Antiretroviral Therapy for the Prevention of HIV Transmission: What Will It Take?

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(See the Editorial Commentary by De Cock on pages 1012–14.)

The evidence in support of use of antiretroviral therapy (ART) for prevention of human immunodeficiency virus (HIV) transmission is encouraging and has stimulated optimism for achieving a dramatic change in the trajectory of the HIV epidemic. Yet, there are substantial challenges that, if not addressed, could be the Achilles’ heel for this concept. These challenges require strengthening every step of the HIV care continuum, including expansion of HIV testing to reach all those with HIV infection, effective linkage to and retention in care, timely initiation of ART, and high levels of treatment adherence with viral load suppression. Also important is the identification of individuals with acute HIV infection whose contribution to HIV transmission may be substantial. Implementation research is needed to identify strategies that address these challenges and to determine the efficacy of ART for prevention in key populations as well as to evaluate the effectiveness of combination strategies for HIV prevention at the population level.

Keywords. HIV; prevention; antiretroviral therapy.

Over the past 2 decades, there have been significant achievements in the response to the global human immunodeficiency virus (HIV) epidemic, particularly in sub-Saharan Africa (SSA), the epicenter of the epidemic. From 2002 to the end of 2010, the number of individuals with access to combination antiretroviral therapy (ART) has increased from approximately 200,000 to >8 million persons in low- and middle-income countries [1, 2]. Scale-up of ART has been associated with a decrease in mortality as well as increased worker productivity, increased school attendance, socioeconomic status, and improved family income status [2–5].

Despite these achievements, the HIV epidemic remains substantial with an estimated 2.5 million new infections occurring per year including 330,000 new infections in children [2]. The evidence for efficacy of ART for prevention of HIV transmission has generated tremendous optimism and has been hailed as a turning point in the epidemic.

EVIDENCE IN SUPPORT OF USE OF ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

The HPTN 052 study reported a 96% decrease in linked HIV transmission among stable serodiscordant heterosexual couples in whom the HIV-positive partner was initiated on ART at CD4+ counts between 350 and 550 cells/µL as compared to those who initiated ART at CD4+ counts between 200 and 250 cells/µL [6]. Observational studies have also supported the role of ART for prevention of HIV transmission among serodiscordant couples in Taiwan, Spain, Brazil, China, and SSA [7–13]. Ecological studies also have provided support for the role of ART for prevention. Studies from San Francisco and British Columbia reported a decrease in the number of new HIV infections associated with expanded ART use by HIV-infected individuals in...
those communities [14, 15]. A more recent study from South Africa demonstrated that increased ART coverage for those eligible based on national guidelines was associated with a decrease in HIV incidence [16].

Modeling studies have provided support for the premise that expanded use of ART for prevention could substantially change the trajectory of the HIV epidemic [17]. However, concerns have been raised regarding the optimistic assumptions used in some models and that, in general, these models did not adequately account for risk of development or drug-resistant virus [17–19]. In response, the HIV Modeling Consortium suggested that future models focus on the effects of ART for prevention in the short term, which may provide useful information in financial and policy planning, and incorporate real-life HIV program performance [19].

Use of antiretroviral drugs by HIV-negative individuals, although not the focus of this overview, has also been shown to have promising results for prevention of HIV acquisition. Preexposure prophylaxis was shown to be efficacious in HIV-negative men who have sex with men (MSM) [20], HIV-negative partners in discordant couples [21], women in Botswana [22], and intravenous drug users in Thailand [23]. However, other studies have not confirmed this finding, largely thought to be due to limited adherence (ie, FemPreP, VOICE studies) [24, 25].

THE CALL TO IMPLEMENT ART FOR HIV PREVENTION

In June 2011, in view of the promise of ART for prevention, the global community embraced an ambitious target of achieving 15 million persons living with HIV (PLWH) on treatment by 2015 along the path to what has been referred to as reaching an “AIDS-free generation” [26]. Although the approach to be used for expansion of ART use for prevention may differ in a generalized epidemic such as in southern Africa from that used in a concentrated epidemic within key populations such as the United States, the need for attention to various steps in the HIV care continuum is equally important [27]. Intervention at each of these steps form the combination strategy that is part and parcel of “treatment as prevention” [28], and each step must be implemented with high coverage and quality to achieve the promise of the overall strategy (Figure 1) [29].

THE ACHILLES’ HEEL OF ART FOR PREVENTION

To advance the strategy of ART for prevention, there is the need to be cognizant of the vulnerabilities in this strategy—what we call the “Achilles’ heel.” In this context, the expression refers to a critical weakness that can threaten the overall potential of ART for prevention (Table 1). This article presents an overview of these vulnerabilities.

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**Table 1. Challenges for ART for Prevention**

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<th>Challenge</th>
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<tr>
<td>Unaware of HIV Status</td>
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<td>Late Diagnosis of HIV Infection</td>
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<td>Failure of HIV-Positive Patients to Link to Care</td>
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<td>Late Initiation of ART</td>
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<td>Inability to Achieve and Maintain Viral Suppression</td>
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**Figure 1.** Challenges for antiretroviral therapy (ART) for prevention of human immunodeficiency virus (HIV) transmission.

**HIV Testing**

HIV testing is the first and critical step for HIV prevention and treatment efforts. In countries with high HIV prevalence, universal access to HIV testing is recommended [30], yet <40% of PLWH in SSA know their status, with proportionally fewer men than women [31]. In the United States, HIV testing is recommended as an opt-out test, and high-risk groups are encouraged for repeat testing at least annually [32]. In 2008, as reported by the National HIV Surveillance System, 80% of the estimated 1.2 million PLWH in the United States had been diagnosed [33]. Yet, within specific groups at substantial risk such as MSM, there is a lag in repeat testing to promptly identify newly infected individuals [34].

Expanded testing may be achieved through increased access to testing through community, home, provider-initiated, and self-testing and through increased demand for tests via amplified HIV awareness and dissemination of information regarding the benefits of knowing one’s HIV status. The Project Accept (HPTN 043) study demonstrated a 9-fold higher volume of HIV testing through use of enhanced community-based testing in 48 communities in South Africa, Tanzania, Zimbabwe, and Thailand compared with clinic-based standard counseling and testing, with an increase of testing by men by 45% [35]. Home testing has also been successfully implemented in several countries and offers the opportunity for reaching entire families and households [36, 37]. HIV self-testing may also be a novel way to expand testing. A systematic review of 21 studies on self-testing for HIV in high- and low-risk groups reported that both supervised and unsupervised self-testing strategies were highly acceptable, preferred to
<table>
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<th>Achilles’ Heel</th>
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<th>Potential Solutions</th>
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| HIV testing                   | • Suboptimal testing coverage for high-prevalence settings and for key populations  
  • Infrequent retesting for at-risk populations  
  • Stigma and discrimination  
  • Fear of knowing status and/or denial  
  • Unaware of importance of knowing status                                                                                       | • Expanded community-based or home-based testing  
  • Expanded provider-initiated testing at health facilities  
  • Increase in uptake of self-tests in at-risk groups, among couples and others  
  • Community engagement to destigmatize HIV, promote HIV testing, and provide information on availability of HIV care and prevention programs                                                    |
| Linkage to care               | • Separate facilities and staff provide testing vs care and treatment services  
  • Structural barriers: distance, transport costs, clinic wait times  
  • Behavioral barriers  
  • Biomedical barriers  
  • Lack of required indicator reporting                                                                                      | • Integration of testing and treatment clinics/programs  
  • Same-day clinic appointments for those found to be HIV infected  
  • Point of care CD4⁺ count testing at time of HIV testing  
  • Case managers/peer educators to navigate PLWH to first HIV clinic appointments  
  • Motivational counseling  
  • Increased patient awareness of importance of linkage to care for health benefits  
  • Requiring testing sites to report on linkage outcomes  
  • Implementation research to evaluate structural, behavioral, and biomedical interventions                                      |
| Enrollment in care at advanced stages of HIV disease | • Late HIV diagnosis  
  • Timely HIV diagnosis but late linkage to HIV care due to stigma, fear, lack of knowledge, distance from clinic, unwelcoming environment in clinics and attitudes by providers | • Earlier diagnosis of HIV through expanded HIV testing efforts including community- and home-based testing efforts  
  • Linkage interventions as above  
  • Community engagement to disseminate information regarding importance of HIV care for PLWH and motivate such individuals to enroll in care  
  • Structural interventions to enhance attitudes among healthcare workers and modify clinic procedures to become more convenient and welcoming  
  • Decentralization of services in order to bring clinical services closer to where PLWH are situated  
  • Attention to the needs of key populations through establishment of special programs that meet these unique needs |
| ART initiation                 | • Obstacles to determining eligibility through CD4⁺ count assays and/or knowledge of WHO staging system  
  • Delay in initiation of eligible patients on ART  
  • Patient refusal to initiate ART  
  • Stock-out of antiretroviral drugs  
  • Paucity of trained, skilled healthcare workers                                                                             | • Routine monitoring and identification of ART-eligible patients who are in care and need ART initiation  
  • Laboratory specimen and result transport and transmission systems  
  • Use of point-of-care CD4⁺ cell count machines  
  • Personalized counseling sessions for patients who refuse ART  
  • Strengthened supply chain management and forecasting of ART needs  
  • Training and mentorship of providers on WHO staging criteria to determine ART eligibility in the absence of CD4⁺ testing  
  • Expanded healthcare workforce including nurse initiation of ART  
  • Research to determine motivators and impediments for initiation of ART in PLWH with early HIV disease |
| Retention in care             | • Suboptimal retention in PLWH who have not started ART as well as those on ART  
  • Lower retention rates in PLWH who are asymptomatic with higher CD4⁺ count  
  • Structural barriers of time to clinic, transport costs, lost wages, child care responsibilities  
  • Limited of real-time systems to track patients who miss appointments                                                   | • Implementation research on HIV program modifications to strengthen retention among PLWH who have not yet initiated ART and those on ART  
  • Implementation research on structural interventions to promote retention, particularly among PLWH with early HIV disease  
  • Utilization of mobile technology, peer educators, and/or community strategies to track PLWH who miss appointments within several days of appointment date  
  • Engagement of community resources to facilitate retention of PLWH                                                             |
| Viral load suppression        | • Suboptimal medication adherence  
  • Limited availability of viral load testing  
  • Discordancy between undetectable viral load in plasma and genital track/semen  
  • Limited availability of resistance testing  
  • Limited availability of second and third-line ART regimens                                                          | • Interventions to promote medication adherence for PLWH on ART, particularly those who initiate ART at earlier stages of disease  
  • Choice of regimens that are well tolerated and convenient  
  • Increased availability of viral load monitoring and resistance testing  
  • Use of viral load monitoring and viral resistance assays, if available  
  • Implementation research on interventions to support adherence and on optimal options for monitoring of PLWH on ART  
  • Research on transmission risk in patients with undetectable plasma viral load                                                |
alternative types of testing, and more often resulted in partner testing [38].

**Linkage to Care**

Gaps in linkage of PLWH from HIV testing to enrollment in HIV care has raised the concern that a “positive HIV test often leads to nowhere” [39]. In many HIV programs, data are not available on linkage to care due to lack of required reporting for this parameter and the separate operations of testing and care services [29]. Current rates of reported linkage vary greatly, from 33% to 88% (median 59%) in SSA [40]. In New York City, 23% of HIV-infected patients identified in one study had delayed entry to care >3 months after diagnosis [41]. In 2012, a panel recommended a target of 85% of newly diagnosed individuals be linked to care within 3 months of testing in the United States [42].

A review of 42 studies, the majority from South Africa, reported that the most commonly cited barriers to linkage to care were transport cost and distance from clinic, followed by stigma and clinic factors such as long waiting times [43]. A recent systematic review of 14 studies examining interventions to promote linkage to or utilization of care among HIV diagnosed persons identified that active care coordination in helping or accompanying clients to care, motivational counseling, and increased education about linkage may be helpful in improving linkage to care [44]. Innovative strategies to improve linkage that have shown promising effects include point-of-care CD4+ testing [45] and case managers [46].

**Enrollment in Care at Advanced Stages of HIV Disease**

Late enrollment in care at advanced HIV disease stages jeopardizes individuals’ ability to garner the benefits of earlier diagnosis, treatment, and disease management for their own health, as well as missed opportunities for prevention of HIV transmission to others. This may be due to late diagnosis of HIV infection or failure of those who are aware of HIV infection to present to care. A study analyzing data from the HIV Outpatient Study (HOPS) found that the baseline CD4+ count at entry into care among 1203 patients was 299 cells/µL and did not change substantially from 2001 to 2009 [47]. In comparison, a study from San Francisco of 3588 HIV-infected individuals aged >13 years from 2004 to 2010 reported an increase in median CD4+ count at diagnosis from 384 cells/µL in 2004 to 623 cells/µL in 2010 [48].

In SSA, late entry into care remains a significant challenge, with median CD4+ counts of 154–274 cells/µL in one meta-analysis [49]. In patients enrolling at HIV care programs in 9 SSA countries, the proportion that enrolled in care with CD4+ count <100 cells/µL or World Health Organization (WHO) Stage 4 decreased from 19.8% to 15.6% (P < .001) from 2005 to 2010 with an increase in median CD4+ count at enrollment in care from 254 cells/µL (interquartile range [IQR], 110–458) to 300 cells/µL (IQR, 139–500), respectively [50]. Nonetheless, further progress is needed to achieve earlier diagnosis of HIV infection and entry of such patients into continuity care promptly after diagnosis.

**ART Initiation**

Delayed ART initiation among eligible patients has been shown to be associated with high mortality. In a study of 1235 treatment-naive ART-eligible adults in South Africa, mortality rates were 33.3 deaths per 100 person-years in the pretreatment interval as compared to 19.1 deaths and 2.9 deaths per 100 person-years in the first 4 months of ART and after 4 months of ART, respectively [51]. More than 84% of deaths occurred prior to ART initiation or during the first 4 months, indicating the need for earlier initiation of ART.

Although ART initiation among eligible patients has increased in both developed and developing countries, many patients are still initiating ART late with CD4+ counts below recommended guidelines. In one US cohort, ART initiation increased from 51% in 2001 to 72% in 2009 (P for trend <.001) in

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Table 1 continued.

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<th>Achilles’ Heel</th>
<th>Challenges</th>
<th>Potential Solutions</th>
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<tr>
<td>Acute HIV infection</td>
<td>Contribution to 5%–95% of new HIV infections</td>
<td>Development of inexpensive rapid point-of-care assays for acute HIV infection</td>
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<td></td>
<td>Lack of simple and inexpensive rapid tests for detection of acute HIV</td>
<td>Increased utilization of laboratory-based HIV testing through multiple platform analyzers</td>
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<td>Limited utilization of HIV testing through multiple platform analyzers that detect early HIV infection</td>
<td>Implementation research on interventions to increase provider and population knowledge of signs and symptoms of acute HIV infection</td>
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<tr>
<td></td>
<td>Lack of clinical provider knowledge of acute HIV signs and symptoms and testing for its detection</td>
<td>Implementation research on interventions to increase testing for acute HIV infection by providers</td>
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<td></td>
<td>Lack of awareness by individuals of signs and symptoms of acute HIV infection</td>
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Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PLWH, people living with HIV; WHO, World Health Organization.
one US cohort [52]. In a study that assessed initiation of ART in 9 countries from sub-Saharan Africa, the proportion of HIV-infected adults who initiated ART late with CD4+ count <100 cells/µL or WHO Stage 4 decreased from 43.3% in 2005 to 30.6% (P < .001) in 2010 with an increase in median CD4+ count at ART initiation from 125 cells/µL (IQR, 56–198) to 178 cells/µL (IQR, 110–458) during this time period [50]. To improve this further, efforts are needed to increase HIV testing, linkage to care, and stigma reduction [53].

High rates of acceptance of ART initiation are also important to achieve the promise of ART for prevention. In a study of newly diagnosed individuals in South Africa who were eligible for ART, 20% refused referral to initiate treatment, of whom 92% continued to refuse after 2 months of counseling [54]. The leading reason for refusal was “feeling healthy.” In addition, of 850 participants randomized to the delayed ART initiation arm of HPTN 052 who were offered ART after the release of the randomized portion of the study results, 19% declined ART for reasons of not feeling ready (37%), believing their CD4 was too high (28%), still deciding (9%), and other reasons [55].

Retention in Care
Retention in care has been cited as a critical challenge for HIV programs. Retention is poorer among patients enrolled in HIV care who have yet to initiate ART as compared to patients who have initiated ART [56–58]. Evidence also indicates poorer retention in patients with higher CD4+ counts, a finding of particular importance as at the core of the concept of ART for prevention is the intent to initiate ART in asymptomatic individuals with early HIV disease. In a study from Rwanda that included 18,955 adult patients who enrolled in care from 2004 to 2011, retention was highest among those with lower CD4+ counts and more advanced HIV disease stage in both patients in care and those on ART [59]. In a study from South Africa of 4223 HIV-infected individuals not yet eligible for ART, retention at 1 year by initial CD4+ count was lowest among those with higher CD4+ count [60]. Overall, it is estimated that 25%–33% of HIV-infected persons have initiated ART [40, 49], with less than three-quarters retained in care 1 year after ART initiation [61].

Viral Load Suppression
Viral load suppression in PLWH is required for optimal individual health outcomes and for the concept of ART for prevention. It is important to note that viral load measurement is not routinely available in SSA; thus, data on viral load suppression are limited from such settings. In a meta-analysis of 11 studies of ART for prevention in serodiscordant couples, the rate of HIV transmission from a seropositive partner with viral load <400 copies/mL on ART was zero with an upper 97.5% confidence limit of 1.27 per 100 person-years [62]. An estimated 19%–25% of PLWH in the United States had viral load suppression [33, 63–65]. More recently, it has been estimated that 32% of PLWH were virologically suppressed in British Columbia, 52% of PLWH in Seattle, Washington, and 50% of PLWH in France [66–68], but even these estimates may not sufficiently decrease HIV transmission [18].

An important potential risk of unsuppressed viral load is the development of HIV resistance [69, 70]. Early use of ART for the purpose of prevention poses the challenge of lifelong adherence for many years, particularly as these individuals are likely to be asymptomatic, a group in which adherence may be more limited [71]. HIV drug resistance in SSA is increasing [72, 73], and the ability to detect resistant strains and access to second- and third-line regimens are limited, factors which may limit the impact of treatment for prevention [72].

For individuals who achieve undetectable viral load in the plasma, recent data suggest that some have detectable virus in semen and genital tract secretions in men and women, respectively, which could potentially pose transmission risk despite high adherence to ART.

Detection of Acute and Early HIV Infection
For HIV treatment to be effective for prevention, identification of as many individuals as possible with HIV infection is required. Studies estimate the proportion of HIV infections attributable to acute or early HIV infection to be between 5% and 95% [74]. In a study from Malawi, an estimate of 38% of HIV transmission was attributable to sexual contact with an individual with acute infection [75]. The absence of simple and affordable tests that detect acute infection, however, poses an important challenge. Two studies that evaluated the point-of-care Determine HIV-1/2 Ag/Ab Combo test, which includes p24 Ag testing, in Malawi and Swaziland demonstrated the failure of this test to detect acute infection [76, 77]. To date, the US Food and Drug Administration has approved 2 laboratory-based fourth-generation HIV diagnostic tests that are able to detect early acute HIV [78].

ART COVERAGE SHOULD BE THE OVERARCHING GOAL

Perhaps the most important measure that will determine the potential for ART for prevention is the extent of ART coverage for PLWH within a community. ART coverage has significantly increased in low- and middle-income countries from 47% in 2010 to 54% in 2011 based on 2010 WHO treatment threshold guidelines that included CD4+ count <350 cells/µL and/or WHO Stage 3 or 4 [79]. In developing countries, ART coverage has rapidly expanded, with some countries such as Rwanda and Botswana achieving >80% ART coverage among eligible adults.
as per 2010 WHO guidelines [31]. However, other countries such as Nigeria and Angola have yet to achieve 30% coverage rates [80]. A study from US HIV clinics reported a 9% increase in ART coverage in eligible adults from 74% in 2000 to 83% in 2008 [81]. The effect of the recent changes in WHO guidelines on ART coverage will be important to monitor [82].

To increase ART coverage to those who need treatment for their own health and beyond for the purpose of prevention, there is a critical need to focus on components of the health system including task shifting to increase nonphysician HIV providers [83, 84], an increase in ART access through decentralization of HIV care to primary health centers, consistency of drug supply and laboratory tests, an increase in demand for HIV testing, care, and treatment and availability of supportive services to PLWH and a supportive community [85, 86].

**RESEARCH QUESTIONS**

There is a paucity of data on the efficacy of ART for prevention in key populations such as MSM, persons who inject drugs, and sex workers —populations that contribute a substantial proportion of new HIV infections in various settings [87–90]. Ecological data provide support of effect of ART expansion on number of new infections in injection drug users in Vancouver and Baltimore [15, 91, 92], whereas a modeling study of MSM in the United Kingdom demonstrated a rise in HIV incidence despite high coverage of ART and only a modest increase in condomless sex [93].

Initiation of ART in individuals with early HIV disease poses unique challenges, particularly with regard to demand generation, enhancing acceptability of ART initiation, and adherence with treatment for the long term. In addition, the balance of risks vs benefits of early ART for such individuals remains unclear [94]. Observational studies have shown conflicting results with regard to this balance, particularly in terms of effect on mortality, and were solely conducted in resource-rich settings [93]. Ongoing studies such as the Strategic Timing of Antiretroviral Treatment (START) study are evaluating the risk and benefit of early ART for individuals with CD4<sup>+</sup> count >500 cells/μL, largely in high- and middle-income settings [95]. Further research is needed to evaluate the individual risk-benefits in resource-limited settings [94].

There is also the need for evidence-based implementation science studies on the “how”—how to improve the performance of the health system as related to all the elements of the HIV care continuum. Such studies should aim to evaluate a combination strategy that includes interventions targeted for various steps in the HIV care cascade and its effect on population outcomes for both treatment and prevention. In terms of determining the effectiveness of ART for prevention, 2 studies are planned to address this question, the HPTN (PopART) study to be conducted in South Africa and another study to take place in Botswana [96, 97].

**CONCLUSIONS**

The promise of ART for prevention has stimulated great optimism in confronting the HIV epidemic. However, for this promise to be fully realized, attention must be given to existing vulnerabilities, or Achilles’ heel, which threaten this potential. Attention to relevant health system elements and improvements in each step of the HIV care continuum, from testing to long-term medication adherence, need to be achieved. Most importantly, respecting individual autonomy and patient preferences and desires are of paramount importance as expansion of use of ART for prevention is considered.

**Notes**

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