Comparison of Drug Treatment Protocols for Children Infected with HIV in Washington, DC and Cape Town, South Africa in Relation to NIH Guidelines

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Abstract

A variety of clinical indicators including CD4 T-lymphocyte counts, HIV viral levels, symptoms of AIDS, and adherence to HIV drug therapies are utilized in selecting and modifying antiretroviral (ARV) drug treatment regimens in individuals infected with HIV. Although guidelines have been published by the National Institutes for Health (NIH) that suggest how these indicators should be used for the treatment of pediatric HIV/AIDS, these recommendations may overlook some of the complications associated with pediatric infection, such as poor adherence, drug intolerance, and inadequate human growth. In order to assess the extent to which published guidelines are used in clinical practice in hospitals located in Cape Town, South Africa and Washington, DC, clinicians responsible for the treatment of children at these hospitals were interviewed using original questionnaires. The results of the interviews were then evaluated and compared to the published guidelines to determine the points of agreement and divergence. Although the NIH recommendations suggest using CD4 counts, HIV RNA levels, and clinical symptoms as the major determinants when prescribing drug therapy, Victoria Hospital in Cape Town, South Africa uses adherence and general health of the child as the primary indicators for initiation and alteration of ARV therapy. The treatment methods of Children’s National Medical Center and Howard University Hospital in Washington, DC differ from the published guidelines in that physicians at these hospitals place all children under the age of one year on drug therapy regardless of any other clinical indicators. The differences that are seen in the application of the published guidelines at these hospitals can be attributed to the dynamics of the specific environments of Cape Town, South Africa and Washington, DC. Because antiretroviral drugs are easily available in the United States, clinicians here are able to treat HIV-infected children in the most aggressive ways. However, since South Africa is bound
by financial limitations that limit access to ARVs, clinicians are forced to alter the published guidelines in order to best serve their pediatric population by using primary indicators other than those specifically recommended by the published guidelines. Thus, depending on the specific population, clinicians of these hospitals prescribe drug therapy differently in order to meet the needs of HIV-infected children within the confines of the specific healthcare system.
Introduction

Curative treatment and complete containment of the Human Immunodeficiency virus (HIV) has escaped medical professionals since HIV first presented itself to the American public in 1981. Although the incidence has declined, Acquired Immunodeficiency Syndrome (AIDS), the disease caused by HIV, remains a lethal condition despite advancement in treatment through highly active antiretroviral therapy (HAART). In the United States, the first known outbreak of HIV occurred amongst homosexual men in San Francisco, California; however, many other populations are vulnerable to contracting the virus. Children of infected mothers comprise one of these populations. Because of the complications associated with the incompletely developed immunity of children, treatment of pediatric HIV infection acquired through perinatal transmission is difficult even under the best of circumstances.

The NIH has published *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* in order to guide clinicians in treating children infected with HIV.¹ These recommendations are based upon the unique clinical progression of disease that is known to occur in the pediatric population. However, it is not known exactly to what degree physicians incorporate these treatment guidelines into their own treatment protocols. A hospital typically uses a set of indicators, each with precise parameters, to define a protocol for treating HIV-infected children. The primary indicators that the guidelines suggest include CD4 count/percentage, HIV viral load, and the appearance of clinical symptoms, as well as adherence and tolerance as secondary indicators. In order for treatment to be initiated, changed, or terminated, one or more of the indicators must be present in the appropriate range as defined by the particular treatment protocol. Although the published recommendations are founded upon clinical evidence, they may overlook some of the complications associated with pediatric HIV
infection and the prescribed treatment. For example, poor adherence to drug therapy, impaired
tolerance to medication, and inadequate growth can all occur and may contribute to disease
progression. Thus, clinicians may choose to apply the published guidelines differently in
shaping their own treatment protocols for children infected with HIV.

Objectives

The primary objective of this study is to compare pediatric HIV/AIDS treatment
protocols used by hospitals in Cape Town, South Africa and in Washington, DC with the
guidelines published by the NIH for the treatment of HIV-infected children. This will establish
to what degree the published recommendations are actually used in clinical practice.
Determining the extent of the relationship between protocols used by various hospitals and the
published guidelines will reveal whether the published guidelines are meeting the needs of the
specific populations to which they are applied.

By interviewing healthcare personnel who treat HIV-infected children in both Cape
Town, South Africa and Washington, DC, several key research questions can be answered. First,
do pediatric hospitals/clinics in both these cities principally rely on specific drug treatment
protocols that include CD4 counts, viral loads, as well as other quantitative measurements to
determine the administration of drug therapy for their pediatric patients? Second, are any
subjective indicators, such as, patient’s family status and support, ability to remain adherent,
tolerance capacity, and maintenance of appropriate growth, considered as mediating the decision
to begin, change, postpone, or discontinue drug treatment for HIV-infected children? Third, do
these hospitals in Cape Town and in Washington, DC fully apply the published guidelines
concerning drug therapy for HIV-infected children or do they define their protocols using
different parameters? The answers to these questions will provide an assessment as to how the
published guidelines are realistically used in a clinical setting in Cape Town, South Africa and in Washington, DC.

**Background**

**Epidemiology of HIV/AIDS**

Both South Africa and the United States are developed countries that do not have national healthcare coverage in any form for their citizens. Thus, this imposes a demanding burden on members of these populations to purchase healthcare as well as medications from privately funded agencies. Therefore, those people who cannot financially afford to purchase health insurance may be less likely to receive optimal treatment for devastating diseases, such as HIV. The consequences of infection with HIV may be exacerbated by the lack of nationally provide healthcare coverage in both South Africa and the United States.

The HIV epidemic has disproportionately affected Africa, with South Africa having one of the highest rates in the entire world among both adults and children estimated at 18.8%.\(^2\) Despite substantial strides in surveillance and drug treatment of infected patients, this value still represents a high proportion of the population. Because most children under the age of 12 who are HIV-positive have contracted the virus through vertical, mother-to-child transmission, the severity of South Africa’s HIV prevalence rate signifies a strong risk for South African children. Although the exact rates for pediatric HIV infection in South Africa as well as major cities within South Africa, such as Cape Town, are not known, it can be assumed, based on the overall prevalence, that pediatric infection is very high in this country.

Treating HIV-infected children effectively with antiretroviral agents remains the only mechanism to reduce morbidity and increase the quality of life. Cape Town, South Africa is currently in the process of undergoing a political transition from a struggling network of small
towns to an impressive industrialized metropolis. With this transition has come access to highly active antiretroviral therapy, but many limitations still exist that can impair its effectiveness. Cape Town largely remains an impoverished city, making access to healthcare for people infected with HIV quite difficult. Even though educational awareness efforts have increased dramatically since the beginning of the HIV epidemic, many people in Cape Town are still unaware of the risk factors that predispose one to contracting HIV. Full adherence to antiviral regimens in the pediatric population is very difficult to accomplish because family members are often not equipped to administer medications effectively often because of their own diseases associated with HIV. These children are then left without an adequate support system due to the poor living conditions associated with extreme poverty. Thus, structuring treatment in a way that is conducive to children living in Cape Town is the only way to minimize the consequences of HIV infection in this population.

While South Africa has been severely affected by the HIV epidemic, the disease also has been widespread and continues to exist in the United States. Here, the HIV/AIDS epidemic first erupted in San Francisco and New York City and then spread to other major cities. In recent years the epicenter in the U.S. has shifted to Washington, DC. The District of Columbia has the highest AIDS prevalence rate for children under the age of 13 estimated to be 74.5 per 100,000. Compared to the estimated rate for the entire country at 3.7 per 100,000 children, this statistic demonstrates the severity of the HIV epidemic in Washington, DC. A similar pattern is seen for adult AIDS prevalence with an estimated rate of 1833.2 per 100,000 in DC compared to an estimate of 167.3 per 100,000 for the entire country. Although the District of Columbia has just begun confidential, name-based HIV infection reporting, data are not yet available for HIV
prevalence rates, so the AIDS prevalence rates serve as the major indicator for the state of the epidemic in DC.

Because Washington, DC has the highest AIDS prevalence rate in the United States for both children and adults, therapeutic drug treatment is a critical issue. For children especially, administering antiretroviral drug therapy in a way that is effective while minimizing harmful side-effects can be a difficult task to accomplish. Thus, the protocols that physicians use should incorporate all the factors that are unique to pediatric HIV infection. For DC specifically, the high rate of infection may reflect certain characteristics of the population such as extreme poverty, lack of adequate access to healthcare, and insufficient awareness of the prevalence of HIV. In order to treat HIV infection effectively, the protocols must take into account the complications caused by these characteristics, such as lack of adherence to drug therapy and the subsequent occurrence of drug resistance. Pregnant women in Washington, DC who are infected often do not receive proper care and treatment during pregnancy, thus leaving their children vulnerable to infection and further complications. Those women who do receive antiretroviral agents are not always compliant with their regimens, thereby increasing the risk that their children will not only be born with HIV, but will also be born with a drug-resistant form of HIV with impaired susceptibility to antiretroviral therapy. Therefore, clinicians treating pediatric HIV infection in the District of Columbia may choose to diverge from the published treatment guidelines in order to target the special circumstances of the pediatric population.

*HIV Infection and Transmission*

In order to understand the treatment process of HIV infection in children, the specific nature of the human immunodeficiency virus must first be discussed in terms of viral structure and reproduction. Two main types of the virus exist, HIV-1 and HIV-2, but HIV-1 remains more
prevalent worldwide. Therefore, for the purpose of this analysis only the characteristics of
disease that pertain to HIV-1 infection will be discussed. HIV-1 is a retrovirus of the lentivirus
family; therefore, its method of replication occurs through converting its own ribonucleic acid
(RNA) genome into deoxyribonucleic acid (DNA) after infecting human host cells. The HIV-1
virus has a spherical shape and an envelope enclosing a capsid, which contains a single-stranded,
positive RNA genome. The envelope consists of a lipid bilayer containing several protein
spikes that function in attachment and replication. The capsid also contains preformed molecules
of reverse transcriptase, integrase, and protease.

HIV infection occurs when the virus attaches and invades cells that have a CD4
membrane receptor molecule, primarily CD4 T-lymphocytes. Although other cells such as
monocytes, macrophages and B-cells are also susceptible to HIV infection, they only serve as a
reservoir for HIV and are not killed by the virus as a result of infection. Upon attachment to the
host cell and virus-cell fusion, the virus can either remain in a latent state or may reproduce itself
through replication. Replication usually occurs and HIV uses reverse transcriptase to transcribe
the viral RNA into a complementary, negative DNA strand, followed by a complimentary
positive strand of DNA, together know as copy DNA, cDNA. Another enzyme, integrase,
ensures that HIV cDNA is inserted into the nucleus of the host cell. Viral messenger RNA
(mRNA) is then produced and is followed by the production and assembly of viral proteins. The
protease enzyme is required for the final stage of viral replication in which infectious viral
particles are formed when protease cuts and reconstructs the viral proteins. Newly produced
virus can now infect other cells with the CD4 surface marker. Human Immunodeficiency Virus
replication is thought of as the fundamental cause of the immune incompetence that follows
infection. Thus, current drug therapy is targeted at two of the enzymes involved in HIV
replication. By inhibiting the replication of HIV, it can be assumed that the disease can be suspended or at least limited to only minimal effects on the immune system.

CD4 T lymphocytes are critical to normal immune function; therefore, their absence leads to profound detrimental effects on the human body. The CD4 membrane receptor enables T-cells to recognize foreign antigens. Once foreign antigens are identified, they can then be targeted for removal by a variety of other cellular mechanisms. Activated CD4 T-cells also release cytokines that activate other cells of the immune system. In this sense, CD4 T lymphocytes can be thought of as the initiators of immune-mediated events in order to enable the body to respond to invasion of foreign pathogens. Because CD4 T-cells are responsible for activating cells of both the cell-mediated immune system and B-cells of the humoral immune system, the decline in CD4 T-lymphocytes results in an insufficient and incompetent immune system. Thus, as CD4 T-cells are depleted from the host, foreign antigens are allowed to invade and replicate unchecked, leading to the development of secondary conditions that define the Acquired Immunodeficiency Syndrome (AIDS).

The human immunodeficiency virus can be found in blood, semen, vaginal and cervical secretions, breast milk, saliva, tears, cerebrospinal fluid, and urine; however, transmission generally occurs through contact with infected blood and semen. Mother-to-child transmission can occur in utero, during the birthing process as the child passes through the birth canal, and through breast feeding from the infected mother. Although HIV-2 is rarely passed from mother to child through vertical transmission, fetuses and infants of HIV-1 infected mothers have a 13-48% chance of contracting the virus. It has recently been established that in the absence of breast-feeding, 20% of vertically transmitted HIV infections take place in utero and the remaining 80% occur during birth. Breast-feeding is thought to contribute an additional 15%
risk of HIV infection for the infant.\textsuperscript{4,7} The pattern of perinatal transmission of HIV follows that of other types of transmission; as maternal viremia increases so does the risk of transmission to the child.

\textit{Clinical Disease Progression}

Following initial invasion and infection of HIV, the virus continues to replicate and invade CD4 T-lymphocytes, causing several notable effects on both molecular and clinical levels. For adult infection, HIV viral load spikes rapidly within approximately 2-4 weeks after infection, corresponding to a moderate decrease in CD4 T-lymphocytes.\textsuperscript{5} The period of primary or acute infection continues to about 12 weeks after the infected individual’s seroconversion from HIV negative to HIV positive.\textsuperscript{5,6,7} The person may experience fever, malaise, diarrhea, lymphadenopathy, and a rash.\textsuperscript{4} During this entire period, high levels of HIV are present in the blood. The initial decrease of CD4 T cells due to their destruction by the replicating virus is followed by an increase to relatively normal levels.\textsuperscript{4} After this stage of infection, the asymptomatic phase begins and can last for a period up to 8-10 years.\textsuperscript{8} A gradual decrease in CD4 T lymphocytes represents the main clinical indicator of disease progression. Even though this phase is often referred to as latent because of the absence of symptoms, the virus continues to replicate and never actually reaches a period of total latency.\textsuperscript{4}

The symptomatic phase is marked by severe immunosuppression with CD4 T cells below that of 300 cells/µL.\textsuperscript{4} Characteristic symptoms include persistent fever, lymphadenopathy, or diarrhea. Significant weight loss, denoted as greater than 10% of normal body weight, can also occur.\textsuperscript{4} This stage continues until the person develops an opportunistic infection.

Acquired Immunodeficiency Syndrome (AIDS) can now be defined as a CD4 T lymphocyte count of less than 200 cells/µL, regardless of any of the other clinical indicators or
There are also 26 conditions, ranging from carcinomas to infections whose development indicates the final stage of disease known as AIDS. As viremia increases and the number of CD4 T-lymphocytes decrease, symptoms of AIDS begin to develop more frequently with increasing severity. Once an adult is diagnosed with AIDS, approximately 18 months may pass until death occurs, making the total time from HIV-positive seroconversion to death between 10 and 12 years.

Differences in the disease progression can be seen between adult and pediatric infection. First, diagnosing a child with HIV is complicated by the presence of maternal antibodies in all children born to HIV-infected mothers. While adult diagnosis entails the identification of HIV-antibodies through both the Enzymed-linked immunosorbent assay (ELISA) and the Western Blot analysis, diagnosis of pediatric infection cannot rely on the presence of antibodies to the virus. These IgG HIV antibodies pass from the mother through the placenta and can remain in the child for up to 10-18 months following birth; therefore, the test cannot differentiate between maternal and infant HIV antibodies. Thus, infant HIV infection can only be truly measured by taking a viral culture, testing for the p24 antigen, or PCR analysis for HIV RNA or DNA.

For children, because of their underdeveloped immune systems, clinical disease progression is often accelerated in that each stage of disease is greatly shortened and more severe. Children proceed to the symptomatic phase much quicker than adults and once AIDS occurs, death is imminent. Not only is the time of the course of disease different for pediatric infection, but the clinical features also vary. Even before changes in the number of CD4 T lymphocytes occur, children may experience B-cell dysfunction leading to reoccurring bacterial infections. This enables the clinical manifestations to be seen throughout infection and not just during particular time periods. These differences in HIV clinical manifestation for infants and
children provoked the Centers for Disease Control and Prevention to reclassify the stages of HIV disease for pediatric infection in 1994. Traditionally, CD4 percentages have been used to define the stage of HIV infection in adults. However, because CD4 T cell counts and percentages are not always accurate indicators of disease progression in children, they are not used as the sole determinants of disease stage classification.9

Rather, three different parameters, infectious status, clinical status, and immunologic status, are used to define the state of disease in an HIV-infected child.9 Infectious status is based on whether or not a child has seroconverted according to positive results of either the HIV viral culture test, HIV polymerase chain reaction, or the HIV p24 antigen on at least two or more occasions. Children older than 18 months may be tested by the ELISA and Western Blot Tests in order to confirm a diagnosis. Clinical status reflects the presence of symptoms of HIV infection as well as opportunistic infections and diseases associated with infection. The categories range from nonsymptomatic to severely symptomatic and each includes specific criteria that must be present in order to classify a child. Immunologic status is based on CD4 T cell counts and percentages. However, because these values do vary in relation to age, this classification is conducted according to the following age groups: less than 12 months, 1-5 years and 6-12 years.9 CD4 counts and percentages are at a maximum following birth and gradually decline with age, so age-specific counts and percentages must be used to account for an accurate immunologic picture of the HIV-infected child.9 Just as classification of the stages of infection was altered appropriately to reflect specific characteristics of HIV infection in children, treatment including drug therapy should also take into account certain complications of pediatric HIV infection, such as impaired adherence, tolerance, and growth.
**Antiretroviral Therapy for HIV-Infected Children**

Treatment for children infected with HIV remains complex and not completely well understood. However, HIV treatment prolongs the duration of life for infected children, as well as improves their quality of life. Drug therapy is currently targeted at two of the enzymes that the virus uses to replicate within human host cells. Reverse transcriptase and protease respectively allow HIV to replicate its RNA and produce infectious viral particles that are then free to invade and replicate within other cells of the host’s immune system. Nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) comprise the three major classes of antiretroviral therapy. These drugs potentially have the ability to disrupt viral replication so that immune function can be maintained. The most effective form of treatment comes in the form of Highly Active Antiretroviral Therapy (HAART), which uses a combination of at least three different drugs from two different classes to allow a multifaceted approach in disrupting viral reproduction in order to minimize detrimental effects on the immune system.

Evidence through randomized clinical trials has shown that HAART is very effective in suppressing viral replication and preserving immune function for the HIV-infected adult when administered soon after infection.\(^\text{10}\) Because there have been similar findings of clinical trials in the pediatric population, it can be assumed that HAART has the same potential for children. Although monotherapy can produce some benefits in terms of viral suppression and immune reconstitution, effects are limited to a transient period of time due to the eventual development of drug resistance.\(^\text{11}\) Inclusion of a PI seems to adequately suppress viral replication while preventing immune function decline according to many studies investigating the effect of PIs on clinical disease progression.\(^\text{12-14}\) Furthermore, when PIs are incorporated into a triple HAART
regimen, a greater percentage of children maintain virologic suppression over time when compared with those treated with only one other a drug and a PI. Similar results are seen in terms of CD4 counts/percentages in that inclusion of PIs into HAART regimens enables CD4 counts to rise and maintain adequate levels well after the initial stages of infection. Since CD4 T-lymphocytes greatly contribute to normal immune function, their viability becomes an important indicator of effectiveness of HAART. Remarkable evidence has shown that HAART is followed by fewer adverse clinical outcomes in terms of opportunistic infections and also prolongs the time to occurrence of AIDS and death in children when it is administered in the early stages of infection before the CD4 count greatly declines. Thus, when applied in the correct ways that consider the factors unique to pediatric HIV infection, HAART can have dramatic beneficial results on the clinical disease progression of HIV in children.

Although evidence from studies on the effective treatment of adult HIV infection can be extrapolated to provide insight on effective therapies for children, treatment of HIV infection in children is complicated by several factors not associated with adult treatment. Children often metabolize drugs much differently than adults; therefore, the pharmacokinetics of antiretrovirals may exert different effects for children. This often requires physicians to alter the drug formulations that are used for adults in order to apply them to children. Furthermore, the course of disease often progresses in much more varied stages for children. First of all, children who have contracted HIV through perinatal transmission exhibit higher baseline viral loads when compared to adults infected with HIV. These children often show peak viral loads within the first two months of life followed by a gradual decline over the next two years. This occurs in contrast to adult infection in which viral loads often peak immediately after infection then
decline rapidly within weeks to months. All these factors that exclusively pertain to pediatric HIV infection must be taken into account when prescribing drug therapy.

Adherence to Antiretroviral Therapy

Drug therapy for HIV-infected children is only likely to be successful if children strictly adhere to the antiretroviral regimen in taking all of their prescribed doses at the appropriate times over a long-term period. For many children, this level of adherence can be difficult to maintain because adherence to drug therapy is often dependent on the primary care giver. Since most children under the age of 13 have acquired HIV through perinatal transmission, both parents might be severely incapacitated with AIDS and therefore unable to give the medications at the appropriate times. Even if children infected with HIV are receiving care from people other than their biological parents, dependence on others to receive medications properly can exacerbate the treatment process for children.

There are many conditions of antiretroviral therapy unique to children that limit adherence such as lack of liquid formulations for some drugs, poor palatability of some medications, and the large volume of medications that the regimens often require. These complications of administering antiretroviral drug therapy to children not only make it difficult for they themselves to take the medications willingly, but they also make it difficult for the primary care giver to force children to comply with regimens that inflict such a daily burden. Some studies have shown that certain characteristics can be predictive of whether a child fully adheres to HAART. Adherence rates for children are typically high if a child’s primary caregiver is someone other than a biological parent and if that person also has a high education level. Also, children who use buddy systems to remember when to take medications and
children who take antipsychotic medications are more likely to remain fully adherent to antiretroviral regimens when compared with those children not exhibiting these characteristics.\textsuperscript{18}

There are several circumstances that are associated with nonadherence for children. Most notably, as the age of the child increases there is a 10\% increase in the odds for nonadherence per year of age.\textsuperscript{18} Thus, encouraging strict adherence for older children should be a major concern for clinicians. Also, children diagnosed with depression as well as children with an unstable family support system have a greater susceptibility of being noncompliant with HAART.\textsuperscript{18} This is important information for the physician to consider when deciding whether to initiate, change or suspend drug therapy for any child infected with HIV.

Not only can full adherence to antiretroviral regimens promote the best possible outcomes for the HIV-infected child, but also the absence of adherence can produce drug-resistant strains, which impede the goals of HAART. Therefore, it is important to be able to assess whether children and their families comply with the drug regimens that are prescribed. Studies have shown that adherence, either reported by the child, a biological parent, or another caregiver, closely follows the degree to which viral suppression occurs.\textsuperscript{17} Therefore, children who comply with their regimens to at least 95\% maintain virologic suppression, defined as less than 400 copies/mL of HIV RNA, when compared to those children who exhibit less than full compliance to the antiretroviral regimen.\textsuperscript{17,18}

\textit{Tolerance of Antiretroviral Therapy}

The ability of HIV-infected children to adequately tolerate the antiretroviral drug regimens is an important aspect of treatment. If tolerance does become a problem for children, they may be less likely to comply with the prescribed drug regimen, thus enabling drug resistance and treatment failure to occur. Since HAART therapy has become the standard of care
for children infected with HIV, side-effects of this type of regimen as well as of specific drugs can be seen more often now. PIs, in particular, can have severe repercussions on the young child. Metabolic and gastrointestinal effects are usually most evident through complications with bone density and unusual body fat distribution. NNRTIs have also shown the ability to cause adverse side-effects. Studies have reported that grade-three rashes are often associated with Nevirapine use. Although side-effects such as these may be managed and controlled to limit further debilitation, they often can demand discontinuation of drug therapy for children who are severely affected.

Even though HAART has been implemented as an effective treatment for adult HIV-infection for many years, its use in children has only come recently with the approval of certain antiretroviral drugs for children with HIV. In turn, because these drug therapies were initially developed and formulated for adult use, the dosages and parameters have been altered in order to apply to children. This has mostly occurred through trial and error of experimenting with which formulations are most appropriate for children in terms of suppressing viremia and preserving immune function, but also in limiting the side-effects that may occur due to toxicity. Studies have often shown that children can have a very narrow therapeutic index with many drugs so the potential for overdose can be relatively strong. This causes tolerance of antiretrovirals to be a much greater concern in children when compared with adults. Furthermore, because of the other complications associated with HIV-infection in children, tolerance must always be a significant consideration when evaluating the effects HAART in children.

Physical and Cognitive Growth Indicators

Although CD4 counts/percentages and HIV RNA levels can give an indication as to the disease progression for children infected with HIV, they do not always solely capture the whole
clinical picture. For instance, children may exhibit high CD4 counts and low viral loads but still rapidly progress to AIDS. Because of this anomaly that seems to occur often in pediatric HIV infection, growth, through both physical and cognitive parameters, is sometimes used as an indicator of disease progression, and thus, also needs to be considered when deciding to begin, alter, or terminate drug therapy.

HIV impairs weight, height, and cognitive growth in infected children. Weight growth failure can be defined as three consecutive months with less than the third percentile for 6-month weight growth velocity according to both gender and age. Incremental growth charts are used to determine the appropriate percentile of growth of each child. Unlike malnutrition, HIV stunts growth in terms of delaying increases in both height and weight. Thus, children with HIV will often be much smaller than normal for their age and gender. Physical growth failure is often related to CD4 counts/percentages in that as they decrease, the child is more likely to suffer from impaired growth. Cognitive growth can be impaired by disease of the central nervous system and thus is also a factor that needs to be considered in the treatment of children infected with HIV. This consequence of HIV infection in children is believed to be unrelated to the immunosuppressive effects of HIV, because cognitive decline is not associated with any decrease in CD4 counts/percentages. Restricted physical growth and diminished cognitive development both increase the chance for mortality among HIV-infected children.

Antiretroviral therapy compounds the effects of HIV on the growth of infected children because it brings both advantages and disadvantages in terms of maintenance of adequate growth. HAART regimens that contain PIs have been shown to improve metabolism and the absorption of nutrients; however, they can also have severe side-effects, such as nausea, vomiting, loss of appetite and diarrhea. Studies examining the effects of PI-containing drug
regimens have documented slight improvements in both height and weight for children receiving these therapies. Although these children did not improve to the extent of acquiring normal weight and height for their appropriate gender and age, drug therapy did allow height and weight decline to be at least temporarily suspended. Therefore, the side-effects imposed by HAART may be outweighed by the potential benefit in terms of limiting the progression of weight and height decline, thereby facilitating at least moderate growth in children infected with HIV.

*Published HIV Treatment Guidelines for Children*

Guidelines for the administration of antiretroviral therapy to HIV-infected patients have evolved as more information concerning effective therapies has become available. Much of this new information has come from clinical trials as well as from general practice and literature regarding drug treatment. For pediatric HIV patients, information through phase III clinical trials has been limited. However, this lack of knowledge has not inhibited clinicians and research scientists from extrapolating the protocols used in the treatment of adult infection and combining them with the application of additional considerations. Currently, the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-infected Children, is the most recent and comprehensive document containing detailed recommendations for treating children.

For infants and young children, infection primarily occurs through perinatal transmission. Thus, HIV-infected children are often exposed to antiretroviral medications, such as zidovudine, in utero, during birth, or after birth. This exposure to antiretroviral therapy should be considered when prescribing further medication once HIV infection is confirmed. Because children are continuing to grow and develop, the pharmacologic parameters of the prescribed medications need to be considered and the dosages and formulations altered appropriately.
lack of a completely competent immune system and the unique clinical picture that is seen in pediatric infection often calls for increased monitoring and altered drug therapy. Therefore, these published guidelines have attempted to take into account these and other factors that are exclusive to pediatric HIV infection.

The Guidelines specifically encourage appropriate monitoring of an HIV-infected child consisting of routine CD4 T-lymphocyte counts and percentages as well as viral loads every three months following diagnosis, and more frequent testing for infants less than one year of age and for children with deteriorating clinical status. Although CD4 counts and percentages provide a standard on which to assess the health and disease status of the HIV-infected child, these values can vary significantly at different times even for the same child. Consequently, it is recommended that alterations in drug therapy should only be made after two consecutive decreased CD4 values or increased viral loads, or after the occurrence of an opportunistic infection. When monitoring HIV viral load in infected children, one must take into account the different pattern that is seen when compared with adult infection. In the initial stage of adult infection, viral load numbers increase sharply and then gradually decrease, whereas children exhibit high levels of HIV RNA throughout infection and for prolonged periods of time. This characteristic difference is probably due to the insufficient immune system of the child and its lack of ability to control viral replication.

Both CD4 cell count and viral load are independently related to disease progression in the HIV-infected child. However, the implications associated with each measurement do differ. Some observational studies have demonstrated that CD4 cell count principally reflects short-term disease progression; whereas viral load is a better predictor of long-term disease progression. Because these indicators are measured at regular intervals at every three months, some
physicians maintain that it is more practical to base initiation and alteration of ARV therapy on the likelihood of short-term disease progression and thus on CD4 counts. However, the published guidelines still suggest that the complete clinical and immunological picture of the HIV-infected child should be taken into consideration as well as the age of the child, since CD4 counts and viral loads fluctuate greatly in children less than one year of age.

Although HAART cannot cure someone with HIV/AIDS, antiretroviral therapy is targeted at improving the quality of life through a reduction in mortality and morbidity, preservation of immune function and suppression of viral replication. Equally important are maintaining adequate growth and cognitive development as well as limiting drug-related toxicity in the HIV-infected child. Although the exact combination of drugs will differ from child to child depending on adherence, HAART history, and the complexity, potency and toxicity of the regimen, there are certain standards that the guidelines encourage. All children who are being treated with antiretroviral therapy should be given a combination of at least three different drugs from two different classes. Future treatment options as well as the possibility of the occurrence of drug resistance should be regarded when prescribing therapy. Changes in drug therapy should not be made without significant evidence of treatment failure. Adherence should be promoted as a necessity for all patients, since lack of adherence is often associated with disease progression and virologic failure.

Much controversy exists when deciding to administer drug therapy to antiretroviral (ARV) treatment-naïve patients, HIV-infected children who have never received antiretroviral medications. Aggressive therapy for these children while they are still asymptomatic can often result in control of viral replication and preservation of the immune system. However, prolonging ARV therapy until a child exhibits symptoms or immune suppression may cause a
reduced occurrence of drug-resistant mutations and greater adherence to medication since the patient is symptomatic. Therefore, both expediting and delaying drug therapy each have their respective benefits. Although a consensus regarding when to initiate treatment has not been definitively reached, treatment of children with HIV generally remains more aggressive than treatment of adults because children already have compromised immune systems.

For children under the age of 12 months, the Working Group recommends that HAART should be initiated for all infants exhibiting symptoms regardless of CD4 T-cell count/percentage or viral load. HAART is also recommended for asymptomatic infants who have a CD4 percentage below that of 25%. For all other infants, the Working Group recommends that HAART should at least be considered. These recommendations are based on the risk of disease progression to AIDS or death, which occurs in children less than one year of age at an estimated rate of 15%. Because evaluation of disease status is so complicated in this age group, CD4 count and HIV RNA levels are often regarded as poor indicators of disease progression. Rather, studies have shown that the prenatal level of maternal viremia as well as the clinical and immunologic status of the mother during pregnancy is more closely related to the risk of disease for infected infants.

For ARV treatment-naïve children older than one year, recommendations for initiation of therapy are slightly less aggressive than those for infants less than one year of age. Drug therapy should be started in those children that are symptomatic regardless of CD4 percentage, count and viral load. Treatment initiation is also recommended for asymptomatic or mildly symptomatic children who have met the age-related CD4 cell count threshold as defined by the Working Group. Consideration for treatment commencement should be given to children who are asymptomatic but exhibit greater than 100,000 copies/mL of HIV RNA. Initiation of HAART
should be deferred for those children who do not exhibit any clinical symptoms or signs of immune suppression and have a viral load of less than 100,000 copies/mL. These slightly altered recommendations represent the decreased risk of disease progression that occurs in HIV-infected children greater than one year of age. In this age group, CD4 count also becomes more predictive of disease progression so its use as an indicator to initiate or change therapy is strongly recommended. Similarly, levels of HIV RNA may also be used to assess whether HAART should be initiated in patients one year and older. Mortality substantially increases when viral load increases to greater than 100,000 copies/mL. However, the ability for viral load to act as a significant indicator of risk of disease progression is not as strong as CD4 count and percentage.

Insert Table 1 here.

For ARV treatment-naïve children, a specific protocol is recommended according to the Working Group. Of the 22 antiretroviral drugs approved for use in adults and adolescents with HIV, 13 are approved for treatment of pediatric infection. Each child regardless of age should receive at least three drugs, including either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), each with two nucleoside analog reverse transcriptase inhibitors (NRTIs). Monotherapy with any of the currently approved drugs is not recommended except to prevent HIV infection in children during the first six weeks of life. Dual NRTI therapy is also not recommended. Triple therapy of only the NRTI class should only be used in special circumstances when the other regimens cannot be initiated because of concern for drug interactions, toxicity, or adherence. For children under the age of three, Nevirapine is the recommended NNRTI. This drug should be given in addition to two NRTIs. For children over the age of three, Efavirenz should be the NNRTI of choice, with Nevirapine as the alternative.
These are the only two NNRTIs approved for the treatment of pediatric HIV infection. For PI-based regimens, the lopinavir/ritonavir combination pill is preferred for all HIV-infected children regardless of age. This should be given with two NRTIs. For children older than two years of age, Nelfinavir is another PI that may be given in addition to two NRTIs. In total, only four out of the ten currently available PIs have been approved for use in children.\(^1\) There are six NRTIs that are currently approved for the treatment of pediatric HIV infection and these can be combined in multiple ways to give a dual NRTI backbone of the HAART regimen. Preference should be given to those combinations delineated by the Working Group to give the most benefit while conferring the least side-effects.

Insert Table 2 here.\(^1\)

There are many advantages to initiating treatment with an NNRTI-based regimen. Generally, NNRTIs have been shown to be less toxic to the child when compared to PIs.\(^1\) Using NNRTIs first allows PIs to be reserved for future use when the child might be better able to tolerate the medication. Nevirapine is available in a liquid formulation, which facilitates treating young children who have difficulty swallowing large pills. There is also a reduced pill burden with NNRTI-based regimens versus those that contain PIs.\(^1\) However, with NNRTI use comes the risk of serious drug resistance with only one viral mutation and entire class resistance is common with prolonged NNRTI use.\(^1\)

PI-based regimens also bring their own advantages and disadvantages. PIs are known to have tremendous potency and are effective in suppressing viral replication. In order for drug resistance to occur, multiple viral mutations must take place.\(^1\) However, PIs can be very toxic to young children and can also cause multiple-drug interactions.\(^1\) Therefore, when considering which regimen to employ, the Working Group recommends that the complete picture of
strengths and weaknesses of the drug combinations as well as the ability of the child to remain adherent be taken into account before any treatment is initiated in the antiretroviral-naïve child.

After initiating drug therapy in HIV-infected children, proper monitoring must be employed in order to identify any adverse effects as well as treatment failure. A physician should first assess children within two weeks of treatment initiation, and then within four to eight weeks to evaluate the child’s clinical status, to check for potential side-effects, and to measure CD4 count/percentage and HIV RNA levels. Routine assessments should then be made every three to four months so that the regimen can be evaluated in terms of effectiveness, tolerability, and adherence.

Once a child has received antiretroviral drugs, and therefore has become treatment-experienced, new considerations should be taken into account as defined by the Working Group guidelines. The decision of whether to change a drug regimen is often not easy; however, the presence of drug resistance, immunologic and clinical status, adherence, and the child’s overall treatment experience should all be taken into account. Most of the time, treatment failure, defined as a suboptimal response or lack of sustained response to therapy, will be the main reason in determining a change in drug regimen. Because complete viral suppression in the treatment-experienced child may not be possible, several factors and measurements should be analyzed to decide if a change in therapy is necessary. A determination of virologic failure should include a comparison of the baseline viral load with current values as well as a second confirmatory test one week after the initial findings. Immunologic failure is slightly more difficult to assess but should include an evaluation of CD4 counts and percentages with a comparison to both baseline values and CDC standards. Clinical treatment failure should only be concluded after at least six months of therapy. Its determination must be based on the
occurrence of either growth failure, cognitive deterioration or recurring AIDS-defining illnesses as well as the state of the virologic and immune responses to drug therapy.¹

When deciding whether to change the regimen of a child who experiences virologic failure, immunologic failure or clinical failure, the child’s history of ARV drugs as well as the degree of adherence should be strongly considered. For instance, if a child has only been limitedly exposed to antiretrovirals and also has minimal drug resistance, the drug regimen should be changed if strong adherence is suspected.¹ In this case, most if not all of the drugs in the current regimen should be changed. If a child has been moderately exposed to antiretrovirals, then the degree to which adherence was a contributor to treatment failure should be assessed before the regimen is altered.¹ If poor adherence is found to be the main contributor to treatment failure, then the current regimen should remain. If that is not the case, then a treatment change can be considered. For those children who have been extensively exposed to drug therapy and have experienced treatment failure due to profound drug resistance, changing or discontinuing current therapy may not be the best option. Because inhibiting clinical progression and preserving immune function are the main goals at this point, viral load may not always be the most accurate indicator of disease progression.¹ Therefore, these children should remain on the current therapy unless it is determined that enough immune function is present to deter clinical progression and suppress viral replication upon a change to a different drug regimen.¹

For the HIV-infected child who has experienced treatment failure and is changed to another drug regimen, HIV drug resistance testing should be performed in order to assess the drugs to which the virus shows sensitivity and resistance. The new regimen should include at least two new drugs and still have an overall total of at least three drugs. If a child experiences
treatment failure on an NNRTI-based regimen, then a PI-based regimen should be given as second line therapy with the opposite situation applying as well. An NNRTI should not be given following the occurrence of drug resistance to an NNRTI because of potential development of entire class resistance.

For certain children, the clinician may determine that either short-term or long-term structured treatment interruption is necessary. Short-term therapy interruptions can be appropriate for surgical procedures and acute illnesses that limit oral intake. All drugs should be stopped at the same time. Long-term treatment interruption can be prescribed for patients who experience tremendous toxicity as well for patients who have exhausted most other treatment options. The theory is that treatment interruption will allow the return of the wild-type virus, which is the original virus without any genetic mutations that confer resistance to antiretroviral drugs. Thus, the wild-type virus will be more susceptible to immune action as well as to antiretroviral therapy. Although this strategy has shown promise in suppressing viral replication and restoring immune function in adults, there is limited knowledge about the effectiveness of such treatments in children.

While these guidelines do provide a template for clinicians to use in how they therapeutically treat their pediatric HIV-infected patients, physicians have complete discretion to use whatever method of treatment they deem best for the patient. Therefore, although these recommendations are meant to provide the best standard of care, other factors may be present that lead the physician to apply these guidelines differently. However, it is unknown to what extent physicians use these guidelines in clinical practice.
Materials and Methods

This study and analysis of the treatment of pediatric HIV infection had its origin in Cape Town, South Africa. A research study was conducted from February to May of 2006 in the pediatric AIDS clinic of Victoria Hospital. In order to determine how published protocols for drug therapy for perinatally HIV-infected children were being used in Cape Town, South Africa, many measures were employed. First, analysis of all the pediatric patient records was performed to find similarities and differences in the drug distribution. The process also facilitated the assessment of the relationship between the health outcomes of children and the antiretroviral regimens that they received throughout the course of treatment, beginning with diagnosis. Permission to review patient records was granted by the hospital board. Extracted patient information was kept on a secure password-protected computer file.

After clinical information was collected, hospital staff and administration were interviewed in regards to their role in treating the HIV-infected children at their hospital. Three clinicians, all with medical degrees, actively oversaw clinic procedure and patient outcomes. These three doctors all agreed to be interviewed. Each interview lasted approximately 30 minutes. An interview guide was used to conduct each interview. First, each doctor was asked what specifically determined the administration of ARV drugs to HIV-infected children. Each doctor was then asked to identify each major component of the clinic’s protocol. For each indicator that they named, the reasons underlying its utilization were also assessed. How the hospital addresses the occurrence of failure to adhere to the drug regimens was determined by several questions. The doctors were then asked questions regarding the concerns of the impact of drug therapy on sustained growth and cognitive development as well as problems with toxicity that may arise with chronic treatment of HIV infection with antiretroviral drugs. Routine HIV
drug resistance testing is not usually available in Cape Town, South Africa so this parameter was not addressed in the interview. The results of each interview were recorded onto a secure password-protected computer file.

To assess how hospitals and treatment centers of pediatric HIV infection Washington, DC apply the published guidelines regarding drug therapy for their pediatric patients, interviews of healthcare personnel from Children’s National Medical Center and Howard University Hospital were conducted. These two Washington, DC hospitals treat the majority of the city’s children infected with HIV. Although there are guidelines for treatment published the National Institutes of Health\(^1\), the true usage of these guidelines in clinical practice is unknown. Whether or not each hospital uses a specific protocol was assessed as well as the factors that determine deviation from those methods.

One clinician from Children’s National Medical Center and one from Howard University Hospital were asked to participate in this study as interviewees. They were informed of the type of study and asked whether or not they could participate in an interview at their respective worksite. In accordance with the inclusion criteria of the study, all subjects who were interviewed are intricately involved in the treatment process at their respective institutions. They have specific knowledge relating to the protocol that is used and any reasons that may cause deviation from that protocol. Although only one person was interviewed from each institution, it can be correctly assumed that the participants represent the hospitals for which they work in terms of identifying and articulating the details of the treatment methods for HIV-infected children. Even though only two hospitals were evaluated, this study details how infants and children with HIV are treated in Washington, DC, since these two hospitals treat the majority of HIV-infected children who reside in this city.
Each interview was conducted in accordance with Georgetown University Institutional Review Board approval, which was obtained on November 3, 2006. Before beginning the interview, each clinician gained permission from their respective hospital board to participate. Informed consent was also obtained from each interviewee. A questionnaire (see Appendix A) was developed and used for each interview. It consists of 25 questions, seven of which pertain to information regarding the background of the healthcare worker. Four of the questions concern the type of services offered as well as the number of children the hospital treats and how often children are seen by physicians. The remaining 14 questions target the specific protocol for pediatric HIV drug therapy that the facility uses, why each protocol is used, and the respective results that have been observed regarding the health outcomes of the patients being treated. Clinicians were asked to give reasons why the hospital uses certain indicators to determine drug therapy. Several questions also focus on whether or not deviation from the current protocol occurs. Clinicians were asked what laboratory results, as well as clinical findings, would necessitate a change in current protocol. Questions concerning drug resistance testing were also asked to the survey participants. Whether or not results of resistance tests play a role in treatment was further assessed. The survey includes both yes or no and open-ended questions. Each interview lasted approximately 30 minutes. Answers to the questions were recorded onto secure password-protected a computer file.

The answers obtained from all the interviews were then assessed and compared to the most current published guidelines. Similarities in treatment indicators and the types of drugs used denoted a strong correlation between hospital protocols and published guidelines. Although conditions at the two hospitals do differ, the comparison pertained to the use of specific treatment indicators and how their use relates to the published guidelines.
Results

As a result of the interviews with clinicians, the protocols used for the treatment of HIV-infected children by Victoria Hospital in Cape Town, South Africa and Children’s National Medical Center and Howard University Hospital in Washington, DC were ascertained. Through the evaluation of these protocols, the indicators used to determine the initiation, alteration, or discontinuation of drug treatment were established. For Victoria Hospital, adherence and general health of the child were regarded as the most important determinants of the initiation of drug treatment. Although CD4 counts/percentages, HIV viral loads, and presence of clinical symptoms were considered the most significant treatment indicators for Children’s Medical Center and Howard University Hospital, all children under the age of one year were placed on HAART independent of any of these clinical findings. Most children over one year of age were also immediately placed on HAART; however, CD4 counts/percentages, HIV viral loads, clinical symptoms, and adherence were considered as factors mediating the decision to begin treatment.

Victoria Hospital

From February to May 2006 when the study at Victoria Hospital took place, the hospital treated 50 HIV-infected children who were 12 years of age or younger at the time. Four of these children were not receiving any antiretroviral drug therapy at the time of the study. There were three doctors and two nurses on staff in the clinic at this time. Children who were treated on an outpatient basis were seen as needed, at varying times from one to six month intervals depending on the clinical stage of disease. CD4 counts/percentages and growth were measured approximately every six months. However, at the end of the study period the hospital was
moving towards a policy of assessing CD4 counts/percentages and growth at regular three-month intervals.

Through a careful analysis of patient records and interviews with clinicians, it was determined that this hospital’s pediatric HIV clinic was forced to use certain indicators more so than others in assessing whether a child needed to be placed on ARV drug therapy. Factors such as adherence and general health of the child were often regarded as more significant than CD4 counts and percentages in determining the initiation, alteration, or suspension in drug therapy. Although CD4 counts and percentages were considered important indicators, they were not solely relied on to predict the treatment that a child would receive. Because of the expense of the test, HIV RNA levels were not routinely measured; however, physicians at Victoria Hospital hoped to institute routine viral load testing in the near future. Although children at this hospital never received HIV drug resistance testing, drug resistance was usually assumed to be the cause of treatment failure when poor adherence to the regimen was observed.

For those ARV treatment-naïve patients, several factors determined whether a child was placed on antiretrovirals. Thus, prescription of medication was not an automatic condition of treatment for children at this hospital. Adherence to drug therapy was regarded as the most significant predictor of virologic suppression by the hospital. Therefore, the hospital chose to delay the prescription of ARV drug therapy to those children who had unstable support systems at home, which might interfere with taking medications properly. Victoria Hospital did institute routine pill counting for all children receiving ART in order to assess compliance with drug regimens. Clinicians also tried to advocate strict adherence to the regimen by talking with the primary care providers; however, no formal counseling took place by trained psychiatrists. Most children on ART who exhibited treatment failure due to poor adherence were either changed to a
different regimen or completely removed from drug therapy regardless of clinical or immunological stage of disease.

Victoria Hospital also often refrained from treating infected children who remained relatively healthy. This postponement in drug therapy did not occur often; however, hospital staff often took advantage of the delay in disease progression of certain children who remained relatively healthy despite being infected with HIV. Although the state of disease was assessed through CD4 counts/percentages, other markers were used as well. For instance, if the child was sustaining adequate growth according to the appropriate range for age and gender, then the state of disease was considered to be minimal. Also, if a child was asymptomatic, then treatment was often delayed regardless of CD4 counts/percentages.

In terms of the types of drug therapy prescribed to children at Victoria Hospital, most children were placed on HAART with at least three or more drugs, including two NRTIs and either one NNRTI or one PI. However, there were some children who only received one or two NRTIs as a result of insufficient adherence, impaired tolerance or delayed clinical progression of disease. The issue of tolerance to the HIV medications was also assessed at Victoria Hospital. This occurrence did result in some children either discontinuing therapy or changing to another cocktail of drugs.

Children’s National Medical Center

In November of 2006 a registered nurse from a Children’s National Medical Center in Washington, DC was interviewed. Along with three doctors, four nurses, four social workers, two psychologists, and one nutritionist, she was a part of the pediatric HIV/AIDS team at this hospital. Approximately 170 children, age 12 and younger, were receiving outpatient care at the time the interview was conducted. At any given time one to five children were receiving
inpatient care. Children are routinely seen every three months with CD4 counts/percentages, viral loads, and growth indicators measured at each of those visits. Upon initiation of drug therapy, children are seen once a month for three months so that CD4 counts and viral loads can be measured. Children who have declining clinical progression of disease are usually seen more often on an as-needed basis.

At Children’s National Medical Center, all infants less than one year of age who are infected with HIV are placed on antiretroviral therapy, regardless of CD4 counts/percentages, viral loads, or other measures. This generally occurs within the first six months of life when HIV infection can be confirmed through viral culture, PCR analysis, or viral antigen testing. Most ARV treatment-naïve children older than one year of age are also automatically placed on HAART; however, the presence of symptoms and or disease related illnesses, as well as CD4 counts and viral loads, can also influence the decision to begin treatment. This hospital has identified these indicators as significant for predicting the course of disease progression that will take place in the HIV-infected child. Since antiretroviral therapy can slow the progression of the disease, physicians at Children’s National Medical Center usually chose to prescribe it when one of these measures changes dramatically.

The interviewee also identified adherence and health status as factors used by the hospital physicians when deciding to initiate or delay drug therapy. These physicians consider the ability and will of the child’s family to properly administer medications at the correct times to contribute to viral suppression and immune reconstitution. Therefore, if a child over the age of one year has a marginal need for ARV therapy and the family situation is poor, then the physicians may decide to postpone treatment until either the child’s condition worsens or his/her home situation improves. For those children on HAART, adherence is often used as an indicator
of whether or not therapy should be changed or discontinued. The hospital does put specific measures in place to address the issue of adherence amongst its pediatric patients. Pharmacists perform adherence assessments through pill counting as well as through helping parents workout a schedule that can be carried out easily and effectively. Psychologists also help young children learn how to swallow large pills to facilitate their role in complying with the regimen. Furthermore, psychologists also work on disclosing the illness with older children so that their awareness may better prepare them to take ARV medications.

Children’s National Medical Center does utilize the method of HIV drug resistance testing through analyzing both virtual HIV phenotypes and genotypes. However, testing is not conducted at regular intervals, but only when resistance is suspected. Although drug resistance is used as an indicator to change drug therapy, it does not supercede general health of the patient, CD4 counts or percentages or HIV RNA levels. Rather it is used in conjunction with these other indicators to confirm treatment failure. The interviewee did not know the prevalence of drug resistant mutations amongst the hospital’s pediatric patients. As for the particular procedures that are used by the hospital to determine treatment for its patients, the interviewee could not specifically name a source of the protocol; however, she did report that the current NIH guidelines and literature are reviewed and considered on a regular basis.

*Howard University Hospital*

The second interview in Washington, DC was conducted in January of 2007 in which a study coordinator from Howard University Hospital was interviewed concerning the treatment protocols for HIV-infected children. She is part of a team of about ten people, including two doctors, two nurse practitioners, study coordinators and psychologists. At the time the interview was conducted this hospital cared for approximately 50 pediatric HIV/AIDS patients, 12 years of
age and younger, on an outpatient basis. At any one time, there are only approximately one to three children admitted to this hospital for treatment. Children are routinely seen by the hospital every three months, when CD4 counts, HIV RNA levels, and growth parameters are measured. Children who experience clinical deterioration are seen by the hospital every six weeks.

When asked about how the hospital chooses to place HIV-infected children on antiretroviral medication, this interviewee disclosed that all infants less than one year of age who are treated at this hospital are placed on ARV therapy shortly after birth or as soon as diagnosis is confirmed independent of CD4 counts/percentages or HIV RNA levels. When children older than one year of age are diagnosed with HIV, they are usually placed on HAART; however, drug therapy initiation may be postponed if the child has remained relatively healthy and has maintained a clinically asymptomatic status. Viral loads and CD4 counts are also used to indicate whether drug therapy is necessary in patients older than one year of age. When considering a change in the ARV regimen, physicians use viral loads and CD4 counts as the main indicators. This hospital relies slightly more on viral load versus CD4 counts and percentages as an indicator of disease progression, and thus, viral loads are used more often than CD4 values in order to determine whether a child needs a change in drug therapy.

Clinicians at Howard University Hospital do consider adherence and the family situation of the child to have a moderate influence on treatment decisions. If the child exhibits poor compliance to the drug regimen as a result of an inadequate home support system, then physicians may decide to prescribe a different regimen that is more easily administered or also may decide to temporarily suspend drug therapy. When children visit the hospital for their routine clinical assessments, pharmacists often conduct pill counting in order to determine the degree to which the child has remained adherent to the regimen. Howard University Hospital
also offers counseling for both children and their families in order to try to increase compliance and determine if any barriers exist at home which may inhibit the children from receiving their medications correctly at the appropriate times. The interviewee confirmed that the principal contributor to drug resistance, and thus, virologic failure has been lack of adherence on the part of the child and the child’s family. The hospital reports that adherence rates for younger children are usually quite high because they are monitored closely and are directly given their medications on a daily basis. However, for older children, who are at least 10 years of age, often too much burden is placed on the child in allowing him/her to take on complete responsibility to take the medication properly. Thus, clinicians at Howard University Hospital have observed poor adherence rates in this pre-adolescent age group.

Although patients from this hospital are tested for HIV genotypic ARV drug resistance, there is no decisive protocol as to how and when this test is used, except for following a dramatic increase in viral load from the previously recorded value. The interviewee reported that in this particular hospital, drug resistance usually increases with age of the child, both because of increased time on ARV therapy and because nonadherence rates increase with age. The average patient who has been on drug therapy for greater than three years has resistance to two to three drugs, with mutations conferring class resistance most commonly to NNRTIs.

Howard University Hospital does not directly follow any one protocol; however, the interviewee could verify that the most recent literature findings and guidelines are taken into account by the all the clinicians and staff involved in the treatment process. Children treated at this hospital do participate in clinical studies, so they can be exposed to experimental protocols, such as prescribed treatment interruption over both short-term and long-term time periods.
Discussion

When comparing the pediatric HIV treatment methods used at the three hospitals in Cape Town, South Africa and Washington, DC, the main contrast is seen in the degree to which each indicator plays a role in the specific HIV treatment protocol. Treatment of children infected with HIV at Victoria Hospital diverged from the published treatment guidelines in that CD4 counts and viral loads were not used as the primary treatment indicators and instead adherence and general health of the child were employed as the main determinants of initiation, alteration and discontinuation of drug therapy. Although the clinicians at Victoria Hospital in Cape Town, South Africa do utilize CD4 counts/percentages as indicators of clinical disease progression, these clinical markers do not solely determine the treatment that the child will receive. This hospital takes into account the ability of the child to remain adherent to the prescribed regimen as well as the general health of the child. Even though the guidelines do recommend consideration of adherence and the health status of the child as mitigating the decision to begin, change, or discontinue treatment, Victoria Hospital uses these indicators to a greater extent.

For instance, when compared to the two Washington, DC hospitals studied, there were more children at Victoria Hospital who remained treatment-naïve due to an insufficient home support system to provide complete adherence to the drug regimen. Also there were more children at Victoria Hospital who did not initiate drug therapy because their health statuses were considered to be adequate in terms of maintenance of normal immune function. Both Children’s National Medical Center and Howard University Hospital in Washington, DC do consider compliance with the drug regimen; however, no children remained treatment-naïve due to fear of poor adherence at the time the study was conducted. Health status and appropriate immune
function are also considered as important factors, but neither of these hospitals delayed drug therapy initiation for any children currently being treated because of these factors.

For treatment-experienced patients at Victoria Hospital, adherence and health status were accorded about equal weight with CD4 counts/percentages in deciding whether a change or discontinuation in therapy was necessary. Upon the identification of treatment failure due to poor compliance to the regimen, children were often changed to a regimen with fewer barriers to adherence, such as decreased toxicity, lower dosage requirements, and non-specific storage conditions for medications. This change was performed even if the former regimen was considered to be more effective than the latter. When comparing this part of Victoria Hospital’s protocol with the Working Group Guidelines, another point of divergence is identified. The published recommendations suggest only changing therapy when poor adherence to HAART is not a contributor to treatment failure. However, clinicians at Victoria Hospital recognize that there are some inherent aspects of HAART regimens that make it difficult for children and their families to comply with drug therapy. Therefore, these physicians believe that changing a child’s regimen to one that lacks these hindrances might actually facilitate adherence to the new drug regimen and consequently result in improved health outcomes.

For children who exhibited drastic changes in CD4 counts/percentages in which poor adherence was not a factor, physicians often changed the drug regimen to facilitate viral suppression and improvement of immune function. When comparing Victoria Hospital’s use of CD4 counts/percentages as an indicator for altering therapy, the methods agree with those recommended by the published guidelines in that drug regimens were changed upon assessment of immunologic failure. However, because Victoria Hospital does not use routine testing of HIV
RNA levels, virologic failure cannot be directly assessed. Therefore, treatment failure can only be determined through evaluation of immunologic and clinic status.

In terms of discontinuing therapy either temporarily or permanently, physicians at Victoria Hospital made the decision on a case-by-case basis by taking into account the history of the child and the current state of disease. It was not uncommon for children at Victoria Hospital to be completely removed from a drug regimen due to poor adherence after several years on HAART, especially if the home situation was a contributing factor. This part of Victoria Hospital’s treatment methods both agrees and differs with the Working Group Guidelines. The recommendations specifically suggest that upon conclusion of treatment failure for children who have been extensively exposed to antiretroviral therapy, discontinuing therapy should not always automatically occur. However, the guidelines also acknowledge that structured treatment interruptions, whether on a short-term, temporary basis or as part of a long-term, permanent solution may be able to actually improve the clinical progression of disease. Because of the financial instability in the funding for antiretroviral drugs, physicians often make the decision to terminate drug therapy for children exhibiting treatment failure due to poor compliance in order to use the available drug therapy to treat other newly infected children.

When evaluating the types of drug regimens used by Victoria Hospital, Children’s National Medical Center, and Howard University Hospital, Victoria Hospital was the only center that used regimens incongruent with the Working Group Guidelines. Although most of the children at Victoria Hospital did receive a triple cocktail with at least two NRTIs and either one PI or one NNRTI, some children also received monotherapy or dual NRTI therapy. These types of regimens were typically reserved for patients who exhibited problems with adherence, toxicity, and also for patients demonstrating delayed disease progression. For children receiving
an NNRTI as part of their ART regimen, Nevirapine was always the drug of choice, conflicting with the Working Group Guidelines that Efavirenz should be the NNRTI given to children older than three years of age.

Children’s National Medical Center and Howard University Hospital had very similar treatment methods in terms of the indicators used to begin, alter, or delay prescription of HAART. Both institutions also used the recommended combinations of antiretroviral drugs as suggested by the Working Group Guidelines. When comparing the methods used by both of these hospitals to the recommended guidelines, there are a few points of divergence.

In contrast to Victoria Hospital’s use of the current guidelines, both Children’s National Medical Center and Howard University Hospital took a more aggressive approach to treating children infected with HIV than recommended by the Working Group. Physicians at both hospitals chose to initiate treatment for all children less than one year of age, instead of relying on CD4 counts, viral loads, or presence of symptoms as treatment indicators. This approach demonstrates a strong concern for preservation of immune function and complete suppression of viremia in the initial stages of infection. Ability for the patient and the patient’s family to comply with the prescribed drug regimen could be a deciding factor in deciding to initiate or postpone drug treatment. Although both of these institutions believe that an aggressive approach with prescription of HAART for all children beginning in infancy provides the best opportunity for the most optimal outcomes, there is presently no clinical evidence at this time to support this claim.

In agreement with the published guidelines, physicians at both hospitals used CD4 counts/percentages, viral loads, and appearance of disease-related symptoms as the main indicators of treatment failure. When considering adherence, both hospitals used this indicator
secondary to other clinical markers, such as CD4 counts/percentages, HIV RNA levels and presence of disease defining symptoms. If treatment failure occurred secondary to poor adherence, there was no set protocol, but a change to a regimen with fewer side-effects and restrictions could occur. Like the situation at Victoria Hospital, this action by Children’s National Medical Center and Howard University Hospital conflicts with the recommendations of the Working Group Guidelines, which specifically suggest that the drug regimen should not be changed for any children with treatment failure caused by noncompliance. However, physicians at both these hospitals felt that it was often in the best interest of the child to try another regimen that may facilitate better adherence. Very few times did physicians decide to discontinue treatment at either of these hospitals due to treatment failure whether or not adherence was a factor. At Howard University Hospital, however, patients often participated in experimental studies in which treatment interruption was used as an experimental condition. It could not be determined at this time whether a suspension in treatment resulted in improvement of the clinical progression of disease of any of these children.

Although this study attempted to capture a realistic picture of how the published recommendations regarding treatment of HIV-infected children are actually used in a clinical setting, several limitations remain. First and foremost, only one hospital in Cape Town, South Africa was used to assess the HIV treatment protocols for infected children. Thus, although it can be assumed with much confidence that similar evidence would be found in other hospitals in Cape Town because of the same constraints on the healthcare infrastructure, this cannot be decisively concluded. Therefore, this limits extrapolation of the results to the whole population of HIV-infected children in Cape Town. Similarly, only two hospitals in Washington, DC were used in the evaluation of the treatment protocols for HIV-infected children. However, these two
hospitals treat the majority of infected children in Washington, DC so the results obtained from the interviews can confidently represent most of the population of HIV-infected children receiving treatment in this city. Therefore, in assessing treatment methods for the pediatric population in each city, the results for Washington, DC provide a much stronger comparison to the published treatment guidelines for HIV-infected children than do the findings for Cape Town, South Africa.

Secondly, interview studies offer some inherent limitations to collecting accurate information. Subjects who are interviewed can present a subjective bias by the way they answer questions. For this study in particular, many open-ended questions were used. This leaves much room for variation in the way the interviewee interprets and answers the questions, as well as how the interviewer translates the answers into recordable results. In the case of Victoria Hospital, the analysis of patient records supported much of the information gained in the interviews with physicians. However, review of patient records could not be performed in Washington, DC due to special requirements enforced by the Health Insurance Portability and Accountability Act (HIPAA) regarding patient privacy. Thus, the interviews conducted at Children’s National Medical Center and Howard University Hospital provide the only measure of treatment protocols for children infected with HIV in Washington, DC.

All three hospitals do not use a defined protocol, but physicians from each were able to identify the primary indicators that are used to treat children infected with HIV in their respective patient populations. Because each child is assessed on a case-by-case basis in each hospital, all circumstances regarding treatment with drug therapy are considered. However, all three hospitals do use certain standards throughout the treatment process to determine any initiation, alteration, or discontinuation in drug therapy. Thus, although limitations of this study
do exist, the interviews did enable a comparison of the treatment methods used in Cape Town, South Africa and Washington, DC, as well as allow an assessment of the degree to which hospitals in these cities used the published treatment guidelines.

Although this study did not explore the relationship between the effects of the alteration in the published Working Group treatment guidelines for HIV-infected children and the health outcomes seen in both Cape Town, South African and Washington, DC, it would be informative to compare the rates of drug resistance and the occurrence of opportunistic infections in each population. Some clinicians have argued that beginning drug therapy too early can decrease the time to which mutations occur that confer mutations to multiple drug therapies. Other experts argue that delaying drug therapy may allow the disease to progression rapidly to a state in which its reversal by ART is not possible. More information on the effects of these adaptations of drug treatment protocols used in these populations needs to be gathered in order for a distinct relationship between the commencement of ART and health-related outcomes in children can be defined.

Conclusions

Although each hospital diverged from the Working Group Guidelines in deciding when to initiate drug treatment for their pediatric patients, the approaches differ dramatically. Physicians at Victoria Hospital in Cape Town, South Africa expanded the published recommendations by using adherence and general health of the child as the main indicators for treatment instead of only using CD4 counts/percentages and HIV RNA levels as the primary indicators. Physicians at both Children’s National Medical Center and Howard University Hospital employed aggressive methods of treatment by initiating HAART for all children under the age of one year regardless of any other clinical indicators. Even though decisions could be
influenced by other factors, such as ability of the child to comply with the drug regimen, rarely did either of the two Washington, DC hospitals refrain from prescribing HAART for their pediatric patients.

The reasons for this striking contrast in the use of the Working Group recommendations can be understood once the setting of each hospital is taken into account. Because HIV drugs are in high demand in South Africa due to the dramatic HIV/AIDS prevalence rate, physicians at Victoria Hospital had to allocate resources in the most efficient way so that children who needed the medication the most could be treated effectively. In order to maintain strong adherence to the antiretroviral regimen, children must have a stable home support system with adults and caretakers capable of distributing medications in the correct dosages at the correct times. The availability of medications is tenuous in South Africa due to their extreme cost, so any children who might not be able to fully comply with the prescribed regimen are initially not placed on antiretroviral therapy. This is an example of how environmental factors can impact the protocols that are used to treat children infected with HIV. The physicians at Victoria Hospital reacted to the limitations imposed by the financial constraints of South Africa by altering the protocols recommended by the published guidelines to meet the needs of the pediatric population of Cape Town South Africa.

The U.S. has much greater access to antiretroviral drugs than does South Africa and infected children and their families have many more available resources in terms of healthcare. Thus, this step to initiate drug therapy for all children less than one year of age regardless of clinical disease indicators is only made possible by certain conditions of the environment surrounding Children’s National Medical Center and Howard University Hospital. By implementing drug treatment for all their patients, the physicians take advantage of the benefits
of living in a first world country with almost an unlimited supply of resources in terms of available drug therapies, testing capabilities, and numerous trained clinical personnel. In particular, because these clinicians treat children in the HIV epicenter of the United States, their awareness of the devastation caused by this disease is heightened. This has caused physicians at Children’s National Medical Center and Howard University to take the most drastic approach in treating children by implementing drug therapy as soon as possible.

The analysis of the treatment protocols used at Victoria Hospital, Children’s National Medical Center, and Howard University Hospital allow the primary research questions of this study to be answered. With regards to the types of indicators that the hospitals primarily employed in prescribing drug treatment, physicians at Victoria Hospital in Cape Town, South Africa chose to use CD4 counts/percentages as secondary to adherence and general health status in deciding when to initiate, change or discontinue drug therapy. Thus, Victoria Hospital regarded these subjective indicators as more influential on the treatment process than the traditional, quantitative clinical measurements. In contrast, even though both Children’s National Medical Center and Howard University Hospital employed CD4 counts/percentages and HIV RNA levels as the primary treatment indicators, physicians at these hospitals took very aggressive approaches in treating all HIV-infected children with HAART, independent of the clinical assessments provided by CD4 and viral load levels. Therefore, all three hospitals do not strictly apply the published guidelines as specifically suggested by the Working Group. Instead, each hospital uses additional methods to determine the drug treatment strategies for children infected with HIV. Although the Working Group recommendations do provide a framework in assisting practicing clinicians who treat HIV-infected children, the conclusions of this study
demonstrate that clinicians often apply the guidelines differently in order to provide the best course of action based on the needs and limitations of the populations they serve.
Appendix A: Survey

1. What is the approximate size of the staff where you work—doctors, nurses, physicians’ assistants, etc?
   Doctors: _____
   Nurses: _____
   Physician assistants: _____

2. Does your facility participate in in-patient treatment, outpatient treatment or both?
   ____ Inpatient only
   ____ Outpatient only
   ____ Inpatient and outpatient

3. How many children are currently receiving drug treatment for HIV?  Outpatient?  Inpatient?
   ____ Outpatient
   ____ Inpatient

4. How often are the children who are treated on an outpatient basis seen by your staff?
   ____ More than once/week
   ____ Once/week
   ____ Biweekly
   ____ Once/month
   ____ Bimonthly
   ____ Once/six months
   ____ Once/year
   ____ More than once/year

5. What indicators does the hospital/clinic use to place an HIV-positive child on ARV drug therapy?
   ___________________________________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

6. Why are these specific indicators used?
   ___________________________________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________
   ___________________________________________________________________________

7. Is the decision to begin drug therapy in children ever mitigated by any other factors?
   ____ Yes
   ____ No
8. If yes, what are some examples?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

9. Has any other protocol been used in the past for placing HIV-positive children on drug therapy?
   _____ Yes
   _____ No

10. If yes, why has there been a change to the current method?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

11. What have been the general outcomes of the implementation of the current protocol?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

12. How does the hospital/clinic address the issue of adherence to ARV therapy among its pediatric patients?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

13. Does the hospital/clinic test for drug resistance among its pediatric patients?
    _____ Yes
    _____ No

14. If yes, what are the recent significant findings concerning drug resistance for the majority of the pediatric patients?
____________________________________________________________________________
15. To your knowledge, can the findings be explained by anything inherent in the method of treatment?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

16. Does the hospital plan on changing its protocol of treating HIV-infected children in the near future?
   _____ Yes
   _____ No
   _____ Possibly

17. If yes, explain why.

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

18. If no, what would necessitate a change in procedure by the hospital/clinic?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

Questions Pertaining to Background of Healthcare Providers

19. Personal Information:
Gender: ______
Date of Birth___________

20. What is your educational background?

______________________________________________________________________________
______________________________________________________________________________
21. What specific training have you had regarding treatment of pediatric AIDS patients?
_______________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

22. How long have you worked for this hospital/clinic?

_____ Less than six months
_____ Six months to one year
_____ 1-2 years
_____ 2-5 years
_____ 5-10 years
_____ More than 10 years

23. What is the title of your position within the hospital/clinic?

______________________________________________________________________________

24. Have you worked anywhere else in the field of HIV/AIDS or pediatrics?

_____ Yes
_____ No

25. If so, where and what was your position?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
References


### Table 1: Indication for Initiation of Antiretroviral Therapy in Children Infected with HIV

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>• HIV-related symptoms OR&lt;br&gt;• Asymptomatic and CD4 &lt;25%&lt;br&gt;• Asymptomatic and CD4 &gt;25%</td>
<td>Treat&lt;br&gt;Treat&lt;br&gt;Consider</td>
</tr>
<tr>
<td>1-&lt;4 years</td>
<td>• AIDS or significant HIV-related symptoms OR&lt;br&gt;• Asymptomatic or mild symptoms and CD4 &lt;20%&lt;br&gt;• Asymptomatic or mild symptoms and CD4 20-24% or HIV RNA ≥100,000 copies/mL&lt;br&gt;• Asymptomatic and CD4 &gt;25% and HIV &lt;100,000 copies/mL</td>
<td>Treat&lt;br&gt;Treat&lt;br&gt;Consider&lt;br&gt;Defer</td>
</tr>
<tr>
<td>≥4-12 years</td>
<td>• AIDS or HIV-related symptoms OR&lt;br&gt;• Asymptomatic or mild symptoms and CD4 &lt;15%&lt;br&gt;• Asymptomatic or mild symptoms and CD4 15-24% or HIV RNA ≥100,000 copies/mL&lt;br&gt;• Asymptomatic and CD4 ≥25% and HIV RNA &lt;100,000 copies/mL</td>
<td>Treat&lt;br&gt;Treat&lt;br&gt;Consider&lt;br&gt;Defer</td>
</tr>
</tbody>
</table>

This table provides the Working Group recommendations that are meant to guide physicians in determining when to begin treatment for HIV-infected children.

### Table 2: Recommended ARV Regimens for Initial Therapy for HIV infection in Children
### NNRTI-Based Regimens

| Preferred                      | Children $>3$ years: 2 NRTIs *plus* efavirenz  
|                               | Children $<3$ years: 2 NRTIs *plus* nevirapine |
| Alternative                   | 2 NRTIs *plus* nevirapine (children $>3$ years) |

### PI-Based Regimens

| Preferred                      | 2 NRTIs *plus* lopinavir/ritonavir |
| Alternative                   | 2 NRTIs *plus* nelfinavir (children $>2$ years) |

### 2 Drug NRTI-Backbone Options (in combination with additional drugs)

| Preferred                      | Zidovudine *plus* (lamivudine or didanosine or emtricitabine)  
|                               | Didanosine *plus* (lamivudine or emtricitabine) |
| Alternative                   | Abacavir *plus* (zidovudine or lamivudine or emtricitabine or stavudine)  
|                               | Stavudine *plus* (lamivudine or emtricitabine) |

A combination ARV regimen in treatment-naïve children should contain 1 NNRTI or 1 PI with a 2-drug NRTI-backbone.