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Acute HIV Infection A Primary Care Dilemma

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Acute HIV Infection A Primary Care Dilemma

Human immuno-deficiency virus (HIV)/ acquired immuno-deficiency syndrome (AIDS) epidemic afflicts approximately 40.3 million individuals worldwide with approximately 2.7million new infections occurring globally as of 2008, and 2 million deaths occurring annually (WHO, 2009). Although the majority of the individuals afflicted by HIV/AIDS are in developing nations, migration patterns are causing emergence of the virus in new areas. Bold steps have been made towards improvement and accessibility to antiretroviral therapy (ART), which slows down the progression of the virus, in turn leading to improved quality of life and extended life expectancy. With these improvements, the incidence of HIV is gradually decreasing while the prevalence is on the rise because of the prolonged life expectancy, which increases the opportunity for HIV transmission to others.

Overview

There are two types of HIV confirmed: HIV-1 and HIV-2. HIV-1, discovered in 1984, is responsible for the global pandemic. It also has extensive genetic diversity classified as subtypes A, B, C, D, and A/G. HIV-1 subtype B is prevalent in North America, Western Europe, and Australia while subtypes A, C, D, and A/G are most common in Africa and other parts of the world. HIV-2 was discovered in 1986 in West Africa although it has been found in several other African countries. It has spread to Portugal, France, and India. Some similarities between the two types include having the same transmission mode, as well as being associated with the same opportunistic infections and conditions. HIV-2 immunodeficiency develops more slowly, appears to be

less transmissible and is milder than that of HIV-1 (Kumar, Abbas, & Fausto, 2005; MDH, 2010).

The initial phase of AIDS is known as acute HIV infection (AHI). It has been found to be diagnosed rarely by primary care clinicians thereby posing a public health concern. This phase is not differentiated from other stages of HIV by the centers of disease control and prevention (CDC) surveillance. According to the CDC (2008), 56,300 new HIV infections occur annually of which 40-90% of these individuals experience symptoms and a substantial number of them will seek medical care. These individuals usually present in primary care settings or emergency care departments. Diagnosing AHI is a challenge because there is no combination of signs and symptoms that reliably distinguishes patients with AHI from other viral illnesses.

AHI usually occurs 2 to 4 weeks after the initial viral exposure and development of HIV specific antibodies. The uninfected individual exposed to HIV usually develops nonspecific symptoms within 5 to 29 days after exposure. Some of the symptoms displayed may include: fever, rash, oral ulcers, pharyngitis, arthralgias, loss of appetite, weight loss > 5lbs, malaise, myalgias, tired or fatigued, nausea, headaches, photophobia, night sweats, confusion, infected gums, diarrhea, genital sores, vomiting, anal sores, and stiff neck (Kelley, Barbour, & Hecht, 2007). Differential diagnoses for AHI include: Epstein-Barr virus, cytomegalovirus, acute viral hepatitis, enteroviral infection, secondary syphilis, toxoplasmosis, herpes virus encephalitis, and influenza during the cold and flu season. However, rhinorrhea and coryza are not typically seen in AHI (Sentangelo, 2001). These individuals are usually unaware of their infection and continue to engage in risky sexual activities and needle sharing, putting others at risk. During this

phase the individual has a significantly higher risk of transmitting the virus because the blood viral load is higher.

There are five groups of adults in the U.S. identified at risk for contracting HIV/AIDS: (a) homosexual or bisexual men, (b) intravenous drug abusers, (c) hemophiliacs, (d) recipients of blood and blood products, and (e) heterosexual contacts. Homosexual and bisexual men account for the majority of reported cases in the U.S. whereas in developing nations, heterosexual transmission is the dominant mode of infection (Kumar et al., 2005). It is noted 1 in 5 people living with HIV in the U.S. are unaware of their infection (CDC, 2008). Also, the transmission of HIV has been found to be at its highest during the initial and final phases of the disease (Pilcher, et al., 2007; 2004; Wawer, et al., 2005).

HIV/AIDS has impacted the economies of both developing and developed countries. Developing countries have experienced decreased life expectancies, reduced earning power for the caregivers, and increased the number of orphaned children. Among developed nations, HIV/AIDS toll is felt on the exorbitant healthcare expenses incurred in maintaining those who have acquired the virus. Therefore, it is important for primary care providers to diagnose and initiate therapy sooner rather than later in order to curb the spread of HIV. This paper focuses on HIV-1, the most common type. Furthermore, the paper addresses the rare diagnosis of AHI by primary care providers and explores the opportunity for HIV surveillance and prevention through presenting symptoms, differential diagnoses, and testing recommendations among the population at risk. Finally the paper utilizes Margaret Newman's nursing theory of health is the expansion of consciousness.

Pathophysiology

On a cell level, the HIV viron envelope contains two viral glycoproteins: surface glycoprotein (gp) 120 which is attached to trans-membrane gp41. Infection occurs through the binding of the gp120 envelope to the CD4 molecule which is one of the T lymphocytes and is a high-affinity receptor for HIV. This leads to a change on gp120 resulting in a new recognition site for other target cell surface molecules known as co-receptors CCR5 or CXCR4. Similarly, change on gp41 occur leading to a fusion peptide insertion into the target cell membrane. The virus then replicates leading to cellular death of the infected cells and nearby bystander immune cells. Acute infection is manifested by a massive viral replication in an environment rich in CD4, CCR5, and CXCR4 target cells and goes unchecked by the host immune system which has not been previously sensitized to HIV antigens (Kumar, Abbas, & Fausto, 2005; Self, 2010). The HIV variants that first appear in more than 90% of AHI use target cell surface molecule CCR5 exclusively regardless of the route of infection (Zetola & Pilcher, 2007).

Sexual transmission is the most common mode of HIV infection worldwide. At the time of sexual contact viral particles cross the genital epithelial layers and infection is started by replicating within the target cells at the point of entry. Infection at the inoculation site and the draining lymph tissue is established within 72 hours of a transmission event. Systemic infection occurs after 7 days as the virus spreads through the lymphatic and circulatory systems. At this point, a viral load measurement is possible. Days 8 to 30 involve massive viral replication with a doubling of the viral load approximately every 8 hours in addition to the death of large numbers of CD4 cells. A dramatic depletion of CD4 cells occurs and is most pronounced in the abdomen which is

the largest lymphoid organ. This depletion is seen as a decrease of the CD4 cell count in a peripheral blood specimen. During this time, the host's immune system is in a state of hyper-activation, leading to the symptoms of acute retroviral syndrome. In this environment, there is increase and activation of CCR5+ T lymphocytes which provides further fuel for viral replication because T cells with an activated phenotype are more susceptible to HIV infection. The immune system begins to mount an HIV specific response, and the first anti-HIV antibodies are produced. These antibodies can first be detected in a patient's serum 3-7 weeks post infection, marking the event of seroconversion. High levels of immune activation among people with AHI, is one of the strongest predictors of progression to AIDS. (Self, 2010; Zetola & Pilcher, 2007).

Peak levels of virus in the blood and genital shedding occur around day 30, followed by a period of abrupt decline in viral load 4 to 10 weeks post infection. The causes for this decline are not clearly understood but are thought to involve the depletion of the reservoir of CD4 or CCR5 cells available for infection and the appearance of specific anti-HIV cytotoxic CD8+ T lymphocytes which limit viral replication and accumulate in significant numbers at mucosal sites after the viral load peak. Week 10 represents the lowest point of viral load in both blood and genital secretions. Weeks 10 to 24 are characterized by interaction between the host immune response and viral replication, eventually leading to a point of equilibrium with a stable viral load and CD4 count termed as the set point. Week 24 is typically considered the end of the AHI infection, after which the patient enters the period of chronic HIV infection (Self, 2010; Zetola & Pilcher, 2007).

Chronic HIV establishes within 30 days of acute infection. The virus propagates within the large number of follicular dendritic cells found in the lymph nodes which trap and retain infectious HIV particles and protect them from degradation for many months. Much smaller numbers of CD4+ T cells with memory phenotype integrate the virus into their chromosome, and do not spontaneously produce virus unless activated. Their long lifespan of 44 months creates one of the main barriers to HIV eradication with current ART. The next section will review literature regarding AHI, screening, diagnostic tests, and management.

Literature Review

The transmission of HIV is dependent upon the infectiousness of the host and the susceptibility of the partner neither of which parameters are uniform over time. Since 80% of HIV is acquired through sexual transmission, understanding viral dynamics in different body fluids is vital for the primary care provider. Pilcher et al. (2007) conducted a cross-sectional study involving 16 men with AHI and 25 men with chronic HIV infection in a sexually transmitted infection clinic in Lilongwe, Malawi. The researchers found the HIV viral load concentration is high in semen during the AHI stage and later in the AIDS stage of the disease shortly before death. The estimated peak time for the viral load was found to be later for semen than in blood with seminal plasma peaking at 4 weeks after infection. For the chronically ill HIV patients with low CD4 cell count the estimated peak time was found to correlate with increased semen and blood viral loads. This study provided a biological explanation for reported increases in HIV transmission during the acute and late stages of infection, thereby emphasizing the importance of early detection of HIV in all individuals especially during the first few days of infection when

infectiousness is amplified and risk for sexual transmission of the virus is substantially increased.

Similarly, a retrospective study involving 235 monogamous HIV-discordant heterosexual couples in Uganda by Wawer, et al (2005) found the highest rate and proportion of HIV transmission per coital act occurred during early and late stages of the disease. The highest rates of acquisition were among partners of patients who recently acquired HIV followed by those with end-stage AIDS. The AHI stage is a time when few seroconverters know their HIV status or receive ART putting them at a higher risk of transmitting the virus.

Early detection of AHI is emphasized because of the capability to predict the progression of HIV to AIDS. This aspect was observed in the prospective study done by Kelley, Barbour, and Hecht (2007) in San Francisco to examine the relation between symptoms, initial viral load, and viral load set point in AHI. These scholars concluded the number of AHI symptoms experienced was strongly related to higher initial viral load in individual first evaluation before seroconversion or recently after seroconversion. The study involved questioning 57 subjects having preseroconversion AHI and 120 subjects having recent seroconversion infection about 21 potential AHI symptoms at enrollment and followed up with viral load measures. The study suggests a low viral load during AHI or soon after seroconversion is a more reliable indicator of which individuals are likely to achieve a low viral load set point and subsequent disease course than the severity of AHI. This information is vital for the primary care provider because it can help in prioritizing care and close monitoring for those patients with higher viral load set point.

Early initiation of therapy has been noted to improve and slow down the progression of HIV to AIDS through various mechanisms. A prospective study by Kassutto, Johnston, and Rosenberg (2005) included 150 patients with symptomatic acute or early onset HIV-1 infection. They were treated with ART and were observed monthly in clinical and laboratory evaluations which utilized serial HIV enzyme-linked immunosorbent assay and Western blots until a fully evolved HIV-1 antibody response was documented. Three of the patients who initiated ART in a mean interval of 8 days after presentation and were observed for a mean duration of 50.2 months did not develop a fully evolved HIV-1 antibody response or demonstrated complete or partial HIV-1 seroreversion despite maintenance of cytomegalovirus- specific humoral responses. Virologic suppression and seroreversion occurred a mean duration of 4.1 months and 15.5 months respectively after the initiation of therapy. All patients maintained complete virologic suppression while receiving therapy and had an undetectable HIV-1 ribonucleic acid (RNA) load at the time of seroreversion. This study suggests that early ART associated with durable virologic suppression in acute HIV-1 infection may stop the formation or detection of HIV-1 specific antibodies. Ongoing antigenic stimulation may be required to maintain HIV-1 specific humoral responses. Incomplete evolution of the HIV-1 antibody response and/or presence of seroreversion underscore the potential unique immunologic effect of early ART in patients with AHI.

Early detection of AHI is also noted to alter the behavior of patients and help curb the transmission of HIV. In the U.S., a meta-analysis study compared the prevalence of high-risk sexual behaviors in HIV positive persons aware of their serostatus with that of HIV positive persons unaware of their status. The study produced 11 independent

findings of which 6 findings compare HIV positive aware persons with independent groups of HIV unaware individuals (between-groups comparison), and the other 5 findings compared seroconverting individuals before and after being notified of their HIV positive status (within-subject comparisons). Outcomes were self reports of unprotected anal or vaginal intercourse (UAV) during specified recall periods. It was found that the prevalence of UAV with any partner was an average of 53% lower in HIV positive persons aware of their status compared to HIV positive persons unaware of their status. Reductions were greater in between-groups comparisons than within-subject comparisons. This study concluded that high-risk behavior is reduced substantially after people become aware of their HIV positive status. Therefore, increased emphasis on HIV testing and counseling is needed to reduce exposure to HIV from persons unaware of their status (Marks, 2005).

Likewise, Wayne, et al (2009) noted short-term behavioral changes influenced by early diagnosis of AHI among 28 participants who completed structured surveys and in-depth interviews shortly after learning of their infection and 2 months later. Quantitative analyses showed significant changes in behavior after diagnosis, including reduction in number of partners, serosorting which involves choosing partners thought to have a similar HIV serostatus especially among homosexual men, and limiting unprotected intercourse with others believed to be HIV positive. However, this study unlike others in the past noted decreased success at increasing condom use. Participants expressed marked discomfort and difficulties with condoms. Seropositioning whereby HIV serodiscordant male couples choose sexual positions in which the likelihood of HIV transmission is believed to be lower was not used by these participants.

Screening

Diagnosis of AHI is a challenge because there is no combination of signs and symptoms that reliably distinguish a patient with AHI from other viral illnesses. Therefore, liberal use of HIV testing among patients with signs of potential AHI and risk factors of the disease is warranted. As of 2006, the CDC recommended screening all high risk individuals. Voluntary HIV screening was found to be cost effective even in healthcare setting with HIV prevalence just as other established screening programs for chronic diseases. Screening reaches a conventional benchmark for cost-effectiveness because of the significant survival advantage resulting from early diagnosis of AHI when therapy can be initiated before severe immunologic compromise occurs.

In an effort to increase the detection and demonstrate the feasibility of AHI surveillance, a study was conducted using a pooled nucleic acid amplification testing (p-NAAT) which detects viral genetic material from patient specimens was conducted. In 2008 the New York City department of health and mental hygiene found using p-NAAT can increase AHI diagnoses among high risk sexually transmitted diseases (STD) clinic patients and indicate that AHI diagnoses can be made apart from p-NAAT screening programs. Pilcher, et al (2005) found adding NAAT to an HIV testing algorithm significantly increases the identification of cases of infection without impairing the performance of diagnostic testing. The detection of highly contagious, acutely infected persons creates new opportunities for HIV surveillance and prevention. Also, it was found specimen pooling resulted in outstanding performance and cost-effectiveness with NAAT. This study led to the CDC recommendation to individuals with very recent high-risk exposures to be encouraged to retest after 4 to 6 weeks, even if p-NAAT is negative.

Diagnostic Testing

In pursuing a diagnosis of AHI two classes of HIV testing should be considered: (a) serologic tests, which detect antibodies produced by the patient in response to HIV infection, and (b) NAATs which detect viral RNA within the patient's blood. A positive serologic test result is the standard for diagnosing chronic HIV infection. However, serologic testing alone is not reliable for AHI because of the timeline between inoculation and sero-conversion known as the diagnostic window. It has been found seroconversion typically occurs 3 to 7 weeks after infection. However, antibodies can be detected as early as 3 weeks in many patients (Self, 2010).

Qualitative and quantitative NAATs have been developed for the detection of HIV RNA. The quantitative test commonly known as viral load can detect as few as 40 copies/ml and shows positive results in the first or second week of infection. Usually, patients have very high viral loads greater than 100,000 copies/ml with the development of AHI. Therefore, NAATs are the standard for diagnosing AHI. False-positive results in NAATs occur in 3% to 5% of patients, depending on the disease prevalence but are usually identifiable by a low viral load (<10,000 copies/ml) which is inconsistent with acute infection. NAATs require several hours to complete and further more, qualitative NAATs screening tests are pooled for cost reduction. Therefore, diagnosing AHI cannot be confirmed in a timely manner of a typical emergency department patient course. Arrangements should be made for the patient to obtain the results or there should be close follow up where a NAAT can be performed (Self, 2010).

An alternative to NAATs for diagnosing AHI are assays that detect the HIV p24 antigen. The p24 antigen test is simpler and the result becomes positive 3 to 6 days after

performing NAATs. However, the p24 test is less sensitive than NAATs, cannot be pooled, and the result is not reliably positive during chronic infection when less than half of the patients have a positive p24 antigen test result because of patient antibodies binding the p24 antigen thereby interfering with the test. Therefore, NAAT is typically chosen over the p24 antigen test for diagnosing AHI (Self, 2010). A summary of the diagnostic testing is shown in table 1 below.

Table 1

Results of Diagnostic Tests during AHI and Chronic HIV Infection

	No HIV infection	AHI	Chronic HIV infection
Serologic Testing (standard/rapid)	Negative	Usually negative*	Positive
Detuned Serology	Negative	Negative	Positive
NAAT	Negative	Positive	Positive
P24 Antigen testing	Negative	Positive	Positive or Negative

*Standard and rapid serologic test results are usually negative during acute HIV infection; however because of the high sensitivity of modern serologic tests and the ability to detect some immature IgM antibodies, serologic tests are rarely positive or indeterminate.

(Self, 2010)

Management

Management for AHI has been summarized by Self (2010) as a holistic approach involving a 4-point system:

1. Considering initiation of ART

2. Arranging for long-term care with an HIV specialist
3. Decreasing the risk of further transmission through patient counseling
4. Providing psychosocial support

There are many benefits associated with early initiation of ART. These include protecting CD4+ cells early in the infection thereby allowing a more robust initial anti-HIV immune response, limiting viral mutations and therefore decreasing the potential for antiviral resistance, improving the symptoms of AHI, and decreasing the risk of viral transmission during peak levels of virus in the blood. However, some disadvantages of early initiation of ART are increased medication toxicity because of early exposure to the agents for longer periods, and the substantial financial costs of the medications. Furthermore, early ART may drive antiviral resistance if the medications do not completely suppress viral replication, especially among patients with poor medication regimen compliance. Studies have shown that patients with the highest likelihood to benefit from immediate ART may be those with severe, unremitting symptoms of AHI and those with an initial CD4 count less than 350cells/uL (Self, 2010; Zetola & Pilcher, 2007). Aggressive treatment may delay progression of the infection and thus preserve treatment options if a more effective and perhaps even curative treatment emerges in the future.

Recommendations for initiating ART are based on HIV viral load and CD4 count as illustrated on table 2 below according to Pagana & Pagana(2009). Genotypic resistance testing should be performed at baseline prior to initiation of any therapy to help guide in the selection of antiretroviral drug regimen (ARV) which will optimize the virologic response (DHHS Panel, 2011).

Table 2

Recommendations for ART Based on Viral Load and CD4 Count

		HIV RNA viral load copies/ml	
CD 4 count, x 10(5)/L	<5000	5000-30,000	>30,000
<350	Recommend therapy	Recommend therapy	Recommend therapy
350-500	Consider therapy	Recommend therapy	Recommend therapy
>500	Defer therapy	Consider therapy	Recommend therapy
<i>Symptomatic</i>		Recommend therapy	

(Pagana & Pagana, pp. 530, 2009)

The next section will focus on utilization of Margaret Newman's nursing theory in executing the strategies.

Application of Nursing Theory in Primary Care

Margaret Newman's nursing theory of "health is the expansion of consciousness" (HEC) is a suitable guide for implementing care in the primary care setting especially when working with chronically ill patients. This grand theory is applicable to any situation across the life span. It is rooted in the Martha Roger's theory of Unitary Human Beings which characterizes health and illness as simple manifestations of the rhythmic fluctuations of the life process therefore being an indivisible process. HEC was inspired by concern for those whom health as the absence of disease or disability is not possible (Newman, 2010). It includes the health of all persons regardless of presence or absence of

disease. It asserts that every person in every situation no matter how chaotic and hopeless it may seem is part of the universal process of expanding consciousness – a process of becoming more of oneself, of finding greater meaning in life, and of reaching new dimensions of connectedness with other people and the world (Newman, 2008).

NPs are nurses first, and this aspect contributes to their connectedness with the patient. While interacting with the patient, the nurse assists the patient in getting in touch with the meaning of their lives through identification of relating patterns. The NP as a primary care provider is in a good position to facilitate pattern recognition by forming relationships with the patients at this crucial time of their lives when they are newly diagnosed with HIV/AIDS. In addition, the NP serves as a partner to the patients in the process of expanding consciousness. Where acquisition of HIV leads to suffering by degradation of the immune system which leads to increased susceptibility to illness, and at the same time it opens up greater sensitivity to themselves and others. In so doing, the NP cultivates an environment which encourages recognition of self awareness (the pattern) thereby leading to acceptance of one's circumstances or limitations in this case living with HIV/AIDS. Realization of one's own pattern/self awareness leads to in depth understanding of one's condition and may pave the way for the patient to engage in activities leading to a positive outlook of the disease process.

The NP may act as a liaison for the patient to establish long-term HIV care in a specialty clinic. This is important for proper disease monitoring, preventative measures such as immunizations and prophylactic antibiotics, initiating and altering ART regimens, and ongoing counseling. From a public health perspective, use of pattern recognition through relationships with patients will assist in identify a network of people at risk for

HIV infection and interrupt ongoing transmission of the disease. Risk reduction counseling should be initiated immediately with clear concise education about infectious potential of acute HIV and strategies to prevent its spread.

Conclusion

Early diagnosis of AHI and initiation of ART should be a priority for all primary care providers in order to curb the transmission of HIV, and potentially alter sexual behavior thereby interrupting the public health risk posed due to a lack of knowledge of one's HIV status. Although advancements in HIV/AIDS treatment have come a long way, it continues to be an enormous economic burden for many countries. Therefore, screening, early diagnosis, and early initiation of therapy takes precedence for all people.

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