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## Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges

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### Abstract

Worldwide, more than three million children are infected with HIV, 90% of whom live in sub-Saharan Africa. As the HIV epidemic matures and antiretroviral treatment is scaled up, children with HIV are reaching adolescence in large numbers. The growing population of adolescents with perinatally acquired HIV infection living within this region presents not only unprecedented challenges but also opportunities to learn about the pathogenesis of HIV infection. In this Review, we discuss the changing epidemiology of paediatric HIV and the particular features of HIV infection in adolescents in sub-Saharan Africa. Longstanding HIV infection acquired when the immune system is not developed results in distinctive chronic clinical complications that cause severe morbidity. As well as dealing with chronic illness, HIV-infected adolescents have to confront psychosocial issues, maintain adherence to drugs, and learn to negotiate sexual relationships, while undergoing rapid physical and psychological development. Context-specific strategies for early identification of HIV infection in children and prompt linkage to care need to be developed. Clinical HIV care should integrate age-appropriate sexual and reproductive health and psychological, educational, and social services. Health-care workers will need to be trained to recognise and manage the needs of these young people so that the increasing numbers of children surviving to adolescence can access quality care beyond specialist services at low-level health-care facilities.

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## Introduction

HIV infection has been established for more than 30 years, with sub-Saharan Africa continuing to have the highest incidence of HIV of any region.<sup>1</sup> The global epidemiology of paediatric HIV mirrors that of adults. Of more than three million children infected with HIV, 90% live in sub-Saharan Africa.<sup>1</sup> The advent of the HIV epidemic resulted in a reversal of the improvements recorded in child health outcomes in the 1970s and 1980s, with global child mortality rates a third to two-thirds higher than they would have been in the absence of HIV/AIDS.<sup>2</sup>

However, since 2004, access to paediatric antiretroviral treatment has expanded globally, resulting in a substantial decline in mortality rates in HIV-infected children.<sup>3</sup> In view of this increased survival, HIV is now evolving into a chronic illness among adolescents.<sup>4</sup> Young adults who have grown up with HIV present an important challenge to HIV care programmes. Longstanding HIV infection acquired when the immune system was not developed results in distinctive chronic clinical complications that cause severe morbidity. In addition to dealing with chronic illness, HIV-infected adolescents have to confront psychosocial issues, maintain adherence to drugs, and learn to negotiate sexual relationships while undergoing rapid physical and psychological changes.<sup>5</sup>

In this Review, we discuss the evolving epidemiology of paediatric HIV infection and the shift of the infection burden onto adolescents. We also consider some of the unique features that characterise HIV infection in survivors of perinatally acquired HIV infection.

## The ageing paediatric HIV epidemic

Unlike the rapid widespread implementation of highly effective HIV interventions in industrialised countries that began in the mid 1990s, antiretroviral treatment for prevention of mother-to-child HIV transmission only became available in much of Africa around 2004. Although in sub-Saharan Africa the number of infant infections has dropped by 24% from 2009 to 2011, treatment coverage remains suboptimum, with only 59% of HIV-infected pregnant women receiving antiretroviral treatment to prevent mother-to-child transmission in the 21 high-burden countries, and about 1000 infants were infected daily in 2011.<sup>1</sup>

Before antiretroviral treatment was available, HIV-infected infants in Africa had a 50% probability of dying by age 2 years.<sup>6</sup> The increasing availability of antiretroviral drugs has resulted in a substantial rise in the life expectancy of children living with HIV in low-income countries, so that escalating numbers of children are surviving to adolescence and beyond.<sup>7,8</sup> For example, more than 40% of the 25 000 children in HIV care in Zimbabwe in 2009 were age 10 years or older.<sup>9</sup> However, the large numbers of adolescents in HIV programmes in sub-Saharan Africa are not accounted for fully by raised survival related to antiretroviral treatment. Over the past decade, substantial numbers of children in sub-Saharan Africa with perinatally acquired HIV have been presenting to health-care services for the first time during adolescence.<sup>10,11</sup> By extrapolation of high early mortality rates associated with untreated HIV in the early days of the HIV epidemic, the widely held perception was that survival to older childhood without treatment in sub-Saharan Africa would be exceptional. However, epidemiological data indicate that at least a third of HIV-

infected infants have slow-progressing infection, with a median survival of 16 years without treatment.<sup>12</sup> In recent years, survival estimates in sub-Saharan Africa for untreated infants infected perinatally have been revised upwards, with about a 20–30% probability of overall survival in untreated HIV-infected infants to at least age 10 years.<sup>12,13</sup>

In industrialised countries, two distinct prognostic groups were recognised in the era before antiretroviral treatment—people with fast-progressing infection and those with slow progression of disease. However, exact survival probabilities for HIV-infected infants in Africa were ill-defined because cohorts were not followed up beyond age 5 years.<sup>14,15</sup> In population-based HIV prevalence surveys in southern Africa, HIV prevalence of 2–6% was reported consistently among adolescents, before antiretroviral treatment became available.<sup>16–18</sup> Up to age 14 years, no difference in HIV prevalence by sex is evident, inferring a non-sexual route of HIV acquisition.<sup>19</sup> However, in children older than 14 years, prevalence of HIV is disproportionately higher in girls than in boys, reflecting the well-recognised increased risk of HIV infection through sexual transmission in young women compared with young men.<sup>19</sup>

As the HIV epidemic matures, as strategies are developed to prevent mother-to-child transmission, and as paediatric antiretroviral drugs become more widely available, the number of HIV-infected infants will decline, whereas the number of children with HIV infection surviving to older ages will increase for some time. Falling prevalence of HIV in adults will compound this trend by reducing the number of infant infections. Such regional trends have been masked by the standard reporting of HIV data in just three age categories: 0–4 years, 5–14 years, and 15–49 years. The number of adolescents infected perinatally accumulated slowly after the onset of the adult epidemic because of the time needed for infants to reach an older age (figure 1). Even with universal access to interventions for prevention of mother-to-child transmission and with scale-up of antiretroviral treatment, a time lag of two decades will be present before the numbers of adolescents infected with HIV perinatally begins to decrease.<sup>12</sup>

## Clinical complications of HIV infection

HIV infection in infancy and early childhood is associated with rapid disease progression and typically presents as failure to thrive, severe bacterial and viral infections and AIDS-defining illnesses, including pneumocystis pneumonia, HIV encephalopathy, and refractory candidosis.<sup>20</sup> By contrast, older children in sub-Saharan Africa with HIV infection are either asymptomatic or typically have a history of multiple, non-specific complaints, including recurrent upper-respiratory-tract infections, diarrhoea, minor skin infections, and suboptimum growth.<sup>21,22</sup> These illnesses are also common in their HIV-uninfected peers and are not recognised as an indication of underlying HIV infection. Health-care workers are only prompted to undertake HIV testing after an individual develops advanced immunosuppression and presents with typical AIDS-indicator illnesses.<sup>21</sup> Therefore, health-care providers must have a low threshold for HIV testing in areas of high prevalence, even for children with no apparent risk factors for HIV infection.

## Infections and malignant disease

In general, the range of opportunistic infections among HIV-infected adolescents more closely resembles that noted in adults with HIV infection than that in HIV-infected infants and young children.<sup>23,24</sup> Cryptococcosis—less commonly seen in younger paediatric patients—is a frequent infectious pathogen in hospitalised HIV-infected young adults in sub-Saharan Africa; further, the incidence of tuberculosis rises in adolescence.<sup>25,26</sup> Social contact widens during a child's teenage years, putting immunosuppressed young people at especially high risk of tuberculosis infection and disease.<sup>26,27</sup> However, tuberculosis is difficult to diagnose and treatment is commonly given on the basis of chronic respiratory symptoms without a definitive microbiological diagnosis.<sup>28</sup> Therefore, the burden of tuberculosis might be over estimated, because HIV-infected adolescents report high rates of longstanding chronic respiratory symptoms.<sup>29</sup>

HIV-infected adolescents are susceptible to vaccine-preventable illnesses, which typically have the greatest effect on young children. A lower response rate to early childhood immunisations, and waning immunity after early vaccination, are likely causes; in outbreak situations, HIV-infected adolescents can be especially vulnerable.<sup>30–33</sup> Of 195 HIV-infected children identified with measles in an outbreak in Botswana in 2009–10, the median age was 13 years (IQR 10–15).<sup>34</sup> The most severely affected patients were HIV-infected adolescents, most of whom had been immunised against measles during early childhood. Further, in a study of young people age 8–17 years in Rwanda who received hepatitis B vaccinations, amounts of HIV RNA and CD4 counts were both independent predictors of hepatitis B antibody response.<sup>35</sup> Revaccination could restore immunity, although currently no robust evidence is available to support this. Also, as adolescent girls become sexually active, cervical cancer is of concern. Human papillomavirus (HPV) is associated strongly with cervical cancer, and HPV infection rates in Africa are high. Cervical dysplasia happens frequently and at a young age in girls infected with HIV, but few screening services are available.<sup>36</sup> Findings of a study in Tanzania showed that 65% of adolescent girls acquired HPV within 1 year of sexual debut.<sup>37</sup> The HPV vaccine has proven safe, immunogenic, and acceptable to adolescents and their guardians.<sup>38</sup> However, policies about HPV vaccination are still being developed for most countries in sub-Saharan Africa.<sup>39</sup>

The range of cancers in HIV-infected children is age-dependent. HIV is associated with a significantly increased risk of Burkitt's lymphoma and Kaposi's sarcoma, with Kaposi's sarcoma being more common in adolescents than in infants and young children.<sup>40–42</sup> Unlike young children, who are more likely to have raised CD4+ T-cell counts at presentation and have lymphatic Kaposi's sarcoma, adolescents present in a similar way to adults, with lower CD4+ T-cell counts and cutaneous lesions.<sup>43</sup> In children, the absolute CD4 T-cell count alone is insufficient to ascertain the risk of malignant disease; duration of immunosuppression is a relevant risk factor, which has important implications for the risk of malignant disease in adolescents.<sup>44</sup> Longstanding HIV infection might predispose to premature malignant diseases in young adults.<sup>45</sup> B-cell and T-cell lymphoproliferative disorders, which are present frequently in HIV-infected children and often at remarkably preserved CD4 counts, potentially represent a preneoplastic state.<sup>44</sup> The risk of these disorders developing into overt malignant diseases in adolescence and beyond is not yet

known. Cases of atypical and rare malignant diseases in HIV-infected adolescents have been reported.<sup>44,46,47</sup>

## Chronic disease

One of the striking features of HIV infection in adolescence is the high prevalence of chronic complications. These disorders can lead to severe disability (figure 2).

### Chronic lung disease

As children get older, they are at increased risk of developing HIV-associated chronic lung disease. This disorder is well-described in HIV-infected younger children, and lymphocytic interstitial pneumonitis was the predominant cause before use of antiretroviral treatment became widespread.<sup>48,49</sup> Lymphocytic interstitial pneumonitis responds well to antiretroviral treatment, but delayed initiation of antiretroviral drugs can lead to long-term sequelae such as bronchiectasis and cor pulmonale in adolescence.<sup>50</sup> The range of chronic lung disease seems to differ in adolescents compared with younger children.<sup>51</sup> In a study from Zimbabwe of 116 adolescents with HIV infection acquired perinatally, more than 30% of children had severe and disabling chronic respiratory symptoms; these findings were confirmed by those of a study from Malawi in 160 older children.<sup>52</sup> Unexpectedly, in the Zimbabwe study, high-resolution CT scanning showed predominantly small-airways disease consistent with constrictive obliterative bronchiolitis, with lymphocytic interstitial pneumonitis being an exceptional finding. Unlike lymphocytic interstitial pneumonitis, obliterative bronchiolitis seemed to have little reversibility with antiretroviral treatment once established; 7% of children had coexisting pulmonary hypertension.<sup>29</sup> Obliterative bronchiolitis, which occurs with graft-versus-host disease and after viral infections and exposure to chemical fumes, is a progressive life-threatening condition, and little is known about its natural history and pathogenesis in people with HIV infection or how it should be managed.<sup>51,53</sup> Chest radiographic findings are non-specific, and high-resolution CT—the gold standard diagnostic method—is not typically available in resource-limited settings.<sup>53</sup> Obliterative bronchiolitis has not been described before in US and European cohorts of HIV-infected adolescents. The availability of antiretroviral treatment during early childhood might be preventive for this disorder, and geographical variability or genetic predisposition could have a role.<sup>54</sup>

### Cardiac disease

Cardiac disease is well-described in HIV-infected infants and young children, and risk increases with age.<sup>55–57</sup> Abnormalities include dilated cardiomyopathy, pericardial effusion, left-ventricular diastolic dysfunction, increased left-ventricular wall thickness or mass, and decreased left-ventricular fractional shortening. Subclinical abnormalities can develop into symptomatic cardiac disease with increasing age, but few data are available on the burden of cardiac pathology in adolescents from Africa with HIV infection.<sup>58</sup> In a cohort of hospitalised HIV-infected adolescents in Zimbabwe, cardiac disease—including cardiomyopathy—was the reason for admission in 12% of cases.<sup>24</sup> An assessment was done of 110 perinatally infected adolescents in HIV care in Harare.<sup>59</sup> 67% had left-ventricular hypertrophy and 24% had impaired left-ventricular relaxation or restrictive physiology.

Moreover, 31% had right-ventricular dilatation and 4% met echocardiographic criteria for pulmonary hypertension, which were both probably secondary to chronic lung disease. Also, exertional dyspnoea was noted in 43% and chest pain in 39%; finally, 37% had a New York Heart Association score of greater than 2, indicating substantial limitation of activity.<sup>59</sup> The effect of antiretroviral treatment on the natural history of cardiac abnormalities is not clear. Prolonged exposure to certain classes of antiretroviral drug—such as protease inhibitors—causes lipid abnormalities and could itself increase the risk of premature cardiovascular disease.<sup>60</sup>

### **Growth failure**

Growth failure, including stunting and pubertal delay, is one of the hallmarks of paediatric HIV infection and generally distinguishes adolescents with perinatally acquired HIV infection from their uninfected peers and from those infected sexually.<sup>21,24,61–64</sup> Growth failure can become especially obvious in adolescence as untreated HIV-infected adolescents lag behind peers who are going through periods of rapid growth and pubertal development. Stunting—a reflection of poor linear growth—happens over a long period and might be the only manifestation of chronic HIV infection in an otherwise seemingly healthy adolescent. Wasting occurs mainly with development of advanced disease and reflects acute illness.<sup>65</sup> The extent of stunting is more profound among HIV-infected children in Africa compared with those in resource-rich settings, possibly reflecting higher background rates of malnutrition and an increased burden of infection.<sup>66</sup> Although catch-up growth can be achieved after initiation of antiretroviral treatment, children who begin treatment in later childhood are typically unable to regain their height potential.<sup>67,68</sup> The dissociation between physical development and cognitive and chronological age can cause considerable psychological morbidity among HIV-infected adolescents; stunting and pubertal delay are visible manifestations of HIV infection and lead to stigmatisation and discrimination of those affected.

### **Neurocognitive disease**

Progressive encephalopathy—characterised by a stepwise or continuous deterioration in brain function—is well recognised in HIV-infected infants and young children. Overall neurocognitive function seems to be within the normal range for older survivors of perinatally acquired HIV infection, although studies vary greatly with respect to methods and generally do not contain a control group, making comparison of findings difficult.<sup>69,70</sup> Seemingly asymptomatic HIV-infected adolescents do have deficits that are difficult to identify by routine testing. These include shortfalls in cognitive function, fine motor function, memory, perceptual performance, quantitative abilities, and mental processing and language abilities.<sup>70</sup> Data for the effect of antiretroviral treatment on neurocognitive outcomes are conflicting and suggest that children who receive antiretroviral drugs in infancy or before the onset of symptoms are likely to have better outcomes than are those who access treatment at an older age.<sup>71–73</sup> Despite treatment with antiretroviral drugs, subtle defects persist and have important implications for adolescents, particularly with respect to adherence to medication, education and career planning, risk behaviours, and overall quality of life.<sup>73,74</sup>

## Skin disease

Skin disease is one of the most common manifestations of HIV infection, and adolescents are affected disproportionately. In a series of 301 young adults admitted to hospital in Harare, those with dermatological abnormalities were 37 times more likely to have HIV infection; furthermore, 70% of HIV-infected adolescents had two or more skin manifestations, a higher proportion than that reported in studies of HIV-infected younger children and adults.<sup>75</sup> HIV-infected adolescents typically report a history of non-specific recurrent rashes occurring throughout childhood. Common manifestations include papular pruritic eruption, angular cheilitis, molluscum contagiosum, herpes zoster, and common warts (*verruca vulgaris*). Moreover, diffuse planar warts—prominent on the face and in other sun-exposed areas of the body—are noted frequently in young people with HIV infection and are typically extensive and stigmatising. Histology and HPV types accord with epidermodysplasia verruciformis, a potentially premalignant condition, and little improvement takes place with antiretroviral treatment, despite immune reconstitution.<sup>76</sup> Use of topical glycolic acid can speed resolution.<sup>77</sup> Other skin manifestations improve with antiretroviral treatment, although transient worsening or initial presentation might be associated with immune reconstitution.<sup>78,79</sup> Similar to growth failure, skin disease is a visible manifestation of HIV infection and—in areas with a high prevalence of HIV—is associated widely with having the infection, resulting in affected children being severely stigmatised (figure 2).

## Renal and bone disease

HIV-associated nephropathy is thought to be due to direct infection of renal epithelial cells.<sup>80</sup> Similar to other chronic complications, risk of HIV-associated nephropathy increases with age; moreover, African people might be at particularly high risk because of the augmented frequency of *APOL1* gene variants in this population, which have been associated with HIV-associated nephropathy in African cohorts.<sup>81</sup> HIV infection is also associated with decreased bone-mineral content and density.<sup>82,83</sup> Factors contributing to low bone density in HIV-infected adolescents include advanced HIV disease, renal disease, vitamin D deficiency, malabsorption, longstanding chronic HIV-mediated inflammation, stunted growth, low body mass, and delayed puberty. Adolescence is an important period for bone-mineral acquisition, and compromised bone mass can increase the risk of premature osteoporosis.<sup>84</sup> Although antiretroviral treatment significantly reduces the risk of kidney disease and is beneficial to bone growth, tenofovir—recommended in first-line regimens for HIV treatment—can cause proximal renal tubular toxic effects and decreased bone-mineral density. The toxic effects of tenofovir are relatively uncommon in adults. However, the risk of adverse effects of tenofovir may be higher in children and adolescents because of their immature physiology and ongoing bone growth.

## Limitations of existing studies

Few data have been published on the range, epidemiology, and pathogenesis of chronic disorders associated with HIV infection in adolescents. Studies to date are limited by their cross-sectional nature, small sample sizes, and absence of controls. Much research has been undertaken in high-income settings, in the era before antiretroviral treatment was introduced.

Studies include a mix of patients—eg, those who have not received antiretroviral drugs before and individuals who have experience of these regimens—and were not disaggregated by age, therefore limiting the generalisability of the findings to HIV-infected adolescents in Africa. Complex clinical issues place heavy demands on already overstretched health-care systems, and optimum screening and management strategies are not well defined

## Antiretroviral treatment in adolescence

In their 2013 guidelines for treatment of HIV, WHO recommend earlier initiation of antiretroviral treatment compared with previous guidelines.<sup>85</sup> Antiretroviral treatment is recommended up to 5 years of age, regardless of clinical or immunological stage of disease; however, in older children, adolescents, and adults, antiretroviral treatment is deferred until the patient develops WHO stage 3 or 4 HIV disease or the CD4 count drops below 500 cells per  $\mu\text{L}$ . Unlike adults, children are infected at a period when the immune system is immature. Compared with adult patients, HIV-driven chronic immune activation in children can lead to premature ageing of the immune system and cause more adverse outcomes on immune health. Delayed treatment also increases the risk of development and progression of end-organ complications in addition to compromising growth potential.<sup>67,72</sup>

Although earlier access to HIV treatment might help to prevent these complications, antiretroviral treatment itself can lead to side-effects, such as lipodystrophy, hyperlipidaemia, and insulin resistance.<sup>67,71,86,87</sup> Use of tenofovir is likely to rise now it is available as a fixed-drug combination for once-daily dosing. The potential risk of tenofovir-related renal and bone toxic effects have been highlighted as a concern by WHO, and recommendations for monitoring of children and prepubertal adolescents receiving tenofovir have been developed.<sup>85,88</sup>

In the 2013 WHO HIV guidelines, the antiretroviral regimens and dosing schedules recommended for adults are also recommended for adolescents heavier than 35 kg. Although this guideline harmonises treatment across age groups, data for the pharmacokinetics of drugs in adolescents are sparse. Pubertal changes and growth delay can affect drug metabolism, and the optimum period when the change from weight-based to age-based dosing should occur is not clear, with a potential risk of under-dosing or over-dosing.<sup>89</sup>

## Psychosocial issues and mental health

Over and above HIV-related issues that are common to any age group, HIV-infected adolescents are likely to face recurrent and cumulative psychological stressors, such as illness and the death of their parents and siblings, responsibility for welfare of younger siblings or other ill family members, stigma and discrimination, the fear of being viewed as abnormal, and confrontation of mortality and an uncertain future.<sup>90,91</sup> HIV/AIDS in the family affects the health and wealth of households, thus aggravating pre-existing poverty.<sup>92</sup> The orphanhood epidemic has matured alongside the HIV epidemic. Thus, more than 50% of AIDS orphans are adolescents.<sup>93,94</sup> Many adverse outcomes of being orphaned have been reported, including loss of effective guidance and supervision, inconsistent care, psychological distress and poor mental health, loss of educational opportunities, impoverishment, increased sexual vulnerability, and high rates of risk taking.<sup>95–99</sup> Issues



with schooling are also prevalent, such as absenteeism because of illness or clinic appointments, disclosure of HIV status to school officials, and stigmatisation from classmates and teachers.<sup>100,101</sup>

The emotional effects of coping with HIV infection can be severe, and the frequency of psychiatric admissions among HIV-infected adolescents is significantly higher compared with that in the general paediatric population in high-income countries.<sup>102,103</sup> This increase is possibly attributable to a combination of the neuropathological effects of HIV infection and environmental factors.<sup>104</sup> In Africa, HIV occurs in the context of social factors such as being orphaned, poverty, and inconsistent guardianship, which results in augmented risk of behavioural problems and psychiatric disorders among adolescents, including post-traumatic stress disorder, depression, and severe anxiety.<sup>105–107</sup> Mental health needs typically receive little attention as families struggle to address immediate medical concerns and the social and economic outcomes of HIV.<sup>92</sup> These factors ultimately affect an adolescent's access to HIV care and treatment adherence, undermining the success of antiretroviral regimens.<sup>108,109</sup>

### Adherence to antiretroviral treatment

Many key life events happen during adolescence, including completion of school, initiation of sexual activity, and becoming economically productive. Furthermore, adolescence is typically a period of experimentation and engagement in high-risk behaviours. Unsurprisingly, adolescents with chronic disease show a poorer adherence to treatment than do adults and young children.<sup>110–112</sup> Likewise, when compared with younger children and adults, HIV-infected adolescents and young adults consistently have disproportionately higher rates of poor drug adherence and virological failure.<sup>113–117</sup> In a study of 154 adolescents and 7622 adults, the rate of optimum treatment adherence declined over time, from 21% at 6 months for adolescents (compared with 41% for adults) to 7% at 24 months (compared with 21%); furthermore, adolescents had a shorter time to viral rebound and were less likely to achieve long-term immunological recovery than were adult patients.<sup>113</sup>

Correlates of poor treatment adherence in adolescence include being orphaned, lack of knowledge, mental health problems, changes of guardianship, attending school, and absence of parental and social support.<sup>109,116,118,119</sup> Delayed disclosure of HIV status to the adolescent, and a resultant lack of autonomy, substantially affect adherence.<sup>118</sup> In Uganda, children whose primary caregiver was the only one who knew the child's HIV status were three times more likely to be non-adherent to antiretroviral treatment.<sup>120</sup> By contrast, good adherence to an antiretroviral regimen was associated with an adolescent's knowledge of their HIV status, valuable social support, and having a strong relationship with parents.<sup>121,122</sup> However, even for adolescents with these apparent advantages, structural barriers of stigma and poverty still affect adherence.<sup>119</sup> The desire for conformity with peers during adolescence, and a fear of stigmatisation, greatly affects treatment adherence. Antiretroviral treatment is a daily reminder of being HIV-positive, and drug fatigue can result in adolescents stopping the regimen.<sup>121</sup> Transition of adolescents from paediatric to adult HIV care services might further disrupt adherence, because the time available for counselling is diminished and health-care providers have little experience of addressing adolescent-specific concerns.<sup>123</sup>

Outcomes of poor treatment adherence include clinical progression of disease, emergence of drug resistance, and the risk of spreading drug-resistant HIV strains when adolescents become sexually active.<sup>124</sup> The importance of addressing adherence in this age group cannot be overemphasised. The high risk of developing drug resistance during this period of life, combined with the fact that patients who began antiretroviral treatment as children will be taking these drugs for a much longer period than will those who were diagnosed as adults, is of grave concern in view of the limited availability of alternative regimens in resource-constrained settings. Additionally, the risk of onward transmission of HIV to a sexual partner is high during adolescence.<sup>117</sup> Thus, maintaining adherence during adolescence is crucial not only to ensure sustainability of treatment success but also to prevent HIV transmission.<sup>124</sup> An evidence base for effective interventions to support adherence among adolescents in low-income settings is absent. Furthermore, no one intervention to maintain sustained adherence is feasible because the process is dynamic and individual.

## Sexual and reproductive health

Adolescents and young adults have been the focus of primary HIV prevention programmes for many years. With growing numbers of HIV-infected children surviving to adolescence and becoming sexually active,<sup>125,126</sup> the need for secondary prevention programmes is increasing. Sexual identity-building in adolescence is complex and culturally specific, and sexual behaviours are shaped partly by societal norms.<sup>127</sup> Many interventions to reduce sexual risk behaviours have been developed in high-income settings, but these might have scant applicability to African young people.

Some factors put adolescents at especially high risk of transmitting HIV infection, including early sexual debut, having multiple sex partners, being at high risk of sexual violence, and adolescent girls engaging in transactional sex with older men.<sup>98,128</sup> Findings of a study at 20 sites in Uganda, of adolescents infected with HIV perinatally, showed low levels of condom use, with 63% of the young people aware of the need to use condoms to prevent HIV infection of their partner or prevention of sexually transmitted infections, but only 30% reporting use.<sup>129</sup> Barriers to use of condoms included fear of rejection, peer pressure, poverty, alcohol use, poor negotiation skills, possible disclosure of HIV status through insistence on condom use, ambivalence about becoming a parent, and impulsivity that is characteristic of adolescence.<sup>130</sup> Oral and anal sexual intercourse is also reported frequently, as a means to avoid pregnancy and to preserve virginity.<sup>131,132</sup>

The desire to have children remains strong, independent of HIV status, and a romantic relationship is typically not regarded as legitimate unless it produces a baby.<sup>133</sup> The cultural value placed on having children means that adolescents living with HIV engage in early relationships to fulfil their obligation to have children before they die.<sup>133</sup> In Uganda, the rate of pregnancy among adolescents living with HIV was similar to that recorded in the general population.<sup>133</sup> Of 1238 adolescents in care at the Paediatric Infectious Disease Clinic in Kampala, Uganda, by the end of 2012, 123 girls had become pregnant since 2008 and at least 12 male adolescents had fathered children (unpublished data; S Bakeera-Kitaka, Makerere University College of Health Sciences, Kampala, Uganda). Management of HIV-infected pregnant adolescents poses specific challenges in terms of ensuring that mother-to-

child transmission does not occur, decreasing the risk of complications in pregnancy in girls who have comorbidities, lessening the stigma associated with HIV infection, and handling the low levels of disclosure to sexual partners.<sup>130,134</sup> Only a few sexually active adolescents report disclosing their HIV status to their current partner (29% in young people age 15–17 years and 42% in adults age 18–19 years).<sup>129</sup> Many adolescent pregnancies are unwanted, and termination of pregnancy is sought from unskilled providers.<sup>128,135</sup>

Awareness of and knowledge about reproductive health, HIV transmission, and contraceptive methods is poor among HIV-infected adolescents.<sup>130</sup> Discrepancy between the information given by health-care providers and the actual needs of HIV-infected adolescents is common, with the concerns of young people sometimes not taken into account.<sup>136</sup> Health-care providers need to recognise that young people perinatally infected with HIV are sexually active or anticipate being so in the future. HIV care programmes should provide age-appropriate information on prevention of HIV transmission and family-planning and give support about disclosure of HIV status to partners and contraceptive services. Without consistent use, condoms are an ineffective contraceptive, and hormonal contraceptives should, therefore, be considered. Use of hormonal contraceptives does not accelerate disease progression but, as with antiretroviral treatment, adolescents adhere poorly to both condoms and hormonal contraceptives.<sup>137,138</sup> Long-acting contraception such as progestogen implants and depots might, therefore, be a pragmatic option for adolescents.<sup>138</sup> However, this option must be accompanied by counselling on the use of condoms to prevent onward HIV transmission and acquisition of sexually transmitted infections.

## Disclosure of HIV status

Although often deferred in early childhood,<sup>139,140</sup> disclosure of HIV status becomes crucial as children approach cognitive maturity and puberty. Young adults have to make decisions about sexual relationships and plan for the future, and these decisions can only be made with an accurate understanding of the nature of their illness.<sup>141</sup> Although the benefits of disclosure are considerable, informing a child of his or her own HIV status is often delayed. Furthermore, deferring disclosure can adversely affect treatment adherence and psychological well-being and might affect family functioning and the adolescent's social and academic life.<sup>120,121,142–145</sup> Delays to the initiation of the process of disclosure increase the difficulty of the eventual revelation. In a study from Kinshasa, Democratic Republic of the Congo, the median age at disclosure of HIV status was 15 years.<sup>146</sup> A child who discovers their HIV status will have many questions about the implications of being HIV-positive and of having HIV in the family, which unfold over time. Adolescents actively desire direct communication with their caregivers about their HIV status, but most adults are ill-equipped to handle this process positively and, thus, prefer to manage HIV infection in silence.<sup>146,147</sup>

Study findings highlight the contextual challenges faced by caregivers in disclosing the HIV status to a child. Reluctance of parents to reveal HIV status is typically attributable to a desire to protect their child from psychological distress, to prevent disclosure of the mother's HIV status, and to avoid not only having to address their own feelings of guilt at having infected their child but also possible blame from their child.<sup>148–150</sup> Other barriers

include the fear of discrimination and stigma toward both the adolescent and the family as a whole.<sup>150,151</sup>

The process of disclosure to children poses several difficulties. Sometimes confusion arises about whether the health-care provider or the caregiver should disclose the information to the child.<sup>149,151,152</sup> Despite recommendations for a developmentally appropriate and incremental process of disclosure, with ongoing support to address questions that arise, caregivers and health-care workers typically think of disclosure as a discrete event.<sup>153</sup> Adolescents report that disclosure is usually a one-point event and that they are not given opportunities to ask questions.<sup>154</sup> Health-care workers sometimes do not have the skills necessary to help caregivers and families deal with the complex issues associated with revealing HIV status to an infected child. With many children receiving antiretroviral treatment through busy clinics, practical approaches to supporting disclosure with limited time and staffing are needed.

## Recommendations for policy and research

Service provision has been affected adversely by an underappreciation of the burden of surviving adolescents living with HIV in Africa and the morbidity associated with HIV in this age group. Strategies to enable earlier identification of HIV infection of children with slow-progressing disease need to be implemented urgently. Specific issues should be taken into account by policy makers: informed consent, confidentiality, and autonomy in a group with evolving capacities; training of health-care providers; and provision of quality care beyond centres of excellence to accessible low-level health-care settings. A global effort, led by WHO and UNICEF, has been initiated to respond to the needs of this previously neglected group of young adults, and guidelines on HIV testing and care have been developed.<sup>155,156</sup> Panel 1 outlines suggestions for interventions and research priorities aimed at addressing issues pertinent to the emerging adolescent HIV epidemic. Many concerns—such as disclosure, adherence, stigma, and transitioning—can be extrapolated to other chronic illnesses in adolescence, and development of policies to address these issues is an opportunity to address the broader agenda of chronic illness in adolescence.

In Africa, dedicated health-care services for young people are the exception rather than the rule, and little or no provision has been made for the special needs of this age group. Without appropriately tailored services, adolescents are likely to fall through the cracks of paediatric-based or adult-orientated HIV care. There is an urgent need to develop and rapidly implement policies and programmes aimed at early diagnosis and improvement of care provided to the expanding numbers of adolescents who are growing up with HIV. A model that integrates HIV clinical care with sexual and reproductive health and psychological, educational, and social services (panel 2) will help to prepare young adults for an independent and productive future and reduce the effect of this devastating epidemic at community and societal level.<sup>155</sup> As these children take an important step towards adulthood, they deserve our support, encouragement, and investment to live their life to its full potential.

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## Panel 1: Suggested interventions and research priorities

### Population-based epidemiology

#### *Epidemiology of HIV infection in adolescents*

- Modelling the effect of strategies to prevent mother-to-child transmission and antiretroviral treatment on the paediatric HIV epidemic
- Identification of competing causes of childhood mortality: malaria, poor sanitation, and unclean drinking water are potential disproportionate hazards for the survival of HIV-infected children
- Surveillance of HIV infection: inclusion of children and adolescents in demographic health surveys (currently include individuals older than 15 years) and population-based surveys
- Reporting of HIV epidemiological data in finer age-bands—eg, 0–5 years, 6–10 years, 11–15 years, 16–19 years

#### Earlier identification of HIV-infected individuals with slow-progressing disease

- Screening algorithms to define at-risk adolescents<sup>157</sup>
- Community-based HIV-testing approaches, including school-based testing, testing at community outlets (eg, churches), home-based testing, self-testing, and voluntary counselling and testing sites<sup>85,155</sup>
- Ethics of HIV-testing—eg, age of consent, testing for adolescents without caregivers
- Context-specific strategies to improve links to HIV care

### HIV care

#### How can virological outcomes after antiretroviral treatment be improved?

- Promotion of retention in care and adherence—eg, integration of HIV testing and care services, peer-led support, adherence clubs, economic enablers, community-based provision of antiretroviral treatment, once-daily dosing, mobile phone technologies, managed problem-solving, point-of-care CD4 count<sup>112,158–160</sup>
- Pharmacokinetic studies in adolescents, to define optimum dosing in relation to stunting and pubertal delay
- Strategies for preservation of long-term treatment options—eg, holding regimens, structured treatment interruption

#### *Chronic complications of HIV infection*

- Earlier initiation of antiretroviral treatment to prevent complications
- Interventions for lung and heart disease: corticosteroids, inhaled or oral antibiotics, preventive treatment for tuberculosis, phosphodiesterase inhibitors

- Investigation of neurocognitive deficits
- Screening and management strategies for chronic complications and long-term toxic effects appropriate for low-income settings<sup>88</sup>
- Implementation of human papillomavirus vaccination

#### *Reproductive and sexual health*

- Mother and child outcomes in individuals who have children: potential for high maternal mortality and risk of HIV to child
- Effectiveness of antiretroviral treatment for prevention of second-generation perinatal HIV transmission in view of the potential for transmission of HIV that is resistant to one or more classes of antiretroviral drug
- Strategies to reduce risky behaviour
- Strategies to prevent onward transmission—eg, male circumcision, health education, pre-exposure prophylaxis

#### *Psychosocial and mental health*

- Strategies directed at health providers, families, teachers and HIV-infected adolescents to manage stigma
- Providing life-skills and vocational support
- Optimum disclosure strategies<sup>161</sup>
- Age-appropriate and culturally valid screening and management of mental health problems

#### **Biomedical research**

##### *Host and viral attributes*

- Genetic and immunological correlates of slow progression of HIV infection
- Pathogenesis of chronic complications

## **Panel 2: Components of a comprehensive care package for HIV-infected adolescents**

### **Early identification of HIV infection and linkage to care**

- Strengthened facility-based testing: opt-out testing in inpatient and outpatient departments, and testing within sexual and reproductive health-care and primary-care services
- Family-based testing: testing all children whose parents and natural siblings are infected with HIV
- Integrated testing and care services—eg, tuberculosis care, sexual and reproductive health care, decentralised HIV care

### **Prevention and management of chronic complications**

- Timely institution of antiretroviral treatment
- Monitoring for chronic clinical complications: growth assessment, lung and cardiac function, learning disabilities, renal disease, dyslipidaemia
- Referral to clinical specialties for investigation and management of systemic complications
- Liaison with disability rehabilitation services
- Human papillomavirus vaccination and cervical screening after sexual debut

### **Psychosocial and mental health**

- Regular assessment of psychosocial status: schooling, guardianship, bereavement
- Screening and treatment for depression
- Counselling for caregivers of HIV-infected children
- Training for teachers about management of confidentiality and discrimination, and communication with caregivers
- Training for health-care workers about adolescent development and adolescent-centred counselling
- Attention to autonomy and confidentiality by health-care workers
- Linkage to community-based psychosocial support services
- Services to address sexual abuse and economic exploitation

### **Adherence support**

- Simplified antiretroviral treatment regimens: once-daily dosing, fixed-drug combinations
- Education about antiretroviral treatment using age-appropriate methods



- Counselling that uses a problem-solving approach and addresses psychosocial context
- Use of peer or paraprofessional treatment supporters
- Use of reminder devices and communication technologies with an interactive component

**Sexual and reproductive health**

- Screening for sexually transmitted infections after sexual debut
- Training on condom use, and provision of condoms and contraception
- Age-appropriate counselling on family-planning and prospects of having children

**Disclosure of HIV status**

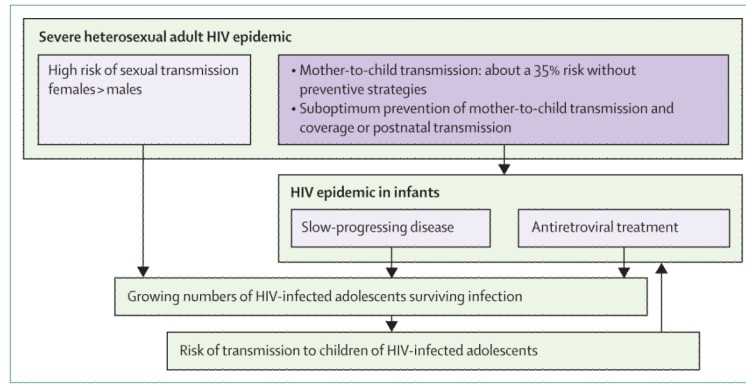
- Timely and developmentally appropriate disclosure of HIV status
- Ongoing post-disclosure support
- Joint involvement of health-care workers and caregivers in disclosure process

**Transition from paediatric to adult care services**

- Liaison between paediatric and adult clinical staff before transition

### Search strategy and selection criteria

We searched PubMed for articles published from January, 1990, to September, 2013, with MeSH terms for HIV, Africa, and “adolescents”, and with MeSH and related terms for specific topic areas (eg, “disclosure”, “lung disease”). We also looked for relevant publications among our personal files and searched Google scholar and abstracts from meetings of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections. Articles resulting from these searches and relevant references cited in those articles were reviewed. We did not set any language limits.



**Figure 1.**  
Evolution of the paediatric HIV epidemic in sub-Saharan Africa



**Figure 2. Clinical manifestations of HIV infection in adolescents infected by perinatal transmission**

(A) Severe stunting in a 14-year-old boy (height-for-age Z score  $-3.5$ ). (B) Diffuse planar warts in a 13-year-old boy. (C, D) Deforming, non-infectious, seronegative arthritis in a 16-year-old boy. All patients and their guardians have provided their consent for pictures to be reproduced.