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

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Abstract

Description—After HIV diagnosis, timely entry into HIV medical care and retention in that care are essential to the provision of effective antiretroviral therapy (ART). ART adherence is among the key determinants of successful HIV treatment outcome and is essential to minimize the emergence of drug resistance. The International Association of Physicians in AIDS Care convened a panel to develop evidence-based recommendations to optimize entry into and retention in care and ART adherence for people with HIV.

Methods—A systematic literature search was conducted to produce an evidence base restricted to randomized, controlled trials and observational studies with comparators that had at least 1 measured biological or behavioral end point. A total of 325 studies met the criteria. Two reviewers independently extracted and coded data from each study using a standardized data extraction form. Panel members drafted recommendations based on the body of evidence for each method or intervention and then graded the overall quality of the body of evidence and the strength for each recommendation.

Recommendations—Recommendations are provided for monitoring of entry into and retention in care, interventions to improve entry and retention, and monitoring of and interventions to improve ART adherence. Recommendations cover ART strategies, adherence tools, education and counseling, and health system and service delivery interventions. In addition, they cover specific issues pertaining to pregnant women, incarcerated individuals, homeless and marginally housed individuals, and children and adolescents, as well as substance use and mental health disorders. Recommendations for future research in all areas are also provided.

The availability of potent antiretroviral therapy (ART) has resulted in remarkable decreases in HIV-related morbidity and mortality in the past 15 years (1, 2). Entry into and retention in HIV medical care is critical to the provision of ART, and adherence to ART is among the key determinants of HIV treatment success (3–6). More than 2 decades of targeted research

in these areas has produced a varied and complex evidence base that, to date, has not been fully evaluated or distilled into concrete recommendations for how to best monitor or support HIV care and ART adherence.

Recent data from the U.S. Centers for Disease Control and Prevention reveal that only 28% of persons with HIV in the United States have achieved viral suppression while receiving ART (7). Of those who knew they had HIV, only 69% were linked to care, and only 59% were retained in care (8). These figures and comparable global data (9, 10) challenge us to explore best practices for improving entry into and retention in care on a global scale. Only with successful care linkage and retention can ART be accessed. Once patients are in care and are receiving treatment, high levels of adherence are required to prevent the selection of resistance mutations and subsequent virologic failure (11). In a global pooled sample of 33 199 adults taking ART in over 84 observational studies, only 62% of persons achieved adherence of at least 90% of doses (12). These data underscore the need for concise and clear evidence-based recommendations to help care providers monitor and support ART adherence.

In this context, the International Association of Physicians in AIDS Care (IAPAC) convened an expert panel to develop evidence-based recommendations to optimize entry into and retention in care and ART adherence and to monitor these processes. Members of the panel are listed in Appendix 1 (available at http://www.annals.org). These guidelines aim to define best practices that can be used by practitioners and health systems to improve adherence and, in turn, health outcomes. Our recommendations are based on the best published science; however, the evidence base remains insufficient in many areas. For that reason, we also highlight areas in which additional research is needed to inform future recommendations. We realize that implementation of these recommendations may, in some cases, require that new resources be identified to bring the benefit of best practices to our clinic populations. We believe that presenting recommendations based on rigorous science is the best avenue to achieve that end.

Guidelines Focus and Target Population

These guidelines focus on interventions to improve entry into and retention in care and ART adherence for people living with HIV, as well as methods to monitor these critical processes. The target audience includes care providers, patients, policymakers, and organizations and health systems involved with implementing HIV care and treatment.

Guidelines Development Process

For these guidelines, a systematic literature search was conducted to produce an evidence base restricted to randomized, controlled trials (RCTs) and observational studies with comparators that had at least 1 measured biological or behavioral end point. For monitoring, correlation between a method and an outcome was required. A total of 325 studies met our criteria. Two reviewers independently extracted and coded data from each study using a standardized data extraction form. Panel members drafted recommendations based on the body of evidence for each method or intervention and then graded the overall quality of the body of evidence and the strength for each recommendation. Table 1 summarizes the quality

and strength scales used. Details on the methods used are available in Appendix 2 (available at http://www.annals.org).

Guidelines

Appendix Table 1 (available at http://www.annals.org) summarizes all recommendations and associated quality and strength scores.

Entry Into and Retention in HIV Medical Care

The associations between entry into and retention in HIV medical care and both individual health outcomes and HIV transmission dynamics mediated by ART have been well established in retrospective, prospective, and mathematical modeling studies (13–19). Accordingly, individual-level monitoring of entry and retention is essential to the development and evaluation of cost-effective interventions required to improve these critical components of clinical care.

Recommendation 1: Systematic monitoring of successful entry into HIV care is recommended for all individuals diagnosed with HIV (II A): Entry into care after HIV diagnosis, defined as a visit with an HIV care provider authorized to prescribe ART, has been associated with improved survival (20). Within a given jurisdiction or service area, providers of testing services, local public health institutions, and medical clinics have a shared responsibility to monitor entry into HIV care. Roles and accountability should be clearly established on a local level. Integration of multiple data sources, including surveillance data, administrative databases, and medical clinic records, may enhance monitoring of initial entry into HIV care (21).

Recommendation 2: Systematic monitoring of retention in HIV care is recommended for all patients (II A): Retention in care is associated with improved individual health outcomes, including HIV biomarker and clinical variables, and may reduce community-level viral burden, with implications for secondary prevention (13, 22). Although monitoring retention is routinely recommended, specific details, such as retention measures to be used and desired visit frequency, vary among jurisdictions and programs and should be in harmony with national and international guidelines. Many retention measures (for example, visit adherence, gaps in care, and visits per interval of time) and data sources (for example, surveillance, medical records, and administrative databases) have been used (23) and may be applied in accordance with local resources and standards of care. As with monitoring of linkage, integration of data sources may enhance monitoring of retention.

Recommendation 3: Brief, strengths-based case management for individuals with a new HIV diagnosis is recommended (II B): The Antiretroviral Treatment and Access Study evaluated entry into and retention in care as part of a multisite RCT in several U.S. care sites comparing strengths-based case management sessions (up to 5 in a 90-day period) with passive referrals for local care among patients with recently diagnosed HIV infection (24). Trained social workers helped clients to identify their internal strengths and assets to facilitate successful linkage to HIV medical care. A significantly higher proportion of the

case-managed participants visited an HIV clinician at least once within 6 months (78% versus 60%) and at least twice within 12 months (64% versus 49%). However, availability of resources may impede implementation in a given jurisdiction or service area.

Recommendation 4: Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered (III C): In a sample of 104 individuals in whom HIV was diagnosed within 6 months before enrolling in the U.S. Special Projects of National Significance Outreach Initiative, 92% attended medical appointments within 6 months of enrollment (25). At study baseline, 14% of individuals had undetectable HIV-1 RNA, which increased to 45% after 12 months of follow-up. This observational demonstration project used a variety of approaches, focusing on individuals considered underserved by the health care system (such as women, youth, and people with a history of substance use or mental illness).

Recommendation 5: Use of peer or paraprofessional patient navigators may be considered (III C): Patient navigation has been described as a model of care coordination and is largely based on peer-based programs established for patients with cancer. Patient navigators are trained to help HIV-infected patients facilitate interactions with health care. In an analysis of 4 patient-navigation interventions from the U.S. Special Projects of National Significance Outreach Initiative, involving more than 1100 patients who were inconsistently engaged in care, the proportion with at least 2 visits in the previous 6 months increased from 64% at baseline to 87% at 6 months and 79% at 12 months in the intervention group (26). In addition, the proportion of patients with undetectable HIV-1 RNA was 50% greater at 12 months than at baseline.

Monitoring ART Adherence

Monitoring adherence is necessary to assess the effect of interventions and also to inform providers of the need to implement interventions. Measurement methods include self-reports, pharmacy refill data, pill counts, electronic drug monitors (EDMs), and drug concentrations from biological samples; each has unique strengths and weaknesses (27, 28). Many of the studies reviewed combined measures to improve sensitivity and specificity, but because of the large variability in these approaches, we will not address these potential combinations here. Regardless of measurement method, adherence is a factor that varies with time and therefore must be repeatedly assessed (29).

Recommendation 6: Self-reported adherence should be obtained routinely in all patients (II A): Self-reported ART adherence has consistently been associated with HIV-1 RNA levels. Although it commonly overestimates adherence (30), self-reported nonadherence has a high predictive value (27). Self-report is less strongly associated with treatment response than are EDM- or pharmacy-based measures, but relative ease of implementation further supports its use in clinical care. Careful attention must be paid to collecting self-report data in a manner that makes reasonable demands on memory. Therefore, questionnaires should inquire only about specific doses taken over a short time interval (for example, in the previous week or less) and about global measures of adherence over a somewhat longer time (for example, in the previous month).

Recommendation 7: Pharmacy refill data are recommended for adherence monitoring when medication refills are not automatically sent to patients (II B): Many observational studies across the globe have demonstrated the validity of pharmacy refill data as an ART adherence measure, including medical records (30, 31), claims data (32), and ad hoc pharmacy contact (33). Pharmacy measures are useful for as long a period as the refill records are maintained. The interval over which refill records can be used depends on the days' supply (that is, the length of time the medication dispensed is intended to last).

Recommendation 8: Drug concentrations in biological samples are not routinely recommended (III C): The concentration of HIV medications in various biological samples has been assessed as an adherence measure in many settings; relatively few analyses have been associated with clinical outcomes (34–36). Results are inconsistent (37, 38) and are limited by assay issues and the relatively short half-life of most antiretroviral medications.

Recommendation 9: Pill counts performed by staff or patients are not routinely recommended (III C): An association between pills counts and biological outcomes has been seen in some studies (39, 40) but not in all (41). Several studies have assessed various operational methods for conducting pill counts, such as making unannounced home visits for marginally housed individuals (3, 39, 42). Clinic-based pill counts are susceptible to pill dumping. The personnel required for pill counts and the burden of bringing medication to visits are further barriers to routine use.

Recommendation 10: EDMs are not routinely recommended for clinical use (I C): Electronic drug monitors have been used to assess adherence in many studies (43–47). Adherence measured electronically is consistently more closely associated with HIV-1 RNA than are other methods (48, 49). In research, EDMs have been the measurement method of choice (50, 51). Unfortunately, these technologies are currently impractical outside of studies because they may be burdensome to patients and incompatible with adherence-promoting strategies, such as pill cases.

Interventions to Improve ART Adherence

Interventions to promote ART adherence are broadly defined as strategies that aim to enhance this critical determinant of successful HIV treatment outcomes.

ART Strategies—Important determinants of ART adherence and the related construct of ART persistence (52), or uninterrupted receipt of treatment, include dosing schedule, pill count, tolerability, and toxicity profiles of ART. Advances in ART now allow simplification of dosing schedules and reduction of pill burden for a majority of patients while maintaining excellent viral suppression. Additional factors to be considered in initiating or changing ART include transmitted or emergent viral resistance, individual ART treatment history, medical and psychosocial comorbid conditions, concomitant medications, and patient preference.

Recommendation 11: Among regimens of similar efficacy and tolerability, once-daily regimens are recommended for treatment-naive patients beginning ART (II B): Many

RCTs in treatment-naive patients have compared once-daily with multiply-dosed regimens containing different drugs. As such, it is impossible to ascertain whether adherence and biological benefits derive from the dosing schedule or the regimen components. Some studies, however, have used identical ART components given once or twice daily and have demonstrated improved adherence and noninferior viral suppression with once-daily dosing (53, 54). Efficacy for once-daily dosing must be confirmed by RCTs before adoption into clinical care.

Recommendation 12: Switching treatment-experienced patients receiving complex or poorly tolerated regimens to once-daily regimens is recommended, given regimens with equivalent efficacy (III B): Several studies have demonstrated successful switching to once-daily dosing for patients with suppressed virus on a multiply-dosed regimen (55–59). Often, studies are limited by small sample size, short follow-up, or changes in ART regimens accompanying the switch to a once-daily regimen, so factors including toxicity, tolerability, and related considerations may contribute to observed findings. Treatment history and prior ART resistance are particularly important considerations when switching regimens for treatment-experienced patients.

Recommendation 13: Among regimens of equal efficacy and safety, fixed-dose combinations are recommended to decrease pill burden (III B): Because fixed-dose combinations (FDCs) are often approved on the basis of safety and bioequivalence rather than noninferiority to the component regimens, few data comparing adherence outcomes between FDCs and individual components are available. Therefore, many of the data in this area come from surveys of patient satisfaction or extrapolation from diseases other than HIV that are, by definition, not included in our evidence base. The evidence base contains 1 RCT and 1 comparative observational study that demonstrated an adherence benefit with FDCs (60, 61). It is important to note that when components of different half-lives are combined, there is potential for a monotherapy "tail" and subsequent resistance when doses are missed or drug is discontinued. On the other hand, the use of FDCs eliminates the possibility of taking an incomplete regimen, as may occur when one drug is not refilled on time or is simply not taken, leading to viral rebound and resistance (62).

Adherence Tools for Patients—Many commonly used self-management adherence tools, including pillboxes and medication planners or calendars, have been associated with improved adherence and HIV-1 RNA suppression (63). It is common for adherence tools to be combined with behavioral and structural interventions. Given their simplicity and observational data supporting their use, they are considered the standard of care despite limited comparative research to establish efficacy. Recommendations regarding use of these tools are limited because of this lack of evidence.

Recommendation 14: Reminder devices and use of communication technologies with an interactive component are recommended (I B): An adherence benefit of dose-time reminder alarms has been reported (64, 65). Strategies using cellular technology (short message service communication) have demonstrated improvement in adherence and HIV-1 RNA. Methods ranged from texting dosing reminders with or without requesting a response

(66–68) to texting weekly check-ins from the clinic with telephone follow-up for those requesting it (69). One study found better ART adherence was achieved with use of texting with expected reply (interactive) than simple 1-way reminders (66).

Recommendation 15: Education and counseling using specific adherence-related tools is recommended (I A): The available literature suggests that some tools may be more beneficial to patient adherence when combined with education or counseling. Seven studies (Appendix Table 2, available at http://www.annals.org) evaluated a particular adherence tool (pill organizer [70], dose planner [71], reminder alarm device [72, 73], or EDM [74–76]) as distinguished from general one-on-one education and counseling. All but 1 demonstrated an effect on adherence, and 3 of the 6 that investigated effects on biological markers found significant positive effects (72, 75, 76). Three studies from the Netherlands and China that used EDMs with counseling about missed doses showed improvement in adherence (74–76), and 2 showed improvement in biological markers (75, 76). A factorial-design RCT and an RCT from Kenya showed the inferiority of using a reminder device without counseling and suggested that tools may be most successful when offered as part of a comprehensive support package (72, 77).

Education and Counseling Interventions—Several systematic syntheses of behavioral interventions targeting ART adherence are available and report generally positive modest effect sizes, but the effect on HIV-1 RNA is less consistent (78–81). Recommendations are limited to those appropriate for general clinic populations; interventions targeting behavioral determinants of adherence in specific subgroups are included in other sections. Because of the volume and breadth of data supporting these recommendations, individual study results are not reviewed in detail, but Appendix Table 2 describes studies and outcomes. Across recommendations, pertinent issues exist with regard to best structure, deliverer, training, duration, timing, frequency, and targets of educational and counseling interventions, as well as optimal modalities for dissemination and implementation.

Recommendation 16: Individual one-on-one ART education is recommended (II A): Of the 14 interventions with ART education components (82–95), 10 had favorable effects on adherence outcomes, 2 had initial effects that deteriorated over time (86, 92), and 2 showed no benefit on adherence (87, 91); only 1 study demonstrated clear benefit on biological markers (94), 6 did not evaluate biomarkers (82, 87–90, 92), and 7 showed no biomarker benefit (83–86, 91, 93, 95). Among effective interventions, education was not the only component; most interventions also included counseling or skills-building, along with activities to promote adult learning. Group-delivered education is addressed in recommendation 18.

Recommendation 17: Providing one-on-one adherence support to patients through 1 or more adherence counseling approaches is recommended (II A): Strategies to support adherence that involve one-on-one discussions targeting enhancement of facilitators and easing of barriers are recommended. Twenty-seven interventions in the evidence base used individual adherence counseling; of the 25 evaluating adherence, 16 established positive

effects (82, 84, 88–90, 93–103), 3 demonstrated as-treated or post hoc effects (83, 85, 104), 3 demonstrated early effects that deteriorated over time (86, 92, 105), and 3 demonstrated no benefit (87, 106, 107). Of the 17 that included biological outcomes, 12 demonstrated no benefit (83–86, 93, 95, 102, 103, 105–108) and 5 demonstrated positive effects (94, 97, 99, 101, 109). Although most interventions are delivered in person, there are also successful examples of telephone-based counseling or mixed in-person and telephone-based models (72, 83, 102) and home visits (95). Further, expanding one-on-one counseling to include serodiscordant partners has demonstrated some benefit on adherence, although not on HIV-1 RNA (110), while inclusion of "caregivers" with ART-naive patients had mixed results (no benefit in 1 study [91] and support for effects on adherence and HIV-1 RNA overall but not over time in another [111]). The evidence base suggests the utility of providing some form of discussion-based support to individuals receiving ART and provides a wide array of potentially effective specific interventions that should be carefully matched to clinic population needs and resources.

Recommendation 18: Group education and group counseling are recommended; however, the type of group format, content, and implementation cannot be specified on the basis of the currently available evidence (II C): The evidence base included 7 studies of group-based education and counseling programs targeting general clinic populations (Appendix Table 2). Although some studies have demonstrated significant improvements in ART adherence, HIV-1 RNA, or CD4 cell counts (112–114) and 1 study demonstrated effects in specific subsets of participants (115), other studies showed no significant improvements in adherence (116, 117). Notably, studies targeted diverse patient groups and used a wide range of interventions, so the evidence does not clearly converge to support one particular approach to offering group education and counseling. Characterizing these interventions as "group" interventions designates their main modality, but several interventions also used an individual component or support for group members.

Recommendation 19: Multidisciplinary education and counseling intervention approaches are recommended (III B): Use of multidisciplinary teams is distinct from multiple team members duplicating efforts or content addressing adherence; multidisciplinary team members have clearly delineated roles and cover content specific to their particular area of expertise. A health-team approach in which 109 ART-naive patients met with a pharmacist, dietitian, and social worker for targeted education and counseling before ART initiation did not produce significant effects on pharmacy-refill-based adherence at 12 months but did significantly affect HIV-1 RNA outcomes (118). Another intervention using nurses and pharmacists targeted multiple factors (such as diet, work, social support, tools, and skills-building); significant effects on adherence were reported, but HIV-1 RNA and CD4 cell count did not change significantly (64).

Recommendation 20: Offering peer support may be considered (III C): Nine studies were reviewed and showed mixed outcomes (119–127). One reported null findings from a peer-based psychoeducational group (120), and 8 studies examining interventions involving treatment partners or peers, or both, demonstrated some success. The evidence base exhibits diverse results for use of peers. Several interventions, including treatment partners to

supervise or directly administer ART (121–123, 127) and peers to provide social support (119, 124–126), showed improvement in adherence or biological markers or both. Combination of use of peers and intervention in these studies limits the ability to draw conclusion on the specific effect of peers versus the interventions they delivered.

Health System and Service Delivery Interventions—We focused on interventions targeting factors believed to be related to adherence but that are associated with systems of care or service delivery (for example, transportation to clinic and food supplements, staffing and service modifications, co-location of services) or influence social determinants, such as HIV-associated stigma.

Recommendation 21: Using nurse- or community counselor– based care has adherence and biological outcomes similar to those of doctor- or clinic counselor– based care and is recommended in underresourced settings (II B): Two RCTs showed noninferiority of nursing ART care to physician-based care. A trial from Uganda found a nurse-peer model was not inferior to the traditional doctorcounselor model in adherence, HIV-1 RNA, and CD4 outcomes (128). Another RCT from South Africa also demonstrated noninferiority of CD4 and HIV-1 RNA outcomes with nurses rather than doctors caring for people on ART (129). A cohort analysis, also from Uganda, with a notable limitation (the exposed cohort differed from control cohort) showed that a system of providing ART through volunteers (trained and supervised by a clinical officer) in a rural community was not inferior, in the short term, to a clinic-based standard of care (130).

Recommendation 22: Interventions providing case management services and resources to address food insecurity, housing, and transportation needs are recommended (III B): Research with US homeless populations have shown mixed results, but HIV-1 RNA levels improved in an as-treated analysis of a housing provision intervention (131). Case management is discussed in Recommendation 32. Cohort studies from Nigeria and Zambia with comparator groups evaluated outcomes of interventions for food-insecure patients and showed that ART adherence, retention in care, and clinical outcomes can be enhanced with food supplementation programs (132, 133). Addressing transportation issues in the context of case management and a home visit also may decrease missed appointments, especially among women with mental health or substance use disorders (134).

Recommendation 23: Integration of medication management services into pharmacy systems may be considered (III C): Pilot pharmacies in California offered services to manage adverse drug effects, evaluate patient adherence in consultation with physicians and case managers, and tailor drug regimens to accommodate specific patent needs. Analysis of claims data for pilot pharmacies found that a larger percentage of pilot pharmacy patients were classified as adherent to ART on the basis of pharmacy refill data, used fewer contraindicated regimens, and had fewer excess medication fills than patients with standard pharmacy care (135).

Recommendation 24: Directly administered ART is not recommended for routine clinical care settings (I A): Although directly administered ART (DAART) has demonstrated benefit for some vulnerable populations (see Recommendations 28, 29, 31,

and 37), well-controlled RCTs from well-resourced as well as resource-limited settings (including South Africa, Mozambique, Tanzania, Kenya, and Peru) have shown no benefit for various forms of DAART (clinic- or home-based; once-daily, twice-weekly, or once-weekly) among general populations (120–123, 127, 136–139) on adherence or biological markers. Thus, strong evidence supports not recommending DAART for routine HIV clinical care settings.

Special Populations

Treatment of a stigmatized and complex medical disorder with associated poor health outcomes is challenging in the best of circumstances for individuals with adequate social support, health literacy, stable housing, and economic resources. The additional challenges of incarceration, poverty, food and housing instability, and substance use and mental health disorders can further complicate adherence and require specialized interventions.

Pregnant Women—More than 50% of the 37.2 million adults with HIV in the world are women, and most are of childbearing age (140). Optimal ART adherence during pregnancy and the postpartum period remains a challenge globally (141–143). The evidence regarding ART adherence interventions during pregnancy comes predominantly from resource-limited settings and is focused only on short-term prevention of mother-to-child transmission (PMTCT) rather than on ART adherence throughout pregnancy and afterward.

Recommendation 25: Targeted PMTCT treatment (including HIV testing and serostatus awareness) improves adherence to ART for PMTCT and is recommended compared with an untargeted approach (treatment without HIV testing) in high-HIV-prevalence settings (III B): A Zambian RCT designed to test universal (without HIV testing) versus targeted (for those testing positive for HIV) single-dose nevirapine for PMTCT found that although nevirapine uptake was somewhat higher in the universal-treatment group, adherence was lower in women who were illiterate and unaware of their HIV status (144). Health literacy education is recommended in these settings.

Recommendation 26: Labor ward–based PMTCT adherence services are recommended for women who are not receiving ART before labor (II B): A cluster RCT in 12 public-sector delivery centers in Zambia found that offering HIV counseling and testing and ART adherence training in the labor ward was feasible and significantly improved nevirapine coverage and adherence (145).

Substance Use Disorders—Individuals with alcohol and other substance use disorders are at increased risk for poor retention in care, poor adherence, and virologic failure (146). Several adherence strategies not recommended for general clinic populations are effective among those with substance use disorders.

Recommendation 27: Offering buprenorphine or methadone to opioid-dependent patients is recommended (II A): Among patients with opioid dependence, both methadone and buprenorphine maintenance treatments improve medication adherence (147–150), ART uptake (149, 150), and biomarkers (147, 151, 152). Integration of buprenorphine into HIV

clinical care settings increased retention in care and ART prescription in 1 RCT, but ART adherence was unchanged because most patients were already adherent to ART at baseline (153).

Recommendation 28: DAART is recommended for individuals with substance use disorders (I B): Four RCTs (154–157) and 3 prospective cohort studies (158–160) of DAART showed significant HIV-1 RNA or CD4 cell count improvements compared with self-administered therapy. Follow-up data from 1 trial, however, failed to demonstrate persistent effects on biological outcomes after DAART was discontinued (157).

Recommendation 29: Integration of DAART into methadone maintenance treatment for opioid-dependent patients is recommended (II B): One RCT and several longitudinal cohort studies report improved HIV-1 RNA and adherence outcomes when DAART is integrated into methadone maintenance. Among 77 stable patients receiving methadone maintenance treatment, DAART compared with self-administered therapy significantly improved ART adherence and viral suppression over 24 weeks (161). Similarly, 3 prospective observational studies of DAART confirm improved CD4 counts and viral suppression over 12 (162, 163) and 24 (164) months compared with contemporaneous controls. Long-term durability of benefit has not been confirmed.

Mental Health—Mental health disorders may predispose individuals to acquiring HIV, are common among individuals living with HIV, and present serious challenges for HIV treatment adherence. A meta-analysis of 95 studies found a significant relationship between depression and ART nonadherence that was consistent across patients in resource-rich and resource-limited settings (165). Research has linked depressive symptoms to poor HIV care engagement and health outcomes, including impaired immunologic response and mortality.

Recommendation 30: Screening, management, and treatment for depression and other mental illnesses in combination with adherence counseling are recommended (II A): Randomized, controlled trials indicate that cognitive–behavioral therapy for depression and psychosocial stress improves ART adherence when conducted in tandem with ART adherence counseling (115, 116, 166, 167). Combined mental health and ART adherence counseling interventions have shown significant reductions in depressive symptoms, improved ART adherence, and improved treatment outcomes in RCTs (115, 166, 167). In contrast, an RCT of a stress management intervention with no ART adherence counseling reduced psychological distress but did not improve ART adherence or treatment outcomes (116). Evidence further indicates that pharmacologic treatment of depression is beneficial for ART adherence and treatment outcomes (168–170).

Incarceration—HIV and AIDS prevalence is higher among incarcerated populations in low-, middle-, and high-income countries (171). Globally, incarceration negatively affects continuity of care; development of trust; and, ultimately, optimal adherence (172). Incarceration provides a public health opportunity to provide ART to HIV-infected persons; however, barriers to ART delivery and adherence exist (173–175), and unintended ART interruptions sometimes occur after release (176). Key challenges to ART adherence among criminal justice populations include identifying successful strategies for medication

distribution that preserve confidentiality and avoid stigma (177–180) and maintaining persistent ART use during transitions from correctional facilities to the community (181–183).

Recommendation 31: DAART is recommended during incarceration (III B) and may be considered upon release to the community (II C): In a small, comparative observational study of 84 Italian prisoners, DAART in prison was associated with a higher proportion of patients with viral suppression to levels less than 400 copies/mL than was self-administered treatment (158). A small RCT compared ART adherence for DAART with that for self-administered treatment in 43 prisoners (184). Overall adherence was high at 92%, with a higher adherence rate in the DAART group than in the self-administered treatment group. Another RCT compared DAART given daily by community outreach workers versus self-administered treatment among 154 post-release patients (155). Six months after release, DAART was superior to self-administered treatment in achieving viral suppression to levels less than 400 copies/mL and less than 50 copies/mL.

Homeless and Marginally Housed Individuals—In communities where stable housing is a societal norm, the homeless represent a special population with respect to ART adherence because of the multiple and often interrelated adherence challenges in this population (such as unstable housing, mental illness, substance use disorders, food insecurity, mistrust of the health care system, incarceration, and inconsistent provider–patient relationships). Homelessness itself often disrupts daily routines, including medication taking, and can make medication storage difficult. In highly resourced countries, many homeless people have concomitant mental illness or substance use disorders that are associated with incomplete adherence (185). Mistrust of the health system and inconsistent provider–patient relationships can contribute to delayed entry into care (186). The homeless have competing survival needs, including food access, which have been associated with incomplete adherence and poor viral suppression (187). Excellent adherence and reliable viral suppression can, however, be achieved despite these multiple barriers (61, 188).

Recommendation 32: Case management is recommended to mitigate multiple adherence barriers in the homeless (III B): Case management includes referral to mental health and substance use treatment and housing (or housing vouchers), as appropriate, and can facilitate continuity when individuals are transitioning into and out of incarceration. However, referrals require the availability of infrastructure and resources, which differ dramatically among communities. One observational study in the United States showed that case management was associated with improved adherence and CD4 cell counts in a marginally housed population (189).

Recommendation 33: Pillbox organizers are recommended for persons who are homeless (II A): Pillbox organizers offer a simple visual reminder of missed doses. In an observational study, their use was associated with improved adherence and higher probability of achieving an HIV RNA level less than 400 copies/mL in homeless people with multiple adherence barriers (63).

Children and Adolescents—HIV-infected young people between birth and 24 years of age are a developmentally diverse group, including those perinatally and behaviorally infected. For perinatally infected children, adherence to medications is determined largely by their caregivers, who often have many challenges, including HIV infection (190). Unique medication-related factors associated with nonadherence for children include difficulty swallowing pills, bad taste of medications, and difficulty timing medication administration around meals (191). Perinatally infected teens often experience deterioration in medication adherence during adolescence, as do their peers with other chronic diseases. Transition from pediatric to adult care settings may create additional adherence barriers because of disruptions in comprehensive services and insurance issues (192). Adolescents and young adults are less likely than their older counterparts to be retained in care and receive prescriptions for ART, and they have worse clinical outcomes (193, 194).

Recommendation 34: Intensive youth-focused case management is recommended for adolescents and young adults living with HIV to improve entry into and retention in care (IV B): Among 174 HIV-infected youth, appointment attendance improved significantly after introduction of individualized case management focusing on increasing self-efficacy and developing group activities to improve support networks (195). In a cohort study of 61 young gay men who were newly diagnosed or in intermittent care, intensive case management, including initially weekly and then monthly meetings, also improved attendance to medical visits, and more intervention visits were associated with increased likelihood of ART prescription (196).

Recommendation 35: Pediatric- and adolescent-focused therapeutic support interventions using problem-solving approaches and addressing psychosocial context are recommended (III B): A cohort study of multisystemic therapy intervention (a form of cognitive–behavioral therapy that considers multiple factors in a youth's environment that contribute to behavior change) in 19 perinatally infected youth with poor adherence showed no significant effect on caregiver-reported adherence but significantly improved virologic outcomes through 3 months after the intervention (197). Two other RCTs showed promising, if mixed, results (198, 199), whereas others demonstrated promising trends but had significant methodological limitations or did not achieve statistical significance (200, 201).

Recommendation 36: Pill-swallowing training is recommended and may be particularly helpful for younger patients (IV B): Pill-swallowing training improved adherence in a small cohort study of 23 patients with identified pill-swallowing difficulties or who needed to switch from other formulations to pills (202).

Recommendation 37: DAART improves short-term treatment outcomes and may be considered in pediatric and adolescent patients (IV C): Three cohort studies of DAART for perinatally infected children and adolescents living with HIV showed improvement in short-term immunologic outcomes (203–205). In the 2 studies where DAART was discontinued, however, this improvement was not sustained at follow-up (203, 204). In 1 study it did help to determine the cause of treatment failure in several patients. Another

study in Cambodia showed improved immunologic outcomes for orphaned children at a cost of $60 for DAART per child per year (205). In some low-resource settings DAART may be a practical, cost-effective, long-term strategy to improve adherence for younger patients, but a plan for increasing disease self-management is needed as children transition to adolescence.

Recommendations for Future Research

Cross-cutting and broadly relevant recommendations for future research are presented here, and topic-specific recommendations are included in Table 2 (206–234). Long-term studies of intervention and postintervention outcomes on adherence and, especially, HIV biomarkers are needed. Formal cost-effectiveness analyses from a range of perspectives are needed to inform institution, government, and policy-level programmatic decisions. Similarly, rigorous implementation and dissemination studies are needed to guide best practices and procedures for replication and scale-up of effective interventions.

Further, there are emerging issues for which insufficient evidence exists to provide recommendations at this time. In settings where ART use has been long-standing and widespread, non-AIDS diseases now account for more deaths among persons with HIV than do AIDS-defining diseases (235). Cardiovascular disease is more common in persons with HIV than those without and accounts for a substantial proportion of serious non-AIDS events (236, 237), and although stopping ART increases this risk (238), certain HIV treatments are also associated with higher risk (239–241). HIV-infected persons have high rates of type 2 diabetes, dyslipidemia, and hypertension (242, 243). High rates of hepatitis C co-infection are seen in Asia, Eastern Europe, and the United States (244). Patients with comorbid conditions often struggle with multiple medications, increased pill burden, drug interactions and side effects, and complex medication scheduling. Comparative research is needed to evaluate intervention strategies to improve adherence and outcomes in the context of multiple comorbid conditions. Finally, new successes in biomedical HIV prevention (pre-exposure prophylaxis [245–247], microbicides [248]) have been tempered by problematic adherence, and comparative research of adherence strategies in these settings will be essential to maximize their benefit.

Conclusions

ART decreases morbidity and mortality, and early therapy is increasingly recommended for its effect on individual health (249–252), as well as for control of HIV transmission (251). Entry into and retention in medical care is a prerequisite for providing lifesaving treatments to persons with HIV. Few validated strategies exist, however, for improving this aspect of care, and the need for robust research is compelling. More data are available on interventions to improve adherence to ART in both general and special populations; however, much of the existing research lacks comparative rigor and correlation to changes in HIV-1 RNA, CD4 cell count, and clinical outcomes. To assure that implementation is feasible for evidence-based recommendations, it will be necessary to strengthen resources, including multidisciplinary linkages, dedicated to ART and care adherence. As the global economy contracts, the identification and implementation of evidence-based strategies to

maximize the individual and societal benefit of HIV treatment will become increasingly important. With proper research and resources, the tools are at hand for substantially decreasing—and perhaps ending—the global HIV epidemic.

Acknowledgments

Appendix 1: Guideline Panel Members

In addition to the authors, the following are members of the Guideline Panel and participated in discussions of the content or review of the manuscript: Magda Barini-García, MD (Health Resources and Services Administration, Rockville, Maryland); Vanessa Elharrar, MD, MPH (National Institute of Allergy and Infectious Diseases, Bethesda, Maryland); Tia Morton, RN, MS (National Institute of Allergy and Infectious Diseases, Bethesda, Maryland); Charles Holmes, MD, MPH (Office of the Global AIDS Coordinator, Washington, DC); Shoshana Kahana, PhD (National Institute on Drug Abuse, Bethesda, Maryland); Peter Kilmarx, MD (Centers for Disease Control and Prevention, Harare, Zimbabwe); Cynthia Lyles, PhD (Centers for Disease Control and Prevention, Atlanta, Georgia); Henry Masur, MD (National Institutes of Health, Bethesda, Maryland); Celso Ramos, MD, MSc (Federal University of Rio de Janeiro, Rio de Janeiro, Brazil); Evelyn Tomaszewski, MSW (National Association of Social Workers, Washington, DC); Marco Antônio de Ávila Vitória, MD (World Health Organization, Geneva, Switzerland).

Appendix 2: Methods for Guidelines Development Process

Summary

A systematic search for studies on interventions to improve entry into and retention in care and antiretroviral adherence and monitoring was performed. A total of 325 studies were identified for inclusion in the evidence base for the guidelines. Two reviewers independently extracted and coded data from each study using a standardized data extraction form. Differences were resolved by consensus with a third reviewer. Reviewers assessed bias in RCTs by using the Cochrane Risk of Bias Tool and in observational studies by using the Newcastle-Ottawa Quality Assessment Scale. Studies were then grouped by intervention type. Adherence monitoring articles were abstracted and graded using a modified Quality Assessment for Diagnostic Accuracy Studies (QUADAS) tool. Panel members drafted a recommendation statement based on the body of evidence for each monitoring method or

intervention type. They then graded the overall quality of the body of evidence for each recommendation on the basis of its risk for bias, quantity, and consistency using methods adapted from the American College of Physicians guidelines and the Grades of Recommendation Assessment, Development and Evaluation (GRADE) System for Rating Clinical Guidelines processes. Finally, panel members graded the strength of each recommendation on the basis of not only the quality and quantity of the body of evidence but also the magnitude of benefit, risk and burdens, costs, and generalizability, recording scores on standardized forms.

Guideline Focus and Target Population

These guidelines focus on interventions to improve entry into and retention in care and ART adherence for people living with HIV as well as methods to monitor these critical processes. The target audience includes care providers, patients, policymakers, organizations, and health systems involved with implementing HIV care and treatment.

Guideline Development Process

IAPAC funded development of these guidelines through a grant from the National Institutes of Health Office of AIDS Research but did not have approval authority over specific recommendations or the completed manuscript. IAPAC convened a panel of 31 members, consisting of experts in clinical care, clinical trials, behavioral science, pharmacy, and guideline methods and patient representatives. From this panel, 20 members volunteered to be on the writing team. Each member completed a written conflict-of-interest disclosure. All potential conflicts of interest were declared, discussed, and resolved by the panel. The panel determined the issues to be covered on the basis of a systematic literature review and developed these guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument for practice guideline assessment (253). This process was conducted in accordance with Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines (254).

Literature Search

Interventions

The following were the interventions of interest: 1) any intervention for improving entry into and retention in care for people with HIV and 2) any intervention for improving adherence to ART. The objective of the literature search was to identify optimal interventions for improving entry into and retention in care and ART adherence to assist with developing guidelines.

To be included, the studies had to meet the following criteria: 1) evaluated an intervention intended to improve entry into and retention in care or ART adherence; 2) had an RCT or observational design that included comparators (if sufficient RCT-level evidence for an intervention was available, then observational studies were not considered in the body of evidence); and 3) reported 1 or more relevant outcomes assessed after the intervention was

completed (biological or behavioral). The following were exclusion criteria: observational studies without comparators, letters, and editorials.

The study participants were children, adolescents, and adults with HIV. The included studies had the following biological and behavioral outcomes of interest: mortality, morbidity, virologic failure, immunologic response, development of HIV resistance, adherence behaviors (as measured by self-report, pill count, electronic drug monitor, pharmacy refill, and other methods), entry into and retention in care behaviors (such as clinic attendance and loss to follow-up), and adverse events.

Identification of Studies

The search largely consisted of a systematic search performed on the Centers for Disease Control and Prevention (CDC) Prevention Research Synthesis Project Database (78), with some specific adaptations for this project. Since 1996, the CDC Prevention Research Synthesis Project has been conducting ongoing systematic searches of the HIV prevention intervention literature, focusing on HIV risk reduction and medication adherence, to establish a cumulative, comprehensive research database for conducting regular systematic reviews. This database has been developed and updated by annual automated electronic database searches, quarterly hand searches of journals, and daily ad hoc searches of the published literature from 1988 to the present. The database created for these guidelines began with pertinent evidence from 1996 and included the most recent annual electronic search of the CDC database (February 2011), hand searching through March 2011, and additional ad hoc searching through November 2011. The searches were performed with no limits for language, setting, or age. The evidence base for these guidelines was restricted to RCTs and observational studies with comparators that had at least 1 measured biological or behavioral end point.

The panel searched the following journal databases: MEDLINE, EMBASE, PsycINFO, CINAHL, and AIDSLINE (before retirement in 2000). The following conference databases were searched from July 2009 to June 2011: Conference on Retroviruses and Opportunistic Infections; IAPAC Adherence Conference; International AIDS Conference; and the International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention.

The clinical trials databases searched were CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov (http://clinicaltrials.gov), Current Controlled Trials (http://www.controlled-trials.com), and Pan-African Clinical Trials Registry (http://www.pactr.org).

Sixteen journals that typically contribute the most relevant citations were also hand-searched for medication adherence and retention studies. We contacted individual researchers and members of relevant organizations working in the field, including panel members, to identify studies and completed or ongoing trials.

We checked the reference lists of all studies identified by the preceding methods and examined the bibliographies of any relevant systematic reviews, meta-analyses, or current guidelines we identified during the search process.

Monitoring

In addition to producing evidence-based guidelines for entry into care, retention in care, and ART adherence interventions, the panel also targeted the identification of strategies and methods for adherence monitoring or assessment, which required separate methods to search, grade, and synthesize evidence. The resulting list of articles was reviewed to include only studies that compared an adherence measurement method with a biological outcome.

Study Inclusion Criteria

The studies must have included one or more methods of adherence measurement and compared clinical or biological outcomes (as listed above).

Search Strategy

Key word searches (*monitoring, measure*) were performed on the original database to identify articles specific to HIV monitoring. One panel member reviewed citations found from key word searches to determine whether they met inclusion criteria. In addition, all articles initially identified as potential intervention articles were screened to see whether they were also of relevance to HIV monitoring. Supplementary searching for relevant articles was also performed as described above.

Data Abstraction and Grading

Articles identified for inclusion were abstracted (for example, study title, date, measures used, and estimates of association) and graded by using a modified Quality Assessment for Diagnostic Accuracy Studies (QUADAS) tool (255).

Evidence Synthesis Strategy

Data on measures from the studies were compiled into summary tables listing ranges of association, quality ratings, and other factors. Quality of the body of evidence and strength of recommendation were then rated according to the methods detailed below.

Overall Grading Scale for Recommendations

We used a grading scale based on the GRADE System for rating Clinical Guidelines and the American College of Physicians methods for development of clinical practice guidelines (256, 257). This pragmatic and systematic approach allowed for transparent, intuitive, and efficient production of these guidelines. Each guideline recommendation has a grade for quality of the body of evidence and a grade for strength of recommendation. Table 1 summarizes the quality and strength scales used. The following sections detail how these 2 grades were derived.

Individual Study Evaluation Methods

Data Extraction and Management—After the initial search and article screening, 2 reviewers independently coded and entered information from the included studies onto a standardized data extraction form; differences were resolved by consensus with a third reviewer. Extracted information included the following: study details: citation, start and end

dates, location, study design; participant details: study population, ages, population size; interventions details: duration, nature, and intensity of the intervention; and outcome details: mortality, clinical disease progression (AIDS and non-AIDS events), treatment response (CD4 recovery and viral load response), adherence, retention, loss to follow-up, resistance, and adverse events. These data were then summarized in a table.

Assessment of Risk for Bias in Included Studies—The 2 reviewers then assessed each of the individual studies for risk for bias; differences were resolved by consensus with a third reviewer. The results were summarized in tables. The Cochrane Risk of Bias Tool was used for RCTs (258, 259). The Cochrane tool assesses risk for bias in individual studies across 6 domains with 3 potential responses for each domain: yes, no, or unclear.

Reviewers assessed observational studies for risk for bias using the Newcastle-Ottawa Quality Assessment Scale (260). This validated scale assesses quality of cohort and case–control studies in 3 main areas by using a "star rating system" ranging from 0 to 9.

Evaluating the Body of Evidence

After each individual study was evaluated, panel members proposed draft recommendation statements based on the evidence gathered and concurrently grouped individual studies together to form the body of evidence for each specific recommendation. The body of evidence for each recommendation was then evaluated according to the factors listed in Appendix Table 3.

All of these factors were considered in decreasing or increasing the quality of the body of evidence and were framed around the standards and interpretation listed in Table 1. Panel members then decided on a grade and, using standardized forms, detailed instances if and why they increased or decreased the quality of the body of evidence, specifically referencing the factor(s) involved.

Moving From Evidence to Recommendation

After recommendation statements had been proposed and the corresponding body of evidence for each recommendation graded, the factors listed in Appendix Table 4 were considered to determine the strength of the recommendation.

Each of the factors was explicitly considered. Panel members then decided on a strength of recommendation and, using standardized forms, detailed how they came to this decision, specifically referencing each factor as appropriate. Note that quality of the body of evidence was only 1 factor considered in the strength of recommendation.

Comments and Modification

An international group of content experts reviewed a draft of these guidelines, and relevant modifications were made to the manuscript. Guideline panel members will review these guidelines periodically and make updates as new evidence becomes available.

Appendix Table 1

Summary of Recommendations With Scores for Quality of the Body of Evidence and Strength of Recommendation[*]

Entry into and retention in HIV medical care

1. Systematic monitoring of successful entry into HIV care is recommended for all individuals diagnosed with HIV (II A).

2. Systematic monitoring of retention in HIV care is recommended for all patients (II A).

3. Brief, strengths-based case management for individuals with a new HIV diagnosis is recommended (II B).

4. Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered (III C).

5. Use of peer or paraprofessional patient navigators may be considered (III C).

Monitoring ART adherence

6. Self-reported adherence should be obtained routinely in all patients (II A).

7. Pharmacy refill data are recommended for adherence monitoring when medication refills are not automatically sent to patients (II B).

8. Drug concentrations in biological samples are not routinely recommended (III C).

9. Pill counts performed by staff or patients are not routinely recommended (III C).

10. EDMs are not routinely recommended for clinical use (I C).

ART strategies

11. Among regimens of similar efficacy and tolerability, once-daily regimens are recommended for treatment-naive patients beginning ART (II B).

12. Switching treatment-experienced patients receiving complex or poorly tolerated regimens to once-daily regimens is recommended, given regimens with equivalent efficacy (III B).

13. Among regimens of equal efficacy and safety, fixed-dose combinations are recommended to decrease pill burden (III B).

Adherence tools for patients

14. Reminder devices and use of communication technologies with an interactive component are recommended (I B).

15. Education and counseling using specific adherence-related tools is recommended (I A).

Education and counseling interventions

16. Individual one-on-one ART education is recommended (II A).

17. Providing one-on-one adherence support to patients through 1 or more adherence counseling approaches is recommended (II A).

18. Group education and group counseling are recommended; however, the type of group format, content, and implementation cannot be specified on the basis of the currently available evidence (II C).

19. Multidisciplinary education and counseling intervention approaches are recommended (III B).

20. Offering peer support may be considered (III C).

Health system and service delivery interventions

21. Using nurse- or community counselor–based care has adherence and biological outcomes similar to those of doctor- or clinic counselor–based care and is recommended in underresourced settings (II B).

22. Interventions providing case management services and resources to address food insecurity, housing, and transportation needs are recommended (III B).

23. Integration of medication management services into pharmacy systems may be considered (III C).

24. Directly administered ART is not recommended for routine clinical care settings (I A).

Pregnant women

25. Targeted PMTCT treatment (including HIV testing and serostatus awareness) improves adherence to ART for PMTCT and is recommended compared with an untargeted approach (treatment without HIV testing) in high-HIV-prevalence settings (III B).

26. Labor ward–based PMTCT adherence services are recommended for women who are not receiving ART before labor (II B).

Substance use disorders

27. Offering buprenorphine or methadone to opioid-dependent patients is recommended (II A).

28. DAART is recommended for individuals with substance use disorders (I B).

29. Integration of DAART into methadone maintenance treatment for opioid-dependent patients is recommended (II B).

Mental health

30. Screening, management, and treatment for depression and other mental illnesses in combination with adherence counseling are recommended (II A).

Incarceration

31. DAART is recommended during incarceration (III B) and may be considered upon release to the community (II C).

Homeless and marginally housed individuals

32. Case management is recommended to mitigate multiple adherence barriers in the homeless (III B).

33. Pillbox organizers are recommended for persons who are homeless (II A).

Children and adolescents

34. Intensive youth-focused case management is recommended for adolescents and young adults living with HIV to improve entry into and retention in care (IV B).

35. Pediatric- and adolescent-focused therapeutic support interventions using problem-solving approaches and addressing psychosocial context are recommended (III B).

36. Pill-swallowing training is recommended and may be particularly helpful for younger patients (IV B).

37. DAART improves short-term treatment outcomes and may be considered in pediatric and adolescent patients (IV C).

ART = antiretroviral therapy; DAART = directly administered antiretroviral therapy; EDM = electronic drug monitor; PMTCT = prevention of mother-to-child transmission.

[*] Refer to Table 1 for recommendation grades.

Appendix Table 2
Evidence Base for Education and Counseling Recommendations

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
McPherson-Baker et al, 2000 (70)	Cohort study with matched controls in 42 "poorly adherent" men	Monthly individual meeting for 5 mo with pharmacist for	X						5 mo	Yes	Yes (T)

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		in the U.S. (majority substance abusers)	focused adherence counseling with weekly pill organizer, compared with pharmacy overview of medications but no organizer								
Milam et al, 2005 (71)	RCT in 437 HIV clinic patients in the U.S.	10-mo period of physician-delivered adherence education and counseling yoked to regularly occurring medical care visits using Vertex "Daily Drug Planners," compared with safer sex intervention	X						10 mo	Yes	No
Mannheimer et al, 2006 (72)	RCT in 928 CPCRA patients in the U.S.	Weekly telephone contact for 3 wk, then monthly for 30 mo, with trained research staff providing adherence support; second condition involved a reminder alarm device; third condition offered both	X						30 mo	Yes	Yes
Simoni et al, 2011 (73)	RCT in 70 clinic patients initiating therapy with CD4 <0.350 × 10⁹ cells/L in the U.S.	Choice of reminder device or three 1-h sessions of counseling alone or with an adherence partner using CBT (LifeSteps) approach	X						25 wk	Yes	No
de Bruin et al, 2005 (74)	Cohort study in 26 treatment-experienced patients in the Netherlands	Nurse delivered 9-step protocol based on Theory of Planned Behavior delivered at each clinic visit if adherence was suboptimal, with EDM feedback for	X						5 mo	Yes	NA

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		about 3 mo of care visits									
de Bruin et al, 2010 (75)	RCT in 133 outpatient clinic treatment-experienced patients in the Netherlands who started treatment after 1996	3-mo nurse delivered AIMS intervention delivered at care visits targeted to EDM adherence rates: 95% received brief "adherence sustaining" discussions and <95% received intensive "adherence improving" discussion (adherence plan, goals with consequences, and EDM data review)	X						9 mo	Yes	Yes
Sabin et al, 2010 (76)	RCT in 68 clinic patients in China taking ART	After a 5-mo habituation period, EDM feedback was provided to patients for 6 mo by a care provider; those with <95% adherence based on EDM received additional counseling with physician or nurse (contrasted to providing counseling to those self-reporting <95% adherence)	X						12 mo	Yes	Yes
Chung et al, 2009 (77)	RCT in 400 HIV outpatients in Kenya	4 arms: SOC alone; SOC with three 45-min educational sessions at ART commencement; SOC with alarm reminder device for 6 mo; and SOC with both educational counseling and alarm device	X						18 mo	Yes (education arms only)	No
Brock et al, 2007 (82)	Quasi-experimental study in 51 outpatient clinic patients initiating or	17-minute video on personal digital assistant targeting ART information and self-efficacy		X	x				1d (immediate)	Yes	NA

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
	continuing ART										
Collier et al, 2005 (83)	RCT in 282 AIDS Clinical Trials Group participants in the U.S.	16 scripted supportive telephone calls over 96 wk delivered by study staff focused on medication-taking behavior, barriers, social support, managing side effects (plus SOC of plastic cards showing pictures of pills and time of day with instructions)	X	X					96 wk	Yes (T)	No
Fairley et al, 2003 (84)	RCT in 43 patients in Australia who had missed 1 ART dose in the last month and were not planning ART change in the next 3 mo	One 2- to 3-hour education program, individualized planning of regimen, choice of adherence aids, and reminder devices delivered by the study nurse with monthly follow-up calls	X	X					20 wk	Yes	No
Golin et al, 2006 (85)	RCT in 140 clinic patients in the U.S. initiating ART or with recent changes in viral load	2 individual MI sessions with masters-level health educators, separated by 4 wk, targeting concerns through reflective listening and reframing, and a 20-minute video, booklets, and booster letters	X	X					12 wk	Yes (T)	No

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
Goujard et al, 2003 (86)	RCT in 326 patients in France receiving ART with 3 drugs (33% with an AIDS diagnosis)	Three 1-hour educational sessions using planning cards with self-adhesive medication stickers and pill boxes delivered by trained staff during first 12 mo; SOC also used planning card	X	X					12 mo	Yes (I)	No
Holzemer et al, 2006 (87)	RCT in 243 clinic patients in the U.S. currently receiving ART	2-phase intervention using assessment questionnaire and Client Adherence Profiling-Intervention Tailoring nursing intervention for an average of 5 sessions covering specific adherence-related content areas tailored to participant's responses and booster telephone-based sessions at 1 and 3 mo	X	X					6 mo	No	NA
Johnson et al, 2007 (88)	RCT in 204 clinic patients in the U.S. with <85% adherence (53% homosexual men)	Five 60-minute individual sessions with trained certified facilitators (Balance Project) based on social problem-solving training and Stress and Coping Theory and monetary incentive for session completion	X	X					15 mo	Yes	NA
Kalichman et al, 2005 (89)	Cohort study in 30 people receiving ART in the U.S. with low health literacy	Two 90-minute nurse-delivered sessions and one 60-minute booster over 4 wk based on the IMB model and health education principles; pictographic	X	X					3 mo	Yes	NA

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		information and pocket-size pamphlets with sticker-pictures of pills									
Murphy et al, 2007 (90)	RCT in 141 HIV clinic patients in the U.S. nonadherent to ART regimen (skipped dose at least once a week)	5-weekly 90-minute social CBT intervention plus four 60-minute booster sessions over a 3-mo follow-up period	X	X					9 mo	Yes	NA
Rawlings et al, 2003 (91)	RCT in 195 outpatient clinic patients in the U.S. (20% injection drug users, 91% receiving initial therapy)	4 modules of Tools for Health and Empowerment education course for patients and their care givers; SOC included routine counseling	X						24 wk	No	No
Safren et al, 2001 (92)	RCT in 56 patients in the U.S.	Single session (LifeSteps) CBT and MI with a video education session before LifeSteps visit and follow-up telephone review 1 wk later	X	X					12 wk	Yes (I)	NA

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
Smith et al, 2003 (93)	RCT in 43 clinic patients in the U.S. initiating PI treatment or switching to new PI regimen	One-on-one education and 3 follow-up visits in approximately monthly intervals with trained nurse or pharmacist based on Social Cognitive Theory and providing patient education and assistance with medication self-management skills (information exchange, skills development, social support enlistment), contrasted to a basic medication education condition	X	X					3 mo	Yes	No
Tuldrà et al, 2000 (94)	RCT in 116 clinic patients in Spain initiating first- or second-line ART (38% MSM, 38% IDU)	4 one-on-one sessions over 48 wk focusing on psycho-education around medication use and self-efficacy	X	X					48 wk	Yes	Yes
Williams et al, 2006 (95)	RCT in 171 patients in the U.S. receiving 3 or more ARTs (majority with a past or current history of substance abuse)	Weekly home visits from trained nurses for first 3 mo, tapered to biweekly for 3mo and monthly for 6 mo, based on social education model; contrast included clinic-based adherence support	X	X					15 mo	Yes	No
Dilorio et al, 2003 (96)	RCT in 20 HIV clinic patients in the U.S. receiving at least 1 PI	3 adherence sessions 2 wk apart delivered by nurse based on MI to promote behavior change using motivational materials (video, journal, calendar, education)			X				8 wk	Yes	NA

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
Dilorio et al, 2008 (97)	RCT in 247 patients in the U.S. initiating or receiving ART (primarily low-income)	5 individual in-person and telephone-based MI counseling sessions with study nurse over a 3-mo period			X				12 mo	Yes	Yes
Johnson et al, 2011 (98)	RCT in 249 patients in the U.S. receiving ART with self-reported high levels of ART side effect distress	Fifteen 90-min CBT sessions delivered by masters-level clinicians covering stress, coping, and adjustment; safer behaviors; and health behaviors over a 10-mo period			X				25 mo	Yes	NA
Knobel et al, 1999 (99)	RCT in 170 viremic patients in Spain taking zidovu- dine + lamivu- dine + indinavir	Individualized education and counseling concerning adaption of treatment to patient lifestyle and information about therapy provided by pharmacists with telephone support available over 2-mo period			X				24 wk	Yes	Yes
Parsons et al, 2005 (100)	Cohort study in 12 SUD patients in the U.S. receiving ART	8-weekly individual 60-min sessions with trained therapist using MI and CBT with focus on adherence and substance use; within-group contrast			X				3 mo	Yes	NA
Pradier et al, 2003 (101)	RCT in 244 HIV clinic attendees in France	Three 45- to 60-min individual counseling and education sessions over 2–3 mo with trained nurse using motivational psychology and client-centered strategies to enhance patients' self-efficacy			X				6 mo	Yes	Yes
Reynolds et al, 2008 (102)	RCT in 109 ACTG patients	4 telephone calls from trained nurse			X				64 wk	Yes	No

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†][‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
	initiating ART in the U.S.	plus a 24-h support line for adherence problem-solving and reminders; contrast condition included nurse- or pharmacist-delivered education that included building strategies and recommending actions for problem-solving									
Weber et al, 2004 (103)	RCT in 60 HIV clinic patients in Switzerland with viral loads < 50 copies/mL within the previous 3 mo	About 11 CBT one-on-one sessions over 1 y with licensed practitioners, including medication adherence as a focus			X				12 mo	Yes	No
Mann, 2001 (104)	RCT in 44 female HIV clinic patients in the U.S. of low socioeconomic status (60% with AIDS diagnosis)	Twice-weekly 10-min writing assignment about a positive future over 4 wk, 5 postcard reminders			X				4 wk	Yes (T)	NA
Wagner et al, 2006 (105)	RCT in 230 HIV clinic patients in the U.S.	5 weekly 30 to 45-min CBT and MI sessions delivered by a research nurse with or without a 2-wk run in (placebo practice)			X				48 wk	Yes (I)	No
Webel, 2010 (106)	RCT in 89 HIV-infected women in the U.S.	7-weekly 2-h trained peer-led support groups based on social cognitive theory; contrast included symptom management strategies and written material			X				14 wk	No	No
Wilson et al, 2010 (107)	RCT in 156 patients in the U.S.	Four visits with physicians trained in MI and with access to and adherence beliefs of			X				12 wk	No	No

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		participant and adherence data via EDM and self-report									
Garcia et al, 2005 (108)	RCT in 76 clinic patients in Brazil beginning ART	20-min motivational home visits every 2 wk by a social worker (based on FRAMES model: feedback, responsibility, advice, menu of strategies, empathy, self-efficacy)			X				6 mo	NA	No
Javanbakht et al, 2006 (109)	RCT in 90 HIV clinic patients in the U.S. with treatment failure due to nonadherence to medication regimen	Weekly for first 3 mo, then every 2 wk for 3 mo, then monthly for 6 mo; 30-min case management with a treatment advocate using contingency management (monetary) for decreased viral load and pill boxes, pagers, reminder calls and social service referrals			X				48 wk	NA	Yes
Remien et al, 2005 (110)	RCT of 215 heterosexual and homosexual patients in the U.S. with nonadherence	Four 45- to 60-min couples sessions (primary partner) targeting education, problem-solving, and optimizing social support vs SOC			X				5 wk	Yes (I)	No
Koenig et al, 2008 (111)	RCT of 226 patients in the U.S. starting ART with their identified treatment partners	5 sessions with nurse-interventionist (ranging in duration from 1.5 to 3 h) during first 2 mo of ART with booster session at 6 mo and telephone check-ins through month 5, targeting education,			X				5 mo	Yes (T)	Yes(T)

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		skills, and support									
Chiou et al, 2006 (112)	RCT in 67 clinic patients and social service agency clients in Taiwan with CD4 count >0.200 × 10⁹ cells/L	3-weekly 60- to 90-min one-on-one or group teaching of a symptom management program with 3 wk of telephone counseling (ASSURE model)				X			3 mo	Yes	Yes
Kalichman et al, 2011 (113)	RCT in 436 patients in the U.S.	7 sessions (45-min one-on-one orientation and goal-setting visit, five 120-min group sessions followed by a 60-min one-on-one session) delivered by trained interventionists based on the conflict theory of decision making, targeting treatment, adherence, sexual health, and substance use				X			9 mo	Yes	No
van Servellen et al, 2005 (114)	RCT in 85 Spanish-speaking patients in the U.S. with detectable viral load and a stated problem with adherence and receiving ART 3 mo	5 small-group sessions (Es Por La Vida); modular content delivered by trained nurse practitioner and health educator targeting knowledge and communication skills with medical staff				X			6 mo	No	Yes
Antoni et al, 2006 (115)	RCT in 130 MSM in the U.S.	10-weekly small-group CBT stress management sessions delivered by postdoctoral fellows and advanced clinical-health graduate students added cognitive restructuring and skills-building to the				X			15 wk	No	Yes (T)

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		SOC (1 h medication adherence training with 2 additional 30-min education sessions)									
Berger et al, 2008 (116)	RCT in 104 Swiss HIV Cohort (Switzerland) study participants	12-weekly 2-h sessions of CBT group therapy with a CBT therapist using psycho-education, cognitive strategies, homework, and relaxation				X			~12 mo	No	No
Sampaio-Sa et al, 2008 (117)	RCT in 107 HIV public health clinic patients initiating ART in Brazil	4 small-group 2- to 3-h education workshops led by psychologist and social worker based on IMB model delivered over 2 mo; contrast was 4 group video sessions with questions and answers				X			12 mo	No	Yes (I)
Levy et al, 2004 (64)	RCT in 68 patients in Australia with <100% adherence and not planning to interrupt or change therapy in next 3 mo	2 phases: general education by the pharmacist or nurse regarding HIV infection and importance of adherence; 2-h pharmacist-delivered examination of the patient's lifestyle and integration of adherence and use of tools (e.g., planner, alarm)					X		20 wk	Yes	No
Frick et al, 2006 (118)	Retrospective cohort study with historical controls in 261 university-based HIV clinic patients initiating ART in the U.S.	3-part intervention consisting of meetings with a pharmacist for an hour, dietitian for 40–60 min, and social worker for 30–60 min, addressing strengths and barriers to adherence with					X		12 mo	No	Yes (T)

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†][‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
		referrals made as needed									
Chang et al, 2010 (119)	RCT in 15 outpatient clinics (1336 patients) in Uganda	Biweekly home visit by health worker, providing clinic- and home-based counseling, clinical and social support						X	24 mo	No	Yes
Mugusi F et al, 2009 (120)	RCT in 621 outpatients in Tanzania	Addition of an educational calendar or a treatment partner or monthly then tapered DAART to SOC clinic-based counseling						X	14 mo	No	No
Muñoz et al, 2010 (121)	Observational matched cohort study in 120 adults in Peru	Community-based support including DAART together with peer support groups or microfinance support, compared with SOC (clinic-based)						X	24 mo	Yes	Yes
Nachega et al, 2010 (122)	RCT in 274 ART initiators in South Africa	Partial (once-daily) DAART with patient selected treatment partner vs. SOC (3 group education sessions pre-ART)						X	12 mo	No	Mixed[§]
Pearson et al, 2007 (123)	RCT in 350 outpatients in Mozambique	Daily visit by trained peers during the week for once-daily DAART						X	12 mo	Yes	No
Ruiz et al, 2010 (124)	RCT in 240 hospital patients in Spain	4 psycho-educational sessions delivered by peers receiving ART; contrast was receiving same 4 visits with a health professional						X	24 wk	Yes (T)	No
Simoni et al, 2007 (125)	RCT in 136 indigent outpatient	6 twice-monthly 60-min trained peer-led support						X	6 mo	Yes (T)	No

Study, Year (Reference)[*]	Study Design	Intervention	Recommendation						Duration	Effectiveness[†‡]	
			15	16	17	18	19	20		Adherence	HIV-1 RNA or CD4 Count
	clinic patients (high levels of substance abuse)	group with weekly telephone calls from peer for 3 wk									
Simoni et al, 2009 (126)	RCT in 224 HIV outpatient clinic patients in the U.S.	Twice-monthly group and weekly telephone-based discussions with trained peers providing psychosocial support, information, and harm reduction for 3 mo, alone or with a 2-way pager alarm and text messages; third arm used pager only; fourth arm was SOC						X	9 mo	No	Yes (T)
Taiwo et al, 2010 (127)	RCT in 499 outpatients in Nigeria	Patient selected treatment partner to supervise medication and remind to attend clinic vs. SOC (2-h group education session pre-ART)						X	12 mo	Yes (I)	No

AIMS = Adherence Improving Management Strategy; ART = antiretroviral therapy; ASSURE = ASSURE = analyze learners, state standards and objectives, utilize technology/media/materials, require learner participation, evaluate and revise; CBT = cognitive–behavioral therapy; CPCRA = Community Programs for Clinical Research on AIDS; DAART = directly administered antiretroviral therapy; EDM = electronic drug monitoring; IDU = injection drug user; IMB = information, motivation, behaviors skills; MI = motivational interviewing; MSM = men who have sex with men; NA = not assessed; PI = protease inhibitor; RCT = randomized, controlled trial; SOC = standard of care; SUD = substance use disorder; US = United States.

[*] Education and Counseling recommendations draw from peer-reviewed evidence-graded studies because the full evidence-base was considered broad and comprehensive enough to warrant exclusion of presentations and abstracts; 6 graded abstract reviews were not included; recommendations would be unchanged with their inclusion.

[†] Yes (I) = initial effectiveness but effect not sustained; Yes (T) = effective in as-treated or modified intention-to-treat population only; mixed = a significant relationship not clearly established but some evidence of effect on biological markers provided.

[‡] See text for details on outcome analyses for specific groups.

[§] Intervention group had significantly lower rates of mortality.

Table A3

Process for Evaluating the Body of Evidence

Factor	Decreases or Increases Quality	Comment
Study limitations	Decrease	As indicated by individual study evaluation tools
Inconsistency of results	Decrease	Widely differing estimates in treatment effect (i.e., heterogeneity)
Indirectness of evidence	Decrease	Evidence does not directly address relevant population or intervention(s) not directly compared
Imprecision	Decrease	Small sample sizes or events with wide CIs
Publication bias	Decrease	Evidence of publication bias found in the systematic review
Large magnitude of effect	Increase	Large or very large estimates of effect increase confidence in results
Dose response	Increase	Evidence for dose–response relationship increases plausibility
Plausible confounding would change the effect	Increase	All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed

Table A4

Factors Considered in Determining the Strength of the Recommendation

Factor	Comment
Quality of the body of evidence	The higher the quality of evidence, the stronger the recommendation.
Magnitude of benefit	The large the benefits, the stronger the recommendation.
Magnitude of risks and burdens	The smaller the risks and burdens, the stronger the recommendation.
Costs	The lower the costs, the stronger the recommendation.
Values and preferences	Key patient and provider values and preferences.

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Table 1

Grading Scales for Quality of the Body of Evidence and Strength of Recommendations

Quality or Strength	Interpretation
Quality of the body of evidence	
Excellent (I)	RCT evidence without important limitations Overwhelming evidence from observational studies
High (II)	RCT evidence with important limitations Strong evidence from observational studies
Medium (III)	RCT evidence with critical limitations Observational study evidence without important limitations
Low (IV)	Observational study evidence with important or critical limitations
Strength of recommendation	
Strong (A)	Almost all patients should receive the recommended course of action
Moderate (B)	Most patients should receive the recommended course of action. However, other choices may be appropriate for some patients
Optional (C)	There may be consideration for this recommendation on the basis of individual patient circumstances. Not recommended routinely

RCT = randomized, controlled trial.

Table 2
Recommendations for Future Research

Monitoring entry into and retention in HIV medical care

Comparative evaluation of monitoring strategies in conjunction with entry into and/or retention in care interventions

Research formally comparing retention in care measures to each other and to biomarker and clinical outcomes

Operational research to optimize and standardize measurement of entry into and retention in care in clinical settings

Entry into and retention in HIV medical care

Comparative evaluation of case management strategies in community-based settings thus far supported only by observational data (206)

Comparative evaluation to identify cost-effectiveness and best practices for case management

Comparative evaluation of other interventions, including peer support, patient navigation, motivational interviewing, and health literacy and life-skills training (207, 208)

Prospective evaluations of "pay for performance for patients" programs, including financial incentives and nonmonetary awards (209, 210)

Monitoring ART adherence

Defining duration of adherence period for longitudinal measures (e.g., refill data or EDMs) that provides the most clinically useful information

Advances in EDM technology to decrease costs and improve real-time monitoring capability

New measurement methods for drug concentrations in biological samples (e.g., standardizing measurement in hair)

Methodological work to optimize the validity of each monitoring modality

Operational research to optimize and standardize measurement of adherence in clinical settings

Improved monitoring methods for nonsolid (e.g., liquid) formulations

ART strategies

Data on adherence, clinical, biological, and cost-effectiveness outcomes of FDCs compared with individual constituents, especially where cost considerations encourage the decoupling of FDCs (211)

Adherence tools for patients

Determination of the relative influence of adherence tools in relation to other behavioral or structural intervention components (e.g., education and counseling)

Well-controlled comparative trials for other noninteractive tools, such as pagers, watch alarms, and keychain alarms

Education and counseling interventions

Research measuring biological outcomes for education and counseling interventions

Research on the influence of community, culture, and available resources in countries other than the United States

Research to identify "active ingredients" in education and counseling or specific strategies that uniquely affect targeted outcomes

Research to improve understanding of the optimum characteristics of interventions, such as duration, longevity, and delivery strategies

Evaluation of dyadic or couples-based counseling approaches

Additional research evaluating cue-based reinforcement (109, 209, 210, 212) or use of medication run-in periods (105, 111)

Research evaluating the efficacy of mandatory attendance at pre-ART group education courses or the identification of a "treatment buddy"

Cost-effectiveness and feasibility of combination interventions

Cost-effectiveness and operational research on interventions adopted as a part of clinical care

Health system and service delivery interventions

Comparative research, particularly cost-effectiveness studies, to better understand the effect of cultural, social, and policy-related factors and associated interventions

Research into interventions to decrease HIV-associated stigma, particularly with a focus on adherence and biological outcomes

Evaluation of programmatic approaches to optimize clinic staffing through decentralizing adherence support into the community in resource-limited settings

Shifting of ART care from medical to nursing staff in more resource-rich settings

Pregnancy

Investigation of specific ART adherence barriers related to pregnancy status

Well-controlled studies to understand adherence barriers for pregnant women and to improve ART adherence antenatally and postpartum

Substance use disorders

Interventions for ART-naive patients with substance use disorders

Creation of transitional models that sustain the long-term benefit of effective interventions

Evaluation of the effectiveness, feasibility, and cost-effectiveness of comanaging HIV and opioid replacement treatment (146, 153, 213, 214)

Evaluation of the efficacy of educational counseling, adherence case management, timer and reminder interventions, and peer-driven and family-support interventions that have shown promising results in pilot studies (215–218)

Exploration of long-term home-visit nursing interventions with peer support (219, 220)

Mental health

Research addressing mental health disorders other than depression, including bipolar disorders, schizophrenia, personality disorders, and the effects of traumatic and stressful events in relationship to ART adherence

Research on mental health disorders in relationship to ART adherence from locations outside the United States

Research on systematic mental health screening in relation to ART initiation or adherence

Research to understand the specific mechanisms through which depression may influence ART adherence and treatment outcomes

An expanded evidence base regarding mental health disorders and symptoms in relation to HIV care engagement and retention

Incarceration

Studies investigating ART distribution and adherence strategies in low- and middle-income countries

Additional studies to determine whether DAART is the optimal strategy within correctional facilities

Studies to determine the optimal length of DAART after release from a correctional facility

Cost analyses of ART adherence interventions

Studies to investigate case-management interventions designed to maintain ART and to maximize linkage to care after release (221–224)

Studies to investigate whether opiate replacement therapy improves ART adherence during incarceration and after release among opioid-dependent persons

Homeless and marginally housed individuals

Better strategies to assess adherence and detect lapses to better tailor support to functional adherence challenges in individual patients

Studies on the effectiveness of DAART, adherence tools, and case management and medical outreach for homeless and marginally housed individuals

Children and adolescents

Better understanding of adherence predictors within subgroups of HIV-infected youth (perinatally infected and behaviorally infected adolescents)

Strategies to improve linkage to and retention in care that are developmentally and culturally appropriate, with particular attention to the vulnerable period of transition from pediatric to adult care

Exploration of relationship of disclosure of HIV diagnosis to medication adherence and retention in care (225–232)

Research on medication formulations, pill burden, and administration methods

Determination of the reasons why adolescents and young adults are less likely to receive prescriptions for ART than their older counterparts

Further research to develop, test, and implement interventions that address adherence barriers in an individual's environment (225–229, 233, 234)

Additional adherence interventions using mobile technology and social networking

ART = antiretroviral therapy; DAART = directly administered ART; EDM = electronic drug monitors; FDC = fixed-dose combination.