

Review

A Review of HIV Antiretroviral Adherence and Intervention Studies Among HIV–Infected Youth

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Advances in antiretroviral medications have resulted in precipitous declines in HIV-associated morbidity and mortality; however, high levels of adherence are crucial to the success of HIV therapies. This article reviews published studies in the United States on HIV-infected youth (ages 13 to 24 years), focusing on adherence to antiretroviral regimens and interventions designed to enhance adherence. A systematic search yielded 21 articles published between 1999 and 2008 that reported data on medication adherence in HIV-infected youth, of which 7 described unique interventions to enhance medication adherence. Five thematic areas were identified to classify factors associated with adherence. Findings suggest psychosocial factors, in particular depression and anxiety, were consistently associated with poorer adherence across studies. Three types of adherence interventions with HIV-infected youth were found. Results suggest that examining adherence within the broader contextual issues present in the lives of youth, including HIV stigma and disclosure, caregiver stress, peer relations, mental health and substance use, and length of time on medications, may be most important to understanding how best to intervene with adherence among this population. Secondary HIV prevention interventions for youth represent a possible mode through which to deliver individually tailored adherence skill building and counseling to improve medication adherence.

According to the Centers for Disease Control and Prevention, an estimated 5259 young people aged 13 years to 24 years received a diagnosis of HIV infection or AIDS in the United States in 2006, a 25% increase from estimated diagnosed cases among youth in this age range in 2003 ($n = 4209$).¹ These youth represented 25% of the estimated 475,871 persons living with HIV or AIDS in 2005 in the 33 states with long-term, confidential, name-based HIV reporting in the United States ($n = 19,134$).¹ Advances in medical treatment, specifically antiretroviral medications, have resulted in precipitous declines in HIV-associated

morbidity and mortality,^{2–5} allowing for HIV-infected adolescents and young adults to manage their HIV infection as a chronic, rather than imminently life-threatening, disease. However, maintaining high levels of adherence (90% to 95%) to antiretroviral therapy is crucial to treatment success,^{6–10} and promoting adherence remains an essential element of modern HIV care.^{11,12}

In providing HIV care for youth, practitioners may follow the US Department of Health and Human Services guidelines.¹⁰ Although substantial advances have been made to simplify regimens and develop combination therapies,¹²

the behaviors associated with adherence (eg, taking doses at the same time every day, following food restrictions, and not skipping doses as the result of irregularity in routines) remain a challenge, especially for young people living with HIV infection.¹³

The normal developmental trajectory of adolescence and young adulthood involves behavioral experimentation, risk taking, and confronting a host of difficult choices with regard to romantic relationships, sexual behavior, alcohol and drug use, and identity formation (eg, Arnett, 2004).¹⁴ The complexity of these choices is compounded for HIV-infected youth and emerging adults,¹⁴ who must negotiate these developmental stages within the framework of having a chronic and stigmatizing disease.^{15–17} Medication adherence may be particularly challenging at a time of life when adolescents do not want to be different or perceived as different from their peers.¹⁰ Moreover, developmental processes, such as concrete thinking,¹⁸ may contribute to difficulties in taking medications when adolescents are asymptomatic, particularly if the medications have taxing adverse effects.

Previous reviews of antiretroviral adherence studies in the United States have focused on HIV-infected adults.^{19–22} This article reviews published adherence studies on HIV-infected youth (ages 13 to 24 years), focusing on rates of adher-

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ence to antiretroviral regimens and interventions designed to enhance adherence. Included are possible directions for future research and suggestions for intervention development to improve antiretroviral adherence among HIV-infected youth.

Methods

Data Sources, Search Procedures, and Inclusion Criteria

Articles were identified through searches conducted on MEDLINE, PubMed, and PsychInfo using combinations of the keywords HIV/AIDS, youth, adolescents, young adults, adherence (or compliance), nonadherence (or noncompliance), medical treatments, highly active antiretroviral therapy (HAART), antiretroviral, resistance, and intervention (also keywords associated with specific types of interventions, such as education, telephone, and peer). In addition, bibliographies of relevant articles were reviewed for additional studies.

Included were quantitative and qualitative studies reporting original data on medication adherence among HIV-infected youth (ages 13 to 24 years) and on exercising an intervention technique to enhance antiretroviral adherence among this population. Studies that included children as well as adolescents and young adults were incorporated for review as long as the mean age of participants fell within the 13- to 24-year-old age range; data relevant to adolescents and youth from these studies were reported where available, with the exception of 2 intervention studies^{23,24} that included data from all participants.

The systematic search yielded 21 articles dating from 1999 to 2008; of the 21 articles reporting data on medication adherence, 7 described unique interventions to enhance adherence among HIV-infected youth. Given the early stage of research in this field, all relevant studies were included in the review, regardless of methodologic rigor. Common methodologic limitations of studies (eg, lack of randomization, lack of control group, or insufficient power) are reported where relevant.

Coding and Abstracting of Adherence Studies

A coding manual was developed to extract descriptive information on setting, study design, population and sample characteristics, definition of adherence used, adherence measurement method, key study variables, and reported findings. In accordance with the approach utilized in prior literature reviews (eg, Fogarty et al, 2002),¹⁹ names and definitions of variables were extracted verbatim from study authors, generating a list of 46 variables. A combination of content analysis²⁵ and an iterative process of variable sorting and concept formation common in qualitative research²⁶ was employed to identify 9 categories in which all the variables could be classified. These categories were further refined into 5 broad thematic areas associated with adherence: (1) demographic factors (eg, age, sex); (2) psychosocial factors (eg, family/caregiver, psychologic/developmental); (3) disease factors (eg, clinical status, disease stage); (4) treatment regimen factors (eg, regimen complexity, adverse effects); and (5) practitioner factors. Intervention components and relevant outcomes are also described.

Variables were often worded in both the positive and negative directions (for example, predictors of adherence and predictors of nonadherence). Findings were classified in 1 of 3 ways: (1) variables statistically significantly associated with adherence, (2) variables statistically significantly associated with nonadherence, or (3) variables inconsistently associated or failing to demonstrate an association with adherence.

Measurement of Adherence

Accurate measurement of HIV medication adherence presents challenges to researchers, and few studies are consistent in their classification of adherence.²⁷ Three categories were used in this review to classify how studies measured adherence: (1) subjective measures of adherence based on self-report or others' report of adherence; (2) pharmacologic measures of adherence (eg, pill count, pharmacy refill records, use

of mechanical monitors of pill or drug use); (3) physiological methods or indicators (eg, plasma HIV RNA level below detection limits, CD4+ count, plasma assay results, other laboratory reports).

Results

Overall rates of adherence in the 30 days before study enrollment ranged from 28.3%²⁸ to 69.8%.²⁹ Table 1 provides a descriptive overview of the 14 adherence studies reviewed.

Factors Related to Adherence Among HIV-Infected Youth

Five broad thematic areas of factors associated with medication adherence among HIV-infected youth were identified (Table 2). Each is described in detail below.

Demographic factors. Age, sex, and race were inconsistently associated with adherence across studies.²⁹⁻³³ For example, 1 study found that younger age was associated with poorer adherence;²⁹ others found no association to either adherence or nonadherence.^{31,32} With respect to education level and socioeconomic indicators, being in school was associated with better adherence,²⁹ whereas having repeated a grade in school and having unstable housing were each associated with poorer adherence to antiretroviral medications among HIV-infected youth.³⁴

Psychosocial factors. Much of the research on adherence among HIV-infected youths (48%) focused on social and psychologic factors.

a. Family/caregiver. Family and caregiver factors associated with adherence were having an adult other than the biological parent as the primary caregiver (eg, relative or other adult) and higher caregiver education level.³³

b. Social support. In the studies that tested it, no association was found between social support and adherence.^{31,35} However, HIV stigma and discrimination by friends and family were strongly associated with nonadherence, and skipping doses was often attributed to fear that friends and family would discover their HIV status.³⁶ Similarly, less HIV disclosure overall was associated

Table 1. Published Studies Assessing Factors Associated With Adherence Among HIV-Infected Youth

Reference Study Design	Sample Measures	Major Results and Health/Immune Outcomes
Becker et al, 2002 ³⁰ Retrospective analysis of pharmacy claims data on nucleoside analogue reverse transcriptase inhibitor prescription refills to estimate adherence	3788 HIV+, treatment-naïve youth (ages 18–24 years) Adherence defined as proportion of days on which drugs were taken during first 365 days of therapy	Overall adherence rate, 53%. No differences by sex detected in adherence rates ($P = .30$). 26% of individuals were 80% adherent or better. Age was associated with adherence by chi-square examination ($P = .001$)
Belzer et al, 1999 ³⁹ Explored correlates of adherence to antiretroviral therapy, including reasons for missing doses, medical and mental health histories, and substance use histories	Surveyed 31 HIV+ youth (ages 13–24 years) from adolescent HIV clinic One-time 22-question interview administered to participants. Demographics, mental health, medical history, and substance use gleaned from medical records. Data analyzed to explore correlates of antiretroviral adherence	61% reported > 90% compliance with medications in previous 90 days. Youth who believed medications would “most definitely” improve quality of life were more likely to have ≥ 90% adherence at 3 months. Most commonly reported reason for missing medications: having too many pills to take
Comulada et al, 2003 ³¹ Examined factors associated with antiretroviral drug use and adherence among young HIV+ people, particularly sexual and substance use transmission acts	Recruited 253 HIV+ youth (mean age, 22.9 years) in Los Angeles, San Francisco, and New York HIV/AIDS clinical care sites 2-hour ACASI interview with each participant; participants queried regarding lifetime and recent behavior, including antiretroviral drug use, health status, sexual behavior, substance use, mental health, quality of life, and social support	54% were currently using antiretroviral drugs; 63% of users adhered to 90% of their medications ($n = 85$). Adherers were less likely than nonadherers to have been sexually abused, attempt suicide, report a lower life satisfaction, and use depression withdrawal or self-destructive escape coping mechanisms. Frequency of recent drug use was statistically significant predictor of antiretroviral adherence
Dodds et al, 2003 ³⁷ Analyzed preliminary data from subset of adolescent/young women from mental health–perinatal HIV care project	Recruited 21 perinatally HIV+ women (ages 20–25 years) from obstetric/gynecologic HIV clinics enrolled in Whole Life project Examined sociodemographic patterns, HIV risk, health status, and mental health status among participants	Central to nonadherence: patient fears about unwanted HIV disclosure, drug adverse effects and their interference with social life, and relationships with partners. Validating and praising small concrete steps proved especially important to help teen mothers Achieving maximum patient adherence required: developmental framework, patient peer culture, meaningful patient-practitioner relationships, careful medication selection, mental health services, substance abuse treatment, and trauma-informed systems for HIV care Suggested program services to these ends: case management, developmental and education services, one-stop/colocation of key services, home visits, transportation provisions, childcare, food, patient incentives, engaging patient in conversation, buddy systems/peer advocates, reminder phone calls and letters, and support groups
Hosek et al, 2005 ³⁸ Self-report questionnaire and 1-hour interview. Data examined for correlation with adherence	Recruited 42 HIV+ youth (age 16–25 years; 25 male, 17 female patients) from CORE Center, Chicago, IL Surveys assessed adherence, perceived reasons for nonadherence, factors to consider before starting a new regimen, cognitive ability, negative affective, and substance use. Regression analysis examined associations to adherence	44% reported being 95% adherent. Only 19% of participants always properly took all medication. 40% of male and 35% of female participants indicated depressive symptoms; 33% of all participants exceeded the cutoff for medium-high trait anxiety. Depression/anxiety and age of first marijuana use were statistically significant predictors of nonadherence ($P < .05$). Most common reason for missing a dose: forgetting

ACASI indicates audio computer-assisted self-interviewing; CI, confidence interval; HIV+, HIV seropositive; OR, odds ratio; PTSD, posttraumatic stress disorder.

Table 1. (Continued)

Reference Study Design	Sample Measures	Major Results and Health/Immune Outcomes
Martinez et al, 2000 ³⁴ Retrospective analysis of patient charts	Consecutive review of 25 charts of HIV+ youths (ages 13–21 years) from 1/1993 to 5/1998 Measures were sociodemographic factors (eg, age, race/ethnicity, sex, housing stability) and health variables (eg, CD4+ count and viral load, length of time on antiretroviral drugs) associated with adherence	13/18 (72%) of patients on antiretroviral therapy were nonadherent; 67% of females and 80% of males reported missing doses. Housing instability and length (months) of treatment with antiretroviral medications correlated with nonadherence ($P < .04$). Living situation stability was the most statistically significant correlate of adherence
Murphy et al, 2005 ²⁹ Longitudinal study of cohort of HIV+ adolescents to investigate long-term antiretroviral therapy adherence and its correlates	231 HIV+ adolescents (mean age, 18.4 years) infected primarily through sexual behaviors Validated self-reported adherence measures by comparison with plasma HIV RNA level; assessed behavioral factors associated with antiretroviral therapy adherence	69% of adolescents reported being adherent. Adolescents in later HIV disease stages were less likely to be adherent. Less alcohol use and being in school were associated with adherence. Median time to nonadherence was 12 months, and failure to maintain adherence was associated with younger age and depression
Murphy et al, 2003 ²⁸ Structured interviews conducted to determine barriers to adherence; principal component factor analysis performed on scores of 19 barrier variables	114 HIV+ adolescents (ages 12–19 years) prescribed antiretroviral therapy and in REACH Project. All participants infected through risk behaviors Main outcome measures were self-report of adherence and barriers to adherence and plasma HIV RNA level	Only 28% of adolescents reported taking all prescribed antiretroviral medications in previous month. Plasma HIV RNA level was associated with self-report of adherence ($P = .02$). Medication-related adverse effects and complications in daily routines accounted for largest proportion of variance. Adherence was tied closely with daily routine; working closely with adolescents to improve their organizational skills may improve adherence
Murphy et al, 2001 ³² Combination of face-to-face interview, ACASI, laboratory analysis, and medical chart review to find associations between self-reported medication adherence, depression, anxiety, social support, and demographics	Recruited 161 HIV+ adolescents (ages 13–18 years) from 13 US cities into REACH Project. All adolescents infected through sexual or injection drug use behaviors Antiretroviral drug adherence investigated. Assessed associations between variables using various statistical methods, including chi-squares, logistic regression, analysis of variance, and Pearson correlation	41% reported consistent adherence. 83% reported taking all medications at least “some of the time,” but only 50% of these subjects reported full adherence. Strong association between adherence and reduced viral load. CD4+ level ≥ 500 cells/ μ L was associated with adherence. Number of drugs prescribed was inversely associated with adherence, with more drugs associated with lower adherence. Higher levels of depression strongly associated with decreased adherence. Adherence was not associated with age, race, or sex
Naar-King et al, 2006 ³⁵ Tested predictors of adherence previously identified in adults among youth (self-efficacy, social support, and psychologic distress)	Recruited 24 HIV+ youth (ages 16–24 years) from single clinic site. 79% infected through risk behavior Self-administered questionnaires measured medication adherence, self-efficacy, social support, psychologic distress, and participant plasma HIV RNA level	Self-efficacy and psychologic distress were correlated with adherence. Social support was not, but social support with medications was correlated with self-efficacy. In regression analysis, self-efficacy and psychologic distress were independently related to adherence (accounting for 47% of the variance)
Radcliffe et al, 2006 ⁴¹ Trained interviewers conducted survey to assess demographic characteristics, sense of connection with care team, trauma history, and traumatic stress responses	Recruited 30 HIV+ youth (ages 18–24 years) from urban pediatric hospital-based HIV clinic Participants asked to identify their “biggest, worst experience” and their next “worst” incident or HIV diagnosis. The PTSD Checklist was used to measure stress responses to both above events	Participants experienced a mean of 6 potentially traumatic events, with HIV diagnosis being traumatic 93% of the time. HIV diagnosis was “biggest, worst experience” 59% of the time. 13% of sample met full criteria for PTSD. Percent of clinic visits kept was correlated with practitioner adherence ratings. No relationship found between adherence and care team connection

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Table 1. (Continued)

Reference Study Design	Sample Measures	Major Results and Health/Immune Outcomes
Rao et al, 2007 ³⁶ HIV+ adolescents and young adults were asked to participate in focus groups, which explored attitudes and experiences around medication adherence	Recruited 25 HIV+ youth (mean age, 22 years) from young-adult clinic where they received HIV treatment. Most participants infected during sexual contact Each focus group was recorded and professionally transcribed. Thematic categories were identified and responses coded accordingly. Frequency with which each theme occurred was tabulated	Social factors and HIV stigma represent strong barriers to adherence for youth; 50% of respondents indicated that they skipped doses because of fear that family or friends would discover status. Youthful feelings of “invulnerability” do not seem to be important barriers to HIV medication adherence. 64% of participants indicated side effects did not bother them
Schwartz et al, 2001 ⁴⁰ HIV+, REACH program adolescents observed for 24 months, assessed every 3 months. Health history, demographics, and laboratory results obtained via patient interviews, ACASI, and medical records	215 HIV+, antiretroviral therapy–naïve adolescents (aged 12–18 years at entry into REACH) seen at 15 REACH clinical sites Generalized estimating equations applied to identify associations between demographics, risk behaviors, perceived health, and clinical status with initiation of antiretroviral therapy during first 24 study months	Antiretroviral therapy prescribed for 115 (53%). Statistically significant univariate associations with antiretroviral prescription: lower CD4+ cell count (OR, 1.7; 95% CI, 1.1–2.6), higher plasma HIV RNA level (OR, 2.7; 95% CI, 1.5–5.0), and calendar year of antiretroviral therapy prescription (OR, up to 2.4; 95% CI, 1.1–5.2). Multivariate results: higher plasma HIV RNA level ($\leq 10,000$ copies/mL), having a high school diploma/General Education Degree but no further education (OR, 2.7; 95% CI, 1.3–5.5), and patient perception of poor health status (OR, 0.99; 95% CI, 0.98–0.99) were independently associated with antiretroviral therapy
Williams et al, 2006 ³³ Cross-sectional evaluation using Pediatric AIDS Clinical Trials Group (PACTG) 219C study data. Medical/clinical histories and sociodemographics obtained via clinic records, reviews, interviews. Follow-up visits held every 3 months	PACTG 219C participants with self-assessed adherence ($n = 772$; median age, 14.4 years). All participants infected through perinatal exposure Obtained and compared information on past antiretroviral therapy, clinical/neurologic diagnoses, CD4+ count, plasma HIV RNA level, and sociodemographics. Age-adjusted logistic regression models measured possible predictors of nonadherence. “Adherent” defined as $\geq 95\%$, measured via self-reporting on medication adherence in the 3 days before the visit	78% reported complete adherence over past 3 days. Variables associated with increased risk of nonadherence: female sex, plasma HIV RNA level, depression, and anxiety. Variables associated with decreased risk of nonadherence: having an adult primary care giver other than a biological parent, primary care giver education level, and CD4+ level

ACASI indicates audio computer-assisted self-interviewing; CI, confidence interval; HIV+, HIV seropositive; OR, odds ratio; PTSD, post-traumatic stress disorder.

with poorer adherence to antiretroviral drug therapy.³⁷

c. Substance use. Less alcohol use in the past week²⁹ and less recent drug use in the previous 3 months³¹ were predictive of adherence. Younger age of first marijuana use was associated with poorer adherence.³⁸

d. Psychologic/developmental and coping skills. Lower levels of psychologic distress,³⁵ higher levels of life satisfaction,³¹ and higher self-efficacy for adopting medication compliance behaviors³⁵ were associated with increased adherence. The belief that medication would “most definitely”

improve quality of life was also associated with better adherence.³⁹

Depression and depressive symptoms were consistently and strongly associated with nonadherence^{29,32,33,38} as were symptoms of anxiety.³¹ Nonadherent youth were more likely to have experienced sexual abuse under age 12 years and to have had a prior suicide attempt.¹³

Youthful feelings of “invulnerability,” defined as participants feeling invulnerable to the consequences of HIV, were not statistically significantly associated with adherence³⁶; however, “concrete” thinking¹⁸ was positively associated

with adherence measures.³⁸ In general, withdrawal or self-destructive escape coping mechanisms were associated with nonadherence.³¹

e. Sexual risk. Only 1 study examined sexual risk among adherers ($n = 85$) versus nonadherers ($n = 51$).³¹ In this study, HIV-infected youth adhering to their medications were more likely to have used condoms with recent sexual partners, were less likely to have bartered sex during their lifetime, and were less likely to have had a sexually transmitted disease since learning they were HIV-infected.

HIV disease factors. Several disease

Table 2. Factors Associated With Adherence or Nonadherence Among HIV-Infected Youth

Patient and Family Factors	Association
Demographic Factors	
Individual patient attributes	Associated with adherence: Being in school ²⁹ Inconsistent or no association with adherence or nonadherence: Age, ^{29,32} sex, ³⁰⁻³³ race ^{31,32}
Socioeconomic status	Associated with nonadherence: Housing instability ³⁴
Psychosocial Factors	
Family/caregiver	Associated with adherence: Having an adult other than the biologic parent as primary caregiver, ³³ higher caregiver education level ³³
Social support	Associated with nonadherence: HIV stigma and discrimination by friends and family (eg, skipping doses out of fear that friends and family will discover HIV serostatus) ³⁶ Inconsistent or no association with adherence or nonadherence: Social support ^{31,35}
Substance use and coping skills	Associated with adherence: Less alcohol use, ²⁹ less recent drug use (past 3 months) ³¹ Associated with nonadherence: Depression-withdrawal coping style or self-destructive escape coping style, ³¹ younger age of first marijuana use ³⁸
Psychologic/developmental	Associated with adherence: Self-efficacy, ³⁵ higher life satisfaction on the quality-of-life scale, ³¹ lower levels of psychologic distress, ³⁵ concrete rather than abstract reasoning skills, ³⁸ belief that medication would "most definitely" improve their quality of life ³⁹ Associated with nonadherence: Depressive symptoms, ^{29,32,33,38} symptoms of anxiety, ³³ sexual abuse under age 12 years, ³¹ prior suicide attempt(s) ³¹ Inconsistent or no association with adherence or nonadherence: Youthful feelings of "invulnerability" ³⁶
Sexual risk	Associated with adherence: Less likely to have bartered sex during their lifetime, ³¹ more likely to have used condoms with recent sex partners, ³¹ less likely to have had a sexually transmitted disease since learning their serostatus ³¹
Disease Factors	
	Associated with adherence: Reduced viral load, ^{28,32} CD4+ level ≥ 500 cells/ μ L ³² Associated with nonadherence: Detectable viral load, ³³ later disease stage ²⁹
Treatment Regimen Factors	
	Associated with adherence: Fewer drugs prescribed, ³² medication-related adverse effects (both physical and psychologic) ²⁸ Associated with nonadherence: Length of treatment with antiretroviral medications, ³⁴ self-assessment of adherence by patient ³³
Practitioner Factors	
	Associated with adherence: Practitioner adherence ratings ⁴¹ Inconsistent or no association with adherence or nonadherence: Care team connection ⁴¹

factors related to HIV were associated with adherence, namely undetectable plasma HIV RNA^{28,32} and CD4+ count greater than or equal to 500 cells/ μ L.³² In contrast, detectable plasma HIV RNA^{33,40} and later disease stage²⁹ were associated with nonadherence.

Treatment regimen factors. Reduced regimen complexity (ie, fewer drugs prescribed)³² was associated with improved adherence. Both physical and psychologic medication-related adverse effects were associated with poorer adherence.²⁸ Notably, length of antiretroviral

medication treatment (eg, longer term in years)³⁴ was associated with poorer adherence. Self-assessment of adherence by the patient was also strongly associated with decreased reports of adherence, compared with reports of adherence by a caregiver or medical practitioner.³³

Practitioner factors. Few studies explore practitioner factors in investigating adherence among HIV-infected youth. The only study that examined this relationship⁴¹ found that maintaining regular follow-up care and treatment with a medical practitioner was associated with increased adherence.

Adherence Interventions With HIV-Infected Youth

Seven intervention studies targeting improved adherence to antiretroviral medications among HIV-infected youth were reviewed (Table 3). Of these, 3 utilized directly observed therapy (DOT), in which participants met with a medical practitioner who administered their HIV medication, and involved a retrospective analysis of chart information.^{23,24,42} Two studies applied regimen-related interventions prospectively that ranged in duration from 12 weeks to 96 weeks,^{13,43} and 2 studies utilized education and counseling sessions to promote adherence to antiretroviral medications with study periods between 8 weeks and 12 weeks.^{44,45}

Directly observed therapy interventions. Hospital-based DOT interventions were associated with substantial changes in the plasma HIV RNA level and CD4+ count of participants. All studies that used DOT involved a retrospective analysis of information from a variety of clinical sources, including admitted children's or adolescents' medical charts, electronic medical records, and a clinic laboratory database. Parsons and colleagues,²⁴ who observed 19 admissions between 2000 and 2003, found the mean plasma HIV RNA level at admission to be 5.7 log₁₀ copies/mL, at discharge to be 4.7 log₁₀ copies/mL, and at 6 months after discharge to be 5 log₁₀ copies/mL. A decrease in plasma HIV RNA level for patients on DOT indicates prior nonadherence when the patient was not under direct supervision. Glikman and colleagues²³ reported a statistically significant decrease in mean plasma HIV RNA level (0.8 ± 0.55 log₁₀ copies/mL) for the DOT period; they also reported a rise in mean plasma

Table 3. Published Studies of Interventions Designed to Enhance Adherence Among

Reference Study Design	Population
Glikman et al, 2007 ²³ Reviewed medical charts of HIV+ patients admitted to Comer Children's Hospital for directly observed therapy. Patients hospitalized for 7 days	9 perinatally infected patients (median age, 13 years), 13 total admissions; 8 patients had been treated with numerous antiretroviral therapy regimens
Lyon et al, 2003 ⁴⁵ Intervention: 6 biweekly family and youth education sessions; 6 biweekly youth-only education sessions. Devices to increase antiretroviral adherence introduced	23 HIV+ youths (ages 15-22 years) and 23 family members or "treatment buddies"; 18/23 youths completed a group
McKinney et al, 2007 ¹³ Prospective observational study at 16 sites of 37 therapy-naïve, HIV+ children and adolescents	37 therapy-naïve HIV+ participants (43% age 14-21 years)
Parsons et al, 2006 ²⁴ Evaluated directly observed therapy of HIV+ children and adolescents with elevated viral loads and nonadherence. Retrospective chart review performed	19 child and adolescent admissions (58% age 13-16 years) included in analysis
Puccio et al, 2006 ⁴³ Pilot—small sample. Patients received free cell phones with local service and reminder phone calls for 12 weeks. Call frequency was tapered at 4-week intervals	8 HIV+ adolescents and young adults (ages 16-24 years) beginning either their initial antiretroviral regimen or a new regimen
Purdy et al, 2008 ⁴² Retrospective chart review to identify subjects and glean relevant health and adherence information	5 patients (ages 14-19 years; all vertically acquired HIV) identified as having received directly observed therapy for ≥ 4 contiguous days after ≥ 8 weeks of a stable antiretroviral regimen
Rogers et al, 2001 ⁴⁴ Longitudinal study of cohort of adolescents enrolled in TREAT program to observe movement through Stages of Change Model toward acceptance of and adherence to antiretroviral therapy	288 HIV+ adolescents (ages 15-22 years) in REACH program: 147 receiving antiretroviral therapy, 29 receiving nonantiretroviral therapy, 112 no therapy (65 accepted TREAT program)

HIV+ indicates HIV seropositive.

HIV-Infected Youth

Measures	Results and Health/Immune Outcomes
Demographics, clinical/immune class category, previous/current antiretroviral medications, drug resistance tests, plasma HIV RNA level, and CD4+ cell count and percentage before and after directly observed therapy	Three patterns of change in plasma HIV RNA level were observed over time: (1) drop at the end of the directly observed therapy period, remaining low thereafter; (2) drop at the end of the period, but not sustained; (3) no change during or after directly observed therapy. Plasma HIV RNA level at end of directly observed therapy was lower than at admission in 8 patients (mean standard deviation, decrease of $0.8 \pm 0.55 \log_{10}$ copies/mL)
Baseline participant viral load, CD4+ count, and HIV knowledge compared with same measurements from 3 months after program completion. Survey administered pre-/post-intervention	91% of youths self-reported increased adherence after completing a group. 4 participants experienced a $1 \log_{10}$ reduction in viral load to levels below detection during intervention. 2 participants continued to decline use of antiretrovirals after intervention and demonstrated no decrease in viral load. Participants tested 5 devices and rated multiple alarm watch as best aid. Family/treatment buddies rated overall program highly helpful, citing social support as most valuable. Unanticipated benefit was increase in other health behaviors
Participants observed for ≥ 96 weeks. Signs, symptoms, plasma HIV RNA level, CD4+ count, and safety laboratory tests measured	32/37 subjects (85%) achieved suppression of plasma HIV RNA level to < 400 copies/mL, and 26/37 (72%) maintained sustained suppression at < 50 copies/mL through week 96. Median baseline CD4+ count increased by 18%. Pill amount reduction (to once-daily) used as intervention
Differences in CD4+ count and plasma HIV RNA level at admission, before discharge, and 6 months after discharge were evaluated using Wilcoxon signed-ranks test	Mean CD4+ count at discharge (492) and 6 months after discharge (429) were statistically significantly higher than at admission (262) ($P < .01$). Mean plasma HIV RNA level at discharge ($4.7 \log_{10}$ copies/mL) and 6 months after discharge ($5 \log_{10}$ copies/mL) were statistically significantly lower than at admission ($5.7 \log_{10}$ copies/mL) ($P < .004$). Majority of admissions (74%) involved a change in antiretroviral regimen. Directly observed therapy resulted in immediate, sustained (up to 6 months) reduction in plasma HIV RNA level and increase in CD4+ count
Participants received a cell phone with 250 free minutes and \$10 for questionnaires. Calls were received for 12 weeks. Assessment at 4-week intervals to determine perceived intrusiveness and helpfulness of calls and missed medication doses. Assessment done at week 24 with the same questions	(1) 5/8 patients recruited completed the 12 weeks of cell phone reminders; (2) participants not experiencing institutionalization or major chaotic life changes did very well receiving phone calls, did well with adherence to medication doses, and experienced statistically significant decreases in plasma HIV RNA levels that tracked positively with adherence to call reminders; (3) initially, call reminders were reported to be "annoying, but helpful" but by 12-week follow-up, subjects reported calls to be "less annoying"
Retrospective chart review obtained plasma HIV RNA level before and after directly observed therapy intervention	All 5 participants were highly treatment experienced (median, 4 previous antiretroviral regimens), and all had genotypic evidence of resistance to antiretroviral drugs. All were prescribed a twice-daily regimen containing ritonavir-boosted protease inhibitors; 3 patients received more complex regimens because of their specific antiretroviral resistance. 4/5 patients had a decrease in plasma HIV RNA level while on directly observed therapy (ranging from 0.5 - $2.46 \log_{10}$ copies/mL; mean, $1.15 \log_{10}$ copies/mL). All patients later exhibited viral rebound
(1) Acceptability evaluated by reaction to program video ($n = 65$); (2) movement across Stages of Change Model assessed by comparing first recorded stage evaluation to last ($n = 18$); (3) acceptance of adherence measured from medical records. Adherence based on self-report, clinical judgment, and suppression of plasma HIV RNA level ($n = 18$)	(1) Acceptability of the program: 25% "expressed real approval," 49% "were positive and found it helpful," 25% "noncommittal," and 1% "negative"; (2) Subject movement across Stages of Change Model: 78% ($n = 14$) moved forward, 11% ($n = 2$) no movement, 11% ($n = 2$) regressed; (3) Subject acceptance and adherence to antiretroviral therapy: 2/3 ($n = 12$) accepted and began antiretroviral therapy, and 1/2 ($n = 6$) maintained adherence "most to all of the time"

HIV RNA level when the participants or their caregivers again became responsible for maintaining treatment in the absence of DOT. Purdy and colleagues⁴² observed 5 admissions, of which 4 had a decrease in plasma HIV RNA level while receiving DOT (range, 0.5–2.46 log₁₀ HIV RNA copies/mL; mean, 1.15 log₁₀ HIV RNA copies/mL). All DOT studies showed that plasma HIV RNA level increased as time after discharge increased, suggesting that hospital-based DOT has a limited effect on adherence among HIV-infected youth, as long-term benefits were not observed.

Regimen-related interventions. One of the 2 regimen-related interventions focused on medication scheduling (ie, reduction to once-daily dosing) and evaluated viral load and CD4+ count as outcomes. Sampling 37 therapy-naïve individuals, McKinney and colleagues¹⁵ evaluated the efficacy of a regimen that included emtricitabine, didanosine, and efavirenz. The median CD4+ count at baseline was 310 cells/mL with an increase to 673 cells/mL by week 96 of the intervention, resulting in a gain of approximately 18% and demonstrating successful viral load decreases and suppression over time.

A second study incorporated the use of cell phone reminder calls to assist HIV-infected adolescents to adhere to their antiretroviral therapy.⁴³ Of the 8 participants recruited, 5 completed the entire 12-week study period of cell phone reminders. Although the intervention technique was reported as “annoying” by participants, the 5 participants who completed the study experienced clinically important decreases in their viral loads (for example, 1 participant had a plasma HIV RNA level of 342,536 copies/mL at baseline and 242 copies/mL at 24-week follow-up).

Education and counseling interventions. One of these studies evaluated the efficacy of an 8-week program that involved antiretroviral therapy education via 2 videotapes, information booklets, and a set of 5 audiotapes using the transtheoretical model to increase adherence across stages of change.⁴⁴ The video- and audiotapes

followed a newly HIV-infected youth coming to terms with her condition as she joins a support group in which other HIV-infected youth receiving antiretroviral therapy answer questions, discuss difficult issues, and model stage-specific processes. Of the 18 of 112 participants who completed the program, two-thirds initiated antiretroviral therapy, and half self-reported maintaining adherence “most” to “all of the time.” An important limitation of this study was difficulty retaining participants.

Lyon and colleagues had more success in retention of study participants.⁴⁵ Initially recruiting 30 pairs of HIV-infected youths between the ages of 15 years and 22 years and a family member or “treatment buddy,” they retained 23 pairs for the final assessment. The program consisted of 12 weeks of education sessions, 6 of which were exclusive to just the HIV-infected youth, and the other 6 of which incorporated all participants. The curriculum focused on the dynamics of HIV; the purpose of antiretroviral therapy; medication choices and managing adverse effects; nutrition, exercise, and alternative treatments; communication with doctors and health care practitioners; and the media.

On alternate weeks, the youths met to discuss issues with medication adherence in a group psychotherapy format. To further help participants adhere to medication, a new device (such as a pillbox, beeper, calendar, multiple-alarm wristwatch, or gym bag) was introduced to the youths at each youth-only session. Upon entry into the program, 43.5% of the 23 HIV-infected youth had a CD4+ count between 200 cells/μL and 499 cells/μL, and the other 56.5% had a count of less than 200 cells/μL. By the end of the 12-week study period, 17.4% had more than 500 CD4+ cells/μL, 30.4% had between 200 cells/μL and 499 cells/μL, 26% had less than 200 cells/μL, and 13% were deceased. In addition to the positive changes in the CD4+ counts, 91% of the study participants self-reported increased adherence to antiretroviral medication as a result of the group education sessions.

Discussion

Consistent with the literature on HIV adherence among adults¹⁹ and general adherence literature,²⁷ our review of research on HIV-infected youth suggests that individual demographic factors and readily observable patient characteristics failed to distinguish adherent from nonadherent individuals. No consistent, predictive sociodemographic relationships with adherence to antiretroviral medications emerged. In contrast, psychosocial factors such as depression and anxiety were most consistently associated with nonadherence across studies. Continuing to examine adherence within the broader contextual issues present in the lives of youth is essential to understanding how to improve medication adherence and long-term survival for young people living with HIV.

The most promising strategies for improving treatment adherence among HIV-infected youth involve patient and caregiver education, self-monitoring, peer support, and telephone follow-up. Consistent with adult adherence interventions,^{21,22,27,46} multicomponent strategies tended to be most effective in improving poor adherence. A commonly cited reason for nonadherence to medication among youths is “simply forgetting.”^{29,38} Interventions that include simple treatment regimens with once-daily dosing¹⁵ seek to address this barrier to adherence.

However, once-daily dosing provides other challenges in a population with adherence difficulty. For example, missing a once-daily dose means 24 hours without medications, whereas missing 1 dose of twice-daily regimens means only 12 hours uncovered. Hosek and colleagues note that nonadherence relates more to difficulty incorporating the medication regimen into patient lifestyle than to regimen complexity itself.³⁸ Thus, interventions might consider skill building around taking medications during a specific time that is integrated into a routine behavior, such as after brushing one's teeth or eating breakfast.

Findings suggest that providing DOT, while considered impractical for

all youth because of its cost, might be important for selected adolescents infected with HIV,^{10,32} such as those with active substance use disorders. To date, no studies have examined the use of multidisciplinary treatment teams (eg, teams with case managers, physicians, nurses, psychologists) versus physicians alone in working with HIV-infected youth.⁴⁷ However, multidisciplinary treatment teams are more successful than physicians alone in providing and implementing successful adherence interventions among adults.^{27,48} Future research with HIV-infected youth may benefit from investigating intervention delivery mode (eg, team treatment vs individual treatment).

An estimated 2% to 6% of US youth have a depressive disorder, and approximately 15% have elevated depressive symptoms.^{49,50} Among HIV-infected youth, elevated levels of psychologic distress have been documented, with rates of depressive symptoms ranging from 18% to 45%.^{15,50} Evidence from studies in adults demonstrates the effectiveness of treating depression as a means of improving adherence.^{51,52} Findings that depressive symptoms are strongly associated with nonadherence among HIV-infected youth^{29,32,33,39} suggest that treatments for adolescent depression may assist in improving medication adherence. A recent study demonstrated that treating HIV-infected adults with cognitive behavioral therapy for depression and adherence skill building effectively reduced depression over time and improved medication adherence.⁵³

Limitations bear mention when interpreting review findings. Given the early stage of research in this field, all relevant studies were included in our review, regardless of methodologic rigor. The few studies conducted to date, small sample sizes, and paucity of research on specific subgroups (eg, gay and lesbian youth, racial or ethnic minority youth) limit generalizability. In addition, studies often presented adherence and nonadherence as opposing or opposite constructs. However, findings suggest that distinguishing between and understanding the differences between these concepts may yield valu-

able insight as to the roles that diverse factors play in adherence and may be especially productive in helping develop new interventions. Thus, differences between adherence and nonadherence should not be reduced but should instead be expanded and each concept thoroughly investigated.

Given the range of complex factors associated with nonadherence, different sets of targeted interventions may be warranted that focus on specific populations of youth (eg, homeless, sexual minorities, substance abusing). Randomized controlled trials are needed that incorporate solid theoretic frames, satisfactory sample sizes, psychometrically sound outcome measures, consistent operationalization of adherence, and better adherence assessment measurements.²² Cost-effectiveness data to assess the practical value of different adherence interventions in the long-term would be beneficial.^{22,54} Finally, because the psychosocial needs of HIV-infected persons are changing to more closely resemble the needs of the chronically rather than the terminally ill individual,¹⁵ investigating how psychosocial issues such as distorted body image, substance use, anxiety, history of childhood sexual abuse, and influence of peer norms relate to antiretroviral adherence may be particularly crucial to promoting long-term survival and quality of life among HIV-infected youth.^{15-17,55} Secondary HIV prevention interventions^{54,56} may provide useful means of not only reducing HIV transmission through sexual risk taking but also improving health outcomes through the incorporation of strategies to increase antiretroviral adherence.

This review indicates that more research on adherence among HIV-infected youth, as well as more rigorously evaluated interventions, are needed. Maximizing adherence may not only be fundamental to the well being of HIV-infected youth but may also have a far-reaching and broader impact on public health.¹² Nonadherence may lead to drug resistance and cross-resistance that may render HIV treatments ineffective and may be implicated in the emergence of drug-resistant strains of HIV.^{9,57,58} Consequently, gaining a

more thorough and contextualized understanding of factors associated with adherence and nonadherence, including individual demographic, social and psychologic, disease-related, treatment-regimen, and practitioner factors, represents an important step in helping people live longer and in intervening to address infectious disease rates. Further culturally tailored, intervention development research for HIV-infected youth is warranted.

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References

1. **Centers for Disease Control and Prevention (CDC).** HIV/AIDS surveillance report, 2006. Volume 18. 2008 revised edition. <http://www.cdc.gov/hiv/topics/surveillance/index.htm>. Accessed November 26, 2008.
2. **CASCADE Collaboration.** Survival after introduction of HAART in people with known duration of HIV-1 infection. The CASCADE Collaboration. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet*. 2000;355:1158-1159.
3. **Gortmaker SL,** Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001;345:1522-1528.
4. **Hogg RS,** Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA*. 1998;279:450-454.
5. **Palella FJ,** Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study

Investigators. *N Engl J Med*. 1998;338:853-860.

6. Bartlett JA. Addressing the challenges of adherence. *JAIDS*. 2002;29(Suppl 1):S2-S10.

7. Chesney M. Adherence to HAART regimens. *AIDS Patient Care STDs*. 2003;17:169-177.

8. Paterson D, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21-30.

9. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis*. 2003;37:1112-1118.

10. US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. January 29, 2008. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Accessed February 19, 2008.

11. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. *J Infect Dis*. 2008;197(Suppl 3):S272-S278.

12. Secord E, Cotronei-Cascardo C. Pediatric and adolescent HIV disease. *Ann Allergy Asthma Immunol*. 2007;98:405-412.

13. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naïve children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics*. 2007;120:e416-e423.

14. Arnett JJ. *Emerging Adulthood: The Winding Road From Late Teens Through the Twenties*. New York: Oxford University Press; 2004.

15. Battles HB, Wiener LS. From adolescence through young adulthood: psychosocial adjustment associated with long-term survival of HIV. *J Adolesc Health*. 2002;30:161-168.

16. Brown LK, Lourie KJ, Pao M. Children and adolescents living with HIV and AIDS: a review. *J Child Psychol Psychiatry*. 2000;41:81-96.

17. DeLaMora P, Aledort N, Stavola J. Caring for adolescents with HIV. *Curr HIV/AIDS Rep*. 2006;3:74-78.

18. Piaget J. *The Essential Piaget*. New York, NY: Basic Books; 1977.

19. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Educ Couns*. 2002;46:93-108.

20. Haddad M, Inch C, Glazier RH, et al. Patient support and education for promoting adher-

ence to highly active antiretroviral therapy for HIV/AIDS (Cochrane Review). *Cochrane Database System Review*. 2002;CD001442.

21. Ickovics JR, Meade CS. Adherence to antiretroviral therapy among patients with HIV: a critical link between behavioral and biomedical sciences. *JAIDS*. 2002;31(Suppl 3):S98-S102.

22. Simoni JM, Frick PA, Pantalone DW, Turner BJ. Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Top HIV Med*. 2003;11:185-198.

23. Glikman D, Walsh L, Valkenburg J, Mangat PD, Marcinek JF. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. *Pediatrics*. 2007;119:e1142-e1148.

24. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: a retrospective study. *AIDS Patient Care STDs*. 2006;20:275-284.

25. Strauss A, Corbin J. *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory*. 2nd ed. Thousand Oaks, CA: Sage Publishing; 1990.

26. Miles MB. *Qualitative Data Analysis*. 2nd ed. Newbury Park, CA: Sage Publishing; 1994.

27. Bosworth HB, Oddone EZ, Weinberger M. *Patient Treatment Adherence: Concepts, Interventions, and Measurement*. Mahwah, NJ: Lawrence Erlbaum Assoc; 2005.

28. Murphy DA, Sarr M, Durako SJ, Moscicki AB, Wilson CM, Muenz LR. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Arch Pediatr Adolesc Med*. 2003;157:249-255.

29. Murphy DA, Belzer M, Durako SJ, Sarr M, Wilson CM, Muenz LR. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med*. 2005;159:764-770.

30. Becker SL, Dezii CM, Burtcel B, Kawabata H, Hodder S. Young HIV-infected adults are at greater risk for medication nonadherence. *MedGenMed*. 2002;4:21.

31. Comulada WS, Swendeman DT, Rotheram-Borus MJ, Mattes KM, Weiss RE. Use of HAART among young people living with HIV. *Am J Health Behav*. 2003;27:389-400.

32. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Adolescent Medicine HIV/AIDS Research Network. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care*. 2001;13:27-40.

33. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medi-

cations in children and adolescents with HIV infection. *Pediatrics*. 2006;118:e1745-e1757.

34. Martinez J, Bell D, Camacho R, et al. Adherence to antiviral drug regimens in HIV-infected adolescent patients engaged in care in a comprehensive adolescent and young adult clinic. *J Natl Med Assoc*. 2000;92:55-61.

35. Naar-King S, Templin T, Wright K, Frey M, Parsons JT, Lam P. Psychosocial factors and medication adherence in HIV-positive youth. *AIDS Patient Care STDs*. 2006;20:44-47.

36. Rao D, Kekwaletswe TC, Hosek S, Martinez J, Rodriguez F. Stigma and social barriers to medication adherence with urban youth living with HIV. *AIDS Care*. 2007;19:28-33.

37. Dodds S, Blakley T, Lizzotte JM, et al. Retention, adherence, and compliance: special needs of HIV-infected adolescent girls and young women. *J Adolesc Health*. 2003;33:39-45.

38. Hosek SG, Harper GW, Domanico R. Predictors of medication adherence among HIV-infected youth. *Psychol Health Med*. 2005;10:166-179.

39. Belzer ME, Fuchs DN, Luftman GS, Tucker DJ. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health*. 1999;25:316-319.

40. Schwarz DF, Henry-Reid L, Houser J, Ma Y. The association of perceived health, clinical status, and initiation of HAART (highly active antiretroviral therapy) in adolescents. *J Adolesc Health*. 2001;29(Suppl 3):115-122.

41. Radcliffe J, Tanney M, Rudy B. Post-traumatic stress and adherence to medical treatment among youth with HIV. *J Adolesc Health*. 2006;38:110-111.

42. Purdy JB, Freeman AF, Martin SC, et al. Virologic response using directly observed therapy in adolescents with HIV: an adherence tool. *J Assoc Nurses AIDS Care*. 2008;19:158-165.

43. Puccio JA, Belzer M, Olson J, et al. The use of cell phone reminder calls for assisting HIV-infected adolescents and young adults to adhere to highly active antiretroviral therapy: a pilot study. *AIDS Patient Care STDs*. 2006;20:438-444.

44. Rogers AS, Miller S, Murphy DA, Tanney M, Fortune T. The TREAT (Therapeutic Regimens Enhancing Adherence in Teens) program: theory and preliminary results. *J Adolesc Health*. 2001;29(Suppl 3):30-38.

45. Lyon ME, Trexler C, Akpan-Townsend C, et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. *AIDS Patient Care STDs*. 2003;17:299-308.

46. Amico KR, Harman JJ, Johnson BT. Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004. *JAIDS*. 2006;41:285-297.

47. **Kunins H**, Hein K, Futterman D, Tapley E, Elliot AS. Guide to adolescent HIV/AIDS program development. *J Adolesc Health*. 1993;14(Suppl 5):1S-140S.

48. **Levy RW**, Rayner CR, Fairley CK, et al. Multidisciplinary HIV adherence intervention: a randomized study. *AIDS Patient Care STDs*. 2004;18:728-735.

49. **Richardson LP**, Katzenellenbogen R. Childhood and adolescent depression: the role of primary care providers in diagnosis and treatment. *Curr Probl Pediatr Adolesc Health Care*. 2005;35:6-24.

50. **US Department of Health and Human Services**. *Mental Health: A Report of the Surgeon General*. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, 1999. <http://www.surgeongeneral.gov/library/mentalhealth/>

home.html. Accessed January 12, 2009.

51. **Crepaz N**, Passin WF, Herbst JH, et al. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. *Health Psychol*. 2008;27:4-14.

52. **Himelhoch S**, Medoff DR, Oyeniya G. Efficacy of group psychotherapy to reduce depressive symptoms among HIV-infected individuals: a systematic review and meta-analysis. *AIDS Patient Care STDs*. 2007;21:732-739.

53. **Safren SA**, Hendriksen ES, Mayer KH, Mimiaga MJ, Pickard R, Otto MW. Cognitive-behavioral therapy for HIV medication adherence and depression. *Cognit Behav Pract*. 2004;11:415-424.

54. **Lee MB**, Leibowitz A, Rotheram-Borus MJ. Cost-effectiveness of a behavioral intervention for seropositive youth. *AIDS Educ Prev*. 2005;17:105-118.

55. **Anaya HD**, Swendeman D, Rotheram-Borus MJ. Differences among sexually abused and

nonabused youth living with HIV. *J Interpers Violence*. 2005;20:1547-1559.

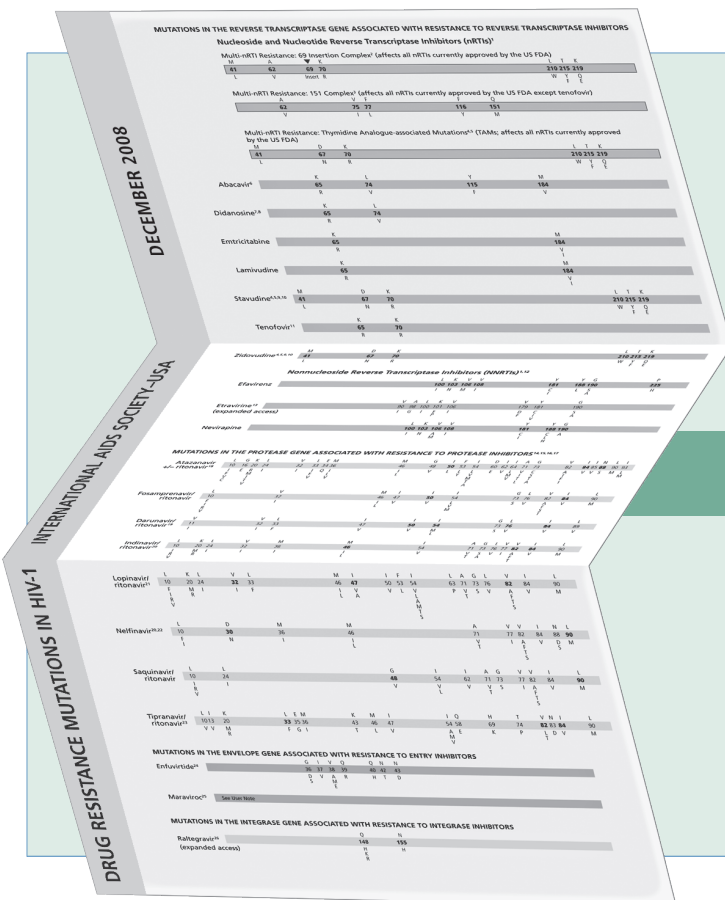
56. **Rotheram-Borus MJ**, Swendeman D, Comulada WS, Weiss RE, Lee M, Lightfoot M. Prevention for substance-using HIV-positive young people: telephone and in-person delivery. *JAIDS*. 2004;37(Suppl 2):S68-S77.

57. **Bangsberg DR**, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS*. 2006;20:223-231.

58. **Liu H**, Miller LG, Hays RD, et al. Repeated measures longitudinal analyses of HIV virologic response as a function of percent adherence, dose timing, genotypic sensitivity, and other factors. *JAIDS*. 2006;41:315-322.

Top HIV Med. 2009;17(1):14-25

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