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# Cascade of Refusal—What Does It Mean for the Future of Treatment as Prevention in Sub-Saharan Africa?

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**Abstract** Recent recommendations by the World Health Organization support treatment for all people living with HIV (PLWH) globally to be initiated at the point of testing. While there has been marked success in efforts to identify and expand treatment for PLWH throughout sub-Saharan Africa, the goal of universal treatment may prove challenging to achieve. The pre-ART phase of the care cascade from HIV testing to HIV treatment initiation includes several social and structural barriers. One such barrier is antiretroviral therapy (ART) treatment refusal, a phenomenon in which HIV-infected individuals choose not to start treatment upon learning their ART eligibility. Our goal is to provide further understanding of why treatment-eligible adults may choose to present for HIV testing but not initiate ART when indicated. In this article, we will discuss factors driving pre-ART loss and present a framework for understanding the impact of decision-making on early losses in the care cascade, with a focus on ART refusal.

**Keywords** Antiretroviral medications · Treatment refusal · Global epidemic · HIV/AIDS · HIV prevention · Science of prevention · ART refusal · Point of testing · Review

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This article is part of the Topical Collection on *The Science of Prevention*

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## Introduction

Over the past 15 years [1], there have been significant advances expanding HIV treatment access in sub-Saharan Africa. Recent studies focused on the timing of antiretroviral therapy (ART) initiation have found that early diagnosis and treatment improves outcomes for people living with HIV (PLWH) [2•, 3•] and prevents HIV transmission to their sexual partners [4]. Based upon these results, the World Health Organization (WHO) has now stated it supports a “test and treat” model of care for all PLWH [5], supported by the Vancouver Statement [6]. If this strategy is ultimately adopted across nations in sub-Saharan Africa, it will lead to an expansive effort to include early-stage individuals in care, many of whom will be asymptomatic.

While there has been a substantial focus on the entire care continuum, the pre-ART period—specifically the time between HIV acquisition, testing, and treatment initiation—deserves special attention. This is a time where barriers to treatment initiation are not yet balanced by the motivation to recover from a debilitating and immediately life-threatening illness. The challenge of expanding treatment to people with earlier disease is supported by the observation that CD4<sup>+</sup> cell counts at linkage to care and at ART initiation have not appreciably increased during the past decade in sub-Saharan Africa, despite multinational efforts to expand ART availability [7].

In this article, we will discuss factors driving pre-ART loss and present a framework for understanding the impact of pre-ART decision-making on early losses in the care cascade, with a focus on ART refusal. Our goal is to provide further understanding of why treatment-eligible adults may choose to present for HIV testing, yet may not initiate ART when indicated. By defining the stages of pre-ART decision-making, we hope to guide future empirical study of the factors related to refusal and corresponding interventions to increase treatment acceptance.

## Identifying the Scope of Loss in the Pre-ART Care Continuum

As of 2014, there were an estimated 36.9 million PLWH. The vast majority of these individuals live in sub-Saharan Africa. Unfortunately, fewer than half (15 million) are currently receiving ART [8], despite widespread voluntary testing and free treatment. This is largely due to losses of PLWH whose CD4<sup>+</sup> counts are too high to render them able to start treatment [9–13] and failure to initiate treatment promptly among those who are already ART eligible at HIV diagnosis [7, 14]. There is a growing body of literature focused on pre-ART losses and the need to understand both structural and socio-behavioral barriers to ART initiation, in order to inform effective combination interventions [15•, 16–18].

Structural barriers to ART initiation exist at every level of the pre-ART care cascade, with continual losses through all stages, from the period prior to testing through entry into care and ART initiation [19–22]. Such barriers can include distance to the testing and treatment center [23–25], costs involved in transport and time lost from work [26, 27], and perceived poor quality of care [28•]. Evidence indicates that decreasing structural barriers to testing through programs such as home-based counseling and testing [29–37] and point-of-care diagnostics [38] may be highly effective in improving rates of treatment initiation. In addition, shifting models of care from centralized top-down programs to more decentralized treatment structures [39, 40], including community-based adherence clubs [41, 42], may decrease barriers to initiating treatment and staying in care [43].

Social factors may also impact the pre-ART care continuum. A particular area of focus has been on the impact of psychological consequences of an HIV diagnosis (e.g., depression [44] and internalized stigma [45–49]) and how it may delay ART initiation [50, 51•, 52]. Other forces, including challenges associated with disclosure [53], fatalistic beliefs [54], and a lack of social support [46] may influence the decision to avoid testing, or treatment initiation. In addition, concerns about medication side effects [55] or a belief that

ART is only reserved for the “sick” may also result in treatment avoidance [51•]. Interventions focused on addressing stigma through alternate means of testing [56, 57] and optimizing disclosure (e.g., through couple’s based counseling) [58] may mitigate some of the challenges associated with test and treat strategies and lead to improved uptake of services in pre-ART care cascade.

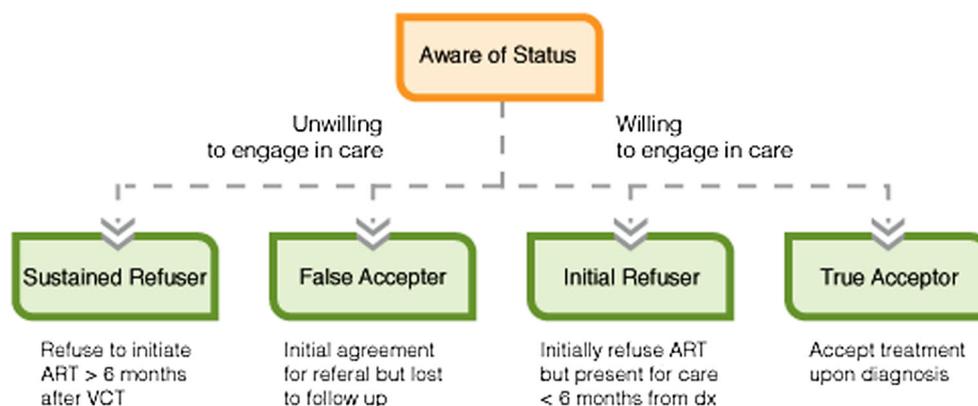
## Four Stages of ART Decision-Making—Developing a Framework for Understanding Its Impact on Early Losses in Care

Pre-ART losses can occur at any point prior to testing, between testing and the receipt of CD4<sup>+</sup> results, and between the receipt of CD4<sup>+</sup> results and ART initiation. As outlined above, social and structural forces may derail PLWH at any of these steps along the continuum. Prior work has focused on losses prior to testing, and between testing and the receipt of CD4<sup>+</sup> results; therefore, we have developed a framework to more clearly define components of treatment initiation.

We have previously explained how ART-related decision-making at the point of testing can be framed in the context of risk aversion and that the pros of known health benefits need to be weighed against the feared risks of medication-associated disclosure and potentially disfiguring side effects of treatment [59]. Based on our research and a growing body of literature focused on developing interventions to reduce pre-ART losses [60], we have refined our understanding of the pre-ART care continuum to encompass four distinct patterns of decision-making among individuals who present for voluntary counseling and testing (VCT) (Fig. 1). While described as four distinct groups, individuals may initially be part of one group and move into another over time.

Individuals may choose to initiate or refuse ART upon learning their eligibility. If they initially refuse and continue to refuse for at least 6 months, they can be classified as “Sustained Refusers.” This group readily acknowledges they are unwilling to start treatment from the time of testing, and

**Fig. 1** Four categories of ART initiation



then continues to be unwavering in this belief, often despite multiple attempts by clinic providers to help engage them in care, including phone calls, text messages, and home visits. While this population presents considerable challenges for care providers, they are often forthright in their desire to forgo treatment from an early stage in the pre-ART care cascade and likely present unique intervention opportunities at the time of testing.

Conversely, those who refuse to initiate upon learning their CD4<sup>+</sup> but change their mind within 6 months are labeled “Initial Refusers.” Initial and sustained refusal may be influenced by different factors. Specifically, concerns about treatment initiation at the point of testing may be related to a sense of wellness and a feeling that they are not yet “sick enough” to start treatment [61]. Whereas those who refuse treatment over a prolonged period tend to express concerns about unwanted disclosure, having a fatalistic worldview, low social support, and fears that medication-associated side effects may render them unable to adhere to a prescribed regimen [50, 51, 62, 63].

Unfortunately, exaggerated beliefs related to ART side effects may have unwittingly been fueled by governmental policies designed to restrict treatment (e.g., the use of CD4<sup>+</sup> cutoffs to guide treatment availability), the usage of medications with severe toxicities early in the HIV epidemic due to cost constraints, and ongoing mandatory pre-adherence counseling sessions [64]. Motivational interviewing may be effective in this population as a way to provide goal-directed, client-centered counseling to elicit behavior change [59, 65–69].

Conversely, individuals may convey a willingness to start treatment at the point of learning of their eligibility. They may then go on to initiate treatment (“True Acceptors”) or fail to start within 6 months (“False Acceptors”). Research on the latter group has shown that structural barriers, including distance from clinic and economic constraints [70], may play a larger role in impeding ART initiation than with “sustained refusers.” Psycho-social factors likely exist, however, including stigma, or poor emotional health, as well as a social desirability bias in reporting intended behavior [28, 70–72]. Rates of “False Acceptors” may be well over 20 % in certain key populations [13, 73, 74] and will likely benefit from combination interventions targeting both structural and psycho-social factors through peer navigation and peer support.

A new long-term strategy for marketing ART should promote more tolerable regimens, and the importance of preventing both long-term complications of HIV inflammation, as well as the benefits of avoiding HIV transmission. Interventions will need to be developed at several levels from public information campaigns to restructuring counseling messages for HIV testing and treatment, to programs that provide direct support for those considering treatment initiation.

## Conclusion

The time between HIV acquisition and ART initiation is a critical period in the treatment continuum. To date, few studies have focused on this vulnerable period [75]. Issues of recruitment and retention remain challenging in this population, and measurement of ART initiation may lack clarity and rigor that has now been well developed and applied in ART adherence research [21, 76, 77]. Yet, it is clear that the cascade of refusal in the pre-ART period remains a critical concern, particularly as treatment is expanded to PLWH earlier in the course of their infection. If a “test and treat” strategy of care is to be adopted in sub-Saharan Africa, there will not only be economic and structural barriers to manage but also deeply held beliefs that ART is associated with illness and even death [51]. Research in this area, which focuses on socio-behavioral intervention design and development, will be critical to the success of treatment as prevention in the time ahead.

## Compliance with Ethical Standards

**Conflict of Interest** Ingrid T. Katz and David R. Bangsberg declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- per cubic millimeter. **INSIGHT and TEMPRANO confirm previous observational studies and add important new evidence that advances our knowledge of the risks and benefits of early ART in patients with CD4+ cell counts of more than 500 cells per cubic millimeter.**
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