



Published in final edited form as:

AIDS. 2013 November ; 27(0 2): S207–S213. doi:10.1097/QAD.0000000000000095.

## Linkage, initiation and retention of children in the antiretroviral therapy cascade: an overview

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### Abstract

In 2012, there were an estimated 2 million children in need of antiretroviral therapy (ART) in the world, but ART is still reaching fewer than 3 in 10 children in need of treatment. [1, 7] As more HIV-infected children are identified early and universal treatment is initiated in children under 5 regardless of CD4, the success of pediatric HIV programs will depend on our ability to link children into care and treatment programs, and retain them in those services over time. In this review, we summarize key individual, institutional, and systems barriers to diagnosing children with HIV, linking them to care and treatment, and reducing loss to follow-up (LTFU). We also explore how linkage and retention can be optimally measured so as to maximize the impact of available pediatric HIV care and treatment services.

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#### Conflicts of interest

There are no conflicts of interest.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the World Health Organization or the U.S. government including the U.S. Centers for Disease Control and Prevention and Agency for Toxic Substances Disease Registry and the United States Agency for International Development. The authors acknowledge the support of UNICEF and the Canadian International Development Agency (CIDA) whose financial assistance made this series possible and the U.S. President's Emergency Plan for AIDS Relief for support of contributing staff time.

## Keywords

antiretroviral therapy; barriers; diagnosis; linkage; loss to follow-up; monitoring; pediatric HIV; retention

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## Introduction

In 2012, there were an estimated 2 million children in need of antiretroviral therapy (ART) in the world [1], with 210 000 new pediatric infections reported from the 21 Global Plan priority countries where 90% of the HIV burden among women is found [2]. Efforts in recent years to expand early care and treatment for pediatric HIV have resulted in historic decreases in HIV-related child mortality [3,4]. The 2013 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection call for ART initiation for all HIV-infected children under the age of 5 years, a recommendation that will substantially reduce HIV morbidity and mortality [5,6]. However, in 2011, ART was still reaching fewer than 3 in 10 children in need of treatment. Despite progress made in early infant diagnosis and early pediatric ART initiation, adult treatment coverage is still twice that of children [7–8]. Whereas ART coverage in children increased by 11% between 2011 and 2012 (from 566 000 to 630 000), adult ART coverage grew by over 20% – the fastest rate ever – during the same period [1,9].

Significantly increasing ART coverage requires early identification of infants and children needing therapy, particularly those missed through traditional prevention of mother-to-child transmission (PMTCT) efforts (see Case Finding article in this series). But even if effective strategies are employed to find these children, linkage to services and retention in care and treatment are key programmatic priorities. With the new WHO treatment guidelines calling for universal treatment for HIV-infected children 5 years and younger [4], attention must be focused at every point that children are lost from care, with a particular emphasis on ensuring proper linkage and retention in care of children known to be HIV-infected. Below, we provide a summary of what is currently known about linking and retaining HIV-infected infants and children into HIV care and treatment. We also summarize the issues around defining retention and monitoring/evaluating retention programs, and provide possible solutions to existing barriers.

## Pre-antiretroviral therapy retention: diagnosing and linking children to care and treatment

‘Pre-ART retention’ has historically been defined as retention during the period between HIV testing and ART initiation. Prior to the release of the 2013 WHO consolidated guidelines, this encompassed a large proportion of adults and children newly diagnosed with HIV but with CD4<sup>+</sup> cell counts (in adults) and CD4<sup>+</sup> percentage (in children) high enough to exclude them from immediate initiation on ART. The goal of pre-ART was to keep individuals engaged in care while monitoring for immunosuppression and disease progression until they became eligible for ART. For children, this period between HIV diagnosis and initiation on ART is critical owing to more rapid disease progression in

children [8]. With the expansion of treatment to below five years of age the pre-ART period for qualifying infants and young children is essentially eliminated. Given that half of untreated, HIV-infected children suffer progressive, multisystem disease and early death before their second birthday, the elimination of the pre-ART period will have an enormous influence on mortality [10,11]. Still, diligent management of HIV-exposed infants throughout the breastfeeding period (including serial testing) remains a key component of pre-ART care, in case these infants become infected.

In adults, 'pre-ART' is still applicable, although attrition during this period is high, with estimates that only 60% of diagnosed HIV-infected adults receive a CD4<sup>+</sup> cell count, and only 70% of immunologically eligible adults initiate ART [12]. Although data are scarce, children also have high rates of lost to follow-up (LTFU) before treatment initiation [13,14]. One systematic review found only eight studies from Africa and two from Asia specifically addressing retention of children in care before ART initiation [15], with consistently low numbers of eligible children (as low as 40%) eventually initiated on treatment. Programs reporting better initiation rates are from internationally-funded, physician-driven programs such as the Baylor International Pediatrics AIDS Initiative [16], Elizabeth Glaser Pediatrics AIDS Foundation [17], and Médecins Sans Frontières [18], and are therefore not representative of the routine services received by the majority of HIV-infected children. Importantly, information on the outcomes of children who did not initially meet eligibility criteria for ART (and thus were started later) was not included in the review.

As more HIV-infected children are identified early and universal treatment initiated in children under 5 regardless of CD4<sup>+</sup> [6], the high-risk pre-ART period will be eliminated. In addition, some countries are proposing universal treatment for children up to 10 or 15 years of age [19]. As guidelines evolve, the bridge between diagnosis and initiation remains critical. As therapy for children becomes routine immediately after a positive test result in children, death and attrition in this age group should decline.

Linkage to care and treatment is a complex issue. Health-seeking behaviors among children, caregivers, and providers are mediated by a complex array of formal and informal relationships; ensuring that children are successfully ushered from diagnosis to treatment requires thought and planning [20]. Whereas losses occur throughout the treatment cascade, losses after diagnosis and prior to ART initiation are needless and costly given the high mortality rates among HIV-infected children (see Case Finding article in this series).

## **Retention of children on care and treatment**

Identifying eligible children, linking them to care and treatment, and initiating ART is just the beginning. Improving the fate of these children requires long-term retention in care, including age-appropriate support and dosage/drug modifications as the child grows. Strategies to optimize retention of children in HIV programs must address key barriers to retention, including: individual barriers, institutional barriers, and systems barriers.

## Individual barriers to retention

Interactions at the patient level – or, especially for a child, at the caregiver level – naturally impact linkage to and initiation of care as well as retention. Whereas several models exist for optimal management of HIV and other chronic diseases in adults, few have been adequately applied to children in resource-limited countries [21]. For the purpose of this discussion, we will focus on the characteristics of individual children, caregivers, and healthcare providers that influence retention in pediatric HIV care programs.

**Patient characteristics affecting retention and lost to follow-up**—In a large cohort of HIV-infected Kenyan children, LTFU was correlated only with severe immune suppression among HIV-infected children. Risk factors for LTFU among untreated, HIV-exposed children included low weight for height, being orphaned, and having clinically advanced disease. These data suggest higher risk of infection and death among HIV-exposed but undiagnosed children. Interestingly, retention was higher among HIV-exposed children who were tested and found positive. Older, exposed children were also more likely to be retained, as were children receiving food supplementation [13], an unsurprising finding but one that has not been carefully examined in other studies. A cohort of HIV-infected children awaiting ART in The Gambia had an approximately two-fold higher LTFU in children less than 2 years compared to those 5 years or older, and a similar increase in risk for children with WHO stage 3 or 4 versus WHO stage 1 or 2 [22].

These data suggest that retention is especially challenging for younger, sicker HIV-infected or exposed children [23]. This is not surprising given that immunosuppression is a major risk factor for mortality in children [13], and that infants and young children often present with advanced and rapidly progressing illness [24].

Delayed, individual disclosure status (to the child) is also a risk factor for LTFU, which ideally begins in mid or late childhood. Retention at 36 months after ART initiation is higher for older children aware of their infection compared to those unaware of it. Despite this, approximately two-thirds of the older children and adolescents in this cohort were unaware of their HIV status [25], and disclosure rates among school children were only 16% [26]. In addition to proactive disclosure, other types of treatment support are effective in school-aged children, including appointment reminders and treatment buddies for those aware of their status [27] (see also Adolescent article in this series).

**Caregiver and provider characteristics affecting retention**—Studies detailing caregiver characteristics influencing pediatric retention are few but consistent. Caregiver decisions regarding whether children receive treatment are influenced by many factors including transport costs, food availability, time constraints, perceptions that the child is healthy, perceived stigma, religious beliefs, and male partner support [28]. In one study, 30% of caregivers reported that children were LTFU because caregivers either had not disclosed their own HIV status or were afraid of family/community stigma related to their HIV status or that of the child [29]. Additionally, caregivers may be unaware that pediatric HIV treatment is available and thus perceive no benefit in seeking these services for children [30].

Healthcare providers also play a critical role in retention. Although patient or caregiver satisfaction with health workers and health facilities is rarely measured in resource-limited countries, it is a potent quality measure that helps to increase retention [31]. Undertrained, overworked providers are more likely to have poor relationships with patients [32]. Stigma, and unprofessional or insensitive attitudes from healthcare workers towards HIV-infected parents and children can be a major disincentive for mothers seeking care for their children [28,33,34]. When children or caregivers do seek clinic services, the child's HIV status is frequently not disclosed [35], perhaps related to caregivers' reluctance to reveal their own status to the provider or from fears of stigma [32]. Finally, children's retention in care and treatment is influenced by health workers' level of comfort with pediatric HIV management. Such discomfort can be due to high patient volumes and the perception that management of children is more time-intensive. Many providers simply receive inadequate training in pediatric HIV management, and do not recognize the importance of early treatment in children [33]. As a result, children frequently go without treatment or are provided services crudely adapted from the more familiar, adult service models.

### **Institutional barriers to retention**

In addition to individual factors, there are multiple site-level issues that influence retention of infected children in care and treatment programs. Long clinic wait times, understaffing, and inadequate clinical/laboratory services are among the most frequently cited barriers [36].

**Long clinic wait times**—Both public and private clinics have shortages of healthcare providers and lengthy wait times, limiting caregiver willingness to seek out services [37]. Convoluted registration processes and complex patient routing through health facilities worsen delays further [38]. Since patients and caregivers often travel long distances to access facilities providing pediatric care, clinic visits can take up an entire day of a child's and caregiver's time [36]. Having different appointment dates, times, or locations for a caregiver and her child can add to this time burden and increase the risk of resulting in LTFU [28].

**Understaffing**—Understaffed clinics naturally find it challenging, if not impossible, to actively track children who are LTFU [36]. Fortunately, a growing number of studies on facility staffing have shown that task-shifting or task-sharing to nurses and community health workers can be effective in alleviating physician workload while increasing retention of mothers and infants [39–41]. A recent Cochrane review found that home-based nursing, well received by patients and caregivers alike, was effective at improving retention by bringing care and treatment services closer to the client [42].

**Inadequate clinical/laboratory services**—Poor quality and reliability of laboratory testing affects retention. Approximately 70% of HIV-infected children give blood for PCR and CD4<sup>+</sup> tests and simply never receive results, or lab samples are simply never drawn [43]. Limited offerings for certain tests, prohibitive costs, and poor communication between laboratories and sites all diminish the quality of lab services, which renders appropriate

follow-up impossible [44]. Similar issues occur throughout the child's care (see also EID article in this series).

In sum, health facility quality and scope of clinical services are important considerations for increasing retention of children in HIV care and treatment. Like any other person living with HIV, infected children require comprehensive, pediatric-specific services, such as age-appropriate counseling and ancillary support services. The availability, efficiency, navigability, and level of coordination between staff and services offered all affect patient outcomes and retention [36].

### **Systems barriers related to linkage and health information**

Factors within the health system affecting delivery of pediatric HIV services and, in turn, retention of patients can be broken down into two categories: structural elements and information systems.

Challenges remain in integrating traditionally fragmented and vertical HIV service delivery into existing healthcare systems. Integration of these services into the existing sectors (e.g. maternal and child health) and ensuring that clinical services themselves are offered in tandem when possible (e.g. utilizing family-centered models) can facilitate better health service delivery and retain children in HIV programs [28].

Inadequate health information systems also interfere with retention. When children transition from one service to another, data needed to provide appropriate longitudinal care and treatment are often lost or of low quality [45]. Patient-level data, such as HIV-exposure status and HIV test results, may not be recorded on a child's health card because of providers' and caregivers' fears that documenting such information leads to discrimination [34]. Moreover, patients who switch clinics may mistakenly be considered LTFU even though they are simply accessing HIV services elsewhere, especially common in highly mobile urban areas [46]. In cases where patients are truly LTFU, the recording of basic patient information such as a phone number can facilitate re-engaging these individuals in HIV care and treatment, but is often not collected [47]. Finally, poor health information and related logistics systems can lead to disruptions in the supply chain of pediatric antiretrovirals and other commodities, which limit the effectiveness of services offered and erode retention [48].

### **Measuring retention and lost to follow-up**

It is essential to identify and characterize specific points where children living with HIV are engaged and lost along the continuum of pediatric care and treatment [49] (see Evidence from the Field: Missed Opportunities for Identifying HIV Infected Children for Early Initiation of ART and Case Finding articles in this supplement). Retention and LTFU are defined and measured differently from country to country, making aggregation and comparison difficult across programs. Consistent and harmonized definitions of pediatric retention and LTFU facilitate measurement, reporting, and monitoring over time at the country level and facilitate communication across countries and globally [50].

## Defining pediatric retention and lost to follow-up

Standardized guidelines on retention and LTFU provide a shortlist of key indicators, a proposed methodology to calculate retention rates, a time frame for calculation, and routine data collection tools.

The HIV-infected child retention continuum is divided into four stages: time of HIV test to enrolment; enrolment to ARTeligibility; ARTeligibility to ART initiation; and initiation to lifelong care and treatment [51]. In pediatric cohorts, the ‘recognition of exposure’ is commonly considered the first step in a pediatric continuum. Historically, the term ‘retention in care’ covers the period from enrollment in clinical services after HIV diagnosis to ART initiation, whereas ‘retention in treatment’ starts with the initiation of ART and continues until a defined end point (e.g. 12 months) as a proxy for long-term care and treatment. As discussed above, ‘pre-ART’ period should, with rare exception, be very brief, with an emphasis on immediate initiation of ART. In other words, the first and the last stages should follow one another in quick succession for all children aged 5 years and under. After a child is initiated on treatment and retained on treatment through adolescence, the transition from pediatric to adult care and treatment services represents the culmination of the pediatric treatment continuum.

Lost to follow-up refers to patients who are not retained in care and treatment with unknown outcomes, rather than those who are lost due to known end points (e.g. death, transfer to another facility, disengagement from care) [51]. A recent WHO working group defined LTFU period as not having accessed the healthcare system for 90 days after the last scheduled appointment [51]. Applying this (or any related) definition of LTFU can be challenging, though, as standard appointment schedule, time frames vary from site to site, even within the same country [50].

## National-level consideration for the measurement of pediatric retention

National HIV programs should provide a common vision on how retention will be measured. Countries should consider standardized tracking metrics to gauge progress on retention in pediatric HIV programs at all levels of the healthcare system. Due to the lack of pediatric patient cohort data disaggregated by age groups in most countries, periodic site(s) assessments can provide a more comprehensive evaluation of retention performance and barriers.

## Facility-level considerations for the measurement of pediatric retention

If national standard strategies to improve measurement of pediatric retention within HIV programs do not exist, the following key components can improve retention measurements at the facility level: effective patient tracking systems tools (paper-based or electronic); use of captured data to minimize patient loss misclassification; and mechanisms for locating and recovering lost patients. The following indicators can be collected routinely and aggregated at pediatric care sites. As feasible, the aggregated data should then be sent to the next higher level in the national M&E system.



### Indicators to monitor retention and lost to follow-up

The following indicators on pediatric retention and LTFU rates can be used until standardized metrics are developed. These indicators are examples that can provide reliable estimates of retention and its trends over time:

1. Age of first HIV test and first positive HIV test; age of first encounter at HIV care clinic and age at initiation of ART
2. Percentage of HIV-exposed, uninfected infants remaining in care until the assessment of the final HIV status at the end of HIV-exposure period
3. Percentage of children alive and on ART at 3, 6, 12, 24, and 36 months after ART initiation, age disaggregated to allow evaluation of interventions that target specific age groups
4. Percentage of children enrolled in HIV care and not initiated on ART but continue to visit health facilities for various services at 3, 6, and 12 months of follow-up, age disaggregated

### Retention rate periodicity and factors affecting accuracy of retention data

The rate of retention in care and treatment should be calculated in accordance with national guidelines (e.g. every 6 months). Retention in ART should be calculated at 3, 6, and 12 months following treatment initiation for children under 5 and then once a year thereafter. LTFU among HIV-infected children on ART should be calculated as the proportion of patients not retained 90 days after their last clinic visit, through following cohorts, standardized record reviews that document appointments kept or other means [51]. LTFU among HIV-infected children who have not yet initiated ART is calculated as the proportion of children initiating clinical care but who have not visited the health facilities for at least 6 months after their last clinic visit or 6 months after birth for an HIV-exposed infant.

Factors affecting the validity and accuracy of retention data include: lack of linked data across HIV points of service; poor patient tracking systems within sites (including the inability to differentiate between deceased, transferred, lost, and disengaged) and across sites; lack and inconsistency, or either of them, of appointment scheduling systems; and limited human resources to identify and follow-up on missed appointments.

Strategies to increase the impact of pediatric HIV care and treatment services must include careful attention to linking and retaining children in those services. Attrition from pediatric care and treatment programs has severe consequences on morbidity and mortality, and 'getting it right' is complex. The best strategies for promoting retention are still inadequately understood and data systems are still inadequate to effectively track simple proxies of retention. However, if we pay attention to and build upon what we know about retaining children on life-saving HIV treatment, we can protect an extremely vulnerable population from death, and usher them safely to adulthood.

### Acknowledgments

The authors thank Ms Victoria Riechers for her assistance revising this manuscript.



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