Clinical Aspects of Human Immunodeficiency Virus Infection (HIV): Background Reading

Students:
On Wednesday, April 10, 2019 at 10:30 am there is an MHD session entitled “HIV—Clinical Aspects” led by Dr. Nina Clark from Infectious Diseases. Clinical issues regarding HIV management will be presented and discussed.

In order for you to get the most benefit from this session on 4/10/19, PRIOR preparation is essential. Because the topic of HIV infection is quite broad, the HIV monograph below written by Dr. Clark contains epidemiologic and clinical background on HIV that supplements the information you will hear during the lecture; the session on 4/10/19 will focus more on HIV testing, complications and treatment. We will also send you a set of questions for a pre-session self-assessment of your understanding of some of the clinical aspects of HIV. You should complete these questions PRIOR to the case-based discussion on 4/10/19.

Learning Objectives for “HIV—Clinical Aspects” monograph and session:

1. Describe the epidemiology and risk factors for HIV infection
2. Compare methods of testing for HIV
3. Discuss the indications for starting antiretroviral therapy and its benefits
4. Recognize the opportunistic infections that occur at various stages of HIV
5. Explain how laboratory markers are used to monitor the course of HIV infection and inform the use of medications to prevent complications
HIV MONOGRAPH

1. The Scope of the HIV Epidemic
The acquired immunodeficiency syndrome (AIDS) is one of the worst pandemics experienced by humans. It began as a zoonosis; the simian relative of HIV, simian immunodeficiency virus (SIV), crossed species barriers into humans and became a new human pathogen, HIV. It is thought that humans encountered SIV through the hunting of African non-human primates (e.g., chimpanzees). 1, 1 AIDS was first recognized in 1981, when a cluster of cases of Pneumocystis pneumonia was reported among young homosexual men in Los Angeles, CA. 2 The retrovirus that causes HIV/AIDS was subsequently isolated in 1983 and the first HIV test became commercially available in the US in 1985. 3 Since that time, the disease has spread to infect >77 million people in the world, and an estimated 25 to 50 million persons worldwide have died from an AIDS-related illness. 4 One million persons died from AIDS-related illnesses in 2016. 5

Figure 1. Worldwide distribution of HIV-1 infections in 2016. 6
In 2017, 36.9 million people were living with HIV and 1.8 million became newly infected. The vast majority of infected persons live in sub-Saharan Africa with the Americas the 3rd most affected region (Figure 1). Fortunately, through intensive prevention and treatment efforts, annual new HIV infections have fallen globally by 36% between 2000 and 2017 and AIDS-related deaths have fallen by 38%. In 2017, approximately 21.7 million persons living with HIV (59%) were receiving antiretroviral therapy, a progressively increasing number since 2010. Continued new infections and longer lifespans due to treatment with antiretroviral medication have led to an increase in US and worldwide prevalence of people living with HIV.

However, not every country has experienced declines in annual new infections, and some regions such as Eastern Europe and central Asia have experienced significant increases. Furthermore, the global prevalence of HIV infection, 37 million persons, is still devastating. As of 2015, HIV/AIDS was no longer the leading cause of death in Africa but was still the second leading cause, after lower respiratory tract infections.

In 2016, the CDC announced that annual HIV diagnoses in the US fell by 19% from 2005 to 2014. There were significant declines in new infections among heterosexuals, injection drug users and African American women, but other subgroups showed increases in HIV infections, particularly Latino gay/bisexual men and black gay/bisexual men. There were still almost 40,000 people diagnosed with HIV in the US in 2016.

2. HIV-1 Transmission and Risk Groups

In sub-Saharan Africa, HIV is spread predominantly through heterosexual contact. Young African women are disproportionately affected; relationships between young women and older men (including those related to sexual abuse/violence), lack of access to education and low condom use contribute to this. Male and female sex workers in Africa are also at especially high risk. Data on HIV infection in men who have sex with men (MSM) are very limited for Africa and injection drug use as a risk factor is relatively low.

In the US, MSM and racial/ethnic minorities are disproportionately affected by HIV, particularly African Americans. MSM represent 3-4% of the male population in the US but accounted for 66% of new infections in 2017. African Americans comprise 13% of the US population but accounted for 43% of new HIV diagnoses. Hispanics/Latinos comprise 18% of the population but account for 26% of new HIV diagnoses. Data on new HIV infections in the US in 2017 are represented below:
Other at risk populations include intravenous drug users (4% of new infections in 2017) and heterosexuals (24% of new infections), especially women.\textsuperscript{12}

For some populations, the lifetime risk of HIV diagnosis in the US is extremely high when using 2010-2014 infection rates, particularly for racial/ethnic MSM:

**Figure 3.** Source: CDC\textsuperscript{13}

The lifetime HIV risk for African American women is 1/48, for Hispanic women is 1/227 and for white women is 1/880.\textsuperscript{13}

HIV is concentrated in urban areas, and the highest rates of new HIV infections in 2017 were in the Southern US states (more than half of new infections), followed by the West, Northeast and Midwest.\textsuperscript{10}
Perinatal infection in the US has declined significantly due to testing pregnant women for HIV and providing prophylaxis with antiretroviral therapy (ART) to infants born to HIV-infected mothers. The rate of perinatal transmission can be reduced from ~25% in the absence of ART to < 1% if appropriate ART is given to the mother and ART prophylaxis given to the infant, Cesarean section provided when a mother’s viral load is elevated and breastfeeding is avoided.\(^\text{14}\) It is recommended that ART be started as early in pregnancy as possible, regardless of CD4 count or viral load.\(^\text{15}\) The CDC recommends routine opt-out HIV testing for women during pregnancy.\(^\text{16}\)

Knowing one’s HIV status and knowing that of one’s partner is ideal to help reduce risky behaviors. In the early years of the HIV epidemic, many states imposed laws that held persons with HIV criminally liable if they knowingly exposed others to HIV through sex or needle use. These laws were largely passed prior to the availability of data which show ART decreases the risk of HIV transmission. In Illinois, persons with HIV are required by law to disclose their HIV status to a partner if there will be unprotected sex or sharing of needles.\(^\text{17}\) Physicians are allowed but not obligated to inform a legal spouse or civil union partner of someone with HIV, after giving the HIV-infected person a chance to inform the partner.\(^\text{18}\)

3. **HIV Testing**

About 15% of HIV-infected persons in the US and a much higher percent of persons globally are unaware of their HIV infection.\(^\text{19}\) Modeling of HIV transmission by the CDC has shown that 38% of transmissions occur from persons who are unaware of their infection, and 43% occur from persons aware of their infection but not in care.\(^\text{20}\) Testing for HIV is not only important for optimal treatment and preventing AIDS but is also vital to interrupting transmission. High viral loads in blood and genital secretions increase infectiousness.

Modes of testing for HIV will be reviewed in the lecture.

4. **Natural History of HIV Infection**

HIV is typically acquired by sexual contact with an infected person but can also occur through exposure to infected blood products or be transmitted from mother to child. A higher risk of HIV transmission is associated with high levels of virus in the blood, the presence of ulcerative sexually transmitted infections (e.g., herpes simplex, syphilis), certain sexual practices (e.g., anal sex, greater number of sex partners) and lack of circumcision.\(^\text{21-23}\)

The level of viremia established after infection can influence the natural history of HIV, with higher viral loads in the weeks after infection being associated with faster progression to AIDS and death in patients who do not receive ART.\(^\text{24,25}\) A very small minority of HIV-infected persons may be “elite controllers” (~1 in 200 to 300 persons with HIV\(^\text{26}\)) and maintain undetectable HIV viral loads for a prolonged period in the absence of ART, although most of these patients will experience some level of HIV progression (elevated viral loads, CD4 decline, AIDS or death) over time.\(^\text{27}\) It is likely that unique host immune genetics are largely responsible for determining elite controller status.
HIV virions infect and destroy CD4+ T cells, and if HIV is untreated, most persons experience a gradual decline in CD4 count after infection (often without symptoms in the initial years) until AIDS occurs at an average of 10-11 years after infection. However, patients may experience enlarged lymph nodes during this otherwise asymptomatic phase and can experience the effects of other sexually transmitted infections sometimes acquired with HIV including syphilis, hepatitis B or C. As CD4 counts decline below normal but prior to significant immunosuppression (i.e., a CD4 < 200 cells/mm3), patients can experience a variety of signs and symptoms of AIDS such as weight loss, night sweats, and fatigue and may have anemia, leukopenia and/or thrombocytopenia. AIDS in HIV-infected adolescents or adults is defined as a CD4 < 200 cells/mm3 or one or more of the following illnesses regardless of CD4 count.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive if age ≥ 13 years
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* pneumonia
- Pneumonia, recurrent if age < 13 years
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

The following 2 conditions are also diagnostic of AIDS in children age < 13 years:

- Bacterial infections, multiple or recurrent
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Some infections and malignancies typically occur only once there is advanced HIV with a CD4 count < 100 cells/mm3:

- *Mycobacterium avium* complex
- Cytomegalovirus retinitis
- Cryptococcal meningitis
- Cryptosporidiosis and microsporidiosis
- Primary central nervous system lymphoma
- Progressive multifocal leukoencephalopathy due to JC virus
- Toxoplasmosis of the brain

We will focus on some of the above opportunistic processes in the session on 4/10/19.

5. **Monitoring HIV and Infection Prevention**

Once HIV is diagnosed, regular medical and laboratory monitoring can help treat and prevent complications of HIV and associated illnesses. There are a number of tests that should be performed after HIV diagnosis including CD4 T-cell count, plasma HIV RNA (viral load), HIV genotype (which can identify mutations in the HIV reverse transcriptase and protease genes that may predict resistance to certain ART medications), screening tests for other sexually transmitted infections and testing for tuberculosis.

HIV viral loads can serve as a marker of response to ART. A persistently “undetectable” viral load (generally < 20-40 copies/ml) is one of the goals of ART.

CD4 cell counts help gauge the immune function of persons with HIV. A CD4 count should be obtained at entry into care, and periodically afterwards, to assess the response to ART. CD4 counts often increase significantly after ART and may reach a normal level over a period of years, particularly if ART is started at CD4 >350 cells/mm3.

Certain opportunistic infections can be prevented with antibiotic prophylaxis or vaccination, and this will be discussed in the session on 4/10/19.

6. **Antiretroviral Therapy**

Effective combination antiretroviral therapy, available since 1996 with the introduction of the protease inhibitor class of medications, dramatically altered the treatment and outcomes of HIV infection, with marked declines in AIDS-defining diagnoses and mortality.

However, ART treatment cannot cure HIV infection and needs to be taken for life. In addition, HIV medications can cause short- and long-term side effects, including diseases associated with aging such as cancers, renal and hepatic dysfunction, osteoporosis, dyslipidemia, diabetes and cardiovascular disease. Drug-drug interactions are another important consideration, as many ART medications are metabolized by cytochrome P450 enzymes and can affect the levels of other common medications. In addition, acid-blocking medications and food can in some cases significantly affect ART absorption. The
development of ART resistance is an additional potential complication, particularly if patients have incomplete adherence to their medication regimen. However, the management of HIV-infected persons has changed significantly in recent years with the availability of very potent, less toxic and once daily ART regimens, many of which can be taken as a single table.

Recommended first-line ART regimens are those that include a 2-nucleos(t)ide analog reverse transcriptase inhibitor backbone plus an integrase strand-transfer inhibitor.\textsuperscript{31} Protease inhibitor-based regimens are now considered first-line only in certain situations, given their less favorable side effect profile (e.g. dyslipidemia, drug-drug interactions).

There are a number of alternative acceptable regimens but specific recommendations should be individually tailored and based on a patient’s HIV genotype, comorbid conditions, concomitant medications, viral load and patient preferences such as pill size and pill burden. Current regimens are extremely effective at treating HIV, typically with minimal or no side effects. A recent study that followed HIV-infected persons starting ART showed a very low risk of ART failure (9\%) over 5 years.\textsuperscript{36}

7. **Pre-exposure prophylaxis against HIV infection**

HIV-uninfected persons at high risk for HIV may minimize their risk for acquiring HIV by taking ART preventively. The combination antiretroviral pill containing tenofovir and emtricitabine (Truvada\textsuperscript{®}), has been approved for use as pre-exposure prophylaxis (PrEP).\textsuperscript{37} In randomized, placebo-controlled trials of tenofovir-emtricitabine in MSM, intravenous drug users and heterosexuals, the combination ART pill was significantly more effective than placebo in preventing HIV infection, and efficacy of the medication correlated with adherence to taking the medication.\textsuperscript{38-40} PrEP must be combined with counseling on risk reduction, condom use and treatment of sexually transmitted infections (STIs) as well as regular monitoring for adherence, medication side effects and testing for HIV and other STIs.\textsuperscript{41} It is unclear what additional benefit PrEP provides to an uninfected partner of a person with HIV who is taking ART and has a suppressed viral load.

References