

VOLUME 2, ISSUE 5

TREATING YOUTH AND YOUNG ADULTS WITH HIV INFECTION



In this Issue...

Thirty years into the HIV epidemic, we can celebrate successes such as combination antiretroviral therapy (cART), effective prevention of mother to child transmission (PMTCT), treatment as prevention, and effective opportunistic infections prophylaxis, all resulting in increased life expectancy of persons living with HIV. Additionally, with the tools we have to prevent (preexposure prophylaxis, condoms, circumcision) and treat HIV, certain groups have experienced declines in HIV incidence. However, youth and young adults (< 25 years of age), especially young men who have sex with men (MSM), comprise a group where the incidence of HIV infection is increasing. Primarily infected through sexual acquisition, their age and their developmental stage (concrete thinking and invincibility), along with the challenges of social marginalization and stigma, make diagnosing, engaging, and treating HIV challenging in youth and young adults. Youth and young adults with HIV infection include those who acquired the infection nonperinatally (nPHIV), primarily through sexual activity, as well as a growing number of children whose HIV infection was acquired through perinatal HIV infection (PHIV) who are now reaching adolescence and young adulthood. Each population has its own unique management issues.

In this issue, we review the recent literature describing the epidemiology, management challenges, and complications of HIV among youth and young adults.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the HIV epidemic among adolescents and young adults in the US.
- Discuss the management challenges in caring for HIV-infected adolescents and young adults, including engagement, retention, and treatment.
- Summarize the emerging data on the clinical implications of HIV infection in adolescents and young adults.

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The incidence of HIV among youth and young adults between 12 and 24 years of age has increased over the past five years, while other populations have experienced a decline in their rates of infection.¹ The increase is probably related to a combination of increased testing, lack of awareness of HIV status, continued high-risk behaviors, and some disinhibition regarding the potential risks and implications of an HIV diagnosis. It is estimated that 50% of persons with HIV acquired the infection during their adolescent or youth years, presenting to care later. It had been speculated, when Gardner et al² and others published the HIV treatment cascade of care, that the cascade among youth was probably worse. Zandoni et al confirmed this with their careful analysis of published literature showing the worst case scenario of only an estimated 43% of youth with HIV being retained in care, and an estimated 6% actually achieving virological suppression. Farmer et al reported at the 2014 Conference on Retroviruses and Opportunistic Infections a rate of retention of 44% in the one year after engaging in care, and 23% at three years after engaging in care for youth with nPHIV infection in the HIV Research Network cohort.³ These estimates have huge implications for immune deterioration and the risk of transmission, particularly in a population that, given their decreased perception of risk and sense of 'invincibility,' often continue to engage in risk behaviors including unprotected sexual intercourse.

Youth may be escaping testing messages as they continue to present with CD4 counts in the advanced stages where treatment is indeed already indicated. In fact, the 2014 study by Agwu et al, reviewed in this issue, showed no improvement in the proportion of youth and young adults presenting for HIV care to 18 HIV Research Network sites with CD4 counts < 350 cells/mm³ between 2002 and 2010, which coincides with the change in the Centers for Disease Control and Prevention recommendations on testing to include all individuals above the age of 13 years.⁴ While the authors cannot comment on whether the youth were previously aware of their status but waited to enter care, or if their HIV were only recently diagnosed, the fact that there have been no changes in their CD4 at presentation is concerning. This study provides additional insight into pockets of youth that may be at particular risk of presenting to care with more advanced immunosuppression — including males, racial and ethnic minorities, those with increased viral loads, and heterosexual youth — that can inform targeted testing interventions and strategies. This study also highlights the fact that those presenting with lower CD4 counts were more likely to have elevated viral loads, again with potential implications for immune deterioration and transmission.

Antiretroviral treatment of adolescents and youth is addressed in the Department of Health and Human Services Guidelines for managing adults, as the disease trajectory of youth with nPHIV infection is more consistent with that of adults.⁵ The CD4 count is the primary measure used to determine treatment initiation (CD4 < 500); however, there is a move in the guidelines to initiate therapy in all patients infected with HIV, regardless of CD4 count, given the increasing data of improved outcomes of earlier initiation, decreased risk of transmission, and the potential benefits of minimizing inflammation and its consequences by suppressing HIV viral load.

Adolescents are treated as a "special population" for which the provider has to understand the unique characteristics (psychosocial, cognitive, and developmental; and logistical issues and barriers) that affect management in this population. Previous studies have demonstrated that youth who meet treatment criteria are less likely to be treated than their adult counterparts, and those who were begun on therapy were less likely to stay on therapy, particularly when followed at an adult treatment site.^{6,7} Further, Ryscavage et al reported that, in a small, single center study, youth were less likely to have virologic suppression than their adult counterparts.⁸ Concerns are that amid the push to initiate cART at higher CD4 counts, clinicians will continue to be reluctant to initiate youth, who historically have higher rates of nonadherence, resulting in a wider disparity between treated adults and youth.

The study by Gagliardo and colleagues, though regionally limited, is promising in that it showed that with the adoption of the 2009 treatment guidelines that pushed the threshold

to initiate therapy to between 350 and 500 cells/mm³, an increased number of youth were actually started on therapy. Troubling, however, is that at six months, only 70% were virologically suppressed on mostly nonnucleoside-based regimens, which have lower barriers to resistance. Further, the increase in resistance mutations in their patients entering care over the study period raises concern for transmission of resistance variants.

When managing youth infected with HIV, it is critical to understand the similarities and differences between the populations that make up this group. Specifically, the nonperinatally HIV-infected cohort predominantly comprises males, the majority of whose transmission risk is unprotected anal intercourse, while the perinatally HIV-infected (PHIV) cohort comprises a mixture of males and females. As discussed in the review on youth and young adults infected with PHIV, the latter have usually been engaged in care since infancy and have longstanding experience with the medical system, although they may or may not have autonomy and health literacy.

The assumption that youth infected with PHIV have adjusted to illness and are capable of managing their disease on their own is fraught with pitfalls. Further, they have usually been treated extensively with antiretroviral therapy, often before effective cART, and may therefore have significant resistance, as well as treatment fatigue and aversion. The non-perinatal HIV (nPHIV)-infected group usually has limited experience with the medical system and limited understanding of how to navigate and advocate for themselves.

Both groups may have challenges with disclosure, mental health (ie, depression and anxiety), and cognitive delay (particularly for those infected with PHIV). The study by Nichols et al (reviewed herein) found that in a well-characterized cohort, up to 49% of youth recently infected with nPHIV have asymptomatic neurocognitive impairment that may affect their ability to successfully adhere to therapy and care. Further, with limited psychosocial supports and resources, the barriers to consistent adherence and engagement in care may appear insurmountable — underscoring the importance of multidisciplinary teams understanding the challenges and barriers in this population (to better facilitate their care and promote retention and adherence) and knowing about interventions that may have the potential to improve outcomes.

In managing youth and young adults infected with HIV, it is important to recognize that while they may currently have limited apparent comorbidities, data are emerging on persistent inflammation,⁹ non-AIDS related comorbidities (renal failure, vasculopathy),^{10,11} and potential risk for future adverse outcomes. As presented in the review of the Patel study, elevated Pathobiological Determinant of Atherosclerosis in Youth (PDAY) scores indicate atherosclerotic disease risk, reinforcing the importance of 1) longitudinal studies to examine cohorts of youth (with PHIV and nPHIV infections); 2) focused studies of inflammation and other markers; and 3) noninvasive techniques to assess their risk for developing complications that may warrant interventions such as modifying cART, adding therapies to address modifiable risk factors, or employing preventive modalities to manage inflammation. Studies of these interventions (eg, aspirin, statins, and immunomodulators) are ongoing in adults and are in their early stages for youth.

In summary, HIV among adolescents and young adults in the US is an evolving epidemic that includes populations who pose unique challenges to treatment and management. The most complicating issue in their management is adherence, which is affected by a multitude of factors (eg, psychosocial, cognitive/developmental) with resultant impact on testing, engagement, retention, treatment, adherence, virologic and immunologic outcomes, and potential transmission. With the rising incidence of infection in this demographic group, continued vigilance is needed to understand these factors and develop interventions and strategies to improve outcomes.

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THE ADOLESCENT AND YOUNG ADULT HIV CASCADE OF CARE IN THE US

Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Pt Care STDs*. 2014 Mar;28(3):128-35.



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This 2014 paper by Zanoni and Mayer examines the now famous HIV cascade — from diagnosis to linkage to care, retention, treatment, and virologic suppression — among youth. Because youth are the only demographic in the US where HIV incidence is increasing, and the unique challenges of engaging and retaining youth in care, the goal of this comprehensive review was to examine the literature for differences in the HIV cascade of care among youth and highlight the areas that could be targeted for interventions to improve engagement, adherence, and retention in this population.

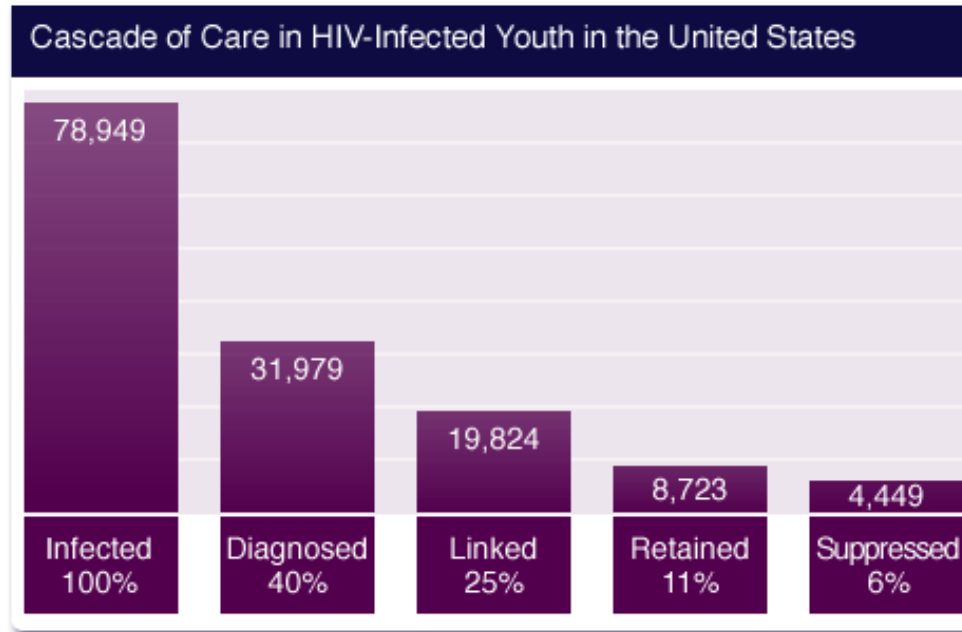
The authors reviewed the published literature by searching several large databases (eg, PubMed, Google Scholar) and conference proceedings between 2000 and 2012, identifying literature with relevance to age (13-29 years) and the HIV Cascade of Care (eg, diagnosis, testing, linkage, retention) written in English. The publications found predominantly reported US data.

The authors describe a 21% increase in HIV incidence among youth between 2006 and 2009, with the largest increases among minority (primarily African American) young men who have sex with men. Of the 1,178,350 persons living with HIV in the US in 2010, 6% were youth between the ages of 13 and 29. Only around 41% were aware of their HIV infection, a number significantly lower than the 80% that has been reported in other studies for adult populations.¹ Further, the publications reviewed describe challenges with undiagnosed infection, poor testing rates, unsuccessful linkage to care (62% of youth compared to 75% of adults link to care within one year of their diagnosis), and primary antiretroviral resistance (up to 15% have transmitted drug resistance). The authors combine data from multiple studies to estimate that only 51% of adolescents and young adults achieve virologic suppression to less than 400 copies/ml. The authors also attempt to decipher retention in care among youth by combining multiple studies and estimate that 43% of youth are retained within 1-3 years after engaging in care, significantly less than the 75% for those older than 25 years of age.

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The authors' review of the literature on the various steps of the cascade led to an estimate of the cascade in youth (below) that shows an alarmingly low rate of virologic suppression of 6%, significantly lower than the 28% that has been estimated for adults.



Source: Zanoni and Mayer, 2014

Though an estimation, the article highlights that youth and young adults have even steeper declines along all steps of the treatment cascade than those seen in the adult population, which may have implications for their own health as well as broader public health implications for increased transmission risk. The authors discuss several youth-focused mechanisms to improve the cascade, including targeted HIV testing with integration into areas where youth may intersect with the health care system, study and expansion of linkage to care interventions, improvement in transition of care, and studies of interventions to improve adherence. Further, the authors underscore the fact that what has been tried in older adults does not necessarily translate to youth and there is a need to examine youth-specific interventions to affect the cascade.

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CD4 COUNTS OF NONPERINATALLY HIV-INFECTED YOUTH AND YOUNG ADULTS

Agwu AL, Neptune A, Voss C, Yehia B, Rutstein R. CD4 Counts of Nonperinatally HIV-Infected Youth and Young Adults Presenting for HIV Care Between 2002 and 2010. HIV Research Network. *JAMA Pediatr.* 2014 Apr 1;168(4):381-3.



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Agwu and colleagues evaluated the CD4 count at presentation to care for youth with nonperinatal HIV (NPHIV) infection at HIV Research Network (HIVRN) sites. The HIVRN is a network of 18 HIV clinical US sites whose goals are to use "real-life" timely clinical data on epidemiologic patterns, service delivery, and resource use. The authors set out to determine whether, with the many public health initiatives to improve HIV testing rates, CD4 counts of youth improve in care (as has been shown for adult populations).

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Thirteen HIVRN sites geographically distributed over the US contributed patients to the analysis. Data from 1,497 youth and young adults who presented for care at the 13 sites, who were not on cART, and had at least one CD4 count, were included. The authors excluded those youth and young adults who had been engaged in care previously. Their specific goal was to examine the proportion of youth who are presenting to care with a CD4 count < 350 cells/mm³, a level of immune decline where there is consensus that treatment should be initiated for all patients.

Of the 1,497 youth who presented for care during the 2002-2010 time frame, 61% were African American, 19% Hispanic, 77% were male, and 63% acquired HIV through men who have sex with men (MSM) activity. The major finding of this article was that 40% of youth presented with CD4 counts < 350 cells/mm³, with 16% presenting with a CD4 count of < 200 cells/mm³, a level that defines AIDS (acquired immunodeficiency syndrome). Further, there was no improvement in the proportion presenting at this CD4 level over the course of the study period.

Certain groups of youth were at greater risk of presenting with CD4 counts < 350; specifically, males vs females (adjusted odds ratio [AOR] 1.63, 95% CI 1.16-1.23); heterosexuals vs MSM (AOR 1.43, 95% CI 1.08-1.88); African Americans (AOR 2.03, 95% CI 1.31-3.15); Hispanics (AOR 1.69, 95% CI 1.21-2.34); and older vs. younger youth/young adults (AOR 1.14, 95% CI 1.06-1.23). Further, those with higher viral load levels were more likely to present with lower CD4 counts. The authors also conducted an in-depth analysis of males only and found that among males, these same factors were also associated with advanced immunosuppression.

The study showed that the CD4 counts of HIV-infected youth have not increased significantly, even as awareness of HIV infection and testing initiatives have highlighted youth as a target population. The authors compare their findings to those in adults entering care in whom CD4 increases have been seen, speculating that the unique challenges of youth (eg, developmental and cognitive stage, testing and engagement challenges) may be affecting the treatment trajectory. This study highlights MSM as the group most at risk of HIV infection among youth; however, when examining the specific subgroups, males and heterosexuals may be at highest risk of presenting with the lower CD4 counts and may be escaping the testing messages. In addition, increasing viral load was also associated with lower CD4 at presentation, highlighting the significant risk of immune deterioration and transmission for youth entering care and underscoring the importance of testing and engagement initiatives for this population.

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INITIATION OF ART AND TRANSMITTED DRUG RESISTANCE IN ART-NAIVE ADOLESCENTS

Gagliardo C, Brozovich A, Birnbaum J, et al. A multicenter study of initiation of antiretroviral therapy and transmitted drug resistance in antiretroviral-naïve adolescents and young adults with HIV in New York City. *Clin Infect Dis*. 2014 Mar;58(6):865-872.



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Gagliardo and colleagues set out to evaluate whether there has been uptake of the December 2009 Department of Health and Human Services recommendation for earlier initiation of combination antiretroviral therapy (cART) at CD4 counts between 350 and 500 cells/mm³ among youth and young adults between the ages of 13 and 25 years infected with nonperinatal HIV who were ART-naïve. They also sought to examine whether there have been changes in transmitted drug resistance mutations (DRMs) over the study period.

In this multicenter retrospective cohort study, eligible youth were between 13 and 25 years old, were ART-naïve, and had HIV diagnosed within one year of presentation to care. They presented for primary HIV care between January 2007 and June 2011. All of the included sites were in New York City. The authors compared the number of youth meeting treatment criteria between January 2007 and December 2009 (CD4 < 350) vs

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January 2010 and December 2011 (< 500). They also examined the prevalence of transmitted drug resistance mutations.

Of the 331 youth included in the study, 90% were male, 76% were between 20 and 25 years old, and 78% had MSM transmission risk, with another 13% reporting sex with men and women as their transmission risk. The mean CD4 at entry to care was 444 cells/mm³ in 2007-2009 vs 470 cells/mm³ 2010-2011. One hundred ninety-one (58%) were started on cART. The mean CD4 at cART initiation was statistically different: 261 cells/mm³ vs 363 cells/mm³ for patients between 2007-2009 vs 2010-2011, respectively. There was also a time-effect on cART initiation, with individuals in 2010-2011 being significantly more likely to initiate cART at CD4 counts of 350-500 than those in 2007-2009 (odds ratio 5.2 [95% confidence interval 1.1-25.1]). There was also a shorter time between presentation to care and cART initiation (12 vs five months in 2007-2009 vs 2010-2011). Of the youth and young adults who were started on cART, 71% had attained virologic suppression by six months after cART initiation, with the mean time to achieve suppression 147 days (range 11-665 days). The most commonly initiated regimen was the coformulation of emtricitabine/tenofovir/efavirenz, which was initiated in 64% of individuals (71% and 60% in 2007-2009 vs. 2010-2011, respectively).

A second aim of the study was to evaluate transmitted drug resistance mutations. The authors report that 64% of the youth had resistance testing, with these tests less likely to be done on females. There was also a difference by site on whether resistance testing was conducted. The authors reported a statistically significant (P = .02) increase from 12% to 25% in the proportion of youth entering care with DRMs over the two study periods, with 5% of subjects with DRMs in 2007 and 28% in 2011. Overall, 18% had major DRMs: specifically, 14% had nonnucleoside reverse transcriptase inhibitor (NNRTI), 7% had nucleotide/side reverse transcriptase inhibitor (NRTI), and 3% had protease drug resistance mutations. No demographic or clinical factors were associated with risk of have DRMs.

The article shows that when guidelines shifted to earlier cART initiation, youth were also started on cART earlier in the course of infection, when CD4 was higher, with a large majority of youth being started on NNRTI-based regimens. Interestingly, the authors report short-term suppression over the six months after cART initiation, with 71% reaching this milestone, a rate lower than that seen in adults. While they do not report subsequent data on virologic suppression, the increasing proportion of youth entering care with drug resistance is of concern, especially since the regimen that was predominantly being started has a lower barrier to resistance in the setting of suboptimal adherence. In addition, it has been well-established in multiple studies that youth/young adults continue to engage in risky behaviors that increase the risk of transmission of resistant virus. The authors conclude that diligence in monitoring resistance at entry into care is critical.

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NEUROCOGNITIVE FUNCTIONING IN NON-PERINATALLY INFECTED ART-NAÏVE YOUTH

Nichols SL, Bethel J, Garvie PA, et al. Neurocognitive functioning in antiretroviral therapy-naïve youth with behaviorally acquired human immunodeficiency virus. *J Adolesc Health*. 2013 Dec;53(6):763-771.

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In this 2013 study by Nichols et al, the authors examined the prevalence of neurocognitive dysfunction among youth who had recently been infected through risk behaviors. It has been previously reported that 30%-50% of HIV-infected adults have evidence of HIV-associated neurocognitive disorders (HAND), with lower nadir CD4 counts and substance abuse being some of the factors that have been associated with that finding.¹ Additionally, data in children and youth perinatally infected with HIV show impairments in language and

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global functioning.^{2,3} As youth with nonperinatally acquired HIV (nPHIV) are at a developmental stage different from those of younger children and older adults, this study is one of the few to examine neurocognitive function in this unique population. Given the high rates of nonadherence and psychosocial chaos seen in the management of this population, it is important to decipher whether neurocognitive effects may be affecting these outcomes.

The authors conducted an Adolescent Trials Network prospective cohort study at US and Puerto Rico sites, examining neurocognitive functioning in youth (aged 18-24) with nPHIV with different illness severities who were treatment-naïve. Those who received combination antiretroviral therapy (cART) to prevent mother-to-child transmission (n = 3) were not eligible for inclusion. The study was conducted when the criteria for cART initiation was CD4 < 350 cells/mm³. English- or Spanish-speaking participants without active substance abuse, psychosis, or significant non-HIV related cognitive or motor impairment were included in the study. Participants underwent a battery of neurocognitive measures to examine memory, motor skills, attention, executive functioning, general cognitive functioning, and everyday functioning. The scores were calculated and classified individuals either with HAND (decline in ≥ 2 activities of daily living) or asymptomatic neurocognitive impairment (ANI); the latter signified by impairment on testing but no reported impact on daily functioning. Participants were also assessed for psychiatric functioning (depression, distress) and queried about education, employment, substance use, income, and living situation.

Of the 220 participants (mean age 20.9 years, 80.4% male, 68% African American, 62% gay/lesbian), approximately 50% had had their HIV diagnosis for < 1 year. The median CD4 count was 397 cells/mm³, with 57% having CD4 counts ≥ 350 cells/mm³. For depression, 73.4% scored in the minimal or mild range, and 53% had evidence of general distress. On a daily basis, 20.4% smoked cannabis, 33.6% smoked tobacco, and 2.8% drank alcohol. The study's major finding was that 62.9% of the youth had evidence of ANI, while 2.4% exhibited syndromic HAND. Lower CD4 counts were associated with HAND and poorer executive functioning, and longer duration of infection was associated with lower intelligence.

While this study is limited by not having a control (uninfected) group, it does provide evidence for a high rate of asymptomatic impairment, which may affect adherence and management of youth with nPHIV living with HIV. The longitudinal component of the study has been completed, but the results have yet to be released. The full results will provide invaluable insight into the impact of treatment and time on the trajectory of the neurocognitive function in this population, and possibly set the stage for interventions to affect the impact on functional outcomes.

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CVD RISK DISEASE AMONG ADOLESCENTS PERINATALLY INFECTED WITH HIV

Patel K, Wang J, Jacobson DL, et al. Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus. Pediatric HIV/AIDS Cohort Study (PHACS). *Circulation*. 2014 Mar 18; 129(11):1204-12.



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Concern is increasing about the long-term effects of HIV and its therapies on end organs such as the heart, particularly in adults. There is limited data for children, in whom there are no hard outcomes such as heart attacks. In this study, Patel and colleagues examined

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the aggregate risk of cardiovascular disease in adolescents perinatally infected with HIV in the multicenter Pediatric HIV/AIDS Cohort Study (PHACS), adolescent master protocol (AMP). The authors used the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scoring, which provides risk estimates for having an advanced atherosclerotic lesion in either the coronary (CA) or abdominal aortic (AA) artery relative to a person of the same age and sex without any cardiovascular risk factors. The measures used to calculate the score include lipids, glucose, smoking, blood pressure, and obesity.

Two hundred twenty-five of the 451 PHACS participants were in the validated age range for the PDAY score (≥ 15 years old) to be eligible; of those, 165 had the necessary clinical measures to be included in the study. The score was then calculated at baseline and at each annual visit after the age of 15. The median age at entry of the participants was 16.7 years; 49% were male, 68% were African American, and 41% had a history of immunosuppression with a $CD4 < 200$ cells/mm³ (though on their most recent assessment for the study, 57% had $CD4 > 500$). 48% and 24% of the PHIV-infected youth had PDAY scores consistent with CA and AA atherosclerosis. Factors associated with high CA and AA scores included elevated non-high-density lipoprotein cholesterol and low levels of high-density lipoprotein. In multivariable regression, male sex (adjusted odds ratio (AOR) 2.47 [95% CI 1.24-4.92]), disease severity (AOR 2.94 [95% CI 1.23-7.05] for CDC category C vs. B), longer cumulative duration of boosted protease inhibitor (AOR 3.97 [95% CI 1.54-10.24] for 5-8 years vs. 0 years), and no prior use of tenofovir (AOR 0.43 [95% CI 0.22-0.87]) were significant predictors of having a CA score ≥ 1 . For AA, current virologic suppression, CDC category C severity, and longer cumulative duration of boosted protease inhibitor use were associated with greater likelihood of scores ≥ 1 . When the authors examined changes in PDAY scores over the four years of study follow-up, there were no significant changes in the scores.

The study is limited by the absence of controls, small sample size, and lack of validation of the PDAY scoring with non-invasive vasculature assessments. Nonetheless, this study adds to the growing literature that describes the potential for premature and increased cardiovascular risk for PHIV-infected patients. The addition of a validated measure, the PDAY score, showing an increased risk of conventional, modifiable risk factors, along with HIV in this population, provides some additional data to stratify risk in patients who need close monitoring, lifestyle modification counseling, glycemic and lipid control, and potentially modification of antiretroviral regimens to more lipid-friendly agents. More data and studies on the functional implications of PDAY are needed to further define and determine risk for these patients.

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ART TREATMENT, MANAGEMENT CHALLENGES AND OUTCOMES IN PERINATALLY HIV-INFECTED ADOLESCENTS

Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. *J Int AIDS Soc*. 2013 Jun 18;16:18579. doi: 10.7448/IAS.16.1.18579.



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In this comprehensive review of the antiretroviral treatment, management challenges, and outcomes among perinatally HIV (PHIV)-infected adolescents, Fairlie and Agwu set out to examine the challenges that are specific to these individuals. This population is often highly treatment-experienced, with resultant mutations and limited treatment options, and comorbidities related to lifelong HIV infection and antiretroviral therapy. Comorbidities can include metabolic syndrome, osteopenia, short stature, psychiatric disorders, cognitive delay, and treatment fatigue, all of which have the potential to complicate management and compromise adherence.

The authors reviewed the global epidemiology of youth infected with PHIV, and then specifically examined and compared the domestic US epidemic to the global epidemic. In the US, with the advent of maternal and infant testing, the scale-up and implementation of prevention of mother-to-child transmission programs, and the early initiation of



combination antiretroviral therapy (cART), most youth with PHIV infection have been on therapy for a long time. Therefore, the management challenges tend to relate to nonadherence, with resultant virological failure and development of drug resistance, immunologic failure, adverse effects, drug-drug interactions, and development of comorbidities. Other concerns include incident sexually transmitted infections (STIs), pregnancy potential, and effective retention and transition to adult care.

With the availability of a cadre of antiretrovirals and the potential to craft palatable "salvage" regimens, adherence is the most crucial barrier to successful outcomes for adolescents and youth infected with PHIV. In fact, longitudinal cohorts described in this review report virologic suppression rates for youth ranging from 28%-78%, lower than rates of 90% or higher reported in adult cohorts. These rates have potential implications for immunologic deterioration as well as public health implications for transmission. In the US, the barriers to adherence are typically related to psychological barriers, such as low self-efficacy or the belief in one's ability to adhere, low outcome expectance (lack of belief that the medicine will work), treatment fatigue, lack of psychosocial support, and mental illness or behavioral disturbance. The authors review specific kinds of barriers, such as medication-related and structural barriers that providers can assess when examining reasons for nonadherence and provide strategies to address them.

Additionally, the authors review the literature on strategies (bridging or minimalist strategies such as treatment deintensification, 3TC monotherapy, and other simplification strategies) that providers who care for youth have employed as they address virologic and immunologic failure. They conclude that if alternative strategies are tried, the strategies should be done with close monitoring and continued adherence support and strengthening.

In summary, the authors provide a comprehensive review of the complex and unique issues surrounding the management of adolescents and youth infected with PHIV that may be instructive for providers who assume the care of this population as they transition into adult care.

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- Many clinicians require education regarding current treatment and new emerging hepatitis C medications in patients coinfecting with HIV/HCV who require antiretroviral therapy.
- Clinicians may need an update on current recommendations for the treatment of HIV with HAART.

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