Chronic comorbidities in children and adolescents with perinatally acquired HIV infection in sub-Saharan Africa in the era of antiretroviral therapy

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Globally, 1·7 million children are living with HIV, of which 90% are in sub-Saharan Africa. The remarkable scale-up of combination antiretroviral therapy has resulted in increasing numbers of children with HIV surviving to adolescence. Unfortunately, in sub-Saharan Africa, HIV diagnosis is often delayed with children starting antiretroviral therapy late in childhood. There have been increasing reports from low-income settings of children with HIV who have multisystem chronic comorbidities despite antiretroviral therapy. Many of these chronic conditions show clinical phenotypes distinct from those in adults with HIV, and result in disability and reduced quality of life. In this Review, we discuss the spectrum and pathogenesis of comorbidities in children with HIV in sub-Saharan Africa. Prompt diagnosis and treatment of perinatally acquired HIV infection is a priority. Additionally, there is a need for increased awareness of the burden of chronic comorbidities. Diagnostic and therapeutic strategies need to be collectively developed if children with HIV are to achieve their full potential.

Introduction

The HIV pandemic has been established for 40 years and, in 2018, 1·7 million children (aged <15 years) worldwide were estimated to be living with HIV, of which 90% were in sub-Saharan Africa. Most children with HIV have been infected by mother-to-child transmission.[1] Because of the remarkable scale-up of effective interventions that prevent mother-to-child transmission, the number of perinatally acquired HIV infections decreased from 280 000 in 2010 to 160 000 in 2018.[1] Additionally, access to combination antiretroviral therapy (ART; a combination of three drugs leading to durable viral suppression) has expanded globally over the past decade, resulting in a substantial decline in mortality and an increased life expectancy in children with HIV. Thus, escalating numbers of children, who would previously have died in infancy and early childhood from untreated HIV infection, are now surviving to adolescence.[2] HIV has therefore changed from a life-threatening illness to a chronic, treatable, albeit incurable, condition.

Key messages

- Despite antiretroviral therapy, long-standing HIV infection in children is associated with multisystem chronic comorbidities, particularly in sub-Saharan Africa where HIV treatment initiation is often delayed and occurs much later in childhood than in high-income settings
- Chronic morbidities in children with HIV are driven by underlying dysregulated immune activation associated with HIV infection, or are a sequela of infections or HIV treatment, or both
- HIV programmes have predominantly focused on delivery of antiretroviral therapy and much less attention has been paid to diagnosis and management of chronic comorbidities
- Validated tools for screening and diagnosis and evidence-based interventions for prevention and treatment of comorbidities need to be developed
- As well as earlier initiation of antiretroviral therapy, HIV care programmes need to identify and address the additional health needs of children with chronic complications, including educational support, rehabilitation, nutrition, psychosocial, and mental health support, if children with HIV are to have optimal health outcomes

In high-income countries, adults on ART with well controlled infection have shown a range of comorbidities, including cardiovascular, renal, neurocognitive, and lung disease, which have been described and termed non-AIDS-defining illnesses. These comorbidities contrast with the opportunistic infections and malignancies that occur at advanced stages of HIV disease due to HIV-mediated immunosuppression. Likewise, there is now increasing recognition that children with HIV, including those taking ART, are at risk of developing chronic multisystem comorbidities and concomitant disability.[3,4] Some reports have suggested a trend from infectious events to non-infectious morbidities associated with inflammation, immunodeficiency, and drug toxicity as these children age.[5]

Many of these comorbidities will be driven by underlying inflammation associated with HIV infection. The spectrum of comorbidities in children might differ from that in adults, most likely related to the timing of HIV infection or ART initiation, or both, and the absence of traditional adult risk factors such as ageing, smoking, and drinking alcohol. Furthermore, there could be differences in the epidemiology of comorbidities in children with HIV in different settings. In high-income settings, combination ART became available in 1996, whereas in much of sub-Saharan Africa, paediatric ART was introduced after 2004. Additionally, children with HIV in sub-Saharan Africa start ART much later than

those in high-income settings. In a global meta-analysis of children who entered HIV care before 10 years of age, the age at ART initiation in Africa was 7·8 years compared with 0·9 years in the USA.[6]

In this Review, we discuss the spectrum of chronic morbidities in children growing up with HIV, focusing on studies in sub-Saharan Africa, the likely pathogenesis underlying the development of comorbidities, the implications for HIV care and management, and implications for HIV programmes that have largely focused on ART delivery until now.

Chronic comorbidities related to HIV

Chronic lung disease

Although the incidence of acute pulmonary infections in children with HIV has declined in the past decade because of co-trimoxazole prophylaxis and ART, several studies have reported a substantial burden of chronic respiratory symptoms and signs in children growing up with HIV who are taking ART. Symptoms and signs include cough, breathlessness, reduced exercise tolerance, hypoxia,[7–9] and reduced lung function (predominantly airflow obstruction with little reversibility with bronchodilators).[10,11] These findings have been reported in the context of delayed HIV diagnosis and initiation of ART in late childhood.

High-resolution CT studies in children with HIV show decreased attenuation in a mosaic pattern as the predominant radiological finding with or without bronchiectasis (figure 1).[12,13] Notably, radiological findings consistent with lymphoid interstitial pneumonitis, the most common cause of chronic lung disease in children with HIV in the pre-ART era, have become rare in the ART era (from around 2004, when ART began to become available in Africa).[12,14] Decreased attenuation correlates strongly with reduced forced expiratory volume in 1 s (FEV_1) and, together with hypoxia and irreversible airflow obstruction, these findings are consistent with constrictive obliterative bronchiolitis.[12] Obliterative bronchiolitis is characterised by inflammation of the bronchiolar epithelium, leading to dense fibrous scarring with small airway obstruction, complicated by recurrent infections and bronchiectasis. This condition has been described following severe lower respiratory tract infections in children, often with adenovirus and more commonly in the southern hemisphere than in the northern hemisphere.[15] A South African study showed that radiological features of obliterative bronchiolitis were associated with a history of tuberculosis or severe pneumonia.[13] Plain chest radiography is insensitive for small airways disease: a definitive diagnosis usually requires high-resolution CT,[12] which is rarely available in low-income settings. Bronchiectasis is another irreversible cause of chronic lung disease in children with HIV and can occur as a sequela of lymphoid interstitial pneumonitis, recurrent pulmonary infections including tuberculosis, and possibly HIV infection itself.[16]

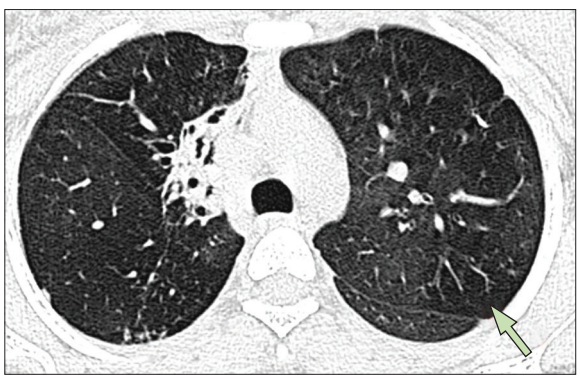

Figure 1: **High-resolution CT scan of the lungs in a child with HIV**
Bilateral black and white lung pattern characteristic of mosaic attenuation, with decrease in the number and calibre of vessels (arrow). There is also atelectasis on the right and bronchiectasis.

Reports of paediatric chronic lung disease associated with HIV mainly come from low-income settings. This difference in reporting might be due to a high prevalence of risk factors in these settings, including recurrent pulmonary infections in early life, delayed ART initiation, household air pollution, malnutrition, and stunting.[17] Malnutrition during the first year of life might be associated with decreased lung function at 1 year of age, and stunting is a marker of delayed somatic growth, therefore, it is possible that stunted children could have smaller lungs and reduced lung volume.[18]

Importantly, lung impairments and decreased lung function in childhood track through adult life and therefore pulmonary injuries in childhood not only prevent an individual from reaching full lung potential but also increase the risk of chronic lung disease in adult life (figure 2A).[19,21] A South African study showed that lung function tracked over 2 years in adolescents with HIV (aged 9–16 years) who were well established on ART.[10] In this study, early life pulmonary tuberculosis or previous admission to hospital for lower respiratory tract infections were associated with reduced lung function.

Availability of diagnostic modalities for chronic lung disease, such as spirometry and high-resolution CT, is scarce in low-income settings. Therefore, chronic respiratory symptoms are often empirically treated with repeated antibiotics and antituberculosis therapy in settings where there is a high prevalence of HIV and tuberculosis is common. The pathogenesis of chronic lung disease associated with HIV is poorly understood and the disease is without specific management guidelines. However, prevention of pulmonary infections can mitigate the burden of chronic lung disease in children with HIV and optimise lung health. Pulmonary infections can be prevented by ensuring routine vaccinations (including pneumococcal conjugate vaccine and annual influenza vaccine),[22] early ART initiation, continued co-trimoxazole prophylaxis and use of isoniazid prophylactic therapy, avoidance of exposure to tobacco smoke and indoor air pollution, and optimisation of nutrition.

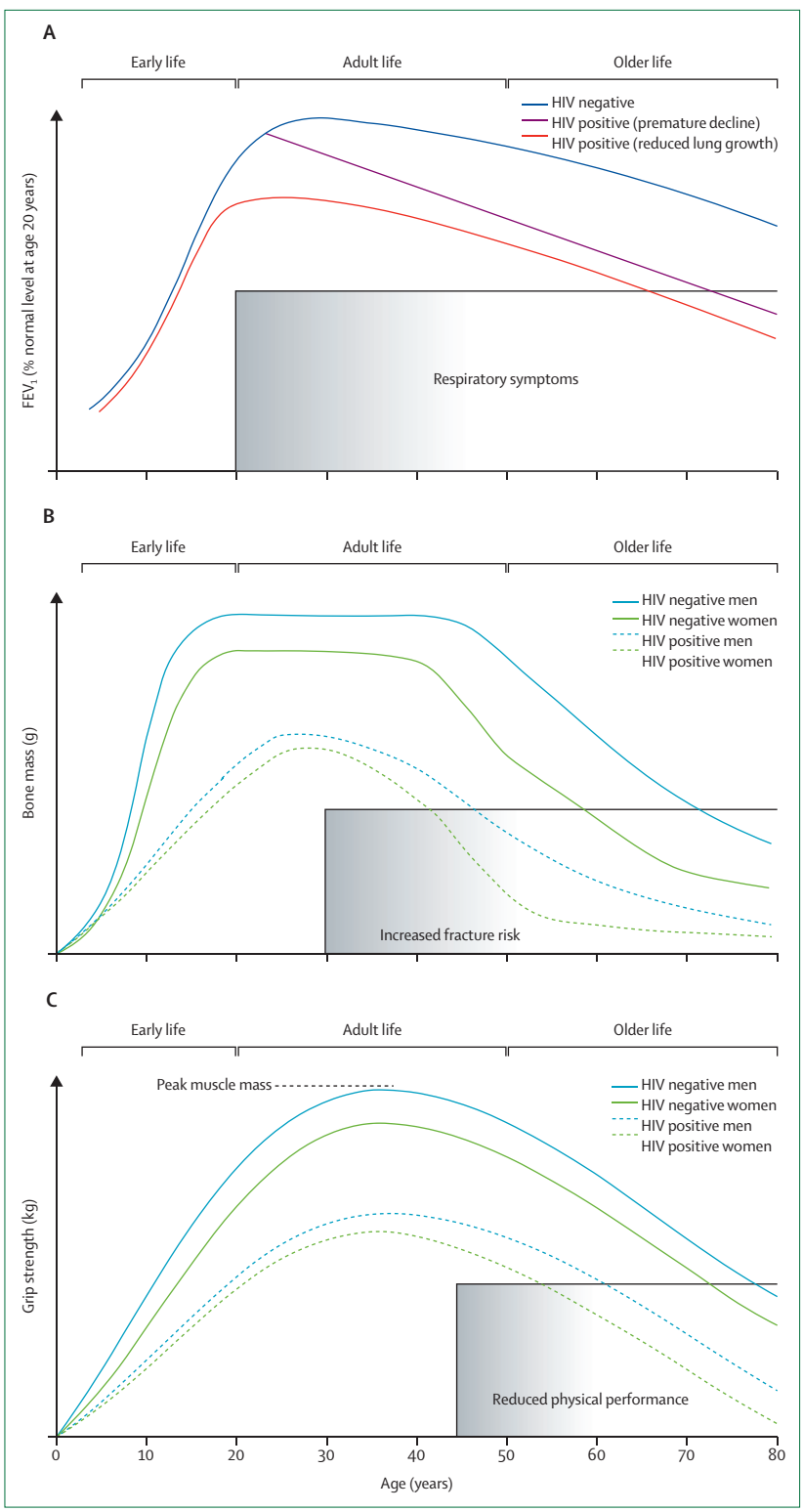

***Figure 2*: Hypothesised effect of HIV infection across the life-course**
(A) Respiratory function (adapted from Weiss).[19] (B) Bone mass (adapted from Arpadi et al).[20] (C) Muscle strength.

Cardiovascular disease

Studies from low-income countries have reported a high burden of cardiac abnormalities associated with HIV in children with HIV taking ART. Prevalence estimates from these studies are wide, ranging between 14% and 89%, most likely reflecting differences in measurements and in the selection of participants.[23–25] The spectrum of abnormalities includes left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, left atrial dilatation, isolated right ventricular dilatation, conduction abnormalities, and in some cases, pericardial thickening or effusion (figure 3).[24–26] In a South African cohort of adolescents with HIV (aged 9–14 years), right ventricular dysfunction was the most common form of cardiopulmonary dysfunction; cardiopulmonary dysfunction was associated with lower body-mass index, height, and previous history of pulmonary tuberculosis compared with adolescents who did not have HIV.[27] Notably, in most studies, children were paucisymptomatic. A prospective study in Zimbabwean children with HIV on ART reported the incidence of left and right echocardiographic abnormalities as 3·52 and 5·64 per 100 person-years, respectively.[28] This study also reported that most abnormalities persisted at 18 month follow-up but children were either asymptomatic or their symptoms had not worsened.[28]

Much less attention has been given to assessment of vascular disease in children with HIV than the attention given to cardiac disease in these children, although there is evidence from high-income countries that HIV and ART, particularly regimens that are protease inhibitor based, are associated with subclinical atherosclerosis even in young individuals.[29] A South African study reported an increased risk of endothelial dysfunction in adolescents with perinatally acquired HIV compared with their age-matched peers who were HIV-negative.[30] Traditional risk factors for cardiovascular disease, including age, hypertension, smoking, and lipid abnormalities, do not play a substantial role in this age group, and HIV or ART, or both, might therefore play a larger role in the pathogenesis of cardiovascular disease.

The natural history and clinical significance of cardiovascular abnormalities are not clear. In contrast to findings from sub-Saharan Africa, a study from the USA reported a decline in rates of cardiomyopathy in the era of ART.[31] The underlying mechanistic pathways of cardiovascular abnormalities are not understood and the abnormalities reported could reflect impairment acquired before ART initiation. Surveillance and studies to investigate pathogenesis and progression are needed to understand whether these abnormalities are likely to result in an increased risk of premature cardiovascular disease as adolescents with HIV enter adulthood.

Renal and metabolic disease

Microalbuminuria is an early marker of glomerular injury and predicts further proteinuria development.

Two studies from Tanzania and South Africa reported a variable prevalence of 20% (49 of 240) and 8% (43 of 511), respectively, for microalbuminuria in children with HIV.[32,33] The children in the Tanzanian study were younger and more immunosuppressed than the children in the South African study, and microalbuminuria was strongly associated with immunosuppression and haematuria.[32] Notably, African people often carry *APOL1* variants G1 and G2, which are associated with increased odds of early renal disease, with HIV infection substantially augmenting the risk.[34]

Tenofovir disoproxil fumarate is associated with an adverse effect on renal function and wasting of low molecular weight proteins, phosphate, and glucose. Although slowly progressive, chronic kidney disease is uncommon.[35] Hyperphosphaturia secondary to tubular dysfunction can disturb renal-bone metabolic regulation, leading to progressive bone loss and hypophosphataemic osteomalacia, as observed in Fanconi syndrome.[35]

Older ART drugs, such as stavudine, didanosine, and early generation protease inhibitors, were associated with abnormal fat distribution (lipodystrophy or lipoatrophy). Although the newer ART regimens are less toxic, children with HIV with established lipid abnormalities or abnormalities in fat distribution show little improvement from switching to newer, less toxic ART.[36] ART is also associated with dyslipidaemia and insulin resistance; however, data are sparse for children with HIV in sub-Saharan Africa. A South African study of children who attended HIV clinics on either a lopinavir and ritonavir or efavirenz based ART regimen (with 90 [90%] of 100 having taken stavudine previously) reported a 10% (10 of 96) prevalence of insulin resistance using the homoeostatic model assessment of insulin resistance (HOMA-IR) index, and similar prevalence of dyslipidaemias.[37] Overall, 40% (38 of 96) had either insulin resistance or at least one lipid abnormality. The adjusted mean LDL cholesterol increased by 0·24 mmol/L for each year of cumulative lopinavir and ritonavir exposure. Notably, the median body-mass index of participants was only 15·1 kg/m² (IQR 14·4–16·0) in children on lopinavir and ritonavir and 15·5 (IQR 14·6–17·0) in children on efavirenz where the healthy range is 18·0–24·9 kg/m². In a trial comparing three different regimens based on nucleoside reverse transcriptase inhibitors in children starting ART in Uganda, HOMA-IR score increased significantly in all three groups 48 weeks after ART initiation, and this increase correlated with monocyte activation.[38] Similarly, in another study, abacavir was associated with increased HOMA-IR score in adolescents.[39] Although the long-term effects of the renal and metabolic abnormalities reported in cross-sectional studies are not known, insulin resistance, dyslipidaemias, and abnormal fat distribution are recognised risk factors for cardiovascular disease, hence monitoring is required. Switching to newer protease inhibitors, such as atazanavir or darunavir, in children taking lopinavir might improve lipid profiles.[40]

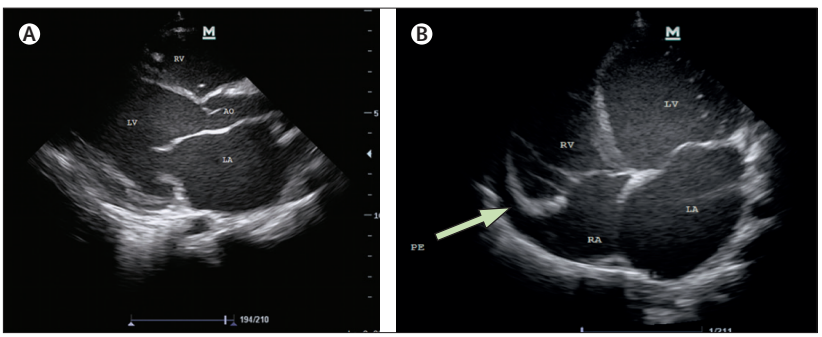

Figure 3: **Echocardiogram of a girl aged 12 years with HIV**
(A) Parasternal long axis view. (B) Apical four-chamber view showing pericardial effusion. AO=aorta. LA=left atrium. LV=left ventricle. RA=right atrium. RV=right ventricle. PE=pericardial effusion.

Musculoskeletal disease

HIV infection is associated with impaired growth, manifested as stunting (impaired linear growth) and as delay of pubertal onset by up to a year.[41,42] Stunting is more profound in children with HIV in low-income settings than in those in high-income settings, most likely reflecting high background rates of undernutrition and intercurrent infections in children with HIV from low-income settings.[43]

Impaired growth could have a deleterious effect on musculoskeletal development and health across the life course. Puberty is a crucial period for musculoskeletal development and bone mass accrual. After cessation of linear growth and skeletal maturation, bone mass reaches a peak,[44] after which bone mass declines at varying rates throughout adulthood (figure 2B). Peak bone mass accounts for 60% of lifetime osteoporosis risk,[45] with a 10% decrease in peak bone mass doubling the risk of adult fracture.[46] Pubertal delay predicts lower adult bone mass and increases future osteoporotic fracture risk.[47] A systematic review of 32 studies reported an increased prevalence of low bone density in children with HIV, and that HIV appeared to be associated with decreased bone accrual throughout childhood and adolescence.[20] However, most studies were in high-income settings and varied with respect to comparison groups, methods of measurement, and adjustment for body size or growth retardation. A Zimbabwean study showed reduced size-adjusted (Z score ≤–2·0) lumbar spine bone density in 14% (14 of 97) and reduced total body less head bone density in 12% (12 of 97) of children with HIV aged 8–16 years taking ART.[48] Notably, this study used gold standard size-adjustment methods to analyse dual x-ray absorptiometry scans, which if ignored, underestimate bone density in stunted children.[49]

Certain ART drugs such as tenofovir disoproxil fumarate can cause accelerated bone loss most likely aggravated by low body mass and vitamin D deficiency.[35] Although studies have reported an association between

tenofovir disoproxil fumarate and lower bone density in children with HIV, this association might not be sustained in the long term and longitudinal studies from sub-Saharan Africa are needed to determine the effect of tenofovir disoproxil fumarate on bone health in children.[35,48,50] Additional factors that are prevalent in children with HIV can further compromise bone health, including low muscle mass, poor nutrition, inadequate dietary calcium, vitamin D deficiency, and the pro-inflammatory milieu associated with HIV.[51–53] Muscle strength and bone strength are closely related; muscles exert forces on bone resulting in bone adaptation in size and strength.[54] HIV infection and consequent ill health could reduce physical activity levels, impairing muscle strength (figure 2C) and skeletal impact loading, and thus bone development.[55]

Although growth resumes after ART initiation, children who have more profound stunting and begin ART in late childhood have a delayed growth spurt and are typically unable to reach their height potential.[43,56,57] Age at ART initiation is an important predictor of bone density. In the Zimbabwean study, children with HIV starting ART after the age of 8 years had, on average, at least 1 standard deviation lower size-adjusted lumbar spine bone density.[48] This level of bone density reduction doubles fracture risk in adults.[58] Given the late average age at ART initiation of CWHIV in sub-Saharan Africa, these findings are concerning.[6]

Neurodevelopmental delay, neurocognitive disease, and mental health

In the pre-ART era, severe neurodevelopmental delay and HIV encephalopathy were common in children with HIV; the prevalence of neurocognitive impairment associated with HIV has declined in the ART era. Early ART initiation and viral suppression in infancy improves neurocognitive outcomes.[59] However, children with HIV who start ART outside infancy can have subtle to severe neurocognitive deficits. A prospective study of children aged 5–11 years from four countries in sub-Saharan Africa compared neuropsychological outcomes in children with HIV, children who had been exposed to HIV but were not infected, and children who had not been exposed to HIV. This study reported that children with HIV did worse in all cognitive domains than did the other two groups. More than 95% (239 of 246) of children with HIV had a suppressed HIV viral load and good immunological status (CD4 percentage greater than or equal to 25%), but only 1% (3 of 246) started ART in the first 6 months of life.[60]

An MRI study found that white matter structural abnormalities occur early after birth, and ART initiation by 8 weeks of age might be too late to prevent white matter abnormalities associated with HIV in the CNS.[61] Second-line ART, a high HIV viral load, low CD4 cell count, and poor cognitive function were associated with poor white matter integrity, measured by diffuse tensor imaging in children with HIV in a South African study.[62] A meta-analysis showed an association between HIV infection in children and adolescents and neurocognitive impairment, mainly in the domains of working memory, executive function, and processing.[63] This study also showed evidence of deficits in visual memory and visual-spatial ability. Geographical bias was notable, with only a third of studies coming from sub-Saharan Africa. The causes of neurocognitive impairment despite effective ART are likely to be multifactorial, including ongoing viral replication in the CNS and resulting neuro-inflammation, irreversible CNS injury before ART, and neurotoxic effects of ART; and could be compounded by socioeconomic and psychosocial factors.[64] Children with neurocognitive impairment can appear asymptomatic with deficits missed by routine testing. Screening tools and standardised definitions that are context-specific and have been culturally validated are scarce. However, a study in South Africa in 2019 has validated a youth international HIV dementia screen.[65]

Several studies report a high prevalence of mental health disorders in children and adolescents with HIV. A large, Ugandan study that recruited more than 1300 children and adolescents with HIV reported a 17·4% (233 of 1339) prevalence of any psychiatric disorder and a 9·6% (128 of 1339) prevalence of a behavioural disorder, most commonly attention deficit hyperactivity disorder. These disorders were more common in adolescents than in children and commonly occurred concurrently with each other.[66] Similarly, a South African study reported that adolescents with HIV had poorer functional competence, self-concept, and motivation; and higher levels of depression, disruptive behaviour, attention-deficit hyperactivity disorder symptoms, and clinically significant anger, compared with their peers who were HIV-negative.[67] Children with HIV face recurrent and cumulative psychosocial stressors that differ from other chronic childhood illnesses, such as stigma and discrimination, responsibility for welfare of siblings or other family members who are ill, illness and the death of their parents, and unstable guardianship. These stressors can hamper development of protective mechanisms and leave children psychologically vulnerable and ill-equipped for coping with challenges, most likely increasing the risk of mental health disorders.[67–69] It is possible that the neuropathological effects of HIV infection could augment risk.[70] Mental health disorders affect an individual's adherence to ART and are associated with an impaired quality of life, yet they typically receive little attention in the face of physical health concerns.

Malignancy

As children with HIV reach adolescence and become sexually active, they are at risk of acquiring human papillomavirus (HPV) infection, with certain subtypes (for example, HPV 16 and HPV 18) known to cause cervical cancer. The risk might be higher in those with

HIV; in an Asian study in Thailand and Vietnam, perinatally infected adolescent girls had a higher prevalence of high-risk HPV and abnormal cervical cytology than adolescents who were not infected, after adjusting for age, sexual history, and pregnancy.[71] In a Kenyan study, the quadrivalent HPV vaccine was safe and highly immunogenic in boys and girls with HIV.[72] WHO recommends a three-dose series (at months 0, 1–2, and 6) for girls with HIV rather than the standard two dose series (given to immunocompetent girls younger than 15 years old), following studies that showed lower antibody titres after HPV vaccination in women with HIV compared with women who were not infected.[72,73] However, HIV testing before vaccination is not recommended, which could mean that adolescents with HIV miss the third dose if vaccination programmes are implemented in schools.

Children with HIV with advanced immunosuppression before ART initiation, or who started ART at an older age, have an increased risk of cancer compared with those with modest immunosuppression or who began ART in infancy.[74] Reliable incidence estimates of cancer in children with HIV are difficult to generate as many cancer registries do not report HIV status, and cancer incidence varies according to regions and study periods. Linked data from five paediatric ART programmes and four paediatric oncology units in South Africa showed an overall incidence of cancer of 82 per 100 000 person-years. The most common cancers were Kaposi's sarcoma with an incidence of 34 per 100 000 person-years and non-Hodgkin lymphoma with an incidence of 31 per 100 000 person-years.[75] The risk of developing cancer was reduced by 70% for children on ART, however, risk increased with age at start of treatment and immunodeficiency at enrolment. The risk of Kaposi's sarcoma is limited to children with HIV in, or from, sub-Saharan Africa. A study reported Kaposi's sarcoma incidence per 100 000 person-years of 81 in children from sub-Saharan Africa living in Europe, 86 in those in Eastern Africa, and 11 in those in southern Africa. There were no cases of Kaposi's sarcoma in Europe and Asia in children who were not from sub-Saharan Africa.[76] Data from Malawi suggest that incidence of Kaposi's sarcoma is increasing. The average annual number of new Kaposi's sarcoma diagnoses was 18 cases per year from 2006 to 2010, increasing to 25 cases per year from 2011 to 2015, despite improved access to ART.[77] Although this rise could be explained by increased awareness and detection, it is also possible that the cumulative risk of malignancy increases with age even in the era of ART. An older study from the USA, which followed up children for 10 years, showed that although the incidence of Kaposi's sarcoma and non-Hodgkin lymphoma decreased in the ART era, the risk of developing non-AIDS-defining cancers did not.[78] This increased risk of non-AIDS-defining cancers highlights the need for continued monitoring of children growing up with HIV. Access to comprehensive cancer services is scarce in most low-income settings and mortality is high.

Other comorbidities

Additionally, there are other comorbidities that are common in children with HIV, such as visual and hearing impairments and dental disease even in the ART era.[79–82] Skin disease (eg, seborrhoeic dermatitis, eosinophilic folliculitis, planar warts, and molluscum contagiosum) is severe and atypical in children with HIV, with children responding less well to treatment and relapsing more frequently than children who are not infected with HIV. Although incidence has declined in the ART era, skin conditions related to HIV are one of the most common management problems faced by health-care workers caring for children with HIV. ART is associated with risk of drug reactions and immune reconstitution inflammatory syndrome skin disease (unmasking of a new skin disease or paradoxical worsening of existing dermatological conditions).[83] These conditions receive little attention as they are not life-threatening. However, they can lead to complications and disability, reduced quality of life, and frequent clinic attendances, which place an additional burden on health services.

Pathogenesis of chronic comorbidities

The mechanisms underlying comorbidities associated with perinatally acquired HIV infection are largely unknown. Some of the underlying mechanisms might be shared with those reported in adult HIV infection, whereas others could be unique to the paediatric age group, in keeping with the distinct clinical features observed in this age group. Pathogenic mechanisms might also differ between populations in high-income and low-income settings.

In adults, the development of comorbidities associated with HIV is thought to be related to levels of persistent immune activation, predominantly reflecting activation of monocytes and macrophages, rather than activation of T cells.[84] Various biomarkers that are associated with adult comorbidities have been described, largely in cross-sectional studies.[85] These include inflammatory markers, such as IL-6, soluble tumour necrosis factor receptors 1 and 2 (soluble TNFR-1 and soluble TNFR-2), interferon-inducible protein 10 (IP10), and high sensitivity C-reactive protein; markers of monocyte activation, such as soluble CD14 and CD163; markers of indoleamine 2,3-dioxygenase-1 activity (IDO-1); markers of coagulation risk, particularly D-dimer levels; and markers of gut barrier dysfunction, such as zonulin and intestinal fatty acid binding protein. Tracking rising levels of these biomarkers in longitudinal studies better predicted the development of non-AIDS-defining illnesses than taking a single value at recruitment.[86] These findings suggest that impaired function of the gut barrier leads to translocation of microbial products from the gut into the circulation, where they activate

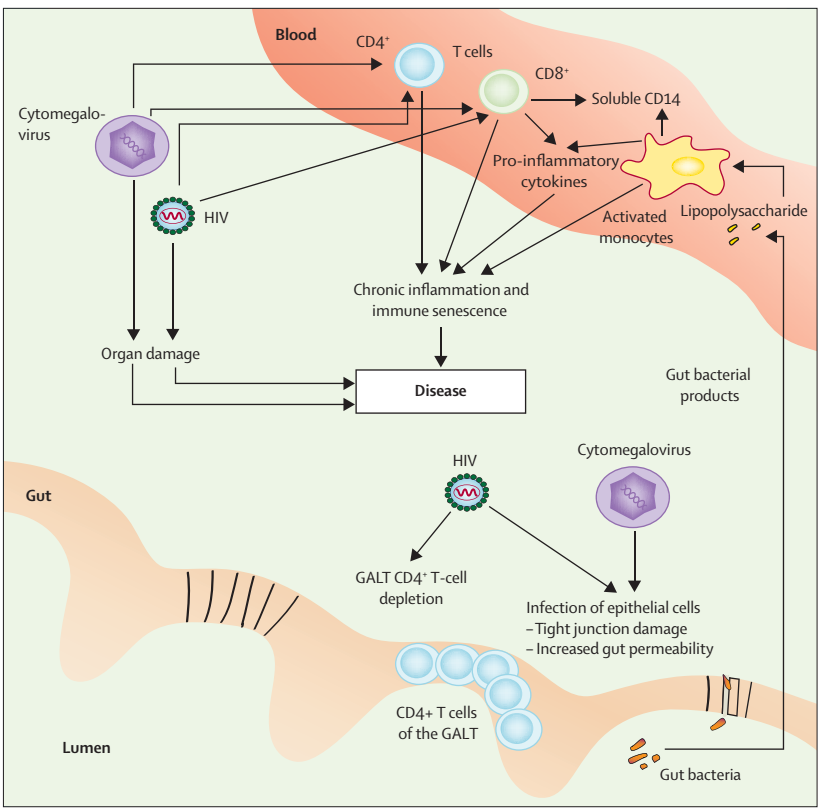

Figure 4: **Pathogenesis of comorbidities associated with HIV**
GALT=gut-associated lymphoid tissue.

monocytes and macrophages, initiating a cycle of chronic inflammation (figure 4).[85] This cycle appears to be related to the activation of a specific subset of inflammatory monocytes that express tissue factor: these monocytes can secrete high levels of pro-inflammatory cytokines and trigger the coagulation cascade, so are particularly implicated in coagulopathy associated with HIV.[87]

Additional factors that contribute to inflammation include vitamin D deficiency and cytomegalovirus co-infection.[88] Vitamin D deficiency is associated with immune activation levels in individuals with HIV, potentially mediated through its immunomodulatory effects on populations of monocytes and macrophages, dendritic cells, and B and T lymphocytes.[89] A trial of vitamin D supplementation in children with HIV who were deficient of vitamin D and well controlled on ART, led to significant reductions in both T-cell and monocyte activation.[90]

The relationship between comorbidities and cytomegalovirus infection is difficult to disentangle, as almost all individuals with HIV have cytomegalovirus co-infection. However, in the few studies that include people with HIV who were negative for cytomegalovirus, people with HIV and cytomegalovirus co-infection had higher plasma levels of IP-10, TNFR-2, and D-dimer,[91] and an increased risk of non-AIDS-defining illnesses, particularly cardiovascular and cerebrovascular disease.[92] Cohort studies have shown associations between inflammatory markers (which in turn are linked with the subsequent development of comorbidities) and the scale of immune response specific to cytomegalovirus (IgG concentration[93,94] and magnitude of T-cell response[95]). This suggests that subclinical cytomegalovirus reactivation or replication, or both, is reflected in elevated immune responses: however, it is important to control for ageing in these studies.[96] For children with HIV in low-income settings, especially when HIV diagnosis and ART initiation is delayed, primary cytomegalovirus infection most likely occurs in infancy at a time of uncontrolled HIV replication. African children acquire cytomegalovirus infection early in life, primarily through breastmilk exposure: studies in The Gambia showed 85% (239 of 281) of infants had acquired cytomegalovirus by 12 months of age, reaching 100% by 18 months.[97] Thus, their situation is distinct from that of adults who mainly acquire HIV after cytomegalovirus infection and would already have generated immune responses leading to viral control in the long term. Therefore, cytomegalovirus reactivation or reinfection might occur more frequently in children with perinatally acquired HIV who were diagnosed late, and could make a greater contribution to the pathogenesis of comorbidities. A study in Zimbabwe reported unexpectedly high levels of cytomegalovirus viraemia in older children with HIV.[98] The detection of cytomegalovirus DNA in plasma was associated with two of the major comorbidities described in older children (aged 6–16 years) with perinatally acquired HIV: chronic lung disease and stunting. Further studies are needed to determine whether similar findings are noted in other settings and if presence of cytomegalovirus DNA in the blood represents reactivation of latent infection or reinfection with new viral strains.

The other key difference between children and adults is the greater potential for lymphopoiesis with enhanced thymic and bone marrow activity: paediatric slow progressors are characterised by what was described as supranormal thymic activity.[99] However, thymic infection leading to impaired function can occur in a proportion of children with HIV, which is associated with significantly more rapid disease progression.[100] Several studies suggest that children with perinatally acquired HIV have markers of premature ageing,[101] including shorter telomere length,[102] distinct epigenetic features of ageing,[103] and accumulation of senescent (CD28 negative and CD57 positive) and exhausted (PD-1 positive) T cells.[102] In children with HIV with these markers, there are also features of thymic dysfunction,[102] which could potentially indicate HIV infection of the thymus, leading to an inadequate response to turnover of T cells driven by immune activation.

In summary, comorbidities in children with HIV are likely to reflect persistent immune activation and premature ageing of the immune system, potentially driven by infection in early life with cytomegalovirus and exacerbated by vitamin D deficiency in low-income

Panel: Addressing comorbidities associated with HIV in children and adolescents

Research priorities

- Epidemiology and clinical spectrum
- Pathogenesis
- Diagnosis and screening
  - Standard definitions of comorbidities based on population-specific normative ranges
  - When to start screening and frequency of screening
  - Age appropriate and culturally appropriate screening tools for mental health and neurocognitive disease
- Interventions for prevention and treatment
  - Preventive and therapeutic drugs—eg, antibiotics, antivirals, anti-inflammatory drugs, and vitamin D
  - Feasible and effective educational and mental health interventions
  - Interactions of drugs used for prevention or treatment, or both, with antiretroviral therapy
- Service delivery
  - How to integrate diagnosis and management of comorbidities associated with HIV within HIV services or maternal, newborn, and child health platforms, or both

Components of comprehensive HIV care

- Earlier initiation of antiretroviral treatment to prevent complications
- Monitoring growth, musculoskeletal, and neurocognitive development
- Screening for cardiac, lung, and renal disease
- Assessment of psychosocial status (schooling, guardianship) and mental health
- Management of common mental health disorders and psychosocial support
- Isoniazid and cotrimoxazole prophylaxis
- Optimal nutrition
- Catch up or revaccination according to WHO guidelines—eg, pneumococcal and influenza vaccination
- Human papillomavirus vaccination for adolescents
- Cervical cancer screening after sexual debut
- Referral to clinical specialties for management
- Liaison with disability and rehabilitation services
- School-based programmes to provide educational support
- Leverage existing early child development platforms for supporting children with HIV
- Linkage to community-based psychosocial support services

settings (figure 4). Interventions aimed at reducing inflammation, cytomegalovirus suppression, or vitamin D supplementation, or a combination, could have potential for control or even reversal of comorbidities and merit further study.

Recommendations for policy and research

Although access to paediatric ART has increased substantially in the past decade, coverage in children lags behind that in adults with about 54% of children with HIV accessing treatment in 2018 compared with about 62% of adults globally.[104] Timely diagnosis and treatment of HIV infection in children remains an essential priority.

In sub-Saharan Africa, there is a large cohort of children with HIV entering adolescence and adulthood that have had delayed ART initiation, and are at increased risk of multisystem impairments and earlier onset of comorbidities than are usually associated with ageing. To date, HIV care has mainly focused on delivery and sustainment of adherence to ART and there is an under-appreciation of the burden of multisystem comorbidities associated with HIV in children. Additionally, complex clinical issues place heavy demands on already over-stretched health-care systems, and optimum screening and management strategies are not well defined. In response to these issues, WHO convened two scoping meetings in 2014 and in 2019 to review available data and policies on management of major comorbidities associated with HIV, and evidence gaps in clinical management and programming.

Comprehensive HIV care should include diagnosis and management of comorbidities and consequent disability. The panel outlines suggestions for interventions and research priorities aimed at addressing comorbidities associated with HIV in children. In Africa, dedicated HIV services for children and adolescents are the exception rather than the rule. Provision of comprehensive HIV care will need to extend beyond centres of excellence to low-level health-care settings, integrate within existing HIV and maternal, newborn and child health platforms, and consider the physiological and psychosocial changes through childhood. Importantly, inclusion of guardians, teachers, and communities as equal partners will be crucial to optimally support children with HIV to achieve their full potential.

Search strategy and selection criteria

This is a descriptive review on comorbidities associated with HIV infection in children, informed by clinical experience and expert opinion. We searched PubMed for articles published from Jan 1, 2014, to July 31, 2019, with MeSH terms for HIV, Africa, and children and adolescents; and with MeSH and related terms for specific comorbidities (eg, cardiac disease and lung disease). We also looked for relevant publications among our personal files. We did not set any language limits. Articles resulting from these searches and relevant references cited in those articles were reviewed. The final reference list was generated on the basis of relevance to the broad scope of this review.

Contributors

RAF and LJF conceptualised and coordinated the Review. RAF wrote the chronic lung disease section with SR-J, and collated the manuscript. RAF and EDM provided clinical pictures. SR-J wrote the pathogenesis section. LJF wrote the malignancy section. CLG and RR wrote the musculoskeletal section. EDM and HJZ wrote the cardiac disease section. JH wrote the neurocognitive and mental health section with

input from LJF and RAF. JJ and CLG wrote the renal and metabolic disease section. WA and LM wrote the policy section with input from RAF and LJF. All authors, including All authors contributed to editing and approved the final version of the Review.

Declaration of interests

We declare no competing interests.

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