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Pediatric HIV Continuum of Care: A Concise Review of Evidence-based Practice

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SYNOPSIS

Children and adolescents living with HIV represent a distinct population that requires a unique approach to HIV care. Prevention, testing, initiation of antiretroviral therapy (ART), and retention and engagement in care are all critical steps in the care of these youth. Each step requires providers to address age-specific barriers, so that successful and prolonged viral suppression can occur. Adherence to ART, disclosure of HIV-positive status, and stigma are all examples of struggles faced by youth, their families, and health care providers. A multifaceted approach and thoughtful transitions of care are needed, but with sustained ART, youth living with HIV can survive and thrive with the expectation of a normal lifespan.

Keywords

HIV; AIDS; children; adolescents; prevention; adherence

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Introduction

Since the discovery of HIV in 1983, momentous advances in the recognition, treatment and prevention of HIV infection has averted an estimated 9 million deaths so far in the new millennium.¹ However, HIV/AIDS remains one of the largest international public health crises. Children and adolescents are especially vulnerable populations, and the identification and care of youth living with HIV presents unique challenges.

There are two distinct populations of youth living with HIV. There are those who acquired HIV through perinatal transmission and require HIV care from the time of their birth, and those who acquired HIV through risk behaviors in adolescence such as unprotected sexual encounters or injection drug use. Both populations of HIV-seropositive youth require tailored approaches in order for their care to be successful. The cascade of care for individuals living with HIV begins with diagnosis, counseling, linkage to care, and initiation of antiretroviral therapy (ART), at which point the work of patients and providers has only just begun. Strict adherence to ART, persistence in ART, and retention in care is necessary for viral suppression and requires collaboration of patients, health care staff, social workers and physicians.⁵

As of 2016, 1.8 million children under the age of 15 are living with HIV and 87 percent of these children live in sub-Saharan Africa.⁶ At the end of 2013, 1,999 children under the age of 13 lived with HIV in the United States, and 73 percent of these children acquired the infection through perinatal transmission.² Approximately three quarters of adolescents living with HIV worldwide represent those that were infected at birth, which is evidence of the positive impact of ART on life expectancy of perinatally-infected children.⁷ The rates of perinatal HIV infection in the United States are very low and the majority of adolescents living with HIV in this country acquired the virus through risk behaviors. Of the approximately 2 million adolescents living with HIV across the world, only 1 percent is from the United States.⁸ This adolescent one percent account for 22 percent of all new HIV infections nationally.² Young male, transgender African American adolescents are the highest risk group.⁹ Globally, however, girls and young women are at highest risk due to culture specific gender norms, sexual abuse,¹⁰ intergenerational sexual relationships,⁹ and enhanced biologic susceptibility.¹¹

Refugees and immigrants represent another special population as up to 14 percent are leaving countries of high HIV prevalence.¹² High rates of pregnancy were noted in one cohort of HIV-infected refugees in Rhode Island, highlighting the need for preventative HIV perinatal care.¹³ Among roughly seven thousand children adopted internationally over a 15 year period (1990–2005), twelve children were found to be infected with HIV.¹⁴

In 2016, only 50 percent of perinatally-exposed children globally were tested within the recommended two months.¹ Of the children who tested positive for HIV only 50 percent are receiving treatment,¹ though this varies by country and region. Compared to Europe and Central Asia where over 95 percent of children younger than 15 years old are receiving ART, sub-Saharan Africa has 1.83 million or 73 percent of their children living with HIV that are untreated.⁶ In the rest of Africa and the Middle East 86 percent of children living with HIV

are untreated. For infants born with HIV, treatment is crucial to prevent rapid progression to AIDS in the early years of life. Without ART, half of these children will die by the age of two years old.⁹

Statistics are similarly bleak for youth who acquire HIV later in life. In the United States 44 percent of young people living with HIV are unaware of their diagnosis.² Adolescents in sub-Saharan Africa are even less informed of their HIV infection status with only 13 percent of adolescent girls and 9 percent of adolescent boys receiving testing in the most recent 12 months.¹ HIV is the number two cause of death of adolescents globally, and it is the number one cause of death of adolescents in Africa.¹ Disturbingly, since the year 2000 deaths have tripled among adolescents with AIDS, which is in stark contrast to other affected groups that have seen improved mortality rates.⁸ Disparities in resources, healthcare infrastructure, stigmatizing cultural influences and a poor understanding of HIV infection all play a role in the current state of HIV care.¹⁵

Preventing HIV/AIDS in Children and Adolescents

The Joint United Nations Programme on AIDS (UNAIDS) and the World Health Organization (WHO) are leading a global program with a goal to end AIDS by 2030, a goal that will require both a greater focus on ART for people already living with HIV infection and a renewed emphasis on preventing new HIV infections.⁹

Overall funding for global HIV/AIDS programs has increased over the past several years, with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) as the largest global funding source for effective prevention programs.¹⁶ However, the proportion of HIV/AIDS resources available for *prevention* of new HIV infections has fallen slightly over that period, in part because the number of people living with HIV who are receiving life-long *treatment* with relatively expensive ART has been increasing rapidly. As a consequence, global progress toward the prevention goal of less than 500,000 new HIV infections per year is considered to be "off-track".⁹ Although progress toward the ultimate prevention goal of a successful HIV vaccine has not yet met expectations, the prevention of mother-to-child transmission of HIV (MCTC) has been both a U.S. and a global success story.

Preventing Mother-to-Child Transmission of HIV in Pregnancy and in the Perinatal period

Globally, MTCT accounts for more than 90 percent of new HIV infections among children. The WHO has put forward a comprehensive approach to prevention of MTCT. (See Box 1)¹⁷ Although overall global progress has been sporadic, significant progress has been made in certain countries. For example, in 21 priority African countries, the proportion of known HIV-infected pregnant women who received ART in pregnancy increased from 36 percent in 2009 to 80 percent in 2015.¹⁸ The numbers of HIV-infected children fell correspondingly by 48 percent between the years 2009 and 2014.¹⁹ Six of these priority countries reduced MTCT by at least 90 percent over that period. Finally, by 2016, Cuba, Belarus, Armenia, and Thailand have each reduced MTCT to the point that it is no longer considered a significant public health problem in those countries.

BOX 1

WHO's comprehensive approach to MTCT among adolescents and other women of childbearing age From World Health Organization. PMTCT strategic vision 2010–2015 preventing mother-to-child transmission of HIV to reach to the UNGASS and millennium development goals. http://www.who.int/hiv/pub/mtct/strategic_vision/en/. Updated 2010. Accessed December 10, 2016

1. Prevent HIV infections among adolescents and other women of childbearing age.
2. Help HIV-infected adolescents and other women avoid unintended pregnancy.
3. Prevent HIV transmission from HIV-infected adolescents and other women to their infants.
4. Provide appropriate treatment care, and support to mothers living with HIV and their children

Without any intervention for HIV-infected pregnant women, the risk of mother-to-child transmission of HIV (MTCT) ranges from 15–45 percent. However, effective interventions can reduce this transmission risk to <5 percent. Within the United States, although about 8500 HIV-infected women give birth annually,² the number of children who are HIV-infected *in utero* or in the perinatal period is now less than 100 per year. The lower rate of perinatal transmission is in part a result of high rates of antenatal HIV testing and counseling. In addition, HIV-infected pregnant women in the United States have good access to anti-retroviral medicines during pregnancy and delivery.^{20,21} It is recommended that pregnant women who do not have maximally suppressed HIV viral loads at the time of labor should have a C-section delivery to further reduce the HIV transmission risk to their newborns.

Prevention of Mother-to-Child Transmission of HIV through Breast Milk

MTCT may still occur beyond the perinatal period due to HIV transmitted via breast milk. Though the HIV transmission risk is lower if breastfeeding mothers are on ART, more than half of all MTCT HIV infections in 2013 were attributed to breast milk transmission.¹⁹ Infant formula feeding is the optimal way to eliminate that risk. However, infant formula use may not be possible in all circumstances due to the cost of formula and poor access to clean water. In such cases, exclusive breastfeeding rather than mixed feeding (the latter of which is associated with greater HIV transmission risk) should continue until weaning. Mothers should continue ART to keep their breast milk viral load suppressed and infants should receive their own ART until they reach six weeks old.

Preventing HIV Infections among Adolescents

In contrast to perinatal infections and infections in older adults, where HIV infection and mortality rates have been falling, the adolescent age group has seen increasing rates of both HIV infection and HIV-related mortality. Nearly two-thirds of these new HIV infections and

deaths are occurring in female adolescents. Effective prevention of new HIV infections among adolescents is a complex issue as the causes of HIV transmission vary in different cultural, social, economic, and geographic settings. Appropriately, there is a broad range of prevention strategies, which include:

1. Raising awareness of HIV/AIDS, its transmission mechanisms, and its behavioral components
2. Encouraging community-based- and school-based sex education
3. Increasing use of male and female condoms
4. Increasing uptake of voluntary male medical circumcisions
5. Increasing use of harm reduction interventions such as clean injection equipment
6. Increasing uptake of Pre-Exposure [drug] Prophylaxis (PrEP) and other ART use to lower viral load
7. Use of vaginal microbicides
8. Approaches to reduce child marriage
9. Other structural approaches to address gender inequality and gender-based violence.

Although each of these individual interventions has been demonstrated to be efficacious in one setting or another, the optimal combination in any one location will necessarily be dictated by local circumstances.

Recently, a group of United Nations agencies along with the U.S. PEPFAR program launched the “ALL IN to End Adolescent AIDS” agenda. This agenda will help address and implement interventions similar to those recently begun by the DREAMS INNOVATION Challenge supported by the U.S. PEPFAR program in collaboration with the Bill and Melinda Gate Foundation, several drug companies and other non-governmental organizations.²² The DREAMS INNOVATION Challenge is focused on: (1) Keeping girls in school; (2) strengthening the service delivery capacity of community-based organizations; (3) linking men to services; (4) supporting the use of Pre-Exposure [drug] prophylaxis; (5) linking adolescents to employment opportunities; and (6) increasing the use of data to inform policy.

Voluntary Medical Male Circumcision

Medical male circumcision may be of particular interest to pediatricians as a prevention strategy. After a compellingly high (>55 percent) efficacy of voluntary male medical circumcision (VMMC) was demonstrated to reduce men’s risk of acquiring HIV infection in several randomized controlled trials, use of that intervention was recommended by the WHO and UNAIDS.²³ By late 2015, nearly 12 million adolescent men and boys had been circumcised in 14 priority African countries. Current program efforts are focused on further integrating VMMC services within routine health systems, investigating safe alternatives to surgical circumcisions, and providing sufficient counseling to ensure that circumcision recipients understand that protection from HIV is not absolute and still requires condom use

and avoiding other high risk behaviors. Expanded use of infant male circumcision as an HIV prevention intervention is also being investigated in a number of African countries.

ART Adherence

Unlike other chronic diseases where even partial adherence to medications may be adequate treatment, poor adherence to ART risks creating resistant HIV strains that are difficult or impossible to treat and may then be transmitted. Adherence rates over 90 percent have been considered necessary to achieve viral suppression.^{24,25} However, adherence rates among adolescents range from 65–90 percent,²⁶ with one study in the United States reporting adherence rates of 65 percent.²⁷ Where ART is available and accessible there are still nearly a quarter of children and adolescents who are not taking their pills regularly. Evidence-based strategies to improve adherence in adolescents are critical for individual health and to prevent transmission.²⁸ Development of these strategies requires understanding of age-specific barriers to adherence.

Barriers in ART Adherence Specific to Infants and Children

For infants and very young children, many logistical factors impede adherence despite the best intentions of caregivers. Liquid ART formulations are often bitter and poorly tolerated;²⁹ their cost is up to four times higher than tablets; and the bulk and weight of multiple months of liquid ART makes them conspicuous and difficult to transport and store.³⁰ Dosing of liquid formulations require medication dispensers with markings, which may present as a challenge for caregivers with poor vision or lack of education. For children over the age of two, tablets are preferred to liquid formulations.³⁰ In order to avoid liquid formulations some caregivers report crushing tablets or opening capsules in order to sprinkle them over food, which may result in inadequate dosing of ART.²⁹ Gastrostomy tubes have been used to provide a more reliable route of administration. Studies showed that gastrostomy tubes were associated with improved adherence in young children and decreased the time required to administer ART.^{31,32} They may also be used for nutritional supplementation, which has been shown to increase weight and was associated with decreased hospital visits and mortality. However, the routine use of gastrostomy tubes is not recommended given the cost, practical limitations and related risks.³³

For children old enough to swallow non-liquid formulations, other barriers remain. Taking ART on an empty stomach can be uncomfortable and lack of food is a reality for many children and adolescents. In a study done in Uganda, 25 percent of children refused to take their medication if food was not available.³⁴ Children reported that lack of assistance from adult caregivers and forgetfulness were reasons for nonadherence.^{34–36} Children with caregivers reporting substance abuse, lower levels of education or poor understanding of ART also had lower adherence.³⁵ While adolescents may have more weighty social and emotional challenges associated with their HIV-positive status, younger children are not unaffected. Young children also reported hopelessness, depression and fear of taking medications in front of other children, which is of special concern in the orphan population or among children at boarding schools.^{34,36} Living in a rural setting is a risk for decreased

ART adherence,²⁶ with one study showing that children and adolescents who live more than 10 kilometers from medical care are more than twice as likely to be non-adherent to ART.³⁵

Disclosure of HIV status to Seropositive Youth

Children may be too young to understand their HIV-positive status and knowing the appropriate time and setting for disclosure is understandably often a challenge for caregivers. The WHO recommends that children of school age should be informed of their HIV-positive status and that younger children should be told in an incremental manner in relation to their cognitive capabilities.³⁷ In the context of a supportive caregiver relationship disclosure has been shown to improve medication adherence,^{34,35,38,39} though full disclosure is only performed 17 to 31 percent of the time.⁴⁰ Complicated family and social factors can also play a major role. Orphans are more likely to be given full disclosure and studies have shown that biological parents have fear of disclosing to their children due to feelings of culpability. Caregivers' fear of stigmatization, negative emotional impacts on the affected child or uncertainty of how to disclose HIV positive status are some of the major motivations for partial or non-disclosure.⁴⁰ Physicians should be aware of the challenges of disclosure and address this as part of a social history assessment in order to provide guidance and refer caregivers to available resources.

Adolescent Specific Barriers to Adherence

Adolescence presents a myriad of challenges for children transitioning into adulthood including discovery of sexuality, independence, and self-identity. HIV infection in adolescents adds an enormous burden and without adequate social support by family or caregivers adherence to ART is jeopardized. Disclosure to other family members, healthcare providers and sexual partners is anxiety provoking and has been reported as a reason for nonadherence.²⁶ In the United States, adolescents who acquire HIV through risk behaviors reported higher rates of non-adherence than those who acquired HIV perinatally.²⁷ Many perinatally-infected adolescents have been linked to care since an early age and are more likely to have an involved caregiver and access to healthcare services such as medication delivery.²⁷ Regardless of the means of transmission, caregivers reported that depression, poor self-image and peer pressure all affected adolescents likelihood of taking their ART regimen. Anticipated or experienced stigma was reported as the main barrier to adherence in adolescents living with HIV.²⁶ Stigmatizing attitudes regarding HIV are prominent throughout the world and youth living with HIV often face discrimination. Several misconceptions about HIV exist that discourage voluntary testing, taking medications in public or going to regular health care appointments. These misapprehensions include the belief that HIV is a result of divine punishment or a result of licentious sexual practices.⁴¹

Facilitators of Adherence

Several themes reappear in discussions of adherence for children and adolescents. Awareness of HIV-positive status and understanding the implications and importance of ART is fundamental in order to foster good habits and find a supportive community. Social support is one of the most important facilitators of adherence,³⁵ which can come from caregivers, other family members, health care workers or from other peers living with HIV. Newer resources include online support groups where those living with HIV can

communicate anonymously with others and offer encouragement or ask questions.⁴² Strategic planning of location, timing and method of ART consumption is helpful for many children and adolescents. Examples given by families included using alarms and log books as reminders as well as keeping ART in a consistent location that is convenient and safe.³⁴ Extra support from health care facilities is also helpful for many, including transportation services, telephone calls and text message reminders for appointments, and food services.²⁶

Access to Care

Many complex factors must work in concert in order for successful HIV care to be delivered to children and adolescents living with HIV. A breakdown in any area of care can lead to loss of follow-up and poor outcomes for youth. (See Table 1)^{7,43–48} Accessible clinics, adequately trained health care providers, funding for ART and laboratory testing, and psychosocial and adherence support are all critical components for linkage to and retention in HIV care.

The cost of care is a major barrier in resource poor countries. Laboratory reagents, particularly nucleic acid amplification tests, are expensive and may not always be available. In some African countries poor reliability of drug supply chains for ART make perinatal prophylaxis and consistent treatment of HIV infections impossible.⁴⁵ Even if ART and laboratory testing are free and available, delivery of these services in a setting that is realistic for patients is still needed. In Burkino Faso, a study evaluating a mother to child transmission prevention program described pregnant women being tested for HIV in one prenatal HIV clinic and being referred for testing and treatment in three separate health care facilities before returning for further prenatal counseling.⁴⁹ Shortages in health care workers and inadequate health care training can result in insufficient services. For example, HIV testing for infants may only be offered on one day of each month despite recommended testing at specific time intervals after birth.⁴⁹

In the United States, the Ryan White HIV/AIDS Program reaches 52 percent of all people diagnosed with HIV by providing primary medical care and support services to those who are uninsured or underinsured. Part D of the Ryan White HIV/AIDS Program focuses on providing services to women, infants, children and adolescents. In 2015, 6.7 million Part D grant dollars were allocated to health care centers across the country making this an invaluable resource for youth living with HIV in the United States.⁵⁰

HIV Therapy

The guidelines for specific ART regimens for infants, children and young adolescents are complex and depend on age, weight and stage in sexual maturity. The WHO and the United States guidelines now recommend that all individuals living with HIV should initiate ART at the time of diagnosis and this should be done independent of CD4 count, viral load or presence of clinical symptoms. Decisions regarding ART regimens should take into account HIV resistance, palatability, dosing frequency and complexity, available formulations and practical considerations including the volume and weight of liquid formulations. As in adults, adherence counseling should be performed routinely before initiating ART.⁴³

In a study evaluating ART outcomes in children in Asia and Africa almost 95 percent of health care sites were able to provide access to first line ART at no cost to patients. Second line ART was provided at no cost in 88 percent of health care sites. Free access to treatments for opportunistic infections was less consistent, ranging from 41 to 100 percent. Free ART has a significant impact on retention in care. Loss to follow-up was five times higher in patients who were required to pay for ART than in those who were provided ART free of cost.⁴⁵

Inter-Agency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mother and Children and the WHO have created an Optimal Formulary and Limited-use List to guide ART use in treatment of infants and children living with HIV. The Optimal Formulary does include two liquid nucleoside reverse transcriptase inhibitors (NRTIs) and one liquid protease inhibitor (PI). In addition, several tablets are dispersible and/or scored for more diverse dosing possibilities and methods of administration.⁵¹ The WHO also recommends using fixed dose combinations and dispersible tablets when these formulations are available. In order to avoid excessive volumes and the potential underdosing of ART it is also recommended that liquids and syrups be avoided and caution be used when transitioning to adult formulations that may require splitting of tablets.⁴³ For treatment-naïve children, a three drug regimen consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a boosted PI or a dual NRTI/NNRTI backbone with an integrase strand inhibitor (INSTI) is recommended. For infants younger than 14 days old, there is no guideline available regarding dosing of ART.⁴³ Much of the available data used to develop guidelines for ART selection and dosing in children and infants relies heavily on clinical trials done in adult populations. Considering the complexity of HIV therapy for children and adolescents, it is expected that general pediatric practitioners seek additional resources and assistance from Infectious Disease subspecialists. Certain national resources are available such as the Clinician Consultation Center, through the University of California in San Francisco, which provides free phone consultation from experts regarding HIV/AIDS management and perinatal HIV/AIDS.⁵²

Transitions in Care

As HIV is now a manageable chronic disease in the context of ART adherence, youth living with HIV will age into an adult population. Transitioning to adult health care is a challenge as many adolescents have developed strong relationships with their pediatric HIV health care providers. Fragmentation of adult health care is difficult for adolescents with comorbid psychiatric conditions and transitions may result in some degree of loss of anonymity or involuntary disclosure that expose youth to discrimination and stigmatizing attitudes. Several models have been proposed to standardize transition of care and prevent loss of follow-up or nonadherence. All models advise early and repeated discussions with adolescents about transitioning care. Several models include a visit to an adult physician while still being seen by their pediatric or adolescent care provider.⁷

Summary

Children and adolescents are significantly and distressingly affected by the HIV pandemic. However, HIV treatment in the context of linkage and retention in care can provide the opportunity for HIV-positive youth to grow and thrive into adulthood. HIV care is multifaceted and challenging, but coordinated efforts to prevent HIV transmission, promote adherence to ART, and retain youth in care can, with current tools, make HIV infection a manageable chronic disease and hopefully a disappearing one.

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KEY POINTS

- HIV remains a major public health crisis in children and adolescents across the world.
- There are two key populations of youth living with HIV, those that acquire HIV perinatally and those that acquire HIV through risk behaviors later in childhood or adolescence.
- Beyond technical and scientific advances, effective prevention of new HIV infections will require addressing a complex combination of social, economic, behavioral, structural, and logistic obstacles.
- In order for youth living with HIV to achieve viral suppression and optimal health outcomes providers should be aware of and address age-specific barriers to HIV testing, linkage to care, ART adherence, and retention in care.

Table 1

Evidence-based recommendations regarding management of HIV in children and adolescents

Data from refs^{7,43–48}

	Perinatal Transmission	Transmission through Risk-Behaviors
<i>Prevention</i>	<ul style="list-style-type: none"> Initiation of lifelong ART for all pregnant women living with HIV. Six weeks of antepartum ART prophylaxis for exposed newborns. Avoidance of breastfeeding for mothers without HIV viral suppression if other feeding options are available. 	<ul style="list-style-type: none"> HIV testing and counseling. Safe condom use. Pre-exposure prophylaxis. Addressing gender norms that perpetuate inequalities. Voluntary male circumcision.
<i>Diagnosis</i>	<ul style="list-style-type: none"> Immunologic testing should not be performed in children younger than 18 months of age. Virologic testing is recommended in exposed infants at 14–21 days, 1–2 months, and 4–6 months. CD4 T lymphocyte count and plasma HIV RNA should be tested at the time of diagnosis if the child is not on active ART. Testing for resistance is recommended. Laboratory monitoring should occur every 3 months. 	<ul style="list-style-type: none"> HIV testing is recommended: <ol style="list-style-type: none"> For key populations in all settings. For all adolescents in generalized epidemics. Should be made accessible to all adolescents in low and concentrated epidemics. Testing should be done in concert with pre-test and post-test counseling and linkage to care. Youth friendly testing centers. Physician and staff knowledge of consent laws, which vary by country.
<i>Linkage to Care</i>	<ul style="list-style-type: none"> Home based HIV testing and counseling results in improved linkage to care. Special attention should be given to high risk groups: adolescent males who have sex with men, sexually exploited, injection drug users, transgender adolescents, young females and orphans who may face stigma or legal consequences when seeking health care. 	
<i>ART Access</i>	<ul style="list-style-type: none"> ART should be available to all children and adolescents at no cost. Dispersible tablets, scored tablets and avoidance of liquid/syrup formulations are recommended when possible to avoid underdosing. 	
<i>ART Adherence</i>	<ul style="list-style-type: none"> Caregivers should be counseled on disclosure of HIV-positive status to the affected child as knowledge of HIV-positive status improves adherence. Community based approaches including specific training of health care workers to help address treatment adherence is recommended. 	
<i>Retention and Engagement in Care</i>	<ul style="list-style-type: none"> Community-based service delivery is associated with improved retention and reduced exposure to stigma. All counseling and supportive services should also address sexual education. Adolescent sexuality should be treated in a non-judgmental and positive way. Adolescents should be counseled about the health benefits and risks of disclosure to others and supported throughout this process. 	
<i>Transitions in Care</i>	<ul style="list-style-type: none"> Optimization of provider communication between adolescent and adult clinics. Engagement in regular multidisciplinary case conferences between adult and adolescent care providers. 	

	Perinatal Transmission	Transmission through Risk-Behaviors
	<ul style="list-style-type: none">• Implementation of support groups and mental health consultation services.• Incorporation of a family-planning component into clinical care.• Preparation of youth for life-skills development:<ul style="list-style-type: none">– Proper use of primary care physicians– Appointment management– Symptom recognition– Self-efficacy with medication and insurance management	