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Application of a Multistate Model to Evaluate Visit Burden and Patient Stability to Improve Sustainability of Human Immunodeficiency Virus Treatment in Zambia

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Background. Differentiated service delivery (DSD) for human immunodeficiency virus (HIV)–infected persons who are clinically stable on antiretroviral therapy (ART) has been embraced as a solution to decrease access barriers and improve quality of care. However, successful DSD implementation is dependent on understanding the prevalence, incidence, and durability of clinical stability.

Methods. We evaluated visit data in a cohort of HIV-infected adults who made at least 1 visit between 1 March 2013 and 28 February 2015 at 56 clinics in Zambia. We described visit frequency and appointment intervals using conventional stability criteria and used a mixed-effects linear regression model to identify predictors of appointment interval. We developed a multistate model to characterize patient stability over time and calculated incidence rates for transition between states.

Results. Overall, 167 819 patients made 3 418 018 post–ART initiation visits between 2004 and 2015. Fifty-four percent of visits were pharmacy refill-only visits, and 24% occurred among patients on ART for >6 months and whose current CD4 was >500 cells/mm^3. Median appointment interval at clinician visits was 59 days, and time on ART and current CD4 were not strong predictors of appointment interval. Cumulative incidence of clinical stability was 66.2% at 2 years after enrollment, but transition to instability (31 events per 100 person-years) and lapses in care (41 events per100 person-years) were common.

Conclusions. Current facility-based care was characterized by high visit burden due to pharmacy refills and among treatment-experienced patients. Differentiated service delivery models targeted toward stable patients need to be adaptive given that clinical stability was highly transient and lapses in care were common.

Keywords. human immunodeficiency virus (HIV); differentiated care; differentiated service delivery; Zambia; sustainability.

The global public health community has embraced differentiated service delivery (DSD), a suite of strategies that varies the timing, location, and intensity of services for persons living with human immunodeficiency virus (PLWHIV) as a principle strategy to address challenges in accessing care and to improve the quality of HIV service provision. In the second decade of the global HIV response, a growing proportion of patients considered clinically stable were still being asked to make frequent (often monthly) facility visits at considerable personal cost. These visits also contributed to congestion at clinic facilities, leaving overstretched clinical providers with little time to provide care to those more acutely ill. DSD models involve various strategies to target these stable patients, including increased spacing between visits (ie, 3- or 6-month antiretroviral therapy [ART] supply or clinical visits) [1–7], provision of ART in healthcare worker–led [8–14] or community-based peer-led groups [13, 15–21], and individual distribution of medications in the community [2, 13, 22–25].

As DSD models for stable patients gain favor in Africa, data about potential visit burden reduction through application of DSD to stable patients, the rate at which patients become stable after starting treatment, and the durability of clinical stability once achieved can help guide DSD implementation strategies. Existing published data are limited to cross-sectional assessments of DSD eligibility [6] and therefore fail to capture the real-world dynamics of patient stability, yielding potentially inaccurate estimates of efficiency gains and programmatic needs with DSD application.

We used data from a network of ART clinics in Zambia to better characterize the incidence, prevalence, and durability of clinical stability according to conventional criteria. Our objectives were, first, to characterize visit volume and appointment frequency to identify visits potentially reducible by application of DSD models to stable patients; second, to understand the

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current system's ability to differentiate care based on clinical stability by identifying predictors of appointment interval; and third, to determine how quickly patients become stable, for how long they remain stable, and the reasons for being or becoming unstable using a novel multistate modeling approach.

METHODS

Patients

We evaluated HIV-positive adults (aged >18 y at evaluation) who made a visit between 1 January 2013 and 28 February 2015 to any of 56 Ministry of Health clinics (n = 30 urban; n =26 rural) supported by the Centre for Infectious Disease Research in Zambia. The Centre for Infectious Disease Research in Zambia is a Zambian nongovernmental organization that receives support from President's Emergency Plan for AIDS Relief Centers for Disease Control and Prevention to support the Zambian Ministry of Health in the provision of HIV care and treatment across 4 of 10 geographically diverse provinces in Zambia.

Measurements

Sociodemographic and clinical characteristics of patients, including all visit and appointment dates, were obtained from the patient's electronic medical record (EMR) in the Zambian national data system, SmartCare. Enrollment CD4 cell count was defined as the closest CD4 cell count recorded within 365 days before or 30 days after the initial visit date. Current CD4 count was defined as the closest CD4 count recorded before a given visit date within the previous 12 months.

On a given visit to the clinic, patients may have encounters with ≥1 providers (ie, clinicians, pharmacists, or adherence counselors). We categorized visits based on the highest level of healthcare provider seen: a "clinician visit" (with or without a pharmacy encounter), a "pharmacy-only visit" (with or without an adherence counter), or an "adherence-only visit." Appointment intervals were defined as the time between the visit date and the next scheduled appointment. In instances where patients encountered both the clinician and the pharmacist at a given visit, the earliest of these two appointment dates was used to define the next assigned return to clinic date or combined appointment interval.

Analyses

Visit Volume

We enumerated the total number of post-ART initiation visits over time made by the cohort and then categorized visits by visit type, year, patient clinical characteristics, and clinic-level factors. We constructed histograms to describe the distribution of visits over calendar time and stratified by visit type and by 2 characteristics commonly included in assessment of clinical stability for DSD eligibility (current CD4 count and time since ART initiation). Visits in which a CD4 count value within 12 months of the visit date was not available were excluded from CD4 stratified analyses.

Predictors of Appointment Interval

To explore the relationship between clinical stability and assigned appointment interval, we used box plots to describe the distribution of appointment lengths by current CD4 count and time since ART initiation. We then used mixed-effects linear regression to estimate the association between markers of stability (eg, current CD4 and time on ART) and assigned return to clinic. We carried out separate models for pharmacist and clinician assigned return intervals. We included patient and clinic as random effects to account for clustering at these levels. We evaluated individual characteristics and clinic-level characteristics (clinic size, province, urban/rural status, and clinic volume on day of visit) for potential inclusion in the final models.

Multistate Model

We used a multistate model to characterize the dynamic nature of stability and retention in a system where patients may become clinically stable and unstable and exit and re-enter care repeatedly over time. Unlike traditional survival analysis (ie, Kaplan-Meier), multistate models allow patients to take on numerous conditions over time. We used this approach to describe the incidence and prevalence of 6 states over time using 2 different methods: time from date of enrollment and time from the calendar date 1 January 2013. We estimated transition rates (overall and stratified by age, sex, time from enrollment, and enrollment year) as events per 100 person-years between different states.

We used the following criteria (based on Zambian National Guidelines [26] and World Health Organization [WHO] consensus criteria for identifying stable patients for DSD in the absence of viral load [27]) to define clinical stability: (1) patient initiated on ART >6 months prior; (2) patient not on second-line ART; (3) no ART regimen switch in previous 3 months; (4) most recent CD4 count >200 cell/mm^3, and not less than 50% maximum CD4 to date, and not less than minimum CD4 to date; (5) no current tuberculosis, WHO stage III or IV diagnosis, or drug toxicity documented in the medical record at visit; and (6) on time to most recent visit (≤28 days late to last pharmacy appointment date). Patients were defined as unstable at a visit if any of these criteria were not met. We defined the states as follows: state 1: never stable on ART, currently in care; state 2: never stable on ART, currently out of care; state 3: history of stability on ART, currently stable, currently in care; state 4: history of stability on ART, currently unstable, currently in care; state 5: history of stability on ART, currently out of care; and state 6: death. Using this classification, pre-ART patients and patients on ART less than 6 months are categorized as being in state 1. Lapse in care was defined as >28 days late to

last pharmacy appointment date. All individuals were censored either at the time of transfer out of the clinic network or at database closure on 28 February 2015.

Ethics Committee Approval

The study was approved by the institutional review boards at the University of Zambia and University of California, San Francisco.

RESULTS

Patient Cohort Characteristics

There were 167 819 patients included in the current clinic cohort (Supplementary Table 1), with 34% enrolling in care after 2013. At enrollment, median age was 28 years (interquartile range [IQR], 34–41 y), 591 (36%) were male, median CD4 count was 182, and 53 627 (32%) had WHO stage III or IV disease. In total, 149 755 (89%) were started on ART.

Visit Volume

Visit Reason

A total of 3.4 million post–ART initiation visits were made between 1 January 2004 and 28 February 2015 (Table 1). A pharmacy encounter occurred at 92% of all visits to the facility, and a pharmacy-only visit was the most common type of visit (54%). The total number and proportion of pharmacy-only visits made by current patients increased over time (47% in 2010 to 60% in 2014) (Figure 1A).

Individual Patient Characteristics

Overall, 78% of all visits occurred in patients initiated on ART >6 months prior, and 76% of visits occurred among patients

Table 1. Visit Characteristics of Post–Antiretroviral Therapy Initiation Visits Made by Current Clinic Cohort (N = 3 418 018)

Characteristic	Clinician Visits	Pharmacy-only Visits	Adherence-only Visits
Primary reason for visit to clinic	1 451 851 (42%)	1 841 543 (54%)	124 624 (4%)
Encounters at each visit			
Encounter with clinician	1 451 851 (100%)	…	…
Encounter with pharmacist	1 301 192 (90%)	1 841 543 (100%)	…
Encounter with adherence counselor	1 041 168 (72%)	1 323 330 (72%)	124 624 (100%)
Patient characteristics			
Visits by males	495 705 (34%)	648 705 (35%)	43 123 (35%)
Time on ART			
0–6 mo	325 505 (22%)	380 972 (21%)	18 758 (15%)
6–12 mo	168 831 (12%)	200 474 (11%)	13 153 (11%)
12–24 mo	266 554 (18%)	314 404 (17%)	21 671 (17%)
24–36 mo	209 532 (14%)	248 161 (13%)	17 853 (14%)
36–48 mo	160 603 (11%)	200 133 (11%)	14 459 (12%)
>48 mo	320 826 (22%)	497 399 (27%)	38 730 (31%)
Most recent CD4 count, cells/mm^3			
0–50	40 165 (3%)	47 608 (3%)	2784 (3%)
51–100	58 960 (5%)	69 622 (5%)	3940 (4%)
101–200	185 635 (16%)	213 070 (15%)	12 692 (14%)
201–350	348 154 (29%)	402 726 (28%)	25 303 (27%)
351–500	258 911 (22%)	316 196 (22%)	21 524 (23%)
>500	291 678 (25%)	372 757 (26%)	27 351 (29%)
Clinic characteristics			
Urban	1 144 846 (79%)	1 510 537 (82%)	101 589 (82%)
Size			
0–1000	33 477 (2%)	24 032 (1%)	2328 (2%)
1000–5000	761 772 (53%)	691 303 (38%)	45 020 (36%)
5000–10 599	651 314 (45%)	1 123 271 (61%)	77 175 (62%)
Appointment intervals			
Median appointment interval assigned by clinician (IQR), d	62 (30–91)	…	…
Median appointment interval assigned by pharmacist (IQR), d	60 (30–90)	32 (29–62)	…
Median combined appointment interval[a] (IQR), d	59 (29–90)	…	…
Combined appointment interval			
≤30 d	485 602 (34%)	667 154 (37%)	…
≤60 d	786 469 (55%)	1 246 938 (69%)	…
≤90 d	1 081 993 (76%)	1 579 837 (88%)	…

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

[a]The combined appointment interval takes the minimum (or earliest) of the 2 appointment dates (clinician-assigned and pharmacy-assigned) for a given visit.

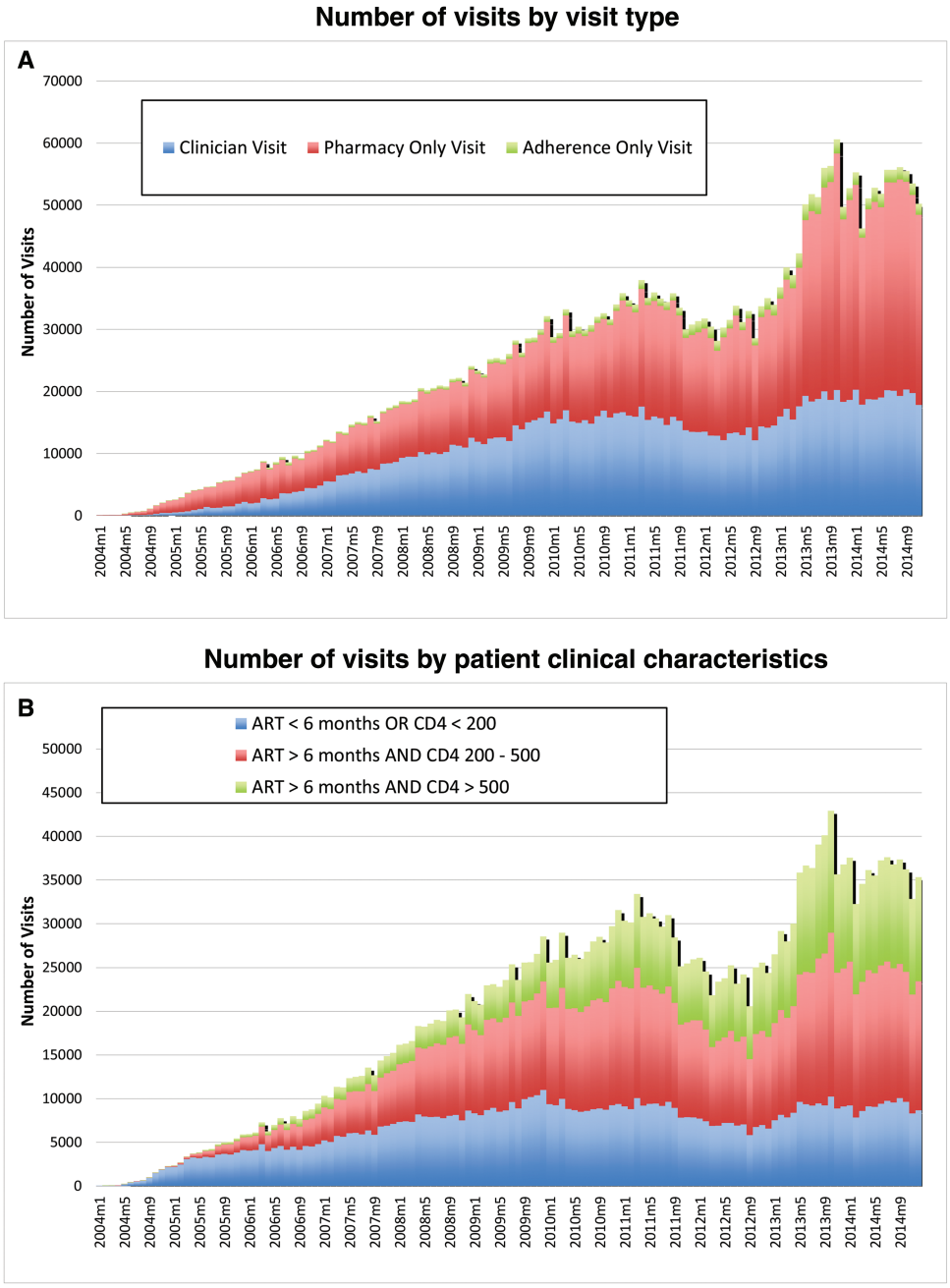

Figure 1. *A*, Number of visits made by current patients between 1 January 2004 and 28 February 2015 in a network of 56 human immunodeficiency virus clinics in Zambia, by primary reason for visit (N = 3 418 018 visits). *B*, Number of visits made by current patients between 1 January 2004 and 28 February 2015, by time since antiretroviral therapy initiation and current CD4 count (cells/mm^3) at visit (N = 2 699 076 visits). Abbreviation: ART, antiretroviral therapy.

with a current CD4 count >200 cells/mm^3 (Table 1). Nearly one quarter (24%) of all visits occurred among patients initiated on ART >6 months prior and with a CD4 count >500 cells/mm^3 (Figure 1B). The total number and proportion of visits made by this population increased over time (4% in 2005 to 32% in 2014).

Appointment Intervals

During clinician visits, the median appointment interval assigned was 62 days (IQR, 30–91 d) by the clinician and 60 days (IQR, 30–90 d) by the pharmacist (Table 1); however, clinician- and pharmacy-assigned appointments were coordinated in only 53% of visits. For 11% of clinician visits, a pharmacy-only visit occurred within 30 days of the clinician visit. Patients were given a combined appointment of <90 days at 76% of clinician visits. For pharmacy-only visits, the median appointment interval assigned was 32 days (IQR, 29–62 d), and 88% received a return appointment of ≤90 days.

Predictors of Appointment Intervals

On initial evaluation using box plots, clinician-assigned appointment intervals at clinician visits appeared to increase with time since ART initiation and CD4 count (Supplementary Figure 1A). However, in linear regression, all effect sizes were small (Supplementary Table 2). For every increase in CD4 count by 50 cells/mm^3, clinician-assigned appointment interval increased by only 1.53 days (0.92 d adjusted) and for every year increase in time since ART initiation, increased by only 4.41 days (2.39 d adjusted). A visit between 2012 and 2015 was associated with an increase in appointment interval by 28.1 days (19.1 d adjusted) compared with a visit between 2004 and 2007.

Multistate Model

We first conducted a survival analysis using enrollment in care as time zero and calculated prevalence of states (Figure 2A), overall transition rates (Figure 3), and subgroup transition rates (Figure 4). The cumulative incidence of becoming stable for the first time was 11.2 (95% confidence interval [CI], 11.1–11.4) at 6 months, 41.1 (95% CI, 40.8–41.4) at 1 year, and 66.2 (95% CI, 66.0–66.5) at 2 years after enrollment and did not vary whether enrolled before or after 2010 (Supplementary Figure 2). The prevalence of stability on ART increased over time since enrollment (30% at 1 year compared with 51% at 6 years) (Figure 2A) However, of those that had achieved clinical stability within the first

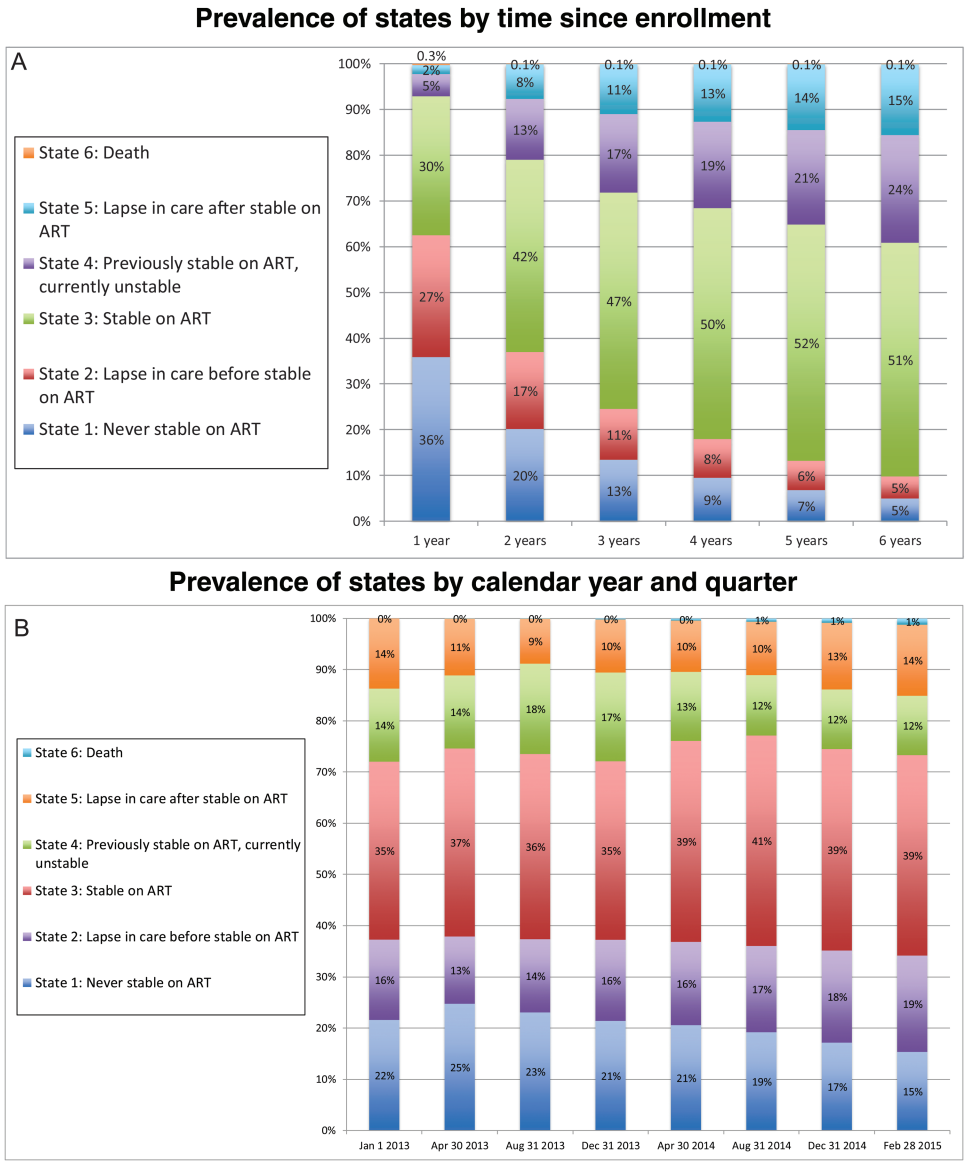

Figure 2. *A*, Prevalence of states in a multistate model from time since enrollment at annual intervals. *B*, Prevalence of states in a multistate model by calendar quarter between 1 January 2013 and 28 February 2015. Abbreviation: ART, antiretroviral therapy.

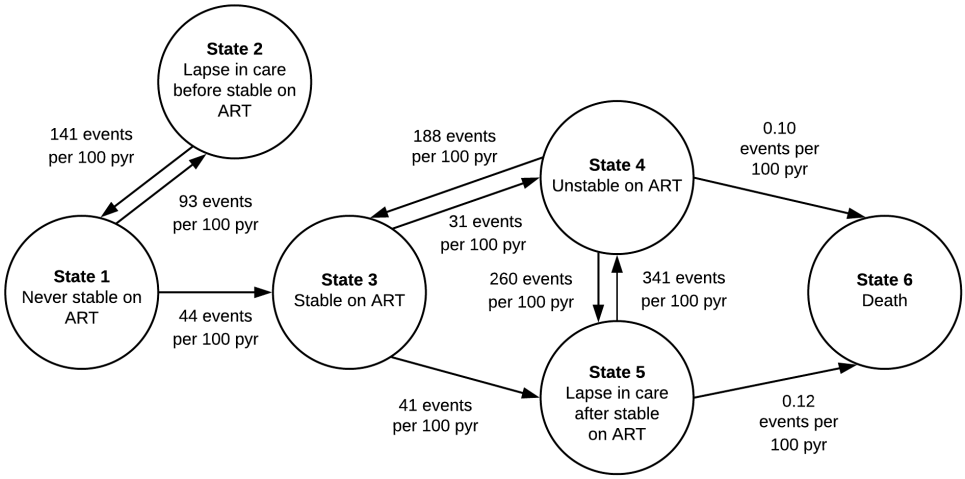

Figure 3. Selected transition rates between states in a multistate survival analysis of clinical stability from time since enrollment in human immunodeficiency virus care. Abbreviations: ART, antiretroviral therapy; pyr, person-years.

year after enrollment, only 39% were continuously stable, whereas 35% became unstable and 34% lapsed in care at least once within the year. The rate of becoming stable for the first time was highest between 12 and 24 months after enrollment (57 events/100 person-years) (Figure 4A). Once stable, the rate of becoming unstable was highest in the first 2 years after enrollment (48 and 39 events/100 person-years in years 1 and 2, respectively) and among those enrolled prior to 2010 (40 events/100 person-years) (Figure 4B) The most common reasons associated with clinical instability after achieving stability were ART switch (58%), drop in CD4 count (22%), and newly documented WHO stage III/IV disease (21%). Rates for lapse in care after being stable on ART were higher for those enrolled after 2010 (65 events/100 person-years) (Figure 4C).

Next, to capture the perspective of an implementing organization, we repeated the analysis using a point in calendar time (1 January 2013) as time zero for all patients (Figure 2B). On 1 January 2013, there were 110 709 people in the cohort: 22% were never stable on ART, 16% were lapsed in care before becoming stable on ART, 35% were stable on ART, 14% were previously stable on ART but currently unstable, and 14% were lapsed in care after becoming stable on ART. Of those who had never been stable on ART at their first visit after 1 January 2013, reasons for lack of stability were as follows: 40% were not on ART, 37% were on ART <6 months, 0.5% were on second-line ART, 4% switched ART regimens in the previous 3 months, 26% had low CD4 count, 1% had documented tuberculosis, 4% had documented WHO stage III/IV disease, and 26% were >28 days late to their most recent visit. Although new patients joined the cohort over time, the proportion that were stable on ART at any specific calendar time remained similar (35%–41%) (Figure 2B). Of the 167 817 total patients in the cohort, by 28 February 2015, 65% had achieved stability; however, 77% experienced clinical instability and 75% lapsed in care after becoming stable. Only 18% had remained continuously clinically stable on ART.

DISCUSSION

Among a network of 56 clinics in Zambia, we found that approximately a quarter of facility visits are being made by treatment-experienced patients with CD4 counts >500 cells/mm^3 and that although the majority of patients became clinically stable within 2 years of engaging in care, most of these patients subsequently experienced clinical instability and/or lapses in care. We identified high visit volume from frequent pharmacy-only refill appointments and among treatment-experienced patients and little differentiation of care based on clinical stability. These findings highlight the opportunity for visit spacing among stable patients to substantially reduce visit burden. However, these data also show that, although a large majority of patients are stable at any given time, stability itself is relatively transient. Differentiated service delivery models for stable patients, including visit spacing, must conceptualize and be able to respond to the large number of patients who might become unstable or experience lapses in care.

Clinical and pharmacy visit spacing among stable patients in DSD models can theoretically reduce visit burden. Short pharmacy appointment intervals and lack of coordination with clinician visits are thought to be driven by actual or anticipated pharmacy stock-outs as a result of poor stock forecasting, inadequate supply buffers, and other pharmacy supply chain challenges [28]. However, interventions to improve pharmacy supply chains and thereby increase capacity for multimonth refills have been shown to effectively reduce clinic visit frequency and congestion in Zambia [29] and elsewhere in Africa [4–7]. Clinical visit spacing among stable patients through application of DSD is another important area for potential visit burden reduction and improvement

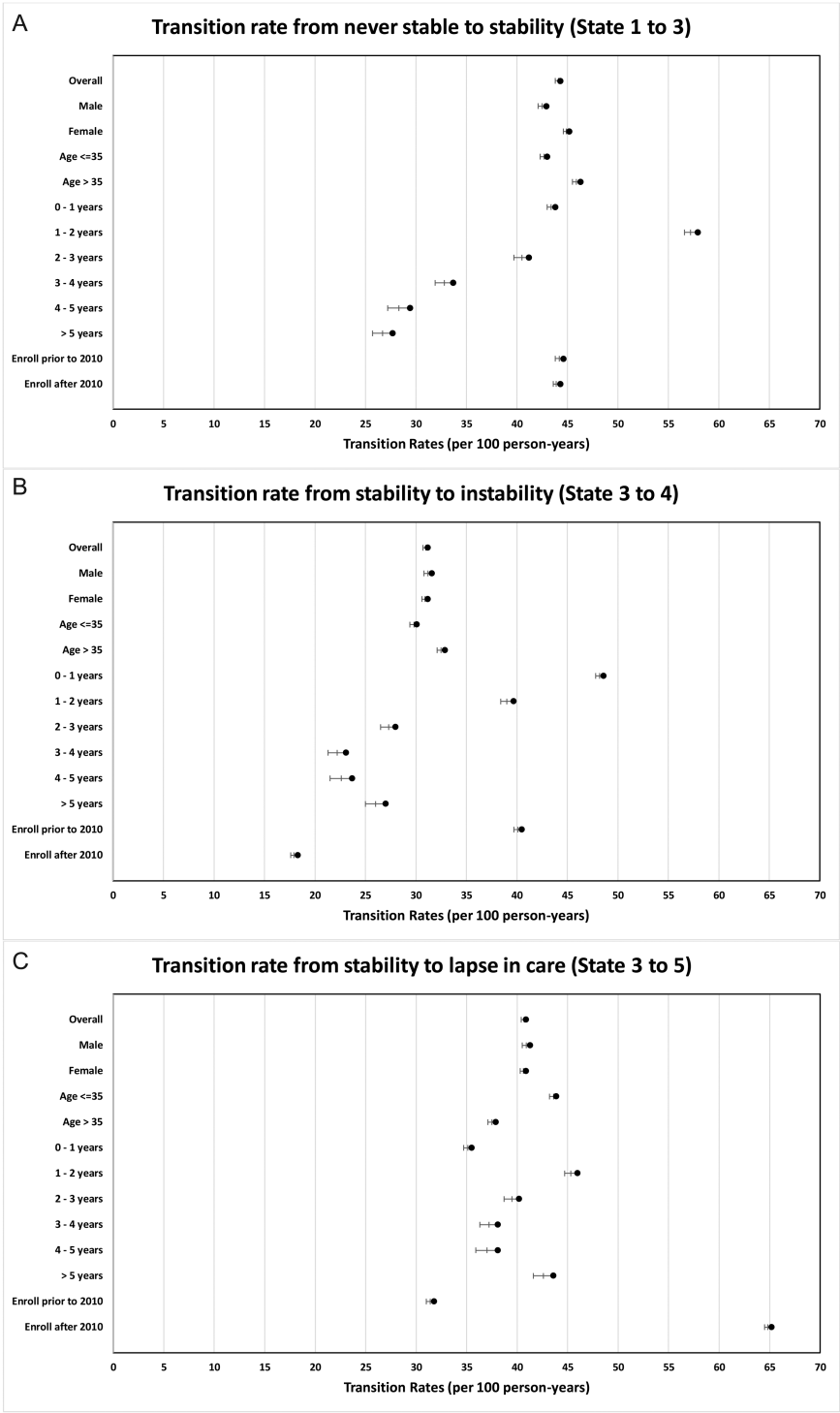

Figure 4. Subgroup analysis of transition rates (events per 100 person-years) between states. *A*, Transition rate from never stable to stability (state 1 to state 3). *B*, Transtion rate from stability to instability (state 3 to state 4). *C*, Transition rate from stability to lapse in care (state 3 to state 5).

in retention [3, 6, 30]. Median assigned appointment intervals in our cohort were approximately every 2 months for clinician visits, in contrast to the 3-month intervals recommended in Zambian national HIV guidelines between 2008 and 2014 and the 3–6-month intervals recommended since 2014.

However, we found that identifying which patients were clinically stable and determining optimal visit spacing within DSD is likely to be challenging because only a minority of patients who became stable remained clinically stable and continuously in care. In Malawi and South Africa, where DSD models have been scaled regionally and nationally, estimates of the

proportion of ART patients considered stable and eligible for DSD are limited by the cross-sectional nature of the data and ranged widely from 26% [9] to 78% [6]. To our knowledge, we are the first to provide a comprehensive description of stability that more accurately captures the dynamics of clinical stability. These data are relevant for estimating not only DSD eligibility but also the challenges that may be encountered once patients deemed stable are enrolled and maintained in a DSD model. Emerging data suggest that lapses in stability and retention continue in DSD models. In South Africa, an evaluation of peer-led adherence clubs revealed a cumulative incidence of loss to follow-up of 26% at 36 months and a referral back to clinic rate of 20.1/100 person-years [31]. Designation of patients as stable, with subsequent visit spacing and without recognition of changing patient stability over time, fails to capture the complexities of DSD implementation in real-world practice.

Our findings have important implications for DSD implementation and underscore the need for systems that are adaptive to patients' changing needs. The inability to detect or respond to changing clinical stability within a DSD model may counteract a primary goal of the DSD approach, which is to provide greater patient-centered care. Qualitative data from a South African study revealed that removing patients from adherence clubs and returning them to facility-based care for viral rebound or missed club appointments created frustration and broke down trust in the healthcare system and providers [32]. Our data suggest that these types of transitions are likely to occur frequently. Rather than discontinue patients from DSD models, systems to rapidly detect (eg, viral load testing) and respond to clinical instability within the DSD model should be developed. Increasingly, DSD models are being considered for virologically detectable and other unstable patients [33]; however, changing clinical needs (in this case, from instability to stability and back again) similarly need to be considered.

There were several limitations in our study. Our analysis focused on the current clinic population and does not reflect visits made by patients who were lost to follow up or died prior to 2013. We were limited by the available chart documentation for covariates of interest in determining clinical stability, including WHO stage, tuberculosis diagnosis, and drug toxicity. Nontuberculosis opportunistic infections, pregnancy (women are followed in Maternal and Child Health), and breastfeeding were not reliably documented and were excluded from analysis. We expect this to have minimal effects on our findings, which already demonstrate high rates of transition to instability. Viral load data were not routinely collected in Zambia prior to 2016. The ability to accurately identify clinically stable patients will be enhanced with widespread programmatic roll out of viral load testing. We elected to use a conservative definition of stability (eg, no recent ART switch and not on second-line ART), and generalizability of our findings may vary based on country-to-country variability in the definition of stability.

As HIV has evolved into a chronic disease and increasing numbers of patients are now on lifelong ART, there is increasing burden on both patients and health systems due to the high number and frequency of healthcare visits. Visit spacing within DSD models has been promoted as a promising solution to decrease access barriers and improve retention in care for stable patients. Our data highlight the large theoretical reduction in visit burden using this approach. However, the transient nature of clinical stability we demonstrated also argue for the importance of adaptive service delivery models that can detect and respond to changing clinical needs over time in order to maximize long-term retention in care.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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