



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy and again before changing regimens (AIII).
- Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence (AIII).
- At least one method of measuring adherence to antiretroviral therapy should be used in addition to monitoring viral load (AIII).
- **Once-daily antiretroviral regimens and regimens with low pill burden should be prescribed whenever feasible (AII*).**
- To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care (AII*).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression.¹⁻³ Prospective adult and pediatric studies have established a direct correlation between risk of virologic failure and the proportion of missed doses of antiretroviral (ARV) drugs.⁴ **Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, as well as sub-therapeutic or partial dosing.**⁵ Poor adherence will result in sub-therapeutic plasma ARV drug concentrations, facilitating development of drug resistance to one or more drugs in a given regimen, and possibly cross-resistance to other drugs in the same class. Multiple factors (including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance) influence the adherence-resistance relationship.⁶ In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens in patients who develop multidrug-resistant HIV and for increasing the risk of secondary transmission.

Poor adherence to ARV drugs is commonly encountered in the treatment of HIV-infected children and adolescents. **A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, child's age and developmental stage, as well as** psychosocial and behavioral characteristics of children and parents—have been associated with non-adherence. However, no consistent predictors of either good or poor adherence in children have been consistently identified.⁷⁻⁹ Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.¹⁰ These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to ensure that adherence education, support, and assessment are integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by the **drug** regimen, patient and family factors, and **patient-provider relationship**.⁸ The limited availability of palatable formulations and **once-daily regimens for infants and** young children is especially problematic.⁴ Furthermore, infants and children are dependent on

others for **medication** administration; thus, assessment of the capacity for adherence to a complex, multidrug regimen requires evaluation of the caregivers and their environments, as well as the ability and willingness of a child to take the drug. Barriers faced by adult caregivers that can contribute to non-adherence in children include forgetting doses, changes in routine, being too busy, and child refusal.^{11,12} Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks,¹³ whereas others themselves face health and adherence challenges related to HIV infection, substance use, or **mental health and** other medical conditions. Other barriers to adherence include caregivers' unwillingness to disclose HIV infection status to the child and/or others, reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, **absence** of social support, and a tendency for doses to be missed if the parent is unavailable. Adherence may also be jeopardized by social issues within a family (e.g., substance abuse, unstable housing, **poverty**, involvement with the criminal justice system).¹⁴

Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A comprehensive assessment should be instituted for all children in whom ART initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may influence adherence by children and their families and can be used to identify individual needs for intervention. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain a patient's explicit agreement with the treatment plan, including strategies to support adherence. It is also important to alert patients to minor adverse effects of ARV drugs (e.g., nausea, headaches, abdominal discomfort) that may recede over time or respond to change in diet or timing of medication administration.

A routine adherence assessment should be incorporated into every clinic visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results and each approach has limitations.¹⁵⁻¹⁷ Viral load monitoring is **the most useful indicator of adherence and should be used routinely for all patients on ART (see [Plasma HIV-1 RNA \[Viral Load\]](#) and [CD4 Count Monitoring](#) in the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)).** In addition, it can be used as positive reinforcement to encourage continued adherence.¹⁸ Use of at least one other method in addition to monitoring viral load to assess adherence is recommended.^{17,19} Other measures include quantitative self report of missed doses by caregivers and children or adolescents (i.e., focusing on missed doses during a recent 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. **Patients, caregivers, and health care providers often overestimate adherence, but admission of missed doses or suboptimal adherence is highly correlated with poor therapeutic response.**²⁰ Targeted questions about stress, pill burden, and daily routine are recommended. **A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment.** Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports.²¹

Home visits can play an important role in assessing adherence. In some cases, suspected non-adherence is confirmed only when dramatic clinical responses to ART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma ARV drug concentrations or therapeutic drug monitoring may be useful measures in situations where non-adherence is suspected. Drug concentrations in hair are currently being studied as an alternative method to measure adherence **but are primarily useful in research studies, as are**^{22,23} electronic monitoring devices (e.g., Medication Event Monitoring System [MEMS] caps, Wisepill) that are equipped with a computer chip that records each opening of a medication bottle. Mobile phone-based and adherence device technologies (e.g., interactive voice response, SMS text messaging) are being investigated to quantify missed doses and provide real-time feedback to patients and caregivers, but studies in the pediatric population are in the pilot phase.²⁴⁻²⁶

Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the first few months after therapy is initiated. This is particularly important if treatment must be started urgently. If there are particular concerns about adherence, patients should be seen and/or contacted (by phone, text messaging, email, and social networking, as allowed within the context of local legal and regulatory requirements) frequently—as often as weekly, or even more often, during the first month of treatment—to assess adherence and determine the need for strategies to improve and support adherence.

Strategies should include optimization of the drug regimen and the development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers—rather than one specific intervention—may be most effective.^{13,27,28} The evidence is mixed as to the efficacy of programs designed for administration of directly observed therapy (DOT) to improve adherence, but DOT may be a useful strategy for particular patients.^{27,29-33} Table 11 summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention offers a web-based toolkit (consisting of four evidence-based HIV medication adherence strategies) to HIV care providers (located at <http://www.effectiveinterventions.org/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx>).³⁴

Regimen-Related Strategies

ARV drug regimens for children often require taking multiple pills or unpalatable liquids, each with potential adverse effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and adverse effects (AEs).³⁵ Efforts should be made to reduce the pill burden and to prescribe a once-daily ARV drug regimens whenever feasible (see [Management of Children Receiving Antiretroviral Therapy](#)). With the introduction of new drug classes and a wider array of once-daily formulations, there are now more options to offer less toxic, simplified regimens particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV drug regimens.³⁶⁻³⁹ When non-adherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can sometimes be masked with a small amount of flavoring syrup or food (see [Appendix A: Pediatric Antiretroviral Drug Information](#)).⁴⁰ Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children aged 4 to 21 years found that training children to swallow pills has been associated with improved adherence at 6 months post-training.⁴¹ Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs or change the particular drug (or, if necessary, drug regimen) when feasible.

Patient/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining a child's medication adherence. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into an HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools

to promote adherence.⁴² Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.⁴³ A gastrostomy tube should be considered for nonadherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications.⁴⁴ If adequate resources are available, home-nursing interventions or DOT may also be beneficial.

Other strategies to support adherence include setting patients' cell phone alarms to go off at medication times; using beepers or pagers as an alarm; sending SMS text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. Randomized clinical trials in adults have demonstrated that text messaging is associated with improved adherence.⁴⁵⁻⁴⁹ Motivational interviews, including computer-based interventions, are currently being evaluated.^{42,50} A study evaluating the efficacy of a four-session, individual, clinic-based, motivational, interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months in youth taking ART. However, reduction in viral load was not maintained at 9 months.⁵¹

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with patients' families. This process begins early in a provider's relationship with a family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important.⁵² Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes.⁵³ Providing comprehensive multidisciplinary care (e.g., with nurses, case managers, pharmacists, social workers, psychiatric care providers) may also better serve more complex patient and family needs, including adherence.

Table 11. Strategies to Improve Adherence to Antiretroviral Medications (page 1 of 2)

Initial Intervention Strategies
<ul style="list-style-type: none"> • Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on the need for treatment and adherence. • Identify depression, low self-esteem, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible. • Identify family, friends, health team members, and others who can support adherence. • Educate patient and family about the critical role of adherence in therapy outcome including 1) the relationship between partial adherence and resistance; and 2) resistance and potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed. • Establish readiness to take medication through practice sessions or other means. • Schedule a home visit to review medications and determine how they will be administered in the home setting. • Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.
Medication Strategies
<ul style="list-style-type: none"> • Choose the simplest regimen possible, reducing dosing frequency and number of pills. • When choosing a regimen, consider the daily and weekly routines and variations in patient and family activities. • Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability). • Choose drugs with the fewest AEs; provide anticipatory guidance for management of AEs. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug-drug interactions. • Assess pill-swallowing capacity and offer pill-swallowing training.

Table 11. Strategies to Improve Adherence to Antiretroviral Medications (page 2 of 2)

Follow-Up Intervention Strategies
<ul style="list-style-type: none">• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.• Use patient education aids including pictures, calendars, and stickers.• Encourage use of pill boxes, reminders, alarms, pagers, and timers.• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.• Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.• Consider DOT at home, in the clinic, or in selected circumstances, during a brief inpatient hospitalization.• Consider gastrostomy tube use in selected circumstances.• Information on other interventions to consider can be found at http://www.cdc.gov/hiv/prevention/research/compendium/ma/complete.html.

Key to Acronyms: ARV = antiretroviral; AE = adverse effect; DOT = directly observed therapy

References

1. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis*. 2004;190(2):271-279. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15216461>.
2. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics*. 2002;109(4):e61. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11927734>.
3. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 1999;18(8):682-689. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10462336>.
4. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793-800. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16148846>.
5. Vreeman RC, Nyandiko WM, Liu H, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. *J Int AIDS Soc*. 2014;17:19227. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25427633>.
6. Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS*. 2009;23(9):1035-1046. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19381075>.
7. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics*. 2006;118(6):e1745-1757. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17101712>.
8. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep*. 2009;6(4):194-200. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19849962>.
9. Malee K, Williams P, Montepiedra G, et al. Medication adherence in children and adolescents with HIV infection: associations with behavioral impairment. *AIDS Patient Care STDS*. 2011;25(3):191-200. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21323533>.
10. Giannattasio A, Albano F, Giacomet V, Guarino A. The changing pattern of adherence to antiretroviral therapy assessed at two time points, 12 months apart, in a cohort of HIV-infected children. *Expert Opin Pharmacother*. 2009;10(17):2773-2778. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19929700>.

11. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS*. 2008;22(8):637-647. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18627275>.
12. Skovdal M, Campbell C, Madanhire C, Nyamukapa C, Gregson S. Challenges faced by elderly guardians in sustaining the adherence to antiretroviral therapy in HIV-infected children in Zimbabwe. *AIDS Care*. 2011;23(8):957-964. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21400306>.
13. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol*. 2009;34(2):187-194. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18586756>.
14. Cluver LD, Hodes RJ, Toska E, et al. "HIV is like a tsotsi. ARVs are your guns": associations between HIV-disclosure and adherence to antiretroviral treatment among adolescents in South Africa. *AIDS*. 2015;29 Suppl 1:S57-65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26049539>.
15. Farley JJ, Montepiedra G, Storm D, et al. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count. *J Dev Behav Pediatr*. 2008;29(5):377-384. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18714204>.
16. Khan M, Song X, Williams K, Bright K, Sill A, Rakhmanina N. Evaluating adherence to medication in children and adolescents with HIV. *Arch Dis Child*. 2009;94(12):970-973. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19723637>.
17. Burack G, Gaur S, Marone R, Petrova A. Adherence to antiretroviral therapy in pediatric patients with human immunodeficiency virus (HIV-1). *J Pediatr Nurs*. 2010;25(6):500-504. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21035017>.
18. Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *J Acquir Immune Defic Syndr*. 2013;64(1):74-78. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23774877>.
19. Muller AD, Jaspan HB, Myer L, et al. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. *AIDS Behav*. 2011;15(2):422-431. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20953692>.
20. Intasan J, Bunupuradah T, Vonthanak S, et al. Comparison of adherence monitoring tools and correlation to virologic failure in a pediatric HIV clinical trial. *AIDS Patient Care STDS*. 2014;28(6):296-302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24901463>.
21. McMahan JH, Jordan MR, Kelley K, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. *Clin Infect Dis*. 2011;52(4):493-506. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21245156>.
22. Gandhi M, Ameli N, Bacchetti P, et al. Atazanavir concentration in hair is the strongest predictor of outcomes on antiretroviral therapy. *Clin Infect Dis*. 2011;52(10):1267-1275. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21507924>.
23. van Zyl GU, van Mens TE, McIlleron H, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. *J Acquir Immune Defic Syndr*. 2011;56(4):333-339. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21239995>.
24. Haberer JE, Kahane J, Kigozi I, et al. Real-time adherence monitoring for HIV antiretroviral therapy. *AIDS Behav*. 2010;14(6):1340-1346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20809380>.
25. Dowshen N, Kuhns LM, Gray C, Lee S, Garofalo R. Feasibility of interactive text message response (ITR) as a novel, real-time measure of adherence to antiretroviral therapy for HIV+ youth. *AIDS Behav*. 2013;17(6):2237-2243. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23546844>.
26. Campbell JI, Haberer JE. Cell Phone-Based and Adherence Device Technologies for HIV Care and Treatment in Resource-Limited Settings: Recent Advances. *Curr HIV/AIDS Rep*. 2015. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26439917>.
27. Simoni JM, Amico KR, Pearson CR, Malow R. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. *Curr Infect Dis Rep*. 2008;10(6):515-521. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18945394>.
28. Barnighausen T, Chaiyachati K, Chimbini N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *Lancet Infect Dis*. 2011;11(12):942-951. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22030332>.

29. Williams AB, Fennie KP, Bova CA, Burgess JD, Danvers KA, Dieckhaus KD. Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2006;42(3):314-321. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16770291>.
30. Bain-Brickley D, Butler LM, Kennedy GE, Rutherford GW. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. *Cochrane Database Syst Rev*. 2011;12(12):CD009513. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22161452>.
31. 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(9):947-953. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20707731>.
32. Ford N, Nachega JB, Engel ME, Mills EJ. Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials. *Lancet*. 2009;374(9707):2064-2071. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19954833>.
33. Hart JE, Jeon CY, Ivers LC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. *J Acquir Immune Defic Syndr*. 2010;54(2):167-179. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20375848>.
34. Centers for Disease Control and Prevention. Medication Adherence. 2014. Available at <http://www.effectiveinterventions.org/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx>. Accessed February 10, 2016.
35. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS*. 2009;23(10):803-807. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19795999>.
36. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*. 2009;48(4):484-488. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19140758>.
37. Campo RE, Cohen C, Grimm K, Shangguan T, Maa J, Seekins D. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *Int J STD AIDS*. 2010;21(3):166-171. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20215619>.
38. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naïve HIV patients. *Int J STD AIDS*. 2012;23(5):351-355. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22648890>.
39. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2014;58(9):1297-1307. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24457345>.
40. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader*. 2000;10(2):88-94. Available at <http://www.medscape.com/viewarticle/410255>.
41. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics*. 2007;119(4):e893-899. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17353298>.
42. Foster C, McDonald S, Frize G, Ayers S, Fidler S. "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(1):28-32. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24428797>.
43. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Ann Behav Med*. 2014;47(3):259-269. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24234601>.
44. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics*. 2000;105(6):E80. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10835093>.
45. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. 2010;376(9755):1838-1845. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21071074>.
46. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database Syst Rev*. 2012;3:CD009756. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/22419345>.

47. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. 2011;25(6):825-834. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21252632>.
48. Finitis DJ, Pellowski JA, Johnson BT. Text message intervention designs to promote adherence to antiretroviral therapy (ART): a meta-analysis of randomized controlled trials. *PLoS One*. 2014;9(2):e88166. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24505411>.
49. Simoni JM, Huh D, Frick PA, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2009;52(4):465-473. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19911481>.
50. Outlaw AY, Naar-King S, Tanney M, et al. The initial feasibility of a computer-based motivational intervention for adherence for youth newly recommended to start antiretroviral treatment. *AIDS Care*. 2014;26(1):130-135. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23869650>.
51. Naar-King S, Parsons JT, Murphy DA, Chen X, Harris DR, Belzer ME. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. *Arch Pediatr Adolesc Med*. 2009;163(12):1092-1098. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19996045>.
52. Molassiotis A, Morris K, Trueman I. The importance of the patient-clinician relationship in adherence to antiretroviral medication. *Int J Nurs Pract*. 2007;13(6):370-376. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18021166>.
53. Van Wingham J, Telfer B, Reid T, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. *BMC Pediatr*. 2008;8:52. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19025581>.