The next decade: cardiovascular risks, outcomes, prevention, and treatment in pediatric HIV infection

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Despite advances in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), the disease continues to be a global problem. As of November 2008, the United Nations Joint Programme on HIV/AIDS (UNAIDS) estimated 33.4 million people were living with HIV or AIDS worldwide, including 2.1 million children.[1] Effective prevention of mother to child transmission through antiretroviral therapies (ART) administered to the mother has lowered the prevalence of perinatal HIV in developed nations and increased access to ART is making a difference for survival and prevention in developing nations. For those children living with HIV/AIDS, ART has enhanced health status, delayed disease progression and improved mortality. In many regions of the world, HIV has transitioned from a life-threatening disease to a chronic illness. However, despite the effectiveness of these therapies on viral suppression and improved clinical outcomes, their toxicities, side effects and long-term sequelae must be acknowledged.

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In the current issue of Jornal de Pediatria, Werner et al. perform a multidimensional evaluation of cardiovascular risk[2] in HIV-infected children. They found that among 43 HIV-infected children evaluated cross-sectionally, over 88% had lipid abnormalities and about 14% had body shape changes consistent with lipoatrophy or lipohypertrophy. However, the effect of specific classes of ART was not assessed. Over 50% of the cohort consumed more than 120% of the recommended energy intake and over 60% of children had a sedentary lifestyle. Since there was no control group, HIV effects could not be distinguished from contemporary trends. Regardless, these findings are highly amenable to lifestyle interventions.

Nutrition has always been central in the care of HIV-infected children. Prior to the advent of highly active antiretroviral therapies (HAART), malnutrition was one of the most frequent and devastating complications of pediatric HIV that was predictive of both morbidity and mortality.[3] There is a well-defined association between nutrition, growth, and immune function in both children and adults (with and without HIV).[4] While HIV can directly impact nutritional status, there is a cyclical effect, as malnutrition can intensify the immunologic effects of HIV, thus leading to a downward vicious cycle of malnutrition, immune dysfunction and advancing HIV disease.[4] This increase in HIV-related mortality associated with malnutrition continues today in many regions of the world that lack adequate access to effective ART.

Yet, as Werner et al.[2] and others show,[5] HIV-infected children have developed concerning metabolic abnormalities that may predispose them to early cardiovascular disease: 1) altered body composition; 2) lipid abnormalities; 3) abnormal glucose metabolism; and 4) vascular abnormalities – all factors leading to increased risk of global cardiovascular disease – are manifestations of drug and HIV effects. These problematic side effects pose a challenge for managing treatment. Many metabolic abnormalities are linked to HAART and even the virus itself.

Changes in body fat were first reported in 1997 among HIV-infected adults on HAART.[6] Fat redistribution varies phenotypically from peripheral wasting of fat (lipoatrophy) in the face, extremities and buttocks to fat accumulation (lipohypertrophy) in the abdominal and dorsocervical spine regions (buffalo hump). The manifestation of these and other metabolic features, whether independently or concomitantly,

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defines one component of the lipodystrophy syndrome. Compared to adults, lipodystrophy in children is more difficult to assess due to growth and puberty. Lipodystrophic changes in children can be subtle and less severe than in adults and are often associated with puberty.

HAART, especially with protease inhibitor (PI) therapy, positively affects weight, weight-for-height, and muscle mass of HIV-infected children. A longitudinal study of 67 HIV-infected children tracked in the pre- and post-HAART era showed these changes were independent of the concurrent decrease in HIV viral load and improved CD4 T-lymphocyte counts.[7] The immediate treatment effects were most apparent with weight and muscle mass and there was a trend toward increased height. Other studies have substantiated the positive growth effects with HAART. Cross-sectional studies of HIV-infected children on HAART estimate up to 29% of pediatric HIV cohorts have lipodystrophy.[8] The European Lipodystrophy Cohort also found fat redistribution in 26% of HIV positive children, yet with clinically inapparent lipodystrophy.[9]

In addition to the increased cardiovascular risk associated with lipodystrophy, the adverse psychological consequences in HIV-infected children can be significant and include reduced adherence to HAART, low self-esteem, depression, and problematic emotional sexual development. These issues are heightened in adolescents who are already prone to these normal developmental phases.

The change in body composition is only one factor that can lead to or represent increased cardiometabolic risk in HIV-infected children. Prior to the introduction of ART, elevated levels of triglycerides and low-density lipoprotein (LDL) cholesterol were reported and associated with HIV infection in adults. These changes point to the effect of chronic immune activation alone on lipid metabolism. One mechanism that has been suggested includes the effect of pro-inflammatory cytokines (as a response to the chronic viral infection) on lipid pathways (such as lipoprotein lipase activity). After the initiation of PI therapy, there can be a 20 to 50% rise in lipid levels of HIV-infected children. The similarities between host cell proteins and HIV-1 protease may be responsible for the PI effects on lipid levels. Other factors associated with hyperlipidemia include successful viral suppression, better CD4 T-lymphocyte counts and demographic factors.[5] The impact of PI on lipid levels, independent of HIV, is effectively described in HIV-seronegative volunteers who developed dyslipidemia following PI treatment.[10]

Abnormal glucose homeostasis was documented in HIV-infected adults with lipodystrophy well before it was reported in children. Insulin resistance is of particular concern in HIV-infected adolescents who naturally experience a relative insulin resistance in puberty. Children with lipodystrophy seem to be at a higher risk for insulin resistence.[11] The etiology of insulin resistance is multifactorial and has been linked to both PI and nucleoside reverse transcriptase inhibitor (NRTI) use singly and in combination, and exact mechanisms have not been well defined. A possible mechanism by which HAART causes insulin resistance is by direct inhibition of the transport function of the Glut4 glucose transporter, which is responsible for insulin-stimulated glucose uptake into muscle and fat. Other potential causes of insulin resistance include mitochondrial DNA (mtDNA) mutations or depletions associated with NRTI therapy, elevated levels of proinflammatory cytokines, or decrease in adiponectin. Although there are fewer studies in children compared to adults, the elevated risk for diabetes mellitus and subsequent cardiovascular risk in HIV-infected children on HAART is becoming increasingly clear.

Vascular endothelial dysfunction as measured by biomarkers, arterial wall stiffness, and increased carotid intima medial thickness (cIMT) also suggest cardiovascular risk in HIV-infected children. These phenomena occur as a result of chronic inflammation and injury to the endothelium, and in HIV specifically, results from oxidative stress due to HAART or direct cytopathic effect of the virus.[11] In addition, dyslipidemia, insulin resistance, and chronic inflammation also contribute to endothelial damage. Endothelial damage, in turn, leads to atherosclerotic changes in the arteries.

Biomarkers of endothelial dysfunction [intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), E-selectin, P-selectin, and high sensitivity C-reactive protein] are elevated in HIV-infected children compared to controls.[12] Atherosclerotic cardiovascular risk can also be defined by other methods including cIMT and brachial artery reactivity (BAR). A British cohort of HIV-infected children found elevated inflammatory markers, with lower flow mediated vasodilatation (increased arterial stiffness) and greater cIMT that increased with age.[13] These changes were particularly evident in PI-treated children.

In addition to the metabolic cardiovascular consequences, HIV-infected children are also at risk for intrinsic myocardial abnormalities. Only a few short years after pediatric HIV was described, Lipshultz et al.[14] reported significant cardiovascular abnormalities in HIV-infected children. In the pre-HAART era, approximately 10-25% of HIV-infected children presented with cardiovascular symptoms including abnormal left ventricular (LV) fractional shortening and LV hypertrophy.[15] In the HAART era, specific echocardiographic abnormalities associated with therapies have been described.[16] Thus, both metabolic and intrinsic myocardial abnormalities contribute to an overall increase in global cardiac risk.

Defining the cardiac risk of HIV-infected children is important, but equally or perhaps more important is to determine whether this risk translates into adverse outcomes. In adults with HIV, the risk of vascular disease leading to myocardial infarction or stroke is greater than the general population, although traditional risk factors

such as age, lifestyle, and family history are all significant contributors as well.[17] Considering the extant evidence, it is clear that HIV-infected children have many critical risk factors for global cardiovascular disease. However, in contrast to adults, children are exposed to these risk factors earlier in life (many since birth and *in utero*), are not typically exposed to other adverse life style risks that potentiate cardiovascular risk, and may not have lived long enough to develop the outcomes of interest, namely myocardial infarction or cerebrovascular events (stroke). Thus, the true risk and prevalence of adverse cardiovascular outcomes in these children have yet to be realized.

In this new decade, we will now have the privilege to care for greater numbers of HIV-infected children living well into adulthood. However, we will also have the obligation to vigilantly monitor these children for adverse consequences of this chronic viral infection and its treatments. It will be necessary to discern cardiovascular risks originating from HIV and its treatments vs. contemporary and societal trends that may follow current patterns in childhood obesity. Practitioners caring for HIV-infected children should implement preventative measures now that impact cardiovascular risk and adverse outcomes later. These measures should start with the careful assessment and treatment of dietary imbalances[18] and promotion of physical activity[19] for all HIV-infected children. These rudimentary measures should be at the core of all interventions that address cardiovascular risk, although investigators need to acknowledge that pharmacologic interventions may need to be implemented.

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