

Initiation of Antiretroviral Treatment and Dosing in Pediatric Patients in Resource Limited Settings

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Allison Agwu: Hello, I'm Dr. Allison Agwu, a pediatric and adult infectious diseases fellow at the Johns Hopkins School of Medicine. And as part of our Center for Global Health Pediatric HIV Lecture series, I'll be discussing with you today the initiation of antiretroviral treatment and dosing in pediatric patients in resource-limited settings.

Our lecture objectives today are as follows: number one, to identify the immunologic and clinical criteria for ARV initiation. Two, to understand the goals of ARV initiation, understand the recommended first line treatment regimens in resource-limited settings, to recognize the challenges of ARV administration in children, and to understand why dosing is particularly important in the pediatric population.

Useful terminology that will be utilized throughout this talk include the following: ARVs, antiretrovirals; HAART, highly active antiretroviral therapy, usually consisting of two to three, at least two but usually three classes or three medications; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; and PI, protease inhibitor.

Why to start ARVs? So, by one year of age, approximately 30% of untreated HIV-infected infants will die. By two years of age, 50% of untreated infants die. Children are at risk for the regular childhood illnesses as well as opportunistic infections that come along with HIV infection. HAART improves the child's ability to respond to infections, and increases survival, with many living through adolescence and beyond with the institution of HAART.

Goals of ARV Therapy. One, to decrease HIV-related morbidity and mortality. Two, to restore immunologic function. Three, to maximally and durably suppress virologic replication. Four, to minimize treatment toxicity, an important one, particularly with HAART initiation in the very young. Five, to promote and maintain normal physical and neurocognitive growth and development in children. And lastly, but very importantly, to improve the quality of life of children.

In this slide, you will see the World Health Organization's recommendations for initiation of antiretroviral therapy in HIV-infected infants and children. And these are according to clinical stage as well as the availability of immunologic markers.

So first, all the way on the left you see the WHO pediatric stage. Importantly, stage four, regardless of CD4, whether it's available or not, all patients greater than or less than the age of 11 months are recommended to receive antiretroviral therapy. In WHO class three, this is essentially also the same, in looking at those

less than 12 months of age, all are treated. Those greater than 12 months definitely all were treated with the CD4-guided approach, and those children with TB, LIP or lymphocytic interstitial pneumonitis, and other opportunistic infections. When there's no CD4 available, all patients are recommended to be treated. Looking at clinical stage one, this is definitely CD4-guided if available. If CD4 counts are not available, recommendations are not to treat those patients if they're in clinical stage one.

Now here is CD4 criteria for severe HIV immunodeficiency. Looking first at those less than 11 months of age with a CD4 percentage of less than 25%, they are required to initiate antiretroviral therapy. This correlates with a CD4 count less than 1,500. Contrast that to those greater than five years of age where a CD4 percent less than 15% and a CD4 count of less than 200 are considered criteria to initiate therapy.

In this slide you see total lymphocyte criteria, and again, looking at those less than 11 months of age, CD4 total lymphocyte count of less than 4,000, actually, is required for therapy. Contrasting in those five to eight years of age where one of less than 2,000 is used.

Importantly to notice between the CD4 and the total lymphocyte count is the fact that HIV RNA is not part of this criteria initiating therapy, usually because of poor availability in many resource-limited settings it's not part of the criteria.

This schematic simply demonstrates what was shown in the prior slide when to initiate antiretroviral therapy. So again, in WHO clinical stage three or four, yes, CD4, whether available or not, WHO clinical stage three or four, antiretroviral therapy is recommended. Now, in CD4 showing advanced disease, and severe HIV immunodeficiency, again, ART is recommended, if they're not in WHO clinical stage three or four. If none of these exist, regular follow up is simply recommended.

Importantly in this slide is recommendations in what to do in patients less than 18 months of age where a confirmed diagnosis of HIV infection is simply not there. Now, in a child less than 18 months of age where there is a positive HIV antibody test, recognizing that a positive antibody test at this age may be more consistent with maternal infection and not necessarily pediatric infections.

However, should this be present, and presumptive diagnosis of HIV infection be suspected, with the following things. Number one, a child with any of the following disorders: PCP, toxoplasmosis, cryptococcal meningitis, candida esophagitis, or persistent and unexplained malnutrition, treatment is recommended. Or, if the infant is symptomatic with at least two of the following conditions below: oral thrush, severe pneumonia, or severe sepsis, or there's been a recent HIV-related maternal death of advanced HIV disease in the mother, or a CD4 percent less than 20%. Again, these are criteria to start antiretroviral therapy. If these are not present, then antiretroviral therapy is not recommended

in those less than 18 months of age.

This is simply a summary of the WHO recommendations for antiretroviral therapy in infants and children, and simply again, reiterates the criteria that were listed in the prior slides. Again, noticing at the bottom for number two, virologic testing is non-available, if non-available, HIV antibody positive infants and children under the age of 18 should be considered for antiretroviral therapy. If they're clinically diagnosed, presume severe HIV disease.

I cannot highlight this point enough as these patients, again, are at higher risk for progression to HIV and AIDS, and again, death.

So, mechanisms of antiviral activity. Here's the HIV life cycle, essentially. To the left you see the HIV virions as they fuse with the human CD4 cell, the target for HIV infection, and highlighted in the yellow are the reverse transcriptase and the protease enzymes. And these are highlighted because these are the major enzymes to which the majority of our antiretrovirals work.

There are other potential mechanisms of blocking the HIV infection and blocking replication of the virus, but those are not necessarily available clinically in the US as of yet, and are definitely not available in resource limited settings. So, first looking down in this circle over here, non-nucleoside reverse transcriptase inhibitors simply work against the reverse transcriptase enzyme, as does nucleoside analogs, who also work there to block the transcription of RNA to DNA.

Protease inhibitors also work at this step where the protease is used to make new HIV from viral material in the nucleus, and protease inhibitors block this step as well.

Just talking more about reverse transcriptase inhibitors, again, they block reverse transcriptase, an enzyme that simply facilitates the conversion of HIV RNA to DNA following the virus fusion with the whole cell as shown in the prior slide. There are two classes of reverse transcriptase inhibitors. There are nucleoside analogs, NRTIs, and non-nucleoside reverse transcriptase inhibitors, NNRTIs. And these are simply based on their structure and how they inhibit reverse transcriptase.

The protease inhibitors block protease, the viral protein vital to the processing of other HIV proteins into their functional forms as they prepare to assemble to fully active virions. There is only one class of protease inhibitors, PIs.

Now this is a list of the potentially available ARVs in resource-limited settings. As you see on the left in the first column, NRTIs. Zidovudine, known by the three-letter words of AZT; lamivudine, 3TC; and emtricitabine, FTC; abacavir, ABC; and TDF, tenofovir. And a list of NNRTIs, the primary third drug used in resource-limited settings, and the PIs, which usually are not recommended as

first-line therapy as we discussed in the further slides. Notably, in the PIs, ritonavir, which is listed in this schematic, is only to be used in combination with another protease inhibitor to enhance activity; never used alone.

The dosing of ARVs and special considerations. In children, dosing by weight or by body surface area and/or Tanner staging in older children is critical. Adolescent patients are Tanner-1 and Tanner-2 criteria utilize pediatric dosing by weight. Later Tanner stages can be dosed by adults. Remember, they may be delayed pubertal maturity in perinatally infected children, and this needs to be taken into consideration as well in designing doses for pediatric patients.

Adolescents who acquire HIV through risk behaviors are usually older and dose according to adult treatment guidelines. Dosing of ARVs, another aspect of this include, due to the more rapid pharmacokinetic clearance in children of certain ARVs, for example abacavir, 3TC, and some of the PIs, the pediatric dosing may actually be higher than one would expect in an adult. Therefore, you must remember to recalculate those in regular intervals with height and weight gain to ensure accurate dosing.

There is a lack of dosing information for children for certain ARVs, and that should be noted by providers as they develop regimens for children. Efavirenz, in kids less than three years of age, there is no dosing information and therefore not recommended.

There are a lack of fixed-dose pediatric combinations, a multitude of them, and also the taste of liquid formulations may be unpleasant for children. Furthermore, cutting unscored tablets can lead to under and/or overdosing and this needs to be appreciated by providers. It is therefore not recommended to utilize doses that require less than half of a pill to be used as this could be unreliable. And definitely of note, there are immediate and long term toxicities of therapies which is another reason why dosing needs to be paid particularly attention to.

This slide is not meant to absorb, but simply to show that there are websites and resources available for providers which allow one to look at weight, and find from weight the specific doses that are recommended. This happens to be from the Columbia Manual of Pediatric HIV Infection. It's a valuable resource for providers providing therapy to children.

First line ARV regimens. So, this is a summary of the recommended and preferred ARV regimens for infants and children. Usually, as stated before, highly active antiretroviral therapy utilizes two drugs: NRTIs plus an NNRTI, so three drugs total. The regimens that are recommended for first-line therapy include a combination of AZT, zidovudine, plus 3TC, plus either nevirapine or efavirenz, again in those less than three years of age, nevirapine would be preferred as efavirenz, as there are no dosing recommendations for less than three years of age or less than ten kilos.

Another regimen, d4T or stavudine, plus 3TC, plus again nevirapine or efavirenz. And the third abacavir plus 3TC plus any of the other NNRTIs listed, nevirapine or efavirenz.

There are notable points about the first line regimen that I felt was important to communicate. One, nevirapine requires an induction period of fourteen days at four mgs per kilo per day and if there is no development of rash, the dose is then increased to either seven mgs per kg, BID, for children less than eight years of age or four milligrams per kilogram BID, or twice daily, for children greater than eight years of age. Nevirapine use exceeding caution in females with CD4 counts greater than 250 cells per millimeter cubed.

Thirdly, efavirenz is again, not approved for children less than three years of age and there is no dosing recommendations for those less than ten kilos. So therefore usually efavirenz is avoided for children who are initiating at that age range or that weight. Efavirenz use should be avoided in first trimester pregnancy or in sexually active adolescent females not on reliable birth control as there is significant teratogenicity associated with efavirenz use in those groups. And FTC, or emtricitabine, can be substituted for 3TC, lamivudine, in children greater than three months of age.

Some advantages and disadvantages of NNRTI-based highly active antiretroviral therapy. Advantages: there is no cold chain required, and these regimens can be stable at room temperature after mixing. They are relatively inexpensive. They are exceedingly efficacious, they are available in generic formulations, and there are some available fixed dose formulations for children and adults.

Disadvantages: they have variable half-lives, and this is critically important to resistance, which will be discussed in a later lecture. There are limitations on efavirenz dosing, as described earlier, and there's a low barrier to development of resistance in NNRTIs, and particularly in 3TC and FTC which can potentially compromise therapy later on.

These are the current WHO recommendations for infants and children with mother-to-child transmission exposure. Now, currently infants who are exposed to antiretroviral therapies for prevention of mother-to-child transmission when nevirapine was used as part of the maternal or the infant component, or for breast feeding infants who are exposed to antiretroviral drugs with the mother taking those drugs, they are still recommended at this point to NRTIs and one NNRTI. This should be cautioned as there is at least one recent trial showing significant virologic failure in infants who received MTCT with NNRTIs and were subsequently treated with an NNRTI-based HAART, and it is possible that in further studies these recommendations may change, however at this time the WHO still recommends this regimen, so stay tuned for changes in that.

These are the recommendations for alternative ARV regimens for infants and children to simplify the management of toxicity, co morbidity, and drug-drug interactions. What's recommended is instead of AZT or d4T plus 3TC, instead of

using an NNRTI, abacavir can be substituted. And this can be a regimen of triple NRTIs.

Now, there are a few situations when alternative ARV regimens may be considered. One, drug intolerability. Patients cannot simply tolerate the NNRTIs. Two, drug interactions. For example, patients on erythromycins for anti-TB therapy where there are significant interactions with the NNRTIs. And three, in adolescent females with CD4 counts greater than 250, and significant concern for initiation of nevirapine due to the potential hepatotoxicity that can be seen.

This slide is exceedingly important as it summarizes the NRTI drug combinations that should not be used, in fact, should be frankly avoided. D4T plus AZT should be avoided. Both drugs work through a common metabolic pathway and are antagonistic. Two, d4T and ddI, as these drugs have overlapping toxicities and can have magnified toxicities in patients, and the following combinations: tenofovir plus 3TC plus abacavir. Tenofovir, 3TC, plus ddI, and tenofovir, ddI, plus an NNRTI. These regimens actually have been associated with a high incidence of early virologic failure and are therefore not recommended.

There are some other antiretroviral mistakes that should be avoided. One is monotherapy, as rapid development of resistance can occur, compromising therapy later on. Two, dual therapy with two NRTIs alone; not recommended. And three, 3TC plus FTC as NRTI backbone, as these drugs have the same mechanism and same pathway and don't necessarily have added benefit to each other.

In terms of expected response to ARVs, rapid virologic decline of 1.5 to two log decline can happen in the first two to four weeks, and after that there is a slower decline. Now 50% of patients in one study reached a viral load of less than 400 at four weeks, and approximately 75% reached a viral load of less than 400 at twenty weeks. By 24 weeks, virologic suppression should occur, and if it has not occurred there should be some concern for adherence, absorption, or some factor interfering with the ability to respond.

In terms of CD4 response, they may be more variable. There is an immediate increase of approximately 9% in CD4 percent in six months of therapy in one study.

In terms of monitoring therapy, ideally the CD4 count should be repeated approximately every two to four months in patients on stable antiretroviral therapy. The viral load should be assessed every three to four months if available. Closer monitoring intervals are always recommended if new therapy or a change in therapy, even for toxicity reasons. Two, there's a significant change in the viral load in the CD4 count or a decline in clinical status it should make providers suspicious of a lack of adherence or a problem with therapy.

So, in conclusion, the initiation of therapy requires the assessment of multiple factors, including immunologic and clinical status, drug availability, palatability, dosing, and adherence. And secondly, virologic failure is not uncommon and will be addressed in a future lecture. And here are a few references utilized in this talk.