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Antiretroviral Therapy Adherence Enhancing Interventions for Adolescents and Young Adults 13–24 Years of Age: A Review of the Evidence Base

Sarah Shaw, MA and K. Rivet Amico, PhD

Introduction: Youth living with HIV are highly under-represented in the evidence base for adherence interventions, despite their diverse and unique needs and barriers.

Objective: This systematic review aimed to identify antiretroviral therapy (ART) adherence interventions specifically targeting adolescents and young adults (defined as ages 13–24) with the goal of characterizing the evidence base.

Methods: Articles were identified using the PubMed database and cover work published through September 14, 2015. Inclusion criteria: (1) average age 13 to 24, (2) HIV positive, (3) on or beginning ART, (4) intervention targeted ART adherence in full or in part, (5) reported adherence, viral load, and/or CD4 count outcomes. Strength of evidence was defined as level 1 [randomized controlled trial (RCT) with significance testing on outcomes], 2 (within group studies with statistical testing on outcomes), 3 (RCTs with descriptive results), or 4 (within group studies with descriptive results).

Results: Of 151 articles, 10 met inclusion criteria. Published between 2003 and 2014, these studies evaluated diverse intervention approaches. Most were conducted in the US and were small pilots that have yet to be replicated despite promising results. Only 3 studies met criteria for highest level strength of evidence; 2 supported a phone-based counseling approach with adherence monitors and 1 for weekly individual and family counseling.

Conclusions: Despite nearly 20 years passing since the wide-scale availability of ART, and clear recognition that adolescents and youth adults fair worse on the cascade of HIV care, the evidence base remains sparse and underdeveloped. Promising approaches need replication and more rigorous studies are desperately needed.

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From the Department of Health Behavior and Health Education, School of Public Health, University of Michigan, Ann Arbor, MI.

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Correspondence to: K. Rivet Amico, PhD, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109-2029 (e-mail: ramico@umich.edu).

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INTRODUCTION

Adherence to antiretroviral medication is a critical component of HIV treatment and management. The probability of the progression to AIDS and death decreases with consistent and proper adherence to antiretroviral therapy (ART), and poor adherence can result in negative health outcomes and treatment-resistant strains of the virus.[1–3] Among adolescents and young adults living with HIV, rates of suboptimal adherence produce poorer outcomes than their adult counterparts.[4] In the US and globally, adolescents living with HIV face unique barriers to maintaining high adherence levels because they progress through major milestones in cognitive and social development and transition to adult HIV care.[5] Compared with adults, adolescents and young adults in the United States have poorer retention in care, a larger delay in the initiation of ART, and lower rates of virological suppression.[6,7]

Of the 33.4 million people living with HIV, 4.9 million are youth.[8] Youth in the US generally have noteworthy challenges in sexual health and self-care[9] and poverty, discrimination, homophobia, and discrimination are well-recognized factors influencing both risk for HIV infection and utilization of HIV care. Despite the high prevalence and incidence of HIV in adolescent and young adult populations across the globe, this population is highly under-represented in evidence bases of effective intervention approaches to promote rapid and durable viral suppression. Adherence interventions, specifically, target viral suppression and have a long history and robust presence in the literature, with multiple meta-analyses and synthesis[10–12] published to date and resources available to implement demonstrated interventions.[13] In contrast, youth-focused interventions, particularly within key populations,[5] have not been as comprehensively represented in the evidence base. A recent systematic review characterized service delivery interventions among individuals 10–19 years of age, finding 11 studies published through 2014 that suggested some promising approaches but ultimately provided limited evidence for effective linkage, retention, and adherence strategies specific to adolescent and young adult populations.[14]

Adolescents and young adults living with HIV, through behavioral or perinatal routes of infection, require specific focused attention. Youth have diverse needs that are unique

from adults and to date the appropriateness of adapting adult interventions to youth remains suspect because of the dramatic differences between adults and youth in executive functioning, emotional development, and self-regulation.[15] Adherence may also be challenging during adolescence because of reactivity to feeling different from peers.[16] Intertwined in these processes are different levels of identification, including ethnic/racial, gender, sexuality, moral and religious identities[17,18] that shape engagement in care and adherence. Strategies and messages to support adherence and well-being should arguably reflect shifts from concrete to abstract thinking and from an invulnerable to self-preserving mindset. It is important to note that the definition of adolescence can vary by culture, yet these developmental themes are persistent throughout and have implications for adherence. Given the ongoing disproportionate burden of HIV in youth worldwide, taking stock of the available evidence on efforts to fully engage adolescents and young adults in adhering to their medication regimens can identify areas of promise and areas that should be addressed in research agendas.

To identify the "front facing" evidence base specific to ART adherence interventions for adolescents and young adults, and gaps in evidence, we selected the most frequently used research database linking to peer reviewed publications among medical care providers,[19] PubMed. This differs substantially from meta-analytic or research syntheses approaches that cull across a wide range of resources, including databases for peer-reviewed publications and conference presentations, cross-referencing, and efforts to contact authors when data are insufficiently detailed in a given publication that allow for characterization of the full research database in a given area. Our work focuses on what faces an individual, organization, or group searching a common access database ("front facing") for interventions that were effective for potential adoption, thus representing the operations and dissemination intersection of consumer (service provider) and evidence (peer-reviewed publications cataloged in PubMed) rather than a full capture of emerging research available through more databases or conference and meeting venues. Also, distinct from work already available,[14] our efforts focused on interventions evaluated within populations ranging from 13 to 24 years of age, the range that the Centers of Disease Control and Prevention (CDC) identifies as accounting for an estimated 26% of all new HIV infections in the US.[9] Additionally, this population faces unique barriers to adequate adherence as they transition from pediatric to adult care settings[20]

METHODS

Search

Adolescent and young adult-focused intervention articles were identified using the PubMed database covering

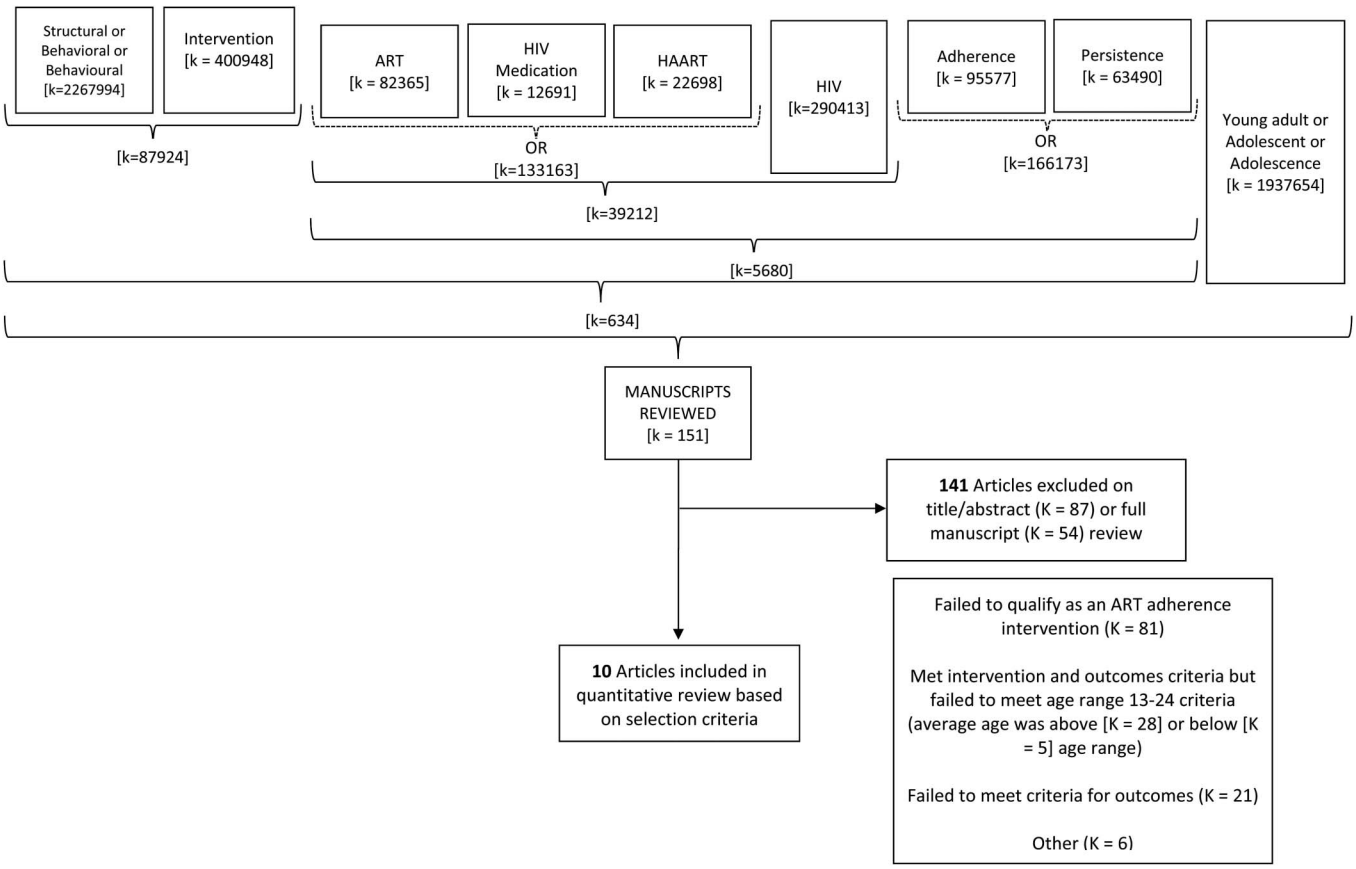

FIGURE 1. Flowchart for reviewed and included articles under searched term [(((((((structural) or ((behavioral) or behavioural))) and intervention)) and ((((((ART) or HIV medication) or HAART)) and ((adherence) or persistence)) and HIV))) and (((young adult) or adolescent) or adolescence)]. HAART, highly active antiretroviral therapy.

work published through September 14, 2015. Search terms evaluated for inclusion and resulting data are presented in Figure 1. Inclusion was based on the following criteria: (1) focus of intervention was on adolescents to young adults (average age range 13–24), (2) participants were HIV positive, (3) participants were on or beginning ART, (4) evaluated an intervention targeting ART adherence in full or in part, and (5) reported adherence, viral load (VL), and/or CD4 count outcomes.

Selection of Articles for Review

As presented in Figure 1, 151 articles were identified by the applied search terms. Title and abstract review excluded 87 articles; complete text review eliminated another 54. In full, only 10 articles met all criteria and were used in the current research synthesis. The main reason for elimination was not having evaluated an adherence intervention followed by exclusion due to average age being outside the range of 13–24 years.

Data Extraction

Each article that met selection criteria was reviewed for characteristics of the cohort or population included in the research (eg, sample size, sex distribution, race, and ethnicity), design features (eg, randomization, study arms/conditions, and sampling strategy), intervention characteristics/adherence strategies in treatment condition (eg, duration, dosage, and targets), adherence support offered or available to control or comparison group if applicable, outcomes measured, methodology for and frequency of measurement, overall outcome of evaluation as reported in article. For articles providing such information, the details were extracted and recorded in an excel worksheet database. All content was extracted by (S.S.) with discussion of all authors to adjudicate or clarify any content that could not be clearly interpreted.

Data Synthesis

Meta-analytic procedures synthesizing effect sizes across the evidence base were not used because of the small set of studies included and diversity in their research, evaluation and inferential statistics strategies, and reporting. Rather, we conducted an iterative review of the 10 included studies to identify commonalities in main results and conclusions, intervention approaches, and outcomes that characterize the current "state of the science" for ART adherence support interventions for adolescent and young adult populations. Data extracted from each article were summarized and iteratively reviewed by both authors to identify common themes and limitations in the current evidence base.

RESULTS

Populations

In full, 10 articles met inclusion (Table 1) and represented a total of 346 youth. The average enrolled sample size was about 35 participants per study, ranging from 4 to 108. The average evaluated sample size was about 23, ranging from 4 to 91. Most studies presented findings from small pilot interventions (only 2 studies had over 60 participants,[21,24] 1 of which included over 100 participants[21]). Only 2 studies were conducted outside the US: 1 at the Thai Red Cross AIDS Research Centre clinics in Bangkok, Thailand[21] and the other in the United Kingdom.[27] Samples were largely drawn from pediatric clinics and 2 studies recruited participants from sites in the Adolescent Trials Network for HIV/AIDS.[22,24] The study populations in all 8 of the US interventions consisted of primarily African American and Hispanic/Latino/a youth. Only 1 study included or reported transgender identity[23] and sexual identity was reported by only 2 studies.[21,24] Mode of HIV infection was commonly reported, with the evidence better representative of cohorts with mixed routes of infection (3 of the 9 studies reporting infection route represented almost exclusively perinatally infected youth[25–27]). The average age of intervention participants ranged from 15 to 23 years of age. A total of 8 out the 10 articles reported an average or median age greater than 18 years of age, whereas only 2[25,26] looked at an average below 18 years of age (15 and 15.5 years).

Project Design/Study Type

Most of the interventions (60%) conducted repeated measures of within-group comparisons, generally including 6 to 9 assessments of outcomes over 24–96 weeks (average 37 weeks). All but 2[28,29] of the studies evaluated outcomes postcompletion of the intervention. Experimental and quasi-experimental designs were used in 4 studies[21,22,24,25] which implemented diverse strategies for allocation and comparison condition. Use of attention control or active intervention comparison arms was common in trials which adopted randomized controlled trial (RCT) designs (3 of the 4 studies using random assignment).[21,24,25]

Interventions

The most frequently evaluated intervention strategy was individual sessions (90%)[21,22,24–30] followed using technology in some capacity (80%).[22,23–26,28–30] Cell phones were evaluated in 3 studies,[22,28,30] pagers in 2,[23,29] and Skype,[25] telephones,[26] computers,[24] and wrist-watches[23] were included in interventions in single studies. Of the included articles, 40% incorporated reminder strategies,[22,28–30] 30% included parents sessions,[23,25,26] 30% employed motivational interviewing,[21,24,27] 20% involved families or family members other than parents,[23,25] and 10% used group sessions.[23] Length of intervention varied from brief (2 sessions a month apart)[24] to a 12-month intervention that consisted of 2 motivational interviewing sessions and financial incentives based on scheduled VL assessments.[27] Most of the interventions were 12 or 24 weeks in length (70%).[21–23,25,28–30]

Intervention Modality

The articles included in the review applied varying modalities to conduct the interventions. Three interventions[21,23,27] were delivered in-person whether at health clinics or a children's

TABLE 1. Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Level 1: RCT studies with significance testing on outcomes							
Letourneau et al[25]	MST for poorly adherent youth with HIV: results from a pilot RCT	N(bl and f) = 34 65% female, 35% male Distributions of sexual identities not reported Mean age = 15 97.1% infected perinatally Ethnicity: 91% African American Inclusion criteria: 9–17 yrs of age, receiving HIV management, residing in stable placement and within a 2-h drive from either clinic and met adherence-related eligibility criteria Participants recruited from pediatric clinic	RCT pilot—30 randomized into MST and MI groups and first 4 participants placed in MST group Between group comparison MST intervention group and single MI session control group Analyses performed using HLM software Collected data before baseline; then 4 assessments (bl, 3, 6, 9 mo) Final assessment: 9 mo from baseline Standard of care (all groups): adherence monitoring, discussion with providers at each clinical care visit, home visits when needed, hospitalization as needed, quarterly clinic visits	N(bl and f) = 20 MST On average, 6 mo long individual and family-level intervention conducted at home, over the internet (eg, Skype for youth in rural locations), at schools, and medical clinics Families seen for a mean of 2.2 visits per week Strategies included cognitive-behavioral therapy, parent training, BFST, and communication skills training	N(bl and f) = 14 Single session MI Individual and family level control condition conducted in clinic and at home if needed	Self-reported adherence (1 mo recall items: % days any medication taken, all doses taken, medication taken according to instructions) as a dichotomous variable <90% VL CD4 count Satisfaction with treatment	Between groups NS difference between MST and MI groups Significant difference in changes in VL with MST group continuing to ↓ over time and MI group increasing NS differences for CD4 Within groups Intervention arm: ↑ medication adherence (significant), ↑ CD4 count (significant), ↓ VL (significant monthly rate of change) Control arm: NS change in medication adherence, rate of change in CD4 count, change (slope) for VL
Rongkavilit et al[21]	Motivational interviewing targeting risk behaviors for youth living with HIV in Thailand	N(bl) = 108; N(f) = 91 81.5% male Sexual identities: 29.6% heterosexual, 20.4% bisexual, 50% homosexual; 70% MSM Mean age = 21.7 Ethnicity: Thai youth 16.7% infected perinatally Inclusion criteria: HIV positive, age 16–25, ability to understand Thai Youth living with HIV attending the Thai Red Cross AIDS Research Centre clinics in Bangkok who were interested in participating were referred by their physicians to the study team	RCT pilot Between- and within-group comparisons VL and adherence measured 4 and 9 mo after baseline (1 and 6 mo after final session) Final assessment: 9 mo from baseline	N(bl) = 55 N(f) = 49 Healthy choices MI-based intervention informed by the Information Motivation-Behavior Skills model targeting risk reduction 12 wks with 4 individuals level sessions (60 min each) Counseling sessions targeted 2 of 3 risk behaviors, including sexual risks, alcohol use, and antiretroviral adherence (selected based on severity of the risk identified at baseline assessment)	N(bl) = 53 N(f) = 42 Time-matched health education control group 4 individualized sessions of general health education (healthy diet, exercise, smoking and health sleep habits, overall review). The content was from the health education materials published by the Thai Ministry of Public Health Interventionist was instructed to avoid discussing HIV-related topics	Self-reported adherence (VAS; global adherence score averaged % of ART medications being taken, % of the time every dose for the day was taken, % of the medications being taken as directed in past 30 d) VL Other: substance use, sexual risk behaviors, mental health, motivational readiness, self-efficacy, condom use	Between and within groups NS within or between groups change on adherence for those on ART (n = 21 intervention arm with 84% adherence at baseline and 89% at 6 mo; n = 18 control condition with 92% adherence at baseline and 88% at 6 mo) NS within or between groups on change in VL (log VL change at 6 mo from baseline was −0.14 for intervention and −1.06 for control conditions)

TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Belzer et al[22]	The use of cell phone support for nonadherent HIV-infected youth and young adults: an initial randomized and controlled intervention trial	N(bl) = 37; N(f) = 31 62.16% male Distributions of sexual identities not reported Mean age = 20.43 Ethnicity: 70.27% African American, 10.81% White, 18.92% Hispanic or Latino/a 45.95% infected perinatally Inclusion criteria: HIV-positive youth between 15 and 24 yrs old with a defined history of nonadherence to one or more components of ART; excluded if there was evidence of a cognitive impairment or other mental/substance abuse condition that limited ability to complete intervention or assessments; youth were also not allowed to be participating in another behavioral intervention trial at same time Participants recruited from 5 ATN sites	RCT Between-group comparison Intervention guided by theories of social support Adherence and VL measured at bl, 24 wks, and 48 wks Final assessment: 48 wks from baseline	N(bl) = 19; N(f) = 12 Cell phone support through problem solving 24-wk individual/interpersonal cell phone support intervention; frequency of calls depended on medication dosage; calls scheduled at a time after youth scheduled to take their ART "Adherence facilitators" placed calls and served as medication monitor using problem solving during the call Facilitators were not permitted to be licensed clinicians or master's level social workers	N(bl) = 18; N(f) = 17 Standard of care Youth were randomized within sites and those in the control group received individual ATN sites' usual care for the 24-wk period	Self-reported adherence (VAS last month and last 3 mo; dichotomous variable at <90% or ≥90% adherence) VL	Between groups ↑ mean % adherence rates (improvements significantly higher in intervention vs. control; improvements seen at 24 wks sustained through week 48) Higher proportion of youth in intervention reported being adherent (dichotomous outcome) at all 4 assessments compared with control group ↓ mean VL intervention group saw greater decreases in VL at 24 and 48 wks compared with control; differences were significant Virologic suppression below the level of detection significantly higher in intervention group over study

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TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Level 2: within-group studies with significance testing on outcomes							
Dowshen et al[28]	Improving adherence to ART for youth living with HIV/AIDS: a pilot study using personalized, interactive, daily text message reminders	N(bl) = 25; N(f) = 21 92% male Distributions of sexual identities not reported Mean age = 23 Ethnicity: 60% African American, 8% White, 24% Hispanic or Latino/a, 8% multiracial 12% infected perinatally Inclusion criteria: HIV positive, age 14–29, use a personal cell phone, English speaking, on ART with adherence problems Sample drawn from a program that provides medical care and other services to YLHV at an LGBT-focused center that services mainly young men who have sex with men of color	Within-group comparison—no control group pilot Convenience sample 5 total assessments of adherence (bl, 6 wks, 12 wks, 18 wks, and 24 wks); 3 assessments of VL and CD4 (bl, 12 wks, 24 wks) Final assessment: 24 wks from baseline	Daily text messages Individual level, 24-wk intervention that consisted of daily text reminders Frequency and time of daily reminders and actual personalized reminder message were chosen by the participant with the help of the research assistant	No control group	Self-reported adherence measured by VAS and AIDS Clinical Trials Group adherence questionnaire and satisfaction surveys CD4 count VL	Within groups ↑ self-reported adherence (significant) NS improvements in CD4 and decreased VL

TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Level 3: RCT studies with descriptive outcomes							
Naar-King et al[24]	MESA: pilot randomized trial of a brief computer-delivered prevention intervention for youth initiating antiretroviral treatment	N(bl) = 76; N(f) = 70 80.26% male Sexual identities: 22.36% straight/heterosexual, 19.74% bisexual, 57.89% gay/lesbian Mean age = 20.32 Ethnicity: 71.05% African American, 2.63% White, 22.37% Hispanic or Latino/a, 3.95% multiracial No data route on infection Inclusion criteria: HIV+, ages 16–24 yrs 11 mo, newly recommended to begin ART Excluded if pregnant, unable to understand written and spoken English, active psychiatric disorder that interfered with study participation, or participation in any concurrent adherence intervention trial Recruited from 8 sites in the NIH Adolescent Trials Network for HIV/AIDS	RCT with blinding of staff to treatment condition Between- and within-group comparison Further follow-up organized in alignment with clinic visits to 6 mo after study entry 3 assessments: bl, 3 mo, 6 mo Final assessment: 6 mo from baseline	N(bl) = 36; N(f) = 33 MESA Computer-based brief individual-level intervention that incorporated MI and is specifically tailored to adolescents living with HIV in the US Two 30-min sessions held in clinic setting Two-dimensional animated character (avatar) delivers personalized health feedback, information related to ART and can deliver MI strategies—designed to mimic the conversational nature of person-delivered brief interventions	N(bl) = 40; N(f) = 37 Nutrition and physical activity control group (MESH) Two-session attention-control intervention that also used the CIAS software with an MI-consistent avatar Software followed same format as intervention component	Self-reported adherence (ACASI VAS; number of doses of HIV medication missed in the last 7 d and last weekend) VL	Findings are effect size estimates (no tests on group differences on measures; differences are effect size differences) Between groups ↑ adherence (6-mo VAS; % past week; % past weekend) seem larger for MESA condition Comparison of effect sizes significantly different in favor of MESA condition for % adherence past week and past weekend ↑ viral suppression by month 6 (52% for MESA arm and 38% suppressed in MESH condition) ↓ log 10 transformed VL from study entry to 6 mo (1.84 drop in MESA and 1.60 for MESH condition at month 6)

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TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Level 4: within-group studies with descriptive outcomes							
Lyon et al[23]	A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project	N(bl) = 23; N(f) = 21 however, only 18 completed the groups 60.9% female, 34.8% male, 4.3% transgender (n = 1) Distributions of sexual identities not reported Mean age = 19.3 Ethnicity: 100% African American 9% infected perinatally Inclusion criteria: patients who reported difficulty adhering to antiretroviral medication (youths with lowest CD4 count or highest VL recruited first) Participants recruited from specialty clinic at an urban children's hospital	Within-group comparison—no control group 3 assessments: start of group, end of group and follow-up 3 mo after group ended Final assessment: 6 mo from baseline	Individual and family level pilot 12-wk intervention 6 biweekly family and youth education sessions and 6 biweekly youth-only education sessions Curriculum covered dynamics of HIV, purpose of ART, medication choices/managing side effects, nutrition/exercise/alternative treatments, communication with doctors/health care providers, the media. Youth-only sessions were in a group psychotherapy format during which a new device was introduced to help patients' adherence to medication doses Group size ranged from 16-20 depending on attendance	No control group	Self-reported adherence (NIH Adherence to Medication Questionnaire and CAPS interview of reasons given for missing doses) and skipped a dose in past 2 wks, past 2 d, and yesterday; adherence measured as dichotomous variable: skipped dose/did not skip dose CD4 count VL	Within group ↓ nonadherence from bl to 3 mo postintervention: report of skipped dose in past 2 wks went from 78% to 36%; report of skipped at least 1 dose yesterday went from 50% to 12%; report of skipped at least 1 dose in past 2 d went from 43% to 18% ↓ VL to undetectable levels in 4 participants at follow-up ↑ CD4 count to >500 in 4 participants at follow-up
Puccio et al[30]	The use of cell phone reminder calls for assisting HIV-infected adolescents and young adults to adhere to highly active ART: a pilot study	N(bl) = 8; N(f) = 5 87.5% male Distributions of sexual identities not reported Mean age = 20.6 Ethnicity: 25% African American, 12.5% White, 50% Hispanic or Latino/a, 12.5% multiracial 25% infected perinatally; 37.5% MSM Inclusion criteria: HIV-positive youth, either going to begin HAART for the first time or were going to start a new HAART regiment for HIV treatment Sample drawn from the Division of Adolescent Medicine at Children's Hospital Los Angeles	Within-group comparison—no control group pilot Adherence measured after 4 wks, after 8 wks, and after 12 wks; VL measured at baseline, after 4 wks, after 8 wks, after 12 wks, and at 24 wks Final assessment: 24 wks from baseline	Cell phone reminders 12-wk individual level intervention Study participants received phone calls for each medication dose (once or twice a day) from research team member; cell phone was provided Tapered schedule—during the first 4 wks, calls occurred on a daily basis, for weeks 5–8, calls were only made Monday–Friday and then weeks 9–12 calls occurred on Sunday, Tuesday, and Thursday Participants chose their call times Participants were terminated from the cell phone reminder and 4-wk surveys if they missed 3 calls	No control group	Adherence (missed medication past 4-wk recall) VL	Within group Number of missed doses at the end of the intervention (12 wks) remained unchanged or increased across all participants Descriptive findings (no statistical tests) ↓ VL overall in 6/8 participants from baseline to 24 wks (but ↑ VL in 4/8 from 12 to 24 wks) ↓ VL associated with adherence to call reminders 4/8 with undetectable VL (<50) at 12 wks, only 2/4 remained undetectable at 24 wks 3 subjects unable to complete study and were dropped b/c of missed calls

TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Gaur et al[29]	DOT for nonadherent HIV-infected youth: lessons learned, challenges ahead	N(bl) = 20; N(f) = 14 65% female Distributions of sexual identities not reported Median age = 21 Ethnicity: 75% African American, 5% White, 20% Hispanic Infection acquired through high-risk behaviors Inclusion criteria: Aged 16 to <25 yrs with behaviorally infected youth continuing, reinitiating, or changing HAART with demonstrated adherence problem Excluded if pregnant, breastfeeding, had a comorbidity that required frequent monitoring and medical follow-up or were receiving HAART that required more than twice daily dosing Sample drawn from patients at community sites in Detroit, Memphis, LA, and San Diego	Within-group comparison—no control group pilot 7 assessments at bl, 4 wks, 8 wks, 12 wks, 16 wks, 20 wks, 24 wks Final assessment: 24 wks from baseline	DOT 24-wk pilot study that intervened at the individual level and took place at a community-based location chosen by the participant In community DOT enhanced with conversations with DOT facilitator guided by Health Belief Model and self-efficacy theory Initial 2-wk period of daily DOT which was then tapered to 5 d a week for 6 wks and subsequently further reduced to self-administered therapy dependent on rates of adherence to DOT (DOT exposure ranged from 12 to 24 wks) While on DOT, participants were provided pagers for site staff to contact them and for automated medication reminders	No control group	Self-reported percent adherence over past 4 wks; dichotomize to >93% in analyses CD4 count VL	Within group Descriptive findings (no statistical tests) 71% had >93% adherence while receiving DOT at week 12 that dropped to 36% at week 24 when participants were tapering or off DOT ↑ median CD4 count at 12 and 24 wk VL suppression (1/20 suppressed at BL) ↑ at week 12 (9/14); not sustained at wk 24 (6/14)

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TABLE 1. (*Continued*) Ten Adherence Intervention Studies Included in Review of Adherence Interventions for Youth Living With HIV Ages 13–24

Study	Title	Sample	Design	Intervention Description	Control Description	Outcomes Measured	Outcomes
Gray et al[26]	Piloting BFST to improve adherence among adolescents with HIV: a case series intervention study	N(bl and f) = 4 75% female Distributions of sexual identities not reported Mean age = 15.5 Ethnicity: not reported 100% perinatally infected Two participants below poverty line Inclusion criteria: adolescents aware of their HIV diagnosis, identified by their physician as having poor adherence to HAART, currently taking medication in pill form, living with parent/legal guardian w/in a 90-min driving distance of clinic; excluded if have major psychiatric illness Participants identified at hospital-based pediatric infectious disease clinic in Southeast US	Within-group comparison—no control group case series pilot 6 study phases which include: (1) initial screening and assessment, (2) baseline monitoring (3–6 wks), (3) pretreatment assessment, (4) treatment (7 weekly sessions), (5) posttreatment assessment, (6) follow-up assessment (3 mo after treatment)	BFST BFST was adapted by including an HIV/HAART education session and tailoring problem solving and family communication to address adolescent-reported barriers to adherence Individual and family level intervention consisting of 7 weekly sessions of adapted BFST that included HIV education and problem-solving training Delivered in the form of alternating home (40–50 min) and telephone (20–30 min) sessions and included joint sessions conducted with the adolescent and parent dyad	No control group	Adherence measured by MEMS TrackCaps, pill counts, and paper-based monitoring log VL	Within group Descriptive findings (no statistical tests) ↑ mean adherence increased for 3/4 adolescents from bl to posttreatment assessment and from posttreatment to follow-up ↓ VL in 2/4 participants from enrollment to final follow-up (one reaching clinical significance)
Foster et al[27]	"Payment by Results"—financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: a pilot program	N(bl) = 11; N(f) = 10 72.7% female Distributions of sexual identities not reported Mean age = 19 Ethnicity: 72.7% African American, 27.3% White 100% infected perinatally Inclusion criteria: perinatally infected, age 16–25, CD4 count ≤200, off ART despite multiple attempts but willing to restart therapy, transitioned from pediatric services to specialist young persons HIV clinic, willing to sign patient agreement Sample recruited from a specialist young person HIV clinic in the United Kingdom	Within-group comparison—no control group pilot 3 major assessments at bl, 12 mo, and 24 mo of VL and CD4 (smaller more frequent assessments aligned with financial incentives) Final assessment: 24 mo from baseline	Financial incentives and MI 12-mo individual level intervention implemented at a young person's HIV clinic 1 MI session at baseline and after initiation of ART Structured adherence support termed the "Incentive Scheme" which combined financial incentives with attendance at motivational interviewing sessions—received vouchers for specific set decreases in VL at certain time markers	No control group	CD4 count VL Sustained viral suppression	Within group Descriptive findings (no statistical tests) ↑ medianCD4 at 12 mo ↑ median CD4 at 24 mo but lower than 12 mo ↑ mean CD4 gain from baseline at 12 and 24 mo ↓ median VL at 12 (105 c/mL) and 24 mo (<50 c/mL)

ACASI, audio computer assisted self interview; ATN, Adolescent Medicine Trials Network; BFST, behavioral family systems therapy; bl, baseline; CAPS, Center for AIDS Prevention Studies; f, follow-up; HAART, highly active antiretroviral therapy; HLM, hierarchical linear modeling; LGBT, lesbian, gay, bisexual and transgender; MESA, motivational enhancement system for adherence; MeSH, Medication Subject Healths; MI, motivational interviewing; MSM, men who have sex with men; MST, multisystemic therapy; N, sample size; NS, non/not significant at $P > 0.05$; Significant, $P \leq 0.05$; VAS, Visual Analog Scale; YLWH, Youth Living with HIV.

hospital with strategies including motivational interviewing and educational sessions. Four of the interventions[21,24,28,30] were delivered through technology. One article described daily personalized text messages,[28] whereas another delivered a computer-based brief intervention.[24] The other 2 were phone-based interventions in which daily calls served as medication reminders and monitors.[21,30] The remaining 3 interventions were delivered both in-person and through technology.[25,26,29]

Delivery of the interventions involved a diverse set of professionals with various educational and career backgrounds: 20% of interventions were delivered by or partially delivered by a case manager,[22,23] 20% by a research assistant,[21,22] 30% by a clinical psychologist, clinical nurse or physician,[21,23,27] and 70% by other professional or academic personnel,[23–26,28–30] including masters level therapists,[25] study coordinators or interventionists hired by the study,[28–30] graduate students,[26] and mental health professionals.[23] One study used computer software to deliver the intervention.[24] Only 1 article stated a focus on using lower-cost staff as the facilitators could not be licensed clinicians such as nurses, psychologists, or master's level social workers.[22]

Type of Adherence-Related Outcome

Reporting on VL or CD4 t-cell counts and/or some measure of adherence was required for inclusion in the review. Thus, all studies report on one or more of these outcomes. All 10 articles included VL as an outcome, 5 included CD4 count,[23,25,27–29] and 9 included a measure of adherence.[21–26,28–30] Of these 9 studies that included an adherence outcome, most were derived from self-report,[21–25,28,29] 1 a combination of directly observed therapy (DOT)[29] and self-report, and 1 used Medication Event Monitoring System (MEMS) data.[26] Measurement strategies included: (1) Visual Analog Scale, (2) AIDS Clinical Trials Group adherence questionnaire, (3) Medication Event Monitoring System (MEMS), (4) TrackCaps, (5) pill counts, (6) paper-based monitoring log, (7) NIH Adherence to Medication Questionnaire, and (8) Visual Analog Scale through audio computer-assisted self-interviewing. The most common operationalizations of self-reported adherence were percent of doses taken over doses prescribed and a count of missed doses. Time periods for these measures ranged from the previous day[23] to past 3 months.[21] A recall interval of 4 weeks was used by half of the studies[21,22,25,29,30] and 40% of studies dichotomized adherence, 2 with a 90% cutoff,[22,25] 1 with whether or not any doses were skipped and the final study used >93%.[29] One study in this review used a MEMS supplemented by pill counts and self-report when MEMS data were missing.[26] MEMS was used to monitor weekly adherence for one of the medications the participations were taking. In this study, adherence data were gathered from MEMS whenever possible but pill count and self-report were also used to measure this variable in 17 incidences (23.8%).

"Graded" Evidence Base

All articles were evaluated in the context of their potential strength of evidence, prioritizing studies of highest methodological rigor and confidence in findings. This resulted in the organization of studies (Table 1) into the following categories: (1) RCT with significance testing on outcomes[21,22,25]; (2) within-group studies with statistical testing on outcomes[28]; (3) RCTs with descriptive results[24]; (4) within-group studies with descriptive results.[23,26,27,29,30]

Evidence Level 1

Three studies contributed the strongest evidence through use of RCT designs and statistical evaluation of outcomes.[21,22,25] The 2 focused on improving ART adherence demonstrated significant positive outcomes on self-reported medication adherence and viral suppression at 6[22] and 9 months.[25] Each targeted nonadherent youth and used some aspect of problem solving, with Belzer et al[22] using cell phone outreach by monitors to work with youth on problem solving around dose times, and Letourneau et al[25] using weekly in-person or internet-facilitated family and patient counseling to target training and skills building. Despite relatively small samples, effects were significant on adherence and biological outcomes and seemed robust over time. Alternatively, the final RCT included in this category[21] was focused in part on adherence but predominantly on reduction of risk behaviors and did not select participants on the basis of known history with nonadherence. In this study of youth in Thailand, the implementation of an evidence-based risk reduction intervention (12-week 4-session Healthy Choices intervention), in comparison to a health education comparison condition, did not impact adherence or VL.

Evidence Level 2

As depicted in Table 1, only 1 study was ranked at the second level of evidence (within groups design using statistical test of effects). Dowshen et al[28] delivered a 24-week intervention among youth with adherence problems which consisted of daily text reminders at dose time, followed by a texted inquiry about whether or not the dose was taken an hour later. Self-reported adherence improved significantly from baseline (75%) to the final assessment at week 24 (93%). Although VL and CD4 patterned in a promising direction (dropping from a VL of over 2700 to 28 from baseline to 24 weeks, and increasing CD4 counts from 501 at baseline to 545 at 24 weeks), significance was not reached. Of note, the text intervention seemed to have been implemented throughout the project period, thus no assessment after removal of texts was provided.

Evidence Level 3

Only 1 study was included in this level.[24] Although the trial was a high methodological rigor RCT and did include some subanalyses with significance testing, we position it in level 3 given the overall approach of description of effect sizes. This study evaluating a 2-session computer-delivered Motivational Enhancement System for Adherence (MESA) for treatment-naïve youth used an active comparison condition (a nutritional and physical activity program: Medication Subject Healths [MeSH]). Evaluation of self-reported adherence at 6 months, proportion of participants suppressed, and change in log VL favored the intervention condition as suggested by small to large effect size estimates. Contrasts of effect sizes on 2 of the adherence measures were significant. Given that the intervention and comparison condition were typically implemented within the first 3

months of enrollment into the study, the final endpoint did reflect a durability of gains, largely evident by month 3.

Evidence Level 4

Most of the intervention studies with youth targeting ART adherence in the literature fall in the lowest level for strength of evidence where within-group designs are used and outcomes are largely descriptive. The 5 studies included in this level[23,26,27,29,30] (Table 1) have final observation sample sizes ranging from 4 to 21 and did not include a comparison group. These studies vary in intervention approach, applying strategies including educational and psychotherapy sessions,[23] phone calls aligned with medication dose,[30] DOT,[29] adapted behavioral family systems therapy with an HIV/HAART education session,[26] and motivational interviewing.[27] Two studies intervened at both the individual and family group level.[23,26] Two studies had notably small samples sizes.[26,30] One involved use of cell phone reminders with a final sample of 5 participants and presented mixed- and short-lived improvements.[30] The other evaluated behavioral family systems therapy with 4 case reports and presented enhanced adherence overall and mixed support for decreased VL.[26] Foster et al[27] implemented a motivational interviewing session at initiation of ART, followed by a financial incentive program, with a final sample of 10 participants at 24 months. The study reported improved a CD4 count and VL at final assessment. The use of DOT within a tapered individual approach was evaluated by Gaur et al[29] with a final sample of 14 youth. Higher self-reported adherence and viral suppression was observed around 12 weeks on DOT, however, improvements were diminished at final assessment (week 24) when participants had stopped or tapered from DOT. Lyon et al[23] implemented an educational curriculum which alternated between family and youth sessions and youth-only sessions with 21 participants at final assessment (month 6). Improvements across self-reported measures of adherence were noted; however, only 20% of the sample had improvements in VL or CD4 counts.

DISCUSSION

Our systematic review of ART adherence interventions for youth ages 13–24 identified 10 articles from the current evidence base. Overall, several of the studies reported results supportive of improvements in adherence outcomes. However, the progress in this area of research seems to continue to lag behind increasingly vast evidence base for adherence support in adults, despite previous calls for investigation of interventions specifically tailored to adolescent and young adult populations.[14] The studies identified in our review were not only few, but were heterogeneous in intervention approach, duration and methodology, creating a scattered picture for what might work best for promoting ART adherence in youth.

Although slightly over half of the studies reviewed joined the evidence base relatively recently (in or after 2012), there is a nascent quality to this area that belies the long-recognized issues with nonadherence encountered by numerous youth living with HIV. Almost all studies were framed as pilots, used within-group designs, and most positioned outcomes as descriptive explorations. Few evaluated the impact of interventions, between or within groups, with sufficient power to detect even moderate effects and many opted for descriptive exploration because of these small-sample limitations. Despite this, our review did identify a number of strong evidence results, including strategies leveraged with nonadherent youth that incorporated texted outreach and multisystem therapy, and good evidence for interactive text-based outreach around dose times. Moreover, promising potential for positive impact through very brief computer-delivered in-clinic support may offer viable low implementation cost opportunities to assist youth.

Because of the diversity in rigor and overall approach, we separated findings relative to strength of evidence, in part to assist in the interpretation of a sometimes mixed profile of evidence. For example, 1 study provided strong evidence in support of interactive outreach phone call approach,[21] whereas a very similar approach evaluated in a very small pilot did not seem to improve outcomes.[30] Results do suggest support for a number of intervention packages, however, as noted within these studies, replication is needed as the evidence base is lacking in this process. Where results were supportive, the cohorts tended to include youth already known to have adherence problems, which is consistent with our earlier evaluations of the adherence literature with adults.[31]

The current state of the evidence for adherence support in youth is limited by a number of shortcomings. These include a paucity of research targeted to specific key populations within youth (eg, interventions specifically targeting sexual and gender minority youth), small sample size and pilots dominating the evidence base, relatedly low power, interventions that require interventionists with advanced degrees, most interventions conducted in the US, and diversity in follow-up periods. Results of this study regarding limitations in methodological rigor in the current evidence base and diversity in intervention strategies and results are aligned with the conclusions of a recently published synthesis of youth focused service delivery interventions to improve linkage, adherence, and retention in HIV care.[14] Our review adds to the characterization of this evidence base as emerging, at best, with potential promise that will require considerable attention to move forward. Aggressive efforts to engage youth in adherence-related trials are needed, which depend in part on better strategies to reduce and manage regulatory challenges in research with minors. Innovative strategies to afford youth added privacy, confidentiality and autonomy in the context of behavioral trials are needed to facilitate a robust and representative evidence base.[32–34]

Limitations in the current review include reliance only on PubMed for identification of the evidence base for adherence interventions targeting youth living with HIV. Although PubMed catalogs peer reviewed research across most medical and social journals, we do not characterize all available research. Interventions presented in conference venues and scientific journals not indexed in PubMed are not included. We recognize that there are often substantial delays between presentation of effective interventions in conference venues and peer-reviewed publication; however, the focus on peer-reviewed publications affords access to the specific data needed for synthesis and offers added confidence in integrity of findings through the peer-review process, which is not available in conference abstracts, presentations, or other "grey literature."

CONCLUSIONS

Almost 20 years have passed since the introduction of ART and near immediate realization that adherence is a major driver of successful treatment outcomes yet the evidence base remains small and dominated by pilots. Nearly half of all new HIV infections are occurring among those aged 13–24, and recommendations are increasingly adopting the rapid initiation of lifelong ART after diagnosis. Improved ART adherence leading to sustained viral suppression within this population is crucial to decreasing onward transmission.[35,36] ART adherence remains an essential component in both individual and public health. The current pace of intervention research remains grossly disproportionate to needs of adolescents and young adults living with HIV. Prioritizing youth in research agendas and calling for innovative, rigorous designs to identify effective interventions are overdue and necessary for world-wide implementation of "90-90-90."

REFERENCES

1. Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *J Antimicrob Chemother.* 2004; 53:696–699.
2. Jensen-Fangel S, Pedersen L, Pedersen C, et al. Low mortality in HIV-infected patients starting highly active antiretroviral therapy: a comparison with the general population. *AIDS.* 2004;18:89–97.
3. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4 + cell strata. *Ann Intern Med.* 2003;138:620–626.
4. Kim SH, Gerver SM, Fidler S, et al. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. *AIDS.* 2014;28:1945–1956.
5. Lall P, Lim SH, Khairuddin N, et al. Review: an urgent need for research on factors impacting adherence to and retention in care among HIV-positive youth and adolescents from key populations. *J Int AIDS Soc.* 2015;18(2 suppl 1):19393.
6. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Patient Care STDS.* 2014;28:128–135.
7. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med.* 2012;156:817–833.
8. UNAIDS. *Adolscents and Young People Fact Sheet*; 2012. Available at: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/factsheet/2012/20120417_FS_adolescentsyoungpeoplehiv_en.pdf. Accessed November 30, 2015.
9. Centers for Disease Control and Prevention. *HIV Among Youth*; 2015. Available at: http://www.cdc.gov/hiv/group/age/youth/. Accessed January 28, 2016.
10. Yang Y. State of the science: the efficacy of a multicomponent intervention for ART adherence among people living with HIV. *J Assoc Nurses AIDS Care.* 2014;25:297–308.
11. Horvath T, Azman H, Kennedy GE, et al. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database Syst Rev.* 2012;3:CD009756.
12. Simoni JM, Frick PA, Pantalone DW, et al. Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Top HIV Med.* 2003;11:185–198.
13. Centers for Disease Control and Prevention. *Compendium of Evidence-based Interventions and Best Practices for HIV Prevention: The Complete Medication Adherence Chapter*; 2014. Available at: http://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html. Accessed December 30, 2015.
14. MacPherson P, Munthali C, Ferguson J, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. *Trop Med Int Health.* 2015;20:1015–1032.
15. Steinberg L. Cognitive and affective development in adolescence. *Trends Cogn Sci.* 2005;9:69–74.
16. Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med.* 2009;17:14–25.
17. Tsang SK, Hui EK, Law BC. Positive identity as a positive youth development construct: a conceptual review. *ScientificWorldJournal.* 2012;2012:529691.
18. Meeus W, van de Schoot R, Keijsers L, et al. Identity statuses as developmental trajectories: a five-wave longitudinal study in early-to-middle and middle-to-late adolescents. *J Youth Adolesc.* 2012;41: 1008–1021.
19. De Leo G, LeRouge C, Ceriani C, et al. Websites most frequently used by physician for gathering medical information. *AMIA Annu Symp Proc.* 2006:902.
20. Dowshen N, D'Angelo L. Health care transition for youth living with HIV/AIDS. *Pediatrics*. 2011;128:762–771.
21. Rongkavilit C, Naar-King S, Wang B, et al. Motivational interviewing targeting risk behaviors for youth living with HIV in Thailand. *AIDS Behav.* 2013;17:2063–2074.
22. Belzer ME, Naar-King S, Olson J, et al. The use of cell phone support for non-adherent HIV-infected youth and young adults: an initial randomized and controlled intervention trial. *AIDS Behav.* 2014;18:686–696.
23. Lyon M, 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.
24. Naar-King S, Outlaw AY, Sarr M, et al. Motivational Enhancement System for Adherence (MESA): pilot randomized trial of a brief computer-delivered prevention intervention for youth initiating antiretroviral treatment. *J Pediatr Psychol.* 2013;38:638–648.
25. Letourneau EJ, Ellis DA, Naar-King S, et al. Multisystemic therapy for poorly adherent youth with HIV: results from a pilot randomized controlled trial. *AIDS Care.* 2013;25:507–514.
26. Gray WN, Janicke DM, Fennell EB, et al. Piloting behavioral family systems therapy to improve adherence among adolescents with HIV: a case series intervention study. *J Health Psychol.* 2011;16: 828–842.
27. Foster C, McDonald S, Frize G, et al. "Payment by Results"—financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: a pilot program. *AIDS Patient Care STDS.* 2014;28:28–32.
28. Dowshen N, Kuhns LM, Johnson A, et al. Improving adherence to antiretroviral therapy for youth living with HIV/AIDS: a pilot study using personalized, interactive, daily text message reminders. *J Med Internet Res.* 2012;14:e51.
29. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses.* 2010;26:947–953.
30. Puccio J, Belzer M, Olson J, et al. Use of cell phone reminder calls for assisting HIV infected adolescents and young adults to Adhere to high active antiretroviral therapy: a pilot study. *AIDS Patient Care STDS.* 2006;20:438–444.
31. Amico KR, Harman JJ, Johnson BT. Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004. *J Acquir Immune Defic Syndr.* 2006;41:285–297.
32. Shaw C, Brady LM, Davey C. *Guidelines for Research with Children and Young People*. London, United Kingdom: National Children's Bureau Research Centre; 2011.
33. DiClemente RJ, Sales JM, Borek N. Barriers to adolescents' participation in HIV biomedical prevention research. *J Acquir Immune Defic Syndr.* 2010;54(suppl 1):S12.
34. Brawner BM, Volpe EM, Stewart JM, et al. Attitudes and beliefs toward biobehavioural research participation: voices and concerns of urban adolescent females receiving outpatient mental health treatment. *Ann Hum Biol.* 2013;40:485–495.
35. Cohen MS, Dye C, Fraser C, et al. HIV treatment as prevention: debate and commentary—will early infection compromise treatment-as-prevention strategies? *PLoS Med.* 9:e1001232.
36. Mayer K, Gazzard B, Zuniga JM, et al. Controlling the HIV epidemic with antiretrovirals IAPAC consensus statement on treatment as prevention and preexposure prophylaxis. *J Int Assoc Providers AIDS Care.* 2013;12:208–216.