

Clinical practice treatment of HIV infection in children

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Abstract Perinatal transmission remains the main cause of HIV infection in the pediatric population. Treatment of HIV-infected children has become less of a problem in resource-rich countries with a remarkable decrease of perinatal infections, resulting in an effective prevention of mother-to-child transmission and antiretroviral treatment of HIV infection in pediatrics because of differences in drug pharmacokinetics, the lack of available licensed drugs, the use of different immunologic markers and age-related adherence issues. This review, for the general pediatrician, summarizes the most recent pediatric data and guidelines for treatment of HIV. Recommendations for when to initiate therapy are more aggressive in children than in adults, particularly in infants because disease progression in children is more rapid. The indications to start therapy differ by age and are based on international immunologic and clinical classification system for HIV infection. At present, combination regimens of at least three drugs are recommended. Moreover, therapies must also consider the potential complications in these children currently treated for a long time.

Keywords Pediatric HIV infection · Antiretroviral therapy · Nucleotide and nucleoside reverse transcriptase inhibitor · Non-nucleoside reverse transcriptase inhibitor · Protease inhibitor · Perinatal HIV infection

Abbreviations

ART	antiretroviral therapy
NRTI	nucleotide and nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
CDC	Centers for Disease Control

Introduction

Perinatal transmission remains the main cause of HIV infection in the pediatric population. In our industrialized countries, prenatal HIV testing, use of antiretroviral regimen during pregnancy, elective cesarean delivery if maternal viral replication is yet detectable, use of antiretroviral prophylaxis to the newborn, and the avoidance of breastfeeding brought the rate of mother-to-child HIV infection to <2% [3, 5, 23].

Initial studies in the early 1990s of monotherapy for HIV infection and AIDS in children showed significant clinical and immunological benefits. Later results showed that combination therapy led to better outcome with a decrease in HIV mortality in children by 70% through reduction of opportunistic infections and other complications of HIV infection. At present, combination regimens of at least three drugs are recommended. Advances in clinical trials and in laboratory monitoring, including resistance testing, have allowed clinicians to better select effective initial treatment regimens. The development of new drugs and drug formulations with less dosing frequency and fewer toxicities is very important for children since the availability of pediatric formulations is still limited. These improvements

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will lead to an improved adherence and decreased resistance [29].

Different classes of drugs

A complete list of the medications and information on drug formulation with pediatric dosing and toxicity for individual drugs and drug interactions can be found on <http://AIDSinfo.nih.gov/> [28]. Over the last two decades, therapeutic strategies for the treatment of patients with HIV infection have expanded dramatically from treatment with single medication to combination therapy that may include in adults up to five different classes of agents. As of July 2008, a total of 25 drugs have been approved for the use in HIV-infected adults and adolescents; 16 have an approved pediatric indication (noted with * below). For a better understanding of the action of the different classes of drugs, the viral invasion mechanism of a T lymphocyte is illustrated (Fig. 1). Here, we describe the five drug classes of which the first three are commonly used in children [15].

Nucleotide and nucleoside reverse transcriptase inhibitors

The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drug available for the treatment of HIV infection. They act at the early stage of replication as potent inhibitors of the HIV reverse transcriptase enzyme responsible for the reverse transcription of viral RNA into DNA, prior to viral genome integration into the host genome. These agents are:

abacavir*, didanosine*, emtricitabine*, lamiduvine*, stavudine*, tenofovir, zalcitabine, and zidovudine*.

Non-nucleoside reverse transcriptase inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) also act at the early stage of replication prior to virus integration into the host genomic material by inhibition of HIV DNA polymerase activities. There are currently four approved NNRTIs: delavirdine, efavirenz*, etravirine, and nevirapine*.

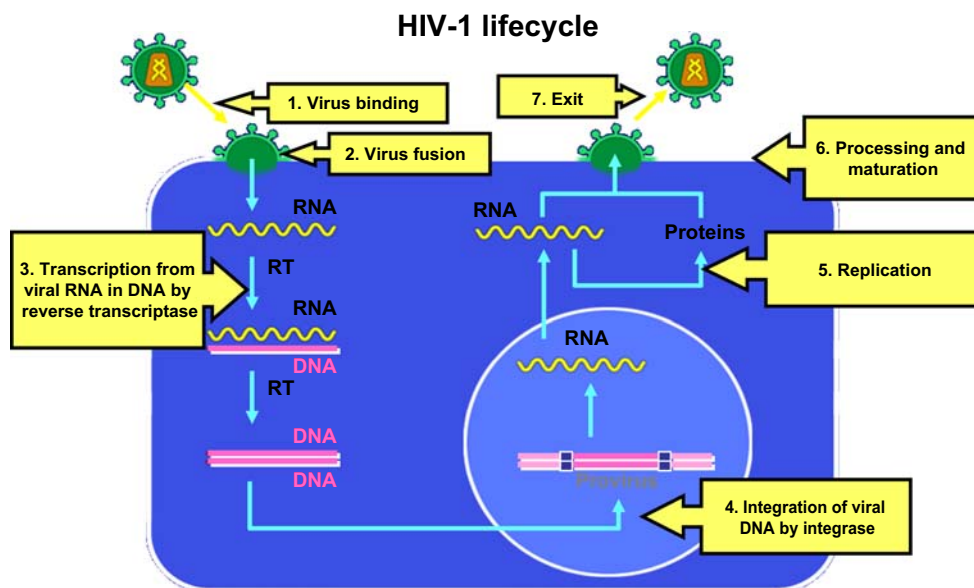
Protease inhibitors

Protease inhibitors (PIs) act at a post-integration step of the viral life cycle. They inhibit the HIV protease enzyme, required to cleave viral polyprotein precursors, and generate new functional viral proteins. They are: amprenavir, atazanavir*, darunavir, fosamprenavir*, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, saquinavir, tripanavir*. “Boosted” therapeutic regimens consisting of two PIs + one or two NRTIs are frequently used in adults with good results. However, with the exception of the coformulation PI lopinavir/ritonavir, there are limited data of combination PI regimens in children.

Entry and fusion inhibitors

Two drugs that interfere with sequential steps involved in the penetration of target cells by HIV are available as options for treatment in experienced patients. Enfuvirtide*

Fig. 1 Different steps of the viral invasion in a T lymphocyte



is the only entry inhibitor currently approved in adults and children, by blocking the fusion of the virus to the target cell. Its subcutaneous administration with frequent local-site reactions limits its use in experienced pediatric patients.

Maraviroc is an oral agent which alters the structure of CCR5 chemokine receptor preventing its use as coreceptor by HIV. This drug has been recently licensed for use in experienced HIV-infected adults.

Integrase inhibitors

These drugs block the viral integrase and the insertion of DNA copy of the viral genome into the host cell chromosome. Raltegravir has been approved for use in adults. There are no pediatric data up to now.

Treatment recommendations

General considerations

At present, combination regimens of at least three drugs are recommended [24]. Preferred first-line regimens in children include two NRTIs plus either an NNRTI or PI [19, 22]. Recommendations for when to initiate therapy are more aggressive in children than in adults, particularly in infants, because disease progression in children is more rapid [2, 16]. CD4+ count varies considerably by age in children and even in uninfected infants and children. Therefore, recommendations to start therapy differ by age [18]. Indications for antiretroviral therapy (ART) initiation in children based on the immunologic and clinical classification system for HIV infection edited for children by the Centers for Disease Control (CDC) and Prevention in 1994 and are summarized on Tables 1 and 2 [4]. In 2008, the NIH Working group released new recommendations based on three age groups (Table 3) [28].

Table 1 1994 revised HIV immunological classification based on age-CD4 cell count [4]

Immunologic categories	CD4 + lymphocyte count (cells per microliter) and CD4%		
	<12 months	1–5 years	6–12 years
1. No evidence of suppression	≥1,500 or ≥25%	≥1,000 or ≥25%	≥500 or ≥25%
2. Moderate suppression	750–1,499 or 15–24%	500–999 or 15–24%	200–499 or 15–24%
3. Severe suppression	<750 or <15%	<500 or <15%	<200 or <15%

Table 2 1994 revised HIV clinical classification system [4]

Category N: not symptomatic Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A
Category A: mildly symptomatic Children with two or more of the following conditions but none of the conditions listed in categories B and C Lymphadenopathy (>0.5 cm at more than two sites; bilateral = one site) Hepatomegaly Splenomegaly Dermatitis Parotitis Recurrent or persistent upper respiratory infection, sinusitis, or otitis media
Category B: moderately symptomatic Children who have symptomatic conditions attributed to HIV infection, other than those listed for category A or category C; examples of conditions in clinical category B include but are not limited to the following Anemia (<8 mg/dl), neutropenia (<1,000 cells per cubic millimeter), or thrombocytopenia (<100,000 cells per cubic millimeter) persisting ≥30 days Bacterial meningitis, pneumonia, or sepsis (single episode) Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children aged >6 months Cardiomyopathy Cytomegalovirus infection with onset before age 1 month Diarrhea, recurrent or chronic Hepatitis Herpes simplex virus stomatitis, recurrent (i.e., more than two episodes within 1 year) Herpes simplex virus bronchitis, pneumonitis esophagitis with onset before 1 month of age Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome Leiomyosarcoma Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex Nephropathy Nocardiosis Fever lasting >1 month Toxoplasmosis with onset before 1 month of age Varicella, disseminated (i.e., complicated chicken pox)
Category C: severely symptomatic Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of lymphoid interstitial pneumonia (which is a category B condition)

Children <12 months of age

A number of US and European cohort studies have reported better outcome in infants receiving early antiretroviral therapy [6, 14, 21, 26]. The recent Children with HIV Early Antiretroviral Therapy trial confirms that early HIV diagnosis

Table 3 Indications for initiation of antiretroviral therapy in children infected with HIV (from the NIH Working Group) [28]

Age	Criteria	Recommendation
<12 months	Regardless of clinical signs and symptoms, immune status, or viral load	Treat
1 to <5 years	AIDS or significant HIV-related signs and symptoms ^a	Treat
	CD4<25%, regardless of symptoms or HIV RNA level ^b	Treat
	Asymptomatic or mild symptoms ^c and CD4≥25% and HIV RNA≥100,000 copies per milliliter	Defer ^d
	Asymptomatic or mild symptoms ^c and CD4≥25% and HIV RNA<100,000 copies per milliliter	
≥5 years	AIDS or significant HIV-related signs and symptoms ^a	Treat
	CD4 < 350 cells per cubic millimeter ^c	Treat
	Asymptomatic or mild symptoms ^c and CD4≥350 cells per cubic millimeter and HIV RNA≥100,000 copies per milliliter	Consider
	Asymptomatic or mild symptoms and CD4≥350 cells per cubic millimeter and HIV RNA≥100,000 copies per milliliter	Defer ^d

Data from [28]

^a US CDC clinical category C and B (except for the following category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

^b The data supporting this recommendation are stronger for those with CD4 percentage <20% than for those with CD4 percentage between 20% and 24%

^c CDC clinical category A or N or the following category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

^d Clinical and laboratory data should be re-evaluated every 3–4 months

^e The data supporting this recommendation are stronger for those with CD4 count <200 than for those with CD4 counts between 200 and 350 cells per cubic millimeter

and antiretroviral therapy reduced infant mortality by 76% and HIV progression by 75% [27]. These data provide strong support for the initiation of treatment from an early age in all infants, regardless of the CD4+ count or percentage, viral load, or clinical parameters, given the high risk of rapid progression of the disease during the first year of life (Table 3).

Children ≥12 months of age

Owing to the lower risk of disease progression in children over 1 year, the option of deferring treatment must be considered. For children with HIV infection and significant signs and symptoms (CDC clinical category classes B/C), treatment is recommended. The prognostic significance of CD4+ count or percentage varies with age [6]. In young patients less than 5 years old, a CD4+ count or percentage of less than 25% warrants the initiation of treatment whereas, in children aged 5 years and older, current adult and adolescent guidelines are used to start therapy (Table 3).

Choice of initial antiretroviral therapy

Treating children is associated with many challenges: preserving effective regimens for the future and avoiding short- and long-term toxicities and drug resistance. The most appropriate regimen for a child depends on multiple factors: child's age, appropriate drug formulations, social

and familial supports, and availability to adhere to the regimen. Other additional factors must also be considered including comorbidities such as coinfections (tuberculosis, hepatitis) and chronic renal or liver disease.

Antiretroviral drug resistance testing

Resistance testing is recommended prior to the initiation of therapy in all newly diagnosed treatment-naïve children because of the risk of maternal transmission of a drug-resistant HIV strain. For antiretroviral drug resistance testing, several genotypic and phenotypic assays are available [20].

Preferred regimens for initiation

The choice of a specific combination is based on drug potency, toxicity, pediatric formulation, and potential drug interactions. A combination antiretroviral regimen in treatment-naïve children generally contains one NNRTI or one PI combined with a two-drug NRTI backbone (Table 4).

(a) NNRTI-based regimens

The preferred regimen for initial treatment in children consists of one NNRTI + NRTI backbone. Choices would include: efavirenz in combination with two NRTIs for children ≥3 years or nevirapine + two NRTIs for children <3 years of age or those who require liquid formulation [25].

Table 4 Recommended antiretroviral regimens for initial therapy for HIV infection in children

Non-nucleoside reverse transcriptase inhibitor-based regimens	
Preferred regimen	Children ≥ 3 years: two NRTIs plus efavirenz ^a
Alternative	Children < 3 years or who cannot swallow capsules: two NRTIs plus nevirapine ^a Two NRTIs plus nevirapine (children ≥ 3 years)
Potase inhibitor-based regimens	
Preferred regimen	Two NRTIs plus lopinavir/ritonavir
Alternative	Two NRTIs plus nelfinavir (children > 2 years)
Use in special circumstances	One or two NRTIs plus nelfinavir plus (efavirenz [children ≥ 3 years] or nevirapine) Zidovudine plus lamivudine plus abacavir Two NRTIs plus low-dose ritonavir plus (indinavir or fosamprenavir or saquinavir), only in adolescents who can receive adult doses
Two-drug NRTI backbone options (for use 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)
Use in special circumstance	Stavudine plus didanosine

Modified from [28]

^a Efavirenz is currently available only in capsule form; nevirapine would be the preferred NNRTI for children < 3 years of age or who require a liquid formulation. Amprenavir should not be administered to children < 4 years of age

(b) PI-based regimens

The preferred PI for treatment-naïve child is coformulated lopinavir/ritonavir based on virologic potency in both adults and children. Advantages of PI-based regimens include excellent virologic potency, high genetic barrier for development of resistance, and sparing NNRTI drug class. However, the PIs have potential multiple drug interactions and may be associated with metabolic complications.

(c) NRTIs in regimens

The preferred dual NRTI combination for initial therapy consists of abacavir, didanosine, or zidovudine combined with either lamivudine or emtricitabine. Due to the potential but rare life-threatening drug-associated hypersensitivity reaction to abacavir in patients with HLA B5701 genotype,

it is recommended to test all the patients genetically prior to start of abacavir [17]. A three-drug NTRI regimen, such as zidovudine, abacavir, and lamivudine, is only recommended in special circumstances when an NNTRI- or PI-based regimen cannot be used as first-line therapy.

Changing retroviral therapy

When treatment fails, children should have both genotype and phenotype resistance testing and should be referred in HIV specialists [10]. The use of both assays can provide information that could be useful in choosing a new drug, particularly in children who have complex antiretroviral histories. It is crucial to reinforce adherence prior to switch to a new regimen in order to improve the chance of success of the therapy.

Discussion

Many challenges faced in the management of pediatric HIV infection result from potential toxicities associated with long-term drug use and poor adherence which may be due to the lack of pediatric formulations and/or high pill burden [12].

Adherence is a critical key in the treatment of HIV patients because lack of adherence will lead to subtherapeutic levels of antiretroviral medications with both risk of development of drug resistance and virologic failure. Unfortunately, adherence is reported to be suboptimal among children and even worse among adolescents. Factors for poor adherence are: high pill burden with high frequency of medication, patients' lack of awareness of their diagnosis, and poor familial and/or social support systems [1].

The *future* is promising with emergence of new classes of medications including the integrase inhibitors, the CCR5 inhibitor, and new NNTRI [9]. None of these drugs have been yet approved in children for whom adequate formulation and pharmacokinetic studies are still needed.

Moreover, future therapies should also consider the *potential complications* in these children currently treated for a long time: metabolic alterations such as dyslipidemia, fat redistribution, insulin resistance or reduced mineral density, osteopenia, and osteoporosis [11, 13].

The work to fight against HIV is huge and varied. More awareness about the infection and sexual transmission prophylaxis are important. In children, it consists not only of treating HIV-infected patients with the most adequate ART but also preventing perinatal mother-to-child transmission to decrease the number of HIV-infected infants [8]. If this prevention has significantly reduced the number of children with HIV in our industrialized countries, we must

not forget that, in resource-limited areas, HIV remains a devastating health crisis with an important morbidity and mortality in the pediatric population [7, 23].

Conclusions

The management of HIV-infected patients evolves rapidly but increases in complexity. Management should include multidisciplinary assistance including HIV specialists, nurses, social workers, and psychologists.

Antiretroviral drug treatment must be initiated in all infants. Compliance is critical in the treatment of HIV infection in children. The development of new drugs and new pediatric formulations as well as more pharmacokinetic data are badly needed.

More energy should be spent to improve prophylaxis and to promote information about HIV infection and AIDS.

All children born from HIV-infected mother must be tested even if they seem healthy, even if they are over 10 years of age.

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References

- Belzer ME, Fuchs DN, Luftman GS, Tucker DJ (1999) Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health* 25:316–319
- Blanche S, Newell ML, Mayaux MJ et al (1997) Morbidity and mortality in European children vertically infected by HIV-1. The French Pediatric HIV Infection Study Group and European Collaborative Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 14:442–450
- Centers for Disease Control and Prevention (CDC) (2007) Revised recommendations for HIV testing of adults, adolescents and pregnant women in health-care settings. *MMWR Recomm Rep* 55:1–17
- Centers for Disease Control and Prevention (1994) 994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Recomm Rep* 43:1–10
- Centers for Disease Control and Prevention (2001) Revised recommendations for HIV screening of pregnant women. *MMWR Recomm Rep* 50:63–85
- Chakraborty R (2005) HIV-1 infection in children: a clinical and immunologic overview. *Curr HIV Res* 3:31–41
- Cross Continents Collaboration for Kids (3Cs4kids) Analysis and Writing Committee (2008) Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. *AIDS* 22:97–105
- Dao H, Mofenson LM, Ekpini R et al (2007) International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update. *Am J Obstet Gynecol* 197:S42–S55
- Day E, Buckberry K, Sharland MR, Chakraborty R (2008) Novel treatment options for pediatric HIV infection. *Curr Opin Investig Drugs* 9:170–175
- Durant J, Clevenbergh P, Halfon P et al (1999) Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet* 353:2195–2199
- Eley B (2008) Metabolic complications of antiretroviral therapy in HIV-infected children. *Expert Opin Drug Metab Toxicol* 4:37–49
- Eley B, Nuttall J (2007) Antiretroviral therapy for children: challenges and opportunities. *Ann Trop Paediatr* 27:1–10
- European Paediatric Lipodystrophy Group (2004) Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS* 18:1443–1451
- Goetghebuer T, Haelterman E, Le Chenadec J et al (2008) Early vs deferred highly active antiretroviral therapy in HIV infected infants: a European Collaborative Cohort Study. *Retrovirology* 5(suppl 1):O25
- Giaquinto C, Rampon O, Penazzato M et al (2007) Nucleoside and nucleotide reverse transcriptase inhibitors in children. *Clin Drug Investig* 27:509–531
- Gray L, Newell ML, Thorne C et al (2001) Fluctuations in symptoms in human immunodeficiency virus-infected children: the first 10 years of life. *Pediatrics* 108:116–122
- Green H, Gibb DM, Walker AS, Paediatric European Network for the Treatment of AIDS (PENTA) et al (2007) Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS* 21:947–955
- HIV Paediatric Prognostic Markers Collaborative Study (2005) Use of total lymphocyte count for informing when to start antiretroviral therapy in HIV-infected children: a meta-analysis of longitudinal data. *Lancet* 366:1868–1874
- Ikeda T, Ch'ng TW, Oleske JM (2007) Recommendations in pediatric antiretroviral therapy. *Expert Opin Pharmacother* 8:155–166
- Lujan-Zilbermann J, Rodriguez CA, Emmanuel PJ (2006) Pediatric HIV infection: diagnostic laboratory methods. *Fetal Pediatr Pathol* 25:249–260
- Luzuriaga K, McManus M, Mofenson L, PACTG 356 Investigators et al (2004) A trial of three antiretroviral regimens in HIV-1 infected children. *N Engl J Med* 350:2471–2480
- McKellar MS, Callens SF, Colebunders R (2008) Pediatric HIV infection: the state of antiretroviral therapy. *Expert Rev Anti Infect Ther* 6:167–180
- Prendergast A, Tudor-Williams G, Jeena P et al (2007) International perspectives, progress and future challenges of paediatric HIV infection. *Lancet* 370:68–80
- Resino S, Resino R, Micheloud D, Spanish Group of Paediatric HIV infection et al (2006) Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. *Clin Infect Dis* 42:862–869
- Starr SE, Fletcher CV, Spector SA, PACTG 382 Study Team. Pediatric AIDS Clinical Trials Group et al (2002) Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 21:659–663
- Van der Linden D, Hainaut M, Goetghebuer T et al (2007) Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J* 26:359–361
- Violari A, Cotton MF, Gibb DM et al (2008) Early antiretroviral therapy and mortality among HIV-infected infants. The CHER Study Team *N Engl J Med* 359:2233–2244
- Working Group on Antiretroviral Therapy and Medical Management of HIV-infected children (2008) Guidelines for the use of antiretroviral agents in pediatric HIV infection and pediatric antiretroviral drug information. <http://AIDSinfo.nih.gov>
- WHO (2008) Paediatric HIV and treatment of children living with HIV. www.who.int/hiv/paediatric/en/index.html