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Monitoring prevalence of advanced human immunodeficiency virus (HIV) disease (i.e., CD4+ T-cell count <200 cells/µL) among persons starting antiretroviral therapy (ART) is important to understand ART program outcomes, inform HIV prevention strategy, and forecast need for adjunctive therapies. To assess trends in prevalence of advanced disease at ART initiation in 10 high-burden countries during 2004–2015, records of 694,138 ART enrollees aged ≥15 years from 797 ART facilities were analyzed. Availability of national electronic medical record systems allowed up-to-date evaluation of trends in Haiti (2004–2015), Mozambique (2004–2014), and Namibia (2004–2012), where prevalence of advanced disease at ART initiation declined from 75% to 34% (p<0.001), 73% to 41% (p<0.001), respectively. Significant declines in prevalence of advanced disease during 2004–2011 were observed in Nigeria, Swaziland, Vietnam, and Zimbabwe, nationally representative ART facilities were captured in the electronic system. In Nigeria, Mozambique, and Namibia, where large, centralized, electronic ART patient monitoring systems are employed, all available data from 2004–2015 were analyzed. In each of these countries, 77%–100% of all ART patients and 67%–100% of all ART facilities were captured in the electronic system. In Nigeria, Swaziland, Vietnam, and Zimbabwe, nationally representative samples of ART facilities were selected, with probability of selection proportional to facility size. In Tanzania, Uganda, and Zambia, investigators purposively selected health facilities to represent the range of ART facilities in each country and ensure that the study remained feasible. Among the seven sample-based surveys, a sample frame of study-eligible ART patients was created at each selected facility, and simple random sampling was used to select the sample of records. Eligibility criteria included initiation of ART ≥6 months before data abstraction, during 2004–2015, and at age ≥15 years. Data were abstracted from ART records onto standardized abstraction forms by trained study personnel. Because of variations in the timing of retrospective data collection for the 10 studies (Table 1), the calendar years of ART initiation included in the analysis varied among the countries.

The CD4+ T-cell count (CD4) measured in the 6 months before ART initiation and closest to the date of ART initiation was considered the baseline CD4. For each of the 10...
TABLE 1. Summary of study designs to assess trends in prevalence of advanced disease at antiretroviral therapy enrollment — 10 countries, 2004–2015

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>ART clinics*</th>
<th>ART enrollment years covered by analysis</th>
<th>Patient sampling technique at selected clinics</th>
<th>Planned sample size</th>
<th>No. eligible medical records analyzed</th>
<th>Date of data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namibia</td>
<td></td>
<td>≥15</td>
<td>2004–2012</td>
<td>Census</td>
<td>165,468</td>
<td>165,468</td>
<td>Dec 2013</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td></td>
<td>≥15</td>
<td>2007–2009</td>
<td>SRS</td>
<td>4,000</td>
<td>3,896†</td>
<td>Jan–Jun 2010</td>
</tr>
<tr>
<td>East Africa</td>
<td>Tanzania</td>
<td>≥18</td>
<td>2004–2009</td>
<td>SRS</td>
<td>1,500</td>
<td>1,214†</td>
<td>Apr–Jul 2010</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>≥18</td>
<td>2004–2009</td>
<td>SRS</td>
<td>1,500</td>
<td>1,466**</td>
<td>Apr–Jul 2010</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>694,639</td>
<td>694,138</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ART = antiretroviral therapy; PPS = probability of selection proportional to size; SRS = simple random sampling.
* To keep sample-based studies feasible, in Zimbabwe, Nigeria, and Vietnam, only facilities with ≥50 adults on ART were eligible for sampling, whereas in Zambia, Uganda, and Tanzania, only facilities that had enrolled ≥300 adults on ART were eligible.
† In Zimbabwe, 23 of 3,919 selected patients with either missing gender (n = 12), or missing outcome (n = 11) were excluded from analysis.
§ In Zambia, among 1,457 records sampled, 243 were excluded because of noncompliance with simple random sampling procedures at one site.
‡ In Tanzania, 1,458 records sampled; one patient was excluded because of absence of age data at ART initiation, and 36 patients enrolled in 2004 were excluded because of small sample size for 2004.
∥ In Uganda, among 1,472 records sampled, six patients were excluded because of absence of age data at ART initiation.
†† In Nigeria, implicit stratification was used in the sampling approach.
‡‡ In Vietnam, among 7,587 records sampled, four observations were excluded because information on gender was missing.

countries and for each calendar year, the percentages of adult patients with baseline CD4 <100, <200, and <350 cells/µL are described with percentages and 95% confidence intervals accounting for survey design. Bivariate logistic regression models accounting for survey design were used to evaluate statistical significance of changes in percentages over calendar years, with the likelihood ratio test used to assess departure from linear trend over time. Trends in median baseline CD4 at ART initiation over time are described, and a linear regression model, accounting for survey design, was used to assess statistical significance of changes.

Across the 10 countries, 694,138 adult ART patient records were analyzed from 797 ART facilities (Table 1). The overall percentage of new ART enrollees during 2004–2015 with missing baseline CD4 ranged from 9% in Swaziland to 53% in Zimbabwe. In the three countries providing more recent national electronic medical record data, prevalence of advanced disease at ART initiation declined from 73% to 37% during 2004–2014 in Mozambique, from 80% to 41% during 2004–2012 in Namibia, and from 75% to 34% during 2004–2015 in Haiti (Table 2) (supplemental figure; stacks.cdc.gov/view/cdc/45821). In addition, over the same periods, prevalence of CD4 <100/µL declined from 39% to 18% in Mozambique, from 39% to 16% in Namibia, and from 49% to 20% in Haiti. Prevalence of CD4 <350/µL at ART initiation also declined over time in all three countries. Over the same periods, significant increases in median CD4 count at ART initiation were observed in Mozambique (from
128/µL to 261/µL; p<0.001), in Namibia (from 125/µL to 230/µL; p<0.001), and in Haiti (from 103/µL to 297/µL; p<0.001) (Figure).

In the seven countries with less recent data, statistically significant declines in prevalence of advanced disease were observed in five countries (Table 2). Prevalence of advanced disease at ART initiation declined from 72% to 54% in Swaziland (2004–2010), from 84% to 53% in Zimbabwe (2004–2010), from 68% to 53% in Nigeria (2004–2011), and from 91% to 80% in Vietnam (2005–2009) (Table 2) (supplemental figure; https://stacks.cdc.gov/view/cdc/45821). Over the same periods in Swaziland, Uganda, and Vietnam, statistically significant increases in median baseline CD4 from 143/µL to 184/µL (p<0.001), 89/µL to 170/µL (p<0.001), and 22/µL to 92/µL (p = 0.014), respectively, were observed (Figure).

**Discussion**

This analysis of 694,138 medical records from 10 low- and middle-income countries (LMIC), contributes several findings relevant for ART programs in resource-limited settings. Observed declines in the prevalence of advanced disease at ART initiation in eight countries and increases in median baseline CD4 at ART initiation in six countries are likely due to increasing access to HIV testing and treatment (e.g., increasing numbers of facilities providing testing and treatment services), and increasingly inclusive ART eligibility guidelines (I). Despite this encouraging progress, however, a significant...
percentage of ART enrollees still started ART with advanced disease in recent years. In Haiti, which provided the most recent data on ART enrollees for this analysis (2015), and which historically has had higher than average median CD4 at ART initiation compared with other LMIC (Table 2) (2,3), the percentage of ART enrollees with CD4 <200/\(\mu\)L was 34% in 2015. Similarly, in Mozambique in 2014, 37% of patients started ART with advanced disease. Although recent data from the 10 countries are limited, these data and data from a recent meta-analysis, which reported mean CD4 count at ART initiation for 27 LMIC in 2011–2013 of 186 cells/\(\mu\)L (3), suggest at least a third of ART patients in LMIC initiated ART with advanced disease in 2015. To reduce prevalence of advanced disease at ART initiation in LMIC, continued attention to programmatic strategies facilitating earlier HIV testing and linkage to care are needed, in addition to adoption of WHO-recommended universal ART eligibility (“treat-all”) guidelines for persons living with HIV (3), which stipulate that all patients become eligible for ART on the day of HIV diagnosis, regardless of CD4 count at HIV diagnosis. Early ART for all persons living with HIV could improve ART program outcomes and HIV prevention impact (4,5). For example, in the Strategic Timing of Antiretroviral Therapy (START) trial, initiating ART for patients with CD4 >500/\(\mu\)L rather than deferring ART initiation until more advanced disease stages, was shown to reduce risk for a composite endpoint of any serious acquired immunodeficiency syndrome (AIDS)–related event, non-AIDS–related event, or death by 57% (5). In addition, early rather than deferred ART for HIV-positive persons in a serodiscordant relationship was found to reduce HIV transmission to the HIV-negative partner by approximately 96% (4). Among the 10 countries studied, “treat-all” guidelines have been adopted nationwide in nine (Haiti, Mozambique, Namibia, Nigeria, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe), whereas Vietnam is beginning to phase in “treat-all” guidelines with nationwide adoption planned by 2020.

Given the low median baseline CD4 from Vietnam in 2009 (92/\(\mu\)L), much lower than Haiti’s median baseline CD4 the same year (219/\(\mu\)L), evaluation of more recent trends in baseline CD4 is warranted. With Vietnam’s epidemic largely
involving men who inject drugs, late presentation for ART might be partly explained by suboptimal health-seeking behavior in this population (6). In Vietnam and similar LMIC, continued monitoring of the prevalence of advanced HIV disease at ART initiation is necessary to inform understanding of ART program access, outcomes, and prevention strategies (because baseline CD4 gives an indication of how long ART enrollees have lived with an unsuppressed viral load). Comparing prevalence of advanced disease at ART initiation among demographic groups (e.g., nonpregnant females, pregnant females, and males) or among more affected population groups (e.g., sex workers and persons who inject drugs) can inform which populations are being reached late and therefore require targeted interventions (1).

Recent WHO guidelines recommend a differentiated approach to treatment of persons living with HIV.5 This approach means that patients initiating ART with advanced HIV disease require additional specialized care to ensure optimal outcomes. For example, tuberculosis (TB) is common among patients starting ART with advanced HIV disease, and remains the most common cause of death, accounting for approximately 40% of deaths, half of which are undiagnosed before death (7). Based on recent evidence from a randomized trial (8), WHO recommends that the lateral flow urine lipoarabinomannan assay may be used to assist in the rapid diagnosis and treatment of disseminated TB among persons living with HIV admitted to hospital with CD4 <100/µL and symptoms of TB. WHO conditionally recommends the same screening approach for adult outpatients. Early identification and treatment of disseminated TB can reduce all-cause mortality (8). In addition, plasma screening for cryptococcal antigen (CrAg) among patients with CD4 <100/µL and consideration of preemptive treatment with fluconazole for CrAg-positive patients might reduce 12-month ART mortality (9). Co-trimoxazole prophylaxis for ART enrollees with CD4 <350/µL has been shown to reduce mortality (10). Use of these adjunctive therapies could help reduce relatively high 12-month mortality among people taking ART in LMIC (11).

Given the importance of baseline CD4 in determining eligibility for adjunctive therapies that have the potential to reduce mortality, it is concerning that 40% of the 694,138 medical records reviewed lacked documentation of the baseline CD4, with country-specific rates ranging from 9% in Swaziland to 53% in Zimbabwe. Quality improvement measures to ensure availability of baseline CD4 data for clinical decision-making are warranted.

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Summary

What is already known about this topic?

Monitoring prevalence of advanced human immunodeficiency virus (HIV) disease (i.e., CD4+ T-cell count <200 cells/µL) among persons initiating antiretroviral therapy (ART) is important to help understand ART program outcomes, inform HIV prevention strategies, and forecast need for adjunctive therapies.

What is added by this report?

In an analysis of 694,138 adult ART records from 10 countries, the prevalence of advanced disease at ART initiation during 2004–2015 declined in eight countries. In Mozambique (2004–2014), Namibia (2004–2012), and Haiti (2004–2015), prevalence of advanced disease at ART initiation declined from 73% to 37% (p<0.001), 80% to 41% (p<0.001), and 75% to 34% (p<0.001), respectively. In the remaining seven countries with data available for 2004–2011, significant declines in prevalence of advanced disease were observed in Nigeria, Swaziland, Uganda, Vietnam, and Zimbabwe.

What are the implications for public health practice?

Declines in the prevalence of advanced disease at ART enrollment over time in most countries are encouraging, but in 2015, approximately a third of new ART patients still initiated ART late. Adoption of World Health Organization–recommended “treat-all” guidelines and strategies to facilitate earlier HIV testing, and treatment are needed. These strategies would help reduce HIV-related mortality and HIV incidence.

The findings in this report are subject to at least three limitations. First, cohort data varied in size and generalizability; statistical significance of trends in baseline CD4 over time is more likely with larger sample sizes and more calendar years of available data. Second, missing data on CD4 at ART initiation might have introduced measurement error for summary estimates. Third, in several countries, data on more recent ART enrollees are needed to inform estimates of the current prevalence of advanced HIV disease at ART initiation.

Encouraging reductions in the prevalence of advanced disease at ART initiation were observed in eight of the 10 countries studied. This reflects the rapid scale-up of HIV testing and treatment services in LMIC since 2004 and evolution of HIV treatment guidelines encouraging earlier ART initiation. However, an estimated one third of new ART enrollees in LMIC in 2015 started ART with advanced disease, indicating that continued scale-up of interventions to facilitate earlier testing and treatment are needed. For those ART enrollees who do initiate ART late (3), ensuring availability of WHO-recommended adjunctive therapies could help reduce morbidity and mortality during ART.

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References


