Adolescent antiretroviral management: Understanding the complexity of non-adherence

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This case-based discussion highlights challenges in adolescent antiretroviral management, focusing on non-disclosure of status and the subsequent impact of suboptimal treatment adherence. Despite the scale-up of antiretroviral therapy (ART) and recommendations made by the World Health Organization (WHO) for ART for all human immunodeficiency virus (HIV)-infected paediatric patients, ART coverage in adolescents lags behind that in adults. Challenges of sustaining lifelong ART in children and adolescents require consideration of specific behavioural, physiological and psychosocial complexities associated with this special group. To preserve future drug options and sustain lifelong access to therapy, addressing non-adherence to treatment is critical to minimising acquisition of ART drug resistance and treatment failure. We review the psychosocial and developmental components that influence the course of the disease in adolescents and consider the complexities arising from perinatal exposure to ART and the growing risk of transmitted ART drug resistance in high-burden resource-limited settings.


Case report

A 13-year-old male adolescent with severe respiratory distress presented to a medical outpatient department. He was admitted to the adult ward with suspected Pneumocystis jirovecii pneumonia. He was known to be HIV-infected and on antiretroviral therapy (ART) for approximately 10 years, with a CD4 count of 10 cells/μL (0.1%) and a viral load of 1.5 million copies/mL (Fig. 1).

On further enquiry, it was noted that his mother had died from an HIV-related illness when he was 3 years old; he was subsequently adopted by his maternal aunt. History of nevirapine exposure for perinatal exposure to ART and the growing risk of transmitted ART drug resistance in high-burden resource-limited settings.

As is common in our setting, the carer had not yet disclosed the patient’s HIV status on medication adherence, and the impact of non-adherence on acquisition of ART drug resistance.

We present a case that highlights the complexity of managing long-term adolescent survivors of HIV acquired through vertical transmission. We describe the impact of non-disclosure of HIV status on medication adherence, and the impact of non-adherence on acquisition of ART drug resistance.

Urgent unmet needs in adolescent HIV care include the challenge of lifelong ART, limited safe, effective and robust drug options, and lack of co-formulated antiretroviral drugs appropriate for once-daily dosing. While the development of a single-pill treatment regimen has resulted in high ART adherence and acceptability, with substantial improvements in quality of care in HIV-infected adults, this option is not yet available to children and adolescents.

What is the burden of disease in adolescents and children?

Globally, adolescence is defined as the period of development between the ages of 10 and 19 years, represents the fastest growing age group of HIV-infected people, and accounts for 5.9% of the burden of HIV. Approximately 2 500 of the 6 300 new HIV infections that
occur daily worldwide, are in adolescents and youth 15 - 24 years of age, while a third of these are in children <15 years owing largely to vertical transmission. Temporal trends analysis of adolescent HIV prevalence conducted between 2006 and 2012 in South Africa (SA), while showing decreases from 22.4% to 19.3% (15 - 24 age group), 13.7% to 14.4% (15 - 19 age group) and 28.0% to 24.2% (20 - 24 age group), still remains alarmingly high. The expanding disease burden among adolescents underscores the need for a greater understanding and suitable adaptation of HIV care and treatment services to adequately meet the needs of this patient population.

Notwithstanding unprecedented investments in ART scale-up and delivery in the past decade, published literature shows that adolescents are less likely to access HIV care and remain in care or achieve virological suppression. Despite guidance in the management of adolescent ART issued by the WHO in 2013 there have, however, been serious impediments to reducing delays in the initiation of appropriate ART, in supporting adherence to treatment and in retention of adolescents in care. Currently, approximately 90% of the estimated 3 million in care. Currently, approximately 90% of the estimated 3 million adolescents living with HIV globally reside in sub-Saharan Africa – only 27% of those who require ART receive it. Furthermore, in SA only 45% of the 369 000 HIV-infected children aged 10 - 14 years, and 14.3% of the 720 000 aged 15 - 24 years, currently receive ART. This may be due to HIV-exposed children often not receiving conclusive HIV test results, poor linkage to appropriate paediatric care, and lack of facilities that specifically cater for children.

As in adults, the benefits of ART in HIV-positive children and adolescents include a decreased risk of death, improved growth, better immune function, and a marked reduction in infectious complications. The benefits and risks need to be considered in the context of safe and sustainable therapeutic options for lifelong ART. In 2013, WHO HIV guidelines recommended that adult ART regimens and dosing schedules be applied to adolescents >35 kg. These recommendations did not take into consideration the pubertal changes and growth delays that affect ART metabolism, a lack of clarity guiding the timing of transition from weight-based to age-based dosing, and a lack of efficacy and safety data on co-formulated agents. HIV resistance in children occurs as transmitted drug resistance (TDR), which is either vertical (from mother to child) or horizontal (through a sexual partner), or has been acquired, and results from poor ART adherence.

The US Reaching for Excellence in Adolescent Care and Health (REACH) study evaluating disease progression, which was conducted in HIV-positive adolescents infected through sexual behaviour or injection drug use, found that only 41% of adolescents aged 12 - 19 years reported >95% adherence to ART. Factors associated with poor adherence included depression, pill burden, advanced HIV status, alcohol use, and dropping out of school. In addition, Murphy et al. reported that only 28.3% of adolescents reported >95% adherence in the previous month. Barriers to adherence included ART toxicity and complications with regard to integrating pill-taking with day-to-day routines. In another US study, the Pediatric AIDS Clinical Trial Group (PACTG) 381, of 120 adolescents (aged 11 - 22 years) infected via high-risk behaviour and receiving triple ART therapy, only 44 (37%) stayed on study treatment for the 3 years of observation. Twenty-nine (24%) reached and maintained viral suppression, and poor adherence was the main predictor of virological failure.

With increases in the number of adolescents on ART, sustaining optimal ART adherence has emerged as a major challenge to maintaining ongoing AIDS-free survival and prevention of sexual transmission for this group. Antiretroviral regimens are often complex, require good adherence for efficacy, and may lead to the development of viral resistance due to treatment non-adherence (defined as < 95% of medication taken, or >1 missed dose per week) or suboptimal levels of antiretroviral agents.

Furthermore, in many HIV-endemic resource-limited settings, the future impact of perinatal HIV transmission strategies, including nevirapine or zidovudine mono- or dual therapy on acquisition of resistance to non-nucleoside-based first-line ART regimens, has not been fully quantified. Our case highlights themes that have already emerged from the literature in developed countries. A meta-analysis
CONTINUING MEDICAL EDUCATION

Recent ART scale-up in SA has allowed more people to access care, but may inevitably engender HIV drug resistance, thereby limiting the benefits of treatment. Increases in paediatric HIV drug resistance in resource-limited settings have been driven by limited access to routine viral load monitoring, limited availability of paediatric drugs for second-line therapy and complexities related to PMTCT, paediatric care and ART adherence, as seen in the presented case.

A recently published review of drug-resistant mutation prevalence rates after first-line ART failure among children in resource-limited settings, showed mutation rates of 80% for NRTIs, 88% for NNRTIs and 54% for boosted protease inhibitors.

A survey conducted in 18 African countries reported an increase in TDR, primarily driven by NNRTI resistance, with moderate levels of TDR (5 - 15%) being documented in KwaZulu-Natal.

This is of concern, as this drug class forms the backbone of first-line ART regimens and prophylaxis for PMTCT.

What are the research gaps in understanding ART resistance in children?

HIV-infected children and adolescents remain at high risk of disease progression and death. Insufficient attention has been directed towards the creation of specialised centres offering HIV testing and care. Evaluating the impact of services that prioritise the needs of children and adolescents in care on long-term ART adherence and retention is warranted. SA has recently celebrated tremendous success in improving PMTCT, offering all HIV-infected pregnant women immediate ART access. This implies that most children who were exposed to HIV during the perinatal period have also been exposed to maternal ART. The magnitude of HIV prevalence in the sexually active age group and the growing risk of transmitted ART resistance emphasise the need for research into the use of pre-ART resistance testing in children and adolescents initiating or changing ART.

Observation of acquisition rates of ART resistance is especially important to inform future drug sequencing, especially in high-burden settings offering a programmatic approach.

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