Linkage to HIV Care and Antiretroviral Therapy by HIV Testing Service Type in Central Mozambique: A Retrospective Cohort Study

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Background: Access to antiretroviral therapy (ART) has increased dramatically in resource-limited settings since its introduction a decade ago. However, ART coverage remains low in countries with the highest disease burden, which may be partially explained by poor testing to care linkages. HIV testing service may impact early attrition in the HIV treatment cascade.

Methods: A retrospective cohort study was conducted in 18 clinics in central Mozambique using routine patient data and monthly reports. Patients referred from voluntary counseling and testing (VCT) were compared with those referred from prevention of mother-to-child transmission (PMTCT) for 3 outcomes: (1) enrollment at an HIV clinic ≤30 days after testing HIV positive, (2) CD4 test ≤30 days after enrollment, and (3) ART initiation ≤90 days after first CD4 test.

Results: Patient retention in the HIV care system dropped at each step from HIV testing to ART initiation. Enrollment in HIV care was not significantly different between PMTCT and VCT [risk ratio (RR) = 0.84, 0.72 < RR < 1.02]. Women tested in PMTCT were less likely to have a CD4 test ≤30 days after enrollment when adjusting for age, education level, and marital status (adjusted RR = 0.84, 0.70 < RR < 1.00), and were less likely to initiate ART ≤90 days after their first CD4 test when adjusting for age, education, and marital status (adjusted RR = 0.56, 0.44 < RR < 0.71).

Conclusions: Poor linkages between HIV testing and care hamper efforts to improve coverage for HIV care and treatment services. Increased loss to follow-up among women diagnosed in PMTCT relative to VCT is worrisome and merits further qualitative research and programmatic attention.

Key Words: linkages, HIV testing, antiretroviral therapy, Mozambique, HIV testing to care, operations research

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INTRODUCTION

Mozambique ranks among the top 10 countries with the highest adult HIV prevalence globally.1 HIV prevalence patterns vary regionally in Mozambique, and in the central provinces of Manica and Sofala, adult HIV prevalence is estimated to be 15.3% and 15.5%, respectively.2 In response to the HIV epidemic, Mozambique rapidly expanded antiretroviral therapy (ART) coverage through a national HIV care plan launched in 2004, and the proportion of eligible adults on ART grew from less than 3% in 2003 to 51.7% in 2011.3 Although this increase in ART coverage is impressive, over a quarter of a million HIV-infected ART-eligible adults are still not accessing ART.3

The success of an ART program depends on its ability to find, enroll, treat, and maintain access to care for HIV-positive patients. Loss to follow-up (LTFU) is high at each step in the HIV treatment cascade, varies greatly between treatment clinics, and is especially high before patients begin ART.4–6 LTFU is a complex issue that can be influenced by multiple factors on the individual, health care system, and societal levels.7–11 Assessing follow-up across the treatment cascade is important in LTFU studies because it identifies bottlenecks that can be targeted to achieve improvements in ART coverage.5

One characteristic associated with LTFU is the type of HIV testing center. Studies conducted previously in Mozambique suggest that pregnant women who were identified as HIV infected at prevention of mother-to-child transmission (PMTCT) centers are less likely to be linked to HIV care and...
initiate ART compared with people identified at voluntary counseling and testing (VCT) centers.7 A number of factors could contribute to this difference in retention among testing service types. First, self-referral has been associated with lower LTFU compared with provider-initiated HIV testing, and PMTCT testing is generally provider initiated.12 Second, PMTCT attendees are often healthier, with higher CD4 counts, which has also been associated with higher LTFU.11,13 Additionally, HIV-positive pregnant women may be particularly vulnerable to the burdens of an HIV diagnosis, including concern for the fetus, stigma, uncertainty about disclosure, and additional health care visits necessary for antenatal care.14

To better understand the impact of HIV testing approach on patient flow through HIV care systems, we retrospectively examined a cohort of patients who were identified as HIV infected at VCT and PMTCT and were followed-up through ART initiation at 18 public sector clinics with ART services in central Mozambique.

METHODS

Study Setting

This study included patients identified as HIV infected at PMTCT and VCT centers within the HIV care networks of 18 public-sector ART clinics in the central Mozambique provinces of Manica and Sofala. The first 4 ART clinics in the region began between 2003 and 2005 as centralized centers that received patients from satellite HIV testing locations.15,16 As the HIV care network expanded, PMTCT centers were integrated into antenatal care, VCT centers were integrated into HIV care facilities, and ART clinics were integrated into primary health care.16 During the study period, 15 of the 18 ART clinics had an integrated delivery model, 10 were urban, and 6 were hospitals. Although HIV testing and care centers became widely available throughout Manica and Sofala provinces during the study period, only 18 ART clinics and associated HIV testing services were included in this study as they had patient-level electronic data systems.

Study Population

Study subjects were patients who tested HIV positive between January 1, 2007, and May 1, 2008, at a PMTCT or VCT center in the direct catchment area of the 18 included ART clinics. Analysis was restricted to ART naive adults (age ≥ 15 years) who newly enrolled in HIV care at the ART clinics. Study subjects were assessed for 3 outcomes: (1) enrollment at an ART clinic ≤30 days after testing HIV positive, (2) completion of a CD4 test ≤30 days after ART clinic enrollment, and (3) initiation of ART (if eligible) ≤90 days after the first CD4 test.

Irrespective of the testing site, newly identified HIV-positive patients were referred to an ART care facility and told to present their HIV test card upon arrival. This HIV test card contained information on HIV test date, location, and results of HIV testing. After enrollment at an ART clinic, patients were told to return within ≤2 weeks for the results of their CD4 test.

Patients were excluded from analyses if they were known to have transferred to another clinic or died within the follow-up period for a given outcome, or if their enrollment date was earlier than their test date, their CD4 test date was earlier than their enrollment date, or if their ART start date was earlier than their first CD4 test date.

Data Sources

This study used routine data from HIV testing centers and ART clinics. HIV testing service data provided the number of patients receiving an HIV diagnosis per month via routine facility monthly reports. ART clinic data included site and date of HIV testing, sociodemographic information collected at the time of enrollment, and clinical, laboratory, and pharmacy information collected at each patient visit to the clinic. Facility-based personnel maintained the databases primarily for routine program monitoring purposes, and the clinic databases have been validated over the study period.5,15–18

Variable Definition and Covariates

Detailed definitions used for linkage outcomes and exclusions are presented in Table 1. For analyses of ART treatment outcomes, LTFU was defined as a patient not returning to pick up their medication for >60 days. Patient-level covariates were considered for inclusion in analysis

| TABLE 1. Variable Definitions and Exclusions for HIV Testing Center Type and 3 HIV Linkage Outcomes |
|---|---|---|
| Factor | Definition | Exclusions |
| HIV testing type | Determined by name of testing center in patient’s ART file compiled from paper referral forms given to patients at HIV testing center | Any males tested at PMTCT centers |
| ART clinic enrollment | Patients “successfully enrolled” at ART clinic if ≤30 d from testing HIV positive | If listed HIV testing center and HIV test date corresponded with missing monthly total of HIV-positive tests at the given center |
| CD4 testing | Those undergoing CD4 test ≤30 d after “successful” ART enrollment | |
| ART initiation | ART initiation ≤90 d after “successful” CD4 testing for all ART-eligible patients. ART eligibility based on national guidelines defined as patients with CD4 <200 cells per mm$, patients with CD4 counts <350 cells per mm$ who were also in WHO clinical stage 3 or pregnant, and all patients in WHO clinical stage 4 regardless of CD4 count | |

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based on their theoretical potential to confound the relationship between HIV testing location and study outcomes.

**Statistical Analysis**

Outcome percentages were calculated by dividing the numerator (the number of patients who went on to the next step in the treatment cascade within the allotted time frame) by the denominator (the number of patients from the previous step minus the patients who were excluded for the outcome being calculated). Cumulative percentages were based on the original number of patients who tested HIV positive and were calculated by multiplying the percentages that moved on at each step in the treatment cascade.

Generalized linear models for the binomial family were used to estimate the association between site of HIV testing and each of the study outcomes. Risk ratios (RR) were estimated using the log link function. Analyses of CD4 and ART outcomes accounted for clinic-level clustering using generalized estimating equations, and analysis of enrollment was clustered at the level of HIV testing service. Analyses of ART treatment outcomes used the standard life table approach and competing risks cause-specific cumulative incidence calculations.

The study was approved by the institutional review boards of the Mozambique Ministry of Health and the University of Washington. All analyses were conducted in Stata 13 (College Station, TX).

**RESULTS**

**Cohort Characteristics**

In the ART clinic databases, 24,820 (74%) of 33,640 patients who tested HIV positive were matched to the testing center data by the month and site of HIV testing (Fig. 1). Of these, 2083 (8.4%) patients did not meet the eligibility criteria due to the following: age <15 years (n = 1628), not the first ART clinic enrollment (n = 263), male tested at PMTCT (n = 113), or enrolled before 2007 (n = 33). Patients were excluded from analysis of outcome 1 because their enrollment date was earlier than their HIV test date. Patients were excluded from analysis of outcome 2 because 341 (1.6%) left the clinic within 30 days of enrollment due to transfer or death, 325 (1.5%) had a CD4 test date listed as earlier than their enrollment date, and 1 (<0.0%) had a CD4 test but did not have a listed CD4 date. Patients were excluded from the ART analysis because 434 (6.3%) died or transferred clinics ≥90 days after their first CD4 test and 12 (0.2%) had an ART start date that was earlier than their first CD4 date.

**FIGURE 1.** Study flow chart stratified by HIV care type (VCT vs. PMTCT). Patients were dropped if younger than 15 years (N = 1628), missing age (N = 30), not HIV positive (N = 16), not the first ART clinic enrollment (N = 263, 1.1%), male tested at PMTCT (N = 113), or enrolled before 2007 (N = 33). Patients were excluded from analysis of outcome 1 because their enrollment date was earlier than their HIV test date. Patients were excluded from analysis of outcome 2 because 341 (1.6%) left the clinic within 30 days of enrollment due to transfer or death, 325 (1.5%) had a CD4 test date listed as earlier than their enrollment date, and 1 (<0.0%) had a CD4 test but did not have a listed CD4 date. Patients were excluded from the ART analysis because 434 (6.3%) died or transferred clinics ≥90 days after their first CD4 test and 12 (0.2%) had an ART start date that was earlier than their first CD4 date.
(n = 113), enrollment before 2007 (n = 33), missing age (n = 30), or not HIV infected (n = 16). Thus, a total of 22,737 patients enrolling in an ART clinic were included in this study.

Of these 22,737 patients, 151 (0.7%) were excluded from the enrollment analysis because their recorded enrollment date was before their HIV test date. A total of 667 (2.9%) were excluded from the CD4 analysis due to transfer or death within 30 days of enrollment (n = 341, 1.6%), having a CD4 test date was earlier than their enrollment date (n = 325, 1.5%), or having a CD4 test without a listed CD4 date (1, 0.0%). A total of 446 patients (6.5%) were excluded from the ART analysis due to death or clinic transfer within 90 days after their first CD4 test (434, 6.3%) or an ART start date that preceded the first CD4 date (12, 0.2%). The proportion of patients who were known to be lost due to death or transfer within 120 days of clinic enrollment was greater in VCT (n = 937, 5.6%) than PMTCT (n = 34, 0.6%).

Demographic characteristics of the 22,737 patients enrolled in ART clinics are presented in Table 2. Briefly, those tested at VCT centers were on average almost 10 years older, had higher education levels, were less likely to be married, had lower baseline CD4 counts, were more likely to be in WHO stage III or IV, and were more likely to attend a vertical ART clinic.

### Measures of Patient Flow

With VCT and PMTCT combined, 21,889 patients (96%) enrolled at an ART clinic ≥30 days after testing HIV positive [22,582 (99%) enrolled at some point]. A total of 13,708 (63%) completed a CD4 test ≥30 days of enrollment at an ART clinic [14,805 (68%) had a CD4 test at some point after enrollment], of which 6875 (50%) were ART eligible. Of the eligible patients, 2886 (42%) initiated ART ≥90 days of their first CD4 test [3635 (53%) initiated ART at some point].

Patient flows stratified by testing service type (VCT vs. PMTCT) are displayed in Figure 1. VCT patient retention dropped by 3% (to N = 16,232) between testing and enrollment, by an additional 34% (to N = 10,773) between enrollment and CD4 test, and of those who were eligible for ART, an additional 54% (to N = 2565) between CD4 testing and ART initiation. By contrast, PMTCT patient retention dropped by 7% (to N = 5657) between testing and enrollment, by an additional 48% (to N = 2935) between enrollment and CD4 test, and of those who were eligible for ART, an additional 75% (to N = 321) between CD4 testing and ART initiation. The overall proportions of HIV-positive patients progressing through the care and treatment cascade out of the total number tested are presented in Figure S1 (see Supplemental Digital Content, http://links.lww.com/QAI/A494).

### Enrollment in ART Clinics (Outcome 1)

ART clinic enrollment was not significantly different between patients referred from PMTCT (58%) and VCT centers (68%) (RR = 0.84, 0.72 < RR < 1.02) (Table 3).

### Table 2. Selected Characteristics of Patients Enrolled in Study Clinics, by HIV Testing Center

<table>
<thead>
<tr>
<th></th>
<th>VCT N (%)</th>
<th>PMTCT N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16,649 (73.2)</td>
<td>6088 (26.8)</td>
<td>22,737 (100)</td>
</tr>
<tr>
<td>Age</td>
<td>33.3 ± 10.1</td>
<td>25.1 ± 5.6</td>
<td>31.1 ± 9.8</td>
</tr>
<tr>
<td>Sex</td>
<td>9886 (59.4)</td>
<td>6088 (100)</td>
<td>15,974 (70.3)</td>
</tr>
<tr>
<td>Education, yrs</td>
<td>0–5: 7498 (45.0), 6–9: 6123 (36.8), ≥10: 2058 (12.4), Missing: 970 (5.8)</td>
<td>2840 (46.7), 2323 (38.2), 523 (8.6), 402 (6.6)</td>
<td>10,338 (45.5), 8446 (37.2), 2581 (11.4), 1372 (6.0)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Single: 4638 (27.9), Married: 9483 (57.0), Widow/separated: 1999 (12.0), Missing: 529 (3.2)</td>
<td>1306 (21.5), 4447 (73.1), 159 (2.6), 176 (2.9)</td>
<td>5944 (26.1), 13,930 (61.3), 2158 (9.5), 705 (3.1)</td>
</tr>
<tr>
<td>First CD4 count (cells per mm³)</td>
<td>Median (IQR): 258 (122–457), Missing (%): 2380 (14.3)</td>
<td>389 (239–584), 4449 (73.1)</td>
<td>289 (143–492), 6829 (30.0)</td>
</tr>
<tr>
<td>First WHO stage recorded</td>
<td>I/II: 5884 (35.3), III: 6107 (36.7), IV: 586 (3.5), Missing: 4072 (24.5)</td>
<td>3335 (54.8), 510 (8.3), 17 (0.3), 2226 (36.6)</td>
<td>9219 (40.6), 6617 (29.1), 603 (2.7), 6298 (27.7)</td>
</tr>
<tr>
<td>Clinic type</td>
<td>Integrated: 9329 (56.0), Vertical: 7320 (44.0)</td>
<td>4656 (76.5), 1432 (23.5)</td>
<td>13,985 (61.5), 8752 (38.5)</td>
</tr>
</tbody>
</table>
CD4 Testing (Outcome 2)

Patients tested in PMTCT centers were less likely to have a CD4 test ≤30 days after clinic enrollment (30%) compared with VCT centers (45%) when adjusting for age, education level, and marital status [adjusted RR (aRR) 0.84, 0.70 < aRR < 1.00] (Table 4).

Initiation of ART (Outcome 3)

Eligible patients tested in PMTCT centers were less likely to initiate ART ≤90 days after their first CD4 test (3%) compared with patients tested in VCT centers (11%) when adjusting for age, education level, and marital status (aRR = 0.56, 0.44 < aRR < 0.71) (Table 4).

Overall Treatment Outcomes

Of the 2886 patients who initiated ART in ≤90 days, attrition from ART care by 180 days for any reason (death, LTFU, or transferring out of the care network) was 8.9% [95% confidence interval (CI): 7.9 to 10.0]. Of the 8.9% who left ART care, 6.1% was due to death or LTFU, and 2.8% was due to transferring to another clinic.

Treatment Outcomes Stratified by Testing Service

For the 2565 patients tested at VCT centers, 180-day all-cause attrition from ART care was 9.6% (95% CI: 8.6 to 10.8) compared with 2.8% (95% CI: 1.5 to 5.3) for the 321
patients tested at PMTCT centers. Of the 9.6% who left ART care and were tested at VCT centers, 6.7% was due to death or LTFU and 2.9% was due to transferring. Of the 2.8% who left ART care and were tested at PMTCT centers, 0.31% was due to death or LTFU and 2.5% was due to transferring.

Delayed Outcomes

The proportion of patients who successfully proceeded onto the next step of treatment, but did so beyond the time restrictions, was higher for all 3 outcomes among patients tested at PMTCT centers compared with VCT centers (enroll at ART clinic: 6.2% of PMTCT versus 1.9% of VCT; CD4 testing: 5.4% of PMTCT versus 4.9% of VCT; initiate ART: 12.0% of PMTCT versus 10.6% of VCT). The median time between HIV test to enrollment and from enrollment to CD4 was the same between the groups (0 and 3 days, respectively), but median time from CD4 to ART was 43 days for VCT (interquartile range, 27–74) and 63 days for PMTCT (interquartile range, 38–106).

Gender

When restricted to VCT alone, the percentage of males and females who had a CD4 test and initiated ART was nearly identical (CD4: 68% of females versus 69% of males; ART: 51% of females versus 49% of males).

DISCUSSION

Our investigation of the relationship between type of HIV testing center and retention in HIV care demonstrated consistent and substantial drop-offs at each step in the HIV care cascade among patients diagnosed at both VCT and PMTCT centers. Patients diagnosed at PMTCT centers were significantly less likely to have a CD4 test and initiate ART compared with patients diagnosed at VCT centers. ART clinic enrollment was also lower among women tested at PMTCT centers, although this result was not statistically significant.

Pre-ART retention across sub-Saharan Africa (SSA) is heterogeneous. Our findings are similar to other studies done from SSA reporting rates of linkage from HIV testing to ART clinic enrollment and CD4 testing. Studies from Uganda and South Africa have reported a higher proportion of ART-eligible patients starting ART than we found in this study. Yet, this study found higher ART initiation than previous studies in Mozambique.

Lower pre-ART retention among HIV-positive pregnant women referred from PMTCT centers is a common finding in other studies. The results of this study in 18 clinics is similar to a previous analysis from 2 clinics in the same region, which demonstrated that compared with those referred from VCT centers, patients referred from PMTCT centers were less likely to enroll at an ART clinic ≤30 days from HIV testing, were similarly likely to have a CD4 test done ≤30 days after ART clinic enrollment, and were less likely to initiate ART ≤90 days of their CD4 test. Another study in Mozambique found that ART-eligible women (including pregnant women) had lower odds of initiating ART compared with men. Two studies in South Africa also found that pregnant women had higher rates of LTFU after starting ART compared with non-pregnant patients. However, this relationship has not been consistent across settings. One study in South Africa found that women tested for HIV at PMTCT centers were more likely to have a CD4 and initiate ART if eligible compared with patients who were tested at VCT centers.

Differences in retention between VCT and PMTCT patients are not surprising given the many factors that influence LTFU. First, gender may influence successful referral and movement through the HIV care system; although the influence of gender on LTFU is not consistent in the literature, nor was gender associated with LTFU among the VCT population in this study. Second, because pregnant women are routinely screened for HIV during antenatal care, they are generally healthier than patients who seek HIV testing at VCT centers. Previous research has found lower CD4 count to be predictive of retention in care, and the women from PMTCT testing centers in this study had a higher median CD4 count and lower WHO stage at enrollment compared with the VCT group. Furthermore, pregnant women who discover their HIV status through routine screening as part of antenatal care may be less prepared for the diagnosis than those who actively seek testing, which may impact subsequent HIV care. This result is consistent with other literature that has found self-referral to HIV testing to be associated with lower rates of LTFU compared with provider-initiated HIV testing. Another potential interpretation is that women, especially pregnant women, may be more vulnerable to stigma associated with an HIV diagnosis, which could easily lead to LTFU. Although previous research on stigma among patients who initiated ART in central Mozambique saw no difference in stigma, depression, or perceived social support between genders, it may be that LTFU in the pre-ART phase of care may be more susceptible to these influences.

HIV testing and health system factors may also influence the higher pre-ART LTFU among women tested at PMTCT centers, especially related to limitations in counseling and referral within busy antenatal care centers. In southern Mozambique, “cultural miscommunication” was documented between the PMTCT staff and patients when it came to breastfeeding and future childbearing, and this miscommunication was found to be a barrier to receiving PMTCT centers. Other studies documented transportation costs and antenatal care wait times as other reasons for LTFU in cohorts of pregnant women.

There are several limitations of this study. First, we were unable to match over 8000 patients who tested HIV-positive at testing sites but were not matched to HIV sites using ART clinic records, and we had moderate amounts of patient exclusion. To be included in this study, a patient had to both test and receive care within the catchment area of the 18 included HIV care clinics. Therefore, if a patient tested outside the network but sought care inside the network or vice versa, they were not included. We cannot infer any information on whether these unmatched patients are different from those who did match; nevertheless, the proportion of tested patients who matched were similar comparing those tested at VCT (77%) versus PMTCT (65%) (Fig. 1). Regarding patient exclusion,
this could contribute to selection bias; yet, most of our exclusions were because patients were younger than 15 years, mainly acting to restrict our generalizability and not expected to bias our findings.

Second, because data from HIV testing services were only available as aggregate monthly reports, our analysis could not follow individuals referred from HIV testing centers to ART clinics. As a result, we could not adjust for individual characteristics in the enrollment analysis (outcome 1), and the lack of individual-level data may have led to inclusion of more individuals under 15 years of age in the group tested in VCT than PMTCT (where the great majority of pregnant women are over 15 years of age). Although this limitation is notable, we expect that this would overestimate LTFU between testing and HIV care center enrollment among those tested in VCT compared with PMTCT, which would have attenuated the observed difference between those tested in PMTCT and VCT. Routine data systems may also contain errors, and although most of the data used in this study came from ART databases that have been previously validated, HIV testing center data systems have not been validated for completeness or accuracy.5,15–18

Another study limitation is the lack of information on reasons for HIV care attrition. Attrition from HIV care can be divided into 4 categories: death, transfer, LTFU, or delayed ART while remaining in care. Based on the available death and transfer data, the proportion of patients tested at VCT who died or transferred to another clinic was 10-fold that of PMTCT, which fits the pattern of more advanced HIV disease among patients seeking VCT centers.25–27,30 It is likely that undocumented mortality and transfers, especially among VCT-referred patients, led to outcome misclassification and attenuated risk estimates. We also have no available information on reasons for delays in moving through the HIV care system because a greater proportion of patients tested at PMTCT centers completed the study outcomes beyond the time restrictions compared with those tested at VCT centers.

A final limitation is that we were unable to include other testing centers of interest, including community-based testing and testing in clinical services (primarily tuberculosis services). Patients tested for HIV at community and clinic-based testing likely have different health and well-being patterns, and different experiences with linkages to the health system.

Despite these limitations, this study has a number of strengths. First, using a novel approach, we were able to link HIV testing and ART clinic data to estimate not only pre-ART LTFU within the HIV care system but also drop-offs between testing and care centers. We were also able to include data from multiple HIV testing centers and ART clinics to describe referral and care patterns within a complex HIV care system environment. A further strength of this study is the large sample of study patients from 18 heterogeneous HIV care systems (including testing centers and care clinics) covering a large geographic area, which provides more stable estimates of the pre-ART LTFU experience.

Further studies are needed to better understand the barriers to initiating and continuing HIV care among pregnant women in Mozambique and other areas of SSA. It is difficult to ascertain reasons for differential retention among pregnant women in different ART care systems without information on reason for LTFU. Further assessment of operational and community factors associated with the high and differential pre-ART LTFU, and testing of approaches to ameliorate this LTFU, is critically needed to improve retention as ART centers continue to expand. Additionally, improvements in retention in HIV care will require further strengthening of the overall health care system to accommodate the larger numbers of patients who are enrolled and maintained in long-term HIV care.

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