

# Adherence to High Activity Antiretroviral Therapy (HAART) in Pediatric Patients infected with HIV : Issues and Interventions

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## ABSTRACT

It has been proven that HAART is effective in suppressing human immunodeficiency virus (HIV) replication, decreasing morbidity and mortality associated with HIV and improving quality of life in adults as well as children infected with HIV. However, drugs don't work in patients who don't take them and in the management of HIV infection it is now well established that optimum adherence to HAART is critical to successful outcome of patients receiving therapy. At least 95% adherence to HAART is optimum and studies have shown that < 95 % adherence is associated with virologic failure rate of > 50 %. Important factors that influence adherence to HAART such as regimen related complexities, patient/family related issues and factors related to healthcare delivery system makes adherence to HAART challenging. Although numerous interventions to improve adherence have been investigated in developed as well as developing countries, majority of work in this area is focused on adherence in adults and data in children is limited. Therefore, in order to facilitate adherence and improve outcome of HAART in pediatric population, it is necessary to have a deep understanding of the factors influencing adherence and interventions that can improve adherence in children. [Indian J Pediatr 2007; 74 (1) : 55-60] E-mail : [chiirag@gmail.com](mailto:chiirag@gmail.com)

**Key words** : HIV; HAART; Children; Adherence

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Acquired immuno deficiency syndrome (AIDS), one of the most destructive epidemics the world has ever witnessed, claimed 3.1 million [2.8–3.6 million] lives in 2005 of which more than half a million (570 000) were children. Presently an estimated 40.3 million [36.7–45.3 million] people are living with HIV world-wide, of which 2.3 million (2.1–2.8 million) are children under 15 years.<sup>1</sup>

HIV management has drastically changed in the current era of effective, potent antiretroviral therapy (ART). Therapeutic strategies have expanded greatly from historical treatments with a single anti-retroviral drug to combination therapy that includes at least three different drugs from up to three different classes, HAART. When compared to monotherapy, combination therapy has shown to delay progression to AIDS, improve survival, result in a greater and more sustained virologic and immunologic response and delay development of virus mutations that confer resistance to the drugs being used. For these reasons HAART is recommended for all infants, children, adolescents and adults infected with HIV.<sup>2,3</sup> Widespread acceptability and use of HAART has thus

turned HIV infection into a chronic manageable disease.<sup>4</sup>

However, many factors can affect the ability of HAART to suppress viral replication, including low potency of one of the drugs in the combination, viral resistance, inadequate drug exposure and inadequate adherence to therapy. The major factor determining the success of HAART is sustained and optimum adherence to therapy<sup>5</sup> as poor adherence increases the risk of virologic failure and viral resistance.<sup>6</sup>

Sustaining adherence represents a significant challenge for children getting the treatment, their caregivers as well as healthcare providers. In order to facilitate adherence to HAART and to improve outcome of HAART in HIV-infected children it becomes necessary to know possible and relevant issues in pediatric patients that influence adherence and to determine the possible interventions to improve adherence in children. This article focuses on these points.

### Definition of Adherence

Adherence to medication, also known as compliance with medication, is the extent to which patient follows medical instructions.<sup>7</sup> This however does not mean that patient is only a passive receiver of medical advice and not an active contributor in the treatment process. In the treatment of patients with HIV infection it is essential to

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achieve more than 95 percent adherence to HAART in order to suppress viral replication and avoid the emergence of resistance.<sup>8</sup> Achieving such high rates of adherence is often very challenging in such patients, because their regimens include multiple, often expensive medicines that may have complex dosing schedules and may cause food interactions and adverse effects resulting in poor tolerability. In addition, lifestyle factors and issues in the patient-provider relationship may make adherence difficult.<sup>8</sup> Considering these issues, a practical definition of adherence in the context of HAART can be stated as the extent to which a person's behavior in taking medication, following dietary specifications and/or executing lifestyle changes corresponds to the agreed recommendations from a healthcare provider. In case of pediatric patients this can be related both to the caregiver's and the child's behavior and agreement on treatment recommendations is required from both the child and caregiver.

### Factors Influencing Adherence

The factors influencing adherence can be divided into three main groups:<sup>9</sup>

1. Patient and family/caregiver related factors
2. Medication related factors
3. Healthcare delivery system related factors

All these factors may influence adherence positively or negatively and both quantitatively and qualitatively. They may also have varying importance depending upon the specific characteristics of patients, cohorts, drugs and healthcare systems. Knowing and understanding these factors is helpful in identifying where and how to improve adherence to ART in children.

#### 1. Patient and Family/Caregiver Related Factors

Family plays a crucial role in any kind of treatment in children. For example younger children are often given medications by their parent or other family member.<sup>10</sup> Major issues related to family or caregiver that influence adherence include: presence of anxiety, depression, active substance abuse, the presence of HIV infection in another family member, fear of disclosure of HIV-positivity of the family, family disruptions, and belonging to racial minorities or other vulnerable groups of the population. If the caregiver himself/herself is infected then he/she is struggling with his/her own illness, psychosocial factors, medication regimens and most often financial burden due to expenses incurred on his/her own therapy, child's therapy and associated cost of medical treatment.<sup>3, 11, 12</sup> These factors along with his/her own knowledge about ART, belief in ART and personal experience on ART, can interfere with caregiver's ability to provide proper care to the child, thereby affecting the necessary adherence to HAART over time.<sup>9, 13-19</sup>

Age (especially infancy and adolescence), refusal of treatment, knowledge of HIV status, clinical stage, and changes in health status (improvement as well as

deterioration) have also been identified as relevant issues in relation to adherence to HAART in pediatric patients.<sup>3, 9, 12, 14, 15, 17, 18, 20-28</sup> For example improvement in health status can be a powerful motivating factor for achieving optimal adherence, while deterioration or lack of improvement can be demotivating. Denial and fear of HIV status, misinformation about HIV, low availability, accessibility and acceptance of therapy are some of the issues in HIV infected adolescents. Also administration of complex regimens at a time when adolescents do not want to be different from their peers can all act as significant barriers for adherence in this age group.

#### 2. Medication Related Factors

Characteristics of the commercially available formulations, such as taste, palatability, size of pills, availability of liquid formulations, storage requirements (e.g. refrigeration for liquid formulations), adverse effects (e.g. metabolic complications, lipodystrophy) can significantly affect adherence. Further, pharmacokinetic and or pharmacodynamic properties of the drugs such as need for daily administration, dietary restriction, drug interactions, frequency of dosing, dosage and therefore pill burden or amount of liquid, also influence child's adherence to therapy.<sup>3, 9, 14-16, 18, 20, 21, 24, 26, 27, 29-33.</sup>

As small numbers of antiretrovirals (ARVs) are approved worldwide for pediatric use (Table 1) and as fewer formulations exist exclusively for this age group compared to adults, above mentioned medication related factors become crucial in determining child's adherence to HAART.

#### 3. Healthcare Delivery System Related Factors

Factors not directly related to patient or drugs can also influence adherence. For example limited availability and accessibility of ARVs and healthcare facilities for diagnosis and treatment of HIV especially in developing countries, high cost of ART and other health services, presence of healthcare providers experienced in pediatric HIV, patient-provider relationship, availability of counseling services and social, economic or psychologic support for people living in both developing as well as developed countries can influence adherence positively or negatively.<sup>3, 14, 21, 23, 34, 35</sup>

#### Interventions to Improve Adherence in Children

Little systematic work has been done to identify ways that can improve adherence in children. However, many authors who have identified key factors related to adherence in pediatric patients have also proposed possible strategies and interventions. These strategies can be divided into three main groups

- A. Interventions to improve patient and family/caregiver related factors
- B. Interventions to improve medication related factors

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C. Interventions to improve healthcare delivery system related factors

### A. Interventions to Improve Patient and Family/caregiver Related Factors

Following are some of the strategies at patient and family/caregiver level that are easy to implement and helpful in improving adherence:

Intensive education of patients and or caregivers/parents about the therapy before starting it,<sup>3, 15, 17, 18, 23, 26, 36-39</sup> setting up an adherence program,<sup>3, 14, 18, 21</sup> use of teaching tools<sup>21</sup> to explain about HIV and medications and viral resistance to children, use of reminders (such as timers, diaries, pill sorters, beepers *etc*),<sup>3, 9, 14, 26</sup> sharing responsibility for remembering medication within household,<sup>13, 14</sup> disclosing HIV infection (to the patient,<sup>17, 21, 40</sup> inside the household,<sup>14</sup> outside the household<sup>13, 14</sup> *e.g.* school), including adolescents and older children in the decision making process about therapy modification,<sup>21, 26, 36</sup> hospital admission when starting new regimen,<sup>40, 42</sup> keeping a treatment diary by the patients,<sup>21</sup> using directly observed therapy or watching children taking therapy,<sup>3, 9, 26, 43, 44</sup> specific counseling on adherence to treatment,<sup>14, 26, 39, 45</sup> tailoring of treatment for each patient,<sup>9, 26, 33, 45, 46</sup> regular assessment of adherence,<sup>28, 36, 45, 47, 48</sup> regular assessment of caregivers attitude towards treatment, warning of the

preparation and adverse effects,<sup>3, 36</sup> involvement of social/community workers,<sup>2</sup> are some of the strategies, if implemented can result in improved adherence to HAART.

### B. Interventions to Improve Medication Related Factors

Clinical trials of ARV agents in HIV-infected children and the development of drug formulations appropriate for administration to children have often been delayed until after the development of adult formulations have been completed and/or the drug has been approved for use among infected adults. Although the treatment regimen for pediatric patients infected with HIV should mirror

TABLE 2. List of Pediatric ARV Formulations and FDCs Available in India

Liquid formulations
Stavudine
Lamivudine
Nevirapine
Efavirenz
Zidovudine
FDCs in the form of liquid
Lamivudine + Stavudine + Nevirapine
Lamivudine + Stavudine
FDCs in the form dispersible tablets
Lamivudine + Stavudine + Nevirapine
Lamivudine + Stavudine

TABLE 1. List of ARVs Approved for Treatment of HIV

Drug class	Approved for pediatric use	Type of formulation				
		Capsule	Tablet	Liquid	Powder	IV <sup>†</sup>
<b>Nucleoside reverse transcriptase inhibitors (NRTIs)</b>						
Abacavir	Yes		√	√*		
Lamivudine	Yes		√	√		
Zidovudine	Yes	√	√	√		√*
Didanosine	Yes	√	√		√*	
Stavudine	Yes		√	√		
Emtricitabine	Yes	√		√		
Zalcitabine*	No		√			
Tenofovir DF	No		√			
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>						
Delaviridine*	No	√				
Efavirenz	Yes	√	√	√		
Nevirapine	Yes		√	√		
<b>Protease inhibitors (PIs)</b>						
Amprenavir*	Yes	√		√		
Lopinavir/ritonavir	Yes	√	√	√*		
Nelfinavir	Yes		√			
Ritonavir	Yes	√		√*		
Saquinavir	No	√	√			
Fosamprenavir*	No		√			
Atazanavir	No	√				
Indinavir	No	√				
Tipranavir*	No	√				
<b>Fusion Inhibitors</b>						
Enfuvirtide (T-20)*	Yes				√‡	

\*Not available in India

†Intravenous administration

‡Mix with water and give as a subcutaneous injection

those of adults at all levels of care, this is currently difficult because of less number of drugs approved for pediatric use along with limited availability of ARVs (Table 1) that is further complicated by lack of appropriate pediatric ARV formulations (Table 1, Table 2). According to Department of Health and Human Services (DHHS), in order to improve adherence, to the extent possible regimens should be simplified with respect to the number of pills or volume of liquid prescribed and frequency of therapy. If a regimen is overly complex, it may be simplified.<sup>2,3</sup> For example adherence is often enhanced by changing from a thrice daily dosing schedule to twice daily dosing. When the burden of pills is too great for a child, provide regimen containing fewer pills. As recommended by World Health Organization (WHO), ARVs in fixed-dose combinations (FDCs) have potential advantages over conventional drug regimens: they are helpful tools for simplifying treatment and promote adherence.<sup>49</sup> Findings of several other studies suggest to improve availability of palatable liquid formulations,<sup>13, 14, 18, 26, 27</sup> preferably not requiring refrigeration,<sup>13</sup> or use of tablets/capsules of smaller size, preferably with less pill burden<sup>13, 14, 16, 18, 23, 27, 30, 31, 37, 47</sup> or those which can be crushed,<sup>47</sup> to improve adherence in children. Further, formulations having less dietary restrictions and less drug-drug interactions<sup>2, 3</sup> and regimens that match child's or family's lifestyle<sup>18, 26, 27, 33</sup> and daily schedule will be helpful in improving adherence.

### C. Interventions to improve healthcare delivery system related factors

All components of healthcare delivery system play an important role in determining adherence. The establishment of long-term relationship between children, families and clinic staff<sup>3, 21, 37, 45</sup> is a key intervention. This increases trust in providers, facilitates communication and makes any kind of counseling easier, hence improving adherence. Wherever possible the healthcare institutions/clinics should be as family and patient-friendly as possible.<sup>21</sup> They should offer experienced staff in managing pediatric HIV, pediatric ARV formulations, counseling and adherence strategy/program.<sup>3, 9, 14, 15, 18, 21, 37, 45, 50</sup> Adherence strategy/program preferably including strategies to enhance and facilitate communication between the family and care providers which also aims to overcome language and cultural barriers<sup>13, 37</sup> should be offered to patients. Countries where ARVs are distributed free through government programs should consider use of exclusive pediatric formulations wherever available instead of adult formulations to improve adherence. Pharmaceutical industry should collaborate more with healthcare providers to find out innovative strategies that can make ARV formulations more child-friendly. Countries where awareness of HIV/AIDS is poor and where cultural differences, taboos and stigma further

reduce acceptance of HIV patients in the community, interventions to increase disease awareness should be determined and interventions implemented. This can be done in a variety of ways. For example, awareness can be increased by conducting campaigns by means of mass communication activities, multilingual posters, HIV/AIDS patient education books, patient counseling/help-lines, online information resource etc. Increased awareness is expected to increase social acceptance of this disease and its therapy. This will go a long way in improving adherence to HAART. Training of healthcare providers is of utmost importance in all aspects of HIV and its management including counseling. Finally, improving availability, accessibility and affordability of pediatric ARV agents and other healthcare services is needed to prevent lack of adherence due to financial constraints of the families especially in developing countries.

### CONCLUSION

Improving adherence in pediatric patients infected with HIV is extremely important for successful outcome of HAART. This calls for greater interventions at the level of patient/family, at the level of drug/medications and at the level of healthcare delivery system. It should also be remembered that adherence is a complex behavior involving education, motivation, skills and reinforcement, therefore, more comprehensive and customized interventions are needed to maintain sustained and high levels of adherence. In addition to standard interventions to improve adherence, wherever possible, use of child-friendly HAART regimens that match daily activities of patient/family should be considered. A greater commitment should therefore be shown by pharmaceutical industry in developing child-friendly ARV formulations. Further, continued research is required to identify specific issues related to adherence in different settings, and to find and test possible interventions to overcome such issues. It should be remembered that, although adherence to HAART in pediatric patients is challenging; with the help of effective interventions, it is not an impossible goal to achieve.

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