

The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

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(See the editorial commentary by Lange, on pages 801–802.)

For individuals with human immunodeficiency virus (HIV) infection to fully benefit from potent combination antiretroviral therapy, they need to know that they are HIV infected, be engaged in regular HIV care, and receive and adhere to effective antiretroviral therapy. Test-and-treat strategies for HIV prevention posit that expanded testing and earlier treatment of HIV infection could markedly decrease ongoing HIV transmission, stemming the HIV epidemic. However, poor engagement in care for HIV-infected individuals will substantially limit the effectiveness of test-and-treat strategies. We review the spectrum of engagement in care for HIV-infected individuals in the United States and apply this information to help understand the magnitude of the challenges that poor engagement in care will pose to test-and-treat strategies for HIV prevention.

Over the past decade, antiretroviral therapy has become more potent, better tolerated, and less complex. Today, most human immunodeficiency virus (HIV)-infected individuals receiving combination antiretroviral therapy achieve an undetectable plasma HIV - RNA level [1, 2]. Nevertheless, deficits in the spectrum of engagement in HIV care (Figure 1) including late HIV diagnosis, suboptimal linkage to and retention in HIV care, insufficient use of antiretroviral therapy, and suboptimal adherence to therapy, pose significant barriers to achieving optimal treatment outcomes [3].

These impediments to engagement in HIV care also pose considerable obstacles to the successful implementation of strategies that suggest that early identification of all HIV-infected individuals (“test”) and initiation of antiretroviral therapy in these individuals

(“treat”) could lead to dramatic reductions in the incidence of HIV infection [4–6]. A test-and-treat strategy for HIV prevention is supported by mathematical models and epidemiological data [5, 7, 8]. In addition, locations with high antiretroviral coverage have decreasing incidence of HIV infection [2, 9, 10]. Despite these initial suggestions of success, the barriers to implementation of test-and-treat strategies need to be more fully evaluated.

The first objective of this review is to describe and quantify the spectrum of engagement in HIV care. We then apply these findings to better understand how gaps in the continuum of HIV care affect virological outcomes in the United States and how these gaps need to be addressed for test-and-treat to become a successful HIV prevention strategy. Finally, we explore the possible effects of interventions to improve components of engagement in HIV care.

HIV Infection in the United States

Prevalence and Incidence of HIV Infection

At the end of 2006, ~1.1 million adults and adolescents were living with HIV infection in the United States

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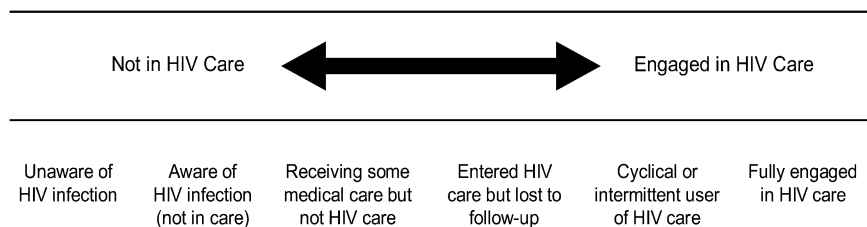


Figure 1. Health Resources and Services Administration (HRSA) continuum of HIV care, describing the spectrum of engagement in HIV care. Adapted from Eldred et al [3].

(prevalence, .45%) [11]. Geographic variability is substantial. In some US cities, HIV seroprevalence exceeds 1%–2%, whereas in populations at high risk of infection, such as men who have sex with men in New York City, HIV seroprevalence exceeds 13% [12–14]. Since 2000, the incidence of HIV infection in the United States has remained stable at ~56,300 new infections per year [15].

Undiagnosed HIV Infection

Of the 1.1 million individuals living with HIV infection in the United States, 232,700 (21%) are estimated to be unaware of their HIV infection [16]. These individuals cannot engage in treatment that reduces morbidity and mortality, may participate more often in high-risk HIV transmission behavior, and have a higher risk of transmitting HIV to others than do those who are aware of their HIV infection [16–20]. Furthermore, among those newly diagnosed, many already have advanced disease. In the United States, 35%–45% of individuals with newly diagnosed HIV infection have AIDS within 1 year after diagnosis [21–27].

Linkage to and Retention in HIV Care

Linkage to Care

Failure to initiate timely HIV care after diagnosis is common. Longer delays in linkage with medical care are associated with greater likelihood of progression to AIDS by CD4 cell criteria. Similar to individuals with undiagnosed infection, HIV-infected individuals not engaged in care pose a greater risk of ongoing HIV transmission [28].

Two prospective, population-based studies have evaluated the extent to which individuals with newly diagnosed HIV infection link to care. In St. Louis, Missouri, 73% of individuals with newly diagnosed HIV infection during 1997–2002 had evidence of having received HIV care within 1 year after diagnosis of HIV infection [29]. In New York City, 64% of individuals with newly diagnosed HIV infection initiated care within 3 months, and 83% entered care within 4 years [30]. In the Antiretroviral Treatment and Access Study, 60% of participants who received only passive referrals to care linked to HIV care within 6 months [31]. In summary, we conclude that ~75% of individuals with

newly diagnosed HIV infection successfully link to HIV care within 6–12 months after diagnosis; 80%–90% link within 3–5 years.

Retention in Care

Successful HIV treatment requires sustained engagement in HIV care [32–34]. Opportunistic illnesses, such as *Pneumocystis jirovecii* pneumonia, are most common in individuals with unknown HIV serostatus and in those who are not receiving HIV care [35, 36]. Three population-based studies from the United States have found that 45%–55% of known HIV-infected individuals fail to receive HIV care during any year [29, 37, 38]. Over longer periods, approximately one-third of HIV-infected individuals fail to access care for 3 consecutive years in some communities [29, 38]. Multiple cohort studies have found that 25%–44% of HIV-infected individuals are entirely lost to follow-up in many settings [39–42], although these individuals may eventually re-establish care. Three European studies found that 27%–60% of out of care HIV-infected individuals return to care in 1–2 years [39,42–44].

In summary, ~50% of known HIV-infected individuals are not engaged in regular HIV care. As a result, these individuals do not have sustained access to antiretroviral therapy, prophylactic medications, or other medical services. Those who receive antiretroviral therapy intermittently are at increased risk of viral resistance [45]. For these reasons, poor engagement in care is associated with poor health outcomes, including increased mortality [32, 33]. In addition, these individuals contribute to ongoing HIV transmission in the community.

Antiretroviral Therapy

HIV-infected individuals who are engaged in care have 4 main barriers to successful treatment with antiretroviral medications: delay or failure to initiate therapy, lack of persistence with therapy, poor adherence to therapy, and viral resistance to antiretroviral medication. In the United States in 2003, ~67% of HIV-infected individuals in care were eligible for antiretroviral therapy on the basis of a CD4 cell count ≤ 350 cells/ μ L; however, 21% of these individuals were not receiving therapy [46]. A more recent analysis from British Columbia found that 89% of

individuals in care required antiretroviral therapy, but ~27% declined or failed to initiate therapy [47]. We estimate that 80% of in-care HIV-infected individuals in the United States should be receiving antiretroviral therapy but that 25% of these individuals are not receiving therapy. Recent guidelines recommend considering antiretroviral therapy initiation when CD4 cell counts decrease to <500 cells/ μ L, which would increase the proportion of in-care individuals eligible for treatment [48, 49].

Persistence with Antiretroviral Therapy

Nonpersistence occurs when therapy is halted prematurely. Patients may stop their medications as a result of medication adverse effects or competing priorities [50, 51], and providers may recommend cessation of therapy in response to clinical or laboratory adverse events or barriers to adherence [52, 53]. In 3 large cohort studies, 4%–6% of individuals who remained in care discontinued their antiretroviral regimen each year [52, 54, 55].

Adherence to Antiretroviral Therapy

A meta-analysis of 31 North American adherence studies found that 55% of HIV-infected individuals achieve adequate adherence [56]. Because antiretroviral therapy has become more potent, better treatment outcomes can be achieved despite lower adherence. With modern initial antiretroviral regimens, 70%–80% adherence leads to durable viral suppression in most individuals [57, 58]. In 2 recent studies from large North American cohorts, 60%–80% of individuals achieved adequate levels of adherence by this new standard [59, 60]. As a consequence of successful viral suppression at lower levels of adherence, the population effectiveness of antiretroviral therapy has increased. Two recent studies found that 78%–87% of individuals receiving antiretroviral therapy, including individuals receiving initial and subsequent regimens, had an undetectable viral load [1, 2].

Resistance to Antiretroviral Medications

Antiretroviral resistance accumulates during virological failure. Antiretroviral resistance also contributes to the failure of antiretroviral therapy. The contribution of antiretroviral medication resistance to regimen failure is unclear but appears to be small, particularly with the advent of new antiretroviral medications and classes. On a population level, rates of transmitted and prevalent resistance are stable or decreasing in some resource-rich settings [1, 61, 62]. This is likely attributable to the high genetic barrier to resistance and/or high potency of the most frequently used regimens [63]. In a large US study from 2006, 15% of individuals with newly diagnosed HIV infection had transmitted antiretroviral resistance—a slightly higher percentage than in prior studies [64].

Nonpersistence, nonadherence, and antiretroviral resistance are barriers to effective antiretroviral therapy, contributing to detectable HIV viremia in 15%–25% of individuals receiving

therapy. However, the majority of individuals receiving antiretroviral therapy in 2010 have undetectable viral loads. Thus, most HIV-infected individuals receiving therapy are at low risk for clinical progression and low risk to transmit HIV to others.

The Spectrum of Engagement in Care: By the Numbers

In Figures 2 and 3a, we synthesize these findings to estimate the spectrum of engagement in HIV care in the United States and the proportion of the HIV-infected population who have an HIV load <50 copies/mL. Approximately 79% of HIV-infected individuals are aware of their HIV infection, but ~50% are not adequately engaged in HIV care. Thus, 60% of HIV-infected individuals in the United States are not receiving regular HIV care because of deficits in diagnosis of HIV infection, linkage to care, or retention in care. Of the remaining 40% of individuals, ~80% require antiretroviral therapy, 75% of whom receive it. Finally, ~80% of treated individuals have an undetectable viral load (defined as < 50 copies/mL). These 210,000 HIV-infected individuals with undetectable viral loads constitute just 19% of the HIV-infected population in the United States. With >80% of HIV-infected individuals in the United States having detectable HIV viremia, it is not surprising that the incidence of HIV infection has not decreased in the United States despite almost 15 years of widespread access to combination antiretroviral therapy. The model in Figure 2 is simplistic, but we are unaware of data from cohorts of individuals tracked over the engagement-in-care continuum that can more precisely determine the true proportion of HIV-infected individuals in the United States with an undetectable HIV load.

These estimates can be used to explore the potential impact of interventions to improve engagement in care on the proportion of HIV-infected individuals with an undetectable HIV load. These simple simulations will also help demonstrate the impact of uncertainty in our engagement-in-care estimates on the projected proportion of HIV-infected individuals in the United States with undetectable HIV loads.

Test-and-Treat Implications

Although there is now a burgeoning interest in the impact of widespread antiretroviral therapy on HIV prevention, this is not new. Approximately 10 years ago, mathematical models were first published to suggest that widespread use of antiretroviral therapy in HIV-infected individuals could reduce the incidence of HIV infection [65–67]. Since that time, epidemiological data have suggested that antiretroviral therapy reduces the risk of HIV transmission in heterosexual sero-discordant couples by 92%–98% [7, 8, 68, 69]. In addition, ecological data have revealed that the incidence of HIV infection may be decreasing

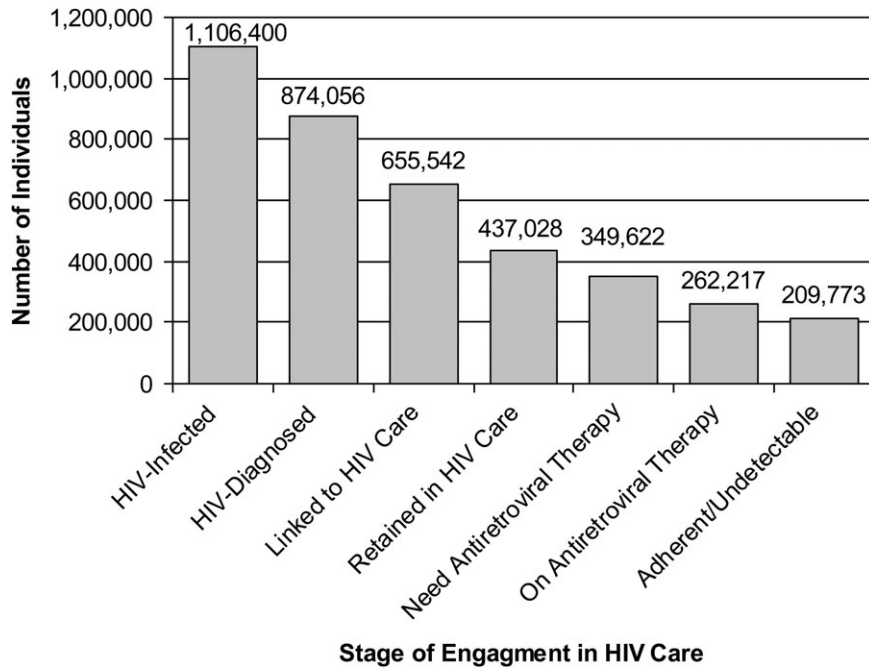


Figure 2. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to full engagement in care, receipt of antiretroviral therapy, and achievement of complete viral suppression. We estimate that only 19% of HIV-infected individuals in the United States have an undetectable HIV load.

in communities with high treatment coverage [2, 9, 10]. Newer mathematical models, using this accumulating data, are more optimistic about the potential usefulness of HIV treatment for the prevention of HIV transmission [5, 70, 71]. In Figure 3, we present simulations of the impact of successful interventions to improve specific components of engagement in care on the proportion of individuals with an undetectable HIV load—a surrogate for individuals unlikely to transmit HIV infection to others. These are not intended to be definitive mathematical

models. Instead, these are presented to provide rough estimates of the magnitude of the barriers that inadequate engagement in care pose to test-and-treat strategies.

Figure 3(b-e) demonstrates that improvement in any single component of engagement in care will have minimal impact on the proportion of HIV-infected individuals in the United States with an undetectable viral load. This occurs because achievement of an undetectable viral load is dependent on overcoming multiple, sequential barriers, each of which has only a modest

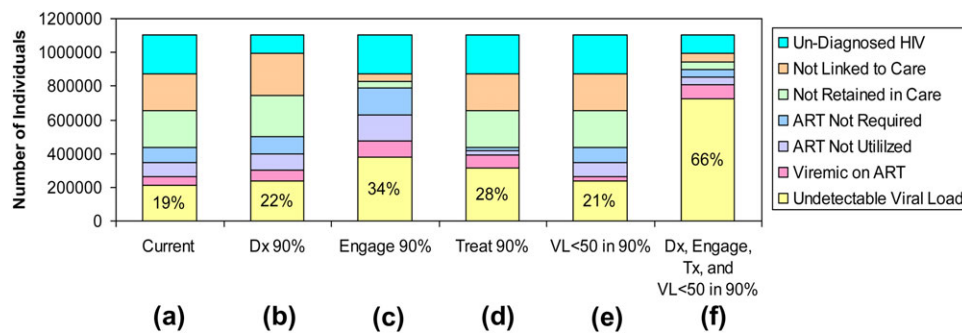


Figure 3. Six simple simulations (a–f) assessing different levels of engagement in care. *a*, Current estimates for engagement in HIV care in the United States: 79% aware of their HIV diagnosis, 50% engaged in care (25% not linked, 25% not retained), 80% require antiretroviral therapy (ART), 75% receive ART, and 80% have an undetectable viral load while receiving ART. For the remaining simulations only the parameter(s) discussed are different. *b*, Assumption that 90% of HIV-infected individuals are aware of their diagnosis. *c*, Assumption that 90% of HIV-infected individuals who have received a diagnosis are engaged in care. *d*, Assumption that 90% of individuals in care receive ART. *e*, Assumption that viral suppression to <50 copies/mL in 90% of individuals receiving ART. *f*, Combination of columns *b–e* by assuming 90% known HIV diagnosis, 90% engagement in HIV care, 90% receipt of ART, and 90% achievement of an undetectable viral load.

impact on overall engagement in care. However, individuals who cannot overcome a specific barrier cannot engage at any subsequent step. Thus, improvement in the entire continuum of engagement in care will be required for test-and-treat strategies to substantially increase the proportion of persons with undetectable viral loads, as shown in Figure 3f. Diagnosis of 90% of HIV infections, achievement of 90% engagement in care, treatment of 90% of engaged individuals, and suppression of viremia in 90% of treated individuals could lead to considerable improvement in the proportion of HIV-infected individuals in the United States with undetectable viral loads. However, even in this ideal scenario, ~34% of HIV-infected individuals will remain viremic, with the potential to spread HIV infection to others.

DISCUSSION

This review demonstrates that incomplete engagement in HIV care is common in the United States and that incompletely engaged individuals account for the largest proportion of HIV-infected individuals with detectable viremia. These findings have direct implications for test-and-treat programs, because disengaged individuals continue to contribute to the ongoing transmission of HIV infection. Although improvements in testing for HIV infection and treatment of HIV-infected individuals will be vital for test-and-treat programmatic success, engagement of HIV-infected individuals in care will be critical for individual health and the prevention of HIV transmission to others.

Although nonadherence to antiretroviral therapy and antiretroviral medication resistance were long viewed as barriers to controlling the HIV epidemic, the advent of more potent regimens has shifted the challenge toward earlier steps in the process of recognition and treatment of HIV infection. A new set of clinical and public health strategies are necessary to address this problem, particularly if test-and-treat programs are to be successful. Little is known about the best ways to link and retain HIV-infected individuals in HIV care. A strengths-based case-management intervention was shown to increase 6-month linkage to care, compared with passive referral, from 60% to 78% [31]. This intervention is widely accepted as the current standard for initial linkage to HIV care, and its results were confirmed in a subsequent community implementation study [72]. The effect of this intervention on retention in care at 1 year was attenuated, however, and overall, less is known about the best ways to retain individuals in care over time.

Soon after the introduction of potent combination antiretroviral therapy, a series of studies funded through a US Health Resources and Services Administration (HRSA) Special Programs of National Significance (SPNS) found that greater engagement in HIV care was associated with greater use of case-management services, mental health services, substance abuse treatment, transportation assistance, and housing assistance

[73]. Subsequently, HRSA identified case management and outreach as a priority for interventions designed to improve retention in HIV care [74]. Interventions funded through a subsequent SPNS initiative included behavioral interventions, intensive case management, patient navigation, life skills training, literacy training, and home-based outreach [75]. As an example of effect size, 4 of the SPNS sites used patient navigation-like interventions, and engagement in care improved from 64% at baseline to 79% at 12 months [76]. The overall conclusion from the HRSA initiative was that outreach activities held promise for engaging and retaining out-of-care persons in HIV medical care [77]. Although costly and labor intensive, such interventions exemplify strategies that simultaneously address several of the barriers described here. Such approaches provide the best current hope for comprehensive management.

Additional research on best practices to link and retain HIV-infected individuals in care is needed. Research will need to be multifaceted to approach the problem of poor retention in care from many angles. Interventions targeting HIV-infected populations, such as provision of mental health or substance abuse services, are important but will need to be complemented by more structural interventions that target the system of health care delivery. The latter may be particularly beneficial, because they should be easier to implement, are more sustainable, and might enhance patient-provider relationships, which clearly promotes successful long-term engagement in HIV care [78]. Patient navigation, intensive case management, cell phone or text-messaging based systems, and integrated informatics to identify at-risk or out-of-care individuals hold promise for further development. Finally, information on the extent to which perceptions of stigma impede engagement in HIV care and interventions should be pursued [79, 80].

One of the limitations of this review is that few studies have assessed the extent to which financial barriers impede access to HIV care in the United States. These barriers include lack of insurance coverage, exclusion of HIV infection as a pre-existing condition, and the high costs of care borne by insured individuals through copayment or coinsurance requirements or coverage limitations. The US Government provides financial support for HIV care for low-income individuals through Ryan White-funded programs [81]. These help support clinical care in many circumstances but do not completely remove the influence and perceived influence of financial barriers on engagement in care. The potential impact of current and future reforms to the US health care system is unknown at this time, but more HIV-infected individuals are likely to qualify for and benefit from coverage under the new system.

Another limitation of this review is the large amount of overlap in the stages of engagement in care. It is difficult to delineate the independent contribution of, for example, poor retention in care, delayed initiation of antiretroviral therapy, and

poor adherence to antiretroviral therapy, when the same individuals are prone to deficits in all of these areas. We have made best estimates from available data, but these are further limited by our cross-sectional representation of the longitudinal process of engagement in care. This limitation in our study is also a limitation of the existing literature, which has not clearly described this series of barriers in patient cohorts over time. Finally, this review is focused on the spectrum of engagement in HIV care in the United States and other resource-rich settings. Obstacles to diagnosis of HIV infection, linkage to and retention in HIV care, and receipt of and adherence to antiretroviral therapy in resource-limited settings are of critical importance to the global HIV epidemic and deserve their own review. Although many of the issues may be similar, the magnitude, causes, and solutions may be quite different.

Proponents of a test-and-treat strategy for HIV prevention are aware of the importance and formidable challenge posed by poor engagement in HIV care [4, 82]. A National Institutes of Health-funded feasibility study called TLC-Plus (Test, Link, and Care-Plus; HIV Prevention Trials Network [HPTN] 065) will assess programs for expanding HIV testing and treatment and linkage to appropriate HIV care and services [83]. Data from this and other studies will help inform the feasibility of test-and-treat strategies. Although complete eradication of HIV infection through test-and-treat programs is unlikely, incremental improvements in methods to overcome the greatest HIV care challenges today in the United States—undiagnosed HIV infection and inadequate engagement in HIV care—will improve the care of HIV-infected populations and decrease the incidence of HIV infection in the future.

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