A Side Door Into Care Cascade for HIV-Infected Patients?

Timothy B. Hallett, PhD and Jeffrey W. Eaton, PhD

Abstract: HIV Prevention Trials Network studies are testing a number of new technologies for preventing HIV infections and reducing AIDS morbidity and mortality, but strengthening existing antiretroviral therapy (ART) programs may be among the most promising ways to generate greater health benefits using available resources. A cascade to care for HIV-positive patients has been described—HIV testing, retention in pre-ART care, treatment initiation, and sustained suppression on ART—and it has been noted that many patients are lost at each stage. We constructed a detailed representation by combining data from different sources about each stage. We found that, although currently available data were not sufficient to specify several key aspects, the traditional model of the cascade could not fully reconcile trends in HIV testing, linkage to care, retention in pre-ART care, and retention on ART with the large numbers of persons on ART and the large percentage of patients initiating treatment at late stages of infection. We hypothesize that supplementing the traditional linear cascade model with patient health-seeking behaviors that allow patients who are not in pre-ART care to be initiated on ART, is essential to fully characterizing the current functioning of ART programs. We have termed this additional channel to care as the “side door.” Understanding the relative roles of the different channels to care will be important to intervening effectively to improve the cascade to care, and we propose several new types of data that should be collected. With these insights, it may be possible to considerably strengthen the impact of ART programs.

Key Words: HIV care cascade, ART programs, surveillance, side door

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INTRODUCTION

Evidence has accumulated about the benefits of antiretroviral therapy (ART), both for the therapeutic impact for patients and the potential public health benefit through reducing HIV incidence, and a substantial global mobilization has improved the availability of ART in the most severely affected settings in sub-Saharan Africa. Several new HIV Prevention Trials Network studies will test the hypothesis that widespread and early initiation of ART could reduce HIV incidence very substantially. However, continuing late HIV diagnosis, low levels of linkage from HIV testing to care and treatment, and high rates of dropping out from pre-ART and ART in settings with broad access to ART have raised concerns about the feasibility of such an intervention in practice.

Given not only the benefits but also the significant costs and challenges of providing ART, much attention has been devoted to examining how existing ART programs could be modified to provide even greater benefits. Investigations have included the use of different treatment regimens, dosing, and patient monitoring. However, one particularly promising direction has been optimizing treatment through addressing the “cascade of care.”

As a framework for conceptualizing the challenges and barriers to successful HIV treatment, a number of steps have been identified through which patients must pass to be successfully treated: (i) HIV testing and diagnosis; (ii) linkage to clinical care; (iii) retention in pre-ART care (ie, between HIV testing until eligibility for treatment); (iv) ART initiation; and (v) viral suppression through retention and adherence on ART. The conceptualization of the cascade is powerful because it connects the patient’s eventual outcomes and experience on ART with events that happen over time, perhaps many years before ART initiation is required, and at different locations in the community and health system. An “ideal” path for achieving the best health outcomes has been described in which HIV infection is diagnosed early and patients are continuously cared for and monitored until they become eligible for ART, at which time they are promptly initiated onto ART and become virally suppressed. However, accumulating evidence from both high- and low-income settings have documented that the cascade is “leaky”: many patients are lost at each stage, even in settings that have achieved high levels of access to ART, many patients initiate treatment later than would be desired, and treatment outcomes are sometimes suboptimal after patients have initiated treatment. The result is that a small proportion of people living with HIV are estimated to have achieved viral suppression in low- and high-income settings alike. In response to these findings, there have been many calls to improve the cascade of care by making it less leaky. One underlying hypothesis is that improving the pre-ART parts would have the benefit of helping more people to start ART at a CD4 cell count closer to the thresholds for eligibility, which is expected to lead to better survival outcomes. Meanwhile, improving the on-ART parts ensures that those patients who initiate treatment receive the greatest benefit from ART. Moreover, it is tempting to think that the interventions required to make these changes to the cascade would be inexpensive compared with the cost of ART provision itself, suggesting that new cheap interventions would leverage substantial existing spending.

Therefore, an important question is how to intervene on the cascade for maximal effect. Answering this question...
requires understanding the system as it functions currently. In constructing mathematical models to quantify the cascade of care, we found that surveillance data were not entirely consistent with the traditional conception of the cascade. In this article, we first describe the data must be reconciled to represent the cascade of care and present an extension to the traditional cascade concept that we hypothesize may more fully capture the pathways to ART. We discuss its implications and describe how further data collection could improve understanding of the cascade to enable interventions to be chosen strategically for maximum impact.

**CAN WE DESCRIBE THE CASCADE OF CARE?**

Fully characterizing the cascade of care and identifying the points of greatest weakness requires accounting for all HIV-infected persons in the population, determining the type of care each should ideally receive, and determining the care that each person is actually receiving. This requires bringing together surveillance data from the community level and from the different loci of engagements in HIV care. There are at least three major challenges in collecting and using these data to confidently establish a representation of the current operation of the cascade. First, traditionally, these streams of data have been unconnected, but it is precisely the transitions between these services that determine the cascade. Second, the data available from clinics and programs have tended to focus on aggregate indicators for populations, such as number of patients ever started on ART and the numbers of HIV tests performed in a year. These indicators obscure the trajectories of individuals that may enter and exit at particular stages. Third, we inherently do not know what happens to people who are “lost to follow-up”; if they cease to attend a clinic, their outcomes usually cannot be recorded. But, it is the persons lost from or never engaged in services who are of greatest interest for characterizing the cascade.

To reconcile the different sources of data, we constructed a mathematical model to represent the cascade of care and applied the model to Zambia, a setting that has reached high levels of ART coverage but in which many patients initiate ART late and retention on ART is not optimal.15 Mathematical models are useful because they impose consistency on different sources of data and produce estimates to characterize populations for which data are not available. In this case, the model brings together program and clinic indicators (numbers getting HIV tests, numbers retained in care, and numbers retained on ART and distribution of CD4 cell count among ART initiators) with separate data on the demography and epidemiology in Zambia (which determines the number of HIV positive people at a point in time and for how long they have been infected).

**TABLE 1. Main Data Sources Used to Assemble a Representation of the Cascade of Care in Zambia With Summary Discussion of Challenges in Interpretation**

<table>
<thead>
<tr>
<th>Aspects of the System</th>
<th>Statistic</th>
<th>Source</th>
<th>Issues of Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>HIV prevalence trends over time</td>
<td>Sentinel surveillance data among pregnant women.</td>
<td>Potential for bias with respect to national prevalence level.</td>
</tr>
<tr>
<td></td>
<td>HIV prevalence level</td>
<td>Household-based nationally representative44</td>
<td>Potential for bias because of nonparticipation.25,26</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Survival times with HIV without ART</td>
<td>African cohort studies27</td>
<td>Data available are not sufficient to robustly characterize CD4 progression.</td>
</tr>
<tr>
<td></td>
<td>Time spent in CD4 cell count categories</td>
<td>International studies on disease progression28,29</td>
<td>Not known if test kits were used; individuals may have been tested multiple times.</td>
</tr>
<tr>
<td>HIV testing</td>
<td>Number of HIV tests performed.</td>
<td>Number of test kits distributed (2012 UNGASS Report19)</td>
<td>Self-report information can suffer from misreporting biases.</td>
</tr>
<tr>
<td></td>
<td>Proportion of adult population who had HIV test last year</td>
<td>Self-report in household-based nationally representative surveys</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion of tests that are repeat tests.</td>
<td>International literature review and analysis7</td>
<td>Assumption/data not available.</td>
</tr>
<tr>
<td>Linkage and retention in pre-ART care</td>
<td>Proportion of persons who had positive HIV test that were linked to pre-ART care and retained until they were eligible for ART</td>
<td></td>
<td>Few studies were able to estimates the rates; studies from different countries and programs had to be combined in some cases.</td>
</tr>
<tr>
<td></td>
<td>CD4 distribution at ART initiation</td>
<td>Retrospective assessment of medical records</td>
<td>Potential for a bias if records not randomly sampled (e.g. records of deceased patients undersampled).</td>
</tr>
<tr>
<td>Retention on ART</td>
<td>Proportion of patients initiated on ART that are alive and on ART 1 year later.</td>
<td>Retrospective assessment of medical records</td>
<td>Potential for bias if transfers to clinics incorrectly classified as dropouts.</td>
</tr>
<tr>
<td></td>
<td>Proportion of patients initiated on ART who are alive and on ART 12, 24, and 60 months later.</td>
<td>Longitudinal follow-up of patients in clinics, averaged to produce national estimate (2012 UNGASS Report19)</td>
<td></td>
</tr>
<tr>
<td>Reconnecting to ART following dropout.</td>
<td></td>
<td></td>
<td>Factors that determine reconnection to care assumed as data not available.</td>
</tr>
<tr>
<td>Numbers on ART</td>
<td>The number of adults receiving ART at midyear.</td>
<td>Aggregated clinics reports</td>
<td>Potential for overcounting if patients transferring to clinics are considered new or if patients are counted who are no longer receiving treatment.</td>
</tr>
</tbody>
</table>

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with data on the natural history of disease (which determines how many people are eligible for ART). For each type of data, careful consideration is given to how the way in which they were collected affect their interpretation, and some required information is not currently available (Table 1).

In constructing this model, we find that the traditional conceptualization of the cascade of care, as described above, is insufficient to explain all the available data. In particular, the number of people estimated to make it through the apparently very leaky cascade would not predict the large growth in numbers on ART. Furthermore, although, at the beginning of an ART program, there may be large numbers of people with low CD4 cell counts to be absorbed into the program, the number of patients continuing to be initiated onto ART with very low CD4 cell counts is not consistent with the traditional cascade model, leading us to hypothesize that many people that do initiate ART had not been retained in pre-ART care since their first HIV test or were reinitiating ART following an earlier dropout.

### SIDE DOORS INTO THE CASCADE OF CARE

Our proposed modification to the cascade of care concept allows for multiple paths through the stages of HIV care, which contrasts with the traditional model that describes patients passing through these states in a particular order (Figure 1). Although some individuals may initiate ART having been continuously retained in pre-ART care since their first HIV test—whom can be said to have entered ART through the “front door”—others can initiate ART following the onset of illness in advanced stages of disease without prior knowledge of their infection status: such persons may be said to have entered ART in a different way, through a “side door.” Similarly, a person lost from pre-ART care on ART may reconnect with care at a later stage following an episode of illness or other event. However, while the 2 “doors” are not equal in terms of the health-benefits for patients, an entry even through the side door will generate much better outcomes than failing to initiate ART entirely.

By including HIV care-seeking behavior informed by an individual’s health status (e.g. experiencing clinical symptoms associated with low CD4 cell count) as an additional driver for patients initiating ART, we were better able to reconcile the representation of HIV testing and pre-ART care with the scale up of numbers on ART and the high proportions of patients initiating ART with advanced disease. Furthermore, we hypothesize that the propensity for individuals to connect or reconnect to care will be additionally informed by their knowledge of their infection and other events. For instance, a person that has previously had a positive HIV test, even if they subsequently were lost to care, may be more likely to connect to care on becoming ill than a person who was never diagnosed. By the same token, a person who has been on ART at one time may more readily return to care when experiencing certain symptoms than would a person that has never been on ART. Persons with such knowledge may also be more responsive to other events, such as a partner’s negative HIV test or the introduction of a new policy (such as treating couples immediately). In this way, the value of an HIV test is not entirely lost when a patient leaves pre-ART care, because that knowledge may help that person to come back to care later on.

The inclusion of these additional channels leads to hypotheses and potential conclusions about the status of ART programs. First, ART programs may actually be more effective at averting HIV-related deaths than “leaky cascade” statistics imply because patients engage or reengage in care via the side door to start ART when they most need it, albeit later than would be considered optimal given the high risk of mortality and poorer long-term treatment outcomes associated with late ART initiation. Conversely, the effect of changes in policies designed to maximize the prevention benefits of ART, such as earlier ART eligibility, may be less than would be implied by current levels of ART coverage if substantial attention is not also given to understanding the motivations for ART initiation and addressing the leaks in the cascade.

Another prediction of the care-cascade model is that there are a group of HIV-infected persons who have been diagnosed but have not been linked to or have been lost from regular pre-ART care and monitoring. We hypothesize that these previously diagnosed persons may be more likely to present for care via the side door on developing symptoms, and hence HIV testing may have an impact in helping patients initiate ART even if they are subsequently lost from care. It may also follow that interventions aiming to improve linkage between testing and the ART program, and the marginal benefit of pairing testing and linkage together over routine provider-initiated testing, may not be as great as currently thought, because, even without immediate linkage and retention, persons who have had an HIV test may still stand a good chance of initiating ART.

Most importantly, it may not be possible to make an evaluation how to improve cascade unless these “side door effects” are quantified. Thus, we suggest it should be a priority to investigate those processes.
COLLECTING MORE DATA TO BETTER UNDERSTAND THE CASCADE

Our preliminary analysis points to several types of data that would be especially valuable in better understanding the cascade of care.

1. How, when, and why are people tested for HIV? To establish how effective testing programs are at finding new HIV-infected persons and the state in which they enter the cascade after testing (health and CD4 level), additional data are needed about testing. In particular, patterns of repeat testing and reasons for testing (i.e., at pregnancy or owing to illness) should be collected in a longitudinal fashion for individuals sampled randomly in communities and retrospectively for persons entering care.

2. Who is initiating ART? Data on the CD4 cell count and health states of those initiating ART, which can be linked to data on the prior experiences of those patients (their first HIV test, first CD4 cell count, and so on), would be essential to establishing the key outcome of the first part of the cascade. Information about patients’ prior experience with HIV diagnosis, CD4 cell count measurement, and prior ART initiations should be recorded, particularly to detect patients who may have received care in different health facilities. Systems that can routinely identify individuals that are reinitiating ART following an earlier dropout, and even record a reason for reconnecting, would also help specify the profile of patients on ART.

3. What really happens to the “dropouts”? Studies that actively follow-up individuals who seem to have lost to care are needed. The pioneering work by Geng et al24 has suggested that many apparent dropouts have in fact only transferred to another clinic. Dropout from ART is an especially important parameter to quantify as it influences the both the assumed scale and performance of an ART program: if apparently high dropout rates actually signify transfers, then it probably also implies an overcounting in the numbers on ART, giving the impression of a larger and more leaky program than is really the case.

4. Are large numbers of AIDS deaths still occurring, and at which point in the care cascade did failure occur? Even with evidence of the epidemiological, economic,22 and social23 benefits of earlier ART initiation, the first goal for ART programs is to prevent AIDS deaths. To ultimately identify the points of weakness, and potential points of leverage, for improving ART programs, it should be a priority to evaluate what, if any, engagement had been with the HIV-care system. For example, many surveillance activities conduct “verbal autopsies” (asking family members of a deceased person about their condition). These should include specific questions about whether the deceased had ever been diagnosed, was known to have been attending a clinic, had started ART, was currently on ART, or had ceased to be on ART. This would provide some information against which models of the cascade could be compared and validated and whether side doors are effectively bringing persons into care.

CONCLUSIONS

Strengthening the cascade to care in ART programs may be among the best ways to generate further health benefits from existing resources for ART, at least in the short term. However, we have found that the data available from programs are insufficient to accurately characterize the cascade to care, although they were enough to suggest the potential importance of patients’ health-seeking behavior in determining ART outcomes. We hypothesize that patients’ trajectories through care can follow multiple paths and are influenced through a powerful interaction of their own health and knowledge of their condition. Indeed, many more elaborations to the care cascade would be possible than we have discussed here, such as reactions to delays in receiving test results, multiple forms of treatment outcomes (suppression, resistance, etc.), and the role of other events that drive people to health settings, such as pregnancy. Collecting the data necessary to develop a fuller understanding of the cascade, of which we have proposed several types, will be essential for a strategic approach to evaluating and improving the care HIV-infected patients receive.

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REFERENCES


