Chapter 4

HIV Care Continuum in Adults and Children: Cost-Effectiveness Considerations

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INTRODUCTION

The management of human immunodeficiency virus (HIV) infection has evolved substantially since the advent of the HIV/acquired immune deficiency syndrome (HIV/AIDS) epidemic in the 1980s. The discovery of effective antiretroviral therapy (ART) transformed the lives of persons living with HIV (Deeks, Lewin, and Havlir 2013) by achieving a substantial drop in morbidity and mortality (Danel and others 2015; START Study Group 2015). Additionally, evidence supports the efficacy of ART in preventing the transmission of HIV infection (Cohen and others 2011).

Progress in controlling the HIV epidemic, however, requires the achievement of virologic suppression among all HIV-infected individuals, which, in turn, requires the identification of such individuals and their retention across the care continuum—from conducting HIV testing, linking HIV-positive individuals to care, retaining them in care, and achieving viral suppression (figure 4.1) (Gardner and others 2011). For each step of the continuum, this chapter discusses the rationale, relevant guidelines, measurements of each parameter, barriers to achieving successful outcomes, interventions demonstrated to be effective, and available data on the costs and cost-effectiveness of interventions.

The chapter includes information from peer-reviewed manuscripts identified through a targeted literature review focused on publications pertinent to low- and middle-income countries (LMICs), with a focus on Sub-Saharan Africa. Studies conducted in other LMIC regions and high-income countries are referenced when they address a key relevant issue. A table summarizing approaches to improving HIV testing, linkage to and engagement with HIV care, retention in HIV care, and adherence to HIV treatment is included in annex 4A.

HIV TESTING SERVICES

Rationale and Coverage

HIV testing services (HTS) are essential for identifying HIV-positive persons in need of care and ART, as well as for identifying at-risk HIV-negative persons for referral and engagement in HIV prevention programs (Celum and others 2013). Despite the importance of HIV testing, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that nearly half of the 36.9 million people living with HIV globally in 2014 were unaware of their infection (UNAIDS 2015a). Similarly, only 44 percent of pregnant women in LMICs access HIV testing (WHO 2014c). Recent findings from

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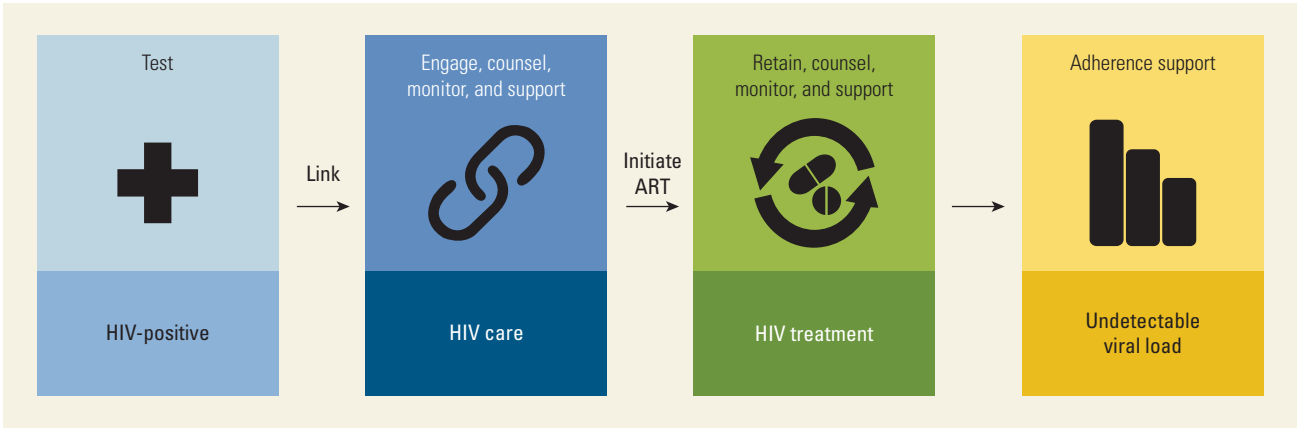
Figure 4.1 HIV Care Continuum



Source: McNairy and El-Sadr 2012. Adapted with permission from Wolters Kluwer.
Note: ART = antiretroviral treatment; HIV = human immunodeficiency virus.

the Population HIV Impact Assessment (PHIA) surveys completed in Malawi, Zambia, and Zimbabwe suggest the need to enhance HIV testing coverage; in these surveys of random samples of households, 70.4 percent of individuals found to be HIV-positive were aware of HIV infection (ICAP 2016).

HIV testing is especially critical for pregnant women and children. HIV-infected pregnant women must be identified early during pregnancy to benefit from ART for their own health and for the prevention of vertical transmission; HIV-negative pregnant and postpartum women require repeat testing during pregnancy and the postpartum period (Drake and others 2014).

HIV testing and ART initiation for HIV-infected infants in the first months of life has been demonstrated to markedly reduce mortality (Violari and others 2008). However, only 46 percent of HIV-exposed infants in LMICs received an early infant diagnostic (EID) test for HIV in 2014 (UNICEF 2015).

Adolescents are another high-risk group in need of increased access to and uptake of HIV testing. In 2015, there were 1.8 million adolescents ages 10–19 years living with HIV (UNAIDS 2015b). Since 2004, mortality has decreased 30 percent among adults but increased 50 percent among adolescents (Porth and others 2014). In the PHIA surveys cited above, only 46.4 percent of young individuals (15–24 years old) found to be HIV-positive in the population surveys were aware of their HIV infection (ICAP 2016).

Guidelines

The World Health Organization (WHO) recommends universal testing in countries with generalized HIV epidemics (WHO 2013b). Provider-initiated testing and counseling (PITC) is recommended for women as a routine component of antenatal care, with retesting before delivery for persons with a first negative test (WHO 2015a).

All infants of HIV-infected pregnant women should be tested for infection at age four to six weeks using a virologic test that directly detects the virus, including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or DNA polymerase chain reaction (PCR) assays (WHO 2015a). Infants testing positive should be initiated on ART, while those testing negative should be tested again with virologic or serologic assays (depending on their age) after the risk period for mother-to-child transmission ends with cessation of breastfeeding.

For children ages 18 months or older, the WHO recommends serological testing when HIV infection is suspected or exposure has occurred; and in high-prevalence settings, HIV testing should be routinely available to children attending immunization, under-five, malnutrition, and tuberculosis clinics; all hospitalized children; and those receiving services for orphans and vulnerable children (WHO 2015a). In generalized HIV epidemic settings, HTS, with links to prevention, treatment, and care, are recommended for all adolescents (WHO 2015a).

For populations at substantial risk for HIV, including persons who inject drugs (PWID), sex workers (SWs), and men who have sex with men (MSM), frequent, voluntary, community-based HTS, linked to prevention, treatment, and care, are recommended.

Measurement

Common measures of HIV testing include the number of tests conducted and the number of individuals

who are tested, counseled, and receive their results (PEPFAR 2013). However, these measures do not assess the effectiveness of HIV testing in identifying all persons with HIV infection in a community. Others have highlighted the importance of measuring the proportion of individuals who test positive for HIV who then link to care (El-Sadr, Gamble, and Cohen 2013).

Barriers

Individual-level barriers to testing include perceived low risk of infection, anticipated psychological burden of living with HIV, fear of HIV-related stigma, direct and indirect financial costs of accessing HIV testing, and gender inequality (Musheke and others 2013). Testing of children and adolescents is complicated by the need to obtain consent from a parent or legal guardian (WHO 2013b, 2014b). System-level barriers include high patient load, test kit shortages, inadequate counseling space, and poor counseling skills (Larsson and others 2011; Nuti, Kabengula, and Msuya 2011). For pregnant women, low uptake of antenatal services in some settings remains an impediment to achieving universal HIV testing.

Approaches to Improve HTS Uptake

Voluntary counseling and testing (VCT) is dependent on individuals' actively seeking HIV testing at a clinic, hospital, mobile health unit, or free-standing site (Matovu and Makumbi 2007). However, VCT is of limited value among individuals who do not perceive themselves to be at risk. Moreover, children rarely access VCT services, because caregivers fear stigma and disclosure of their own serostatus (Ahmed and others 2013).

In 2007, the WHO and UNAIDS released guidance recommending PITC for all patients in high-prevalence settings and for all patients, irrespective of epidemic setting, whose clinical presentation suggests HIV infection (Kennedy and others 2013; Roura and others 2013; WHO 2007). A systematic review of PITC in Sub-Saharan Africa reported increased uptake of HIV testing after PITC was implemented in antenatal and family planning, tuberculosis, sexually transmitted infection, and outpatient clinics (Kennedy and others 2013). PITC uptake is lower among men and among women who are not pregnant, however (Baggaley and others 2012; Hensen and others 2012; MacPherson and others 2012). PITC has been effective in identifying HIV-infected and -exposed infants in inpatient settings, but it is not widely implemented for children (Kankasa and others 2009).

Community-based testing (CBT) strategies, including testing in homes, schools, the workplace, or other community venues (Bateganya, Abdulwadud, and Kiene 2010; Coates and others 2014), have demonstrated promise for expanding knowledge of HIV status. Compared with facility-based testing, CBT has been associated with increased testing, higher proportions of first-time testers, higher proportions of HIV-infected individuals identified with CD4 cell count greater than 350 cells per microliter, and an overall lower seropositivity rate (Suthar, Ford, and others 2013). Home-based testing has been highly acceptable, with 83 percent accepting testing in a meta-analysis (Sabapathy and others 2012). It was also found to be cost-effective for reaching youth, men, and rural populations (Sweat and others 2011; van Rooyen, McGrath, and others 2013; Wachira and others 2014). Home-based testing has also been more effective than facility-based testing at diagnosing people with less advanced disease and has increased linking of HIV-positive persons to care (Wachira, Kimaiyo, and others 2012).

CBT has also shown promise for pediatric case finding (Ahmed and others 2015). Among members of households with HIV-infected individuals in Uganda, home-based testing increased identification of HIV-infected persons, including children, compared with clinic-based care (Lugada and others 2010).

Mass campaigns that provide HTS in conjunction with other health services have also been used. In Kenya and Uganda, HTS were provided along with free bed nets, water purification kits, condoms, and cotrimoxazole to those who tested HIV-positive (Lugada and others 2010; Tumwesigye and others 2010). In Kenya, 80 percent of the population in a catchment area was tested for HIV in a period of one week; in Uganda, 63 percent of households were tested through such a campaign. In Tanzania, a CBT campaign for children identified 108 new pediatric cases (3.6 percent) (Shea and others 2013). Mass campaigns that include HIV testing have been less successful in reaching young adults and adult males (Chamie and others 2014; Ostermann and others 2011).

Couples' testing is another approach to identifying concordant HIV-positive couples in need of ART and serodiscordant couples in need of ART for positive partner or preexposure prophylaxis (PrEP) or voluntary medical male circumcision for negative partner (Baeten and others 2012; Gray and others 2007).

Self-testing for HIV holds promise (Choko and others 2011; Pant Pai and others 2013; Thirumurthy and others 2016). In Malawi, self-testing with oral test kits was acceptable among 92 percent of persons, and 99 percent of results were accurate (Choko and others 2011).

More research is needed to evaluate linking of HIV-positive patients to care, as well as disclosure of results to partners among persons who self-test positive.

Limited access to the specialized tests (nucleic acid tests including DNA and RNA PCR) for diagnosis of HIV infection in infants resulted in high mortality among HIV-infected babies (Creek and others 2008). The introduction of new laboratory technology at centralized laboratories in many Sub-Saharan African countries, coupled with the use of dried blood spots for specimen collection, improved access and uptake of early infant diagnosis (Essajee and others 2015; Ghadrshenas and others 2013). The use of text message printers and computerized tracking systems has increased the rate of return of EID results to clinics and families (Essajee and others 2015; Finocchario-Kessler and others 2014).

In South Africa, couples-based HIV testing in MSM appears to be effective (Stephenson and others 2013). In China, peer-driven counseling sessions significantly increased testing rates among MSM (Menzies and others 2009). Text reminders also increased testing rates (Bourne and others 2011). For PWID, venue-based testing at methadone clinics and drop-in sites was successful in increasing knowledge of HIV status (Xia and others 2013). Additionally, a qualitative study noted that female sex workers (FSWs) in Benin would more likely access HIV-testing services if paired with outreach strategies (Dugas and others 2015).

A systematic review of seven partner notification studies in LMICs to achieve testing of partners described the use of email, text messaging, and social networking, with most clients choosing to send notifications via text rather than email to enhance testing of partners of HIV-positive individuals (Hochberg, Berringer, and Schneider 2015). In a study from Malawi, only 25 percent of partners in the passive referral arm returned for HIV testing, compared with 51 percent in both the contract and the provider referral arms ($p < 0.001$) (Brown and others 2011). Similarly, a cohort study in Cameroon reported that 46 percent of partners in the passive referral group returned for testing as compared with 60 percent in the provider group and 61 percent in the contract referral arm (Henley and others 2013).

Cost-Effectiveness Considerations

Table 4.1 describes cost and cost-effectiveness studies regarding HTS.

Voluntary Counseling and Testing

Evidence suggests that while VCT and CBT have low costs per person tested, the cost per HIV-infected person tested is lower for PITC.

In East Africa, VCT can be delivered for US$10–US$30 per person tested, and the overall cost-effectiveness of VCT has been favorable in the few available studies (Grabbe and others 2010; Menzies and others 2009). In Tanzania, the cost per disability-adjusted life year (DALY) averted was estimated to be US$13–US$18 and the cost per HIV infection averted to be US$249–US$346 (Sweat and others 2000). Offering VCT for free was highly cost-effective (Thielman and others 2006). Because utilization levels for VCT services are an important driver of the costs per client, demand creation for VCT is essential for reducing costs. In addition, many studies underestimate the cost-effectiveness of HIV testing by neglecting the prevention benefits of knowing HIV-positive status, which leads to a decrease in risk behaviors, and the cost-effectiveness of ART provision to individuals identified as HIV-infected.

The costs of VCT approaches to HIV testing are higher when calculated per HIV-infected person identified rather than per individual tested. Costs per HIV-infected person identified are often lower for alternative testing approaches such as PITC (including hospital-based testing) than for VCT. In Uganda, hospital-based testing costs US$12 per client tested and US$43 per HIV-infected person identified (Menzies and others 2009). In contrast, VCT costs US$19 per person tested and US$101 per HIV-infected person identified.

Community-Based Testing

Evidence is emerging on the costs of approaches to CBT. Studies have found the costs of such approaches to be lower than or comparable to the costs of VCT, at approximately US$8–US$15 per person tested (Grabbe and others 2010; Menzies and others 2009). In Kenya and Uganda, mobile HTS had a lower cost per person tested than VCT. The cost per HIV-infected person identified was lower for mobile HTS than VCT in Kenya, but higher in Uganda. A modeling analysis for South Africa that estimated the incremental cost-effectiveness ratios (ICERs) per DALY averted of home-based HIV testing and counseling along with enhanced links to care found a high level of cost-effectiveness (Smith and others 2015). The cost per DALY averted was US$1,340 at an ART threshold of CD4 count less than 200 cells per microliter and US$1,360 at universal access to ART.

Although not high-prevalence settings, studies conducted in China and India have provided additional evidence on the cost-effectiveness of targeted use of VCT among key populations and high-risk groups. In China, among populations at higher risk of HIV acquisition, such as MSM, VCT was cost saving (Wang, Moss, and Hiller 2011). In Indonesia, costs per HIV-infected person identified were lower in prisons than in

Table 4.1 Cost-Effectiveness of Approaches to the HIV Care Continuum

Intervention	Study	Region or country	Cost per outcome	Cost (C) or cost-effectiveness (CE)	Unit of outcome	Currency as presented (year)	Cost in 2012 US$
HIV testing and counseling							
	Grabbe and others 2010	Sub-Saharan Africa, Kenya	$26.75	CE	per HTC client	2007 US$	$41.81
			$43.69	CE	per new HTC client	2007 US$	$68.28
			$189.14	CE	per HIV-positive client	2007 US$	$295.59
			$237.60	CE	per new HIV-positive client identified	2007 US$	$371.32
All mobile compared with stand-alone			$14.91	CE	per HTC client	2007 US$	$23.30
			$16.58	CE	per new HTC client	2007 US$	$25.91
			$157.21	CE	per HIV-positive client	2007 US$	$245.69
			$178.10	CE	per new HIV-positive client identified	2007 US$	$278.34
Community-site mobile compared with stand-alone			$8.82	CE	per HTC client	2007 US$	$13.78
			$9.73	CE	per new HTC client	2007 US$	$15.21
Semimobile container compared with stand-alone			$17.23	CE	per HTC client	2007 US$	$26.93
			$20.06	CE	per new HTC client	2007 US$	$31.35
Fully mobile truck compared with stand-alone			$20.38	CE	per HTC client	2007 US$	$31.85
			$23.39	CE	per new HTC client	2007 US$	$36.55
VCT	Sweat and others 2000	Sub-Saharan Africa, Kenya	$12.77	CE	per DALY averted	1998 US$	$17.47
VCT, enrolled as couples			$2.75–$3.48	CE	per DALY averted; HIV-1-positive males and females	1998 US$	$3.47–$4.73
			$19.48–$21.86	CE	per DALY averted; HIV-1-negative females and males	1998 US$	$26.38–$29.60
Free VCT campaign	Thielman and others 2006	Sub-Saharan Africa, Tanzania	$5.40	CE	per DALY averted	2003 US$	$8.09
Sustained free VCT			$4.72	CE	per DALY averted	2003 US$	$7.07
Scaled-up, community-based VCT	Tromp and others 2013	East Asia and Pacific, Indonesia	$9.17	CE	per DALY averted	2008 US$	$12.59

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Table 4.1 Cost-Effectiveness of Approaches to the HIV Care Continuum (continued)

Intervention	Study	Region or country	Cost per outcome	Cost (C) or cost-effectiveness (CE)	Unit of outcome	Currency as presented (year)	Cost in 2012 US$
VCT	Wang, Moss, and Hiller 2011	East Asia and Pacific, China	1,087,669 yuan	CE	Incremental cost per HIV infection averted (including averted cost) in general population	2002 yuan	$228,514.82
			53,317 yuan	CE	Incremental cost per DALY averted (including averted cost) in general population	2002 yuan	$11,201.68
Stand-alone HTC	Menzies and others 2009	Sub-Saharan Africa, Uganda	$19.26	C	Cost per client tested	2007 US$	$25.07
Hospital-based HTC			$11.68	C	Cost per client tested	2007 US$	$15.20
Household-member HTC			$13.85	C	Cost per client tested	2007 US$	$18.03
Door-to-door HTC			$8.29	C	Cost per client tested	2007 US$	$10.79
Stand-alone HTC			$100.59	C	Cost per HIV-positive individual identified	2007 US$	$130.92
Hospital-based HTC			$43.10	C	Cost per HIV-positive individual identified	2007 US$	$56.09
Household-member HTC			$231.65	C	Cost per HIV-positive individual identified	2007 US$	$301.49
Door-to-door HTC			$163.93	C	Cost per HIV-positive individual identified	2007 US$	$213.35
HTC in prisons, HIV community clinics, and hospitals	Siregar and others 2011	East Asia and Pacific, Indonesia	$23.00	C	per VCT in prison	2008 US$	$31.58
			$39.00	C	per VCT in HIV community clinics	2008 US$	$53.56
			$65.00	C	per VCT in STI community clinics	2008 US$	$89.26
			$74.00	C	per VCT in hospitals	2008 US$	$101.62
VCT	Sweat and others 2000	Sub-Saharan Africa, Kenya and Tanzania	$249.00–$346.00	CE	per infection averted	1998 US$	$473.46–$722.66
Free VCT	Thielman and others 2006	Sub-Saharan Africa, Tanzania	$92.00	CE	per infection averted	2003 US$	$137.78

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Table 4.1 Cost-Effectiveness of Approaches to the HIV Care Continuum (continued)

Intervention	Study	Region or country	Cost per outcome	Cost (C) or cost-effectiveness (CE)	Unit of outcome	Currency as presented (year)	Cost in 2012 US$
VCT at community health centers	Tromp and others 2013	East Asia and Pacific, Indonesia	$248.00	CE	per HIV infection averted	2008 US$	$340.56
VCT	Wang, Moss, and Hiller 2011	East Asia and Pacific, China	165,067 yuan	C	Lifetime cost of HIV care and treatment per person in MSM population and in general population	2002 yuan	$34,679.90
VCT	Venkatesh and others 2013	India	$800.00–$1,900.00	CE	per YLS	2010 US$	$912.27–$2,166.65
Home-based HTC with enhanced link to care	Smith and others 2015	Sub-Saharan Africa, South Africa	$1,090.00–$1,360.00	CE	per DALY averted	2013 US$	—
DNA-PCR for EID compared with use of rapid HIV tests to screen out HIV-uninfected infants	Menzies and others 2009	Sub-Saharan Africa, Uganda	$1,489.00	C	per infant correctly diagnosed and informed of result for DNA-PCR versus modified algorithm	2007 US$	$1,937.90
Improvement of retention and adherence							
HBC, FBC, and MCC for provision of ART	Babigumira and others 2009	Sub-Saharan Africa, Uganda	$2,615.00	CE	per QALY, ICER for MCC versus FBC	2008 US$	$3,200.86
			$2,814.00	CE	per QALY, ICER for HBC versus FBC	2008 US$	$3,444.44
			$2,241.00	CE	per life year, ICER for MCC versus FBC	2008 US$	$2,743.07
			$2,251.00	CE	per life year, ICER for HBC versus FBC	2008 US$	$2,755.31
Interventions to prevent LTFU: $22/intervention/person/year	Losina and others 2009	Sub-Saharan Africa, Côte d'Ivoire	$1,200–$3,100 depending on efficacy in reducing LTFU (10%–75%)	CE	per YLS	2006 US$	$1,489.27–$3,847.28
Interventions to prevent LTFU: $41/intervention/person/year			$1,500–$4,900 depending on efficacy in reducing LTFU (10%–75%)	CE	per YLS	2006 US$	$1,861.59–$6,081.18

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Table 4.1 Cost-Effectiveness of Approaches to the HIV Care Continuum (continued)

Intervention	Study	Region or country	Cost per outcome	Cost (C) or cost-effectiveness (CE)	Unit of outcome	Currency as presented (year)	Cost in 2012 US$
Interventions to prevent LTFU: $77/intervention/person/year			$2,000–$8,400 depending on efficacy in reducing LTFU (10%–75%)	CE	per YLS	2006 US$	$2,482.12–$10,424.88
Patient tracer to follow up lost patients	Rosen and Ketlhapile 2010	Sub-Saharan Africa, South Africa	$432.00	C	per patient returned to care	2009 US$	$552.10
Patient tracer to follow up lost patients			$18.00	C	per patient attempted to be traced in the intervention, including those who could not be found through tracing	2009 US$	$23.00
Peer health workers for adherence monitoring and social support	Chang and others 2013	Sub-Saharan Africa, Uganda	$189.00	C	per virologic failure averted	2012 US$	$231.34
			$1,025.00	C	per LTFU averted	2012 US$	$1,254.64
Case management to improve adherence	Marseille 2011	Sub-Saharan Africa, Ethiopia	$33.00	C	per patient served	2009 US$	$42.11
Case management to improve adherence			$84.00	C	per "successful exit" from the case management program	2009 US$	$107.20

Note: — = not available; ART = antiretroviral therapy; DALY = disability-adjusted life year; DNA = deoxyribonucleic acid; EID = early infant diagnostic; FBC = facility-based care; HBC = home-based care; HIV = human immunodeficiency virus; HTC = HIV testing and counseling; ICER = incremental cost-effectiveness ratio; LTFU = loss to follow-up; MCC = mobile clinic care; MSM = men who have sex with men; PCR = polymerase chain reaction; QALY = quality-adjusted life year; STI = sexually transmitted infection; VCT = voluntary counseling and testing; YLS = year of life saved.

hospitals, underscoring the importance of identifying high-risk locations for HIV testing (Siregar and others 2011). In India, one-time voluntary HIV testing in the population was found to be very cost-effective (ICER of US$1,100 per life year saved). The cost-effectiveness of such screening was even greater in high-prevalence areas (ICER of US$1,100 per life year saved) and high-risk groups (US$800 per life year saved) (Venkatesh and others 2013). A strategy of annual screening in high-prevalence districts and high-risk groups was also found to be cost-effective, as was screening every five years in the national population.

Early Infant Diagnosis

In Uganda, one study assessed the cost-effectiveness of incorporating initial screening with rapid HIV tests into the conventional testing algorithm of DNA-PCR to screen out HIV-uninfected infants (Suthar, Ford, and others 2013). Costs per infant were US$23.47 for DNA-PCR screening, compared with US$7.58 and US$22.75 for the modified algorithm that used rapid HIV tests. The modified algorithm was significantly less costly for infants older than age three months. Cost-effectiveness was assessed by calculating the incremental cost per infected infant correctly diagnosed, with parents informed of results. The conventional algorithm had cost-effectiveness ranging from US$539 to US$7,139 per infant correctly diagnosed and with family informed of result, suggesting that screening infants with rapid HIV tests before DNA-PCR is potentially cost-effective in infants older than age three months.

LINKING TO AND ENGAGEMENT WITH HIV CARE

Rationale and Coverage

Linking to HIV care and treatment services after a positive HIV test is a critical, but poorly documented, step in the HIV care continuum. The verbal or written referral process is often insufficient, with significant loss to follow-up (El-Sadr, Gamble, and Cohen 2013; Mugglin and others 2012). In a systematic review of 28 studies from Sub-Saharan Africa, a median of 59 percent of patients testing HIV-positive linked to care (Rosen and Fox 2011). It is important to note that based on the PHIA surveys completed and reported, of all HIV-positive individuals identified through the populations surveys in Malawi, Zambia, and Zimbabwe, a substantial proportion (87%) indicated that they were receiving ART, suggesting excellent ART initiation (ICAP 2016). However, these data do not inform the time from an HIV-positive test to linkage to care and treatment.

A systematic review of linkage of HIV-infected pregnant women revealed a failure to initiate ART among 38 percent to 88 percent of women known to be eligible (Ferguson and others 2012; Psaros and others 2015). Although infants born to a known HIV-infected mother should be engaged in care, linking HIV-exposed infants to appropriate follow-up services has been inadequate (Ahmed and others 2013; Chatterjee and others 2011; Ghadrshenas and others 2013). For children found to be HIV-infected, linking with and entry into care is similarly difficult (Phelps and others 2013).

Guidelines

The WHO identifies linking to HIV care as necessary to realize the full health and prevention benefits of ART (WHO 2013a). However, no consistent guidance exists on the optimal timing from receipt of a positive HIV test to linking to HIV care. The International Association of Physicians in AIDS Care and the Centers for Disease Control and Prevention recommend that individuals testing HIV-positive be linked to care within three months of diagnosis (CDC 2013b; Thompson and others 2012).

Measurements of Linkage to Care

Measuring successful linkage from HIV testing to care is often not feasible because HTS typically record aggregate data on number of tests without individual identifiers (McNairy and El-Sadr 2012). In addition, some studies report links within 30–90 days of an HIV-positive test, while others do not specify the time interval (Medley and others 2013; van Rooyen, Barnabas, and others 2013).

Some HIV programs require HIV-positive individuals to register in the HIV clinic and receive a medical record number and an appointment date for a clinic visit, but not necessarily documentation of an encounter with a clinician (Elul and others 2014). Other programs prefer evidence of receipt of clinical evaluation or a CD4 cell count test (Rosen and Fox 2011).

Barriers

One review of 24 studies (21 of which were from Sub-Saharan Africa) cited the multiple steps needed to enroll HIV-positive individuals into care (Bogart and others 2013; Govindasamy and others 2014). Reasons reported for not linking include fear that HIV-positive status will be purposefully or inadvertently disclosed (Hatcher and others 2012), fear of discrimination and spousal violence or separation (Bogart and others 2013;

Gari and others 2013), and distance to the health facility and transportation costs (Bogart and others 2013; Hensen and others 2012; Posse and Baltussen 2009).

System-level barriers include inconvenient clinic hours; long waiting times; shortages of skilled health care workers; and delays in CD4 cell count, viral load, and EID results. Furthermore, improperly trained or overworked health care workers and clinics where space limits privacy discourage patients from engaging in care (Fayorsey and others 2013; Hensen and others 2012; Posse and Baltussen 2009; Tran and others 2012).

Approaches to Improving Linkage to Care

Individual-Level Approaches

A study from Uganda demonstrated that patients who received extended posttest counseling and monthly visits by peer support workers were 80 percent more likely than other patients to access HIV care (Muhamadi and others 2011). Such programs are encouraged among populations less likely to access and sustain HIV care (Wouters and others 2012). Training for counseling that emphasizes linkage could be a simple and feasible approach to more effectively engage HIV-infected individuals in care.

Use of community health workers (CHWs) and peer educators, who are often themselves HIV-positive, to provide support, guidance, and help with navigation to HIV-positive individuals has shown considerable promise for improving linkage to care (Ackerman Gulaid and Kiragu 2012; Hatcher and others 2012; Kim and others 2012). A study from the United States found that newly diagnosed HIV-positive persons were more successfully linked to care when supported by a case manager (Craw and others 2008). In Kenya, 63.2 percent of patients who received home visits by peers were enrolled in ART within three months (Kohler and others 2011). Similarly, when CHWs were assigned to HIV-infected pregnant women in Malawi at the time of diagnosis, more than 70 percent of eligible women and eligible children received ART (Ahmed and others 2015; Kim and others 2012).

Incentives, including food, conditional cash transfers, and vouchers, have been used to encourage linkage to care (Kundu and others 2012; Solomon and others 2014). In India among PWID, modest voucher incentives significantly improved linkage to HIV care (Solomon and others 2014).

Text messages can help remind patients of appointments, testing, and medication adherence (van Velthoven and others 2013). The HIV Infant Tracking System in Kenya improved linkage to HIV services for HIV-exposed infants, with increased uptake of EID testing and linkage to care for those found HIV-positive, as well as prompt ART initiation (Finocchario-Kessler and others 2014).

Structural-Level Approaches

Point-of-care (POC) CD4 testing has been shown to increase likelihood of timely access to care (Wynberg and others 2014); for those eligible for ART, it has been shown to increase likelihood of initiating ART (Faal and others 2011; Larson and others 2012; Larson and others 2013; Patten and others 2013; Wynberg and others 2014). In South Africa, initiating POC CD4 testing at the time of HIV diagnosis more than doubled the likelihood that patients would initiate ART (Faal and others 2011).

Many countries, particularly in Sub-Saharan Africa, have successfully decentralized HIV care to the primary care level, reducing transport time and costs for patients (Govindasamy, Ford, and Kranzer 2012; Suthar, Hoos, and others 2013). Task-shifting and task-sharing—allowing trained peer health workers, nurses, and other nonphysician cadres to administer HIV services—has enabled decentralization and the scale-up of HIV services. These approaches were implemented in Malawi and Uganda with improved linkage to care and minimal increases to costs (Arem and others 2011; McCollum and others 2010).

Colocating HIV testing and care services may also enhance linkage to care (Torian and others 2008). The effectiveness of this approach has perhaps been best demonstrated with the integration of prevention of mother-to-child transmission into antenatal care services, with dramatic increases in enrollment into care for HIV-infected pregnant and breastfeeding women (Ferguson and others 2012).

Home-based services, including HIV testing, POC CD4 testing, and immediate initiation of ART, may increase linkage to care, especially in rural areas and in settings with high stigma (Helleringer and others 2009; Lahuerta and others 2013; Myer and others 2013). In South Africa, home-based HIV testing, followed by POC CD4 testing, counseling, and referral, was associated with 86 percent of patients' initiating ART within three months (van Rooyen, Barnabas, and others 2013). In Malawi, a program that offered self-testing and immediate ART initiation for those testing HIV-positive showed a significant increase in ART initiation (MacPherson and others 2014).

Cost-Effectiveness Considerations

Individual-Level Approaches

Few of the studies assessing individual-level approaches to promoting linkage to care have evaluated their

cost-effectiveness. In a study of nonmonetary incentives to promote linkage to care in India, an incentive worth US$4 was effective in increasing ART initiation, suggesting that relatively low-cost interventions are capable of making a difference in this step of the care cascade (Solomon and others 2014).

Given that HIV-infected patients gain individual health benefits and generate positive health externalities once they initiate ART, allocating resources to approaches that promote linkage to care has the potential to be more cost-effective than allocating resources to approaches that promote HIV testing in the general population.

Structural-Level Approaches

A study of home-based HIV testing and counseling accompanied by POC CD4 testing and lay counselor follow-up visits in South Africa reported ICERs of US$1,090–US$1,360 per DALY averted depending on the ART initiation criteria used (Smith and others 2015).

RETENTION IN HIV CARE

Rationale and Coverage

Based on evidence of the benefits of ART when initiated at early stages of HIV disease, it is anticipated that the period from diagnosis to ART initiation will be shortened with adoption of the WHO's 2016 guidelines for universal ART (START Study Group 2015; WHO 2015b). A systematic review of 28 studies from Sub-Saharan Africa found that mean retention of adult patients before ART initiation was only 46 percent, and mean retention from determination of ART eligibility to ART initiation was 68 percent (Rosen and Fox 2011). A systematic review indicated that retention on ART among adult patients was 80 percent, 70 percent, and 65 percent at 12, 24, and 36 months, respectively (Fox and Rosen 2010). Loss to follow-up and death were more frequent among men, adolescents and young adults, and pregnant women (DeSilva and others 2009; Lamb and others 2014; Lawn and others 2008; Phillips and others 2014).

Retention in care remains a major challenge for prevention of mother-to-child transmission programs, including those implementing the Option B+ approach—universal treatment for all pregnant and breastfeeding women. Studies demonstrate significant loss to follow-up for pregnant women on ART, especially those newly diagnosed during antenatal care, those who are diagnosed late in pregnancy, younger women, and those at earlier HIV disease stages (Haas and others 2016; Tenthani and others 2014).

A systematic review of eight studies from Sub-Saharan Africa, with a total of 10,741 children, reported that 78 percent to 97 percent of HIV-infected children had a CD4+ cell count measured; 63.2 percent to 90.7 percent of children were assessed for ART initiation; and 39.5 percent to 99.4 percent of eligible children started ART (Mugglin and others 2013). Loss to follow-up and death are significantly higher among children younger than age one year and among those with advanced disease (McNairy and others 2013).

Globally, approximately 1.7 million PWID are living with HIV, only 38 percent of whom are estimated to be receiving ART (WHO 2014c). A systematic review found that loss to follow up among FSWs was only 6 percent, albeit from few available studies (Mountain and others 2014). In a study from Zimbabwe, an estimated 50 percent to 70 percent of HIV-infected FSWs reported being enrolled in HIV care, and only 25 percent to 35 percent accessed ART (Cowan and others 2013). Among MSM in LMICs, data on access to HIV treatment remains limited (Arreola and others 2012; UNAIDS 2014).

Guidelines

The WHO guidelines highlight the importance of retention in care to enable achievement of viral suppression (WHO 2016), including for adults, children, adolescents, and pregnant women. Strategies to increase retention in care include community-level interventions for adults and interventions to enhance retention among pregnant women during the postpartum period, highlighting the importance of follow-up among caregivers for children and development of adolescent-friendly services.

Measurement of Retention in Care

Retention in care is defined as the proportion of patients who remain in care as evidenced by a clinical visit or pharmacy visit within a defined period. For example, for an HIV program that recommends a clinical visit every 3 months, a patient is retained at 12 months if the patient has completed a visit within 3 months of the scheduled 12-month visit.

Barriers

Barriers to retention in care are multifactorial (Bogart and others 2013; Geng and others 2010; Ware and others 2013). Structural barriers include financial constraints such as transport costs and lost work wages, long wait times and inconvenient clinic hours, mobility to seek employment, health care worker attitudes, and perceived low-quality care (Geng and others 2010; Maskew and others 2007). Psychosocial and behavioral barriers

include anxiety and hopelessness, stigma, lack of perceived severity of HIV disease, lack of social support, and reluctance to return after a hiatus from clinic attendance (Wringe and others 2009). Biomedical barriers include inadequate opportunistic infection prevention and management that may hinder clinic attendance and contribute to deteriorating health (Brinkhof, Pujades-Rodriguez, and Egger 2009). In a meta-analysis of 17 studies evaluating loss to follow-up in patients on ART, the most common reasons reported were lack of money, improving or deteriorating health, and transfer to another HIV care site (Brinkhof, Pujades-Rodriguez, and Egger 2009).

Women are often lost to care when they return to their home villages or towns for delivery and postpartum care, and postdelivery when they make the transition to routine ART services (Colvin and others 2014; Phillips and others 2015; Schnippel and others 2015). Retention is particularly challenging for children, who depend on caregivers to bring them for clinic visits. Caregiver fear of disclosing HIV status to the child, unstable family structure, and unsympathetic school environments may lead to loss to follow-up for children (Busza and others 2014; Wachira, Middlestadt, and others 2012).

Engagement and retention in care are particularly difficult for key populations because of systematic exclusion, social and institutionalized stigma, harassment, and other psychosocial barriers that discourage engagement in care after an HIV-positive diagnosis (Baral and others 2012; Mtetwa and others 2013; WHO 2014c).

Approaches to Improving Retention

Several interventions have been noted to enhance retention in care.

Provision of free cotrimoxazole improved 12-month retention by 20 percent among pre-ART patients in Kenya (Kohler and others 2011), and food assistance was associated with increased clinic attendance in Haiti (Ivers and others 2010). Weekly mobile phone communication via text messages to encourage retention is being evaluated in an ongoing study in Kenya (van der Kop and others 2013). HIV treatment programs that include staff or peer workers who conduct outreach for patients who fail to attend clinic visits had higher retention, higher estimated mortality (resulting from more accurate ascertainment of outcomes among those lost to follow-up), and lower loss to follow-up (McMahon and others 2013).

Task-shifting from physician- to nurse-led HIV management has been associated with improved patient retention in several studies from Sub-Saharan Africa (Assefa and others 2012; Brennan and others 2011; Emdin, Chong, and Millson 2013; Fairall and others 2012; Iwu and Holzemer 2014; Sherr and others 2010; Shumbusho and others 2009; Thurman and others 2010). Evidence suggests improved retention for patients who initiate and maintain ART at primary health facilities (full decentralization) versus patients who initiate at secondary health facilities and are maintained at primary health facilities (partial decentralization) (Auld and others 2015; Reidy and others 2014).

In a study from rural Uganda, provision of US$2.50–US$7.00 to patients on ART to cover transportation costs was associated with increased retention at 12 months of between 87 percent and 92 percent (Emenyonu, Thirumurthy, and Muyindike 2010). Several programmatic and research studies are now examining how best to optimize retention of HIV-infected pregnant women (Sturke and others 2014).

Patient ART groups in Mozambique and South Africa, in which one individual is designated to pick up medications for the group, showed more than 95 percent retention in care of patients over 12 months, as well as favorable longer-term outcomes (Luque-Fernandez and others 2013; Rasschaert and others 2014).

For key populations, intensified posttest counseling combined with follow-up counseling by CHWs significantly increased the proportion that were enrolled and retained in HIV care (WHO 2014b; Wouters and others 2012).

Cost-Effectiveness Considerations

Few studies have assessed the cost-effectiveness of approaches to improve retention in HIV care (table 4.1).

Using Treatment Supporters

The cost-effectiveness of approaches that rely on treatment supporters has been assessed in South Africa, where the costs of using patient tracers to determine the status of patients lost to follow-up and to assist patients in returning to care were determined (Rosen and Ketlhapile 2010). Although the average cost per patient attempted to be traced in the intervention (including those not found through tracing) was reasonably low at US$18, because information systems to track deaths and monitor patients who transferred to other sites were not available, the cost of the intervention per patient returned to care was high at US$432.

Eliminating Patient Costs and Providing Incentives

A modeling study estimated the long-term clinical benefits and cost-effectiveness of retention interventions in Côte d'Ivoire (Losina and others 2009), including

eliminating ART copayments, eliminating charges to patients for opportunistic-infection-related drugs, improving personnel training, and providing meals and transportation reimbursements for patients. The intervention costs varied from US$22 per person per year to US$77 per person per year. The results suggest that for a US$22 per person per year intervention that reduces loss to follow-up by 10 percent, the cost-effectiveness ratio of the intervention (compared to no intervention) would be US$3,100 per year of life saved. Using the WHO threshold for cost-effectiveness of 3 × per capita GDP, such an intervention would be cost-effective if it had an efficacy of at least 12 percent (WHO 2014a). Similarly, the more costly US$77 per person per year intervention is also cost-effective, with an efficacy of at least 41 percent.

ADHERENCE TO HIV TREATMENT

Rationale and Coverage

The clinical effectiveness of ART for individuals and to reduce transmission depends on adherence to treatment (Cohen and others 2011; START Study Group 2015). A meta-analysis published in 2006 found that adherence among patients on ART in Sub-Saharan Africa and North America was 77 percent and 55 percent, respectively (Mills, Nachega, Buchan, and others 2006). However, a systematic review of findings from 53 countries indicated that 62 percent of adolescents and young adults (ages 12–24 years) receiving treatment were at least 85 percent adherent to ART (Kim and others 2014). Among children, adherence varies considerably by age and medication formulation but has been estimated to be 75 percent in Sub-Saharan Africa (Vreeman and others 2008). A systematic review of 51 studies reporting on adherence during and after pregnancy found that 77 percent of pregnant women had adequate adherence, but adherence decreased during the postpartum period to 53 percent (Nachega and others 2012).

Lastly, a systematic review of HIV-infected PWID found that ART adherence ranged from 33 percent to 97 percent in LMICs (Feelemyer and others 2015); another systematic review determined that 76 percent of FSWs globally adhered to ART (Mountain and others 2014). ART adherence rates among MSM populations in LMICs have not been reliably estimated.

The lack of broad availability of viral load measurement in LMICs has limited the ability to assess adherence through the effect on viral suppression (Lecher and others 2015). The recently conducted PHIA surveys provide encouraging findings. Overall, the first three surveys completed in Zimbabwe, Malawi and Zambia showed that 88.6 percent of HIV-positive patients who indicated that they were on ART had viral suppression.

Guidelines

Guidelines from both the WHO and the International Association of Providers of AIDS Care recommend a once-daily, fixed-dose regimen, with the goal of facilitating adherence (Thompson and others 2012; WHO 2016). The guidelines also recognize the centrality of excellent adherence to the success of ART for individual as well as population health and the complexity of maintaining adherence to lifetime treatment. To support patient adherence, the WHO recommends implementation of evidence-based interventions, including peer counselors, mobile phone text messages, reminder devices, cognitive behavioral therapy, and behavioral skills training.

Measurement

Adherence measures include self-reporting, pill counts, and pharmacy claims, or more reliably, directly observed therapy (Chaiyachati and others 2011; Kabore and others 2015; Simoni and others 2006). In research contexts, measures include determination of drug concentration in blood samples and use of Medication Event Monitoring System caps on prescription containers (Bulgiba and others 2013; Liu, Ma, and Zhang 2010; Thompson and others 2012).

Barriers

A systematic review of patient-related barriers found that fear of disclosure, stigma, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, high pill burden, decreased quality of life, work and family responsibilities, food insecurity, and limited access to medication are commonly reported barriers (Mills, Nachega, Bangsberg, and others 2006; Young and others 2014). System-level barriers include lack of awareness about ART, stigma, perceived high costs for antiretrovirals and related services, lack of financial means, distance and duration of travel to health providers, lack of consistency and coordination across services, limited involvement of the community in the program planning process, poor clinical practices and health care worker attitudes toward patients, and stock outs of antiretroviral drugs (Bezabhe and others 2014; Coetzee, Kagee, and Vermeulen 2011; Kagee and others 2011).

For pregnant women, additional barriers to adherence include medication side effects, disparate locations for delivery of ART (antenatal care versus ART clinic), and health worker attitudes (Gourlay and others 2013; Hodgson and others 2014; Thompson and others 2012). For children and adolescents, barriers include high pill burden, poorly tolerated formulations, ART side effects, concerns about stigma and discrimination, and a lack of youth-friendly clinical services (Denison and others 2015; Hudelson and Cluver 2015; Lall and others 2015).

Among MSM (Beyrer and others 2010), PWID (Feelemyer and others 2015), and SWs (Mountain and others 2014), mental illness, stigma and discrimination, lack of confidentiality, health worker discrimination, violence, and lack of tailored services, as well as structural barriers such as social and legal critical enablers, frequently discourage HIV-infected patients from adhering to ART care (Grubb and others 2014; WHO 2014b).

Approaches to Enhancing Adherence

A systematic review of adherence interventions in Sub-Saharan Africa identified six interventions that demonstrate efficacy: text messages and other reminder devices, treatment supporters, directly observed therapy, education and counseling, food supplements, and different care-delivery models (Bärnighausen and others 2011).

Data on patient-reported barriers to adherence suggest that efforts to reduce pill burden (with fixed dose combinations) and drug-specific side effects may result in higher adherence (Nachega and others 2014). While data on other strategies targeting HIV-infected pregnant women are limited, adoption of Option B+ may improve adherence when it consists of a once-daily, fixed-dose combination regimen (Ahmed, Kim, and Abrams 2013; Vitalis 2013).

In Sub-Saharan Africa, two randomized trials have shown that text message reminders to patients to take their medication can significantly increase adherence. The overall effect of text messaging was influenced by level of education, gender, and timing and interactivity of the message (Lester and others 2010; Mbuagbaw and others 2013). A recent review of studies evaluating the effect of text messaging on ART adherence noted one study that found that weekly one-way text messages to patients increased the proportion of patients with greater than 90 percent adherence, while another study found that weekly two-way messages (that is, messages sent to the patient with provider follow-up based on the patient's response) increased the proportion of patients with greater than 95 percent adherence and viral suppression (Horvath and others 2012). Another meta-analysis of eight studies reported higher adherence among text message recipients than among controls (Finitsis, Pellowski, and Johnson 2014).

Community adherence support delivered by peers—peer educators or patient advocates—improved retention among both adults and children on ART in South Africa and was associated with decreased mortality (Bemelmans and others 2014; Grimwood and others 2012; Root and Whiteside 2013).

Studies also report significantly improved viral load suppression among patients in HIV programs with peer workers (Chang and others 2010; Pearson and others 2007; Taiwo and others 2010). A randomized controlled study in Rakai, Uganda, observed decreased virologic failure rates among patients at clinics with peer workers compared with those without peer workers (Chang and others 2010).

Decentralizing HIV services from secondary and tertiary health facilities to primary care facilities or community-based adherence clubs has improved virologic suppression (Chishinga and others 2014; Grimsrud and others 2015). Adherence clubs implemented in Cape Town, South Africa, that decentralize care to CHWs and include peer support and self-management features demonstrated only 6 percent loss to follow-up, and fewer than 2 percent of patients experienced viral rebound (Grimsrud and others 2015).

Interventions have been explored to enhance ART adherence among children and adolescents, including counseling, peer support group therapy, medication diaries, directly observed therapy, and improved antiretroviral formulations (Denison and others 2015). A qualitative study of HIV-infected adolescents in Zimbabwe suggested benefit from support group interventions (Mupambireyi and others 2014). A study in Zambia highlighted the importance of family support and life-skills training to enhance adherence to ART for adolescents living with HIV (Denison and others 2015). The introduction of Option B+ with a simplified once-daily, fixed-dose combination regimen is expected to improve adherence among pregnant and breastfeeding women (CDC 2013a).

Among PWID, those who receive care in supportive environments have ART outcomes similar to outcomes of non-PWID HIV-infected individuals (Wolfe, Carrieri, and Shepard 2010). Creating an enabling environment is also critical, including supporting legislation, making policy and financial commitments, decriminalizing behaviors of key populations, addressing stigma and discrimination, empowering specific communities, and addressing violence against people from key populations

(WHO 2014b). Among PWID, opioid substitution therapy was associated with greater ART adherence, supporting the need for integration of drug treatment and HIV treatment services (Malta and others 2008; Milloy, Montaner, and Wood 2012). Among SWs, interventions similar to those mentioned above but tailored to the specific needs of this population have been noted to be effective in improving ART adherence, including adherence counseling and monthly support groups (Graham and others 2013; Huet and others 2011; Konate and others 2011).

Food incentives provided at scheduled appointments have increased ART adherence and have modestly enhanced nutritional status (Cantrell and others 2008).

Cost-Effectiveness Considerations

Only a few approaches to promoting adherence have been assessed for cost-effectiveness (table 4.1). A number of studies that evaluated the efficacy of adherence interventions did not include cost-effectiveness analyses (Bärnighausen and others 2011). In South Africa, it has been estimated that higher ART adherence can reduce health care costs, particularly hospitalization costs (Nachega and others 2010), suggesting that effective adherence approaches could be highly cost-effective and possibly cost saving as well.

Peer Counseling

While the cost-effectiveness of using peer health workers has not been determined in studies, one study has reported on the costs of this approach. In Uganda, an approach that used peer health workers to provide clinical and adherence monitoring and psychosocial support to patients at clinics and during monthly home visits cost US$189 per virologic failure averted and US$1,025 per patient loss to follow-up averted (Chang and others 2013).

Decentralized Care

A study in Uganda that assessed the cost-effectiveness of facility-based care (FBC), home-based care (HBC), and mobile clinics indicated that facility-based ART provision was the least costly, and the ICER for mobile clinic care relative to FBC was US$2,615 per quality-adjusted life year (Babigumira and others 2009). The ICER for HBC relative to FBC was US$2,814 per quality-adjusted life year. Thus, though patient outcomes are often better with mobile care and HBC, their costs result in cost-effectiveness ratios that in some countries exceed the threshold of three times per capita GDP. Nevertheless, these approaches may be warranted in cases in which patient populations reside far from facilities or if the costs of these approaches can be reduced.

CONCLUSIONS

The global HIV response is at a critical crossroads. Although declines in the number of new infections and in HIV-related mortality have been noteworthy, more remains to be done, both to sustain these gains and to accelerate epidemic control (Piot and others 2015).

Achievement of optimal outcomes for HIV-infected individuals and for the prevention of transmission to others is dependent on optimizing every step of the HIV care continuum. As described in this chapter, many promising and efficacious approaches exist to address specific gaps. The findings from the PHIA surveys are encouraging and demonstrate, at least for the first three countries surveyed, good progress toward the UNAIDS 90/90/90 targets, with certain gaps identified particularly in terms of reaching the first 90 target, engaging men and adolescents and young adults. However, for key populations, large gaps remain in achieving the 90/90/90 targets and in addressing the gaps in the HIV care continuum (ICAP 2016).

It is important to note that enhancing one step in the continuum will be insufficient to achieve the overall desired outcome of HIV programs. Thus, research efforts should focus on identifying effective combinations of interventions that target multiple steps along the continuum. Similarly, research studies need to assess the cost-effectiveness of such interventions and packages of interventions across the care continuum. Having information on cost-effectiveness is critical to motivating policy change and resource mobilization.

Now more than ever, identifying cost-effective methods that enable the achievement of high service coverage and quality is essential to controlling the HIV epidemic.

ANNEX

The annex to this chapter is as follows. It is available at http://www.dcp-3.org/infectiousdiseases.

- Annex 4A. Effectiveness of HIV Interventions

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NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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