylactic treatment decreases the risk of HIV infection

A recent study published by *The New England Journal of Medicine* evaluated HIV negative homosexual men and transgender women who have sex with men on emtricitabine and tenofovir. These patients were found to be 44% less likely to contract HIV.

This placebo controlled study followed 2499 people for up to 2.8 years. They were monitored for HIV and other sexually transmitted infections, given condoms, and counseled on how to reduce their risk of developing AIDS at every visit. The most common side effects associated with emtricitabine and tenofovir use were nausea, diarrhea, weight loss and an elevated serum creatinine level.

Based on this study, providers can now recommend prophylactic treatment to their high risk patients. This is another big step in the fight against HIV and AIDS.

Grant R, Lama J, Anderson P, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men [Internet]. *N Engl J Med*. 2010 Nov 23 [cited 2010 Dec 2]. Available from: www.nejm.org

The last "dose" …

You're the only one who can make the difference.
Whatever your dream is, go for it.

-Magic Johnson

An electronic bulletin of drug and health-related news highlights, a service of …
Auburn University, Harrison School of Pharmacy, Drug Information Center
• Phone 334-844-4400 • Fax 334-844-8366 • http://www.pharmacy.auburn.edu/dilrc/dilrc.htm
Bernie R. Olin, Pharm.D., Director
Archived issues are available at: http://pharmacy.auburn.edu/dilrc/au_informed.htm