Finding solutions for HIV’s lost generation: adolescents and young adults

By Mark Mascolini

Interviews with:

Patricia M. Flynn, MD:
Understanding antiretroviral adherence, HIV stigma, and HIV prevention in adolescents

Bill G. Kapogiannis, MD:
Preventing HIV acquisition and transmission—and improving identification and management of HIV—in youth
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EDITOR
Mark Mascolini

CONTRIBUTING WRITER
Mark Mascolini

GRAPHICS & LAYOUT
Teresa B. Southwell

AIDS RESEARCH CONSORTIUM OF HOUSTON dba The Center for AIDS Information & Advocacy
P.O. Box 66346, Houston, Texas 77266-6306
1407 Hawthorne, Houston, Texas 77006
Voice 713.527.8219
888.341.1788
713.521.3679
Fax 713.521.3679
Web Site http://www.centerforaids.org
E-mail  rita@centerforaids.org
Dear reader,

In the last issue of RITA! (Spring, 2010), editor Mark Mascolini examined the causes and mechanisms of premature aging in people with HIV, a subject of widespread attention. In this issue, he takes an in-depth – and sometimes heartrending – look to the other end of the lifespan and at the pandemic’s lost generation: the adolescents.

According to Mascolini, “Children who reach their teens burdened by HIV since birth often arrive at this epochal nexus with bodies lagging their peers in maturity, with the stigmata of their infection, and with aimless, abusive, or absent parents” (p. 5).

Other teens enter adolescence free of HIV but at heightened risk for acquiring it. In the U.S., HIV is spreading fastest among 15-to-24 years olds. Among gay males in the U.S., 13-to-24 year olds were the only age group to see an increase in new infections in a five-year survey by the federal government.

In 1984, when Ryan White became the most famous American teenager ever diagnosed with HIV/AIDS, probably no one would have guessed that 20 years later, 15-to-19 years would represent nearly 60% of new diagnoses.

What works – and what doesn’t – in both preventing and treating HIV and its social sequelae among teenagers is the focus of this issue. The data suggest the focus is timely.

Until there’s a cure,

Paul Simmons, RN, ACRN
Executive Director
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Finding solutions for HIV’s lost generation: adolescents and young adults
By Mark Mascolini

No longer children and not quite adults, adolescents straddle a maturational divide marked by rapid growth, raging hormones, rebellious autonomy, and an unquenchable appetite for anything new. Bedroom-mirror and beach-blanket scrutiny confirm exciting somatic changes that demand reciprocal heed from peers of the opposite or same sex. And almost everything that makes adolescents adolescent ratchets their risk of sexually transmitted infection, most notably HIV. Children who reach their teens burdened by HIV since birth often arrive at this epochal nexus with bodies lagging their peers in maturity, with the stigmata of their infection, and with aimless, abusive, or absent parents.

No one can define when an adolescent becomes a “young adult” because the transition is more continuum than threshold and because it differs for everyone. But if one considers people in their late teens and early twenties young adults, a sprawling segment clearly clings to the attributes of adolescence. Even relatively mature young people tend to be more often transient, single, and insouciant than middle-aged and older adults, and so still more liable to pick up HIV or pass it to a partner.

An anomaly of HIV medicine—and all medicine for that matter—is the lack of specialization in adolescent and young adult care, even though this chronologically delimited group plainly differs from its pediatric antecedents and its mellowing supersedents in behavior, biology, and yen for risk. To their credit, HIV researchers have hollowed a special niche for this pivotal age group when studying an array of issues, from psyche to cytology to antiretroviral response. And they do this for good reason: The 15-to-24 age group is the fastest-growing in the US HIV tally, and countless countries surely share that demographic.

Centers for Disease Control and Prevention (CDC) data baldly reflect this explosive growth in HIV cases among adolescents and young adults. A 2004-2007 survey of 34 states and five US-dependent areas with confidential name-based HIV reporting charted a 25% skid in HIV cases among children under 13, a 2% dip among 13-to-14-year-olds, a 57.5% vault among 15-to-19-year-olds, and a 32% surge in 20-to-24-year-olds (Figure 1). Dividing teens and adults into four age groups (13 to 29, 30 to 39, 40 to 49, and 50 or older), the CDC figured that the 13-to-29 contingent accounted for the largest share of new HIV infections in 2006 among both males (34%) and females (35%). Similarly, in a 2001-2006 survey of HIV cases among gay men in the United States, the CDC tracked an upswing in only one of five age groups, 13-to-24-year-olds.
Teens seem to comprise a lost generation of HIV-positive people: Adolescents with and without HIV begin experimenting—sometimes avidly—with so-called risk behaviors that make them more liable to infect others or to get infected themselves. Yet these youngsters differ decidedly from older HIV groups in sundry ways that affect their risk of HIV infection, HIV transmission, and response to antiretroviral therapy.

This issue of RITA! explores HIV care in teens and young adults in high-income countries, examining HIV risk, HIV testing, stigma, response to antiretroviral therapy, antiretroviral toxicity, and long-term consequences of HIV infection. Interviews with Pat Flynn (St. Jude Children’s Research Hospital, Memphis) and Bill Kapogiannis (Eunice Kennedy Shriver National Institute of Child Health and Human Development) offer expert insights on many of these issues. An ad hoc panel of experts in adolescent HIV gives their advice on antiretroviral adherence and management faux pas.

**HIV risk behavior in seronegative youth**

No one over the age of 12 needs to be told that young people spend lots of time thinking about sex—and making some of those thoughts come true. Although it’s a mistake to assume that all older adults drastically curtail their time copulating, teens and young adults typically are more rarely tied to a single partner and much more likely to let their libido do their bidding as often as circumstance allows. And because youngsters often know or care less about the consequences of frequent sex, they put themselves at a higher risk of sexually transmitted infections (STIs), including HIV.
US researchers estimated about 19 million new STIs in the year 2000, and 15-to-24-year-olds accounted for almost half of them.\(^4\) According to a 2010 report on the National Survey of Family Growth, 37.5% of 2007 18-to-22-year-olds in the United States reported any high-risk HIV behavior.\(^5\) In Sweden, surveys of almost 17,000 people in 1989, 1994, 1997, 2000, 2003, and 2007 found that the likelihood of “holding a restrained attitude” to sex outside a steady partnership swooned significantly over the study period, particularly among 16-to-24-year-olds.\(^6\) Among women in that age group, prevalence of having several sex partners and having sex without a condom doubled from 1989 to 2007.

Startling misconceptions about HIV risk and transmission remain rife among US college students. A 650-student survey at a Midwestern university in 2008 found that, although 77% of respondents claimed familiarity with HIV and its modes of transmission, 14% believed mosquitoes could transmit the virus and 20% could not say whether mosquitoes were likely culprits.\(^7\) Although many of these students reported chancy sexual habits, 87% did not think they had a high risk of HIV infection.

**Perilous doings among already-positive youth**

Like their elders, HIV-positive youngsters do not become models of rectitude when they learn they carry the retrovirus. As a result, young people with HIV risk transmitting the virus to others, while they face shorter odds of acquiring other STIs or superinfection with a second, nastier HIV. A CDC study of 105 sexually experienced 13-to-21-year-olds infected with HIV perinatally or by their own doing found that 49 of them (47%) had unprotected sex since learning they had HIV infection.\(^8\) Among 55 sexually experienced girls and women, 19 (35%) had already been pregnant. Among 86 recent sex partners interviewed, 51 (59%) got exposed to HIV through unprotected vaginal, anal, or oral sex, and 69 (80%) did not know their sex partner had HIV.

A study of 254 perinatally HIV-infected or exposed 10-to-16-year-olds in the US-based Pediatric HIV/AIDS Cohort Study found that nearly half, 46%, met study criteria for one or more behavioral health problems, including unprotected sex, mental health problems, and recent substance use (usually involving alcohol or marijuana).\(^9\) Among sexually active youngsters with HIV, half had a detectable viral load and one third acknowledged recent nonadherence to antiretroviral therapy. Among all children with HIV, care by the birth mother almost tripled the risk of having two or more study-defined negative health outcomes (odds ratio [OR] 2.86, 95% confidence interval [CI] 1.04 to 7.88). The investigators postulated that this apparently counterintuitive finding could reflect poor child care from mothers coping with violence, substance abuse, and other troubles.

Screening 352 HIV-positive youngsters in five US cities, Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) researchers found that 68% had at least one of three risk behavior problems involving substance use, sexual risk, or medication adherence.\(^10\) One third of the study group reported no problem behavior, one third reported one problem, 95 (27%) reported two problems, and 20 (6%) reported three. The ATN team determined that 211 adolescents (60%) had “problem-level” substance use, and 148 (42%) claimed a sexual risk problem. Among 165 youngsters taking medications, 91 (55%) had a tough time with adherence, and that group had

continued...
higher viral loads than adolescents without adherence difficulties.

Lower CD4 percent almost tripled the risk of substance use in a study of HIV-positive and negative 12-to-18-year-olds enrolled in IMPAACT P1055, a multisite US cohort study.\textsuperscript{11} This comparison of 196 youngsters with HIV and 103 HIV-negative youth in families affected by HIV found that similar proportions (13% and 16%) reported substance use when they entered the cohort. For the whole group, substance use proved more likely in adolescents who met clinical criteria for attention deficit hyperactivity disorder (20\% of adolescents, adjusted odds ratio [AOR] 4.0, $P = 0.01$), oppositional defiant disorder (15\% of adolescents, AOR 4.8, $P = 0.001$), mild or major depression (11\% of adolescents, AOR 4.0, $P = 0.01$), or conduct disorder (12\% of adolescents, AOR 15.4, $P = 0.001$).

HIV-positive youth with a CD4 percent below 25\% had nearly a tripled risk of substance use (AOR 2.7, $P = 0.03$), even after statistical adjustment for age and other risk factors. Notably, though, substance use or its association with psychiatric symptoms was no more likely in adolescents with HIV than in HIV-affected youth. These investigators proposed that “targeting of both HIV-infected youth and those living in households affected by HIV who have psychiatric conditions is extremely important for public health programs; intervention programs should address both populations for maximum benefits.”

Pregnancy is one tangible measure of sexual risk taking in HIV-positive youth, and one fraught with potentially dire consequences for young HIV-positive mothers and their infants. A study of 2575 perinatally infected US youngsters, half of them girls, identified pregnancy-related conditions as the most frequent newly diagnosed non-infectious condition, at an incidence of 6.16 per 100 person-years.\textsuperscript{12} These conditions included intrauterine fetal demise or spontaneous miscarriage, ectopic pregnancy, chorioamnionitis, preeclampsia, intrauterine growth retardation, and premature delivery. Among all noninfectious conditions assessed in this study, pregnancy-related conditions and gynecological dysplasias were the only two for which incidence rose over the 2001-2006 study period.

Mixed results with risk-reduction programs

Researchers in high-income countries have devised and tested programs that aim to reduce HIV and STI risk exposure in young people with and without HIV. Although some tested approaches yielded at least modestly promising results over the short term, no one doubts the difficulty of changing behavior in young people—especially those prone to risky excursions—with a crafty learning protocol or few counseling sessions.

For example, a randomized trial tested a 12-month risk-reduction intervention involving two group sessions and four phone calls in African-American girls and women who reported an average of nine lifetime sex partners and 13 episodes of vaginal sex in the past 60 days.\textsuperscript{13} Before the study began, only 22\% of these 15-to-21-year-olds reported consistent condom use, and only 43\% used a condom the last time they had sex. Through 12 months of follow-up, young women randomized to the intervention had a 35\% lower risk of chlamydial infection ($P = 0.04$), the study’s primary endpoint. Even so, 42 of 348 young women (12\%) randomized to the intervention had a new chlamydial infection, compared with 67 of 367 (18\%) randomized to the comparison group. Proportions of new gonorrhea cases (6.6\% versus 6.8\%) and new trichomoniasis
(14.9\% versus 15.5\%) were virtually identical in the two groups.

A randomized trial involving 484 HIV-negative US adolescents in juvenile detention facilities compared three interventions to lower the risk of STIs including HIV.\(^1\)\(^4\) One intervention combined group-based sexual and alcohol risk reduction with group motivational enhancement therapy, a second intervention focused only on sexual risk reduction, and a third program merely offered information on preventing HIV and other STIs. Condom use decreased through 12 months of follow-up in all three study groups.

Other research confirms that merely instructing youngsters about HIV provides no guarantee that they will use condoms consistently and eschew other risks. The CDC study of 105 sexually experienced, HIV-positive 13-to-21-year-olds in three cities traced an association between greater knowledge about HIV and recent unsheathed sex (AOR 1.29, 95\% CI 1.00 to 1.66).\(^8\) The CDC researchers speculated that HIV-positive youth who engage in risky sex may know more about HIV because they set out to learn more about their illness. That explanation fits with recent findings that adolescents who start having sex earlier and use condoms inconsistently tended to know more about HIV infection.\(^15\) “Regardless of the reason,” the CDC team wrote, “these findings reconfirm what is now conventional wisdom—simply knowing about HIV infection is not sufficient to change behavior.\(^16,17\)

In youngsters already infected with HIV, a four-session individual motivational interview delivered over 10 weeks had only a short-term impact in lowering viral load.\(^18\) Researchers randomized 186 young adults (16 to 24 years old) at five adolescent HIV clinics to the intervention, which targets several risk behaviors, or to no intervention. Most study participants were African American, and all had at least one of three risk behaviors: nonadherence to antiretrovirals, substance abuse, and unprotected sex. After 6 months, viral loads of the young people randomized to the intervention were significantly lower than viral loads in the control group (\(P = 0.03\)), but the difference was no longer significant after 9 months.

What do these lackluster results say? One possibility is that, despite hard work and good intentions, behavioral scientists remain in the dark on what will make youngsters desist from risky exploits. Grim as that hypothesis sounds, the alternative is bleaker: Risk avoidance cannot be taught once an adolescent embarks on a hazardous lifestyle. If that’s true, researchers might more profitably direct their attention to wider HIV testing and better referral to care.

**Impact of child abuse and response to interventions**

Even the most inspired risk-reduction strategy delivered to the most motivated youngsters will have no impact on one HIV risk factor—sexual abuse. Numerous studies, reviewed by Clum\(^19\) and Mugavero,\(^20\) establish that childhood abuse rates in people with HIV easily outstrip those in the general population. For example, at an adolescent clinic in Washington, DC, half of 34 HIV-positive youngsters interviewed had a documented history of sexual abuse.\(^21\) Besides heightening the risk of HIV infection, abuse has been linked to worse antiretroviral adherence, high-risk sex, and other unhealthy escapades in people with HIV. Workers in this field theorize that abuse during childhood leaves victims with a sense of helplessness that cripples their ability to establish and maintain healthy relationships.\(^22\)

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One study based on in-depth life-story interviews with 40 young HIV-positive women who suffered sexual or physical abuse before age 18 describes a knotty skein of consequences, from avoidance of sex and sexual dysfunction on the one hand, to being “boy crazy” or “addicted to sex” on the other.\textsuperscript{19} Thirty of these 40 young women from three US cities endured sexual abuse, 32 physical abuse, and 22 both. The researchers rated post-traumatic stress syndrome symptoms moderate to severe in 12 of these women (30%) and severe in 6 (15%).

Abuse or violence drove many of these teens to the streets or forced them into group homes or residential centers, but “the new environments often function as contexts that appeared to increase vulnerability to risk behavior and additional abuse situations.”\textsuperscript{19} Many young women described difficulty trusting people in general, and sex partners in particular. The investigators observed that “trust and intimacy have been identified as important to negotiations of safer sex practices.” Some young women traded sex for drugs or a place to stay. Current substance use was common, though the researchers deliberately recruited some substance users (23 of 40) to study the impact in abused women.

Child abusers prey on boys as well as girls. A longitudinal study of 844 children and adolescents, 49% of them boys, defined a link between a history of sexual abuse from ages of 2 through 12 years and HIV risk behavior at age 14.\textsuperscript{22} The Longitudinal Studies of Child Abuse and Neglect (LONGSCAN) assess the antecedents and consequences of child abuse and neglect by interviewing children and their primary caregivers at age 4 and then approximately at ages 6, 8, 12, 14, 16, and 18.

This LONGSCAN analysis found boys somewhat more likely than girls to report physical abuse (35.5% versus 29.1%, \( P = 0.06 \)), and girls more likely to report sexual abuse (18.8% versus 9.9%, \( P < 0.001 \)). Similar proportions of boys and girls reported neglect (58.4% and 56.1%), emotional abuse (32% and 33.6%), and witnessed violence (77.2% and 76.4%). Statistical analysis examining various risk models linked childhood sexual abuse alone to two behaviors—alcohol use and sexual intercourse—that raise the risk of HIV infection. However, physical and emotional abuse contributed to development of HIV risk behavior beyond the risk imbued by sexual abuse alone. The LONGSCAN investigators proposed that similar maltreatment experiences predict HIV risk behaviors in both boys and girls.

As damaging as child abuse can be, it may afford HIV clinicians an earlier opportunity to diagnose and treat seropositive youngsters. A US prospective cohort study associated childhood sexual or physical abuse with a twice-higher likelihood of entering HIV care with a CD4 count still above 200 cells/mm\(^3\).\textsuperscript{20} This study involved 186 members of the Southeastern US CHASE cohort, all of whom entered HIV care after January 1996 as adults and had a CD4 count within 6 months of their first visit. Most study participants (91%) were African American, 58% had a CD4 count above 200 cells/mm\(^3\) at their first HIV clinic visit, 23% experienced childhood sexual abuse, and 33% experienced sexual or physical abuse as a child. Sexual or physical abuse doubled the chance of seeking care at a CD4 count of 200 cells/mm\(^3\) or higher (AOR 2.12, 95% CI 1.08 to 4.17, \( P = 0.03 \)). The CHASE team suggested that abuse survivors may find their way into HIV care earlier because they use health services more as a result of their traumatic histories. Earlier presentation for care...
by abused children, the researchers proposed, gives clinicians the chance to deploy “interventions that may improve patient outcomes and prevent secondary HIV infections.”

Several studies offer at least preliminary evidence that such interventions for HIV-positive people abused as children can modify risk behavior and improve antiretroviral adherence. These results seem more promising than in the risk-reduction trials in youngsters reviewed above, perhaps because the abuse intervention trials involve adults, who may respond better to such programs.

A 147-woman trial that randomized seropositive sexual abuse victims to an 11-session psychoeducational intervention or to standard care found greater sexual risk reduction and some evidence of better antiretroviral adherence in the intervention group. Another trial randomized 247 HIV-positive men and women with a history of child abuse to 15 weekly 90-minute sessions of a coping intervention or a control support group. Over 12 months of follow-up in this New York City study, alcohol and cocaine use were significantly lower in the coping intervention group. A separate analysis of this same program charted significant drops in frequency of unprotected intercourse with all partners (P < 0.001) and with HIV-negative or serostatus-unknown partners (P < 0.001).

**HIV awareness and testing in young people**

Young people may be more sexually active and risk-prone than their elders, but those traits apparently provide a negligible prod to get tested for HIV or even to consider that they may carry the virus. Part of the problem, at least in the United States, appears to be a dwindling in HIV education curiously coincidental with the arrival of robust antiretroviral regimens. The CDC reckons that the percentage of students taught about HIV/AIDS in school rose from 83% in 1991 to 91.5% in 1997, then slumped back to 88% in 2005.

Johns Hopkins University researchers compared HIV/AIDS counseling rates in 15- to 19-year-old boys who responded to the 1995 National Survey of Adolescent Males (n = 1729) or the 2002 National Survey of Family Growth (n = 1121), both nationally representative surveys. In 2002 only one third of teenage boys who reported three or more female partners, anal sex with female partners, or oral/anal sex with male partners received HIV or STI counseling from a doctor or nurse. Only one quarter who reported having sex often, with a prostitute, or with an HIV-positive person got such counseling in 2002. These rates had not improved from those recorded in 1995.

The CDC’s 2007 Youth Risk Behavior Survey figured that only 12.9% of high school students across the country ever had an HIV test, a rate slightly higher in girls (14.8%) than boys (11.1%). Black students were more likely to get tested than Hispanics or whites (22.4% versus 12.7% and 10.7%). Among students who ever had sex, 22.3% got tested for HIV, compared with a 4.0% testing rate in students with no sexual experience. The CDC now recommends that health care providers offer HIV testing as part of routine medical care for everyone between 13 and 64 years old.

Among 2007 18- to 22-year-olds who responded to the National Survey of Family Growth in 2002-2003, 34.2% had an HIV test, but students were 46% less likely to get tested than nonstudents. Among the 37.5% of survey respondents who
reported high-risk behavior, only 28.3% had an HIV test in the preceding year, and this rate did not differ between students and nonstudents.

Clinicians should not assume that youngsters who reach age 13 with no obvious HIV symptoms are seronegative, at least not in countries where black Africans make up part of the adolescent population. A nationwide United Kingdom study identified 42 adolescents 13 years old or older who apparently got the virus from their mother. Thirty of them (95%) were black African, 36 (86%) were born in sub-Saharan Africa, and 23 (55%) were girls. Half of these youngsters got screened after a relative tested positive for HIV. Only half of these teens had HIV symptoms.

Some work suggests that using rapid HIV tests can promote more testing of young people—but the type of rapid test offered could be critical. Researchers at a Cincinnati hospital-based adolescent primary care clinic offered HIV testing to 99 young people from 13 to 22 years old, giving them a choice of a rapid oral test, a rapid fingerstick test, and traditional venipuncture. While 50.5% of study participants picked the rapid oral test, 30.2% opted for traditional blood sampling and 19.2% chose the rapid fingerstick test ($P < 0.01$). Those who picked one of the two rapid tests were more likely to get their results within the study follow-up period (91.3% versus 46.7%, $P < 0.001$).

Rapid HIV testing and the CDC revision in testing advice appeared to improve testing rates in 13-to-22-year-olds studied at the same Cincinnati hospital. This retrospective review compared testing rates in 9491 young people in three periods: (1) before publication of the new CDC guidelines in 2006, (2) between that date and the introduction of rapid HIV testing in 2007, and (3) after introduction of rapid testing. The rate improved from 12.6% in period 1 to 27.7% in period 2 ($P < 0.001$) and to 44.6% in period 3 ($P < 0.001$ versus period 1 or 2). Older youngsters and boys and men got tested more than younger adolescents, girls, and women; and a genitourinary diagnosis made testing more likely.

CDC number crunchers figured that 13-to-24-year-olds account for 4.4% of HIV infections in the United States, but for 9.9% of undiagnosed infections. A 21-city CDC study of gay men in 2008 found that 44% of HIV-infected men did not know they had HIV, and that rate was highest in the youngest age groups (Table 1) and in nonwhites (54%).

### Table 1. HIV prevalence and awareness among gay men in 21 cities in 2008

<table>
<thead>
<tr>
<th>Age</th>
<th>Number tested</th>
<th>HIV prevalence (%)</th>
<th>Unaware of HIV status (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 19</td>
<td>423</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>20 to 24</td>
<td>1466</td>
<td>12</td>
<td>68</td>
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<tr>
<td>25 to 29</td>
<td>1529</td>
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<td>30 to 39</td>
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<td>21</td>
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<tr>
<td>40 to 49</td>
<td>1712</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>50 or older</td>
<td>792</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention.
An Adolescent Medicine Trials Network study of 611 gay teens and young men and 606 young lesbians reported in 2010 found HIV rates of 15.3% in the men and 0.3% of the women. While 60% of HIV-positive men did not know they had HIV when tested, none of the 18 infected women suspected they carried the virus. This study assessed the value of HIV testing in venues—where youngsters hang out, rather than where they live—including clubs, parks, streets, and neighborhood service or commercial centers. Venue-based testing appeared to be an effective strategy for young gay and bisexual men, but less so for young lesbians.

**HIV stigma and its impact on young people**

Ryan White, a hemophiliac diagnosed with AIDS in 1984, died 6 years later. But he survives as the first nationally known teenage victim of HIV stigma, after the Kokomo, Indiana school district barred White from classes because of his illness. White won his legal battle to return to school and played an inspiring role in raising awareness of the disease.

Although people with HIV now have legislated rights that White lacked, stigma often remains a crushing burden, especially for youngsters. Stigma can affect every aspect of HIV care, from diagnosis through antiretroviral adherence, while posing countless emotional and psychological threats to young people with HIV. For example, a computer-assisted telephone survey of 18-to-39-year-old blacks and Hispanics in Broward County, Florida, linked perceived stigma to a lower chance of getting tested for HIV (AOR 0.78, 95% CI 0.62 to 0.99, \(P = 0.046\)) and failure to participate in HIV-prevention efforts (AOR = 0.53, 95% CI 0.34 to 0.85, \(P = 0.008\)). In 2004 and 2005, interviews with 42 young gay men and transgendered people (average age 21) in Chicago showed that those diagnosed with HIV in the past year had stigma scores just as high as those diagnosed in earlier years. The study correlated high stigma scores with depression, romantic loneliness, poor social support, and low self-esteem.

A 2006 study of stigma experienced or perceived by 147 substance-using HIV-positive youth in Los Angeles, San Francisco, and New York found that 131 (89%) of these 18-to-29-year-olds perceived stigma and 46 (31%) reported stigma-related experiences. While 80% said someone refused to eat with them because they had HIV, 54% reported they had to move, 28% were shut out by a family member, 20% lost a friend, and 13% were “hassled or verbally threatened.” Reported stigma-related experiences did not differ by age, gender, ethnicity, years since first testing HIV positive, or antiretroviral use. Among gay or bisexual study participants, symptomatic HIV infection or an AIDS diagnosis raised chances of stigma-related avoidance by others 10 times, but symptomatic HIV or AIDS did not have this impact in heterosexual study participants. Women and study participants with a lower proportion of friends and family members who knew their HIV status had higher levels of perceived social rejection, shame, and overall perceived stigma.

Among 40 young (16-to-24-year-old) black gay or bisexual men in Philadelphia, 90% reported sexual minority stigma, 88% reported HIV stigma, and 78% reported both. The men felt social avoidance reflected their sex preference more than their HIV status (\(r = 0.63\)), but feelings of shame were more strongly tied to HIV infection than to their sex preference (\(r = 0.54\)). Men feeling high-level HIV stigma were more likely
to have unprotected sex while high on drugs or alcohol and more likely to have receptive anal intercourse. Feelings of HIV stigma did not wane as time since HIV diagnosis grew.

In interviews with RITA!, Pat Flynn and Bill Kapogiannis suggest approaches to helping youngsters cope with HIV stigma. In some Memphis communities stigma has become so ingrained, Flynn observed, that health workers advise HIV-positive youth to move to another part of the city. Kapogiannis believes clinicians can start addressing stigma by nurturing active dialogs with the community.

**Second-rate response to antiretroviral therapy**

Epidemiologists divide HIV-positive teens and young adults into two groups—the “aging-up” contingent that got infected perinatally and survived into their teens and early 20s, and a newly infected covey that picked up HIV in their teens and 20s through high-risk behavior. Antiretroviral histories of the aging-up cluster often mirror those of adults who began treatment in the pre-HAART era with single or double nucleosides, then added a protease inhibitor (PI) or non-nucleoside (NNRTI) to a faltering antiretroviral duo and ended up with multiple resistance mutations and multiclass failure. You might think that newly infected youngsters, as a group, would respond to triple antiretroviral therapy as consistently as adults starting their first regimen. But recent studies found they don’t.

The earlier study, reported in 2006 and 2007, involves the Pediatric AIDS Clinical Trials Group (PACTG) 381 cohort. The 120 study participants had a median age of 18.8 years, and all began a first antiretroviral regimen including two nucleosides and a PI or efavirenz. After 24 weeks of treatment, only 69 of 118 evaluable cohort members (59%) had a viral load below 400 copies, a rate far below those seen with the same regimens in adult trials. At week 60 the response rate dropped to 46%, and at week 148 to 24%. In virologic responders, CD4 counts reached levels equivalent to those in HIV-negative youth. But CD4 percent, CD8 count and percent, and CD8 activation markers remained significantly different from levels in the HIV-negative population. Among study participants who reached week 148 without a sub-400 viral load, the CD4 count had not changed from pretreatment levels.

COHERE cohort investigators compared virologic and immunologic responses in 10 age groups including 49,921 Europeans starting their first antiretroviral combination between January 1998 and July 2006: younger than 2, 2 to 5, 6 to 12, 13 to 17, 18 to 29, 30 to 39 (the reference group for statistical comparisons), 40 to 49, 50 to 54, 55 to 59, and 60 years or older. Defining virologic response as consecutive loads below 50 copies 12 months after starting therapy, the COHERE team charted improving response rates starting after age 18. The 13-to-17-year-old group had a lower response rate than any adult group (Figure 2).
Compared with the 30-to-39 group, 13-to-17-year olds were 22% less like to meet this virologic response criterion (adjusted hazard ratio [AHR] 0.78, 95% CI 0.65 to 0.94) and 18-to-29-year-olds were 10% less likely to get under 50 copies after 1 year of treatment (AHR 0.90, 95% CI 0.88 to 0.93). The 13-to-17 group was 31% more likely to stop therapy than the 30-to-39 group (AHR 1.31, 95% CI 0.99 to 1.73), and the 18-to-29 group was 11% more likely to quit (AHR 1.11, 95% CI 1.06 to 1.17). Despite the worse virologic response in the teen and young adult groups, their CD4 responses matched those of 30-to-39-year-olds, and the younger groups had nonsignificantly lower rates of new AIDS diagnoses or death: 4.8% for 13-to-17, 5.2% for 18-to-29, and 7.0% for 30-to-39.

Virologic response rates proved similarly pallid in a 2010 analysis of a French cohort of perinatally infected children who survived into adolescence. Everyone in the cohort was born before December 1993 and included in the French Perinatal Cohort at birth. Of 348 children who entered the cohort, 210 (60%) were alive and in follow-up at the time of this analysis; their median age stood at 15 years. While 77% had started triple therapy, 5% were taking two nucleosides, 16% had stopped treatment, and 2% never started. Although median CD4 count reached 557 cells/mm$^3$ and 94% had more than 200 CD4s, only 43% had an undetectable viral load, including only 54.5% taking triple therapy. The antiretroviral response rate was even worse in a 13-city US study of 154 adolescents in the REACH group. Only 50 (32.5%) of these youngsters reached and maintained an undetectable viral load.

What explains these poor virologic response rates? In PACTG 381 three factors predicted virologic failure: “complete” adherence during the first 16 weeks of the study halved the failure risk (relative risk [RR] 0.48, 95% CI 0.27 to 0.87, $P = 0.016$), every 10-fold higher pretreatment viral load raised the risk more than 50% (RR 1.53, 95% CI 1.11 to 2.12, $P = 0.010$), and every 100-cell higher naive CD8 count upped the risk almost 20% (RR 1.18, 95% CI 1.01 to 1.38, $P = 0.034$).
In COHERE, the 6-to-12 group, the 13-to-17 group, and the 18-to-29 group were 13%, 22%, and 10% less likely to reach an undetectable load in 1 year than the 30-to-39 group. Those results, the investigators proposed, could reflect “the more disordered lifestyles that may be present among adolescents and younger adults, which, in turn, may have an impact on adherence.” REACH study investigators calculated that better than 50% adherence lowered the odds of a poor virologic response 60% (AOR 0.40, 95% CI 0.2 to 1.0), while suboptimal treatment before triple therapy more than doubled chances of poor virologic response (AOR 2.6, 95% CI 1.1 to 5.7).

No one doubts that antiretroviral therapy is essential to the survival of HIV-positive children and adolescents. A 2008 analysis of 1236 children and adolescents enrolled in PACTG 219/219C calculated a 76% lower risk of death in the 866 who began an NNRTI-based or a PI-based triple combination rather than some other regimen through 10 years of follow-up (HR 0.24, 95% CI 0.11 to 0.51, \( P = 0.003 \)). This analysis adjusted for age, gender, race/ethnicity, week of follow-up, and calendar year at baseline, plus baseline and time-varying values of CDC clinical category, CD4 cell percent, total lymphocyte count, white blood cell count, hematocrit, and albumin. In the same analysis, factors that independently raised the risk of death were more advanced CDC clinical category, lower CD4 percent, and lower total lymphocyte count upon entering the study:

- CD4 percent <5% (vs >25%): HR 45.94 (95% CI 12.42 to 169.97, \( P < 0.0001 \))
- CD4 percent 5% to 14% (vs >25%): HR 22.07 (95% CI 6.19 to 78.68, \( P < 0.0001 \))
- CD4 percent 15% to 24% (vs >25%): HR 3.77 (95% CI 1.04 to 13.66, \( P = 0.04 \))
- Total lymphocytes <1500 cells/mm\(^3\) (vs higher): HR 2.10 (95% CI 1.04 to 3.92, \( P = 0.04 \))

All these youngsters were infected perinatally, and none had taken antiretrovirals before entering the PACTG studies.

**Improving adherence to antiretrovirals in young people**

Two studies that charted low virologic response rates in adolescents and young adults starting antiretrovirals—PACTG 381 and REACH—both pinpointed poor adherence as an independent driver of poor response. Adherence could not be determined in the huge COHERE cohort but probably played a role. Research suggests at least two dozen reasons for wobbly adherence in young people, summarized by Patricia Flynn of St. Jude Children’s Hospital (Table 2).
Table 2. Characteristics associated with reduced antiretroviral adherence in adolescents

| Patient characteristics | • Younger age  
|                         | • Male gender  
|                         | • Not in school  
|                         | • Distrust of health care providers  
|                         | • Lack of knowledge about HIV  |
| Structural factors      | • Unstable housing  
|                         | • Home in rural area  
|                         | • Problems with insurance  
|                         | • Transportation barriers  |
| Antiretroviral-related factors | • Increasing regimen complexity  
|                         | • Side effects  
|                         | • Longer time on antiretroviral therapy  |
| Social factors          | • Parent as caregiver  
|                         | • Lower education level of caregiver  
|                         | • Disorganized family  
|                         | • Poverty  
|                         | • Fear of stigma and discrimination  
|                         | • Lack of HIV status disclosure  
|                         | • Prior sexual abuse  |
| Mental health factors   | • Drug or alcohol use  
|                         | • Depression  
|                         | • Psychic distress  
|                         | • Decreased life satisfaction  
|                         | • Decreased self-efficacy (belief in one’s ability to accomplish goals)  
|                         | • Decreased outcome expectancy  |

Adapted from Patricia Flynn.⁴⁶
In reporting long-term results of PACTG 381, the investigators defined perfect adherence as missing no doses in the 3 days before each of four study visits. Adolescents with perfect adherence in weeks 4 to 16 had better 24-week and 144-week virologic responses than less adherent youth. The PACTG investigators later reanalyzed the impact of five adherence measures on three long-term outcomes: (1) controlled viral load (viral load ≤400 copies/mL by week 24 and sustained to each time point versus a confirmed rebound above 400 copies/mL), (2) immunologic reconstitution (a CD4 gain of at least 100 cells/mm³), and (3) good adherence (on treatment with self-reported adherence greater than 95% versus adherence 95% or less or off treatment). Among 102 adolescents treated for at least 24 weeks, those with good long-term outcomes at weeks 48, 96, and 144 were more likely to have perfect adherence, higher mean adherence in weeks 4 to 24, and lower variability in adherence over the first 24 weeks. Higher average adherence at week 24 predicted virologic control through week 144.

Considering these results, the PACTG team offered specific adherence recommendations for clinicians: “Health care providers should monitor self-reported adherence by patients as they start new antiretroviral regimens and over the first few months. We recommend they ask about numbers of doses missed and over how many days, rather than just asking if subjects have missed any doses (yes/no). If providers identify problems, they can intervene early to establish better adherence patterns, which will result in better longer term outcomes.” Table 3 summarizes adherence advice from this study and those considered below.

A systematic review of 60 nonintervention adherence studies in children and adolescents included 42 studies of 7427 youngsters in high-income countries and 18 studies of 3729 youths in low- and middle-income countries. Good adherence, defined as taking at least 80% of antiretroviral doses, was less prevalent in high-income countries (average 61%, 95% CI 54% to 68%) than in low-income countries (average 73%, 95% CI 66% to 80%), a difference that approached statistical significance (P = 0.06). In the richer countries, rates of at least 80% adherence were similarly low in studies with fewer than 3 months of assessment (62%, 95% CI 55% to 69%) and studies with 3-month or longer assessment (65%, 95% CI 51% to 78%).

Another recent systematic review of 21 US studies on adherence in 13-to-24-year-olds determined that “psychosocial factors, in particular depression and anxiety, were consistently associated with poorer adherence across studies.” After analyzing these 21 studies, the investigators recommended assessing adherence in a context that considers (1) HIV stigma and disclosure, (2) peer relations, (3) caregiver stress, (4) mental health, (5) substance use, and (6) duration of antiretroviral therapy. They suggested secondary HIV prevention interventions as “a possible mode through which to deliver individually tailored adherence skill building and counseling to improve medication adherence.”

Perhaps the most important finding of this multi-study review is that “individual demographic factors and readily observable patient characteristics failed to distinguish adherent from nonadherent individuals.” The most promising strategies to improve adherence in young people involved patient and caregiver education, self-monitoring, peer support, and telephone follow-up. This
helpful article is online at http://www.iasusa.org/pub/topics/2009/issue1/14.pdf, and Table 3 details some of the reviewers’ advice on improving adherence. The table on page 60 of this issue offers adherence tips from some leading HIV clinicians. In an interview in this issue, Bill Kapogiannis stresses the value of creating an “adolescent-friendly” practice and offers practical pointers on doing so.

**Table 3. Adherence advice from recent studies of adolescents and young adults**

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| Adherence assessment          | • Adherence should be assessed in a broad context including HIV stigma and disclosure, peer relations, mental health, substance use, length of time on antiretrovirals, and caregiver stress.  
  • Assessing adherence regularly improves adherence. |
| Adherence counseling          | • Interventions aimed at secondary prevention in youth may provide a good opportunity to offer youngsters individually tailored adherence counseling. |
| Responsibility for adherence  | • Determining when youngsters may assume partial or complete responsibility for adherence requires careful assessment for cognitive or emotional difficulties that may interfere with the ability to behave responsibly. |
| Demographic factors           | • Race and primary language did not affect adherence in two large studies of US adolescents. |
| Family and friend involvement | • Psychosocial support for families may be essential to good adherence by young people.  
  • Using a buddy system as a dosing reminder greatly lowered the risk of poor adherence in a large PACTG analysis. |
| Depression                    | • Depression consistently correlates with poor adolescent adherence across studies.  
  • Depression is underdiagnosed and therefore undertreated in adolescents.  
  • Adolescents with symptoms of depression may need antidepressant therapy, counseling, and more intense adherence interventions. |
| Other emotional factors        | • Studies of young people associated poor adherence with anxiety symptoms, withdrawal, and self-destructive escape coping mechanisms.  
  • Antipsychotic therapy lowered the risk of poor adherence almost 90% in one study. |
| Alcohol and marijuana         | • Drinking alcohol upped the risk of poor adherence on the preceding Saturday and in the preceding month of an Adolescent Medicine Trials Network study.  
  • Marijuana use emerged as the sole independent predictor of poor appointment keeping in an 18-month study of 178 young women with HIV. |
| Education level               | • High-school dropouts probably need more intense counseling to maintain good adherence. |
| Antiretroviral duration        | • Studies consistently document waning adherence with longer antiretroviral treatment duration. |
PACTG 219C researchers studied 2088 perinatally infected children and adolescents in this prospective cohort to identify predictors of adherence to all antiretrovirals over the preceding 3 days. Most children, 84%, reported complete adherence by this measure. That high rate may reflect attention devoted to adherence at PACTG sites, the motivation of PACTG trial participants, or a combination of those factors. Or they may reflect the short (3-day) adherence recall period. Whatever the reason, this high adherence rate strongly suggests that good adherence is feasible in young people, at least in the short term. Among all cohort members assessed, median age stood at 11.5 years (interquartile range [IQR] 8.7 to 14.1). Among 772 youngsters who assessed adherence themselves, median age measured 14.4 years (IQR 12.6 to 16.5). Girls made up slightly more than half of the study group (52%), 59% were African American, and 25% were Hispanic.

The final multivariate model to predict nonadherence in this study incorporated age and important variables from six areas: demographics, health indicators, antiretroviral and psychiatric medication use, adherence assessment characteristics, quality-of-life measures, and neurologic or psychiatric diagnoses. Among variables that can be modified, three independently lowered the risk of nonadherence: use of antipsychotic medication cut the risk of nonadherence 88% (estimated OR 0.12, 95% CI 0.02 to 0.88, \( P = 0.04 \)), using a buddy system as a dosing reminder trimmed the risk 42% (estimated OR 0.58, 95% CI 0.34 to 0.98, \( P = 0.04 \)), and each additional previous adherence assessment lowered the risk 21% (estimated OR 0.79, 95% CI 0.65 to 0.95, \( P = 0.01 \)).

Lowered nonadherence risk
- Adult caregiver other than biological parent: OR 0.66, 95% CI 0.51 to 0.86, \( P = 0.002 \)
- Each additional caregiver education level: OR 0.84, 95% CI 0.75 to 0.95, \( P = 0.003 \)

Raised nonadherence risk
- Each year of age: OR 1.05, 95% CI 1.00 to 1.10, \( P = 0.07 \)
- Female gender: OR 1.36, 95% CI 1.05 to 1.77, \( P = 0.02 \)
- Viral load above 400 copies/mL: OR 2.46, 95% CI 1.85 to 3.26, \( P < 0.001 \)
- Depression or anxiety diagnosis: OR 1.85, 95% CI 0.95 to 3.61, \( P = 0.07 \)
- Repeating a grade in school: OR 1.36, 95% CI 1.02 to 1.81, \( P = 0.03 \)
- Recent stressful financial life event: OR 1.55, 95% CI 1.14 to 2.09, \( P = 0.005 \)
- Adherence assessed by child/adolescent: OR 1.90, 95% CI 1.36 to 2.65, \( P < 0.001 \)

This analysis found no association between nonadherence and race, primary language, knowledge of HIV status, antiretroviral doses per day, CD4 count or percent, current PI use, or current HAART use.

A longitudinal study of 231 adolescents in 13 US cities linked poor adherence to dropping out of high school, more alcohol use, and depression. This study by the Adolescent Medicine Trials Network involved only adolescents taking an antiretroviral combination including a PI or an NNRTI who reported adherence over the last month, on the preceding Saturday, or on the preceding weekday during a face-to-face interview. For monthly adherence, youngsters rated their pill taking as (1) none, (2) once in a while, (3) half the time, (4) most of the time, or (5) all the time. For Saturday or weekday adherence, study participants were considered adherent if they correctly identified the number and timing of prescribed

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antiretrovirals. The investigators assessed depression with the 20-item Center for Epidemiologic Studies Depression Scale.

Of the 231 study participants, 168 (73%) were girls or young women, 173 (75%) were African American, two thirds had an undetectable viral load, and CD4 counts were below 200 cells/mm³ in 12%, 200 to 499 cells/mm³ in 45%, and 500 cells/mm³ or higher in 43%. At the first study visit, the group’s age averaged 18.4 years and ranged from 15 to 22. At that visit, 70% of these young people reported taking antiretrovirals all or most of the time in the preceding month, 70% had good adherence on the preceding weekend day, and 63% had good adherence on the preceding Saturday.

Multivariate analysis identified only one factor that predicted adherence on the preceding weekday: CDC late-stage disease lowered chances of good adherence more than 50% (AOR 0.47, 95% CI 0.28 to 0.80). High-school dropouts had a 40% lower chance of adherence on the preceding Saturday (AOR 0.61, 95% CI 0.39 to 0.94), and drinking more alcohol (measured on a 5-point scale) lowered Saturday adherence chances 33% (AOR 0.67, 95% CI 0.55 to 0.82). Each 10-fold higher CD4 count almost doubled chances of good adherence on the preceding weekday (AOR 1.89, 95% CI 1.13 to 3.15). High-school dropouts and heavier alcohol users had a lower chances of good adherence in the preceding month (AOR 0.54, 95% CI 0.36 to 0.80, for dropping out, and 0.80, 95% CI 0.66 to 0.98, for alcohol).

Next the investigators assessed adherence in 65 adolescents who had good adherence at the first visit and at least four consecutive visits at 3-month intervals. Follow-up averaged 10.6 months and ranged from 3 to 21 months. In this study phase, the researchers considered good adherence as taking prescribed doses most or all of the time, while nonadherence meant never taking doses or taking antiretrovirals once in a while or half the time. Median time to becoming nonadherent was 12 months (95% CI 9 to 15). Univariate analysis determined that younger age lowered the risk of nonadherence (HR 0.11, 95% CI 0.4 to 0.30), while depression more than doubled the risk of becoming nonadherent (HR 2.21, 95% CI 1.1 to 4.42). Race or gender did not affect adherence in this longitudinal analysis.

The researchers noted that earlier study of the cohort from which these adolescents were drawn found that “depressive symptoms and disorders in adolescents are often underidentified and, therefore, undertreated.” They recommended depression screening for adolescents being considered for antiretroviral therapy. “Those who are depressed,” they proposed, “may need both treatment for depression as well as interventions to assist them in adhering to their new treatment regimen for successful long-term adherence.” The link between alcohol use and poor adherence suggested to these investigators that adolescents should be taught to plan their pill taking for times when they are not drinking or using recreational drugs, and that some adolescents may need referral to treatment for substance use.

Chances of steady antiretroviral adherence are slimmer in young people who cannot keep their HIV clinic appointments. An 18-month US study that identified an array of symptoms and behaviors that may thwart antiretroviral adherence and appointment keeping singled out just one—marijuana use—as an independent predictor of poor appointment keeping. This five-city survey of 178 young women with an average age of 20.6 years found that 47% used alcohol, 37% smoked marijuana, 42% had depressive symptoms, and continued...
10% had a diagnosable mood disorder. Study participants kept only 67% of their HIV clinic appointments. Statistical analysis that factored in age and health status identified only marijuana use as an independent driver of poor appointment keeping.

**Gauging lifelong cardiovascular risk in HIV-positive youth**

Cardiovascular disease emerged as a mortal concern for people with HIV when triple therapy rescued them from an early AIDS death but PI regimens raised the risk of myocardial infarction in big cohort studies.\(^53,54\) Apportioning the risk due to antiretrovirals versus HIV itself proved problematic. The SMART treatment interruption trial, for example, found that continuous antiretroviral therapy lowered the risk of serious cardiovascular disease compared with intermittent treatment.\(^55\) SMART investigators strongly linked inflammation and coagulation markers to all-cause mortality in SMART, and levels of those markers were higher during treatment breaks.\(^56\)

Still, swelling lipid readings with certain antiretrovirals and lifelong exposure even to low levels of HIV stir valid worries that infected children and adolescents face a heightened heart disease risk over several decades. Research on cardiovascular risk in children on and off antiretroviral therapy, reviewed below, links higher lipid levels to treatment with both PIs and NNRTIs. Some work ties HIV and antiretroviral therapy to increased arterial stiffness or carotid artery intima media thickness (IMT) in youngsters. But, as in adult studies, these findings can be hard to interpret.

A 2-year cohort study at London’s Imperial College charted climbing but stabilizing levels of total cholesterol as antiretroviral therapy continued in perinatally infected children up to 16 years old.\(^57\) Both “bad” low-density lipoprotein (LDL) cholesterol and “good” high-density lipoprotein (HDL) cholesterol rose throughout the study, but the total-to-HDL cholesterol ratio improved. This analysis involved 146 children whose nonfasting lipids were measured during 1208 appointments from January 2000 to June 2003. Two thirds of the children were African, and 75 (51%) were taking antiretrovirals.

At the first study visit, antiretroviral-treated children had significantly higher total cholesterol (162 versus 135 mg/dL, \(P < 0.0001\)), LDL cholesterol (92 versus 82 mg/dL, \(P = 0.0003\)), and HDL cholesterol (40 versus 32 mg/dL, \(P < 0.0001\)) than did untreated children. Lipid levels rose as antiretroviral therapy continued, but appeared to stabilize. After 2 years total cholesterol in antiretroviral-treated children rose 36 mg/dL (\(P < 0.0001\)), and 29 (20%) had total cholesterol levels above the 95th percentile. Over that period, LDL cholesterol rose 27 mg/dL and HDL cholesterol 12 mg/dL (\(P < 0.0001\) for both changes). For most children, lipid levels remained within the normal range.

Multivariate analysis associated non-PI regimens with a significantly lowered (improved) total/HDL ratio. Although the ratio rose with PI regimens, that effect did not reach significance in multivariate analysis. More than half of study participants had very low HDL cholesterol concentrations at their first study visit, but these levels rose to normal as treatment continued. The Imperial College researchers suggested that “this rise in cardio-protective HDL may represent a positive effect of treatment.”
A US study of 178 perinatally infected children found that 47% had high cholesterol (at or above 200 mg/dL) and 67% had high triglycerides (at or above 150 mg/dL) at some point during a 1999-2004 cohort study. This PACTS-HOPE cohort analysis considered 2694 cholesterol measurements and 2541 triglyceride values. Multivariate modeling determined that children taking a PI-based regimen had more than a quadrupled risk of high cholesterol (OR 4.3, 95% CI 2.3 to 8.2, \(P < 0.001\)) and more than doubled the risk of high triglycerides (OR 2.5, 95% CI 1.5 to 4.3, \(P < 0.001\)). Median total cholesterol rose significantly after a PI regimen began and continued to climb through 24 months of treatment, but not after that. PI duration had no impact on triglycerides. Like the London researchers, this US team recommended regular lipid monitoring in youngsters taking antiretrovirals.

The PACTG 219C cohort study linked high total cholesterol to both PIs and NNRTIs, to good adherence, and to low viral loads. A 2005 report on this cohort assessed hypercholesterolemia in 1812 perinatally infected children and adolescents from 4 to 19 years old and in 187 HIV-negative children. In the HIV group, 229 youth (13.0%) had hypercholesterolemia, compared with 9 (4.8%) in the seronegative group.

In a 2008 report, after the investigators excluded 13% of the children who had high cholesterol at their first visit, they focused on 2122 perinatally infected children and adolescents. The study group included 1027 boys (48%), 1095 girls (52%), and 414 youngsters (19%) 13 years old or older. The cohort consisted mostly of blacks (59%) and Hispanics (27%). The PACTG team defined incident hypercholesterolemia as two consecutive total cholesterol quotients of 220 mg/dL or higher in children with a value below that when they entered the cohort. The investigators chose 220 mg/dL as the cutoff instead of 200 to avoid misclassification, because cholesterol was usually measured in nonfasting samples. The investigators did not consider antiretroviral duration but rather whether a child had begun a specific regimen at each time point.

Through a median follow-up of 50.4 months, hypercholesterolemia developed in 277 children (13%) to yield an overall incidence of 3.4 cases per 100 person-years. Most children (78%) used a boosted or an unboosted PI at some point during follow-up. A statistical model that considered antiretroviral use, viral load, age, and self-reported adherence at first visit found that use of PIs or NNRTIs independently raised the risk of hypercholesterolemia when compared with no antiretrovirals at the noted adjusted hazard ratios (Fig. 3) \(P < 0.001\) for all comparisons).

**Figure 3.** Three antiretroviral variables independently predicted a confirmed new cholesterol level above 220 mg/dL in a PACTG study of 2122 perinatally infected children and adolescents.
In this analysis, treatment with lopinavir/ritonavir did not magnify the risk of high cholesterol more than use of other boosted PIs, and there was no risk difference between efavirenz and nevirapine. Having a viral load above 400 copies/mL independently lowered the risk of high cholesterol, as did age under 13 years. Children with self-reported 100% adherence over the past 3 days had a 62% higher risk of hypercholesterolemia than children with imperfect adherence (AHR 1.62, 95% CI 1.07 to 2.45, \( P = 0.01 \)). Gender, race, and CD4 percent when entering the study had no impact on hypercholesterolemia.

Because incidence of hypercholesterolemia remained constant over time, instead of leveling off as in the two smaller longitudinal cohort studies, the PACTG team proposed that “the proportion of children with hypercholesterolemia is likely to continue to increase over time.”

High cholesterol levels in children with HIV are similar to elevations measured in people heterozygous for familial hypercholesterolemia; thus the researchers suggested HIV-positive children with high cholesterol may have a similar risk of premature atherosclerotic disease.

A 2010 comparison of 173 behaviorally infected adolescents and young women and 61 HIV-negative controls found high proportions of overweight, cigarette smoking, and drug use in both groups and higher triglycerides, total cholesterol, and non-HDL cholesterol in antiretroviral-treated HIV groups than in women without HIV. The youngsters with HIV were 14 to 24 years old (median 20), while the 61 HIV-negative young women also had a median age of 20. Both groups were recruited from the Adolescent Medicine Trials Network. In the HIV group, 85 young women (49%) had no antiretroviral experience, 33 (19%) were taking an NNRTI but no PI for at least 3 months, 36 (21%) were taking a PI but not an NNRTI for at least 3 months, and 19 (11%) were taking a regimen containing neither a PI nor an NNRTI for at least 3 months. The investigators measured lipids, glucose, and other values in fasting blood samples.

The HIV group included a higher proportion of blacks (77% versus 56%, \( P = 0.005 \)), a higher proportion of current drug users (59% versus 36%, \( P = 0.02 \)), and a lower proportion of regular exercisers (32% versus 53%, \( P = 0.005 \)). More than 60% in both groups drank alcohol, and one third in each group smoked cigarettes. About 40% in each group had a family history of diabetes, and about 30% had a family history of cardiovascular disease. More than 40% in each group were overweight or obese (body mass index at or above 25 kg/m²).

Among young women with HIV, time since diagnosis ranged from 0.9 year in the antiretroviral-naive group to 3.9 in the PI group. Median CD4 counts were in the high 400s across all the HIV groups. Median current viral load lay below 400 copies/mL in the three antiretroviral-treated groups and at 6066 copies/mL in the untreated group. Cholesterol and triglyceride levels were consistently higher in the young women with HIV than in HIV-negative controls:

- Triglycerides significantly higher in all HIV groups than in HIV-negative controls
- Triglycerides significantly higher in NNRTI group than in antiretroviral naive
- Total cholesterol significantly higher in NNRTI and PI groups than in antiretroviral-naive women or HIV-negative controls
• “Good” HDL cholesterol significantly lower in antiretroviral-naive and no-PI/no-NNRTI groups than in HIV-negative controls
• Non-HDL cholesterol significantly higher in NNRTI and PI groups than in HIV-negative controls

Nearly 30% in all antiretroviral-treated groups had triglycerides above 130 mg/dL, while more than 25% taking a PI had total cholesterol above 200 mg/dL. About 30% of antiretroviral-naive and NNRTI users had HDL cholesterol concentrations below 35 mg/dL, while more than 40% on a no-PI/no-NNRTI regimen had HDL cholesterol that low. More than 20% taking a PI had LDL cholesterol levels above 130 mg/dL or non-HDL levels above 160 mg/dL. The investigators stressed that the antiretroviral-naive HIV group had significantly higher triglycerides and significantly lower HDL levels than women without HIV. High-sensitivity C-reactive protein, a marker of inflammation and a heart disease risk factor, topped the upper limit of normal in approximately 40% of young women taking antiretrovirals.

Comparison of 42 HIV-positive perinatally infected children with 4437 age- and gender-matched children in the nationally representative US NHANES cohort found significantly higher triglycerides and significantly lower HDL cholesterol in the HIV group. The HIV-positive children came from sites in Boston and Rochester; 48% were black and 19% Hispanic. Their age averaged 10.1 years (range 2.7 to 18.9), 27 (64%) were girls, two thirds had CDC class B or C HIV infection, and 32 (76%) were taking antiretrovirals at their first study visit. Average fasting triglycerides in the HIV group measured 136 mg/dL, compared with 90 mg/dL in NHANES controls (P < 0.001). Respective average HDL cholesterol concentrations were 47 and 54 mg/dL (P < 0.001). In multivariate analyses, PI therapy was independently associated with higher triglycerides, higher LDL cholesterol, and lower HDL cholesterol, while NNRTI therapy was associated with lower visceral fat and higher “good” HDL cholesterol. Of the four lipid studies reviewed here, this is the only one to find a protective effect with NNRTIs.

Several studies of children and adolescents link HIV infection and/or antiretroviral therapy to increased arterial stiffness or greater carotid intima media thickness (cIMT), two validated harbingers of heart disease in adults. But one study suggested cIMT can improve with continuing antiretroviral therapy.

University College London researchers compared arterial stiffness measured by pulse wave velocity in 83 children with HIV (average age 11.0 +/-3.1 years) and 59 healthy controls (average age 12.2 +/- 2.8 years). Forty-eight children (58%) in the HIV group were taking antiretrovirals, including 23 (28%) taking a PI. Pulse wave velocity was significantly greater in children with HIV than in the control group (P < 0.05), and it rose significantly with age in the HIV group, but not in controls. Pulse wave velocity and total cholesterol were significantly greater in antiretroviral-experienced children than in untreated children with HIV (P < 0.001). Multivariate analysis found four independent predictors of increased arterial stiffness: antiretroviral therapy, higher systolic blood pressure, HIV disease severity, and higher total cholesterol.

A single-center cross-sectional study compared cIMT in 31 children with HIV and 31 HIV-negative controls. Everyone with HIV was taking a stable antiretroviral regimen (for a median of 64...
months), 84% had a viral load below 400 copies/mL, and median CD4 percent was 34%. Two thirds of study participants were girls and two thirds were black. Median age was 9 years and ranged from 2 to 21. Nobody had hypertension or diabetes, and no one smoked or had a family history of premature cardiovascular disease. Left and right common carotid IMT and left and right internal carotid IMT were significantly greater in the HIV group. Longer antiretroviral duration was the only factor associated with greater cIMT in the HIV group. Longer PI duration, HIV disease factors, and classic atherosclerosis risk factors did not predict cIMT in the HIV-positive children.

Another single-center case-control study compared 19 young adults with HIV and 19 HIV-negative controls matched by gender, age, and body mass index. Age ranged from 17 to 23 years in this study group, and body mass index from 16 to 25.6 kg/m². Average common carotid IMT was significantly greater in the HIV group (0.5 versus 0.1 mm, \( P < 0.001 \)). HIV infection and male gender were both associated with greater cIMT (\( P < 0.001 \)), as was longer duration of treatment with a PI or an NNRTI (\( P = 0.019 \)).

The first longitudinal study of cIMT in children with or without HIV also found significantly greater cIMT in the HIV group, but only at the first study visit. After 48 weeks of antiretroviral therapy, cIMT levels in children with HIV declined to match those of the HIV-negative group. In this single-center study at Emory University in Atlanta, median age stood at 10 years and ranged from 2 to 21 in the HIV group. Thirty youngsters with HIV (86%) were taking antiretrovirals, 27 (77%) had a viral load below 400 copies/mL, and median CD4 percent stood at 32%. At the first study visit, internal carotid IMT was significantly greater in the HIV group (0.90 versus 0.78 mm, \( P = 0.01 \)), as was common carotid IMT (1.00 versus 0.95 mm, \( P = 0.05 \)). After 48 weeks, as the CD4 percent rose and LDL cholesterol fell in the HIV group, internal carotid IMT dropped by a median of 0.23 mm and common carotid IMT fell by a median of 0.15 mm (\( P < 0.01 \) for both declines). At that point, internal and common carotid IMT no longer differed significantly between children with HIV and HIV-negative controls.

The investigators believe their findings “suggest that HIV-infected children/young adults are at high risk of cardiovascular disease, but lipid control, immune restoration, and viral suppression with continuous antiretroviral therapy may prevent its worsening.”

Studies of antiretroviral-treated adults with HIV have not documented cIMT regression. For example, a small Spanish trial that randomized people to aggressive versus standard strategies to lower LDL cholesterol recorded equivalent median cIMT gains in the two groups (+1.63% and +1.79%, \( P = 0.59 \)). A Dutch study charted increasing cIMT through 24 months in 37 antiretroviral-naive people who started lopinavir/ritonavir plus zidovudine/lamivudine or lopinavir/ritonavir plus nevirapine (+0.061 mm and +0.044 mm). A 12-month analysis of common carotid IMT in a 346-person French cohort documented a small but significant increase over that time (from 0.54 to 0.56 mm), though there was no significant association with type or dura-
tion of antiretroviral exposure. A US study of 62 HIV-positive adults and 32 healthy controls does suggest a rationale for lower cIMT in people responding to antiretroviral therapy: two inflammation markers, tumor necrosis factor alpha and interleukin 6, correlated with common carotid IMT in the HIV group, while tumor necrosis factor alpha and high-sensitivity C-reactive protein correlated with common carotid IMT in the HIV-negative group.

Together the findings in children and adolescents indicate that HIV and antiretrovirals do conspire to heighten the risk of cardiovascular disease in the youngest patients. The finding that cIMT declines from high levels (relative to HIV-negative children) as antiretroviral therapy continues needs confirmation and further analysis in bigger groups. But it offers hope that HIV infection and its treatment may not send youngsters down a one-way road to heart disease. On the other hand, the largest longitudinal study of lipid ramblings in youngsters yielded evidence that there is no lipid plateau with ongoing antiretroviral therapy, as two smaller longitudinal studies suggested.

Most HIV clinicians probably routinely monitor lipids and perhaps other cardiovascular markers in children and adolescents. Current US guidelines call for fasting lipid and glucose measures in adolescents and adults “if the patient is considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy.” The panel argues that “HIV suppression with antiretroviral therapy may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other comorbidities reported in HIV-infected cohorts.” But these experts do not address the longer-term risk of antiretroviral cardiotoxicity in children and adolescents.

The US pediatric HIV panel says “it is unclear what the long-term risks of lipid abnormalities are in children receiving combination antiretroviral therapy. However, persistent dyslipidemia in children is likely to lead to premature cardiovascular disease.”

What should clinicians do about high lipids in young patients? For children with high cholesterol, PACTG investigators suggest dietary and lifestyle modifications or switching from a PI to efavirenz, though they note that switch options may be limited for perinatally infected children and teens who have already tried several regimens. And efavirenz is not a good option for young women who may become pregnant.

Switching from a boosted PI to boosted atazanavir is a popular strategy in adults with abnormal lipids. But the PACTG notes that atazanavir/ritonavir did a poor job controlling viral replication in a single-center observational study of 23 children with heavy antiretroviral experience. The US pediatric antiretroviral panel lists boosted atazanavir as an alternative first-line choice for 6-year-olds and older children. In US adult and adolescent guidelines, boosted atazanavir is one of five preferred first-line choices. The integrase inhibitor raltegravir, not available at the time of the PACTG report, also has a good lipid profile.

Because there are no HIV adolescent-specific lipid guidelines, Adolescent Medicine Trials Network researchers suggest reference to advice for HIV-positive adults or HIV-negative youth.
Bone growth, HIV, and antiretrovirals in youngsters

Bones grow fast in childhood and early adolescence, and peak bone mass attained in adolescence and young adulthood determines bone mass in later life. So stunted bone growth in this protean life period ignites concern, and study after study shows that children with HIV have lower bone density than children without HIV. As with cardiovascular disease, the relative contribution of HIV and antiretrovirals to blunted bone growth remains a focus of intense study, though little work has assessed bone changes in antiretroviral-naive children and adolescents.

All published case-control studies from the past 6 years comparing bone density in children or adolescents with HIV versus without HIV found less dense bones in the HIV group—except for the only study that evaluated perinatally infected antiretroviral-naive children with HIV. Alessandra Vigano and colleagues in Milan used DEXA scans to measure lumbar spine and whole-body bone density in 16 HIV-positive children with an average age of 9.3 years (+/- 3.9) and two comparison groups: 119 healthy HIV-negative children (average age 9.7 +/- 3.3) and 13 HIV-negative children matched to the HIV-positive group by age, gender, and body measurements. Neither comparison disclosed a significant difference in bone density in the spine or total body. Another study by these investigators, summarized below, found no bone density difference between healthy controls and HIV-positive antiretroviral-naive youngsters or those taking a non-PI regimen.

The same investigators reported one of two published prospective case-control studies of bone density in youngsters with or without HIV. The HIV group included 15 girls and 17 boys from 6.3 to 17.7 years old who had taken antiretrovirals for several years at the baseline visit. The control group included 381 age-matched youngsters. DEXA scans showed significantly lower spine and whole-body bone density in the HIV group at the baseline visit. Spine density in the HIV group increased at a rate similar to the control group through 1 year of follow-up, but whole-body bone density increased significantly more slowly in the HIV group ($P < 0.04$). Levels of markers of bone formation (bone-specific alkaline phosphatase) and bone resorption (N-terminal telopeptide of type I collagen) were significantly higher in the HIV group at baseline and follow-up, findings indicating abnormally rapid bone turnover in the youngsters with HIV.

Boston clinicians reported the other prospective case-control study, comparing bone mineral density in 37 children with HIV (30 taking antiretrovirals) and 9 HIV-negative siblings. These researchers figured age- and gender-adjusted $z$ scores for total-body bone mineral density, body mass index, weight, and height. Median age was 11.6 years in the HIV group and 10.4 in sibling controls. HIV-positive children had bone mineral density $z$ scores significantly lower than population norms ($P = 0.004$), while the 9 siblings had normal $z$ scores. An analysis adjusted for height and weight discerned no significant bone density $z$ score difference between children with HIV and their siblings, possibly because of the small size of the sibling group.

Among HIV-positive children, lower bone density $z$ scores were independently associated with lower weight $z$ scores ($P < 0.0001$), lower height...
z scores \((P = 0.01)\), more advanced (stage B or C) HIV infection \((P = 0.01)\), and age older than 8 years \((P < 0.0001)\). The same statistical model linked better bone-density z scores with multivitamin use \((P = 0.009)\), black race \((P = 0.001)\), and (marginally) nevirapine use \((P = 0.06)\). The researchers had serial bone mineral density readings in 18 children with HIV and 5 siblings. Bone mineral density did not change or increased in all 5 siblings but in only 8 children with HIV \((44\%, P = 0.09)\). Of the 18 HIV-positive children studied over time, 8 of 18 had increasing bone mineral density z scores (range 0.07 to 1.83 standard deviation per year) and 10 had decreasing bone mineral density z scores (range 20.005 to 21.13 standard deviation per year). **Figure 4** outlines risk factors for bone abnormalities and protective variables and strategies identified in recent research.

A cross-sectional case-control study by an Italian group linked higher bone density in HIV-positive children to longer antiretroviral duration. The analysis compared an HIV group of 23 girls and 21 boys from 3 to 17 years old with 568 girls and 641 boys from 3 to 18 years old in a healthy population. All youngsters in the HIV group were perinatally infected, 4 had no antiretroviral experience, 7 were taking two nucleosides, and 32 were taking triple therapy. Instead of measuring bone mineral density by DEXA, these researchers used quantitative ultrasound to gauge bone mineral quality as amplitude-dependent speed of sound and bone transmission time. By both measures, bone mineral quality was significantly lower in the HIV-positive children, even after statistical adjustment for age and body size. However, both bone-quality parameters were positively associated with longer antiretroviral duration \((r = 0.31, P = 0.04)\), as well as with age \((r = 0.59, P < 0.0001)\) and height \((r = 0.66, P < 0.0001)\). The investigators caution that the small size of their HIV group limits this analysis.

Studies weighing the impact of specific antiretrovirals and antiretroviral classes on bone in youngsters implicate PIs (especially full-dose ritonavir) and stavudine. Whether tenofovir depletes bone mineral density, \(16,18,22,40,62,63\) bone density, \(64,65\) or both \(66\) is not clear. Additional studies are needed to determine whether bone density is restored in those who discontinue or who were never exposed to tenofovir.
minerals may depend on a child’s age. Alessandra Vigano’s group compared DEXA-measured bone mineral content in 86 HIV-positive youngsters with ages ranging from 4.8 to 22.1 years and 194 healthy controls with ages from 4.9 to 21.9 years.\textsuperscript{82} In the HIV group, 15 youths remained naive to antiretrovirals, 11 were taking two nucleosides, 32 were taking a PI, and 28 were taking an NNRTI. Statistical analysis that factored in age, gender, and body measurements found significantly lower lumbar spine and whole body bone mineral content in PI-treated HIV-positive youngsters than in controls ($P < 0.05$). But bone content measurements in antiretroviral-naive youngsters and those taking non-PI combinations did not differ from levels in healthy controls.

HIV-positive youngsters taking full-dose ritonavir had significantly lower lumbar spine bone mineral content than other HIV-positive youth. Lumbar spine and whole body bone mineral content was significantly lower in youngsters taking stavudine than in healthy controls, antiretroviral-naive youth, or youngsters taking regimens lacking stavudine. Multivariate analysis linked both full-dose ritonavir and stavudine to lower bone mineral content in both the lumbar spine ($P = 0.0033$) and the whole body ($P = 0.05$).

Lopinavir/ritonavir was associated with lower total-body bone mineral content and density in a study of 236 perinatally infected youngsters and 143 HIV-negative youth matched by Tanner stage and sociodemographic background.\textsuperscript{86} The PACTG investigators found an association between nevirapine use and higher spine bone mineral density, a result reflecting results of the Boston study.\textsuperscript{85} Median age stood at 12.6 years in the HIV group and 11.9 years in matched controls. Compared with HIV-negative boys, boys with HIV had significantly lower total body bone mineral content and total body and spine bone density at Tanner stage 5, and lower total body bone content at Tanner stages 3 and 4. In girls, the investigators found a marginally significant trend between HIV and Tanner stage for spine bone mineral density.

A 5-year study by Vigano’s group found no correlation between tenofovir-containing regimens and decreasing bone density.\textsuperscript{87} The finding is surprising because tenofovir has been tied to lower bone density in adults.\textsuperscript{88} This study involved 21 perinatally infected white youngsters—11 girls and 10 boys—whose ages ranged from 4.9 to 17.9 years. The investigators tracked lumbar spine and whole body bone density over time and measured levels of bone-specific alkaline phosphatase as a bone formation marker and urinary N-telopeptide of type I collagen as a bone resorption marker. Levels of the markers were higher in these youngsters than in a reference group at the first measure and remained higher throughout follow-up. All study participants took tenofovir with lamivudine and efavirenz. Baseline $z$ scores were -0.7 (+/- 0.9 for lumbar spine and -0.13 (+/- 10) for the whole body and did not change significantly for 5 years.

But US National Institutes of Health researchers reported evidence tying tenofovir use to declining bone density—followed by improvements after withdrawing the drug.\textsuperscript{89,90} The first analysis involved 15 youngsters from 8 to 16 years old (average 12 +/- 2) who began a tenofovir-containing rescue regimen after heavy antiretroviral experience.\textsuperscript{89} Tenofovir doses, calculated to match adult exposure, ranged from 175 to 300 mg/m\textsuperscript{2} daily. After 24 and 48 weeks of tenofovir, $z$ scores for lumbar spine, femoral neck, and total hip were
lower than when tenofovir began, but z scores for the group stabilized after that. Six children with an absolute decrease in bone mineral density were significantly younger than children with stable bone density (10.2 +/- 1.1 versus 13.2 +/- 1.8 years). Two children stopped tenofovir because their bone density drop exceeded protocol limits, and they had partial or complete bone mineral recovery by week 96.

The same research group more recently reported bone mineral density findings in 6 children enrolled in a trial that planned to recruit 40 participants but ended for administrative reasons unrelated to study drugs. These 6 perinatally infected youngsters—2 girls and 4 boys—were 11.3 to 17.5 years old (median 12.8) and had height z scores from -1.8 to -3.4 (median -2.5). They took 300 mg of tenofovir daily (median 268 mg/m²) as part of a new regimen including a ritonavir-boosted PI and at least two other antiretrovirals. Children had DEXA scans for bone mineral density before starting tenofovir, then 12, 24, and 48 weeks into treatment, and later in some children.

Five of the 6 children had absolute decreases in bone mineral density during treatment with the new regimen, and these declines were small (1% to 5%) in 3 children. Two children who had 10% and 27% plummets in bone mineral density 24 weeks after starting tenofovir were both prepubertal. The first dropped tenofovir from the regimen and had a bone density rebound to 2% below baseline. The second had poor adherence (indicated by a rebounding viral load), and bone density recovery to 6% below baseline. (In this child it is more difficult to discount the possibility that the PI contributed to declining bone density.)

These researchers observed that youngsters in the Italian study were older (middle to late puberty or postpubertal) and had greater height and weight z scores than children in the US study. They stressed the urgency of determining the impact of tenofovir on bone in children because of the popularity of fixed-dose combinations including this agent and the possibility that it may be used to prevent mother-to-child transmission. These investigators recommend DEXA scanning before starting tenofovir and every 6 to 12 months during treatment.

If one sets aside the question of antiretroviral use, what can be done to prevent or reverse low bone density in youngsters with HIV? Results of a Brazilian study underline the importance of nutrition. This prospective analysis of 57 perinatally infected youngsters correlated gains in weight, height, and lean mass over 1 year with bone mineral density. Age averaged 16 years (+/- 1.9) in this group, and 20 (35%) had low bone density, defined as a z score below -2 for L1-L4 spine or total body bone mineral density. Vitamin D (measured as 25OHD) was nonsignificantly lower in the group with low bone density (36.9 versus 44.0 ng/mL, P = 0.079), but the groups did not differ in calculated consumption of calories, protein, fat, carbohydrates, calcium, or vitamin D. Nor did treatment with a protease inhibitor or tenofovir differ between bone-density groups.

Lumbar spine bone density correlated positively with weight (r = 0.559), body mass index (r = 0.492), and total body fat percent (r = 0.278), while total body bone mineral density correlated with weight (r = 0.496), body mass index (r = 0.446), and total body fat percent (r = 0.268) (all P < 0.05). Gains in weight, height, and lean mass through 1 year correlated positively with spine and total body bone mineral density. For total...
body bone mineral density, these correlations were $r = 0.50$ for weight, $r = 0.523$ for height, and $r = 0.672$ for lean mass (all $P < 0.05$). The investigators suggested that “attempts to reverse the state of nutritional risk [in HIV-infected youth] can be beneficial to those with low bone mineral density.”

US experts in HIV-related bone disease recently published guidelines on screening and treating bone abnormalities,\textsuperscript{92} noting that these problems may be worse in youngsters taking antiretrovirals, those with advanced HIV,\textsuperscript{83,93-95} and pubertal boys.\textsuperscript{86} These physicians believe “there have been no properly powered studies to date that have linked tenofovir use to fracture” in HIV-positive people of any age. For youngsters they emphasize “optimal nutrition, exercise, and lifestyle changes” to maintain healthy bones. Lifestyle advice they give for all people with HIV includes stopping smoking, getting enough vitamin D and calcium, engaging in weight-bearing exercise, and getting enough sun exposure. But they add that the line has not been drawn between enough sun exposure to promote vitamin D synthesis and the amount that heightens skin cancer risk. They do not recommend regular DEXA screening for anyone under 50, except possibly for people with a history of fragility fractures. Table 4 lists conditions these experts believe are linked to osteoporosis and fractures in people with HIV.

Table 4. Conditions associated with a risk of osteoporosis and fractures in people with HIV

<table>
<thead>
<tr>
<th>Lifestyle choices or habits</th>
<th>More than three alcohol drinks daily, dietary calcium deficiency, methadone/opiates, physical inactivity, tobacco use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadal states</td>
<td>Early menopause, low testosterone in men, premenopausal oligomenorrhea</td>
</tr>
<tr>
<td>Other endocrine disorders</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Hemophilia, sickle cell disease</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Medications</td>
<td>Antiretrovirals, glitazones, glucocorticoids, proton pump inhibitors, excess thyroxine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Chronic metabolic acidosis, chronic infection, chronic kidney disease, depression, vitamin D deficiency</td>
</tr>
</tbody>
</table>

Source: McComsey et al.\textsuperscript{92}
Antiretroviral breaks—and words of advice

Long-term risks of antiretroviral therapy encourage some pediatric and adolescent HIV experts to continue studying treatment interruptions as an option for young people. A year ago, when RITA! invited a panel of HIV experts to predict how HIV care would change over the next decade, none warmly advocated this strategy for children, and they ranked it low on the research agenda.\(^6\) (See pages 15 to 17 of that issue, online at the link listed in the references.) Notably, though, that panel lacked researchers who study HIV in children and adolescents. Both of the adolescent HIV maven interviewed for this issue of RITA! think it’s too early to abandon work on antiretroviral breaks for youngsters.

Although this review exceeds 13,000 words, it barely scratches the surface of what’s known and what remains to be learned about HIV infection in adolescents and young adults. To offer some front-line perspective on these problems, RITA! invited two leading HIV clinicians and researchers—Pat Flynn (St. Jude Children’s Research Hospital, Memphis) and Bill Kapo- giannis (Eunice Kennedy Shriver National Institute of Child Health and Human Development)—to field questions on HIV research and care in this volatile population. We also randomly invited US and UK stalwarts in teen care to answer three questions:

- If you could give HIV clinicians one piece of advice about caring for adolescents and young adults with HIV, what would you say?
- What are the most prevalent mistakes clinicians make in caring for adolescents and young adults with HIV?
- What’s the best way you know to improve antiretroviral adherence in young people?

Some of this advice will sound familiar. Some may surprise you. Adolescents are, after all, surprising creatures. Remember, says Caroline Foster of London’s Imperial College and St. Mary’s Hospital, “they are young people in transition between childhood and adulthood—neither dependent children nor dependable adults.”

References


If you could give HIV clinicians one piece of advice about caring for adolescents and young adults with HIV, what would you say?*

George K. Siberry, MD, MPH
National Institute of Child Health & Human Development
Bethesda, Maryland

Work on good communication, nonjudgmental interactions, and clear commitment

Keep youth engaged with you. Like any relationship, that of a maturing adolescent and his/her clinician will have its ups and downs. If the clinician works on good and open communication, nonjudgmental interactions, and clear commitment to the youth for the long run, I think most young people respond very well. There will still be tough periods when things seem like they’re not going well. But if you remain committed and available to that young person, things will usually get better over time and be more likely to succeed in the long run.

Diana F. Clarke, PharmD
Boston Medical Center
Boston, Massachusetts

Keep it simple

Keep it simple! Simple regimens, simple instructions as to how to take their medicines, and how best to take care of their health! Appropriate care and treatment regimens cannot always be kept simple, especially in our patients who are highly treatment experienced and require therapy with more complicated regimens. In that setting, provide as much support as possible and encouragement when instructions are followed and patients are adherent.

Caroline Foster, MB BS, MRCP
Imperial College and St. Mary’s Hospital
London, UK

Adolescents are conformists

Remember that adolescents are not rebellious—they are the most conformist group in society. They just want to fit in with their peer group and this may not coincide with the wishes of their parents, care givers, and health professionals.

continued...
They will tell you what you’ve taught them are the right answers

Be patient when the truth eventually comes out about how/what they have been doing to take care of their health/partners. It takes time to build their trust. Until then, they will tell you what they think you want to hear and what you’ve taught them are the right answers. Don’t ask open-ended questions. Ask questions they have to answer with some degree of conversation. Show an interest, and remember HIV is only one part of their life, not their central/primary focus as you the care provider think it should be.

Meet them where they are

You have to “meet them where they are” and then bring them to where you are at a pace that they can relate to. Recognize that they may not do things you want, but stick with them through that. Assume compliance is a problem and work to help—not scold.

Discuss adherence, sex, and drugs

Talk to them frequently. Discuss adherence, sex, and drugs.
Ross E. McKinney, Jr, MD  
Duke University Medical Center  
Durham, North Carolina

**Consider stopping therapy during “the great gulf” in adherence during early adolescence**

The early years of adolescence are nearly always marked by abysmal adherence, but most teens begin to take responsibility during the high school years. We refer to the gap as “the great gulf,” and during that period we’d rather stop antiretroviral drugs than induce resistance through intermittent adherence, especially since so many of the teens improve in their late teen years.

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Jerilynn Radcliffe, PhD  
*The Children’s Hospital of Philadelphia*  
Philadelphia, Pennsylvania

**Be compassionate . . . be patient**

Be compassionate. Having or getting an HIV diagnosis is traumatic for youth these ages. Respect them as adolescents, understanding that young teens are different from mid-teens are different from late-teens. Be patient while they get things sorted out about managing their health needs.

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*All advice represents individual views of the authorities listed, not official views of their institutions.*
Dr. Flynn directs pediatric AIDS research at St. Jude Children’s Hospital in Memphis and is a member of the Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children. Actively involved in the International Maternal Pediatric and Adolescent Clinical Trials Network and the Adolescent Trials Network, Dr. Flynn published recent research on antiretroviral response, adherence, and pharmacokinetics in children and adolescents.

**Antiretroviral response and adherence**

**Mascolini:*** The PACTG 381\(^1\) and COHERE\(^2\) cohort studies documented poor virologic response rates to antiretroviral therapy by adolescents. What explains these poor results?

**Flynn:** In one word, adherence. In 381 most of our patients were on a nelfinavir regimen or an efavirenz regimen, and we saw no response difference between the two (Table 1).\(^1\) Through 3 years of follow-up, 44 of 120 study participants stayed on study treatment, and 24 reached and maintained an undetectable viral load. I think we’re now having somewhat better success with antiretroviral regimens, and that may be related to their greater potency. But in general the poor response in PACTG 381 and COHERE can be attributed mainly to poor adherence.

**Table 1.** Role of adherence in PACTG 381 regimen switching through 3 years\(^1\)

<table>
<thead>
<tr>
<th>Reason for regimen switch</th>
<th>Initial efavirenz regimen ((n = 71))</th>
<th>Initial protease inhibitor regimen ((n = 47^*))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study on original drug class</td>
<td>13 (18%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Switched regimen because of adherence difficulty</td>
<td>29 (41%)</td>
<td>17 (36%)</td>
</tr>
<tr>
<td>Stopped treatment because of adherence difficulty</td>
<td>10 (14%)</td>
<td>8 (17%)</td>
</tr>
</tbody>
</table>

*Forty-four began nelfinavir.
Mascolini: If you take adherence out of the equation, is there any reason adolescents should not respond to today’s regimens as well as adults?

Flynn: I think some people would argue that we don’t really know the answer to that question because we don’t have a lot of information about antiretroviral pharmacokinetics in adolescents—perhaps they sometimes need different doses than adults. But to be honest, when we’ve looked at responses to newer regimens in some adolescents, the pharmacokinetics have not differed markedly from those in adults. So my answer would be yes, if adolescents take their medications as prescribed, they should have responses similar to what we see in adults. And we certainly do have adolescents who take their meds and have great responses to therapy.

Mascolini: What general recommendations would you make for improving adherence in adolescents?

Flynn: Why many adolescents have such poor adherence to medications is a very, very complex question. The reasons that usually come forward involve the disenfranchisement of these kids: they often don’t have a permanent home; they’re moving from place to place; they have a very disorganized life. More often than not, there is some degree of substance abuse, even if it’s just smoking marijuana. Adolescents with poor adherence typically have no structure to their lives on which they can build a medication-taking pattern. I think that’s probably the most important reason that we see poor adherence, and of course it’s one that’s not easy to address.

But there is a whole host of other reasons that also play into the picture. Many adolescents link medication to their infection. Because they don’t want to think about their infection, they’re inclined to avoid taking their medications. Antiretroviral side effects also contribute to poor adherence, but I tend to believe that’s true only for a minority of adolescents. Particularly with some of the better regimens we have now, we don’t see a lot of the disabling side effects that kept adolescents from taking their medications in the early days of HAART.

Mascolini: Besides working toward better adherence with young people, are there specific things HIV clinicians can do to improve antiretroviral responses?

Flynn: Empowering youth to participate in their health care and help make medical decisions is important. When talking to youth—or to any patient—about starting a complex medication regimen they may have to take for the rest of their lives, it’s very important to explain the status of antiretroviral therapy today, when antiretrovirals are prescribed, the expected outcome, and the risks of taking these medicines. We try to give as much information as we can about the regimens, what the side effects may be, and how treatment may affect their life.

Also it’s very informative for the kids and for us as medical staff to try a regimen of placebos for a week or two before we start antiretrovirals. We get a pill box and dispense candies that are about the size and color of the pills they will be taking to see how well the kids do with that. Often we’ll have kids who are very enthusiastic about starting and apparently ready to start, but they will have difficulty with their placebo regimen. That gives us an insight into which people we’re going to need to follow up a little bit more closely. They may need reminders, or some additional contact, or an additional clinic visit before we anticipate they’ll do very well on medications.

continued...
From short-term side effects to long-term comorbidities

Mascolini: What antiretroviral toxicities should clinicians check for when young people start therapy?

Flynn: The ones we start looking for in the short term are mostly metabolic toxicities that affect the lipid profile or glucose metabolism. If we’re starting a patient on atazanavir, we monitor bilirubin to check for elevations. With bilirubin, sometimes it doesn’t matter what the lab sheet says: If the patient is jaundiced and doesn’t want to be, that’s a reason they’re going to stop taking the drug, so you have to listen to how they’re responding. Those are the key values to monitor when you’re first starting antiretrovirals in adolescents—as well as adults.

Over the long term—particularly in kids who were perinatally infected and are older now—we’re beginning to see a lot more lipodystrophy or fat redistribution syndrome. We’re seeing fat atrophy in the face, a lot of skinny arms and legs, and sometimes a distended abdomen. In our experience, it takes a number of years for lipodystrophy to emerge, but we’re seeing fat redistribution in a significant number of our adolescent patients now.

Mascolini: At your institution, do kids 13 to 18 years old generally start the same first-line regimens prescribed for most adults today?

Flynn: There’s a split in that age group. Most HIV-positive adolescents in the US between 13 and 15 or 16 years old are perinatally infected kids. Often they’ve been on multiple other therapies already, so you have to gauge what antiretrovirals they’ve already been exposed to before picking a regimen. As a result, you may wind up with a more complicated combination than typical first-line regimens in adults.

We see very few 13- to 16-year-old adolescents coming into care who are infected through high-risk behavior. Patients entering care around age 16 or 17 are the ones usually getting infected by high-risk behaviors, and that makes sense because they’re getting infected most often through sex. Normally we start these older adolescents on standard adult regimens.

Mascolini: You’re well aware that clinicians and researchers thinking about older people with HIV, people in their 50s and 60s, have lots of concern about cardiovascular, bone, and neurologic disease—trying to figure out the impact of the virus itself versus the impact of antiretroviral therapy. Those long-term concerns must be much greater when you’re treating a 13-year-old or 15-year-old who may be taking these regimens for their whole lives.

Flynn: There’s a lot of conflicting information on this issue; it’s hard to separate the effects of the drugs from the effects of HIV disease itself. Often there may be an interaction between the drugs and the disease that produces a poor consequence, particularly for cardiovascular health and bone health, which are long-term outcomes that we’re seeing.

To prevent or minimize these problems over the long term, right now our approach is to reinforce healthy lifestyles in our adolescent patients. For instance, we know that a lot of our kids have issues with diet and exercise, so we really encourage...
them to develop a program, to get some exercise, to maintain a reasonable weight. We focus a lot of education on vitamins and diet, and we look for signals like vitamin D deficiency. Of course we also encourage adolescents not to smoke. Cigarettes are one thing, but so many of our young patients smoke marijuana. We encourage them to cut back on that as much as possible.

Genetic factors also contribute to these problems when you come from a family that has a long history of cardiovascular disease and risk factors. Some of these young people have the odds stacked against them genetically, and you can't change those risk factors. But you can change lifestyles.

**Antiretroviral interruption and simplification for adolescents**

**Mascolini:** Antiretroviral interruption strategies fell out of favor in adults after the SMART trial and other studies. But because of the risks of long-term antiretroviral exposure in children and adolescents, should planned treatment interruption remain on the research agenda for them?

**Flynn:** It probably should. I’m sure you’ve seen the study that Bret Rudy published on a structured treatment interruption of 4 days on meds and 3 days off. (See box, “Short-cycle therapy proof-of-principle trial.”) This was a very tightly controlled study requiring a return to 7-days-a-week therapy for any confirmed viral load above 400 copies/mL or significant decreases in CD4 count. Many study participants, especially those infected by high-risk behavior, did quite well on that on-and-off regimen. But it’s hard to get support from the scientific community for this type of research because of the SMART study and other studies that found worse long-term outcomes with structured treatment interruption than with continuous therapy. But I don’t think we’re done assessing that strategy in the adolescent population.

There is another approach that is not really a treatment interruption but is getting some attention now in adults, though it is not broadly recommended. This strategy is regimen simplification, in which patients who reach an undetectable viral load and have a good immunologic response on a full regimen stop some of the drugs and continue others, usually continuing a ritonavir-boosted protease inhibitor. I think that strategy needs testing in adolescents. Patients would still take meds every day, but at least they would reduce the number of drugs taken and potentially reduce some of the side effects.

**Stigma and HIV education hurdles**

**Mascolini:** Everyone knows that stigma has many negative consequences for HIV-positive youth. Can clinicians take concrete steps to help youth deal with HIV-related stigma?

**Flynn:** It’s a very difficult problem. In our clinic stigma comes from many different sources. One of the biggest ones we deal with is family stigma. What we can do as providers is to offer information not only to the infected adolescent but also to the family, even to partners and friends. It’s really a matter of how many people they’re willing to bring into the clinic for you to talk with. Even simply providing this information is somewhat helpful for families and the infected adolescent.
In our area, a lot of young men who have sex with men are in communities where their sexual preference is fairly well accepted. They do well within their community, but when they go out to look for jobs, they have some issues. Also, within our community there are small pockets where HIV prevalence is very high and there are huge amounts of stigma. Ironically, a lot of the bullying behavior about HIV is coming from people who are positive. In addition to offering support, we try to empower the youth to move beyond the stigma, even if that means literally moving out of their familiar territory into a different area of the city.

**Mascolini:** Do you and other clinicians trying to educate HIV-positive and at-risk youth feel you’re getting the support you need from other groups like schools, churches, and community groups?

**Flynn:** In Memphis there are still a lot of people who close their eyes to the reality of what’s going on. We’re located in the Bible belt, and it is sometimes very hard to provide the types of education and intervention needed by these youth. We can’t talk about condoms and we can’t talk about sex because—even though the rate of teenage pregnancy is very high—for some reason there is the perception that talking about it and providing condoms will make teens have more sex.

In my community we have a lot of proscriptions put on us when it comes to HIV education, particularly by churches. Even though so many kids are dropping out of school before they graduate, school still is a reasonable place to provide this type of education. But what you really need to be educating the kids about is subject matter that is taboo, and that’s a horrible thing.

**Research priorities for adolescents and young adults**

**Mascolini:** What are the biggest unmet research priorities involving adolescents and young adults with and at risk for HIV infection?

**Flynn:** Certainly prevention is a huge priority. How do you reach them with the message and the tools to avoid getting infected in the first place? I think this is a huge issue, particularly because in my community—and really across the US—HIV prevalence in young men who have sex with men is increasing at a very rapid rate. This is a population that really deserves a lot of special intervention and a lot of research to try to figure out how to get the message to where it needs to go. I think that’s probably number one on my list—prevention in young men who have sex with men.

Beyond that educational and prevention piece, there’s a lot of attention now on pre-exposure prophylaxis for young people. That’s one thing that we have to address in this very high-risk population of young men who have sex with men.

Barriers to getting kids tested and into care, and keeping them in care, are problems that deserve more research. In our clinic, anywhere from 20% to 30% of young people who begin care for HIV infection come and go and don’t really engage in care the way they should. Once they come to clinic and we can manage them, particularly if they will cooperate and take their meds, prevention and behavioral issues become somewhat easier to deal with.

**Mascolini:** What are your own research goals?

**Flynn:** We’re continuing to look at some of the newer antiretrovirals to see if there are differenc-
es in pharmacokinetics between adolescents and adults or children. Luckily, most findings from this kind of work suggest that adult doses work reasonably in older adolescents.

Another key issue, particularly for perinatally infected youth, is long-term follow-up research to assess the effects of all these agents that we’ve been giving them for a number of years. Even some adolescents infected by high-risk behaviors have now been on therapy for 10 years or more. Studying long-term antiretroviral effects is also important in this group.

One thing we haven’t even started talking about in adolescents and young adults has become a hot topic in management of 40- and 50-year-old people with HIV—early senescence and whether people with HIV are really aging faster than people without HIV. This is a question we’re going to have to start asking in this younger population.

**Mascolini:** Before we wrap up, are there other issues you’d like to address?

**Flynn:** The other big thing that strikes me is the need to focus on HIV prevention in adolescents as they are reaching their sexual debut. In many of our kids, the struggles in their lives and the risk factors that put them at risk for HIV begin in young childhood. I’m talking about broken households, poor supervision, substance-abusing parents, and so on. Sometimes I think those issues might be solved preschool and all through grade school before the children reach puberty.

**References**

Short-cycle therapy (SCT) proof-of-principle trial

Objective: Evaluate the impact of SCT—4 days on treatment followed by 3 days off—in adolescents and young adults with good viral suppression on a protease inhibitor regimen.

Inclusion criteria: At least 6 months of viral suppression below 400 copies/mL, a pre-entry viral load below 200 copies/mL, and an entry CD4 count above 350 cells/mm³.

Study population: Thirty-two 12-to-24-year-olds infected perinatally or later via risk behaviors. The trial enrolled 17 behaviorally infected and 15 nonbehaviorally infected young people, including 19 between 20 and 24 years old and 17 African Americans.

Main findings: Mean preentry CD4 count did not differ significantly between the behaviorally infected youth (706 cells/mm³) and the nonbehaviorally infected group (909 cells/mm³).

- Twelve patients (37.5%) had a confirmed viral load above 400 copies/mL and 18 (56%) stopped the intermittent regimen for any reason.
- Significantly more nonbehaviorally infected patients than behaviorally infected patients stopped intermittent therapy because of viral load rebound, a 30% drop in CD4 count, or other reasons (12 of 15 versus 6 of 17, \( P = 0.016 \)).
- Return to a viral load below 400 copies/mL with the same continuous regimen was achieved by 6 of 7 in the nonbehavioral group and 3 of 5 in the behavioral group.
- Average adherence to the SCT regimen was nearly identical in patients with a virologic rebound (95%) and those without rebound (96%).
- SCT had no major impact on CD4 count in patients with or without virologic rebound.
- One adverse event, worsening depression, was judged possibly related to SCT.

Conclusions: “Our study suggests that short-cycle therapy may be a viable management strategy for some adolescents. However, for subjects with long-standing HIV infection treated with multiple regimens, caution should be taken with this approach.”
Mistakes clinicians make

Don’t assume they fully understand their sexual orientation

Being judgmental is the biggest mistake. Youth pick up on it right away, and will then drop out of care or tune out what you say. Another mistake is to try to do too much, too soon. If youth feel overloaded with information or with too many demands from health care professionals, they will drop out/tune out and then won’t do even a little of what they need to do for their health.

Don’t assume that they are all heterosexual, or that they fully understand their sexual orientation. Use language like “your boyfriend or girlfriend” to refer to a love interest; don’t assume. If youth refer disparagingly to someone being gay or lesbian, gently correct the use of this term and provide some statement like, “here, we provide care and respect for everyone, regardless of whether they’re boys who like boys, or girls who like girls, or whatever.” It will create a safe environment for youth to let you know who they are.

Include teenagers in the plan

Talking to the parents and not including the teenagers in the plan. Remember, as these kids age they need to be transitioned by their health care provider to care for themselves.

Their ability to rationalize is impressive

Accepting what adolescents can say with a straight face. I’m afraid that excess trust is often misplaced during early adolescence. That’s not to say that they aren’t great kids, but their poor decision making and ability to rationalize is impressive.
Reinforce the preventive aspect of health care

Assuming when viral load goes up, they are not taking their medications: they may very well be taking them, just not taking them as prescribed. Threats of what can happen if they don’t take their medications usually do not work, nor do pictures, movies, etc. of what AIDS looks like . . . it is too abstract and not a part of their experience as it was for youth in the 90s. Do not assume youth not taking their meds is passive suicide. Usually there is more going on mentally, emotionally, spiritually that needs to be addressed. Reinforce the preventive aspect of health care to sustain health to lead as normal a life as possible.

Caroline Foster, MB BS, MRCP
Imperial College & St Mary’s Hospital
London, UK

Neither dependent nor dependable

Failing to treat them as adolescents: they are young people in transition between childhood and adulthood—neither dependent children nor dependable adults.

Diana F. Clarke, PharmD
Boston Medical Center
Boston, Massachusetts

Giving too much responsibility

Not treating the patient in an age-appropriate way and giving the patient more responsibility for his/her own care according to ability and maturity. And making things too complicated.
George K. Siberry, MD, MPH
National Institute of Child Health & Human Development
Bethesda, Maryland

Young women and men are eager to hear about how they can have children safely

Too often, clinicians assume that youth are not listening to them and will not follow our advice. On the other hand, clinicians may think that youth will/should listen to all the advice we give them. The key, of course, is for the clinician to work on his/her communication skills and to build a trusting relationship with each adolescent patient. Most youth want input from their clinicians but they want to make sure it fits their particular circumstances and beliefs, too. It’s amazing what we can accomplish with this type of collaborative approach.

We often focus on pregnancy prevention with youth, but many young women and men are eager to hear about how they can have children safely (ie, in a way that avoids HIV infection in their partner and child). Giving youth with HIV infection the opportunity to discuss their future plans for family and answer questions they may already have is an important part of our counseling with them.

*All advice represents individual views of the authorities listed, not official views of their institutions.*
Dr. Kapogiannis is the NIH scientific director of the 15-center Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), which evaluates biomedical, behavioral, and community-level interventions for treatment and management of HIV infection and its complications in youth. In 2005 he joined the Pediatric, Adolescent & Maternal AIDS Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, where he specializes in pediatric and adolescent HIV/AIDS and the immunology of HIV infection. Board certified in pediatrics and internal medicine, Dr. Kapogiannis has helped plan trials involving HIV vaccines and pre-exposure prophylaxis for young people.

**Primary and secondary HIV prevention in adolescents**

**Mascolini:** First, can you explain what the Adolescent Trials Network is and what you do?

**Kapogiannis:** The Adolescent Medicine Trials Network for HIV/AIDS Intervention, or ATN, is a multicenter basic science and clinical research network with 15 clinical sites across the US and Puerto Rico. The ATN’s scientific mission is to conduct independent and collaborative research that evaluates interventions for treatment and management of HIV infection and its complications among youth, as well as the prevention of HIV transmission. The network explores promising behavioral, microbiidual, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV at-risk adolescents, ages 12 through 24 years (https://www.atnonline.org/default.htm). Much of the work we do spans three realms—behavioral medicine, community prevention science, and biomedical science.

**Mascolini:** Within those board research goals, what are the top unmet HIV research priorities in adolescents with HIV?
Kapogiannis: For adolescents who are infected, I think there are two distinct priorities that need to be addressed. First and foremost is the priority of finding youth who are unaware they are infected and bringing them in to care. Within this priority, there are three related goals: we need to find novel ways to identify youth with undiagnosed infection in the United States and then study how best to link them to care and, once they are in the clinic, understand how to most effectively keep them engaged in care. The other priority is the broader issue of adherence, and that includes adherence to the medicines and adherence to visits for clinical care, psychological care, and any type of care an adolescent needs.

Adherence is probably the biggest challenge that adolescent medicine doctors face today. It’s a huge concern in adolescent HIV medicine because these are kids facing the transition from a concrete thinking process to a process of reasoning and abstract thinking as adults. Adolescents are maturing from an egocentric view that “it’s all about me . . . it’s all about what’s here today” to thinking about consequences in the future. This evolution takes years for people to master as they develop psychologically. Depending on how quickly they mature, adolescents are in that vulnerable time when they think “it’s all about me and all about my physical image,” so taking medicine is not a big priority, especially when they don’t feel sick. We need to identify and implement innovative youth-friendly adherence interventions and simplified therapeutic strategies to help manage their infection.

Planning prevention strategies for youngsters

Mascolini: What are the biomedical HIV prevention strategies on the front burner in research and when might such strategies be deployed?

Kapogiannis: Three main biomedical prevention strategies for HIV are being studied actively right now. Before I go into those, I will say there is one additional biomedical strategy that has proven successful in the international arena, which is male circumcision. In the United States it is much more difficult to tease out the protective benefits of circumcision because the large-scale international efficacy trials all involved heterosexuals and the US epidemic is not demographically similar to international settings. Here a major proportion of at-risk and infected people are men who have sex with men (MSM). Circumcision efficacy is difficult to estimate in MSM because many men practice both receptive and insertive anal intercourse, and circumcision more clearly lowers the HIV risk of the exclusively insertive partner.

The other three actively pursued prevention interventions are HIV vaccines, microbicides (topical agents applied to the rectal or vagina mucosa to prevent transmission of the virus), and pre-exposure prophylaxis, or PrEP (an antiretroviral medication taken orally to stave off transmission). Among uninfected youth, study of these primary biomedical HIV prevention interventions is a major unmet HIV research priority, despite the clear future need for data to support approval of products in youth when those products are shown to be effective.

An HIV vaccine has been the most sought-after intervention since the earliest days of HIV prevention work. A vaccine would be a particularly attractive strategy for youth because adherence is so problematic in young people and a vaccine would ideally require only one or two visits. But we’ve had some setbacks in developing a vaccine, most recently with the STEP trial, which found not only lack of efficacy but also increased HIV acquisition in some people who received the active vaccine.
That higher acquisition rate later got attributed to circumcision status and adenovirus type 5 status. Then a trial in Thailand showed about 30% efficacy with a different vaccine. Although almost 28% of the study’s 16,000 participants were 20 years old or younger, the trial population did not have a high risk of HIV infection.

Before the STEP study, we at ATN had forged a collaboration with the HIV Vaccine Trials Network and the IMPAACT Group (International Maternal Pediatric Adolescent AIDS Clinical Trials Group) to conduct an adolescent HIV vaccine trial with a product similar to the one in STEP. When the STEP results were released, development of this collaborative adolescent study was deferred. But the Thai trial has helped reinvigorate that agenda, and we will stay at that table and be there when more promising vaccine candidates come along that we can study.

Tailoring microbicides and PrEP for youth

Mascolini: Where does work stand with microbicides and PrEP for young people?

Kapogiannis: With microbicides there has been more promise and progress than with vaccines. CAPRISA 004, the results of which were released at the 2010 International AIDS Conference in Vienna, found that a microbicide gel containing tenofovir was 39% effective in preventing HIV acquisition by African women. CAPRISA was a milestone study for the microbicide field since all other trials—which had not yet assessed antiretroviral-based microbicides for efficacy—were unsuccessful. VOICE (Vaginal and Oral Interventions to Control the Epidemic), a flagship study of the Microbicide Trials Network that we cosponsored here at the National Institute of Child Health and Human Development (NICHD) along with other NIH institutes, is assessing the efficacy of tenofovir gel in addition to oral medicine, so VOICE has a pre-exposure prophylaxis arm. Results of this study will not be available for some time, but regulators may look at the this as a licensing study.

In the ATN we have done a phase 1 safety, feasibility, and acceptability study of a different (nonantiretroviral) microbicide in female youth aged 18 to 24 years. Given results of CAPRISA 004, the next step is to try to conduct an expanded safety studies in youth using antiretroviral-based microbicides.

The antiretrovirals being used in PrEP efficacy trials right now are tenofovir by itself or with emtricitabine coformulated as Truvada. Results of one of these studies, called Chemoprophylaxis for HIV Prevention in Men (also called iPrEX), were released in November 2010 in the New England Journal of Medicine. This study compared daily Truvada to daily placebo to see if Truvada prevented HIV infection in men who have sex with men. The study took place in South America, South Africa, Thailand, and the United States and enrolled 2499 participants, about half of whom were 18 to 24 years old. Overall results showed that Truvada reduced the risk of HIV infection by 44% compared with placebo. Effectiveness increased if participants took medications more consistently and didn’t miss doses. Results of another large PrEP efficacy trial should be available in 2011—a CDC-sponsored placebo-controlled trial of tenofovir in intravenous drug users in Thailand.

In the ATN we have begun a feasibility and acceptability study with Truvada in 99 youth. We have accrued about three quarters of study participants. I had concerns that adherence could be a problem in healthy youth, but so far participant enthusiasm to learn more about preventing HIV infection seems high. Although the youth know this is only a feasibility and safety study, not an efficacy trial, they’re
adhering to the protocol well. On completion of that trial, we will be poised to go into a potential effectiveness study.

A July 2010 supplement to *JAIDS* discusses all of these biomedical prevention strategies in youth (http://journals.lww.com/jaids/toc/2010/07011).

**Mascolini:** If PrEP and microbicides prove effective in clinical trials, which high-risk adolescent populations in the United States would be candidates for those strategies?

**Kapogiannis:** Of these two strategies, PrEP is the one we will probably want to focus on in US youth. In the United States the epidemic is MSM-predominant and even more so for youth. Of course girls and young women are getting infected heterosexually in the United States, but at-risk young women are harder to identify in the numbers needed to do a prevention effectiveness trial. Current efforts in the ATN are aimed at improving methods of identifying young women with undiagnosed HIV infection. Among MSM, more than a third getting newly infected in the United States are adolescents and young adults. That is the youth group we will need to target in a US PrEP effectiveness study. I say “effectiveness” instead of “efficacy” because the key question, as we just saw in iPrEX, will be how these youth take the medicine in real-world scenarios reflecting what we already know about youth adherence and psychosocial problems.

We will most definitely need a biomedical prevention study combined with a behavioral intervention. A risk-reduction intervention must be incorporated in the trial or we’re not doing due diligence, considering what we know about risk behaviors, particularly in youth. We’re going to need to ensure that we give them the most effective behavioral intervention possible aimed at reducing risk.

**Improving adherence in young people**

**Mascolini:** You’ve mentioned adherence hurdles in youth several times. Two cohort studies, PACTG 381 and COHERE, demonstrated poor virologic response rates to antiretroviral therapy in youth. How much does poor adherence account for these results?

**Kapogiannis:** In PACTG 381, adherence was the most central factor in virologic failure. It was by far the most important predictor of failure. This is also often true in adult studies, which consistently correlate poor adherence with failure.

**Mascolini:** What can HIV clinicians do to improve adherence in young people?

**Kapogiannis:** There isn’t any single approach that will work, but there are a few strategies that will get a better response from adolescents. The basic problem with adolescents is that it’s difficult to get them to focus on what is important—healthcare for themselves. Among the things that I’ve found helpful, the first is to have an adolescent-friendly environment. For adolescents seeing a physician who doesn’t focus on adolescent medicine, it can be daunting for them to come in and face a waiting room full of older people with all sorts of morbidities, with canes and walkers: Adolescents don’t want to feel that they’re that sick.

Of course physicians can’t control some of these things, but there are some factors they can control, such as flexibility with scheduling. Youth don’t like morning appointments. They don’t like waking up early to go to a 9 o’clock appointment somewhere that’s 20 miles away. That will never happen.

_________________________ continued…
The staff and their interactions with the youth are very important. They have to be very patient and understanding of the psychodynamics I discussed earlier in the development of youth. They have to understand how young people think and be willing to do a little more hand holding. In the conventional adult HIV arena, many people tend to be more independent when it comes to care, but staff has to work harder to make sure adolescents keep appointments. Adolescents need reminder calls. They require text messages. Youth don’t communicate the same way we old folks do. They text most of the time they’re using a phone. It’s also helpful to have youth group sessions, as part of an adolescent-friendly environment, to address behavioral aspects with the help of a psychologist or social worker.

**Antiretroviral toxicity and treatment interruptions**

**Mascolini:** Antiretroviral toxicity is a big factor in adherence. What are the short- and long-term toxicities clinicians should monitor in adolescents starting a new regimen?

**Kapogiannis:** All the toxicities you worry about in adults taking antiretrovirals are ones you should worry about in youth. Biomedically, adolescents with HIV are not too different from adults. There are some pharmacokinetic differences between youth and adults in antiretrovirals agents—differences in the capacity with which the body metabolizes the drugs. These pharmacokinetic differences are not consistent from one drug to the next. You can’t say all youth need higher or lower doses of all antiretrovirals: It varies by drug and also individually. If ignored, antiretroviral pharmacokinetic differences between adolescents and adults can result in ineffective underdosing or toxic overdosing, particularly in younger youth.

Short-term toxicities include diarrhea, nausea, stomach upset, headaches, vivid dreams, and all the antiretroviral class-specific toxicities that we deal with in adults. Longer-term toxicities are also similar to those seen in adults. Adolescent medicine physicians are likely to be concerned about the long-term cardiovascular health of youth (see pages 22 to 26 of this issue). We have to pay attention to what the drugs and the virus may be doing in concert—watching not only for signs of cardiovascular disease but also for signals of other non-AIDS morbidities that are coming to the forefront and may affect the central nervous system, bones, kidneys and/or other organs. Concerns about toxicities, comorbidities, and metabolic complications are amplified in youth because they will have longer lifetime exposure both to HIV and to antiretrovirals.

**Mascolini:** Antiretroviral toxicity spurred interest in treatment interruption strategies, but those strategies fell out of favor in adults after the SMART trial. I know you’ve been involved in studying on-and-off therapy in young people. Why do you think this strategy still deserves consideration in youngsters?

**Kapogiannis:** The adult strategy in SMART and most other adult trials involved significant interruption periods. I think prolonged periods of antiretroviral replication and the intermittent spiking viremia you might see with 4 days on therapy and 3 days off may have different consequences. The ATN trial that assessed a 4/3-day on/off strategy was a feasibility study in no way powered to look at efficacy. We didn’t see significant signals of toxicity or resistance to regimens used while youth were in that trial, and we learned that youth were willing to try this approach (see box on page 48).
If we as adolescent medicine physicians focus on trying to bridge a tumultuous time in their lives, if we can get them across this, we might get them to a point where they can assume more responsibility for their health. We tested an on/off strategy like this to see if we could maintain their CD4 T cells without causing any harm, for example, though viral load rebound and evolution of new resistance mutations or emergence of archived resistant virus.

We were thinking about interruption strategies from that vantage point. The goal was not to produce evidence supporting on-and-off treatment for 20 years or an indefinite period of someone’s life. It was a small proof-of-concept trial for potential intervention which showed that it might work for a short period in selected youth who might not have a long history of HIV infection with a lot of antiretroviral exposure. Because it was a small trial, it had significant limitations and did not address some of the safety signals that may be less frequent. Treatment interruption in such select youth requires more study before it could be recommended in clinical practice.

**Taking a community approach to countering HIV stigma**

**Mascolini:** HIV stigma has many negative effects on adolescents. What should clinicians do to address stigma-related problems in youngsters with HIV?

**Kapogiannis:** Stigma is a significant problem that goes beyond the individual and must be considered at the community level. The best way clinicians can help address this problem is to have access to their communities and to have a dialog with their communities. Many of the ATN clinics are affiliated with community-based organizations that refer youth to them (see “Connect to Protect”). They cooperate on health fairs and other activities with community groups. We have specific community-level prevention activities and dialog that happens as a result of being part of the ATN. This kind of community-based approach can yield incremental progress toward destigmatizing HIV.

That doesn’t solve the immediate problem of helping youth when they’re sitting in front of you—or when they’re not in front of you because stigma makes them afraid to come to the clinic. That’s a much more difficult topic to tackle, but it begins with building trust within the community so there’s a general sense of confidence in your clinic that gets transmitted to the youth and makes them less reluctant to see the provider.

Also important is building trust with the youth themselves. Thus, another part of the solution is the “adolescent-friendliness” I was talking about before. If the clinic’s sign outside says “Northwest HIV Clinic,” adolescents are not likely to come. If it says “Northwest Healthcare,” it’s a different story. You also have to look closely at what you give patients to take home and what you send in the mail.

Addressing this issue appropriately requires being culturally and socially sensitive to these concerns and trying to remove any cues that would potentially be perceived as threatening—not just for adolescents but also for adults. I know some adults will not visit certain clinics because they have a strong reputation as an HIV clinic in the community. They’d rather go to a community clinic that’s not the renowned HIV/AIDS center of the region. All of these things are important because there are still significant levels of HIV stigma in the community.
References


Connect to Protect—linking adolescent HIV practice to the community

https://www.atnonline.org/public/resources_form1.asp

ATN—The Adolescent Medicine Trials Network for HIV/AIDS Interventions—offers HIV clinicians and people with HIV contact information on scores of community groups with services for HIV-positive youth. As the NICHD program director of ATN, Bill Kapogiannis stresses in this interview that forging and sustaining strong community ties is an essential step toward creating an adolescent-friendly medical practice and improving clinic visit and antiretroviral adherence in young people.

An ATN online tool, the Connect to Protect Online Resource Directory, helps users track down nearby organizations and agencies that offer health and community services to pre-teens, teens, and young adults with HIV. All listed group have activities or programs related to sexual health and well-being. And many organizations offer additional youth-oriented services, including learning opportunities.

Connect-to-Protect currently lists services in nine states, Washington, DC, and Puerto Rico:

- California
- Florida
- Illinois
- Louisiana
- Massachusetts
- Maryland
- New York
- Pennsylvania
- Puerto Rico
- Tennessee
- Washington, DC

Once users select a region, they can pick between centers that offer outreach or education services, or both. Besides street addresses and phone numbers, the listings include Web links, an e-mail contact, and a list of services.
Adherence tips

What’s the best way you know to improve antiretroviral adherence in young people?*

Caroline Foster, MB BS, MRCP
Imperial College and St. Mary’s Hospital
London, UK

Try all avenues including DOT

Tailor treatment to the individual young person—fit it into their lives, try all avenues including DOT and for those who fail to take treatment keep the door open so they can come back.

Diana F. Clarke, PharmD
Boston Medical Center
Boston, Massachusetts

Address mental health and social issues

Addressing the mental health issues and social issues that get in the way of antiretroviral adherence. Oftentimes, the patients are not receptive to mental health services and it is difficult to find appropriate providers. The most adherent patients tend to be the ones with the most support at home.

Pill boxes, printed medication schedules, alarms on cell phones, etc. These all help, but the patient has to want to take their meds.

George K. Siberry, MD, MPH
National Institute of Child Health & Human Development
Bethesda, Maryland

This is the period when they need their family’s support more than ever

I wish there were a magic formula to help youth adhere fully to their HIV medicines. But, of course, there isn’t. Having strong parent or other family support can make a really big difference. Many families think that their adolescent children should be able to start managing their medicines on their own; in fact, this is the period when they need their family’s support more than ever. It is true that the young person needs to take on some—and eventually all—of the responsibility for taking his medicine (and other aspects of his/her health and life), but this is a gradual process that takes place over the course of adolescence into young adulthood. And ongoing encouragement and support from family and friends continues to make a big and positive difference in successful outcome, even when the young adult has reached independence.
Jerilynn Radcliffe, PhD  
*The Children’s Hospital of Philadelphia  
Philadelphia, Pennsylvania*

**No one-size-fits-all approach**

Make an individualized plan with them, based on knowing them well, and respecting what they say as to what works for them. There’s no one-size-fits-all approach to adherence in HAART among teens and young adults.

Patricia A. Garvie, PhD  
*St. Jude Children’s Hospital  
Memphis, Tennessee*

**Pill swallowing is a skill to learn and develop**

Reminder text messages, routine monitoring of refills, and asking about dose timing (not just are they taking it, but are they taking it with appropriate dose intervals as prescribed). Do not assume they can easily swallow pills. Assess ability and provide pill swallowing training if indicated. Most of these youth prior to HIV have little or no experience with taking medications of any kind, and like anything else, pill swallowing is a skill to learn and develop. Make pill taking not a big deal—30 seconds of your day and done.

Ross E. McKinney, Jr, MD  
*Duke University Medical Center  
Durham, North Carolina*

**Leave parents engaged in monitoring medications**

I’m sorry to say it’s to leave the parents engaged in monitoring medications until the teens begin to take personal responsibility for their own health. We start preaching personal responsibility early in the teen years in hopes that it will eventually soak in as a concept.

Sharon Nachman MD  
*State University of New York Stony Brook  
Stony Brook, New York*

**Use whatever the teenager thinks might work**

No one thing fits all the teenagers all the time. What works at age 16 may not work at age 17. Use whatever the teenager thinks might make them take their meds. Ask them what they want us to try.

*All advice represents individual views of the authorities listed, not official views of their institutions.*
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