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Loss to follow-up of adults in public HIV care systems in Mozambique: Identifying obstacles to treatment

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Abstract

Introduction—Access to antiretroviral treatment (ART) has expanded dramatically in resource-limited settings. Evaluating loss to follow-up from HIV testing through post-ART care can help identify obstacles to care.

Methods—Routine data was analyzed for adults receiving services in two public HIV care systems in central Mozambique. The proportion of people passing through the following steps was determined: (1) HIV testing, (2) enrollment at an ART clinic, (3) CD4 testing, (4) starting ART if eligible, and (5) adhering to ART.

Results—During the 12-month study period (2004–2005), an estimated 23,430 adults were tested for HIV, and 7,005 (29.9%) were HIV-positive. Only 3,956 (56.5%) of those HIV-positive enrolled

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at an ART clinic ≤ 30 days after testing. CD4 testing was obtained in 77.1% ≤ 30 days of enrollment. Of 1,506 eligible for ART, 471 (31.3%) started ART ≤ 90 days after CD4 testing. Of 382 with ≥ 180 days of potential follow-up time on ART, 317 (83.0%) had pharmacy-based adherence rates $\geq 90\%$.

Discussion—Substantial drop-offs were observed for each step between HIV testing and treatment, but were highest for referral from HIV testing to treatment sites and for starting ART. Interventions are needed to improve follow-up and ensure that people benefit from available HIV services.

Keywords

HIV treatment; HIV care utilization; loss to follow-up; resource-limited settings

INTRODUCTION

Over the last several years, access to antiretroviral (ARV) medications has expanded dramatically in resource-limited countries, where the majority of people with HIV live. From December 2003 through December 2007, the number of people on antiretroviral treatment (ART) in low- and middle-income countries increased from 400,000 to almost 3 million people, with a concurrent 20-fold increase in Sub-Saharan Africa alone.¹ Mozambique is one high HIV prevalence country that has greatly expanded ARV coverage to its citizens. HIV services were initially provided in “HIV Care Networks”, a model of care that linked HIV testing services, ART centers, and community-based groups. Since free ARVs became available in the public sector in June 2004, the number of people on ART increased from $<2,000$ in 2003 to over 125,000 in December 2008.²

Despite increased access to ARVs, only about 30% of those estimated to need ARV therapy are on treatment.^{1, 3} In areas where services exist, poor service utilization and high rates of loss to follow-up can dramatically limit the population coverage of HIV treatment programs. While prior studies have identified problems in utilization and follow-up in components of HIV care, such as HIV testing or follow-up after starting ART,^{4–7} few have systematically described HIV care utilization and follow-up at the population level through all steps in HIV care.⁸

The aim of this paper is to systematically examine the flow of people from HIV testing to treatment in two urban HIV Care Networks in central Mozambique, to identify bottlenecks that contribute to low service utilization and loss to follow-up. This approach could lead to interventions to improve program effectiveness, and may also be applied to similar resource-limited settings where rapid and equitable expansion of ARV treatment is a priority.

METHODS

Setting and Data Collection

This study used routinely collected data from HIV testing and treatment facilities in two HIV Care Networks in the cities of Beira and Chimoio in central Mozambique. Beira, in Sofala Province, is the 2nd largest city in Mozambique (population approximately 430,000) with one of the highest adult HIV seroprevalence rates in the country at 29% in 2007.⁹ Chimoio, in Manica Province, has a population of about 240,000 and an adult HIV seroprevalence rate of 25%.⁹

This study used data from a retrospective cohort of people testing for HIV between July 1, 2004 and June 30, 2005, the first complete 12-month period after free ARVs became widely available in the public sector. During the analysis period, the HIV Care Networks in both cities included multiple HIV testing centers, but only one primary public ART clinic that provided

free HIV clinical services, including CD4 testing and ART. These two ART clinics were the only source of public-sector ART in their respective provinces. The ART clinics enrolled an average of 353 (Beira) and 219 (Chimoio) new patients per month, and started an average of 66 (Beira) and 47 (Chimoio) new patients on ART per month which was well below the supply of ARV medications at these sites. While Beira city did have one other small NGO-run treatment clinic, this clinic was not included as it was segregated from the larger public system and provided services predominately to pregnant women receiving prenatal care at that site.

This study utilized routinely collected data from HIV testing centers and ART clinics. These data included information entered into paper registers or computerized databases by facility or NGO personnel for program monitoring purposes. From HIV testing centers, two data sources were used: (1) monthly reports of the number tested, and testing HIV-positive, compiled from anonymous site-based paper registers; and (2) computerized databases that captured information from testing registration forms, including a unique HIV test code, sociodemographic information, reasons for testing, sexual practices, and test results. At ART clinics, computerized databases were used that captured sociodemographic and clinical information from medical records, including information about age, gender, site and date of HIV testing, HIV test code, CD4 testing, and antiretroviral treatment. National identification numbers were not recorded at HIV testing sites to maintain anonymity, and were not captured by ART clinic databases.

Measures

To examine the flow of people through these HIV Care Networks, we identified five key steps (the “HIV treatment cascade”) that were required to identify and treat patients with HIV: (1) test for HIV, (2) enroll for care at the local ART clinic, (3) undergo CD4 testing, (4) start ART (if eligible), and (5) adhere to ART (Figure 1). The first step (test for HIV) occurred in HIV testing centers, while the remaining steps occurred in ART clinics. These steps are similar to the 4 steps identified by the Centers for Disease Control and Prevention’s Serostatus Approach to Fighting the HIV Epidemic^{8, 10}, although our model included an additional step within utilization of care and treatment services (CD4 testing) to better measure ART-related aspects of care.

We used routine data to separately calculate the number and proportion of people passing through each step, following the cohort tested for HIV between July 2004 and June 2005. We restricted analyses to adults ≥ 15 years of age, since initial ARV expansion efforts focused on adults and pediatric ARV preparations were not available until mid-2005. The procedure for calculating flow through each of these five steps includes:

Step 1. Test for HIV—We determined the monthly number of adults tested for HIV, and HIV-positive, at three types of public HIV testing facilities between July 2004 and June 2005: voluntary counseling and testing (VCT), prevention of mother-to-child transmission (pMTCT), and youth-VCT centers. VCT centers primarily served people wishing to know their status on their own initiative, although they also provided testing for outpatients referred by clinicians. pMTCT and youth-VCT centers offered “targeted” testing for pregnant women and youth. While pMTCT centers also provided testing to infants and male partners of pregnant women, we only included women testing at these sites since program reports focused on this population. All testing centers performed pre-and post-test counseling by trained counselors, and used rapid HIV tests (Determine®, and Unigold® for confirmation) with results given the same day. The majority (97%) of people tested at these sites are informed of their results. While HIV testing also occurred at hospitals, recording at these sites was not standardized and therefore not included in these analyses. Routine HIV testing of adults did not occur at ART clinics.

As described above, two sources of data were available from HIV testing sites: monthly reports including numbers of people testing, and testing positive, for HIV, and computerized databases which also included the age of testees. Data from monthly reports were generally considered more accurate for total numbers tested, since this only required abstraction of data from in-clinic registers without individual-level data entry. To assess the comparability of these data sources, we compared cumulative and monthly figures during the 12-month study period for the 2 indicators (testing and HIV-positive) obtained from the databases and monthly reports. In only 4 sites were cumulative figures similar (within $\pm 5\%$) for both indicators, and in no site were all 12 individual month figures similar (within $\pm 5\%$), with discrepancies most commonly due to incomplete data entry into computerized databases. After review of the data and consultation with local program managers, 2 strategies were used to determine the number of adults tested at these sites. For 2 sites, we used only the information on testing and age from the computerized databases: one site where discrepancies were low ($<1\%$ cumulative with a maximum individual month discrepancy of 5.6%); and one site where monthly report figures for 2 months appeared to be duplicated with a subsequent year and where discrepancies for the remaining 10 months were low ($<1\%$ cumulative with a maximum individual month discrepancy of 7.5%). In the remaining 9 sites, overall and/or individual month discrepancies were high ($>15\%$) most frequently due to incomplete data entry into computerized databases, and figures from monthly reports were therefore used. For these sites, the number of adults ≥ 15 years of age was estimated by multiplying monthly report figures by the overall proportion of adults testing (and HIV-positive) at that site, as calculated from demographic information in their respective computerized database.

Step 2. Enroll for care at the local ART clinic—HIV-positive persons identified at testing sites included in this study should have been referred by testing counselors to the local ART clinic, as they were the only public clinics offering free HIV treatment services in the respective provinces. The number and proportion of HIV-positive adults who enrolled for care within 30 days after their HIV test was used as a measure of successful referral to the ART clinic. The 30-day time period allowed a time-defined calculation, and included most (95%) of those eventually enrolling for care. The numerator was determined using information on age (and gender for those tested at pMTCT sites), date of ART clinic enrollment, and date/site of HIV testing from the ART clinic database, and the denominator was the monthly totals of HIV-positive adults calculated in Step 1. While the HIV testing and ART clinic databases were theoretically linked by an HIV test code, formal linking was not necessary for our calculations, and capture of this code was often incomplete and non-standardized precluding its use.

Step 3. Undergo CD4 testing—During the analysis period, CD4 tests in the public sector were only available at ART clinics. The number and proportion of ART clinic enrollees who had CD4 tests drawn within 30 days of their enrollment and whose results were received and registered at the ART clinic was used as the measure of CD4 testing. The date recorded in the database and used for this analysis was the date CD4 tests were drawn. As above, the 30-day time period allowed a time-defined calculation, and also included most (91%) of those who eventually underwent CD4 testing. While the number of CD4 tests “lost” between the lab and ART clinic and the lag-time for CD4 results to become available at ART clinics also contribute to patient flow, this data was not collected routinely. In Beira, CD4 tests were drawn daily and run in an on-site laboratory, and results took several days to weeks to arrive at the ART clinic because of batch testing and logistical delays. In Chimoio, CD4 tests were initially shipped to an off-site central laboratory and blood was only drawn several days per week, and results often took several weeks to arrive at the ART clinic. In mid-October 2004, Chimoio acquired on-site CD4 testing which allowed daily blood draws and shortened the time to receive results.

Step 4. Start ART (if eligible)—The clinical criteria for starting ART in Mozambique was similar to those recommended by the WHO for resource-limited settings,¹¹ and included all patients with CD4 counts <200 cells/mm³, patients with CD4 counts <350 cells/mm³ who were also in WHO clinical stage 3 or pregnant, and all patients in clinical stage 4 regardless of CD4 count. The process for starting ART in Mozambique followed Ministry of Health guidelines, and included (1) clinical visits to determine ART eligibility, start cotrimoxazole prophylaxis, and treat opportunistic infections, and (2) a goal of 3 visits with an ART counselor to address psychosocial issues, help patients identify an ART treatment-partner, and counsel patients on ART side effects and adherence; together these visits were expected to take several weeks or months to complete. We determined initial ART eligibility for those patients who successfully passed through steps 1–3 above, using initial CD4 counts and WHO clinical staging information through 30 days after enrollment. For those eligible for ART, we calculated the proportion that started ART within 90 days after their CD4 test. A 90 day time period was used to allow a time-defined calculation, and because CD4 reporting and pre-ART preparation were expected to take less than this period of time.

Step 5. Adhere to ARV medications—Adherence to ARV medications is critical to achieve the benefits of ART and prevent the emergence of resistance.^{12–15} We estimated adherence to ARV medications through 180 days after ART initiation using pharmacy refill data in the ART clinic database. Adherence was defined as the number of medication-days dispensed between the date of ART initiation and the first refill at least 180 days later, divided by the number of days during the same time period. While pharmacy refill data cannot determine whether patients took their medications,¹⁶ pharmacy-based estimates of adherence correlate with self-reported adherence^{17–19} and clinical outcomes.^{16, 17, 20} For adherence calculations, we excluded patients who left the clinic prior to 180 days for reasons unrelated to adherence (i.e. died, transferred to another clinic, or suspended ART by a clinician). Patients otherwise lost to follow-up prior to 180 days were included in adherence calculations and assigned an adherence rate of “0”. We then dichotomized patients as having either good (≥90%) or bad (<90%) adherence.

Analyses

Trends in HIV testing over time were determined using Pearson correlation between study month and the monthly number tested and HIV-positive. Differences in the proportions of patients moving through subsequent steps based on type of HIV testing center, city, and over time, were determined using Chi-squared tests for independence and trend. Multivariate logistic regression was then used to determine the independent relationships between the proportion passing through each step (dependent variable) and city and type of HIV testing center (independent variables). While differences in flow based on type of HIV testing center may seem most relevant to steps 1 and 2, we analyzed flow through subsequent steps based on this variable to determine if the different populations coming from various HIV testing centers had different follow-up rates even after ART clinic enrollment.

Using the results of the calculations for each step, a model was then constructed to determine the flow of people through all steps of the HIV treatment cascade. This model was used to determine the number of people lost at each step (the difference between those eligible for, and those successfully passing through, each step). The model was also used to calculate the additional number of people who would complete all 5 steps if each step was individually improved, assuming that drop-offs for all other steps remained constant and that the rates of ART eligibility were similar among those that did and did not pass through each step. For step 1, we calculated the extra number completing all 5 steps if the HIV testing rate was independently doubled; for steps 2–5, we calculated the extra number completing all 5 steps if each drop-off was independently eliminated (reduced to 0%).

Statistical analyses were performed with SPSS for Windows statistical software (Standard Version 13.0; SPSS Inc, Chicago, IL), and the flow model was produced using Microsoft Office Excel (Edition 2003, Microsoft Corporation, Redmond, WA).

RESULTS

At the beginning of the study period, the HIV Care Network in Beira included 6 HIV testing centers (3 VCT, 2 pMTCT, and 1 youth-VCT) and 1 ART clinic; in Chimoio, there were 5 HIV testing centers (1 VCT, 3 pMTCT, and 1 youth-VCT) and 1 ART clinic. By the end of the study period, 1 additional HIV testing center was added to these HIV Care Networks—a pMTCT center in Beira that began referring patients to the Beira ART clinic in June 2005. Because this site only entered the Care Network in the final month under consideration, it was not included in the analysis.

Step 1. Learn of HIV status

An estimated 23,430 adults were tested for HIV during the study period, and 7,005 (29.9%) were HIV-positive. Seropositivity rates were higher at VCT centers (44.7%) compared with pMTCT (15.5%, X^2 $p<0.001$) and youth-VCT (13.7%, X^2 $p<0.001$) centers. While there was no significant increase in the total number of patients tested for HIV per month over the study period ($r=0.37$, $p=0.23$), there was a significant increase in the number of HIV-positive people identified per month ($r=0.75$, $p=0.005$, Table 1). The number tested and HIV-positive increased significantly in VCT centers in Beira, although testing reduced in pMTCT centers overall and particularly in Chimoio.

Step 2. Enroll for care at the local ART clinic

Of the estimated 7,005 HIV-positive adults passing through step 1, 3,956 (56.5%) enrolled at the local ART clinic within 30 days of their HIV test. In bivariate analyses, successful referral rates were higher for people tested at VCT centers (67.0%) compared with pMTCT (26.4%, X^2 $p<0.001$) and youth-VCT centers (23.5%, X^2 $p<0.001$), and higher in Chimoio compared with Beira (62.4% vs. 53.3%, X^2 $p<0.001$). In multivariate analyses, there was a significant interaction between city and type of HIV testing center, prompting stratified analyses. The relationship between referral and type of HIV testing center was similar when stratified by city (Figure 2). When stratified by type of HIV testing center, referral rates were higher in Chimoio for VCT centers (78.0% in Chimoio vs. 61.3% in Beira, X^2 $p<0.001$), higher in Beira for pMTCT centers (29.3% in Beira vs. 21.7% in Chimoio, X^2 $p=0.001$), and similar in both cities from youth-VCT centers (23.6% in Beira vs. 23.4% in Chimoio, X^2 $p=0.97$). In only 2 sites (one VCT and one pMTCT site from Chimoio), referral rates significantly increased over time (X^2 test for trend $p<0.05$).

Step 3. Undergo CD4 testing

Of the 3,956 adults passing through step 2, 6 enrollees were already taking ART at the time of their enrollment and were excluded from further analyses. Of the remaining 3,950, 3,046 (77.1%) had a CD4 test done within 30 days after ART clinic enrollment. In bivariate analyses, there were no significant differences in CD4 testing between those tested for HIV at VCT (77.4%), pMTCT (75.2%), or youth-VCT (73.3%) centers. The rate of CD4 testing was higher in Beira than in Chimoio (81.5% vs. 70.2%, X^2 $p<0.001$), although in Chimoio the rate of CD4 testing significantly increased over time (X^2 test for trend $p<0.001$) likely due to the availability of on-site CD4 testing in mid-October 2004. Multivariate analyses were similar to bivariate analyses, demonstrating a higher rate of CD4 testing in Beira compared with Chimoio (OR 1.9, 95% CI 1.6, 2.2; $p<0.001$) with no significant differences by type of HIV testing center.

Step 4. Start ART (if eligible)

Of the 3,046 HIV-positive adults passing through step 3, 1,506 (49.4%) were eligible for ART based on information in the database. However, eligibility could not be definitively determined for 735 (24%) patients because of missing WHO staging information; while these patients were classified as ineligible, this classification may have changed with additional staging information. The proportion of those eligible for ART was significantly higher among those tested in VCT centers (51.7%) compared with pMTCT (31.4% , X^2 $p<0.001$) and youth-VCT (34.1% , X^2 $p=0.02$) centers.

Of the 1,506 adults eligible for ART, 735 (48.8%) started ART before July 1, 2006 (the censorship date of our database) at a median time of 71 days after the initial CD4 test, and 471 (31.3%) started ART within 90 days of CD4 testing. In bivariate analyses, the proportion starting ART within 90 days of CD4 testing was higher in Chimoio compared with Beira (36.3% vs. 28.0%, $p=0.001$), and was lower among those tested at pMTCT centers (19.8%) compared with VCT (32.0%, X^2 $p=0.01$) and youth-VCT centers (40.0%, Fisher's Exact $p=0.10$). The results of multivariate analyses were similar, with a higher rate of starting ART in Chimoio (OR 1.4, 95% CI 1.2, 1.8; $p=0.001$) and a lower rate among those tested at pMTCT compared with VCT centers (OR 0.5, 95% CI 0.3–0.9; $p=0.02$). There was also a significant trend for a higher proportion of patients starting ART over time in each city (X^2 test for trend: Beira $p=0.02$; Chimoio $p=0.001$).

Step 5. Adhere to ARV medications

Of the 471 patients passing through step 4 above, 89 (18.9%) patients left the clinic prior to 180 days for reasons unrelated to adherence and were therefore excluded from adherence calculations. Reasons for exclusion included death ($n=75$), transfer to another facility ($n=13$), and suspension of medications by a clinician ($n=1$). Chimoio had a higher proportion of deaths (19.6%) compared with Beira (12.8%, $p=0.045$).

For the remaining 382 patients not excluded from the adherence analysis, 317 (83.0%) had adherence rates $\geq 90\%$. No significant differences in adherence rates were noted in bivariate or multivariate analyses between cities, type of HIV testing centers, or over time.

Overall flow of people through the HIV treatment cascade

Using data from the preceding analyses, figure 3 provides a summary of the overall flow of patients through the HIV care systems in Beira and Chimoio for the 12-month study period. Based on the model, the greatest number of people were lost at step 1 (348,614 people) and 2 (3,049 people). The greatest increase in people completing all 5 steps would occur if the drop-off at step 4 was eliminated (697 people), although substantial increases would also be seen if step 1 was doubled (317 people) or the drop-off in step 2 was eliminated (244 people). Similar relationships were observed when the model was stratified by city and type of HIV testing site (data not shown).

DISCUSSION

This analysis demonstrates the feasibility of applying a systematic approach to identify bottlenecks within HIV care systems in resource-limited settings. Based on our analyses, it is apparent that each step in the HIV treatment cascade is associated with an attrition of people. First, we found that a relatively low proportion of people were tested for HIV (step 1 of our framework). An expansion of testing centers would likely improve coverage of testing; indeed, over 20 new testing sites have opened since July 2005, and HIV testing is being integrated into tuberculosis and outpatient facilities. However, obstacles to testing in existing centers is likely also present, for reasons such as those identified in developed and resource-limited settings

related to education and knowledge of HIV, proximity to facilities, confidentiality, and stigma.^{4, 5, 21, 22} The declines we noted in testing women in pMTCT centers may also be related to other factors, such as staff availability or the use of opt-in (vs. opt-out) testing.

We also observed substantial drop-offs in the referral of HIV-positive people to ART clinics (step 2), particularly from pMTCT and youth-VCT sites. Referral variations could be related to a number of factors, including the reasons for HIV testing, the quality of counseling, community perceptions of ART clinics and ARV medications, the distance from people's homes to ART clinics, and differences in the demographic characteristics of people tested at these sites. The consistently lower rates of referral we observed from pMTCT centers may also result from testing relatively healthy populations not actively seeking HIV testing, or stigma associated with the social vulnerability of women. Other studies of service utilization among HIV-positive pregnant women in pMTCT programs found that frequently less than half receive simple ARV prophylaxis regimens to prevent mother-to-child transmission of HIV,^{23–26} and that issues of stigma, lack of social support, negative interactions with program staff, lack of preparation for HIV testing, and inability to afford transportation costs, may contribute to this low rate of service uptake.^{27, 28} Different strategies may be needed to ensure that women tested at these sites understand their results and are offered sufficient support to access treatment.

Our results also indicate that even among those who were identified as HIV-positive, arrived to the HIV clinic, and underwent CD4 testing within the defined time-periods for these steps, less than 50% of ART-eligible patients started treatment, and less than 33% started treatment within 90 days after CD4 testing. Similar to step 2, loss was most pronounced among women tested for HIV at pMTCT centers. Again, however, this drop-off is not uncommon. In one study from Côte d'Ivoire, only 34% of patients screened in an ARV program did not return for a follow-up visit, and only 51% of those returning and eligible for ARVs actually started treatment.²⁹ While other studies from resource-limited settings report higher rates of starting ART,^{30, 31} these studies do not specifically report denominators of all determined to be eligible within the relevant HIV care system, and may therefore not be comparable to our figures. In studies in developed countries, uptake of ART among eligible patients is also not universal, but rather varies between clinics³² and provider types,³³ and is particularly low among vulnerable groups such as women and those with competing subsistence needs.^{34–38} Follow-up with chronic care, which is strongly associated with starting ART in developed countries,^{35, 39, 40} is also influenced by the perceived need for treatment, satisfaction with care, and the quality of provider-patient relationships.⁴¹ Additional factors such as stigma, an unfamiliarity with chronic care, limited human resource capacity, a cumbersome pre-ART preparation process, and transportation difficulties, may also contribute to the low rates of starting ART that we observed. These issues suggest potential interventions that could improve follow-up in care, such as improved counseling, rapid CD4 testing, reduced pre-ART preparation visits, decentralization of care (including CD4 testing and ART), and nutritional and transportation subsidies.

Our results also indicate that for those successfully passing through steps 1–4 of the HIV treatment cascade, mortality rates are still high within the first 180 days, likely due to delays in HIV testing and moving through the required steps prior to starting ART. However, among those that did not die, transfer to another facility, or suspend ART for clinical reasons prior to 180 days, the short-term ART adherence rates were relatively high, similar to results from other programs in sub-Saharan Africa.⁴² The ART clinics in this study utilized several adherence support strategies, such as requiring several pre-ART counseling visits, involving peer counselors and community-based groups in adherence support, encouraging patients to identify treatment partners before ART, providing modified directly observed therapy, and tracing patients who did not refill medications. However, the high adherence rates we observed may also be because the proportion of eligible patients who actually started ART was quite low,

such that those able to follow-up with stringent pre-ART requirements may be those who can also overcome barriers to ART adherence. The high adherence rates may additionally reflect our inclusion of only patients that successfully navigated the previous steps within defined time periods; future comparisons of outcomes to other groups of patients may help clarify this issue. Further operations research is also needed to determine if reducing pre-ART care requirements may increase ART initiation and reduce mortality, without reducing adherence rates. In addition, assessments of adherence beyond 6-months are required to ensure that capacity exists to support long-term adherence, particularly as loss to follow-up may be substantial over time.⁷

While a number of factors may contribute to the drop-offs we observed in each of the steps in the HIV treatment cascade, many may be related to the centralized model of HIV care that was initially implemented in these sites. Progressively decentralizing HIV services into primary health care facilities, as is currently being done in Mozambique and other resource-limited settings, may improve capacity and patient flow by increasing the number of health workers involved in HIV care and locating services closer to peoples' homes. In other areas, additional operations research may be necessary to specifically identify the causes of drop-offs prior to developing interventions to improve flow. For example, research to understand the reasons for high attrition among women tested at pMTCT centers could point to improved staffing or counseling at these sites, community-based interventions to improve readiness for testing, or strategies to improve the understanding and perception of care at treatment facilities. In all cases, the effectiveness of interventions should be evaluated for their ability to improve flow through the entire system while avoiding negative consequences, such as health worker overload and burn-out, poor adherence levels, and poor quality of care.

Equally important, however, is determining the priorities for achieving the greatest improvement in treatment access over the short and long term. While efforts should be made to improve follow-up at all steps, increasing the flow of patients into ART clinics without improving systems to handle increased workload may over-saturate the clinics and worsen their efficiency. Our data suggest that improving the efficiency of step 4—starting eligible patients on ART—would have a substantial and immediate impact to increase the number of people on ART. Further research is urgently needed to better identify the causes of poor follow-up among ART-eligible patients, and to develop and test strategies to increase ART initiation without reducing post-ART follow-up and adherence.

This study has several limitations. First, our use of routine data raises the possibility of poor data quality, and also limits our analyses to events captured in our data systems. Our routine data systems, for example, do not evaluate whether people received care outside the public system we evaluated, whether they were tested for HIV multiple times, or why they may have dropped-out of care. However, we found that data quality was acceptable, and produced relatively consistent measures between and within sites over time. Prior evaluations of the reliability of the ART clinic databases also showed high concordance between the databases and patient records.^{43, 44} Although our analyses may have misclassified people who sought care at other locations as lost to follow-up, the care systems we evaluated had only one public free ART clinic in the province to which HIV-positive people could be easily referred. When the ART databases were used to detect transfers between Beira and Chimoio for our study population, we identified only 12 HIV-positive adults who tested in one city but enrolled in the ART clinic of the other city, and only 24 adults who transferred cities after ART clinic enrollment (inclusion of all data for these 24 patients would not have affected any time-defined analyses presented here). While developing a research cohort may help reduce data errors and increase the number of measured variables, this method also has limitations inherent in sampling, the introduction of bias caused by study-team follow-up procedures, the need for repetition to evaluate different sites and trends over time, and the diversion of resources away

from improving monitoring systems. Our use of routine data allowed a simple and operational assessment of the key steps in HIV care that could be easily replicated in other care systems and followed over time. More detailed studies could then be undertaken as necessary to better understand and solve the bottlenecks identified in these analyses.

Secondly, we focused our framework to identify obstacles for one component of HIV care: that of providing ART. While other important aspects of HIV care are also important, we focused on the system fundamental to ensure that people have access to appropriate treatment. While other frameworks for providing ART are possible, our steps represented distinct events relevant to the care system in Mozambique that could be discreetly measured using routine data collection systems.

Thirdly, our use of time-defined measures to reflect flow means that those passing through the steps but outside the defined time-period are categorized as “lost”. However, as our intent was to evaluate the efficiency of the HIV care system, we used indicators that incorporated some measure of time. The time definitions we chose were not intended to represent an optimally efficient system; indeed, an optimal system may be one that facilitates ART clinic enrollment on the day of HIV testing, obtains CD4 testing on the day of (or prior to) ART clinic enrollment, and starts ART on eligible patients within days or weeks of eligibility. Rather, our time definitions reflect a conservative estimate at which point all patients should have passed. Future analyses focused on individual steps and including all data regardless of time are necessary to evaluate additional variations in flow and their effects on patient outcomes.

Despite these limitations, efforts to systematically analyze the flow of people through all components of HIV care is a feasible and important step to evaluate the effectiveness of care systems in resource-limited settings. While previous efforts have focused on examining isolated steps in care, simultaneously analyzing all relevant steps can help identify additional programmatic bottlenecks that limit the population effectiveness of HIV treatment programs. It can also serve to help prioritize interventions and policies to overcome the bottlenecks within systems of care, and follow the effects of these interventions over time. In Mozambique, many interventions have occurred since 2005 to address the bottlenecks identified in this analysis, including the expansion of HIV testing locations, changing from opt-in to opt-out testing at PMTCT centers, decentralizing ART care to primary health care clinics, and increasing community involvement in follow-up. Future analyses, similar to those presented here and based on simple and routine data systems, could help evaluate changes in patient flow over time in Mozambique and elsewhere, to ensure that expanded availability of ARVs reaches the people who need it.

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REFERENCES

1. WHO/UNAIDS/UNICEF. Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector: Progress report 2008. World Health Organization: Geneva; 2008.
2. National ART data for December 2008. Mozambique Ministry of Health. 2009
3. Universal Declaration of Commitment on HIV and AIDS: Mozambique Progress Report for the United Nations General Assembly Special Session on HIV and AIDS, 2006–2007. Maputo, Mozambique: Mozambique National AIDS Council; 2008.

4. Hutchinson PL, Mahlalela X. Utilization of voluntary counseling and testing services in the Eastern Cape, South Africa. *AIDS Care* 2006 Jul;18(5):446–455. [PubMed: 16777636]
5. Sherr L, Lopman B, Kakowa M, et al. Voluntary counselling and testing: uptake, impact on sexual behaviour, and HIV incidence in a rural Zimbabwean cohort. *Aids* 2007 Apr 23;21(7):851–860. [PubMed: 17415040]
6. Temmerman M, Quaghebeur A, Mwanyumba F, Mandalisa K. Mother-to-child HIV transmission in resource poor settings: how to improve coverage? *Aids* 2003 May 23;17(8):1239–1242. [PubMed: 12819526]
7. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med* 2007 Oct 16;4(10):e298. [PubMed: 17941716]
8. Giordano TP, Suarez-Almazor ME, Grimes RM. The population effectiveness of highly active antiretroviral therapy: are good drugs good enough? *Curr HIV/AIDS Rep* 2005 Nov;2(4):177–183. [PubMed: 16343375]
9. HIV Epidemiological Surveillance Round, 2007. Maputo: National Directorate of Medical Care, National STD/HIV/AIDS Control Program, Mozambique Ministry of Health; 2008.
10. Janssen RS, Holtgrave DR, Valdiserri RO, Shepherd M, Gayle HD, De Cock KM. The Serostatus Approach to Fighting the HIV Epidemic: prevention strategies for infected individuals. *Am J Public Health* 2001 Jul;91(7):1019–1024. [PubMed: 11441723]
11. WHO. Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach, 2003 Revision. Geneva: World Health Organization; 2004.
12. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 2002 Apr 15;34(8):1115–1121. [PubMed: 11915001]
13. Haubrich RH, Little SJ, Currier JS, et al. California Collaborative Treatment Group. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. *Aids* 1999 Jun 18;13(9):1099–1107. [PubMed: 10397541]
14. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000 Jul 4;133(1):21–30. [PubMed: 10877736]
15. Press N, Tyndall MW, Wood E, Hogg RS, Montaner JS. Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence. *J Acquir Immune Defic Syndr* 2002 Dec 15;31:S112–S117. [PubMed: 12562032]
16. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005 Feb 1;191(3):339–347. [PubMed: 15633092]
17. Fairley CK, Permana A, Read TR. Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting. *HIV Med* 2005 Sep;6(5):366–369. [PubMed: 16156886]
18. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001 Sep 1;28(1):47–58. [PubMed: 11579277]
19. Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001 Dec;13(6):709–720. [PubMed: 11720641]
20. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. *J Acquir Immune Defic Syndr* 2000 Apr 1;23(4):360–361. [PubMed: 10836763]
21. Kalichman SC, Simbayi LC. HIV testing attitudes, AIDS stigma, and voluntary HIV counselling and testing in a black township in Cape Town, South Africa. *Sex Transm Infect* 2003 Dec;79(6):442–447. [PubMed: 14663117]
22. Fortenberry JD, McFarlane M, Bleakley A, et al. Relationships of stigma and shame to gonorrhea and HIV screening. *Am J Public Health* 2002 Mar;92(3):378–381. [PubMed: 11867314]
23. UNICEF. Evaluation of United Nations-Supported Pilot Projects for the Prevention of Mother-to-Child Transmission of HIV. New York: United Nations Children's Fund (UNICEF); 2003.
24. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet* 2002 Jun 15;359(9323):2097–2104. [PubMed: 12086778]

25. Malonza IM, Richardson BA, Kreiss JK, Bwayo JJ, Stewart GC. The effect of rapid HIV-1 testing on uptake of perinatal HIV-1 interventions: a randomized clinical trial. *Aids* 2003 Jan 3;17(1):113–118. [PubMed: 12478076]
26. Perez F, Mukotekwa T, Miller A, et al. Implementing a rural programme of prevention of mother-to-child transmission of HIV in Zimbabwe: first 18 months of experience. *Trop Med Int Health* 2004 Jul;9(7):774–783. [PubMed: 15228487]
27. Painter TM, Diaby KL, Matia DM, et al. Women's reasons for not participating in follow up visits before starting short course antiretroviral prophylaxis for prevention of mother to child transmission of HIV: qualitative interview study. *Bmj* 2004 Sep 4;329(7465):543. [PubMed: 15345628]
28. Bwirire LD, Fitzgerald M, Zachariah R, et al. Reasons for loss to follow-up among mothers registered in a prevention-of-mother-to-child transmission program in rural Malawi. *Trans R Soc Trop Med Hyg.* 2008 May 14;
29. Djomand G, Roels T, Ellerbrock T, et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. *Aids* 2003 Jul;17:S5–S15. [PubMed: 14565604]
30. Stringer JS, Zulu I, Levy J, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *Jama* 2006 Aug 16;296(7):782–793. [PubMed: 16905784]
31. Lawn SD, Myer L, Harling G, Orrell C, Bekker LG, Wood R. Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clin Infect Dis* 2006 Sep 15;43(6):770–776. [PubMed: 16912954]
32. Sackoff JE, McFarland JW, Shin SS. Trends in prescriptions for highly active antiretroviral therapy in four New York City HIV clinics. *J Acquir Immune Defic Syndr* 2000 Feb 1;23(2):178–183. [PubMed: 10737433]
33. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med* 2005 May 23;165(10):1133–1139. [PubMed: 15911726]
34. Andersen R, Bozzette S, Shapiro M, et al. Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. *Health Serv Res* 2000 Jun;35(2):389–416. [PubMed: 10857469]
35. Gebo KA, Fleishman JA, Conviser R, et al. Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001. *J Acquir Immune Defic Syndr* 2005 Jan 1;38(1):96–103. [PubMed: 15608532]
36. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. *Jama* 1998 Aug 12;280(6):547–549. [PubMed: 9707146]
37. Celentano DD, Galai N, Sethi AK, et al. Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users. *Aids* 2001 Sep 7;15(13):1707–1715. [PubMed: 11546947]
38. Cunningham WE, Andersen RM, Katz MH, et al. The impact of competing subsistence needs and barriers on access to medical care for persons with human immunodeficiency virus receiving care in the United States. *Med Care* 1999 Dec;37(12):1270–1281. [PubMed: 10599608]
39. Giordano TP, White AC Jr, Sajja P, et al. Factors associated with the use of highly active antiretroviral therapy in patients newly entering care in an urban clinic. *J Acquir Immune Defic Syndr* 2003 Apr 1;32(4):399–405. [PubMed: 12640198]
40. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported Antiretroviral Therapy in Injection Drug Users: Am Med Assoc. 1998
41. Griffin SJ. Lost to follow-up: the problem of defaulters from diabetes clinics. *Diabet Med* 1998 Nov 15;15:S14–S24. [PubMed: 9829764]
42. Mills EJ, Nachega JB, Buchan I, et al. Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America: A Meta-analysis. *JAMA* 2006;296(6):679. [PubMed: 16896111]
43. Stubbs B, Micek MA, Pfeiffer J, Gremu A, Montoya P, Gloyd S. Understanding the effect of the treatment partner program on adherence to HAART in central Mozambique. 2008(in preparation)
44. Gimbel-Sherr, K.; Micek, MA.; Pfeiffer, J.; Tomo, MI.; Gimbel-Sherr, S.; Gloyd, S. Task shifting to mid-level clinical health providers: an evaluation of quality of ART provided by tecnicos de medicina and physicians in Mozambique. Paper presented at: XVII International AIDS Conference; August 3–8, 2008; Mexico City.

Figure 1.

The HIV treatment cascade, representing the steps required to identify and treat patients with HIV in central Mozambique. The first step (test for HIV) occurs in HIV testing centers, while the remaining steps occur in ART clinics.

Figure 2.

Step 2: Successful referral rates from VCT, pMTCT, and youth-VCT centers in Beira and Chimoio, Mozambique. The proportion of HIV-positive people who enrolled at an ART clinic within 30 days of HIV testing differed among those tested at the various types of HIV testing centers in Beira (left section of figure) and Chimoio (right section of figure).

Figure 3.

Summary of the flow of people through the HIV care system, and major bottlenecks in care. The flow of people through the HIV care systems in Beira and Chimoio is depicted moving from left to right, with the percentage drop-off at each step calculated using the denominator from the previous box. Green boxes represent the 5 steps in the HIV treatment cascade. Yellow boxes represent denominator adjustments based on the results of HIV testing and other relevant clinical information. Pink boxes indicate (1) the number lost at each step, and (2) the number of additional people who would complete all 5 steps of the HIV treatment cascade if the drop off in each step was individually eliminated (or, in the case of HIV testing, if testing rates were doubled) while holding the drop-offs in all other steps constant. As the figure depicts, the greatest number lost are at steps 1 (348,614 people) and 2 (3,049 people), while the greatest additional number starting ART (697 people) could be achieved by individually eliminating the drop-off at Step 4.

Footnotes for Figure 3:

* Total adult population of Beira and Chimoio cities estimated using 2007 census figures; the total population was multiplied by the estimated proportion of adults in Mozambique ≥ 15 years of age (55.1%)

[†] ART eligible based on Mozambique guidelines at the time of this analysis (see text)

[§] Not excluded prior to 180 days for reasons unrelated to adherence (i.e. death, transfer, or ART suspension by a clinician)

^Δ ART adherence calculated as the proportion with $\geq 90\%$ adherence based on pharmacy refill data though 180 days post-ART; patients lost to follow-up assigned an adherence of 0%.

[^] Number lost at each step calculated as the difference between those that completed the step and the denominator from the prior box

[¥] Calculated as the number of additional people who would complete all 5 steps of the HIV treatment cascade if the drop off in each step was individually eliminated (or, in the case of HIV testing, if testing rates were doubled) while holding the drop-offs in all other steps constant

Table 1

Step 1: Average monthly number of people tested for HIV in VCT, pMTCT, and Youth-VCT sites in Beira and Chimoi

City	Testing center type	Number of sites	Avg. tested per month*	Avg. HIV+ per month*	% HIV+ per month	Trend in number tested per month over 12-month study period†		Trend in number HIV+ per month over 12-month study period†	
						r	p-value	r	p-value
Beira	VCT	3	613	286	46.7%	0.89	<0.001	0.86	<0.001
	pMTCT	2	380	81	21.2%	-0.29	0.36	-0.22	0.49
	Youth-VCT	1	67	12	17.9%	-0.18	0.58	-0.27	0.40
Chimoi	Total	6	1,060	379	35.7%	0.70	0.01	0.81	0.001
	VCT	1	359	148	41.3%	0.18	0.56	0.72	0.009
	pMTCT	3	446	48	10.7%	-0.51	0.09	-0.85	0.001
Both	Youth-VCT	1	88	9	10.5%	0.75	0.005	0.59	0.04
	Total	5	893	205	23.0%	-0.18	0.58	0.51	0.09
	VCT	4	972	434	44.7%	0.81	0.001	0.86	<0.001
Total	pMTCT	5	826	128	15.5%	-0.49	0.10	-0.65	0.02
	Youth-VCT	2	155	21	13.7%	0.53	0.08	0.40	0.20
	Total	11	1,953	584	29.9%	0.37	0.23	0.75	0.005

Avg. = average

r = Pearson correlation coefficient

* Average tested and HIV+ per month are monthly averages for the entire 12 month study period

† Trend over the entire 12 month study period is based on Pearson correlation between the study month and the number testing and testing HIV-positive per month