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Combined estimation of disease progression and retention on antiretroviral therapy among treated individuals with HIV in the USA: a modelling study

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Summary

Background: Accurately estimating rates of HIV disease progression and retention on antiretroviral therapy (ART) can help inform interventions to help control HIV microepidemics and mathematical models used to inform health resource allocation decisions. Our objective was to estimate on-ART CD4+ cell count progression, mortality, ART dropout, and ART re-initiation rates using a continuous time multi-state Markov model. Secondly, we aimed to validate health state transition probability estimates to ensure they accurately reproduced the regional HIV microepidemics across the United States.

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Contributors

LW, EK, JEM, and BN designed the study. LW and EK contributed equally to this article, conducted analyses and wrote the first draft of the article. JEM and BN assisted with analysis and contributed to manuscript development. WCM, AN, CS, JAA, RDM, and KAG aided in study design, interpretation of results, and provided critical revisions to the article. KAG led the procurement of the database. All authors approved the final draft.

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Methods: We considered a cohort of patients from the HIV Research Network (HIVRN) cohort, a consortium of 17 adult and pediatric HIV care providers located in the northeastern (n=8), southern (n=5), and western United States (n=4). Individuals aged 15 years who were in care (defined as one CD4 test and one HIV care visit) with at least one ART prescription (2010–2015) were included in the analysis. Continuous-time multi-state Markov models were used to estimate transitions between CD4 strata, and between on- and off-ART states. We examined and adjusted for differences in transition rates by region, race/ethnicity, gender, HIV risk group, and baseline clinical status.

Findings: The median age of the 32,242 individuals included in the analysis was 44 years [IQR: 35–51]. Over a median follow-up of 4.9 years [2.6–6.0], 26.7% interrupted ART and 4.1% died. Women, men who have sex with men and individuals with no prior ART utilization had increased rates of CD4 improvement whereas Blacks and people who inject drugs had increased rates of ART dropout, and faster disease progression. Regardless of CD4 strata, individuals had increased hazard rates of ART dropout if they were from the South (aHR 1.91–2.45) or the West (aHR 1.29–1.66), compared to individuals from the Northeast.

Interpretation: This study illustrates heterogeneities in disease progression during ART and ART retention rates across race/ethnicity, HIV risk groups and regions. These differences should be viewed as targets for intervention and should be incorporated in mathematical models of regional HIV microepidemics in the United States.

Introduction

More than 1.1 million people were living with HIV in the United States (US) by the end of 2015. Despite the dramatic decreases in mortality and HIV transmission achieved in the US, inadequate retention on antiretroviral therapy (ART) and suboptimal continuity of care are among the biggest challenges to realize the full public health benefits from sustained viral suppression,^{1,2} and public health departments are continuously under pressure to use available resources efficiently.

The HIV epidemic in the US features substantial geographic variation and is best characterized as a set of diverse microepidemics dispersed mostly across large urban centers.³ Given the heterogeneity in care engagement⁴ and structural conditions affecting the HIV response across cities,³ locally-oriented combination implementation strategies are imperative to prioritize resources according to the greatest public health benefit.

Dynamic HIV transmission models are increasingly being used to facilitate decision-making in HIV/AIDS.^{5,6} These models can capture all relevant costs and benefits attributable to HIV care interventions over an extended time horizon;⁷ however, accurately estimating rates of disease progression and ART retention that capture the heterogeneity across individuals and settings is of central importance to accurately predict the current and future burden of disease for the HIV-infected population.⁸

Given the strong relationship between CD4+ T-lymphocyte counts and the risk of mortality,⁹ healthcare costs¹⁰ and health-related quality of life,¹¹ modelling disease progression via transition between CD4-based health states is commonplace in health economic evaluations.

Markov chains have previously been applied to model disease progression via CD4 cell count deterioration.^{12,13} Multi-state Markov regression models can account for competing risks and censored observations from observational cohort data and are thus suited to estimate health state transition probabilities between multiple disease stages.^{14,15} Furthermore, generating estimates using multivariable regression models can account for characteristics of both individuals and settings to represent the heterogeneity observed across microepidemics.

Previous studies have estimated HIV disease progression using multi-state Markov models;¹² however, these estimates have usually not been validated for use in the modeling of specific locations and contexts. For instance, observed differences across cities in the availability and distribution of HIV care may impact ART engagement.³ Generally, the credibility of model inferences are largely determined by the quality and representativeness of input data used for key parameters. Thus, explicit assessment of the representativeness of disease progression estimates used for locally-oriented modelling can help decision makers evaluate their validity and therefore the credibility of the model's inferences.

Our objective was to estimate on-ART CD4 progression, mortality, ART dropout, and ART re-initiation rates using a continuous time multi-state Markov model. Secondly, we aimed to validate health state transition probability estimates to ensure they accurately reproduced the current state of diverse regional HIV microepidemics across the United States.

Methods

Study population

The HIV Research Network (HIVRN) is a consortium of 17 adult and pediatric HIV care providers located in the northeastern (n=8), southern (n=5), and western United States (n=4). HIVRN sites abstract specified data elements from individuals' medical records, and abstracted data are assembled into a single database after quality assurance review. All sites participating in the HIVRN for all years between 2002 and 2015 were included in the analysis.

We considered all individuals reporting male or female gender age ≥ 15 years who were in HIV care (defined as having at least one CD4 count and one HIV primary care outpatient visits in a one calendar year period) between January 1st, 2010 and December 31st, 2015. Individuals in HIV care without prior ART utilization at the start of the study period were included upon ART initiation from the date of initiation up to September 30th, 2015 in order to have at least a 3-month period of follow-up. Consequently, individuals without any ART utilization prior to the study period or throughout the study period, i.e. they did not initiate ART, were not considered for inclusion. We did not consider transgender people for inclusion given the insufficient number of observations. We excluded individuals with a single observed disease status measurement (either a CD4 measurement while on ART, off-ART status, or death) or missing covariate information. Loss to follow-up was defined as having no records of medical care at HIVRN sites for at least 18 months prior to the study end date. The end of the observation period for individuals lost to follow-up was set to either the date of their last HIVRN visit date or the final day of their medication supply.

Measures

HIV disease progression for individuals on ART, mortality, ART dropout and ART re-initiation rates were of primary interest in this study. Disease progression was represented by changes in longitudinally-collected CD4 measurements, and all CD4 measurements while on ART during the period of January 1st, 2010 to December 31st, 2015 were included in the analysis. We categorized CD4 cell count measurements as ≥ 500 , 200–499, and <200 per μL . The CD4 metric is known to exhibit considerable variability resulting from intra-individual temporal fluctuation and measurement error¹⁶ that may lead to biased estimates of disease progression. To address these potential issues, we applied an “ad hoc smoothing” technique shown to perform best in terms of bias reduction, whereby transitions between CD4 categories were only allowed when 2 consecutive CD4 measurements were observed.¹⁷ We classified individuals as off ART if there was a minimum 90-day gap without an active ART prescription.¹³

In order to generate estimates of disease progression and ART retention capturing heterogeneity across settings and individuals, we included covariates to adjust for differences in transition rates by region (Northeast, South, West), sex (male, female), race/ethnicity (Black, Hispanic/Latino, and non-Hispanic white/others), and HIV risk group (men who have sex with men (MSM), people who inject drugs (PWID), MSM who inject drugs (MWID), and heterosexual (HET)). To address multicollinearity between gender and risk group covariates, individuals were categorized in mutually exclusive categories of HET female, HET male or MSM and we defined PWID status as a binary variable (yes/no).

We also considered other potentially confounding factors hypothesized to influence disease progression and ART retention, including age at study entry, time since diagnosis and whether an individual had prior ART utilization at study entry (yes/no). Since sustained high plasma viral load (pVL) periods are associated with CD4 declines, we also controlled for an individuals’ historical average pVL prior to study entry as measured by the area under the log pVL curve. Lastly, we did not control for insurance status as it is often considered as a potentially mediating factor of individual characteristics (e.g., race/ethnicity, risk group) that are of primary interest to our analysis.¹⁸

Statistical analysis

We used a parametric, continuous-time, Multi-state Markov model to estimate monthly transition probabilities between CD4 categories, and between on- and off-ART states, controlling for the covariates listed above. The estimation was operationalized by a matrix with 14 instantaneous transitions among five states (three on ART states defined as CD4 ≥ 500 , 200–499, and <200 , off ART and death), allowing for transitions to and from given states where possible (Figure 1). Multi-state Markov models efficiently handle heavily censored data, such as when the exact time of disease onset is unknown or when an individual is observed over a portion of their disease history.¹⁹ Further, the variation in elapsed time between CD4 measurements is inherently controlled for in this methodology.¹⁹

The effects of the covariates in this model are assumed to be multiplicative and constant over time, both assumptions being consistent with the conventional proportional hazards model.

Therefore, the interpretation of exponentiated coefficient estimates are equivalent to that of the adjusted hazard ratio in a Cox model. The likelihood ratio test was used to select covariates which improved model fit, and the most parsimonious model was chosen. The analysis was conducted on the full sample and on region-specific study samples to examine potential differences in covariate effects across regions.

In order to generate a matrix of transitions probabilities for each region and for each subgroup defined by gender, race/ethnicity and HIV risk group, we estimated all monthly transition probabilities, except mortality, by using region-specific stratified models for each subgroup, holding the other covariates at the region-specific study sample average level. Given the low number of deaths captured in the data within each region, mortality estimates during ART for each subgroup were obtained from the full sample model consisting of all three regions.

Model validation

We utilized transition probability estimates from the region-specific model to project over a 5-year period the number of individuals expected to be in each health state at 3-month intervals, equivalent to the median time between observations in the study sample. The estimated probability of being in health state i at time t given an individual's initial health state r is thus $P(t)_{r,i}$. Assuming all individuals are at time $t = 0$ at study entry, and given $n(t)$ individuals observed at time t , the expected number of individuals in health state i at time t is $n(t)P(t)_{r,i}$.

The selection of validation targets depends on the quality of available data,²⁰ and an external validation is considered dependent if the source for the targets was used to estimate model parameters.²¹ We derived validation targets from the observed number of individuals in each health state at each interval, and we assumed an individuals' health state was the same as their previous when it was not observed at time t . We compared projections from the multi-state Markov model to the observed CD4 disease progression during ART, proportion off ART and mortality over a 5-year period. The percentage deviation from each target was calculated at 3-month intervals, and we calculated the mean percentage deviation to evaluate how close the model projections were to the targets.²²

Role of the funding source

The funders had no direct role in the conduct of the analysis or the decision to submit the manuscript for publication. The corresponding author had final responsibility for the decision to submit for publication and full access to all the data.

Results

A total of 38,472 individuals met our inclusion criteria and were in HIV care during the study period. We excluded 3,376 (8.8%) due to having a single observed disease status measurement, and another 2,854 (7.4%) due to missing covariate information. Among the, 32,242 (83.8%) included in the study sample, the majority were male (75.4%) and the median age was 44 years [interquartile range (IQR), 35–51 years]. At study entry, 27,550 (85.4%) were on ART including 8,342 (25.9%) who had no prior ART utilization. Over a

median follow-up of 4.9 years [IQR, 2.6–6.0 years], 8,614 individuals (26.7%) interrupted ART. Table 1 provides baseline characteristics on the study sample by region.

The five-state, multivariable multi-state Markov was fitted to produce parameter estimates for each of the 14 possible transitions modeled. Selected independent determinants of transition rates from the full sample model are shown in Table 2 (full results on appendix page 4). We found that both heterosexual females and MSM had an increased hazard of CD4 improvement when compared to heterosexual males, and that the improvement was more likely to be sustained. For example, the adjusted hazard ratios (aHR) during ART for transitions from CD4 200–499 to 500 and from CD4 500 to 200–499 among heterosexual females were 1.35 (95% confidence interval [CI], 1.26–1.45) and 0.71 (95% CI, 0.65–0.77), respectively. In contrast, when compared to heterosexual male individuals with CD4 200–499, MSM had reduced hazard of ART drop out (aHR: 0.89 [95% CI, 0.82–0.96]) whereas heterosexual females had increased hazard of ART drop out (aHR: 1.14 [95% CI, 1.04–1.23]). Individuals with no prior ART utilization had increased hazard of sustained CD4 improvement (aHRs from 1.31–1.39) and reduced hazard of CD4 deterioration (aHRs 0.84–0.86). Regardless of CD4 strata, individuals had increased hazard rates of ART dropout if they were from the South (aHRs from 1.91–2.45) or the West (aHRs from 1.29–1.66), compared to individuals from the Northeast. However, those from the South were more likely to re-initiate ART (aHRs from 1.30–1.79) whereas individuals from the West were less likely (aHRs from 0.49–0.94). Moreover, in analysis of the full sample model, reporting injection drug use was independently associated with increased rates of ART dropout and faster disease progression (CD4 decline or death) (Table 2). Finally, our results were robust to sensitivity analysis examining potential bias from exclusion of individuals with missing covariate information (appendix pages 8–9).

In the region-specific stratified models, we found the hazard ratios of death from CD4<200 and ART dropout across CD4 categories to be highly heterogeneous for PWID (Figure 2). For example, injection drug use was associated with increased hazard of death from CD4<200 in the Northeast (aHR: 2.45 [95% CI: 1.66–3.62]), and South (aHR: 1.69 [95% CI: 1.26–2.27]), but not in the West. In contrast, CD4 deterioration for PWID was generally consistent across regions (appendix pages 5–7 present full results for the region-specific stratified models). In addition, results from the region-specific models highlighted heterogeneity in CD4 deterioration for heterosexual females (compared to heterosexual males), with aHRs associated with CD4 deterioration from 500 to 200–499 ranging from 0.66 [95% CI: 0.59–0.74] in the South to 0.85 [95% CI: 0.67–1.07] in the West. We also found heterogeneity across regions in the reduced hazard of ART dropout from CD4>200 among MSM (compared to heterosexual males), with the largest reductions in the Northeast (aHR: 0.61 [95% CI: 0.52–0.71] from CD 500; aHR: 0.76 [95% CI: 0.64–0.90] from CD4 200–499) compared to the other two regions (aHRs ranged from 0.90 [95% CI: 0.81–1.00] to 1.17 [95% CI: 0.94–1.47]) (Figure 2).

We present in Figure 3 the predicted probability of ART dropout among individuals with CD4<200 and of any ART re-initiation regardless of CD4 count, by risk group and region. The fitted values were estimated on an annual basis, generated from the region-specific stratified multivariate multi-state Markov models, and using mean values of covariates

observed in the region-specific study samples. The annual probability of ART dropout was markedly higher in the southern region across all risk groups, and ranged from 16% for Hispanic / Latino MSM to 39% for Black PWID. Compared to the other regions, differences were the greatest for southern Blacks. For example, male PWIDs were 23% more likely to dropout compared to those in the Northeast and heterosexual females 8% more likely than those in the western region. Furthermore, fitted values within the Northeast region were more homogeneous across risk groups and race/ethnicity compared to the other regions (complete fitted values for monthly transition probabilities, by region & subgroups, on appendix pages 10–22).

Validation results from comparing the multi-state Markov model projections to the validation targets are presented in Table 3. The dependent validation showed the model to slightly under-predict individuals in each CD4 strata during ART for the western region, ranging from -2.2% for individuals with CD4 500 to -7.4% for those with CD4 200–499. In contrast, the model slightly over-predicted individuals in only two CD4 strata during ART for the southern region, by 1.6% for individuals with CD4 200–499 and 6.3% for those with CD4<200. Mean deviations for each CD4 strata in the Northeast were relatively small and ranged from -2.1% for CD4 500 to 1.0% for CD4<200. The probability of being off ART was over-predicted across regions from 3.5% (South) to 22.7% (West), while mortality was under predicted across regions from -4.4% (Northeast) to -18.4% (West).

Discussion

This study illustrates the heterogeneity found across settings and individuals in ART engagement and its effect on HIV disease progression. We found the probability of disease progression during ART and ART retention rates varied across HIV risk groups, race/ethnicity and regions of the United States. Prior studies have estimated CD4 transition probabilities using comparable methodologies.^{12,13} However, this multivariable regression analysis conducted using region-specific models to jointly estimate the ART dropout and re-initiation in addition to CD4 progression is the first, to our knowledge, to demonstrate heterogeneity across individuals and settings. These findings have important implications. Clearly, simulation models which employ CD4 transition probabilities estimated from national estimates that do not account for race/ethnicity or HIV risk groups may mischaracterize the optimal set of interventions for treating and preventing HIV across distinct microepidemics. This is an important result to communicate as public health departments aim to implement locally-oriented combination implementation strategies necessary to achieve the ambitious goal of eliminating the HIV epidemic in the United States.

Our findings also have important implications for clinical practice. Delivering continuous care to people living with HIV (PWH) is critical to the control HIV microepidemics^{23,24} and the differences we found should be viewed as targets for interventions. As more than a quarter of all individuals included in our study interrupted ART at least once, treatment initiation must be recognized as an opportunity to improve ART persistence. Our results that individuals without prior ART experience had accelerated CD4 improvement and had a lower hazard of discontinuing ART are consistent with prior findings of successive treatment

episodes that tended to decrease in duration whereas episodes off ART remained relatively constant.²⁵ Given the paucity of evidence on effective and cost-effective interventions to improve ART persistence^{26,27} careful attention must be given to emerging evidence of promising ART engagement programs that target recently diagnosed individuals and individuals in need of comprehensive care assistance, particularly in states that did not expand Medicaid under the Affordable Care Act.

In addition, the increased hazard of both ART dropout and re-initiation in the full sample model for individuals in the southern region are indicative of substantial levels of ‘churn’ (a cyclical process of engagement, disengagement, and reengagement in HIV care) among PWH.¹ This pattern was also noticeable when comparing other race/ethnic groups to non-Hispanic whites. Compared to individuals in the Northeast, those in the South with higher CD4 counts had the highest hazard of ART dropout. Furthermore, those off ART and with low CD4 counts had the highest hazard of ART re-initiation. With HIVRN sites in the South all located in states that did not expand Medicaid under the Affordable Care Act, this observed gradient effect of CD4 count levels may be indicative of the disparity in access and quality of care between the South and Northeast. This disparity between the South and other regions of the United States has also been noted in studies on HIV-related mortality, which is now predominantly concentrated in poorer southern counties.²⁸ Addressing the complex needs of PWH struggling to remain engaged in ART is a key strategy in the United States’ new initiative for “Ending the HIV Epidemic”. It is essential to address the ART persistence challenges to realize the reductions in morbidity, mortality and transmission associated with sustained viral suppression.

Models used to make recommendations of targeted, locally-oriented combination implementation strategies should accurately reflect the current state of a given microepidemic. Several factors might explain the relatively larger deviations of our model projections from mortality and off-ART targets. Prior studies have suggested a higher risk of mortality among individuals lost to follow-up compared to those retained in care,²⁹ and individuals lost to follow-up were more likely to be in poorer health as measured by CD4 counts. Therefore, our analysis using multi-state Markov models that assume non-informative censoring might have resulted in the underestimation of mortality. Moreover, the estimation of ART re-initiation rates by CD4 category, not feasible in our study, might have improved off-ART model projection. Our validation results thus offer further support for the need to locally validate models, a best practice that can be supported by the calibration of key input parameters.^{21,30} Additionally, conducting one-way sensitivity analyses and probabilistic sensitivity analysis in economic evaluations to quantify the uncertainty in model recommendations resulting from parameters with greater uncertainty is critical. Efforts to collect population-based health administrative and surveillance data that could be used for estimating disease progression with greater precision would greatly enhance the validity of modeling recommendations. Given the paucity of data describing disease processes that are specific to the distinct microepidemics across the United States, increasing transparency and standardizing methods for model calibration and validation can ultimately promote better integration of locally-oriented modelling in decision-making.

This study has some limitations that are worth noting. First, although HIVRN sample demographics are comparable to those of PWH in the United States in general, our results may not generalize to all HIV care sites. However, most of the study population received care from urban academic and community-based clinics, thus closely mirroring the HIV epidemic in the United States, which is dispersed mostly across large urban centers.³ In addition, our analysis included multiple sites across broad geographic areas affording greater generalizability than single-site studies. Second, our analysis was restricted to males and females with at least two disease status measurements and with complete covariate information. Comparatively, a greater proportion of excluded individuals were MSM, had been diagnosed after 2007, and had no prior ART utilization (appendix page 3). In addition, our results may not be generalizable to individuals identifying as transgender or non-binary as our analysis was restricted to individuals reporting sex categorized as male or female. Third, the determination of ART interruption and loss to follow-up relied on medication prescription information and receipt of care in the HIVRN network, respectively. HIVRN data does not always reliably capture HIV treatment received elsewhere but this potential measurement bias did not impact disease progression estimates during ART. Data linkages to other databases such as Medicaid Claim data and AIDS Drug Assistance Program (ADAP) data could help improve measures of both ART and HIV care retention. Fourth, we could not determine how immune recovery may have been affected by previous ART regimens among treatment experienced individuals; however, we accounted for differences in disease progression between ART naïve and treatment experienced individuals. Lastly, multi-state Markov models assume non-informative censoring and definitions of loss to follow-up in longitudinal studies may influence event rates.¹⁹ Our multivariable regression analysis accounted for several factors that could be related to propensity of censorship thus mitigating potential attrition biases.

This study reveals heterogeneities in disease progression on ART and ART retention rates across racial and ethnic groups, HIV risk groups and regions. These differences should be viewed as targets for intervention and otherwise should be incorporated in mathematical models of regional HIV microepidemics in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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Research-in-Context

Previous Evidence

We searched PubMed for titles and abstracts of literature published in English between Jan 1, 1996, and July 13, 2018, using the search terms “HIV” AND “CD4” AND “Antiretroviral Therapy” AND (“Survival” OR “Mortality” OR “Prognosis” OR “Disease progression” OR “CD4 change” OR “Treatment interruption” OR “ART dropout” OR “ART interruption” OR “ART retention” OR “ART adherence”) AND (“Determinants” OR “Predictors” OR “Factors” OR “Disparity”) OR (“Rate”, OR “Estimate”). Search results were reviewed to identify publications reporting estimates and determinants of rates of disease progression (measured by CD4 changes) and/or ART retention. A number of factors have been noted in the literature to correlate with accelerated disease progression, including male, injection drug use and race/ethnicity minorities, whereas earlier diagnosis and treatment initiation and improved treatment adherence were associated with improved prognosis. In addition, younger age, injection drug use, and race/ethnicity minorities have been frequently found to be associated with reduced ART retention or adherence. Among them, three studies adopted multivariable multi-state Markov models to estimate rates of CD4 progression adjusting for a list of key covariates: one focused on the natural history of CD4 progression among seroconverter cohorts from 25 countries, while the other two were conducted in a Canadian setting, estimating probability of CD4 progression and mortality among population-based samples who have initiated ART, and interrupted ART, respectively. However, there was no study reporting estimates on rates of CD4 decline and ART retention accounting for heterogeneity across subgroups and geographic regions in the United States.

Added value of this study

We have used comprehensive clinical and ART prescription data from a large multi-site observational cohort to estimate rates of CD4 progression and mortality during ART and ART retention for several population subgroups across geographic regions of the United States. Using a continuous multi-state Markov model, we found that women, men who have sex with men and individuals with no prior ART utilization had increased rates of CD4 improvement whereas Blacks and people who inject drugs had increased rates of ART dropout, and faster disease progression. Finally, regardless of CD4 strata, individuals from the South or the West had increased hazard rates of ART dropout compared to individuals from the Northeast.

Implications of all the available evidence

Our study highlights the heterogeneity in HIV disease progression and ART retention across geographic locations and subgroups. These differences should be viewed as targets for intervention and otherwise should be incorporated in mathematical models of regional HIV microepidemics in the United States. Simulation models which employ CD4 transition probabilities estimated from national estimates that do not account for race/ethnicity or HIV risk groups may mischaracterize the absolute and relative cost-effectiveness of interventions to treat and prevent HIV in distinct microepidemics. This is an important result to communicate as public health departments aim to implement

locally-oriented combination implementation strategies to reduce the public health burden of HIV/AIDS.

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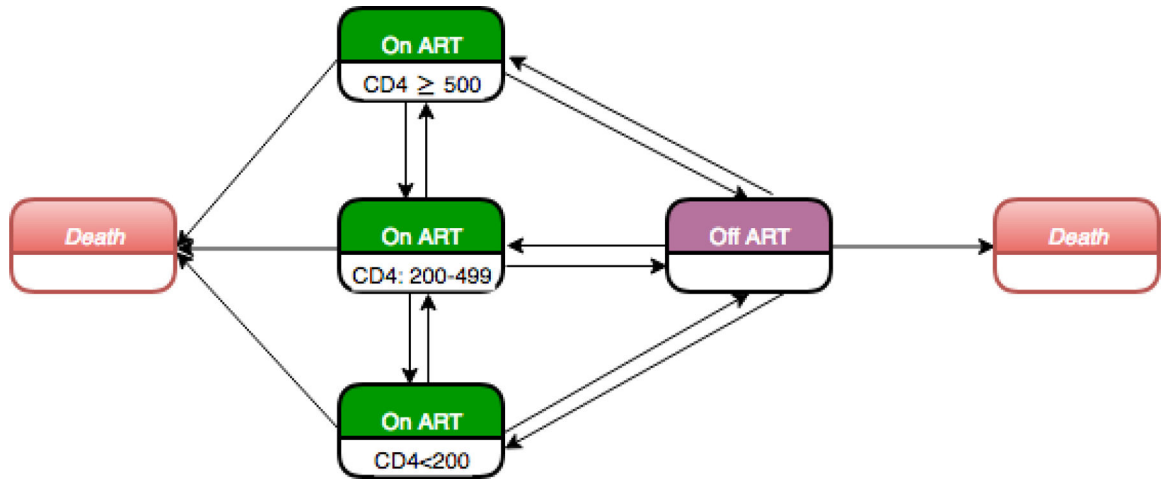


Figure 1.
Diagram for the Multi-state Markov model.
ART: Antiretroviral treatment; CD4: CD4 T-lymphocyte cell count per μL .

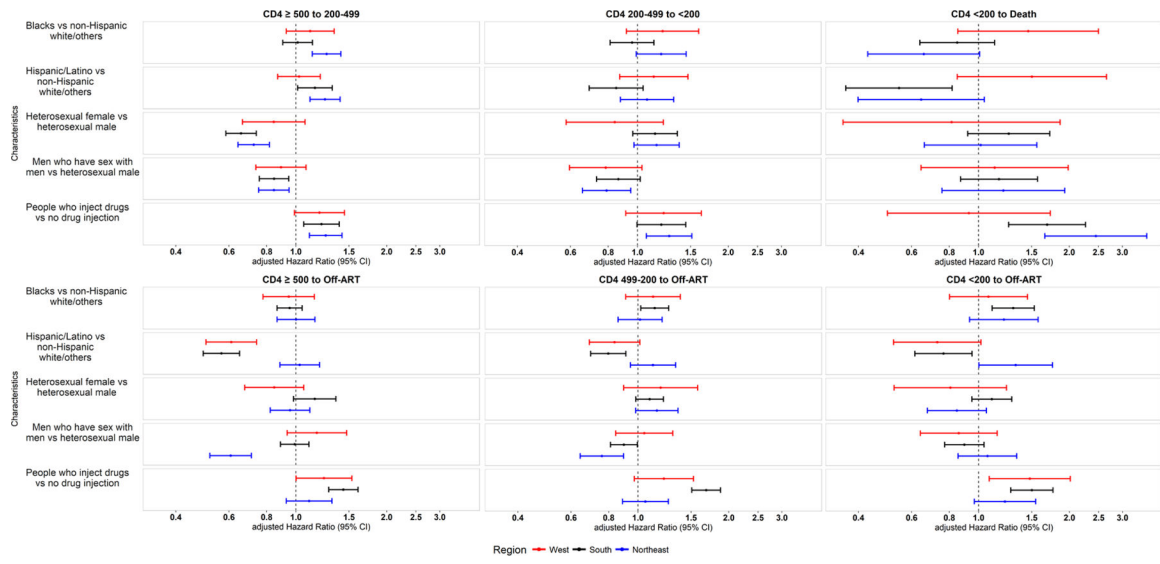


Figure 2. Adjusted hazard ratios associated with CD4 deterioration during ART, including mortality, and ART dropout, by region. ART: Antiretroviral treatment; CD4: CD4 T-lymphocyte cell count per μL .

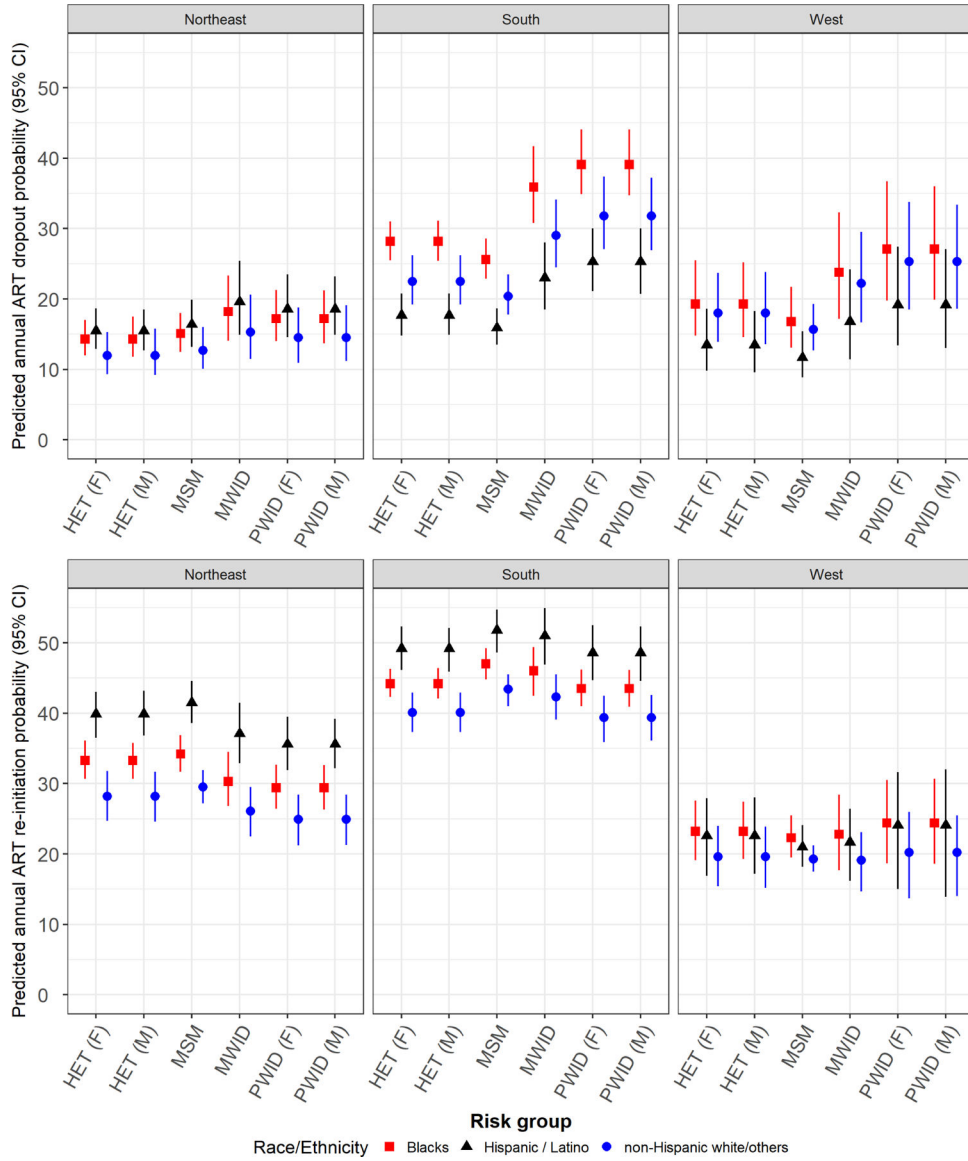


Figure 3. Predicted annual probability of ART dropout among individuals with CD4<200 (top) and of any ART re-initiation regardless of CD4 count (bottom) by region, risk group and race/ethnicity.

CD4: CD4 T-lymphocyte cell count per μL ; MSM: Men who have sex with men; PWID: People who inject drugs; MWID: MSM who inject drugs; HET: Heterosexuals; F: Female; M: Male. Predicted values from region-specific stratified models for each gender, risk group and race/ethnicity adjusting for age at study entry, prior ART utilization at study entry (yes/no) and historical average plasma viral load (pVL) (control values equal to the region-specific study sample average level).

Table 1.

Characteristics of the HIV Research Network study participants, by region (N=32,242)

Characteristics	Region		
	Northeast n=13,563 (42.1%)	South n=13,345 (41.4%)	West n=5,334 (16.5%)
Age at study entry (Median (IQR))	45.4 [36.5, 51.7]	43.3 [33.1, 50.4]	44.3 [36.4, 50.8]
Follow-up in years(Median(IQR))	4.8 [2.8, 6.0]	5.1 [2.6, 6.0]	5.3 [2.5, 6.0]
Male	10,224 (75.4)	9,486 (71.1)	4,595 (86.1)
Race/ethnicity			
<i>Black</i>	5,866 (43.3)	7,627 (57.2)	1,072 (20.1)
<i>Hispanic / Latino</i>	3,749 (27.6)	2,439 (18.3)	1,308 (24.5)
<i>non-Hispanic white / others</i>	3,948 (29.1)	3,279 (24.6)	2,954 (55.4)
HIV risk group			
<i>MSM</i>	6,768 (49.9)	5,483 (41.1)	3,344 (62.7)
<i>PWID</i>	1,580 (11.6)	1,336 (10.0)	362 (6.8)
<i>MWID</i>	272 (2.0)	316 (2.4)	363 (6.8)
<i>HET</i>	4,943 (36.4)	6,210 (46.5)	1,265 (23.7)
Year of diagnosis			
<i>1996</i>	4,701 (34.7)	2,875 (21.5)	1,634 (30.6)
<i>1997–2006</i>	5,261 (38.8)	5,318 (39.9)	2,057 (38.6)
<i>2007–2015</i>	3,601 (26.6)	5,152 (38.6)	1,643 (30.8)
Year of ART initiation			
<i>1996</i>	690 (5.1)	673 (5.0)	517 (9.7)
<i>1997–2006</i>	3,289 (24.2)	4,398 (33.0)	1,729 (32.4)
<i>2007–2015</i>	4,555 (33.6)	6,488 (48.6)	2,282 (42.8)
<i>Unknown</i>	5,029 (37.1)	1,786 (13.4)	806 (15.1)
No prior ART utilization at study entry	2,610 (19.2)	4,377 (32.8)	1,355 (25.4)

MSM: men who have sex with men; PWID: people who inject drugs; MWID: MSM who inject drugs;

HET: heterosexual; ART: Antiretroviral treatment.

Table 2.

Multivariate multi-state Markov model results of disease progression during ART, mortality and ART engagement from full sample (N=32,242)

Reference	HET female		MSM	Black	Hispanic/Latino	PWID	No prior ART*		South	West
	aHR (95% CI)	HET male aHR (95% CI)	aHR (95% CI)	non-Hispanic white/others aHR (95% CI)	aHR (95% CI)	non-PWID aHR (95% CI)	Prior ART aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	Northeast aHR (95% CI)
CD4 improvement during ART										
<200 to 200-499	1.37 (1.24,1.51)	1.25 (1.14,1.37)	1.08 (0.98,1.19)	1.06 (0.95,1.18)	0.98 (0.88,1.10)	1.39 (1.26,1.53)	1.16 (1.07,1.26)	1.05 (0.94,1.17)		
200-499 to 500	1.35 (1.26,1.45)	1.10 (1.03,1.18)	0.98 (0.92,1.05)	0.93 (0.87,1.00)	0.97 (0.90,1.05)	1.31 (1.22,1.40)	0.85 (0.80,0.89)	0.84 (0.78,0.90)		
CD4 deterioration during ART										
500 to 200-499	0.71 (0.65,0.77)	0.85 (0.79,0.91)	1.13 (1.06,1.22)	1.18 (1.09,1.27)	1.23 (1.13,1.33)	0.86 (0.78,0.94)	1.18 (1.11,1.26)	1.18 (1.09,1.28)		
200-499 to <200	1.12 (1.00,1.26)	0.82 (0.74,0.92)	1.11 (0.99,1.25)	1.02 (0.90,1.15)	1.23 (1.10,1.38)	0.84 (0.73,0.95)	1.01 (0.91,1.11)	1.04 (0.92,1.19)		
ART dropout										
500 to off-ART	1.04 (0.95,1.12)	0.88 (0.81,0.95)	0.97 (0.90,1.04)	0.73 (0.67,0.80)	1.36 (1.25,1.49)	1.10 (1.00,1.20)	2.45 (2.29,2.62)	1.66 (1.51,1.82)		
200-499 to off-ART	1.14 (1.04,1.23)	0.89 (0.82,0.96)	1.12 (1.03,1.21)	0.91 (0.83,1.00)	1.45 (1.34,1.58)	0.92 (0.84,1.01)	1.95 (1.81,2.10)	1.41 (1.27,1.56)		
<200 to off-ART	1.00 (0.89,1.13)	0.91 (0.82,1.02)	1.23 (1.09,1.39)	0.89 (0.77,1.03)	1.42 (1.26,1.61)	0.73 (0.64,0.84)	1.91 (1.71,2.13)	1.29 (1.10,1.51)		
ART re-initiation										
Off-ART to 500 on-ART	1.39 (1.27,1.52)	1.25 (1.14,1.38)	1.02 (0.94,1.12)	1.20 (1.08,1.32)	0.88 (0.79,0.96)	1.14 (1.03,1.26)	1.30 (1.21,1.41)	0.49 (0.43,0.55)		
Off-ART to 200-499 on-ART	1.02 (0.93,1.11)	1.02 (0.93,1.12)	1.16 (1.05,1.27)	1.37 (1.23,1.52)	1.02 (0.93,1.12)	0.86 (0.78,0.96)	1.43 (1.32,1.55)	0.59 (0.52,0.67)		
Off-ART to <200 on-ART	0.81 (0.73,0.90)	0.82 (0.74,0.91)	1.39 (1.24,1.57)	1.55 (1.36,1.77)	0.94 (0.84,1.05)	0.60 (0.52,0.68)	1.79 (1.62,1.99)	0.94 (0.80,1.09)		
Mortality										
500 to death	0.77 (0.51,1.15)	0.80 (0.53,1.20)	0.88 (0.61,1.26)	0.50 (0.31,0.83)	2.31 (1.62,3.29)	0.76 (0.42,1.36)	1.24 (0.89,1.73)	1.05 (0.68,1.63)		
200-499 to death	1.01 (0.75,1.38)	0.70 (0.51,0.95)	0.81 (0.60,1.08)	0.54 (0.38,0.78)	1.56 (1.18,2.06)	0.91 (0.60,1.36)	1.12 (0.86,1.46)	1.28 (0.93,1.76)		
<200 to death	1.08 (0.85,1.37)	1.12 (0.90,1.40)	0.90 (0.72,1.13)	0.77 (0.59,1.01)	1.61 (1.30,2.00)	0.93 (0.72,1.21)	1.93 (1.56,2.40)	1.37 (1.02,1.84)		
Off-ART to death	1.34 (0.80,2.22)	1.21 (0.70,2.08)	0.63 (0.39,1.01)	0.74 (0.41,1.33)	1.36 (0.86,2.16)	0.75 (0.36,1.54)	1.15 (0.76,1.76)	0.38 (0.18,0.80)		

Bold indicates statistically significant adjusted hazard ratios at p<0.05

ART: Antiretroviral treatment; CD4: CD4 T-lymphocyte cell count per µL; dx: Diagnosis; aHR: adjusted hazard ratio; CI: confidence interval.

HET: heterosexual; MSM: men who have sex with men; PWID: people who inject drugs.

* No prior ART utilization at study entry compared to prior ART utilization at study entry.

Table 3.

Comparison of multi-state Markov model projections and validation targets.

Regional validation targets	Mean deviation from regional stratified model projections		
	Northeast	South	West
CD4 during ART			
500	-2.1%	0.0%	-2.2%
200–499	0.6%	1.6%	-7.4%
<200	1.0%	6.3%	-7.1%
Off-ART	15.9%	3.5%	22.7%
Mortality	-4.4%	-11.8%	-18.4%

ART: Antiretroviral treatment; CD4: CD4 T-lymphocyte cell count per μL .

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