

Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings

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Abstract: The rollout of antiretroviral therapy (ART) significantly reduced human immunodeficiency virus (HIV)-related morbidity and mortality, but good clinical outcomes depend on access and adherence to treatment. In resource-limited settings, where over 90% of the world's HIV-infected population resides, data on barriers to treatment are emerging that contribute to low rates of uptake in HIV testing, linkage to and retention in HIV care systems, and suboptimal adherence rates to therapy. A review of the literature reveals limited evidence to inform strategies to improve access and adherence with the majority of studies from sub-Saharan Africa. Data from observational studies and randomized controlled trials support home-based, mobile and antenatal care HIV testing, task-shifting from doctor-based to nurse-based and lower level provider care, and adherence support through education, counseling and mobile phone messaging services. Strategies with more limited evidence include targeted HIV testing for couples and family members of ART patients, decentralization of HIV care, including through home- and community-based ART programs, and adherence promotion through peer health workers, treatment supporters, and directly observed therapy. There is little evidence for improving access and adherence among vulnerable groups such as women, children and adolescents, and other high-risk populations and for addressing major barriers. Overall, studies are few in number and suffer from methodological issues. Recommendations for further research include health information technology, social-level factors like HIV stigma, and new research directions in cost-effectiveness, operations, and implementation. Findings from this review make a compelling case for more data to guide strategies to improve access and adherence to treatment in resource-limited settings.

Keywords: HIV, antiretroviral therapy, access, adherence, resource-limited settings

Introduction

In 2010, the World Health Organization (WHO) estimated there were 34 million people living with the human immunodeficiency virus (HIV).¹ The emergence of antiretroviral therapy (ART) transformed HIV from a terminal illness to a chronic disease and resulted in significant decreases in HIV-related morbidity and mortality;^{2,3} however, good clinical outcomes depend on access and adherence to treatment. In low- and middle-income countries (LMIC), home to over 90% of the HIV-infected population, access to ART has dramatically expanded in the last decade, yet it is estimated that only 47% of adults and 23% of children who are eligible are accessing treatment.¹ Recent studies suggest adults and children in resource-limited settings maintain or achieve better rates of adherence compared to those in resource-rich settings,⁴⁻⁶ but suboptimal adherence remains a threat for opportunistic infections,⁷ HIV disease progression,⁸⁻¹⁰

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and viral resistance to ART.^{11–13} Evidence-based strategies to improve access and adherence in LMIC are critically needed. This paper reviews the current scientific literature on strategies to improve access and adherence to ART in LMIC. Important gaps in the literature are highlighted and future directions for research are proposed.

Access to ART requires successful passage through various stages of care, including diagnosis, linkage, disease-stage monitoring, and finally initiation of treatment. Following treatment initiation, good clinical outcomes require retention in care and high rates of adherence to therapy.¹⁴ A number of quantitative and qualitative studies reveal a myriad of barriers at all stages of access and adherence. While some barriers exist across settings, others act more frequently in resource-limited settings. Reviews of barriers to access and adherence often conceptualize and organize barriers according to levels of action^{15–17} consistent with a social–ecological framework

discussed elsewhere.^{18,19} Table 1 summarizes commonly cited barriers to access and adherence in LMIC at the levels of intrapersonal, interpersonal/social, and system. Barriers more common to those living in resource-limited settings may include lack of knowledge of HIV status and treatment options, fear of stigma and discrimination, and system-level barriers, sometimes referred to as structural barriers,²⁰ that constrain individual and community-level efficacy to access and adhere to treatment through poor health care infrastructure and resources. Factors such as entrenched poverty and inequality operate at all levels and may especially affect treatment opportunities for women and children. Improving access and adherence to ART will require interventions that address barriers at each level of action while also considering how these barriers operate at the multiple stages of treatment, across different contexts, and among diverse populations.

Table 1 Barriers to access and adherence to antiretroviral therapy in low- and middle-income countries

Level of action	Barriers
Intrapersonal	Knowledge of serostatus and treatment options ^{200–204,**} Difficulty understanding/managing treatment, ^{108,116,117,120,205–207,**} complicated regimens, ^{116,207–213} ART side effects ^{117,208–210,212–218} Simply forgetting to come to clinic or take medicines, ^{205,207,208,213–215,219} falling asleep ^{210,214,219} Emotional distress (eg, depression), ^{108,214,217,220} substance addiction ^{205,213,221,222} Perceptions of health, ^{206,213,214,223,224} treatment, ^{205,217,225,226} and alternative/traditional medicines ^{227–229} Available financial resources, ^{230,231,*} food insecurity ^{232–234}
Interpersonal/ social	Lack of family or social support, ^{180,235,236} dependency on partners for financial resources ^{201,237,*} or permission for treatment ^{106,*} Household conflict, ^{108,116,216,**} Low parental education level ^{117,**} Fear of violence and/or abandonment ^{202,238,*} Lack of disclosure of own* or child's status ^{108,120,207,211–214,216,217,220,239,240,**} Negative perception of providers ^{206,241} and poor patient–provider communication ^{242,243} Lack of community involvement in ART programs ^{16,201} Stigma and discrimination ^{108,207,216,220,239,*}
System	Costs of care and treatment, ^{205,208,213,215,244,245} distance to clinic ^{205,212,213,219,246–251} Lack of integration/coordination with other health services ^{252,253} Drug shortages and stock-outs ^{218,254,255} Long waiting times at clinics ^{229,234,256} Inadequate laboratory infrastructure/resources ²⁵⁷ Confidentiality of services ²⁵⁸

Notes: *Significant barrier for women; **significant barrier for children and adolescents.

Evidence-based strategies

A review of the literature reveals limited empirical data to guide strategies to improve access and adherence to ART (Table 2). Few randomized, controlled trials (RCTs), widely considered the gold standard in scientific rigor and methodology,^{21,22} evaluate interventions in LMIC and strategies often rely on small case and observational studies. The most compelling data from well-designed observational studies and RCTs conducted in LMIC are reviewed here according to three stages of treatment: HIV testing and diagnosis; linkage to and retention in care; and adherence to ART.

HIV testing and diagnosis

As availability of ART in resource-limited settings expands, voluntary counseling and testing (VCT) services act as critical gateways to testing, early diagnosis and treatment.²³ Despite massive scale-ups in national HIV testing programs,^{24,25} studies suggest that up to 80% of HIV-infected adults do not know their status in some sub-Saharan African settings,^{26,27} although rates of testing vary substantially by country. A national survey in Lesotho found that the percentage of women who had been tested for HIV in the past 12 months had increased from 6.3% in 2004 to 42% in 2009, while a similar national survey in the Congo only showed rates of testing increasing from 3.2% in 2004 to 6.5% in 2009.¹

Low uptake in testing and barriers to accessing traditional, client-initiated VCT services have led to new approaches in HIV testing, including provider-initiated, home-based and mobile or community testing.²⁸ Routine “opt-out” testing by providers, which is now recommended by the WHO as part of standard medical care in certain settings,²⁹ is reported to

Table 2 Evidence base for strategies to improve access and adherence in LMIC

Level of support	Stage of care		
	Testing and diagnosis	Linkage to and retention in care	Adherence
Limited or weak evidence	Provider-initiated testing ^{30,259} Targeted HIV testing: Inpatient testing ^{40,*} Couples' testing ^{46–48,*} Workplace testing ^{44,*} Testing of family members of ART patients ^{45,*} Mass-media campaigns ¹⁹⁰ School-based HIV educational programs ^{128,*}	Referral programs (referral forms, transport stipends, patient navigators); ⁵⁷ patient navigators ⁵⁸ Point-of-care CD4 testing; ^{60–62,64} pre-ART prophylaxis ²⁶⁰ Free services; ²⁶¹ cash transfers for transportation to clinic; ^{77,*} food-assistance programs ²⁶² Home-based ART program; ^{80,*} community group-based ART program ¹⁸² Patient-centered care (ex-child-friendly clinics, ¹²⁹ family-based care ^{263,264}) Health information systems (ie, electronic medical records) ^{162–166} Decentralization of HIV services ^{70–72} and integration into primary care, TB, antenatal services ^{72–74,76}	Adherence support through peer health workers ^{92,*} and treatment supporters ^{94,95,*} Peer-delivered DOT-ART ^{96–98,*} and nurse-delivered DOT-ART ^{99,*} Targeted DOT-ART for HIV-TB patients ^{141–143} and children ¹³⁰ Adherence counseling with EDM ^{87,*} Disclosure of HIV status to children ¹³³ Food-assistance programs ^{90,91}
Strongest evidence	Non-standard approaches to VCT: Home-based testing ^{32–34,36–38,41,†} Mobile or community-based testing ^{24,35,37,42,109,†} Testing in antenatal care settings ^{111–113,†}	Task-shifting to nurse-based, PHW care ^{66–69,78,79,81,265,†}	Adherence counseling/ education ^{85,86,266,†} Mobile phone SMS ^{100–102,267,268,†}

Notes: *Evidence from RCTs; †evidence from RCTs and observational studies.

Abbreviations: DOT-ART, directly observed antiretroviral therapy; HIV, human immunodeficiency virus; PHW, peer health worker; SMS, short message services; RCT, randomized controlled trial; VCT, voluntary counseling and testing; TB, tuberculosis.

increase early diagnosis and access to treatment,³⁰ especially within antenatal care settings.³¹ A number of observational studies show promising early results in increased testing uptake with home-based^{32–34} and mobile^{24,35} services. A large cohort study in rural Uganda found that 1 year after offering home-based testing services, receipt of HIV tests increased more than 5 times compared to previous clinic-based testing.³⁶ Studies assessing the cost-effectiveness and feasibility of home- and mobile-based testing in resource-limited settings have begun to emerge,^{37–39} but more research is needed.

There are few RCTs evaluating interventions to increase uptake of HIV testing in LMIC. An RCT investigating inpatient testing found that patients in an urban hospital in Uganda were significantly more likely to receive testing if it was offered during their hospital stay (intervention = 98.8%) compared to patients who were offered referral cards and travel reimbursement for testing one week after discharge (control = 68.7%).⁴⁰ A randomized population-based study in Zambia found that individuals in the intervention group who were offered VCT at a location of their choice (84% chose home-based VCT) were 4.7 times more likely to be tested than individuals in the control who were offered VCT at the local health clinic.⁴¹ In the largest RCT to date,

Sweat et al reported on Project Accept, a community-based intervention among communities in Tanzania, Thailand and Zimbabwe.⁴² Intervention components included community mobilization through HIV working groups and outreach coordinators, mobile VCT in community centers and other public places, and post-test support services.⁴³ A mean difference of 40.2% (95% confidence interval [CI]: 15.8–64.7) was reported in the proportion of patients receiving HIV testing in intervention versus control communities, plus intervention communities had more first-time testers compared to controls (Tanzania, 37% vs 9%; Thailand, 69% vs 23%; Zimbabwe, 51% vs 5%).⁴² RCTs investigating on-site testing at occupational health clinics,⁴⁴ and home-based testing offered to family members of ART patients⁴⁵ also found significantly increased testing rates compared with controls. RCTs using antenatal care settings to encourage couples counseling and testing of sexual partners have revealed mixed success.^{46–48}

Linkage to and retention in HIV care

The potential benefits of early HIV diagnosis through increased uptake in counseling and testing rely on effective linkage to and retention in HIV care systems. There is growing evidence that individuals testing positive are not

effectively linked to HIV care programs, leading to late presentation for treatment and increased risks of HIV-related morbidity and mortality.^{49–51} Recent studies suggest between 30%–62% of individuals who test positive are linked to care in resource-limited settings.^{40,52–54} Data on retention in care is also concerning. A review of data from 15 large-scale HIV treatment programs in LMIC revealed an average of 21% of patients were lost to follow-up by 6 months and 4% were lost after receiving their first ART prescription.⁵⁵ In South Africa, home to over 17% of the world's HIV-infected population, losses to follow-up have actually been increasing in recent years,⁵⁶ a possible indicator of the burden placed on under-resourced health care systems as more individuals access treatment.

Strategies to improve linkages and retention are emerging, although many studies suffer from weak study design and small sample sizes. In a case study in rural Tanzania, introduction of simple referral forms, along with transportation stipends and community navigators, showed success in increasing and monitoring linkages to care.⁵⁷ A cross-sectional study in Kenya supported mobile testing alongside patient navigators to improve linkage.⁵⁸ Utilization of point-of-care CD4 count technology is being evaluated to enhance CD4 monitoring, improve referral services for timely initiation of ART and decrease loss to follow-up.^{59–63} In a cohort study in Mozambique, implementation of point-of-care CD4 testing at primary health centers resulted in a decrease in loss to follow-up before completion of CD4 staging (from 57% to 21%), decrease in loss to follow-up before treatment initiation (from 64% to 33%) and an increase in enrolled patients initiating ART (from 12% to 22%).⁶⁴ In accordance with global guidelines for HIV care in LMIC,⁶⁵ HIV care systems are implementing various system-level changes to improve linkage and retention. Observational studies generally report positive impacts on linkage, retention and overall treatment outcomes with task-shifting from doctor-based to nurse-based care,^{66–69} decentralization of HIV services from higher level facilities to satellite clinics,^{70–72} and integration of HIV care into tuberculosis (TB), antenatal and other primary care services.^{73,74} Other studies highlight the need for careful implementation in the transition of these services to ensure personnel are trained properly and resources are available.^{75,76}

Evidence from RCTs evaluating linkage to and retention in HIV care is limited. A randomized trial in Uganda found that inpatient HIV testing resulted in only 56% of patients enrolling in HIV care, actually lower than the control group that was offered referral to outpatient testing.⁴⁰ An RCT in rural Uganda found that cash transfers (approximately

US\$5–\$8 per patient per month) for transportation to clinic appointments significantly decreased loss to follow-up ($P = 0.04$) among the intervention group, although sample size was small.⁷⁷ Supporting the efficacy of task-shifting to nurse-managed care, a randomized non-inferiority trial in Uganda found that a nurse–peer model achieved comparable rates of adherence, viral load, and CD4 counts compared to standard clinician-based care.⁷⁸ An RCT in South Africa found nurse-based care to be equivalent to doctor-managed care in treatment failure and retention in care, with hazard ratios of 1.09 (95% CI: 0.89–1.33) and 1.13 (95% CI: 0.81–1.59), respectively.⁷⁹ A cluster-randomized trial found that home-based HIV care through trained lay workers who supported drug delivery and monitored clinical status and adherence in patients was as effective as standard clinic-based care in Uganda in achieving equivalence in its primary endpoint, viral failure (relative risk [RR] 1.04, 95% CI: 0.78–1.40), and in secondary endpoints, mortality (RR 0.95, 95% CI: 0.71–1.28) and proportion of patients who reported 100% adherence (94% in home-based intervention group versus 91% in standard care group).⁸⁰ While the study reported no significant difference in loss to follow-up, home-based ART reduced overall HIV care costs incurred by patients by 50% in the first year and by 66% in subsequent years compared to clinic-based care. An RCT in Kenya found that an intervention using trained HIV-infected individuals as community care coordinators delivering monthly home assessments with clinic visits every 3 months resulted in similar clinical outcomes, including viral load, CD4 count and risk of opportunistic infections, compared to a control group with monthly clinic visits.⁸¹

Adherence to ART

A recent meta-analysis of adherence rates found 77% of adults achieved adequate adherence in sub-Saharan Africa compared to 55% in North America⁶ but rates vary significantly by setting. The literature on adherence interventions is relatively broad. Major reviews of adherence interventions, conducted mostly in resource-rich settings, reveal that the most effective are typically patient-based, behavioral interventions designed to build patient knowledge and efficacy through practical medication management skills.^{82–84} While the evidence base from resource-limited settings is much more limited, it is still significantly wider than for testing, linkage, and retention interventions and provides several RCTs for evaluation.

A number of patient-based counseling and education interventions have been evaluated in LMIC, and some show

positive impacts on adherence.^{85,86} Individual adherence counseling at ART initiation reduced the risk of poor adherence ($P = 0.055$) and viral failure ($P = 0.01$) at 18 months follow-up compared to controls in an RCT in Kenya, although only reduced risk of viral failure was statistically significant.⁸⁶ A small RCT in China found that using feedback from electronic dose monitoring (EDM) during counseling led to significant increases in mean adherence rates ($P = 0.003$) but not mean CD4 counts ($P = 0.07$) at 12-month follow-up compared to controls who received counseling only.⁸⁷ Busari et al investigated the effect of a structured teaching method compared to standard clinic care among 620 ART patients in Nigeria.⁸⁵ Intervention group members received education in 10 modules including benefits of treatment, adverse drug effects, self-efficacy, and social support. At 8 months follow-up, the intervention group achieved significantly higher rates of adherence ($P < 0.001$), CD4 counts ($P < 0.001$), decreased frequency of opportunistic infections ($P = 0.002$), and lower mortality ($P = 0.008$). Two Brazilian RCTs investigating interventions delivered by social workers showed no effectiveness in improving adherence or biological markers.^{88,89} One study used social workers to deliver motivational interviews and counseling through home visits⁸⁹ while the other study compared the effect of small educational workshops versus group video sessions.⁸⁸ Supplementing counseling and education with material support to address poverty-related barriers needs further investigation. Cohort studies in Zambia⁹⁰ and Nigeria⁹¹ support the use of food assistance for improving adherence among food-insecure patients.

Several RCTs have investigated the use of peer health workers, treatment supporters and directly observed therapy (DOT-ART), with mixed results. An RCT in Uganda using peer health workers to deliver clinic- and biweekly home-based adherence counseling and social support did not find significant improvements in adherence over controls, but did show significant decreases in the risk of viral failure after 96 weeks (RR 0.50, 95% CI: 0.44–1.49) until end of follow up at 192 weeks (RR 0.07, 95% CI: 0.006–0.71).⁹² A mixed-methods evaluation of the intervention found that the use of peer health workers improved access to care, care delivery, and patient-provider communication.⁹³ In another RCT in Uganda, use of a patient-nominated treatment supporter, a family member, friend, or neighbor educated on HIV and who agreed to attend counseling and clinic sessions with the patient, did not significantly increase adherence or clinic attendance against a standard adherence support program.⁹⁴ A study in Tanzania evaluated the impact of a treatment

supporter alongside standard adherence counseling and found no significant differences in adherence or mean CD4 counts compared to controls.⁹⁵ A clinic-based, once-daily DOT-ART intervention delivered by trained peers in Mozambique found mean adherence rates and CD4 counts at 6 and 12 months follow up did not increase significantly compared to controls although achieving >90% adherence was significantly more likely for the intervention arm at 6 months (odds ratio [OR] 2.0, 95% CI: 0.93–4.5).⁹⁶ RCTs in Nigeria⁹⁷ and South Africa⁹⁸ using patient-nominated DOT-ART treatment supporters and one in Kenya⁹⁹ using nurse-based DOT-ART revealed initial improvements in adherence, but failed to demonstrate significant increases in adherence, CD4 counts, and viral suppression at study endpoints.

While limited in number, studies assessing interventions using mobile phones have shown positive results. Two RCTs in Kenya investigated the use of mobile phone short message service (SMS) in improving adherence.^{100,101} Pop-Eleches et al found that an intervention group receiving weekly SMS reminders to take ART were significantly more likely to achieve >90% adherence rates ($P = 0.03$) and less likely to experience treatment interruptions ($P = 0.03$) at 48 weeks' follow-up compared to controls.¹⁰¹ Lester et al found significant improvements in adherence ($P = 0.006$) and viral suppression ($P = 0.04$) among an intervention group that received weekly interactive SMS (inquiring about health and well-being), with follow-up calls for nonrespondents after 48 hours.¹⁰⁰ Another RCT in Pakistan found that weekly phone reminders significantly improved adherence and decreased viral load, although sample size and length of follow-up were significantly less than the studies in Kenya.¹⁰² In an RCT in Uganda discussed previously investigating the impact of peer health workers,⁹² a substudy evaluated a mobile phone intervention whereby health workers called and text messaged higher-level providers with patient-specific clinical information and adherence data.¹⁰³ While the intervention did not find significant improvements in adherence, biological markers or loss to follow-up in patients randomized to health workers in the intervention arm, a mixed-methods evaluation revealed mobile phones improved care delivery and was widely believed by patients, clinic staff, and peer health workers to improve clinical care. Two RCTs investigating the impact of SMS on adherence to ART are ongoing in Cameroon¹⁰⁴ and India.¹⁰⁵

Special populations

There are a number of populations that face higher burdens of HIV, worse clinical outcomes and additional and/

or unique barriers in accessing and adhering to ART. These populations require particular consideration, especially in LMIC where they may be further marginalized and isolated from HIV care.

Women

In LMIC in 2010, women represented 51% of those still requiring treatment and 58% of those currently on ART.¹ It is estimated that coverage – the percentage of individuals needing treatment who are receiving it – among women is higher than men, especially in Asia and sub-Saharan Africa, while coverage rates for women in Latin America are slightly lower. Young women face an especially high burden of HIV in sub-Saharan Africa, where women make up 71% of HIV-positive young adults aged 15–24 years old.¹ Preventing mother-to-child transmission, which is the route of infection in 90% of HIV-positive children in LMIC, hinges on expanding access and adherence to ART among pregnant mothers. In 2010, only 35% of pregnant women in LMIC received an HIV test and 48% of HIV-infected pregnant women accessed ART regimens as recommended by the WHO to prevent vertical transmission.¹ Women in many settings face additional barriers to access and adherence to treatment. Qualitative studies suggest important sex-based barriers may dissuade women from accessing and adhering to HIV treatment, including requiring a male partner's permission to seek testing and treatment services.¹⁰⁶ Women in some settings fear disclosing their HIV status to their partner because of potential negative consequences of emotional or physical abuse¹⁰⁷ or forcible displacement from their homes.¹⁰⁸ In many LMIC, women are particularly vulnerable to poverty and socioeconomic inequalities that create additional barriers to access and adherence such as low levels of education, social status, and financial resources.

Few studies in LMIC evaluate interventions aimed specifically at improving women's access and adherence to HIV care. Qualitative studies of home-based and mobile VCT services reveal that these approaches may be more available to women as they do not require travel to clinic or permission and/or money from partners.^{109,110} Provider-initiated counseling and testing for women in antenatal care settings has been shown to be well-accepted and to significantly increase testing uptake and participation in prevention of mother-to-child transmission care.^{111,112} A cluster RCT in Zambia found that counseling and testing services in hospital labor wards increased the number of women on ART during birth and improved adherence.¹¹³

Children and adolescents

In 2010, there were an estimated 3.4 million children under 15 years living with HIV. Adolescents represent one of the fastest-growing HIV-infected populations in the world. Young people aged 15–24 years now make up 41% of new HIV infections in persons older than 15 years.¹¹⁴ Children and adolescents in resource-limited settings bear an alarming burden of the HIV epidemic, but are less likely to achieve adequate adherence and to have good clinical outcomes compared to their adult counterparts.¹¹⁵ Children and adolescents face complex barriers to access and adherence as the extent of their autonomy varies over the developmental course and they frequently rely on caregivers for treatment. Caregiver beliefs,¹¹⁶ education,¹¹⁷ and stress,¹¹⁸ as well as type of family structure,¹¹⁷ all influence pediatric access and adherence to ART. Vulnerable children, such as orphans, often face additional barriers to care.¹¹⁹ Disclosure of the child's HIV status, essential for long-term disease management, is associated with improved adherence,¹²⁰ emotional health,¹²¹ and reduced conflict with caregivers,¹²² but disclosure rates vary and are generally low in resource-limited settings (Vreeman et al, unpublished data, 2012). Children, as adults, report experiencing various levels of HIV-related discrimination.¹²³ Furthermore, issues that arise as children and adolescents transition from pediatric to adult care settings in LMIC have not been investigated sufficiently.¹²⁴

Evidence for strategies to improve access and adherence to ART for children and adolescents is lacking. Two major reviews of interventions to improve adherence among children revealed limited support for home-based nursing care, peer support, and education sessions for caregivers and children to improve adherence; however, many studies suffered from weak methodologies, small sample sizes, and few were conducted in LMIC.^{125,126} Other reviews suggest that, along with child and caregiver-level interventions, improved ART regimens for children (palatability, pill burden/size) and relationships with providers can lead to better adherence to ART in children.¹²⁷ Fewer studies evaluate access to treatment in children. An RCT in Swaziland showed the effectiveness of a school-based educational intervention in increasing HIV testing rates among students.¹²⁸ A comprehensive care program in Kenya offering individual and group psychosocial support and treatment literacy for children and caregivers within a tailored, child-centered care model found improved clinical outcomes; however, individual components of the program could not be evaluated.¹²⁹ Evaluation of a clinic-based DOT-ART program in Cambodia showed significantly improved CD4 counts ($P < 0.001$) after 18 months

for orphaned children.¹³⁰ Few studies examine the impact of disclosure on emotional health and adherence,¹³¹ but evaluation of one clinic-based disclosure program in Puerto Rico found improved rates of adherence after implementation¹³² and disclosure was linked to higher rates of adherence among children in Zambia.¹³³

Other high-risk populations

Additional high-risk populations for HIV that need to be considered for targeted interventions include: individuals with comorbidities such as HIV–TB, substance abusers and individuals with mental disorders, men who have sex with men (MSM), sex workers, and prisoners. In 2010, there were 8 million new cases of TB worldwide with 13% of newly infected individuals also being HIV-positive.¹³⁴ The vast majority of individuals living with HIV–TB, an estimated 82%, reside in sub-Saharan Africa.¹³⁴ The prevalence of substance abuse and psychiatric disorders is high among HIV-infected individuals, with many suffering from all three comorbidities.¹³⁵ While substance abuse and mental disorders are associated with poorer adherence and treatment outcomes in resource-rich settings,¹³⁶ less is known about prevalence and impact in LMIC.¹³⁷ A recent meta-analysis of studies from LMIC found MSM were almost 20 times more likely to be infected with HIV than the general population, highlighting the risks faced by this population.¹³⁸ In LMIC, prevalence of HIV among female sex workers was estimated at 11.8% (95% CI: 11.6–12.0) while among the 26 countries with the highest HIV burden, the overall prevalence jumped to 30.7% (95% CI: 30.2–31.3).¹³⁹ Finally, prisoners represent another high-risk population for HIV, but there is little data on HIV prevalence and treatment in LMIC. Small surveys in sub-Saharan Africa suggest high rates of HIV among prison populations, as high as 40% in a sample in South Africa.¹⁴⁰

These populations face significant and, in some cases, unique barriers to HIV treatment, for example, criminalization in the case of homosexuality and lack of control over treatment for prisoners. Research to improve access and adherence among these populations is virtually nonexistent in LMIC. Interventions that fail to show effectiveness in general populations may prove efficacious among targeted populations. While the evidence from RCTs for DOT–ART is not convincing among the general population, targeted DOT–ART, such as for HIV–TB patients, may be more effective and has demonstrated feasibility and efficacy in small observational studies in resource-limited settings.^{141–143} Evidence from RCTs in resource-rich settings supports the use of DOT–ART for individuals with substance abuse

disorders^{144–146} and prisoners.¹⁴⁷ Depression, one of the most common mental disorders worldwide,¹⁴⁸ has been shown to be associated with nonadherence to ART and poor engagement in care in all settings.¹⁴⁹ Evidence from resource-rich settings suggests improved adherence and clinical outcomes with combined adherence and mental health counseling.^{150,151} No major studies have been conducted among MSM, sex workers, and prisoners, as most research and recommendations focus on prevention.¹⁵² A small observational study in London found a targeted multimedia campaign aimed at young gay men resulted in increased uptake in clinic-based HIV testing.¹⁵³ Another small observational study in Vancouver found increased adherence and viral suppression with a peer-delivered intervention including support groups, patient advocates, outreach, and onsite nursing care among a group of female sex workers using illicit substances, although there was no comparison group.¹⁵⁴

Evaluating the evidence base

While there is increasing data on barriers to treatment, a review of the scientific literature reveals limited evidence for strategies to improve access and adherence to ART in resource-limited settings. Interventions broadening HIV testing approaches, such as home-based, community, and mobile testing, show early evidence of increasing HIV testing and diagnosis. Observational and case studies generally support shifts in HIV care to improve retention through decentralization and integration of services, but only task-shifting to nurse- and peer health worker-based care is supported by RCTs. A larger evidence base is found for interventions directed at improving adherence. Adherence counseling and education interventions have been effective in some settings, and recent evidence supports a role for mobile phone technologies. RCTs to date do not provide sufficient evidence for using treatment supporters and DOT–ART to improve adherence among general populations; however, these strategies may be efficacious for certain populations such as children, HIV–TB patients, and substance abusers.

Studies assessing interventions directed at women, children, and adolescents and other special populations are scarce in LMIC. Provider-initiated inpatient testing has demonstrated feasibility and improved access for women in antenatal care settings, but few other interventions have been investigated adequately. This review also highlights the limited geographic variability among intervention studies to improve access and adherence, with the vast majority of the studies conducted in a few sub-Saharan African countries, including Kenya, South Africa, Uganda, and Zambia. While

sub-Saharan Africa represents the epicenter of the HIV epidemic, studies investigating access and adherence are needed in other resource-constrained parts of the world where population and system-level contextual factors necessitate different approaches.

There are a number of critical weaknesses in studies evaluated for this review. A lack of standardization in evaluating linkage, retention, and adherence is an issue for both research and delivery of clinical care. While there are no common protocols to assess linkage, retention may be measured through gaps in care, clinic visits per interval of time, and number of missed visits.¹⁵⁵ Further, individuals with HIV are a mobile population, moving through different stages of care, but also to different clinics and providers for care.^{156,157} Systems that monitor and link patients between points of care are essential for improving treatment and continuity of care. Adherence measures vary in different settings and common measures include self and proxy reports, pill counts, pharmacy refills, EDM, virologic markers (CD4 counts, viral loads), and blood draws for drug concentrations. No gold standard for measuring adherence has been proposed,¹⁵⁸ and studies often use multiple measure to improve estimates.¹⁵⁹ Long-term, routine monitoring of adherence is required to ensure optimal delivery of care, as adherence often decreases over time,^{160,161} but also to evaluate the effectiveness of interventions to improve adherence. Improving the methods that studies and care systems utilize to monitor linkage to and retention in care and adherence to ART will strengthen findings of intervention effectiveness.

Directions for future research

There are several critical gaps in the current evidence base that need to be addressed in future research. As HIV care systems transition through task shifting, decentralization, and integration and as more individuals need to be retained in treatment, monitoring of patients is critical to improving and expanding delivery of HIV care. Early rollout of health information systems, including electronic medical records, has been mostly positive in LMIC,^{162–166} but more research on technology-based information and surveillance systems and their potential to monitor and track patients throughout care is needed, along with how patient navigators and community outreach workers may supplement these systems. As HIV care systems horizontally integrate with other primary care services, there is an opportunity to implement various technologies into patient-based care that will improve not only HIV care, but strengthen local health care systems more broadly.

HIV-related stigma and discrimination remain major barriers to HIV treatment in LMIC, but this review found no major studies evaluating interventions to improve access and adherence through reducing stigma and discrimination against people living with HIV. A recent systematic review of interventions aimed at reducing HIV stigma evaluated 19 studies, of which nine were conducted in LMIC; however, studies suffered from various methodological weaknesses and no studies examined the association between reduced HIV stigma and health outcomes such as access and adherence to treatment.¹⁶⁷ Very few studies investigating interventions to improve access and adherence include measures of stigma as secondary outcomes, although this review did find two such studies: a cohort study in Peru using community health workers delivering DOT-ART¹⁶⁸ and an RCT in Kenya discussed previously assessing nurse-based DOT-ART.¹⁶⁹ Further research on interventions aiming to reduce stigma, validation of stigma measures, and examining the association between intervention effects and health outcomes such as access and adherence are vital for addressing the significant challenges in HIV treatment due to stigma and discrimination. Issues in disclosure of HIV status, impacted by levels of perceived stigma, also deserve further investigation.

Social support networks have been identified in qualitative studies as important facilitators of HIV treatment, including adherence.^{170–172} Evidence for treatment supporters among qualitative and observational studies generally reveals more positive impacts on adherence and treatment outcomes than RCTs,^{173–178} and their findings warrant further investigation into the potential role for patient-nominated, family, friend or peer supporters in improving access and adherence. In sub-Saharan Africa, O’Laughlin et al suggest that treatment partners go beyond encouraging adherence to restoring access to social and community resources.¹⁷⁹ In this way, treatment supports are sources of social capital and are important for obtaining treatment-sustaining resources such as money for transportation or food.¹⁸⁰ As more patients in LMIC become ART experienced, “expert patients” from the community can likely play a crucial role in interventions to increase access and adherence as they have intimate knowledge of barriers and facilitators of care.¹⁸¹ This review only found two studies using persons living with HIV to deliver interventions.^{81,182} Increased involvement of this population in the design and implementation of interventions deserves investigation.

Simple, low-cost adherence tools such as pillboxes, medication planners, and calendars have not been investigated thoroughly in resource-limited settings. The use of pillboxes has shown efficacy in improving adherence in a US

cohort,¹⁸³ but has not been investigated in resource-limited settings. There may be variations in efficacy of such tools in settings where keeping medications secret is highly prized or where health literacy is more limited. Educational treatment calendars showed no impact on adherence or CD4 counts in an RCT in Tanzania comparing adherence counseling versus adherence counseling plus calendar.⁹⁵ While electronic dose-timing alarms show positive effects in resource-rich settings,^{184,185} an RCT in Kenya found that the use of an alarm device did not significantly improve adherence.⁸⁶ A small pretest–posttest intervention study reported on the delivery of a culturally sensitive educational videotape to improve adherence to ART in South Africa and showed increased knowledge of ART, side effects, and overall adherence strategies, although there was no control group.¹⁸⁶ Combining low-cost adherence tools with counseling and education may offer benefits to adherence, but are not well studied in resource-limited settings. Another low-cost strategy to increase uptake in testing and utilization of services is mass media campaigns that can educate communities, raise awareness of availability of services,¹⁸⁷ and may address issues of stigma.¹⁸⁸ A Cochrane systematic review of mass media campaigns to increase uptake in HIV testing found that these interventions can increase testing rates, although no studies included in the review were from LMIC.¹⁸⁹ This review found one study conducted in a resource-limited setting – a retrospective cohort study in Kenya.¹⁹⁰ Further research is needed on the efficacy of mass media campaigns and their potential to increase access and adherence.

Cost-effectiveness research is needed to evaluate the feasibility of implementing effective interventions in resource-limited settings and is just beginning to emerge. Overall, cost models have shown that high levels of adherence are associated with overall lower total health care costs in the US¹⁹¹ and in South Africa.¹⁹² There is limited research available on the cost-effectiveness in LMIC of various HIV-testing approaches,^{35,37,38} task-shifting to nurse-based care,⁶⁷ and home-based ART care.¹⁹³ There is a need to expand cost research in terms of overall reductions in health care costs associated with improved access and adherence to ART and the cost-effectiveness of efficacious strategies. With these data, programs can reliably estimate overall cost savings projections for efforts to improve access and adherence. Still, cost factors related to the price of ART remain outside the control of local HIV programs. Global partners, pharmaceutical companies, and national governments in LMIC need to continue to work together to create favorable global markets for ART whereby HIV programs in resource-limited

settings gain increased access to the best available HIV medicines in line with WHO guidelines.¹⁹⁴

Finally, new and creative directions in research are needed to address challenges in identifying effective strategies to improve access and adherence to ART in LMIC. RCTs are commonly considered the gold standard, but as research on HIV interventions moves forward, it is important to balance the strengths and weaknesses of RCTs against those of well-designed observational studies. For public health and sociobehavioral interventions, there is a place for observational studies, and complete reliance on RCTs is not always good practice.¹⁹⁵ The use of qualitative data alongside RCTs is still relatively uncommon and not without methodological issues,¹⁹⁶ but may be positioned to evaluate complex and multicomponent interventions. Beyond the scope of studies assessing intervention effectiveness is operational and implementation research. Operational research, using systematic research techniques to improve program operations and decision-making¹⁹⁷ will be a critical endeavor for health care systems in LMIC to strengthen health infrastructure, human resources and capacity for local program design and evaluation.¹⁹⁸ Implementation research, investigating how health systems implement and deliver evidence-based interventions,¹⁹⁹ will be critical to guide governments and policy makers in replicating, adapting, and scaling up interventions.

Conclusion

Individuals living with HIV encounter many barriers to access and adherence to treatment. This nonsystematic review revealed few effective evidence-based strategies to guide clinicians, public health practitioners, and other health care providers. These findings make a compelling case for more data on improving delivery of ART in LMIC.

Disclosure

The authors report no conflicts of interest in this work. The views expressed in this article are those of the authors and do not necessarily represent the view of the Indiana University School of Medicine. The authors take full responsibility for the integrity of this review.

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