

*Invited Review***Preventing and Diagnosing HIV-Related Comorbidities in Adolescents****Hasiya Eihuri Yusuf, MD, MPH; David Griffith, MD; Allison Lorna Agwu, MD, ScM**

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Adolescents with HIV are growing into adulthood and are at risk for comorbidities. Comorbidities in adolescents often go unrecognized, increasing morbidity and mortality, and contributing to poorer outcomes for youth with HIV. Youth with perinatally and nonperinatally acquired HIV are at risk of developing HIV-associated and non-HIV comorbidities, including cardiovascular diseases, diabetes, mental health disorders, renal diseases, and bone disorders. Youth with HIV are also at risk for altered fat distribution and weight gain associated with certain classes of antiretroviral therapy. Sexually transmitted infections from inconsistent condom use pose a sexual health challenge for youth with HIV. Prompt interventions through comprehensive history taking, physical exams, regular screening, and prevention and treatment of clinically evident comorbid conditions are needed to prevent progression and complications.

Keywords: comorbidities; adolescent; HIV; young adults; youth; prevention

Background

Global accessibility and scale-up of effective antiretroviral therapy (ART) have transformed HIV from a potentially progressive, life-threatening disease to a chronic, but manageable, lifelong infection.

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As a result, adolescents with HIV are growing into adulthood. Presently, more than 45,000 adolescents and young adults (AYA) aged 12 to 24 years in the United States are living with perinatally or nonperinatally acquired HIV.¹ Compared with older adults, youth with HIV are less likely to be diagnosed, access care, remain in care, and achieve and maintain

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virologic suppression, which is the current end goal of HIV treatment.² HIV-associated comorbidities are not limited to older adults and are becoming prevalent in youth with HIV, often going unrecognized due to failure to anticipate and probe for them.³ Unidentified comorbidities can lead to morbidity or mortality, or worsen the quality of life for youth with HIV. We discuss common comorbidities prevalent among adolescents with HIV, and strategies for their prevention, prompt diagnosis, and treatment.

Epidemiology of HIV in Adolescents

The majority of children who acquired HIV in infancy are now 13 years old or older, and up to 40% of them are 25 years old or older.⁴ Youth with HIV also include those who acquire HIV as adolescents or

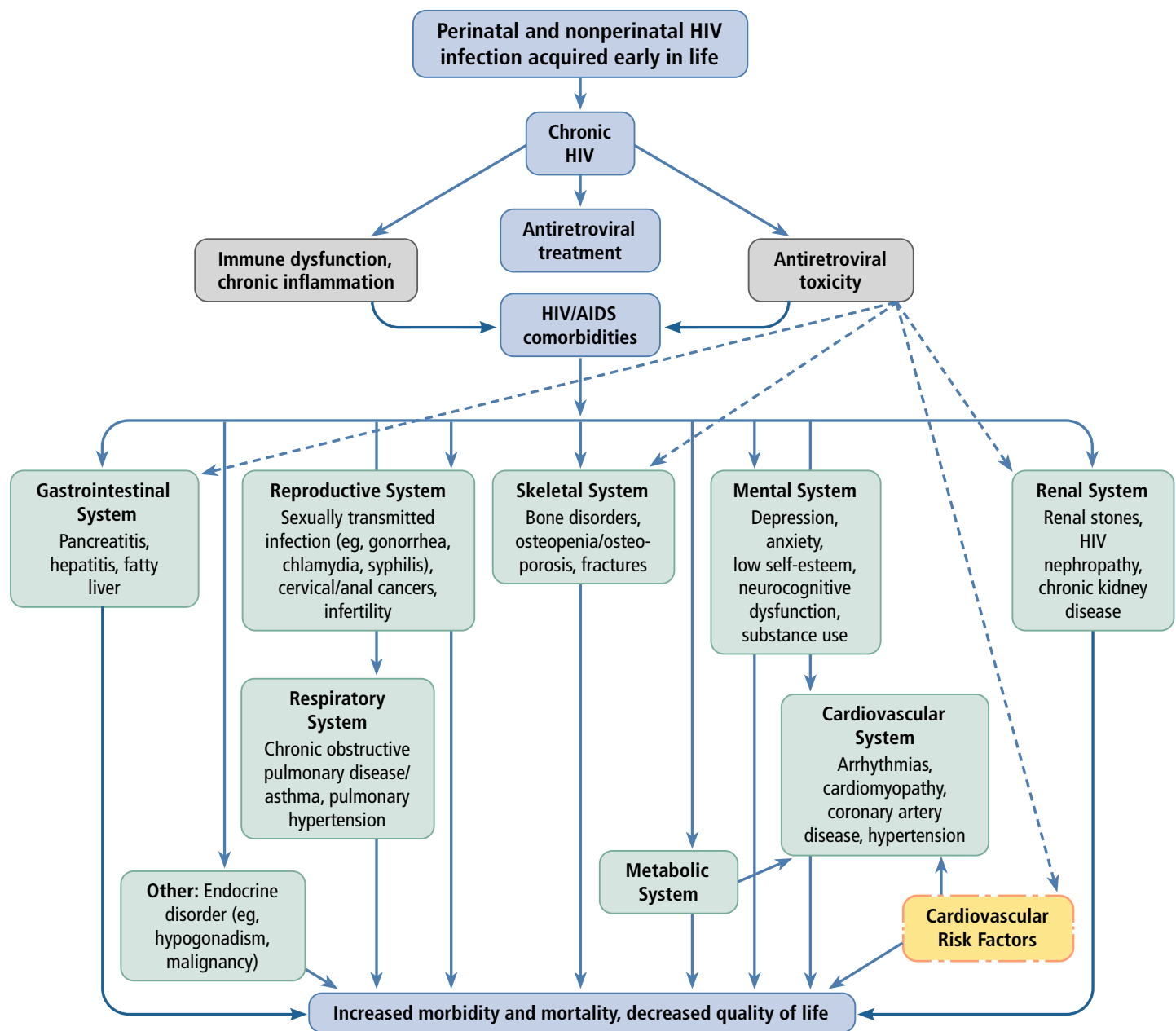


Figure. Chronic comorbidities in adolescents and young adults with chronic HIV infection.

young adults, often characterized as nonperinatally acquired HIV. Of the 34,800 new infections diagnosed in 2019, 7648 (21%) occurred in the 13 to 24 year age group.^{5,6} Although the HIV epidemic has changed in many ways, the demographics of those affected have remained relatively consistent. Most new infections in AYA are diagnosed in men who have sex with men (MSM), representing 83% of HIV diagnoses in that age group.⁵ Racial disparities also characterize the distribution of HIV transmission in

the United States. Nearly 70% of new HIV infections in 2019 occurred among African American and Hispanic or Latinx people, who together make up approximately 30% of the US population.⁵ In 2019, 51% of MSM aged 13 to 24 years and diagnosed with HIV were African American, and 32% were Hispanic or Latinx.¹

The HIV continuum of care (CoC) is a model that examines the level of engagement in care from diagnosis to the attainment of virologic suppression.

Along the continuum, youth with HIV have lower rates of engagement in care, receipt of care, and viral suppression than older adults.² Growing awareness of the poor HIV outcomes in youth has motivated clinicians and researchers to focus on optimizing care for this group, with the aim of strengthening treatment adherence and achieving virologic suppression. Although the CoC is a useful framework, comprehensive care for youth with HIV goes beyond achieving viral load suppression. Other aspects of care must be addressed to ensure well-rounded care delivery and to prevent adverse outcomes for youth. Although rigorous efforts in diagnosis and treatment have been instrumental in reducing HIV transmission among AYA,⁶ many challenges remain in the management of HIV in AYA that must be addressed.

HIV Comorbidities in Youth

More than a quarter of American adults older than 65 years of age are reported to have 2 or more co-

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morbid conditions, and these figures are projected to rise as the elderly population increases.⁷ The prevalence of comorbid conditions is even higher among adults with HIV, who are at greater risk for kidney diseases, cardiovascular events, neurocognitive disorders, and malignancies, and at an earlier age than persons who are HIV negative.⁸ Chronic immune activation by HIV is thought to be the major contributor to developing HIV comorbidities.⁸

Like older adults with HIV, youth with HIV are exposed to the immunologic effects of chronic HIV infection and long-term effects of ART. Youth with perinatally and nonperinatally acquired HIV are therefore at risk of HIV-related comorbidities, including cardiovascular diseases, diabetes, liver disease,

mental health disorders, renal diseases, and bone disorders.⁴ Despite this evidence, efforts to identify and address comorbid risks in youth with HIV have been limited. For example, in a cohort of South African youth with HIV, 55% had clinically recognizable comorbidities, independent of the route of HIV acquisition.³ Only a limited number of those with existing chronic comorbidities or risk factors for comorbidities received intervention. There is therefore a need to identify comorbid risks in this group and to implement measures to prevent progression in their early stages.

Diabetes

Adults with HIV have been found to have higher rates of diabetes than adults who are HIV seronegative.⁹ ART has been identified as a risk factor for diabetes in adults with HIV. Early ART regimens, in particular protease inhibitors (PIs), and thymidine analogs are associated with increased risk of diabetes and metabolic complications from alterations in fat distribution.¹⁰ Though many of the early ART regimens are no longer in common use, prior use remains an important metabolic risk factor.¹⁰ The increasing risk of diabetes in the general population has also been seen in AYA. In a large study, new cases of type 1 and type 2 diabetes among youth increased by 45% from 2009 to 2017 to a prevalence of 0.67 per 1000 youths aged 10 to 19 years.¹¹ A high risk of diabetes has also been reported in youth with HIV. Nearly 15% of adolescents in the PHACS (Pediatric HIV/AIDS Cohort Study) group were found to have evidence of insulin resistance, and observational cohorts have shown an increase in diabetes as youth with HIV age.¹²

Insulin resistance in youth with HIV is multifactorial. As in adults with HIV, insulin resistance in youth with HIV may result from HIV infection itself or the use of ART, especially PIs and nucleoside reverse transcriptase inhibitors (nRTIs) like thymidine analogues (eg, stavudine and zidovudine).¹³ Thymidine analogue use has become less common, and the use of PIs as first-line treatment for HIV has been overtaken by the ease and availability of the integrase strand transfer inhibitor (INSTI) drug class. INSTI

use has been associated with weight gain, which may pose additional diabetes risk.¹⁴ In addition to traditional risk factors (eg, obesity, family history) and the effects of ART, chronic HIV infection is believed to play a role in the development of insulin resistance, although its mechanism is not fully clear.¹⁵

Hypertension and Cardiovascular Risk

Among adolescents in the general population, 15% to 19% of boys and 7% to 12% of girls have signs

Chronic HIV infection causes changes in the structural integrity of the vasculature, and increases intimal and media thickness in carotid vessels. Among youth with HIV, cardiovascular abnormalities such as ventricular hypertrophy, abnormal cardiac rhythms, and cardiomyopathies have all been reported

of elevated blood pressure (BP).¹⁶ As expected, elevated BP in AYA occurs more frequently in those with comorbid conditions, including chronic kidney disease, obstructive sleep apnea, and obesity.¹⁶ Among youth with HIV, wide variations exist in the reported prevalence of elevated BP, with a range of 3% to 20% across several studies.^{3,17} Chronic HIV infection causes changes in the structural integrity of the vasculature, and increases intimal and media thickness in carotid vessels.¹⁸ Among youth with HIV, cardiovascular abnormalities such as ventricular hypertrophy, abnormal cardiac rhythms, and cardiomyopathies have all been reported.⁴ Youth with HIV have substantially greater coronary arterial wall thickness and markers of cardiovascular disease than youth who are HIV negative.¹⁹ These markers are associated with arterial stiffness, irritation, and other signs of compromised vascular integrity. In

youth with HIV, the elevations in inflammatory markers associated with cardiovascular disease appear to be independent of virologic suppression.²⁰ Although hard outcomes of cardiovascular diseases in youth with HIV are not very common, these changes are concerning as evidence emerges of long-term cardiovascular comorbidity in this group. In a recent case report, a 23-year-old with long-standing perinatally acquired HIV developed sudden acute chest pain and marked ST elevations on electrocardiogram from 95% left anterior descending artery occlusion, requiring emergent coronary angiography.²¹ Such occurrences, though rare, emphasize the need for HIV clinicians to proactively seek out and address cardiovascular risks early, and to intervene to avoid the development of and progression to clinically evident cardiovascular diseases.

Weight Gain

Currently, 21% of 12- to 19-year-olds in the United States are obese.²² Data on weight gain in adolescents with HIV are still emerging and appear to be linked to newer drugs in the InSTI class and tenofovir alafenamide (TAF).²³ Guidelines currently recommend InSTI-based regimens as first- and second-line regimens in adolescents, adults, and, more recently, the pediatric age group. InSTI-based regimens are efficacious for achieving virologic suppression and improvement in treatment outcomes; however, they are also associated with substantial weight gain and changes in BMI, both in the adult and youth populations.^{14,24} Among the InSTIs, dolutegravir is associated with the greatest weight gain;¹⁴ however, there are emerging data that bictegravir is also associated with weight gain.²⁵ Other drugs in the class (eg, raltegravir, elvitegravir) cause weight gain, but to a lesser degree and comparable with levels of weight gain with PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).¹⁴ TAF is associated with more weight gain when paired with dolutegravir than tenofovir disoproxil.²³

Several studies on the association between InSTIs and weight gain have been reported, and additional data continue to emerge. The greatest risk of weight gain with InSTIs occurs in women, non-Hispanic

Black individuals, and older adults (>60 years) with HIV.¹⁴ Youth-specific data are comparatively few, and further research is warranted. Nonetheless, available evidence showing a likelihood of weight gain in this group suggests a need for caution and monitoring for weight changes in young patients prescribed InSTIs.

Sexually Transmitted Infections

AYA aged 15 to 24 years have the highest rates of sexually transmitted infections (STIs) in the United States, and these rates are increasing. In 2018, more than half of the 26 million diagnosed STIs in the United States occurred among AYA.²⁶ The rates of gonorrhea, chlamydia, and syphilis increased between 2013 and 2017 among individuals 15 to 24 years of age.²⁶ STI rates among youth with HIV are similar to the general population, and like those without HIV, youth with HIV also engage in sexual risk behaviors that increase their STI risk.^{27,28}

Youth with HIV engaging in sexual activity report high levels of inconsistent condom use.²⁹ There is a risk for the sequelae of STIs including cancers, ectopic pregnancy, infertility, and chronic pelvic pain. Hence, there is a clear need for STI risk reduction interventions among youth with HIV.

Mental Health and Substance Use

Mental health disorders in youth with HIV can negatively impact risk-taking behaviors, treatment adherence, and treatment outcomes.⁴ There is a disproportionately high prevalence of mental health disorders in people with HIV, including youth. For example, people with HIV are twice as likely to be depressed than persons who are HIV negative.³⁰ In one study, the lifetime prevalence of mental health disorders including depression, substance use disorders, and conduct disorder was substantially higher in adolescents who are HIV positive than adolescents of the same age who are HIV negative.³¹ Mental and behavioral disorders are also prevalent, with depression, anxiety, and substance use being among the most commonly reported mental health comorbidities in youth with HIV.^{3,32}

Despite the risk of mental health disorders, substance use, and their consequences in adolescents with HIV, many clinicians do not frequently conduct mental health assessments of their young patients.³³ Racial disparities in the mental health assessment of youth is also common. African American youth with HIV are less likely to receive mental health

It is crucial to identify and address these comorbidities through prevention, prompt diagnosis, and early interventions to prevent adverse outcomes and to improve HIV management outcomes for youth with HIV

services including psychotropic medications than youth of other races.³⁴ Assessment of youth with HIV for mental health disorders including substance use is essential, as untreated psychiatric disorders in people with HIV increase mortality, contribute to morbidity, and hinder treatment adherence.³¹

Way Forward

Patient History

Tackling current HIV comorbidities for youth with HIV and reducing their occurrence in the future demands a keen sense of observation by everyone involved, especially patients and their clinicians. Prevention of comorbidities begins with interventions that focus on identifying early warning signs and risk behaviors. A good place to begin is with a comprehensive history that takes every aspect of the patient's life into consideration. Adequate history taking ought to include a thorough assessment of comorbid conditions and risks, including tobacco and nicotine products, alcohol and other substances of abuse, and a comprehensive sexual history. History of use of other substances (eg, methamphetamines) with rising rates of use among youth should

also be sought. Sexual history must be obtained in a nonjudgmental and nonstigmatizing manner to perpetuate openness. Clinicians need to ask about sexual activity, not just for STI intervention, but also for counseling on contraception and pregnancy intentions for all populations of young people.

History of other activities that may result in unintentional injury (eg, use of helmets, driving, owning or living in a home with firearms) also needs to be taken. Clinical encounters should include a detailed family history, not merely limited to the first encounter but continually updated as patients and their families evolve. Physical examination must be thorough and geared toward identifying clinical signs that may be of concern (eg, abnormal BMI, elevated BP, central obesity, signs of substance use or abuse). Prompt intervention should be the goal for modifiable risk factors (eg, smoking, diabetes, physical inactivity, elevated BP, high blood cholesterol) of comorbid conditions identified in the course of history taking, examination, and laboratory investigations.

Counseling

The false perception of invincibility that often characterizes adolescence can lead young people to engage in unhealthy habits. Physical activity as a normal lifestyle should be encouraged for all patients without medical contraindications, and linkage to available weight management services can be considered for patients who require them. All adolescents ought to be educated on the health hazards of tobacco products (e-cigarettes, cigarettes, cigarillos, pipes) and given true information on their composition and long-term effects on health. Youth with HIV are able to engage in the use of smoking cessation tools. Lifestyle modifications should be encouraged and counseling incorporated into every component of the visit until the desired change is initiated and ultimately achieved.

Screening


According to HIV primary care guidance, metabolic profiles should be assessed for youth with HIV.³⁵ Baseline lipid profiles, hemoglobin A1c (HbA1c), and glucose levels need to be monitored given concerns of the metabolic effects of ART. An initial

assessment of metabolic profile sets the tone for future monitoring. HbA1c above 6.5% should raise concern for diabetes and the need for further evaluation and intervention. Regular assessment of weight and BMI and monitoring for weight gain are also essential. Management guidelines also recommend screening for STIs, hepatitis infection, mental health and substance use disorders, and BP, as well as assessing the need for vaccines.³⁵ Most risk calculators' cardiovascular risk assessment components are not validated for youth. Other methods of assessment should be employed, particularly among youth considered at high risk.

Treatment

Clinicians should initiate prompt treatment for clinically evident comorbid conditions to limit progression and prevent complications. Persistently elevated BP should be treated after exclusion of secondary causes such as renal artery stenosis, chronic kidney disease, and obstructive sleep apnea. Elevation in lipids should be treated with dietary modifications, nutritional counseling, and promotion of physical activity, as well as referral to structured weight loss intervention if indicated. If substantial elevations persist despite these interventions, first-line therapy with statins should be considered, although data is limited in youth with HIV. STI counseling, screening, and treatment, as well as family planning and contraception for interested youth, are crucial. Reproductive intentions should be inquired about with both male and female patients. Youth with HIV with substance use disorders should be offered needed treatments to facilitate recovery. Other mental health disorders can be treated if promptly identified and addressed. It is crucial to intervene early and prevent human papillomavirus (HPV)–associated cancers in youth with HIV with HPV vaccination and screening for abnormalities. Vaccination against hepatitis A and B, as well as other important vaccines protecting against tetanus/diphtheria/pertussis, meningococcus, influenza, pneumococcus, measles/mumps/rubella, and now SARS-CoV-2, can substantially reduce comorbidities.

In conclusion, adolescents with HIV, whether perinatally or nonperinatally acquired, are surviving

into adulthood. Clinicians must be aware of potential comorbidities that may arise in adolescence or early adulthood and set the tone for the patient's health as they move into adulthood. It is crucial to identify and address these comorbidities through prevention, prompt diagnosis, and early interventions to prevent adverse outcomes and to improve HIV management outcomes for youth with HIV. 

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