HIV: Treatment approach to a unique and elusive virus

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A manuscript submitted in partial fulfillment
Of the requirements for the degree of
MASTERS OF NURSING

Washington State University, Yakima Branch
College of Nursing
April 2010
To the Faculty of Washington State University:

The members of the Committee appointed to examine the manuscript of MARK RICHARD TAYLOR find it satisfactory and recommend that it be accepted.

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HIV: Treatment approach to a unique and elusive virus

Abstract

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April 2010

Chair: Lorna Schumann

Submitting to the *Journal of the Association of Nurses in AIDS Care*.

Over the last twenty-five years, HIV-1 has circled the globe as a pandemic affecting millions of people. HIV-1 has unique and elusive biochemical properties. It is unique in that it uses immune system cells to infiltrate the body. It is elusive in that it reproduces at an astounding rate with large numbers of mutant strains evolving constantly. Given these characteristics, one would expect rapid development of resistance to antiretroviral treatments. This has occurred in the United States. In Africa, generalized epidemics account for 22 million carriers of HIV-1 with a multitude of genetic variants. The anticipated result of HAART rollout is that current drugs become obsolete as viral resistance quickly develops. This has not been the case according to recent studies following the efficacy of HAART implementation in Botswana, South Africa, and Tanzania. Further studies must continue to track HIV-1 subtype proliferation and the development of resistance to HAART protocols.

*Key words*: diversity, drug resistance, HIV, HIV-1, Sub-Saharan Africa
Section I. Introduction

The global epidemic of human immunodeficiency virus (HIV) has received worldwide attention as it has amassed millions of victims and contributed significantly to morbidity and mortality. Currently, HIV prevalence stands at 1.1 million people in the United States, with 56,000 new cases each year (Centers for Disease Control and Prevention, 2007). Globally, the prevalence is much greater with 33 million people currently living with HIV, and 2.7 million new cases each year. There are 2 million yearly deaths associated with acquired immune deficiency syndromes (AIDS) (World Health Organization, 2007). The virus continues to spread with disproportionate representation geographically in Sub-Saharan Africa, where 22 million cases exist accounting for two-thirds of the global pandemic. Treatment approaches to HIV have hinged on the use of highly active antiretroviral therapy (HAART), which is the use of three drugs with different mechanisms working against the virus in tandem. Tremendous success has been achieved in decreasing mortality and morbidity in developed countries. Despite over 25 years of intensive research, however, scientists have yet to develop a safe and effective vaccine. Though great strides have been made with HAART, the individual drugs used to treat HIV are feared to possess short life spans, due to the nature of HIV.

HIV is a unique and elusive retrovirus, first recognized in 1981 as the disease manifestation of AIDS. It is unique in that the subunit associated with human cell binding, the viral envelope protein (env), has affinity for CD4 receptors. These are transmembrane glycoproteins that are expressed on the surface of T-Helper lymphocytes, macrophages, dendritic cells, and brain microglia. When internalized in the human cell, an enzyme, reverse transcriptase, translates the viral RNA into the host cell’s DNA (Anderson, Kakuda, & Fletcher, 2007). HIV is elusive in its biochemical pathogenesis. Reverse transcriptase in the HIV virus is
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A problematic enzyme in that it creates mutations at a high rate without correction leading to millions of variations daily in an infected individual (Taylor, Sobieszczyk, McCutchan, & Hammer, 2008). The virus can replicate at a rate of several billion virus per day. So, the direct attack on immune system cells, the high mutation rate, and the high replication rate combine to create the perfect storm for human immune defenses. Thus, HIV often overwhelms its human host, escaping the defense mechanisms that are otherwise formidable.

The epidemiology of the disease helps explain its current pandemic status. HIV is thought to have been a cross-species infection from primates. Its first verified appearance by historical testing was in 1959 in the Congo River region of central Africa. HIV was most likely well-established in Central Africa at this time and probably originated at the turn of the century (Worobey, et al., 2008). HIV-1 has three main groups: M, N, and O. These are recognized as three distinct viral crossover events from African primates evidenced by distinct genetic sequence differences. Crossover events most likely occurred in hunting and preparing game for food. In this process, blood was exchanged and HIV-1 evolved in the infected humans. HIV-2 is a distinct and less virulent form of the virus that remains fairly isolated in West Africa and will not be discussed in this paper. Group M of HIV-1 is the dominant player in the worldwide pandemic. Given the affinity for mutation of the HIV virus, the disease has proliferated in numerous forms categorized by sub-types: A-D, F-H, and J-K. Sub-sub types have evolved for Subtype A and F. When two different viral strains have entered the same cell in the same individual, recombination can occur creating new forms of viral DNA, and when these are isolated in three different individuals, a new circulating recombinant form (CRF) is named (Perrin, Kaiser, & Yerly, 2003). Unique recombinant forms (URFs) are the innumerable result of unique genetic variation within individuals. The high error rate of reverse transcriptase, the
massive viral replication rate, and the propensity for recombination have created a genetic environment where mutations and diversity evolve at a rapid rate.

Human risk groups and their behaviors have helped catalyze HIV’s rapid progression around the globe. Perrin, Kaiser, and Yerly (2003) described human travel as one of the fundamental behaviors contributing to the world pandemic. Six risk groups were described along with the effects of their movements on HIV prevalence: Internal and external migrants, intravenous drug users, military troops, tourists (especially tourists engaging in sexual activity), long-distance truck drivers and seamen, and expatriates. Factors in Africa have contributed greatly to the evolution of HIV as rural populations have moved from isolated communities into Western style urban complexes. The resulting political and socioeconomic upheaval, especially in Central and Southern Africa have contributed to the epidemic with HIV spreading along tracts of geography related to the movements of the groups defined above. The logical consequence of behaviors such as unprotected sex or sharing needles among HIV infected individuals was the proliferation of HIV in all of its forms. Up to 45% of HIV infected people with known disease have unprotected sex at some point during a two year time interval (Kozal, Amico, Chiarella, Fisher, Fisher, & Friedland, 2006).

Iatrogenic causes are a human behavioral contribution to the HIV pandemic as well. Blood transfusions, needle reuse for injections, and various other blood contamination vectors contribute to generalized outbreaks of the disease in developing countries. The contribution is difficult to calculate due to poor health care infrastructure in many of the generalized outbreak epicenters. Gisselquist in 2008 proposed that widespread vaccination programs in Africa have contributed an unknown amount to generalized HIV epidemics due to poor infection control practices. For example, he points out that needle reuse as a practice has been common and
HIV: Treatment approach to a unique and elusive virus widespread throughout the 20th century. Thus human behaviors have contributed to the proliferation of the disease in its genetic diversity along geographical and high risk behavior lines.

Western Europe and North America have been fairly isolated in the diversification of HIV’s genome. Western countries have been dominated by subtype B of HIV-1 which had remained stable until the advent of antiretroviral drugs. With the advent of these drugs, the HIV virus has shown its power to mutate and develop drug resistance rapidly. It seems that some form of resistance develops with each application of drug which leads to treatment failure and increased mortality. Remembering the rapid proliferation of HIV virus combined with its propensity to create mutants, it is not improbable that the advent of resistance would proceed rapidly. In fact, recent studies in the USA of the prevalence of HIV resistance strains found that 75% of the adult HIV positive population with detectable viral load had drug resistance, and 48% had multidrug resistance (Kozal, 2009). As travel has grown across borders and continents, HIV-1 followed leading to the introduction of African strains to Europe and drug resistant strains to Africa. These travel and immigrant lines can often be traced by historical colonial relationships.

II. Problem Statement

Therefore, a number of questions arise: How many variant strains currently exist of HIV-1 and what is their current geographic proximity? This question is significant because it recognizes the implications of HIV-1’s behavior: the dilemma that each characterization of HIV is immediately outdated by the sheer reproductive and diversifying power of the virus. Second: will development of drug resistant HIV in Africa overwhelm our ability to create new
antiviral drugs? Finally, what is the prudent response of a primary care practitioner to a patient presenting with newly diagnosed HIV in light of this information?

These questions capture the importance of the global community’s commitment to monitoring HIV and implementing change in policy so that the unknown threat of HIV in its future forms can be curtailed. As knowledge about drug resistance and the viral behavior of HIV increases, it is necessary to know the extent to which the virus has established itself. The paradigm of war is helpful in this instance: what general would not scout his enemy’s position and gain a detailed description of his strengths before the battle? For if you know the scope and strength of your enemy’s position, you can then wisely deploy your own resources in such a way as to increase the odds in your favor. And if we know the diversity and location of HIV in all its forms, we can wage war in a wise and efficient manner. The cost of not curtailing the HIV/AIDS epidemic, especially in Africa, will be the continued incapacitation of a new generation with political and economic consequences greater than those seen today.

III. Purpose and Aims

In its limited scope, the purpose of this paper is to describe the current status of the HIV virus in selected states in Sub-Saharan Africa using a limited online search of the current literature. A continuously updated picture of HIV’s progeny allows for a detailed knowledge of the extent and power of the virus. Sub-Saharan Africa was chosen because of its historic relationship with HIV and its origin. Given the variants found in Africa, the virus could change the most, produce the most problematic drug resistance, and possibly evolve to a more penetrating disease all in the most resource-poor nations affected in the pandemic. Given the response of HIV to the introduction of HAART in the United States and Europe, with mutant polymorphisms quickly outdating drugs, the treatment response in Sub-Saharan Africa is
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postulated to be overwhelmingly wrought with failure. This is made more probable given that many programs in Africa began as simple antiretroviral treatment (ART), which used one or two drugs on treatment naïve patients. As well, the predicted problems associated with resource poor settings, such as lack of follow-up, drug shortages, and adherence issues are predicted to further complicate drug resistance. To answer this theoretical challenge to the latest therapies, the analysis of one strain, HIV-1, subtype C, will be explored in the context of three nation’s HAART campaigns over the last decade. This will help establish a base of knowledge on the proliferation of HIV and drug resistance in order to guide primary care practice as HIV is encountered in the United States and internationally. The final analysis of this paper will present simple steps to be taken by primary care practitioners as they approach treatment of this unique and elusive virus.

IV. Search Strategies

In the first part of this literature review, Pub Med was investigated with the following search criteria: HIV New Strains and HIV-1 diversity, with the time limit of studies published between January of 2008 and the present. As well, only studies in the English language and studies that were related to human populations were selected. These criteria generated 92 and 133 results, respectively. A number of reviews were selected from this list based on their relevance to the research question, purpose and aims of the paper. The search was then narrowed to the “HIV-1 diversity” search with the addition of the key word Africa. Thirty-two results were obtained and only studies with the intent of describing an HIV variant were selected for study. All articles described the genetic diversification of HIV-1 within a political boundary. The following countries were then detailed: Mozambique, Cameroon, Tanzania, Mali, Botswana, South Africa, Gabon, and Kenya. This list was not intended to be all-inclusive, but to
elicit a descriptive generalization of the current status of HIV. Secondly, Pub Med was again utilized to search “drug resistant HIV Africa” with slightly different criteria: English articles published in the last five years with human subjects with links to full free text online. This resulted in thirty articles for review, which were further narrowed to exclusively deal with HIV-1 Subtype C in the nations of Tanzania, Botswana, and South Africa. These results were crosschecked with further searches substituting the country name for “Africa” to check for other relevant articles.

V. Biochemical Framework

The basis for biochemistry and genetics as applied to actual practice in nursing carries unique and developing frameworks. The working theme applied to this paper was developed from ideas probed in 1997 during a global meeting of scientists in Tanzania discussing the implications of genetic variation in the HIV virus (European Commission and the Joint United Nations Programme on HIV/AIDS, 1997). The consensus emerged that in order to properly put HIV biochemistry in context with vaccine development and disease treatment, the subsequent classifications and tracking of subtypes is of paramount importance. In this way, treatment of disease can be tailored to the biochemical platform on which the disease rests: in other words, the unique polymorphism of the virus in the individual. This central theme is the backbone of the following literature review.

VI. Review of the Literature

Table I displays data from eleven studies that look at the genetic diversity of HIV within national borders in Sub-Saharan Africa. There are a number of trends that can be noted in this review of subtypes. First Mozambique, Botswana, and South Africa were dominated by HIV-1, Subtype C, and with very high prevalence of disease. West-Central African nations have the
most divergent types of HIV-1, but have less overall prevalence. East African nations lie in the middle with prevalence and have mainly Subtypes A, C, and D. East Africa and Southern Africa are connected by historic trade routes, while West/Central Africa is the geographical origin of HIV in humans. All of the studies dealt with one, two, or all three sections of genetic material in HIV known as the \textit{gag} (which codes the viral core), \textit{pol} (which codes reverse transcriptase, integrase, and protease), and \textit{env} regions, which were isolated, sequenced, and classified. In its various forms, HIV-1 Subtype C was found to be most diverse. It is the most widespread subtype accounting for 50\% of the pandemic (McCutchan, 2006). As well, HIV-1 genetic diversity followed more risky behaviors by the testing subjects. The weakness of most of the studies was their lack of breadth. They tended to focus on one or two gene loci and failed to sequence large portions of the viral genome. This needs to be noted as a financial restraint as well as simply a design decision. Another interesting theme in the data is that women and men carried the virus at high rates regardless of risk group in some of the countries. The data points to other factors being involved in the definition of high risk in Africa. This is important because high-risk groups were often associated with higher genetic diversity.

Botswana was the first African country to initiate a HAART program through its public health infrastructure in 2002 (Mujugira, Webster, Kim, Bussmann, & Gaolathe, 2008). Researchers followed this group for a number of different studies. The longitudinal two and five year studies are most interesting in relation to the questions posed in this paper. Although HIV-1 Subtype C was thought to be the virus most likely to cause clinical treatment failure quickly, both studies found excellent immune recovery and sustained gains in CD4+ counts (Bussmann, et al., 2008). Most importantly, the clinical outcomes at five years showed low mortality and greater then 90\% adherence to the medication regimen. Most unexpected was the low virologic
failure rate (<10%). The predictors of failure were not measured due to the high death rates in the beginning, which would censor the data. Botswana’s program was unique in Africa in that treatment was not withheld for patients with poor prognosis. This resulted in high mortality rates especially in the first year, where 86% of all deaths occurred. There were also high numbers of patients lost to follow up due to the expansion of the program to community based clinics and patient movement. If high numbers of these patients left the program due to treatment failure, then the data would be more favorable then reality. Another study followed this same cohort looking for virologic failure (Doualla-Bell, et al., 2009). Four percent of the patients who enrolled in the five-year period beginning in 2002 experienced treatment failure. These patients were found to have a 78% chance of expressing mutations associated with protease inhibitors (PI), and an 87 or 90% chance of expressing mutations associated with nucleoside reverse transcriptase inhibitors (NRTIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), respectively.

In Tanzania, where HIV-1 subtype C is prevalent, as well as subtype A and D, similar results were seen except that greater resistance emerged as time passed (Johannessen et al., 2009). Clinically significant mutations arose at the following rates at year one, two, three, and four of ART: 3.9%, 8.4%, 16.7%, and 12.5%. Rate increases were only associated with duration of HAART therapy, as opposed to factors such as age, sex, clinical stage, body mass index, or initial drug choice. Unfortunately, correlations were not checked with HIV-1 subtype. The greatest unknown is the actual management practices of the study at the point of care for the patient. The patients in this study were rurally based which may give rise to greater treatment adherence issues, though this was not measured and could not be correlated with urban patients. Overall, drug resistance was calculated to be 8.5% of the patient load. Of particular interest in
this study was the emergence of dual drug resistance reaching 13.9% in year three and 6.3% in year four. This may have implications for rural, resource poor areas in Africa where adding drugs to the regimen is not possible.

In South Africa, roughly 190,000 people diagnosed with HIV-1 were receiving HAART by the end of 2005. Roughly 4.4% of the patients treated at two clinics developed virological failure of their regimen within 24 months of starting HAART. Resistance patterns were similar among treatment naïve and prior HAART therapy patients. Risk factors were not associated with genotypic drug resistance. At least one resistance mutation was detected in 83% of the patients experiencing virologic failure. Two-drug resistance was found in over 50% of the cases, but three-drug resistance was very low at 2.6%. Adherence was measured above 95%, overall. The majority of mutations were associated with NNRTI and NRTI resistance, and few were associated with PI's. This was noted as a common finding among HIV-1 subset C patients.

In a unique study, comparing the rollout of HAART in South Africa with patients in Switzerland (Keiser et al., 2007), researchers found that similar virologic outcomes were achieved in both locations regardless of subtype of HIV-1 and model of care delivery. These two nations were chosen for the comparison study due to the ability to apply the same eligibility criteria to both cohorts, and for the two differing models of care delivery: individualistic in Switzerland and public health approach in South Africa. Though the populations and treatment protocols were very different in the two settings, two-year virologic response was found to be similar. Expected findings were that patient load increased greatly during the study period in South Africa and remained stable in Switzerland. As well, patients were admitted into the study in worse shape clinically in South Africa with higher viral loads and more advanced disease. The conclusion of the study is that “antiretroviral anarchy” (Keiser et al., 2007, p. 1108) has not
occurred in South Africa as predicted by many in the West. The findings point, though, to earlier treatment initiation for patients in South Africa. Also, high adherence and follow up rates were observed in both settings.

VII. Discussion

HIV-1 subtype diversity was found to be extensive in Sub-Saharan Africa as predicted by examining the unique and elusive nature of the virus. In fact, the diversity increased geographically as you approach the epicenter of the disease origin. As well, human behavior has influenced the proliferation of HIV-1 subtypes and their geography. To quantify and categorize HIV-1 in Sub-Saharan Africa, genetic sequencing was performed on various blood samples from a variety of subjects in the studies cited in this paper. Researchers used the pol, env, and gag genes to compare and map diversity. Table I shows the diversity by country and in percentages of subtype found. Countries, like Cameroon, with a known historically lengthy epidemic of HIV have large varieties of HIV subtypes inhabiting people from various risk groups. Countries with historically short epidemics, like Mozambique, have a single form of HIV that is traceable in terms of travel vector, and with little genetic variety. As predicted, these results flow directly from HIV’s unique biochemistry and genetics.

Surprisingly, this genetic climate in Sub-Saharan Africa did not produce drug resistance and treatment failure at rates greater than in the West. This has been shown without adjusting for resource poor treatment modalities, and lack of individualized care. As well, the rates of mutation and adherence are within global norms (Cane, 2009), though other reviews point out that there is a need for further deepening of our understanding of HIV-1 genetic diversity on drug resistance in the context of clinical outcomes, especially with longer follow-up cycles (Martinez-Cajas, Pai, Klein, & Wainberg, 2009). Future studies are needed to study the significance of
polymorphisms in non-B subtypes of HIV-1 that increase after HAART exposure. The studies above showed that they exist, but did not look for clinical significance. As well, pre-study genotyping would help yield more information on the mutational pressure exerted on HIV-1 by HAART therapy in Africa. Expert panels worldwide have recommended this practice (Hirsch, et al., 2008). The continued sequencing of HIV-1 as antiretroviral therapy is introduced in Sub-Saharan Africa will be key to tracking drug resistance and subtype diversity. HAART therapy, at this point, is effective as advised by the public health institutions in Botswana, Tanzania, and South Africa, especially given their resource poor circumstances. Primary care practitioners, nurses, and public health officials will be key to recognizing new resistant strains of HIV as they develop in this environment. They also will be key in promoting and advocating continued testing and banking of blood for genetic sequencing.

VIII. Recommendations and Conclusions

The framework and data suggest that further genetic sequencing of HIV-1 as it continues to proliferate in Sub-Saharan Africa will be key to understanding HIV and developing a generalized vaccine for this unique and elusive virus (Butler, Pandrea, Preston, & Apetrei, 2007). Paramount to retaining this paradigm will be understanding the role of human intervention in the midst of the epidemic: factors like social upheaval, new medical technology, and new transportation have combined with human social behavior to oil the gears of HIV genetic diversity (Butler, Pandrea, Preston, & Apetrei, 2007).

Primary care practitioners and public health officials who work on the front lines of this battle must have adequate knowledge in order to implement the best strategies when dealing with HIV. The following steps are proposed in light of the literature review:
1. Name the subtype through genetic testing. The right treatment regimen can then be selected for therapy and the database of genotype diversity can be updated continuously by geographical location.

2. Take a sound clinical history. This is crucial for patient care, especially taking into account past antiretroviral therapy.

3. Drug resistance testing for virological failure. The next drug choice must be guided by knowledge of mutation presence. This will aid in the tracking of resistance strains within specific HIV-1 subtypes.

In summary, the most important recommendation from this review is the continued genetic sequencing of HIV in its entirety throughout the world, and especially in Sub-Saharan Africa, where the epidemic is proportionally most prevalent. Secondly, the careful adherence to established protocols for treatment of HIV or referral to a specialist regardless of where one practices is very important. Timely genetic sequencing or testing for mutations can then occur without delay.

The fight against HIV must be balanced with knowledge of its genetic and biochemical characteristics. Otherwise programs and interventions could be created that do not address its unique and elusive nature.
Reference List


http://www.cdc.gov/hiv/topics/surveillance/basic.htm#international

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Retrieved July 15, 2009 from UNAIDS:

http://www.who.int/hiv/data/2008_global_summary_AIDS_ep.png

Table I.

*Summary of HIV-1 genetic diversity in selected countries in Sub-Saharan Africa*

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