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ADULT ADHERENCE TO TREATMENT AND RETENTION IN CARE

AIDSTAR-ONE TECHNICAL BRIEF

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BACKGROUND

Advances in highly active antiretroviral therapy (ART) have dramatically changed the course of HIV disease, reducing both HIV-related morbidity and mortality. Adherence to treatment, most importantly ART, has proven essential to achieving these benefits in studies conducted in both high-income and resource-limited settings (Bajunirwe et al. 2009; Paterson et al. 2000). Recent studies have expanded the focus of adherence to include retention in care, which includes attending regular follow-up visits (see definitions below). Promoting adherence to treatment and retention in care requires an understanding of the potential barriers that patients face and developing interventions that overcome these barriers. Long-term maintenance of adherence requires that these interventions be integrated into sustainable programs that provide a consistent supply of medications, education, and ongoing support as barriers arise (Rosen, Fox, and Gill 2007).

Both adherence to treatment and retention in care are necessary to optimize clinical outcomes in people living with HIV (PLWH). However, most of the studies conducted in resource-limited settings have focused solely on adherence to treatment and have provided limited information on effective and practical approaches to improve both adherence to treatment and retention in care. This brief will address both aspects of adherence in adult patients and 1) explore barriers associated with poor adherence to ART and retention in care; 2) outline current methods to measure and monitor adherence; 3) review program strategies to retain individuals on effective treatment for life and discuss the applicability of these interventions for integration into ART programs; and 4) provide programs with guidance on key steps to strengthen efforts to promote adherence to ART and retention in care.

DEFINITIONS OF ADHERENCE

Although most studies have focused on adherence to medication, total adherence extends beyond taking prescribed drugs to include other health-related behaviors. These behaviors may include seeking timely medical attention, attending follow-up appointments, obtaining immunizations, and implementing behavioral modifications needed to improve the outcomes of care and treatment such as self-management of disease, smoking, and diet. With this in mind, the World Health Organization (WHO) defines adherence as, "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider" (WHO 2003).

In many models of HIV care, patients refill prescriptions during routine follow-up visits; thus, retention in care is thought to be synonymous with adherence to medication. This, however, may not be accurate for several reasons: patients who are adherent to clinic appointments may not necessarily be adherent to medication, and patients who are adherent to medication may miss clinic appointments crucial for monitoring treatment failure, treatment side effects, and occurrence of other comorbidities. Furthermore, monitoring retention in care is extremely important for those patients who have engaged in HIV care but have yet to initiate treatment, a population with very low rates of retention in many settings. Therefore, while many of the facilitators and barriers may be the same, adherence to treatment and retention in care will be addressed separately for the purpose of this brief and defined as follows.

The Importance of Adherence

Adherence to Treatment

The full and sustained benefits of ART can only be derived from high levels of adherence to an antiretroviral (ARV) regimen. Studies conducted in the United States and Europe have found that adherence at or

Adherence to treatment: The ability to start, manage, and maintain a given medication regimen at the times, frequencies, and under specified conditions as prescribed by a health care provider.

Retention in care: The ability to adhere to critical aspects of care—attend regular follow-up appointments, scheduled lab tests, and other monitoring activities—according to health system standards and as prescribed by a health care provider.

above 95 percent is required for viral suppression, with 80 percent of near-perfect adherers maintaining an undetectable viral load over six months (Paterson et al. 2000). Although data from the United States suggest that some ART regimens may allow patients with lower levels of adherence to also achieve treatment success (Bangsberg 2006), the highest levels of adherence possible should be maintained for maximal benefit of medication. Non-adherence to ART allows for inconsistent drug levels and persistent viral replication, increasing the likelihood of the formation of viral variants resistant to the currently prescribed medication (Friedland and Williams 1999; Hermankova et al. 2001; Kozal et al. 2007). In addition to viral rebound and drug resistance, low adherence to treatment has been associated with higher hospitalization rates, productivity loss, disease progression, and death in both high-income and resource-limited settings (Bajunirwe et al. 2009; Bangsberg et al. 2000; García de Olalla et al. 2002; Hogg et al. 2002; Paterson et al. 2000; Sokol et al. 2005; Van Dyke et al. 2002). In certain resource-limited settings, there is neither the capacity to monitor viral loads and drug resistance, nor the funds for large numbers of second-line therapies, which can cost more than 10 times the price of first-line drugs (Hardon et al. 2007). In such environments, low adherence to ART is particularly dangerous for both programs and patients (Cohen 2007).

Retention in Care

More recently, retention in care has been highlighted as an important element of clinical success for the patient and the program. Whereas attending clinical appointments is associated with favorable patient outcomes among individuals with HIV on ART (Berg et al. 2005; Lucas, Chaisson, and Moore 1999; Nachega et al. 2006b; Rastegar, Fingerhood, and Jasinski 2003), poor retention in care has been associated with higher mortality for both ART and pre-ART patients in both high-income and resource-limited settings (Amuron et al. 2009; Giordano et al. 2007; Rosen, Fox, and Gill 2007). A recent study from Kenya found that patients not retained in care are generally sicker than those who are retained in care and may therefore experience poorer long-term outcomes (Jarrett and Mwamburi 2009). In addition to retrieving medication, clinical follow-up visits are crucial for monitoring drug toxicity, clinical HIV progression, and to diagnose and treat new opportunistic infections (OIs) and other concurrent diseases that may occur.

Current Rates of Adherence

Adherence to Treatment

Initial findings about adherence to ART regimens in sub-Saharan Africa have been encouraging. A meta-analysis found that a pooled estimate of 77 percent of patients in African settings achieved adequate treatment adherence, defined as taking 95 percent of prescribed pills, compared with just 55 percent of patients in North American settings (Mills et al. 2006). A subsequent multi-site study from Africa confirmed these high levels of adherence to medication (Hardon et al. 2006); however, adherence to ART in Southeast Asia was reported to be lower (60 percent) (Cauldbeck et al. 2009).

Retention in Care

Identifying patients who are not retained in care can be challenging as poor retention can include a range of behaviors such as missing a single scheduled clinical visit to lost-to-follow-up (LTFU), a term used to describe patients who fail to present to clinic for a certain period

of time and are not known to have died (Rosen, Fox, and Gill 2007). Although overall treatment adherence among sub-Sahara African patients has been high, recent evidence suggests that a large number of PLWH in the region who have started in treatment programs are not retained in care. A review of 33 patient cohorts taking ART in 13 African countries suggested only 60 percent of patients remain enrolled in programs after two years, with LTFU accounting for 56 percent of all attrition (Rosen, Fox, and Gill 2007). Furthermore, a study conducted in Uganda found that over 25 percent of patients eligible for ART did not complete screening or begin treatment (Amuron et al. 2009). The potentially high attrition rates suggest the need for a better understanding of how PLWH integrate ART and care seeking behavior in the context of their daily lives to support adherence to treatment and program retention.

BARRIERS TO ADHERENCE TO TREATMENT AND RETENTION IN CARE

Adherence to treatment and retention in care are complicated and dynamic issues, influenced by internal and external factors that include the patient, the health system (including clinic environment, providers, supporting services [counseling, nutritional support, case management], and other critical systems [supply chain, laboratory, pharmacy, etc.]), the community, and medication barriers in the case of treatment adherence. Many of the same barriers to treatment adherence have also been noted as barriers to retention in care, although less research has been done in that area. These are summarized in Table 1.

Barriers to Adherence to Treatment

Patient Factors

Patient factors can be demographic, psychosocial, socioeconomic, and/or clinical in nature. While increasing age was found to correlate with a higher adherence in both resource-rich and more limited settings (Mehta et al. 1997; Orrell et al. 2003), most demographic factors, such as gender and ethnicity, alone do not seem to predict adherence. However, gender and ethnicity have been associated with variations in drug levels, efficacy, and in susceptibility to adverse effects of ART, which in turn may affect adherence to treatment. For example, one study found that women are seven times more likely to develop a severe rash from the common non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine, than men and as a result, are significantly more likely to discontinue treatment (Bersoff-Matcha et al. 2001). Similarly, patients of African-American descent have been shown to have significantly greater efavirenz concentrations during HIV therapy, explaining susceptibility to efavirenz-related central nervous system side effects, such as dizziness and insomnia, and lower rates of treatment adherence (Clifford et al. 2005; Haas et al. 2004).

Psychosocial factors have been found to strongly influence adherence (Bogart et al. 2000; Singh et al. 1996). Depression and other psychiatric illnesses have been shown to be related to poor adherence to ART regimens as well as having a significant impact on the overall quality of life for PLWH in both high-income and resource-limited countries (Amberbir et al. 2008; Byakika-Tusiime et al. 2009; Dalessandro et al. 2007; Starace et al. 2002). In addition, both perceived and experienced stigma have profound effects on the mental health of PLWH and those caring for them and thus can negatively influence adherence to treatment in Western settings as well as in sub-Saharan Africa and India (Cluver, Gardner, and Operario 2008; Kip, Ehlers, and van der Wal 2009; Kumarasamy et al. 2005; Vanable et al. 2006). Patients reported that perceptions of stigma and fear of discrimination prevented them both from purchasing and taking their medication. They were less likely to disclose their status to colleagues, friends, and others. Non-disclosure may lead to patients taking their ARV medicines secretly and irregularly because of inadequate social support and encouragement (Golin et al. 2002a; Hardon et al. 2007). Active alcohol or substance abuse also makes it more difficult for patients to adhere to treatment

TABLE 1. BARRIERS TO ADHERENCE TO TREATMENT AND RETENTION IN CARE

Barriers		Treatment	Care
Patient Factors			
Psychosocial	Depression	X	
	Stigma	X	X*
	Substance/alcohol abuse	X	X*
Socioeconomic	Cost of transport	X	X
	Food insecurity	X*	X*
	Lower literacy	X	X*
Demographics	Younger age	X	
	Gender		
Clinical	Prior and/or current medical comorbidities	X	X*
System Factors			
Access	Distance	X	
	Long wait times	X	X
	Cost of co-pay for medication	X	
Environment		X*	X*
Provider relationship		X*	X*
Support services		X	X*
Community Factors			
Lack of knowledge/awareness		X*	
Stigma		X	X*
Medication Factors			
Pill burden		X	
Dose frequency		X	
Dietary restrictions/requirements		X	
Side effects		X	

X, statistically significant association in a published study; X*, suggested from the literature but evidence not as strong in literature reviewed.

(Golin et al. 2002b; Spire, Lucas, and Carrieri 2007; Weiser et al. 2006). In a recent meta-analysis of 40 studies, alcohol drinkers were about twice as likely to be non-adherent compared with abstainers (Hendershot et al. 2009). In a similar study in Botswana, nearly 40 percent of patients surveyed admitted to missing a dose because of alcohol consumption (Kip, Ehlers, and van der Wal 2009).

Patient-level socioeconomic factors, such as income and education, have been shown to contribute to suboptimal adherence to treatment. Cost of transport and medication co-pays are consistently noted as barriers to adherence. Patients have expressed difficultly balancing their need for transportation to the clinic and any medication costs against the need to pay for food, school fees, and other necessities for themselves and their families and as a result, have missed pharmacy pick-ups and other follow-up appointments (Crane et al. 2006; Hardon et al. 2007; Mills et al. 2006; Tuller et al. 2009). Other factors reported to have a significant effect on adherence include unemployment, lack of effective social support networks, unstable living conditions, and/or incarceration (Beyene et al. 2009; Kidder et al. 2007; Small et al. 2009). Illiteracy and a low level of education can also lead to an inadequate

understanding about the effectiveness of medications, resulting in reduced adherence to treatment (Kalichman, Ramachandran, and Catz 1999).

Clinical factors, such as OIs, may also interfere with adherence because of increased risk of drug side effects due to OI-related treatment. For example, severe side effects from treatment of Pneumocystis pneumonia have been reported in 44 to 100 percent of PLWH compared to mild side effects in just 8 percent of HIV-negative patients (Lin et al. 2006). Overlapping toxicities of medications used to treat tuberculosis (TB), a common OI in resource-limited settings, could also result in similar challenges with concurrent treatment of HIV and TB (Pepper et al. 2007). This is discussed in more detail below (see "Medication Factors"). One study, however, showed that patients who have had serious OIs may perceive their illness to be severe and adhere better to their treatment (Singh et al. 1996). Similarly, pregnant women who are living with HIV tend to be more adherent to ART during pregnancy for fear that they will transmit the virus to their unborn child. Adherence rates have been shown to decline, however, during the period after delivery (Mellins et al. 2008; Park, Tochuku, and Grigoriu 2007; Zorrilla et al. 2003).

As PLWH live longer, multiple comorbidities are becoming increasingly common, creating challenges with drug interactions, adverse effects, and adherence. For example, in parts of Africa and Asia, where chronic hepatitis B (HBV) infection is estimated to occur in 10 to 20 percent of PLWH, recent studies show that co-infection with HBV increases the risk of hepatotoxicity from ARVs from three- to five-fold (Hoffmann and Thio 2008; Idoko et al. 2009). An increase in adverse events and decreased adherence are also seen in patients co-infected with hepatitis C virus, a common infection in patients with histories of needle sharing or HIV exposure through infected blood products (Fumaz et al. 2008).

Although it is well known that a patient's belief, trust, and confidence in his or her therapy and health care provider is positively associated with ART adherence in U.S.-based settings (Altice, Mostashari, and Friedland 2001; Beach, Keruly, and Moore 2006; Golin et al. 2002a; Remien et al. 2003), recent evidence from resource-limited settings suggests that an understanding of a patient's medication regimen and the relationship between non-adherence and disease progression predict better adherence (Crane et al. 2006; Watt et al. 2009). In a Ugandan study, near-perfect adherence was motivated by a belief that ART was responsible for keeping the patients healthy and by a desire to stay alive to look after the well-being of family members (Crane et al. 2006). Similarly, in Tanzania, the belief in therapy came from the patient's own experience of transitioning from debilitating illnesses to improved health and function after initiating therapy (Watt et al. 2009).

System Factors

Patient adherence to treatment may be influenced by health system barriers, such as access to the facility and to medication, the overall environment of the facility, the patient–provider relationship, and support services that are incorporated into care. One common challenge faced by HIV treatment programs in resource-limited settings is ensuring a regular and timely supply of medication to patients. An unreliable supply of medications can severely depress patient adherence rates. With the number of patients initiating treatment rapidly growing and a median price for first-line treatment of US$143 per person per year in low-income countries, many health systems are finding it difficult to ensure that there are adequate drugs, supplies, and trained health care providers (WHO 2009b). These countries are often undermined by weak procurement and supply management systems, resulting in frequent shortages of ARVs and other essential commodities. In 2008, of the 91 low- and middle-income countries surveyed, 34% had experienced at least one stockout of a required ARV drug (WHO 2009b).

Similarly, individuals and households often lack the means to pay for ART care and treatment services or

may be unable to bear the indirect costs of seeking services, such as loss of productive time, medication, and transportation. In Uganda, patients reported the price of medication (rather than side effects, stigma, or inconvenience) as the principal challenge to sustaining treatment (Byakika-Tusiime et al. 2009; Crane et al. 2006), a finding consistent with those reported in other African countries and India (Hardon et al. 2007; Safren et al. 2005). Poor adherence to treatment can also be the result of the lack of access to the health facility to pick up medications due to distance to the facility, constrained facility hours, and waiting times (Hardon et al. 2007; Kip, Ehlers, and van der Wal 2008; Weiser et al. 2003). For example, over half of patients surveyed in a rural Indian clinic traveled over 200 km to attend their appointments (Cauldbeck et al. 2009). Similarly, patients in rural Botswana reported clinic wait times of up to 12 hours (Hardon et al. 2007).

Although existing data are limited, aspects of the clinical environment may be associated with improved adherence to treatment. For example, in the United States, a friendly, supportive, and non-judgmental attitude of health care providers and facility staff has been shown to contribute to improved adherence to treatment (Altice, Mostashari, and Friedland 2001; Beach, Keruly, and Moore 2006). Less is known about how the clinic environment affects ART adherence in resource-limited settings. In Tanzania, however, the inclusion of PLWH staff reinforced the benefits of ART and motivated patients to adhere to medication regimens and live with HIV long-term (Watt et al. 2009). In resource-rich settings where patients have a single provider, a better patient–provider relationship is associated with higher adherence (Altice, Mostashari, and Friedland 2001; Beach, Keruly, and Moore 2006). The role of this relationship in resource-limited settings has not been as well studied, although the potential role of counselors and nurses to provide this type of relationship may be possible (Watt et al. 2009). The availability of social support services, such as counseling or peer support groups in resource-rich and -limited settings, also helps patients adhere to treatment better through a deeper understanding of their disease and a more trusting environment (Ickovics and Meade 2002; Watt et al. 2009). Support of access to food and other nutritional support have also been found to be a strong predictor of adherence in more resource-limited settings (Cantrell et al. 2008; Mwadime and Castleman 2009).

Community Factors

A supportive community or interpersonal environment is critical for PLWH. High levels of stigma within the community due to lack of education and awareness of HIV can lead to reduced levels of adherence to treatment. For example, community members from resource-limited settings in Asia and Africa reported fear and disgust of PLWH in their communities who were at the end stages of the disease, as well as social isolation and public shaming of patients and their families (Maman et al. 2009; Watt et al. 2009).

Medication Factors

Early regimens of highly active ART were often complex with up to 20 pills daily, food restrictions, and dosing three to four times a day—all characteristics associated with lower adherence (Chesney et al. 2000). Although most first-line regimens are now one to two pills once or twice daily, second-line regimens can be more complex. A larger problem remains regarding ART-related side effects, including those related to treatment initiation and others that appear only after the initial months of treatment. For example, nucleoside reverse transcriptase inhibitors, such as zidovudine and stavudine, are associated with nausea, fatigue, and headaches that usually resolve two to four weeks after initiation. Other toxicities, including anemia (zidovudine), neuropathy (stavudine), fat redistribution (lipodystrophy), and lactic acidosis, can take weeks or months to appear. Efaverinz, a common NNRTI, causes central nervous system symptoms, such as dizziness, insomnia, and confusion, which can also result in lower adherence (McNicholl 2009). Studies looking at early and longer term adherence have consistently shown that when patients experi-

ence side effects, they tend to stop treatment or take medication irregularly (Nachega et al. 2009; Remien et al. 2003; Weiser et al. 2003).

In addition to a high pill burden, concurrent HIV and TB therapy is associated with increased risks of adverse drug effects such as nausea, gastrointestinal tract disturbance, peripheral neuropathy, cutaneous reactions, renal toxicity, and potentially fatal liver toxicity (Dean et al. 2002). These toxicities may require therapy discontinuation, resulting in greater immune suppression and predisposition to worsening TB and other OIs. In addition, treatment of TB with rifampicin has been shown to reduce the blood levels of many ART drugs and may result in treatment failure even with high levels of ART adherence (Kwara, et al. 2005).

Barriers to Retention in Care

Aside from direct medication-related characteristics, all patient, system, and community barriers to adherence to treatment noted previously also are associated with suboptimal retention in care (see Table 1). Although few formal studies have been done, the most common reasons for missed appointments are thought to be 1) patient barriers such as forgetfulness, sickness/illness, lack of belief about ARV drugs, and traditional and religious beliefs; 2) system barriers such as clinic distance resulting in transport difficulties and cost, schedule conflicts including inability to take time from work (both in the formal and informal sector), long wait times, hospital staff attitude, and poor knowledge about ART; and 3) transferring to another health care provider or migration due to different reasons including stigma (Aidi et al. 2009; Babb et al. 2007; Booysen and De Wet 2009).

In addition, poor clinical environment and gaps in domains of health system responsiveness (access, environment, communication [WHO, 2003]) are also barriers to retention in care. Many public facilities in sub-Saharan Africa scaled up ART without a comparable increase in personnel to accommodate the larger number of patients (Barnighausen et al. 2007; Van Damme, Kober, and Kegels 2008). As a result, health workers are overworked, leading to longer waiting times and deteriorated patient interaction. Long waiting times were cited as a major challenge to adherence to visits in a Botswana study, where most of respondents reported that they spent four hours or more at the clinic. Having to take a half or full day off from work to attend clinic visits is especially challenging for those patients who have not disclosed their status to their employer (Hardon et al. 2007). A recent study in South Africa found that patients who had to take leave or time off work or lost income as a result of having to visit the clinic were nearly four times more likely to miss a visit. Improvements in retention were observed with improvements in self-reported health and higher levels of service quality (Booysen and De Wet 2009).

ASSESSING AND MONITORING ADHERENCE

For most patients, viral suppression is achieved early when adherence tends to be high. However, because adherence has been shown to decrease over time (Liu et al. 2006; Mannheimer et al. 2002), which can result in viral rebound and possible drug resistance, careful monitoring of adherence to treatment and retention in care is needed at all stages of the disease. Effective adherence monitoring, coupled with improved clinical follow-up, will allow health care providers to target interventions and guide regimen selection.

Monitoring Adherence to Treatment

Accurately measuring adherence can be challenging. Although no gold standard exists for the precise assessment of adherence to ART in clinical care, levels of adherence can be estimated by a number of approaches. Common methods include patient self-reports, pill counts, and pharmacy refill records. Biological markers, such as viral load (VL) and CD4 cell count, can also be used as a proxy for suboptimal adherence, although a number of studies have shown

discordance between viral suppression and adherence in the context of HIV drug resistance. Furthermore, lower rates of adherence may still result in viral suppression in patients on longer term treatment (Rosenblum et al. 2009). While uncommon, drug levels are used in some research studies. Each method has advantages and disadvantages, as summarized in Table 2.

Self-reports

Self-reports are the most commonly used approach to measure adherence in the clinical setting. Patients are often asked to report their own adherence in a self-report, such as a questionnaire or personal interview. Different periods of recall may be used—four-day, one-week, one-month, or most-recent recall of missing a dose. The Center for Adherence Support Evaluation Index uses three standard measures of self-reported adherence that are simple to apply and can be employed by both researchers and clinicians in the field (Mannheimer et al. 2006). The widely used Aids Clinical Trials Group adherence instruments employ a four-day recall period (Chesney et al. 2000). A visual analog scale, with values ranging from 0 to 100 percent, can be used to indicate how much of each HIV medication has been taken over a specific time period and has been validated in resource-limited settings (Oyugi et al. 2004). These tools can be found in the Appendix.

Pill Counts

Health care providers, pharmacists, and providers of directly observed therapy (DOT) may conduct pill counts, where the number of remaining pills are counted and assessed to measure adherence to treatment over a specific period of time based on the refill date and daily dosage. This can be done at the time of refill or through unannounced home visits.

Pharmacy Refill Records

Pharmacy refill data has been used as an additional indicator of adherence. Patients collecting their medica-

TABLE 2. ADVANTAGES, DISADVANTAGES, POTENTIAL BIAS, AND COMPARATIVE ACCURACY OF TOOLS TO MONITOR ADHERENCE TO TREATMENT IN CLINICAL PRACTICE

Method	Advantages	Disadvantages	Direction of Potential Bias	Comparative Accuracy
Patient self-report	Simple, cheap	Subjective; accuracy affected by poor patient recall, failure to recognize mistimed doses, and lack of patient candor	Overestimates	Weak yet significant association with VL (Bangsberg et al. 2000; Liu et al. 2001; Simoni et al. 2006)
Pill counts	Simple, objective	Accuracy affected by throwing away remaining pills prior to count, inability to confirm who took the pills, and the timing of doses	Overestimates	Moderate associations with VL and CD4 cell count; unannounced pill counts are more predictive of VL than self-reported measures (Bangsberg et al. 2000; Liu et al. 2001)
Pharmacy data	Simple, cheap, objective	Requires that patients bring in bottles; inability to confirm who took the pills and the timing of doses	Overestimates	Moderate to strong associations with VL, CD4 cell count, and AIDS-related mortality (Farley et al. 2003; Grossberg, Zhang, and Gross 2004; Nachega et al. 2006a; Steiner and Prochazka 1997)
VL testing	Objective	Expensive; technically difficult; invasive (uncommon in resource limited settings)	Overestimate or underestimate	May vary based on viral resistance, prior treatment failure, or poor absorption of the drug

tions regularly on due dates are assumed to be adhering to treatment. An effective record keeping system is essential for pharmacy refill data to be used.

Biological Markers

Because the goal of ART is viral suppression, monitoring VL can be used as an indicator of effectiveness of treatment and, thereby, of medication intake. While suboptimal adherence remains a common reason for detectable viremia in patient on ART, in some patients, VLs may remain high despite high adherence due to viral resistance, treatment failure, or poor absorption of the drug. In settings where VL testing is unavailable—common in many resource-limited settings—monitoring CD4 counts as a marker of response to treatment may detect non-adherence. However, because of the long time lag between non-adherent events and immunologic failure, measurement of VL and CD4 counts are not particularly useful tools to detect and address non-adherent events in a timely manner.

Although all of the adherence measurement tools have been validated to be sensitive in measuring adherence, no single tool can produce a valid and reliable measurement of adherence. Therefore, the use of a multi-method approach that combines feasible self-reporting and reasonable objective measures, such as pill counts, is recommended (Hirschhorn et al. 2002; WHO 2003).

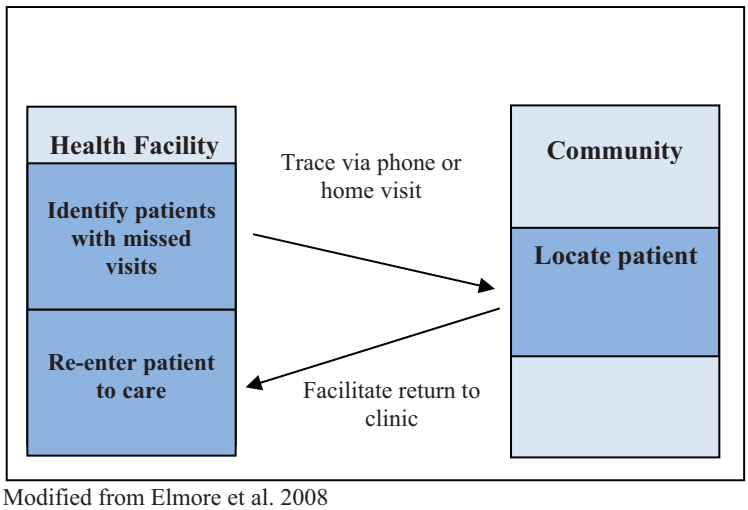
Monitoring Retention in Care

To monitor retention in care, reliable patient tracking and tracing systems are needed to identify patients who have missed visits or are LTFU. This can involve a number of systems, ranging from simply putting aside the charts of no-show patients to as complex as electronic medical records that use global positioning system tracking to locate a patient's home to determine if the patient is not retained or has moved or died. In either case, as shown in Figure 1, this process involves a method of identifying a patient who has missed a visit, followed by tracing the patient's whereabouts and facilitating his or her return to care (Krebs et al. 2008).

APPROACHES TO PROMOTE ADHERENCE

To enhance ART adherence and help achieve clinical goals such as viral suppression, increased immune response, improved quality of life, and reduced morbidity and mortality, interventions should be focused on lowering the unique barriers present. Following are a number of approaches that have been used in resource-limited settings to overcome barriers and promote adherence.

Figure 1. Community tracking and tracing program.



Modified from Elmore et al. 2008

Strategies to Enhance Adherence to Treatment

Psychosocial Assessment and Treatment

To address psychosocial barriers to adherence, mental health assessments and treatment can be integrated into primary care services. Studies in income-rich countries have shown that treatment of mental health illness results in improved adherence and outcome of ART, as well as reducing the risk of HIV drug resistance development (Baingana, Thomas, and Comblain 2005; Cournos, Wainberg, and Horwath 2005; Hartzell, Janke, and Weintrob 2008; Leserman 2008; Starace et al. 2002; Yun et al. 2005). A retrospective cohort study of the effect of antidepressant treatment (ADT) on ARV adherence in the United States showed that ARV adherence was significantly lower among depressed patients not on ADT versus those on ADT. The study also showed an association between adherence to ADT and adherence to ARVs; patients adherent to ADT (compared to those who were not) showed significantly higher adherence to ARVs (Yun et al. 2005).

While there have yet to be similar studies in more resource-limited settings, the association between depression and non-adherence has been established (Amberbir et al. 2008; Byakika-Tusiime et al. 2009). Interventions to reduce depression in resource-limited settings are currently being implemented (Box 1; Bolton et al. 2003).

Primary care providers can learn to assess the mental health needs of PLWH to best treat patients or refer them to the appropriate services (Olley et al. 2005; WHO 2008). However, diagnosis of depression may be difficult among patients with HIV because many symptoms of depression disorder, such as fatigue, lethargy, low libido, diminished appetite, and weight loss, may also be manifestations of HIV-related illnesses. This suggests the need for health care provider education and training as well as more active screening for depression among all patients with HIV, particularly among those with suboptimal adherence to therapy (Yun et al. 2005).

BOX 1. GROUP INTERPERSONAL PSYCHOTHERAPY FOR DEPRESSION, RURAL UGANDA (Bolton et al. 2003)

Background of intervention: In a controlled clinical trial, each Interpersonal Psychotherapy (IPT) group met for 90 minutes weekly for 16 weeks. Groups were led by a local person of the same sex. The group leaders each received two weeks of intensive training in IPT. During each session, the group leader reviewed each participant's depressive symptoms. The participant was then encouraged to describe the past week's events and to link those events to his or her mood. The group leader then facilitated support and suggestions for change from other group members.

Main findings:

- Mean depression score was significantly reduced for intervention groups compared to controls.
- Post intervention, 6.5% of the intervention met the criteria for major depression compared with 86% prior to intervention.
- Mean dysfunction score was significantly reduced in intervention groups compared to controls.
- Post-intervention, participants showed significant increases in the ability to perform individual tasks, such as heading the home, participating in community development, and socializing.

Anticipated secondary outcomes:

- Because low depression scores have been significantly associated with poor adherence to ART in the same population, implementers of IPT believe that this mental health intervention will increase treatment adherence and clinical outcomes.

A number of mental health assessment tools are available. General tools include the General Health Questionnaire, the WHO Mental Disorders Checklist, the Hopkins Symptom Checklist, and the Beck Depression Inventory (see Resources 14–17). In addition to knowledge of signs and symptoms, health workers must understand the patient's world and beliefs by creating a respectful non-judgmental environment where patients feel comfortable discussing their troubles (see Box 1; WHO 2008).

Medication Adherence Counseling

Medication adherence counseling can improve patient knowledge and understanding of his or her disease. Adherence counseling, preferably in the client's native language, should be provided both before and after initiation of ART as a means of promoting adherence to treatment. Preparatory counseling should assess the patient's readiness to engage in long-term treatment, the types of support that will optimize the patient's adherence, as well as addressing individual learning needs (WHO 2003). Early and ongoing education should emphasize the importance of adherence to treatment to achieve VL suppression. Patients should understand the link between regular intake of medication or higher adherence with a decrease in VL, increase in CD4 cell counts, and treatment success. Consequences of non-adherence such as increase in VL, decrease in CD4 cells and immune function, and disease progression should also be discussed. Counselors should emphasize the need for taking every dose every day and correctly, with respect to time intervals and dietary instructions, as well as help patients develop reminder cues or planned dosing schedules that coincide with daily activities such as meals (WHO 2003). The training of lay providers for peer counseling and adherence support has been suggested as an effective way to increase adherence. Not only can the use of PLWH to provide adherence counseling help reduce the burden on already overworked clinic staff, PLWH peers are thought to be in a better position than health care workers to provide emotional support (Box 2; Torpey et al. 2008).

Provider Training on Patient Education

Several qualitative studies and editorials have suggested that effective patient–provider relationships and communication may improve adherence to therapy among PLWH (Altice, Mostashari, and Friedland 2001; Beach, Keruly, and Moore 2006). Regardless of regimen selected, strategies to improve the patient–provider relationship and transfer of knowledge include providing the patient with a scientific basis for treat-

BOX 2. ZAMBIA PREVENTION, CARE, AND TREATMENT PARTNERSHIP PROGRAM (Torpey et al. 2008)

Background of intervention: PLWH adherence support workers (ASWs) were trained to improve adherence support among PLWH and bridge the human resources gap. The ASWs, who worked alongside doctors and nurses and were supervised by a professional health care worker, provided patients with educational and psychosocial support, referrals, and other encouragement to improve adherence, as well as conducted community visits to track patients who had missed clinic appointments.

Key findings:

- ASWs helped reduce waiting times and reduced LTFU (patients who no longer came for services, no longer took the prescribed treatment, and could not be contacted by the program) from 15 percent to 0 percent.
- ASWs effectively educated patients on side effects of treatment as seen through an increase in reporting of side effects to clinicians by patients.
- ASWs served as role models, increased clients' self-efficacy and positive attitudes toward ART adherence, and gave them hope that they could lead longer and healthier lives.
- ASWs reduced the workload of health facility staff, enabling better quality services.

ment, providing access between visits for questions or problems, using counselors who speak the same language and understand the cultural context of the patient, consistently reviewing regimen information with the patient at each visit, and verbally repeating the adherence message with problem solving strategies around episodes of non-adherence. In addition, ensuring a team approach that includes the prescribing provider nurses, pharmacists, peer educators, volunteers, case managers, and drug counselors will help to reinforce the message of adherence to treatment (WHO 2003).

Pillboxes, Medication Diaries, and Pill Charts

Pillboxes, which are containers for storing medication with dividers for each day, can be an effective aid to treatment adherence. Approaches have included preloading by pharmacists or by the patient at home. While making it easier for patients to remember to take doses correctly and to monitor adherence, discussion before use is important. Some challenges with pillboxes include increased stigma and discrimination toward the patient due to unintentionally disclosing that the patient is on ART. In addition, patients who are illiterate or very sick may need help to fill the pillboxes correctly. Medication diaries are notebooks in which patients are to record the time and date of medication intake, missed doses, and reasons for missed doses. Medication diaries can serve as useful records of side effects or other problems patients may experience and may also help long-term adherence. Pill charts, as shown in Figure 2, are used to visually display pills (color and shape), names, and dosage for each medication and are used by health providers during counseling and have been found to be helpful in educating illiterate patients (Safren et al. 2006).

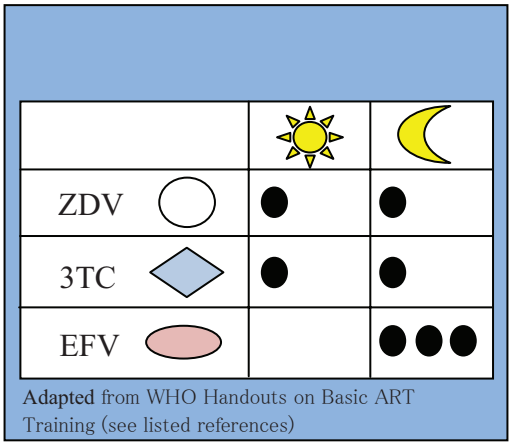
Electronic Reminder Devices

When patients find it difficult to remember to take medication at prescribed times, electronic reminders, such as beepers, pagers, cell phones, wristwatches, and pillbox alarms, can be used to prompt patients to self-administer their medications at set times. Ideally, these devices are mobile and readily incorporated into patient daily routines; however, the devices must be discreet to avoid issues of stigma and confidentiality. While access to certain devices may be difficult especially in resource-limited settings, cell phones are becoming increasingly more prevalent worldwide. A recent study from China showed that cell phone alarms were one of the most common tools used by patients to remember to take their medication on time (Wang et al. 2008).

Home Visits/Buddy System

The buddy system relies on a friend or family member to help the patient to take medications regularly as well as providing some social and logistical support. This would include reminding the patient to take their medication on time, offering encouragement to keep going, helping to keep clinic appointments, and providing emotional support (Nachega et al. 2006b). In a study in Botswana, patients who achieved excellent treatment adherence were those who had accepted their HIV status and engaged an encouraging confidante in their care (Nam et al. 2008). The use of clinic buddies as treatment supporters is relatively low cost and limits risks of forced disclosure because the patient selects his or her own buddy (Birbeck et al. 2009).

Figure 2. Example of a pill chart for low-literacy PLWH.



Adapted from WHO Handouts on Basic ART Training (see listed references)

Directly Observed Therapy

DOT can be thought of as an intensive buddy program in which patients take their medication under the supervision of a health care worker. This method confirms adherence because the health care worker observes the patient taking the medicine (Lanzafame et al. 2000) and is an objective way of measuring adherence. In the management of HIV infection, a modified DOT strategy (observing a proportion of doses over a set period of time) is used as a behavioral intervention that helps patients to 1) develop an understanding of the treatment; 2) develop good treatment-taking behavior; 3) receive support, especially during the first few weeks of ART when patients have short-term side effects; and 4) develop a trusting relationship with health care workers (Box 3; Farmer et al. 2001a, 2001b; Koenig et al. 2006; Singler and Farmer 2002). Some challenges with DOT can be the cost in some settings, the potential to increase stigma through inadvertent disclosure, and that DOT may require complex logistics for a life-long treatment (Katamba et al. 2003; Myung, et al. 2007). The adherence of patients after DOT is discontinued is an area for which more information is needed.

BOX 3. THE USE OF ACCOMPAGNATEURS TO PROVIDE DOT IN CANGE, HAITI (Farmer et al. 2001a, 2001b)

Background of intervention:

- Local community members, called accompagnateurs, are responsible for observing patients taking their medication to promote high rates of adherence.

Most accompagnateurs are peasant farmers or market women, educated in:

- Patient confidentiality and emotional support.
- Clinical presentation and management of HIV infection and TB, including proper use of medications, management of side effects, and prevention of HIV transmission.

Key findings:

- Patients experienced weight gain, improved functional capacity, and suppressed VLs.
- In addition to aiding adherence, accompagnateurs reported sharing food with, baby sitting for, and running needed errands for patients.

Improving Clinic Accessibility

Although there have been significant improvements worldwide in making HIV medication more accessible, clinic accessibility remains a formidable barrier. There remains a deficit in the number of ART sites in rural areas with respect to the location of those in need of treatment. A comparison of the proportion of health facilities with HIV testing and counseling services in four countries (Burkino Faso, Ethiopia, Haiti, and Zambia) shows that the median density of HIV facilities per 100,000 persons was higher in urban districts than in rural districts (Global Fund 2009). In Haiti, though coverage estimates as of 2007 were fairly good (41 percent), 90 percent of clinics offering ART were located in urban areas (Global Fund 2009). A study in rural South Africa using geographical information system technology found a median travel time of 81 minutes to the nearest clinic and a significant decline in usage with increasing travel time (Tanser, Gijsbertsen, and Herbst 2006). Patients in rural settings have corroborated these findings by suggesting care services in closer proximity to the patient's residence, including decentralization of health care services or the provision of home-based care in rural areas (Box 4; Family Health International [FHI] 2004).

After-hours clinics and Saturday clinics can also be arranged for those participants that are employed, and transport reimbursement provided for patients who experienced financial difficulty getting to the clinic on their own. Appointments should also be scheduled so that patients can complete all required appointments with their physicians, counselors, social workers, and pharmacists as required during the same clinic visit.

Incentives/Social Support

Because competing demands of family expenses have been found to affect treatment adherence negatively,

BOX 4. MOBILE CARE AND TREATMENT CENTER, BABATI DISTRICT, RURAL TANZANIA (Robert 2009)

Background: Despite free ART in Tanzania, only an estimated 20% of those in need access therapy. Support for International Change partnered with Mrara District Hospital to bring Community-based Therapeutic Care (CTC) to rural locations with high concentrations of PLWH.

Intervention:

- Promotion of free access to HIV/AIDS services in rural villages each month.
- Mobile CTC staffs a doctor, nurses, a lab technician, and a data manager from the hospital for HIV testing, counseling, clinical exams, and treatment.
- ARV drugs and prophylaxis are provided for new and current patients.
- Community health workers and HIV-positive support groups are available to inform patients of the mobile CTC schedule and to follow-up missed appointments.

Key findings:

- Clinic attendance, including regular follow-up appointments and prescription refills, has increased from 13 to 100 residents in only one rural area in the first three months of the intervention.

BOX 5. A PILOT STUDY OF FOOD SUPPLEMENTATION TO IMPROVE ART ADHERENCE IN LUSAKA, ZAMBIA (Cantrell et al. 2008)

Background: A home-based adherence support program at eight government clinics assessed patients for food insecurity. Four clinics provided food supplementation, and four clinics acted as controls.

Key findings: Over 70% of patients in the food group achieved a medication possession ratio (days supply of medication divided by the days between refills) of 95% or greater versus 48% among controls. This finding was unchanged after adjustment for sex, age, baseline CD4 count, baseline WHO stage, and baseline hemoglobin.

improving access to food, shelter, clean water, sanitation, education, and economic opportunities may help to improve adherence. Because ARV drugs are most effective when taken by people who are adequately nourished (Tang et al. 2002), food support can play an important role in ensuring that PLWH receive the full benefits of treatment (Box 5).

Community-based Outreach and Education

Engaging with individuals and communities effectively around ART can improve health outcomes, contribute to greater understanding of adherence benefits, lead to a stronger belief in the effectiveness of ART, and reduce stigma in the community (Box 6). Some community-based strategies to encourage adherence to treatment include participating in support groups, developing links with community-based organizations to support adherence, encouraging links with support groups, and creating links with patient advocates (FHI 2009; Zachariah et al. 2006).

Strategies to Enhance Retention in Care

As one might expect, many of the approaches to promote adherence to treatment also apply to enhancing retention. This is particularly true for interventions aimed at access, such as mobile care and treatment (see Box 4), social support, and education. Medication adherence counseling sessions and patient–provider interactions should emphasize the importance of attending scheduled follow-up appointments for ongoing monitoring of disease progress, adverse side effects of medication, as well as OIs and other severe illnesses that may occur and interfere with HIV treatment progress.

BOX 6. HIV AWARENESS CAMPAIGNS BY THE ENTEBBE WOMEN ASSOCIATION (EWA) IN GULU, UGANDA

Background: With the help of the World Association of Christian Communication, EWA carried out HIV sensitization sessions designed to increase HIV awareness by highlighting issues surrounding stigma, the care and support of PLWH, and the community's role in HIV prevention.

Interventions:

- Drama and music sessions highlighting issues surrounding stigmatization and support of PLWH.
- Training and advocacy for PLWH in positive living, positive prevention, and drug adherence.
- Radio programs focusing on reducing stigma and increasing care and support of PLWH.

Key findings: Post-intervention, EWA found an increase in the number of referral cases for integrated HIV support through advocacy and an increase in testing and disclosure rates. In addition, requests for additional information through radio calls and letters were also observed.

BOX 7. REDUCING LTFU BY INTEGRATING CLINICAL DATA MANAGEMENT IN COMMUNITY SUPPORT SYSTEMS, RWANDA (Umuhoza, Moen and Byicaza 2009)

Background: In ART clinics in rural Rwanda implementing the AIDSRelief model of care, data teams alerted clinicians to a high number of missed ART appointments. Actions to reduce LTFU (missed appointments >90 days) across 10 ART sites were monitored over a seven-month period.

Intervention:

- Data teams developed electronic data systems to generate a missing patient list based on clinic data.
- Community teams consisting of a coordinator, social workers, and community volunteers were assigned to each patient.
- Teams located the patients, determined the reasons for the missed appointments, and coordinated with clinicians and data teams to facilitate patient re-entry into care.

Key findings:

Integrated clinical data management and community-based support activities resulted in an impressive reduction in missed appointments. While a large number of patients were incorrectly documented as missing due to data entry errors, 88% of those patients that were defined as LTFU were re-enrolled in care.

As the association between poor clinical outcomes and LTFU becomes stronger, other interventions are needed to both monitor and promote retention in care for both pre-ART and ART patients. This includes reliable tracing and tracking systems through improved integration of clinical data management, such as data flow, entry, patient appointment, and transfer systems, with community-based outreach activities to improve retention rates (Box 7; Umuhoza, Moen, and Byicaza 2009).

While having a reliable system to reverse LTFU is critical for keeping patients in care long-term, recent data from Cotê d'Ivoire found that interventions that prevent LTFU would substantially improve survival and be cost-effective by international criteria even with modest to moderate efficacy (Losina et al. 2009). With an estimated 11,000 patient-years of lost life due to poor retention rates, the study found that removing user co-payment from the cost of ARV drugs, an intervention estimated to cost $22 per patient per year, would only have to result in a 12 percent improvement in LTFU in order to be considered cost-effective (Losina

et al. 2009). These data highlight the importance of LTFU prevention strategies.

With increased access to technology in resource-limited settings, the use of electronic reminders is becoming an increasingly popular tool to avoid missed appointments for both pre-ART and ART patients (Box 8). For example, the use of fortnightly telephone calls from the health care provider to patients in Cameroon resulted in significant outcome improvement and fewer patients LTFU. Patients reported that provider-initiated calls served as a motivator for adhering to treatment because it showed interest and support (Muko, Chingang, and Yenwong 2009).

BOX 8. TXTALERT PILOT IN THEMBA LETHU CLINIC, JOHANNESBURG, SOUTH AFRICA (Neethling et al. 2009)

Background: TxtAlert is a mobile technology tool developed to improve clinic attendance. The system aims to reduce rates of LTFU by sending patients SMS alerts for future clinic appointments and offering a free "Please Call Me" mechanism to reschedule missed appointments. A dynamic dashboard allows administrators to flag patients who frequently miss scheduled appointments.

Key findings:

- Scheduled appointment attendance increased as did the voluntary opt-in rate for TxtAlert.
- Proportion of individuals attending the clinic within a week after their scheduled date increased from 87 to 96% during a three-month period.
- Average of 52% of all "Please Call Me" messages received by the TxtAlert administrator led to the successful rescheduling of patient appointments.
- Steady increase of patients who used the "Please Call Me" mechanism to reschedule their appointments.

OTHER PROGRAM CONSIDERATIONS AND CHALLENGES

Enhancing Adherence to Treatment and Retention in Care for Postpartum Women

A number of studies suggest that women are less likely to adhere to medication and be retained in care postpartum than when pregnant in both Western and resource-limited settings (Mellins et al. 2008; Park, Tochuku, and Grigoriu 2007; Van Cutsem et al. 2009; Zorrilla et al. 2003). Poor adherence during the postpartum period can impact the health of the mother and increase the risk of mother-to-child transmission during breast feeding. Recently updated WHO guidelines highlight the increasing importance of adherence support during the postpartum and breastfeeding periods. ART initiation is recommended for pregnant women who are in need of treatment irrespective of gestational age. Medically eligible women should continue treatment throughout delivery and thereafter both for maternal health and for prevention of mother-to-child transmission (PTMCT). The use of triple drug regimens as prophylaxis for PMTCT during breastfeeding has been found to be effective in women who are not yet eligible for ART, an option reflected in the updated guidelines (WHO 2009a).

The implementation of these guidelines in the postpartum period may prove challenging. A complex set of factors are presumed to affect adherence among postpartum women with HIV; however, few targeted studies to identify specific barriers have been performed. A preliminary study in Soweto, South Africa, identified several barriers to both ART and visit adherence in the postpartum year, including tension in relationship with main partner over his HIV testing and treatment, intimate partner violence, lack of economic and social support, non-disclosure in household, lack of transportation, food insecurity, alcohol abuse,

postpartum depression, and competing family needs. Key motivators of adherence included disclosure and support from another person, economic support from partner, peer support groups, and the desire to "live to see my children grow" (Sayles et al. 2009).

The consequences of non-adherence in this group may be treatment failure for the women and increased risk of mother-to-child transmission; therefore, appropriate and effective adherence interventions must be targeted toward this population. This need will continue to grow as more women with HIV on treatment choose to have children and the use of more efficacious PMTCT regimens, including triple drug regimens as prophylaxis for PMTCT, expands.

Cost and Mobilization of Resources

Costing programs and mobilizing adequate financial resources to ensure high adherence can be a challenge, especially in resource-limited settings. A multitude of structural barriers that prevent access to health care and a regular supply of ARV drugs must be addressed by the health care facility. For example, in one comprehensive model to promote higher adherence to treatment and retention in care in Haiti, the cost of monitoring and adherence promoting interventions is roughly US$186 per person per year (Mukherjee et al. 2006). This package of services includes waived user fees for clinic attendance for all patients with HIV; free HIV testing that has been integrated into the provision of primary care services in addition to voluntary HIV counseling and testing; free medications and monitoring tests; and reimbursement for transportation costs for follow-up appointments. Patients are also provided home-based adherence support, including psychosocial support and DOT, from a community health worker. A recent study in Cotê d'Ivoire examining the cost-effectiveness of patient retention strategies reported that the combination of eliminating ART co-payments, providing free OI-related medications, increased training for health care workers, and reimbursing for transportation and breakfast costs a total of US$77 per person per year, with individual interventions ranging from US$12 to US$24 per person per year (Losina et al. 2009). When implemented effectively, strategies to promote adherence to treatment and retention in care will yield a return by delaying the need for second-line HIV therapies (costing about US$1500 per patient per year) and reducing the likelihood hospitalization (Mukherjee et al. 2006).

Human Resource Needs

As noted above, many public facilities in resource-limited settings scaled up ART without a parallel increase in personnel to accommodate the larger number of patients (Barnighausen et al. 2007; Van Damme Kober, and Kegels 2008). To deal with health worker shortages and to ensure training and support of adequate human resources to support patient retention and adherence to treatment, many programs have begun to employ task shifting, or the practice of delegating adherence tasks from more specialized clinicians to less specialized lay workers, such as community volunteers. Currently, a wide variety of community health workers are active in many ARV treatment delivery sites (see Boxes 2 and 3; Farmer et al. 2001a, 2001b; Samb et al. 2007; Torpey et al. 2008).

Unanswered Questions

A significant gap remains between what is known about the barriers to adherence to treatment and retention for PLWH and what is being currently done to address these barriers. A number of questions remain including the following:

1. What are the long-term challenges and efficacy of current and future adherence promoting interventions?
2. How can these strategies be replicated and adapted to improve adherence in diverse environments, such as conflict settings?
3. What other potential barriers to adherence exist?
4. How cost-effective are different types of adherence-promoting strategies?

Due to the complex and dynamic nature of lifelong adherence to medication and retention in care for PLWH, health care providers must have the time, motivation, and skills to not only recognize barriers of adherence through ongoing monitoring, but must also implement tailored interventions to effectively lower these barriers, ensuring treatment success.

RESOURCES

The following resources (with hyperlinks) provide up-to-date information, guidelines, tools, and recommendations for addressing adherence to HIV medication and retention in care.

1. WHO. 2003. *Adherence to Long-term Therapies: Evidence for Action*. Geneva: World Health Organization. Available at **http://whqlibdoc.who.int/publications/2003/9241545992.pdf**
2. Panel of Antiretroviral Guidelines for Adults and Adolescents. November 2008. *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents*. Washington, DC: Department of Health and Human Services. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf**
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8. USAID. 2007. *Adherence to ART Practices in Resource-Constrained Settings, USAID*. Available at **http://pdf.usaid.gov/pdf_docs/PNADJ116.pdf**
9. Family Health International. 2007. *Adherence Support Workers Training Material Facilitators Guide*. Available at **http://www.fhi.org/NR/rdonlyres/ez7jwe4qdytdhkweuuwiueiepgdwwsu4cgwy6zob3qesx4btbexzmuk5la5u5vrfxya6pzbi2jzdvp/ASWFacilitatorsGuideHVenhv.pdf**

   Participants Guide. Available at **http://www.fhi.org/NR/rdonlyres/e3bilmw3oojh344u2z7idbpkkmy7gwovn5boc3umepp626olklihg3pqvbivaiwkrfrs454utyiz6b/ASWParticipantsGuideHVenhv.pdf**
10. International Training and Education Center on HIV. *ART and HIV*. Available at **http://www.searchitech.org/pdf/p06-db/db-50918.pdf**

    This illustrated brochure may be used by doctors to counsel patients with low literacy about ART. It answers basic questions about the uses and possible side effects of ART.
11. WHO. 2006. *Chronic Care with ARV Therapy, 3 by 5 Initiative*. Geneva: World Health Organization. Available at **http://www.who.int/entity/3by5/capacity/chronic_care_3_may_06.pdf**
12. Horizons/Population Council International Centre for Reproductive Health Coast Province General Hospital, Mombasa. 2007. *Adherence to Antiretroviral Therapy in Adults: A Guide for Trainers, Horizons/Population Council*. Available at **http://www.pop council.org/pdfs/horizons/arvadhrnctrngguide.pdf**

13. IeDEA. *International Epidemiological Database to Evaluate AIDS (IeDEA)*. Available at **http://www.iedea-hiv.org**

14. WHO. 2005. *Handouts for the WHO Basic ART Aid Training Course*. Available at **http://www.wpro.who.int/NR/rdonlyres/9365248D-9393-4446-B619-20DE731A4780/0/Handouts_WHO_Basic_ART_Aid_Training_Course.pdf**

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APPENDIX: SELF-REPORT ADHERENCE MONITORING TOOLS

ACTG Adherence Baseline Questionnaire

Date: _____ Self Interviewer Both

Patient ID: _____ How Administered? ☐ 1 ☐ 2 ☐ 3

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficult schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your study nurse to help. Thank you for helping in this important study.

INSTRUCTIONS: Please answer the following questions by placing a circle around the appropriate number response.

A. How sure are you that:

Please circle one response for each question.

		Not at All Sure	Somewhat Sure	Very Sure	Extremely Sure
1.	You will be able to take all or most of the study medication as directed?	0	1	2	3
2.	The medication will have a positive effect on your health?	0	1	2	3
3.	If you do not take this medication exactly as instructed, the HIV in your body will become resistant to HIV medications?	0	1	2	3

B. The following questions ask about your social support.

Please circle one response for each question.

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
1.	In general, how satisfied are you with the overall support you get from your friends and family members?	0	1	2	3

		Not At All	A Little	Somewhat	A Lot	Not Applicable
2.	To what extent do your friends or family members help you remember to take your medication?	0	1	2	3	4

C. People may miss taking their medications for various reasons. Here is a list of possible reasons why you may have missed taking any medications within the **past month**.

If you have **NOT** taken **any** medications within the **past month**, please check this box and skip to Section D. ☐ 1

In the past month, how often have you missed taking your medications because you:

Please circle one response for each question.

	Never	Rarely	Sometimes	Often
1. Were away from home?	0	1	2	3
2. Were busy with other things?	0	1	2	3
3. Simply forgot?	0	1	2	3
4. Had too many pills to take?	0	1	2	3
5. Wanted to avoid side effects?	0	1	2	3
6. Did not want others to notice you taking medication?	0	1	2	3
7. Had a change in daily routine?	0	1	2	3
8. Felt like the drug was toxic/harmful?	0	1	2	3
9. Fell asleep/slept through dose time?	0	1	2	3
10. Felt sick or ill?	0	1	2	3
11. Felt depressed/overwhelmed?	0	1	2	3
12. Had problem taking pills at specified times (with meals, on empty stomach, etc.)?	0	1	2	3
13. Ran out of pills?	0	1	2	3
14. Felt good?	0	1	2	3

D. When was the last time you missed taking any of your medications? Check one box.

☐ 5 Within the past **week**

☐ 4 1-2 **weeks** ago

☐ 3 2-4 **weeks** ago

☐ 2 1-3 **months** ago

☐ 1 More than 3 **months** ago

☐ 0 **Never** skip medications or **not applicable**

E. In the <u>past week</u> how often did you:

Please circle one response for each question.

		Never/ Rarely	Sometimes	Often	Mostly or Always
1.	Feel like you couldn't shake off the blues even with help from your family or friends?	0	1	2	3
2.	Have trouble keeping your mind on what you were doing?	0	1	2	3
3.	Feel that everything you did was an effort?	0	1	2	3
4.	Have trouble sleeping?	0	1	2	3
5.	Feel lonely?	0	1	2	3
6.	Feel sad?	0	1	2	3
7.	Feel like you just couldn't "get going"?	0	1	2	3

F. In the <u>past month</u>, how often have you:

Please circle one response for each question.

		Never	Almost Never	Sometimes	Fairly Often	Very Often
1.	Been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	Felt unable to control the important things in in your life?	0	1	2	3	4
3.	Felt nervous and “stressed”?	0	1	2	3	4
4.	Felt confident in your ability to handle your personal problems?	0	1	2	3	4
5.	Felt that things were going your way?	0	1	2	3	4
6.	Found that you could not cope with all the things that you had to do?	0	1	2	3	4
7.	Been able to control irritations in your life?	0	1	2	3	4
8.	Felt that you were on top of things?	0	1	2	3	4
9.	Been angered because of things that happened that were outside of your control?	0	1	2	3	4
10.	Felt problems were piling up so high that you could not overcome them?	0	1	2	3	4

G. People have various health habits. The following questions ask about your alcohol and drug use, past and current.

1. How often have you had a drink containing alcohol – a glass of beer, wine, a mixed drink, or any kind of alcoholic beverage – in the last 30 days? Check one.

Daily	Nearly Every Day	3 or 4 Times A Week	Once or Twice A Week	2 or 3 Times A Month	Once A Month	Never
☐ 6	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

⇩

*If **Never**, skip ahead to question **#4**.*

2. On days when you drank any alcoholic beverages in the last 30 days, how many drinks did you usually have altogether? By a drink we mean a can or glass of beer, a 4-ounce glass of wine, a 1-1/2 ounce shot of liquor, or a mixed drink with 1-1/2 ounces of liquor? Check one.

1 or 2 Drinks Per Day	3 or 4 Drinks Per Day	5 or 6 Drinks Per Day	7 or 8 Drinks Per Day	9 - 11 Drinks Per Day	12 or more Drinks Per Day
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the past 30 days, how often have you had 5 or more drinks of alcohol in a row, that is, within a couple of hours (e.g. 2-4 hours)? Check one.

Daily	Nearly Every Day	3 or 4 Times A Week	Once or Twice A Week	2 or 3 Times A Month	Once A Month	Never
☐ 6	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

4. Please check "Yes" or "No" for each question.

a. ☐ 1 Yes ☐ 2 No **Have you ever used marijuana?**
If you used this drug, have you used it within the past 6 months?
☐ 1 Yes ☐ 2 No

b. ☐ 1 Yes ☐ 2 No **Have you ever used cocaine (powder, crack, or freebase)?**
If you used this drug, have you used it within the past 6 months?
☐ 1 Yes ☐ 2 No

c. ☐ 1 Yes ☐ 2 No **Have you ever used heroin?**
If you used this drug, have you used it within the past 6 months?
☐ 1 Yes ☐ 2 No

d. ☐ 1 Yes ☐ 2 No **Have you ever used amphetamines (speed)?**
If you used this drug, have you used it within the past 6 months?
☐ 1 Yes ☐ 2 No

5. **Are you <u>currently</u> in methadone treatment?** ☐ 1 Yes ☐ 2 No
If Yes, skip to Question H.

If No, have you <u>ever</u> been in methadone treatment? ☐ 1 Yes ☐ 2 No

H. These last questions ask about your background.

1. What is the highest level of education you have completed? (check one)

☐ 0 11th grade or less

☐ 1 High school graduate or GED

☐ 2 2 years of college / AA degree / Technical school training

☐ 3 College graduate (BA or BS)

☐ 4 Master's degree

☐ 5 Doctorate / medical degree / law degree

2. What is (are) the most likely way(s) that you became infected with HIV? (check "Yes" or "No" for <u>each</u> question.)

a. Sex with a man who was HIV+

☐ 1 Yes ☐ 2 No

b. Sex with a woman who was HIV+

☐ 1 Yes ☐ 2 No

c. Shared needles with a person who was HIV+

☐ 1 Yes ☐ 2 No

d. Blood transfusion or other medical procedure

☐ 1 Yes ☐ 2 No

e. Don't know

☐ 1 Yes ☐ 2 No

f. Other (needle stick at work, etc.)

☐ 1 Yes ☐ 2 No

Please specify: _____

3. Do you work for pay outside the home? ☐ 1 Yes ☐ 2 No

4. Do you have any children? ☐ 1 Yes ☐ 2 No

If <u>Yes</u>, how many live with you? ☐☐

I. The following questions ask about symptoms you might have had during the past four weeks. Please check the box that describes how much you have been bothered by each symptom.

		I DO NOT HAVE THIS SYMPTOM	I HAVE THIS SYMPTOM AND …			
			It doesn't bother me	It bothers me a little	It bothers me a lot	It bothers me terribly
1.	Fatigue or loss of energy?	0	1	2	3	4
2.	Fevers, chills or sweats?	0	1	2	3	4
3.	Feeling dizzy or lightheaded?	0	1	2	3	4
4.	Pain, numbness or tingling in the hands or feet?	0	1	2	3	4
5.	Trouble remembering?	0	1	2	3	4
6.	Nausea or vomiting?	0	1	2	3	4
7.	Diarrhea or loose bowel movements?	0	1	2	3	4
8.	Felt sad, down or depressed?	0	1	2	3	4
9.	Felt nervous or anxious	0	1	2	3	4
10.	Difficulty falling or staying asleep?	0	1	2	3	4
11.	Skin problems, such as rash, dryness or itching?	0	1	2	3	4
12.	Cough or trouble catching your breath?	0	1	2	3	4
13.	Headache?	0	1	2	3	4
14.	Loss of appetite or a change in the taste of food?	0	1	2	3	4

15.	Bloating, pain or gas in your stomach?	0	1	2	3	4
16.	Muscle aches or joint pain?	0	1	2	3	4
17.	Problems with having sex, such as loss of interest or lack of satisfaction?	0	1	2	3	4
18.	Changes in the way your body looks, such as fat deposits or weight gain?	0	1	2	3	4
19.	Problems with weight loss or wasting?	0	1	2	3	4
20.	Hair loss or changes in the way your hair looks?	0	1	2	3	4

Thank you very much for completing these questions.
The information that you provided will help with the development of better drug regimens for all patients with HIV.

PLEASE NOTE: Section "I" on this questionnaire was developed by Amy Justice and Linda Rabaneck. To cite this 20-item symptom index, please contact Dr. Amy Justice at Amy.Justice@med.va.gov.

ACTG Adherence Follow Up Questionnaire

Date _____ Self Interviewer Both

Patient ID _____ How Administered? ☐ 1 ☐ 2 ☐ 3

THIS PAGE IS TO BE COMPLETED BY THE PATIENT AND STUDY PERSONNEL TOGETHER.

A. You are currently taking the following drugs at the frequency and doses listed.

Study Drug Name/Dose	# Pills Each Time (Pills Each Dose)	# Times Per Day (Doses Per Day)

INSTRUCTIONS: Complete this worksheet with the patient.

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficult schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your study nurse to help. Thank you for helping in this important study.

PATIENT ONLY continue here.
The next section of the questionnaire asks about your HIV study medications that you took over the last four days.

Most people with HIV have many pills to take at different times during the day.
Many people find it hard to always remember their pills:

- Some people get busy and forget to carry their pills with them.
- Some people find it hard to take their pills according to all the instructions, such as "with meals," or "on an empty stomach," "every 8 hours," "with plenty of fluids."
- Some people decide to skip doses to avoid side effects or to just not be taking pills that day.

We need to understand how people with HIV are really doing with their pills. Please tell us what you are **actually** doing. Don't worry about telling us that you don't take all your pills. We need to know what is really happening, not what you think we "want to hear."

1. **The next section of the questionnaire asks about the study medications that you may have missed taking over the last four days. Please complete the following table by filling in the boxes below.**

IF YOU TOOK ONLY A PORTION OF A DOSE ON ONE OR MORE OF THESE DAYS, PLEASE REPORT THE DOSE(S) AS BEING MISSED.

Step 1 Names of your anti-HIV study drugs	HOW MANY DOSES DID YOU **MISS** . . .			
	Step 2 Yesterday	**Step 3** Day before yesterday (2 days ago)	**Step 4** 3 days ago	**Step 5** 4 days ago
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses

The following questions pertain to the study regimen on page 2.

If you took only a portion of a dose on one or more of these days, please report the dose(s) as being missed.

B. During the past 4 days, on how many days have you missed taking all your doses?

- ☐ None
- ☐ One day
- ☐ Two days
- ☐ Three days
- ☐ Four days

C. Most anti-HIV medications need to be taken on a schedule, such as "2 times a day" or "3 times a day" or "every 8 hours." How closely did you follow your specific schedule over the last four days?

Never	Some Of The Time	About Half Of The Time	Most Of The Time	All Of The Time
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

D. Do any of your anti-HIV medications have special instructions, such as "take with food" or "on an empty stomach" or "with plenty of fluids?"

☐ 1 Yes ☐ 2 No

If Yes, how often did you follow those special instructions over the last **four** days?

Never	Some Of The Time	About Half Of The Time	Most Of The Time	All Of The Time
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

E. Some people find that they forget to take their pills on the weekend days. Did you miss any of your anti-HIV medications last weekend—last Saturday or Sunday?

☐ 1 Yes ☐ 2 No

F. When was the last time you missed any of your medications? Check one.

- ☐ 5 Within the past **week**
- ☐ 4 1-2 **weeks** ago
- ☐ 3 2-4 **weeks** ago
- ☐ 2 1-3 **months** ago
- ☐ 1 More than 3 **months** ago
- ☐ 0 **Never** skip medications or **not applicable**

*If you **Never** skip medications, please go to **Section H** on page 5.*
Otherwise, please continue by answering the next set of questions.

G. People may miss taking their medications for various reasons. Here is a list of possible reasons why you may miss taking your medications. How often have you missed taking your medications because you: (Circle one response for each question.)

	Never	Rarely	Sometimes	Often
1. Were away from home?	0	1	2	3
2. Were busy with other things?	0	1	2	3
3. Simply forgot?	0	1	2	3
4. Had too many pills to take?	0	1	2	3
5. Wanted to avoid side effects?	0	1	2	3
6. Did not want others to notice you taking medication?	0	1	2	3
7. Had a change in daily routine?	0	1	2	3
8. Felt like the drug was toxic/harmful?	0	1	2	3
9. Fell asleep/slept through dose time?	0	1	2	3
10. Felt sick or ill?	0	1	2	3
11. Felt depressed/overwhelmed?	0	1	2	3
12. Had problems taking pills at specified times (with meals, on empty stomach, etc.)?	0	1	2	3
13. Ran out of pills?	0	1	2	3
14. Felt good?	0	1	2	3

H. The following questions ask about symptoms you might have had during the past four weeks. Please check the box that describes how much you have been bothered by each symptom.

		I DO NOT HAVE THIS SYMPTOM	I HAVE THIS SYMPTOM AND …			
			It doesn't bother me	It bothers me a little	It bothers me a lot	It bothers me terribly
1.	Fatigue or loss of energy?	0	1	2	3	4
2.	Fevers, chills or sweats?	0	1	2	3	4
3.	Feeling dizzy or lightheaded?	0	1	2	3	4
4.	Pain, numbness or tingling in the hands or feet?	0	1	2	3	4
5.	Trouble remembering?	0	1	2	3	4
6.	Nausea or vomiting?	0	1	2	3	4
7.	Diarrhea or loose bowel movements?	0	1	2	3	4
8.	Felt sad, down or depressed?	0	1	2	3	4
9.	Felt nervous or anxious	0	1	2	3	4
10.	Difficulty falling or staying asleep?	0	1	2	3	4
11.	Skin problems, such as rash, dryness or itching?	0	1	2	3	4
12.	Cough or trouble catching your breath?	0	1	2	3	4
13.	Headache?	0	1	2	3	4
14.	Loss of appetite or a change in the taste of food?	0	1	2	3	4

15.	Bloating, pain or gas in your stomach?	0	1	2	3	4
16.	Muscle aches or joint pain?	0	1	2	3	4
17.	Problems with having sex, such as loss of interest or lack of satisfaction?	0	1	2	3	4
18.	Changes in the way your body looks, such as fat deposits or weight gain?	0	1	2	3	4
19.	Problems with weight loss or wasting?	0	1	2	3	4
20.	Hair loss or changes in the way your hair looks?	0	1	2	3	4

Thank you very much for completing these questions.
The information that you provided will help with the development of better drug regimens for all patients with HIV.

PLEASE NOTE: Section "H" on this questionnaire was developed by Amy Justice and Linda Rabaneck. To cite this 20-item symptom index, please contact Dr. Amy Justice at Amy.Justice@med.va.gov.

Case Adherence Index questionnaire

Please ask each question and circle the corresponding number next to the answer, then add up the numbers circled to calculate Index score.

A1. How often do you feel that you have difficulty taking your HIV medications on time? By 'on time' we mean no more than two hours before or two hours after the time your doctor told you to take it.

4 Never

3 Rarely

2 Most of the time

1 All of the time

A2. On average, how many days per week would you say that you missed at least one dose of your HIV medications?

1 Everyday

2 4–6 days/week

3 2–3 days/week

4 Once a week

5 Less than once a week

6 Never

7

A3. When was the last time you missed at least one dose of you HIV medications?

1 Within the past week

2 1–2 weeks ago

3 3–4 weeks ago

4 Between 1 and 3 months ago

5 More than 3 months ago

6 Never

INDEX SCORE: _____

>10 = good adherence

≤10 = poor adherence

Mannheimer, S., et al. 2006. "The CASE adherence index: A novel method for measuring adherence to antiretroviral therapy." AIDS Care 18(7):853-61.

Visual Analogue Scale Used in a Research Study

Now I'm going to ask some questions about your HIV medications.

Most people with HIV have many pills or other medications to take at different times during the day. Many people find it hard to always remember their pills or medicines. For example:

- Some people get busy and forget to carry their pills with them.
- Some people find it hard to take their pills according to all the instructions, such as "with food" or "on an empty stomach," "every 8 hours," or "with plenty of fluids."
- Some people decide to skip pills to avoid side effects or to just not take pills that day.

We need to understand what people with HIV are really doing with their pills or medicines. Please tell us what you are actually doing. Don't worry about telling us you don't take all your pills or medicines. We need to know what is really happening, not what you think we "want to hear."

Which antiviral medications have you been prescribed to take within the last 30 days?

INTERVIEWER: LIST CODES FOR ALL ANTIVIRALS THAT SUBJECT WAS PRESCRIBED TO TAKE IN LAST 30 DAYS--IDENTIFY UP TO 4 DRUGS

DRUG A		DRUG B	
DRUG C		DRUG D	

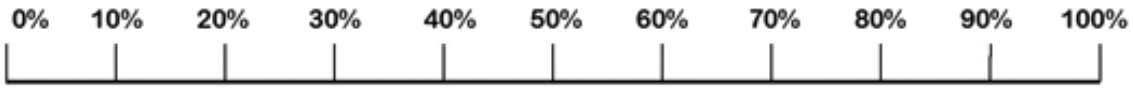
Now I am going to ask you some questions about these drugs. Please put an "X" on the line below at the point showing your best guess about how much **(DRUGS A-D)** you have taken in the last three to four weeks. We would be surprised if this was 100% for most people.

HAND INSTRUMENT AND PEN TO RESPONDENT

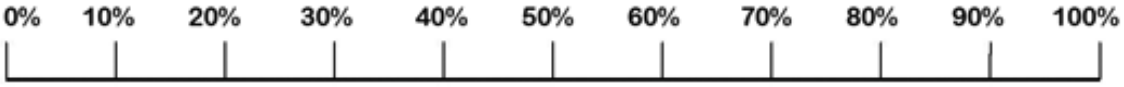
e.g. **0%** means you have **taken no (DRUG A)**
50% means you have **taken half your (DRUG A)**
100% means you have **taken every single dose of (DRUG A)**

Machtinger EL, Bansberg DR. *Adherence to HIV Antiretroviral Therapy* . HIV InSite, May 2005. Available online at http://hivinsite.ucsf.edu/InSite?page=kb-03-02-09. Accessed October 28, 2009.

A1. (DRUG A)



B1. How About (DRUG B) ?



C1. How About (DRUG C) ?

D1. How About (DRUG D) ?

Machtinger EL, Bansberg DR. *Adherence to HIV Antiretroviral Therapy* . HIV InSite, May 2005. Available online at http://hivinsite.ucsf.edu/InSite?page=kb-03-02-09. Accessed October 28, 2009.