Longitudinal Engagement Trajectories and Risk of Death among New ART Starters in Zambia

Aaloke Mody, Ingrid Eshun-Wilson, Sheree R. Schwartz, Kombatende Sikombe, Sandra Simbeza, Njekwa Mukamba, Paul Somwe, Carolyn Bolton, Nancy Padian, Charles Holmes, Izukanji Sikazwe, Elvin Geng

Adherence 2018

June 9, 2018

UCSF University of California San Francisco

CIDRZ

Georgetown University

Berkeley School of Public Health

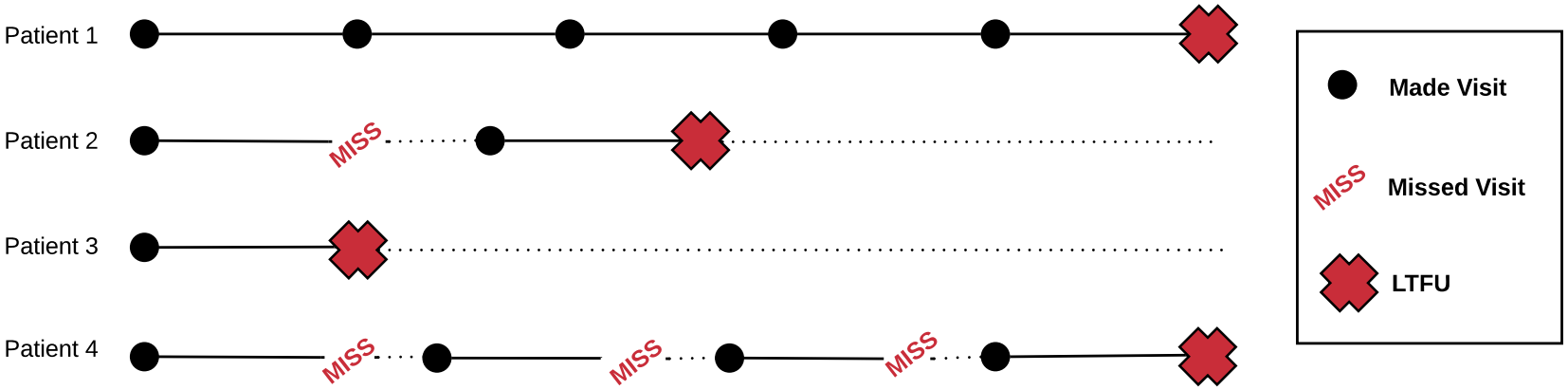
UAB

Motivation

- Retention in HIV care is widely suboptimal across sub-Saharan Africa

- Previous studies have described how patients often transition in and out of HIV care, but current analyses often:
  - Reduce highly-dimensional retention histories into cross-sectional summaries (i.e., LTFU)
  - Obscure patient heterogeneity behind population-level averages

Different Retention Patterns with LTFU



Motivation

- Better characterization of these complex longitudinal retention patterns can give us a deeper understanding of patient retention and behavior

- May help uncover distinctive underlying behavioral phenotypes
  - Similar retention patterns may point to similar challenges to remaining in care
  - Improves our ability to target interventions for a diverse population

- We use group-based trajectory analysis—a form of latent class analysis—to better understand the temporal dynamics of patient retention and the heterogeneity in patient behaviors

Study Objectives

- To identify subgroups with distinct patterns in adherence and retention among patients newly started on ART in Zambia
- To identify predictors of belonging to subgroups with a specific engagement trajectory
- To estimate the association between different patterns of engagement and subsequent mortality

METHODS

Study Population

- HIV-infected adults newly started on ART between Aug 1, 2013 and Feb 1, 2015 in Zambia

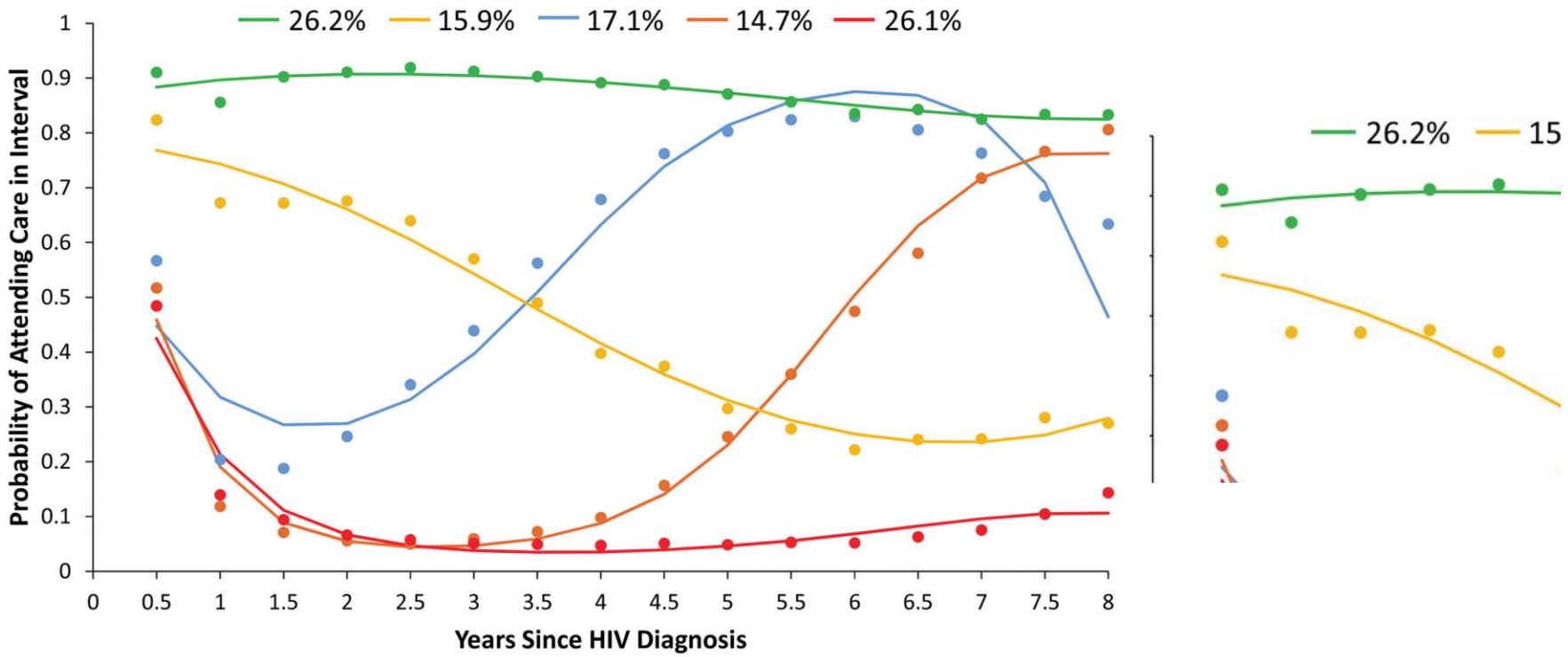
- 64 clinics supported by the Centre for Infectious Disease Research in Zambia (CIDRZ) in Lusaka, Eastern, Western, and Southern Provinces

Measurements

- Better Info for Health study
  - EMR system used in routine HIV care in Zambia (SmartCare)
  - Active tracing of a random sample of patients lost to follow-up (LTFU) as of July 31, 2015 to accurately ascertain mortality

Group-Based Trajectory Analysis

- Identify subgroups that follow distinct longitudinal trajectories
  - Assume population made of distinct, but *unobserved*, subpopulations with different behavioral patterns
  - Use observed data to identify these groups (form of latent class analysis)



Powers *JAIDS* 2017

Group-Based Trajectory Analysis Steps

1. Use observed outcomes to simultaneously estimate 1) shape of trajectories and 2) their population-level distribution
   - Trajectories modeled as a function of time using flexible polynomials

2. Systematically assess various specifications and choose final model based on BIC
   - Number of groups and polynomial order *unknown* a priori

Nagin *Annu Rev Clin Psychol* 2010; Bray *Struct Equ Modeling* 2015; Backk *Struct Equ Modeling* 2016

Model Specifications

- Outcomes for Trajectories (defined at every 30 day interval)
  - Medication possession ratio (MPR) over the past 3 months
  - LTFU Status (>90 days late to the last appointment)

- Observation Period
  - Time zero was date of ART initiation
  - Patients censored at the time of death, transfer, or end of observation (i.e., July 31, 2015).

- Excluded patients with less than 180 days of observation time (i.e., early deaths, transfers)
  - Allow individuals sufficient time to differentiate into a trajectory

- Sampling weights to account for tracing

Group-Based Trajectory Analysis Steps

1. Use observed outcomes to simultaneously estimate 1) shape of trajectories and 2) their population-level distribution
   - Trajectories modeled as a function of time using flexible polynomials

2. Systematically assess various specifications and choose final model based on BIC
   - Number of groups and polynomial order *unknown* a priori

3. Estimate an individuals' probability of belonging to each trajectory groups given their observed outcomes (i.e., posterior probability)
   - Application of Baye's Theorem

4. Assign individuals to the trajectory group they are most likely to belong to based on posterior probabilities

5. Weight observations by the inverse of their classification error (i.e., the probability that they were assigned to one trajectory group when they belong to another) in regression analyses
   - Account for misclassification of group membership (BCH method)

Nagin *Annu Rev Clin Psychol* 2010; Bray *Struct Equ Modeling* 2015; Backk *Struct Equ Modeling* 2016

Analyses by Trajectory Group

- Predictors of Trajectory Group Membership
  - Multinomial Logistic Regression that included individual and clinic-level characteristics

Analyses by Trajectory Group

- Predictors of Trajectory Group Membership
  - Multinomial Logistic Regression that included individual and clinic-level characteristics

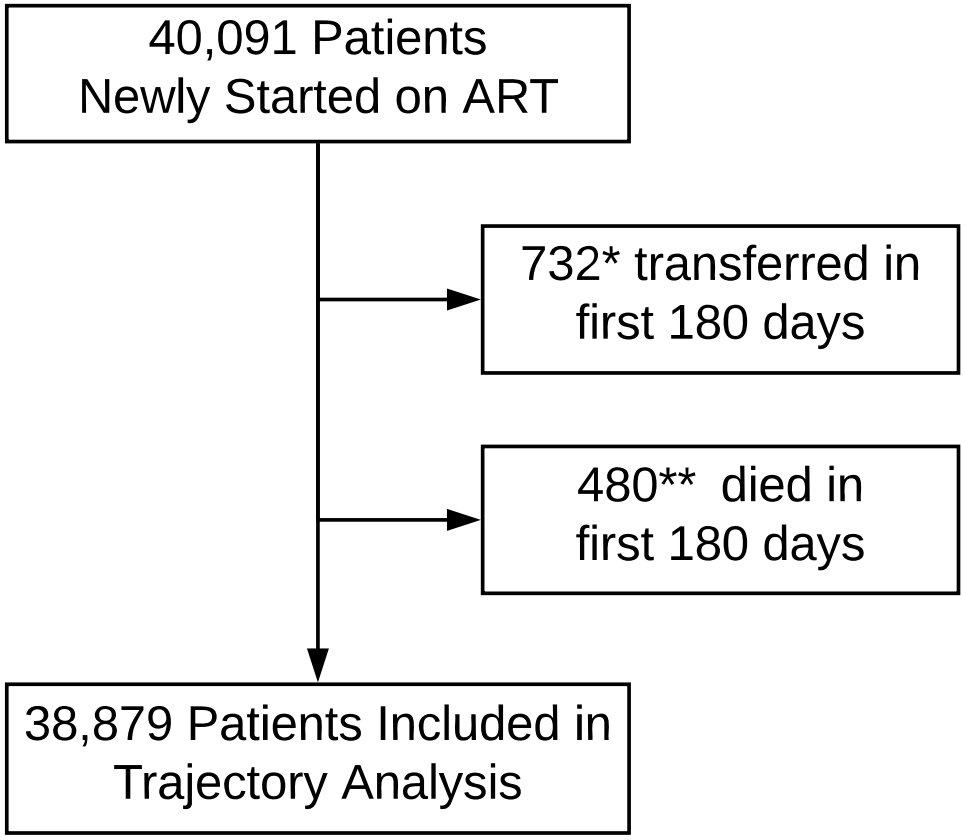
- Mortality Risk by Trajectory Group
  - Survival analysis stratified by trajectory group
    - Time zero was date of ART initiation
    - Administrative censoring at the time of transfer or end of observation
    - Bootstrapped confidence intervals
  - Adjusted Poisson Regression to estimate incidence rate ratios*

- Models weighted to account for classification error and sampling
- Multiple imputation (n=20) to address missingness in predictor variables

*Cox PH model inappropriate due to non-proportional hazards

RESULTS

Study Population



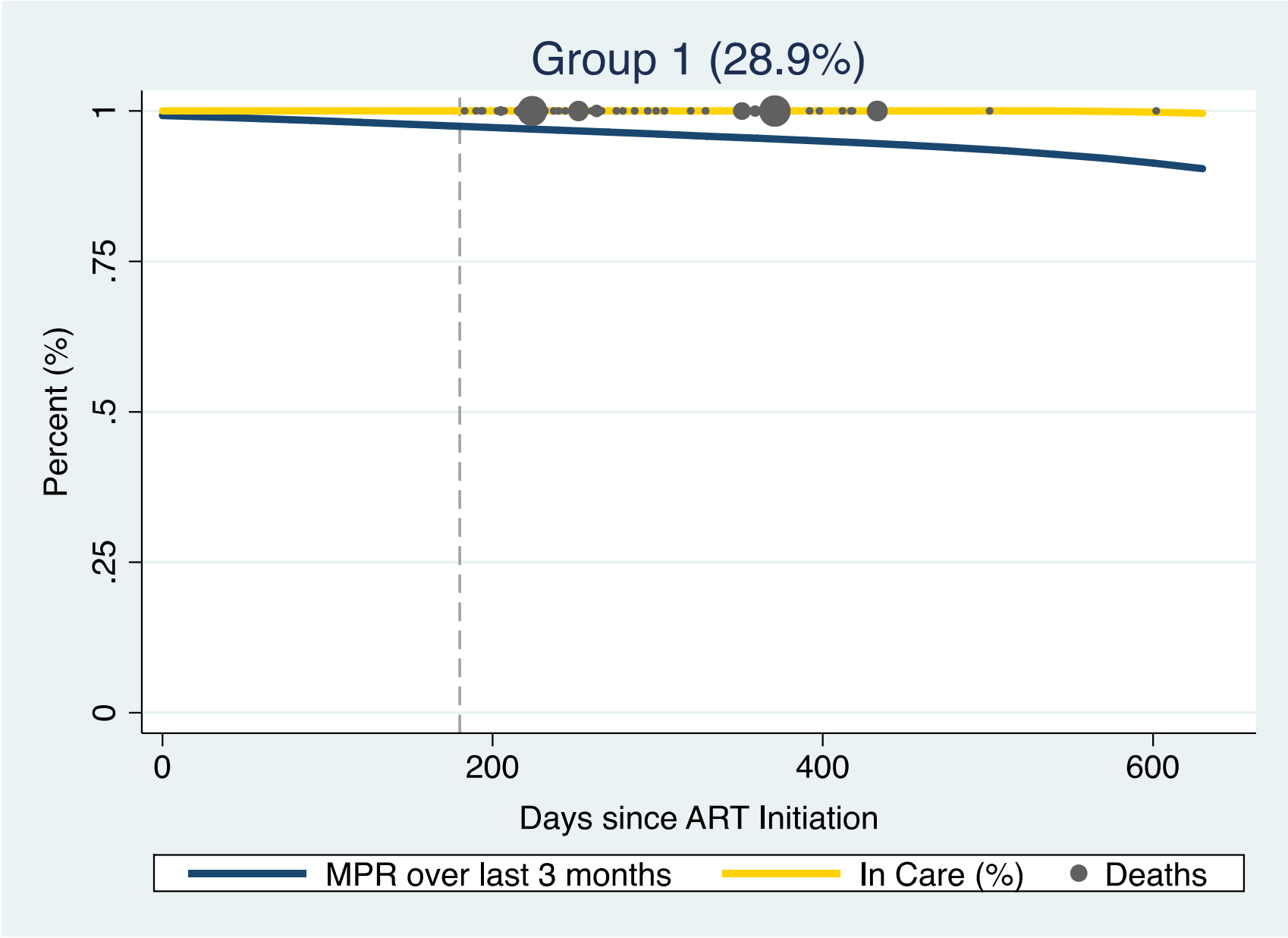
*1.8% of population accounting for sampling weights
**3.2% of population accounting for sampling weights

Patient Characteristics

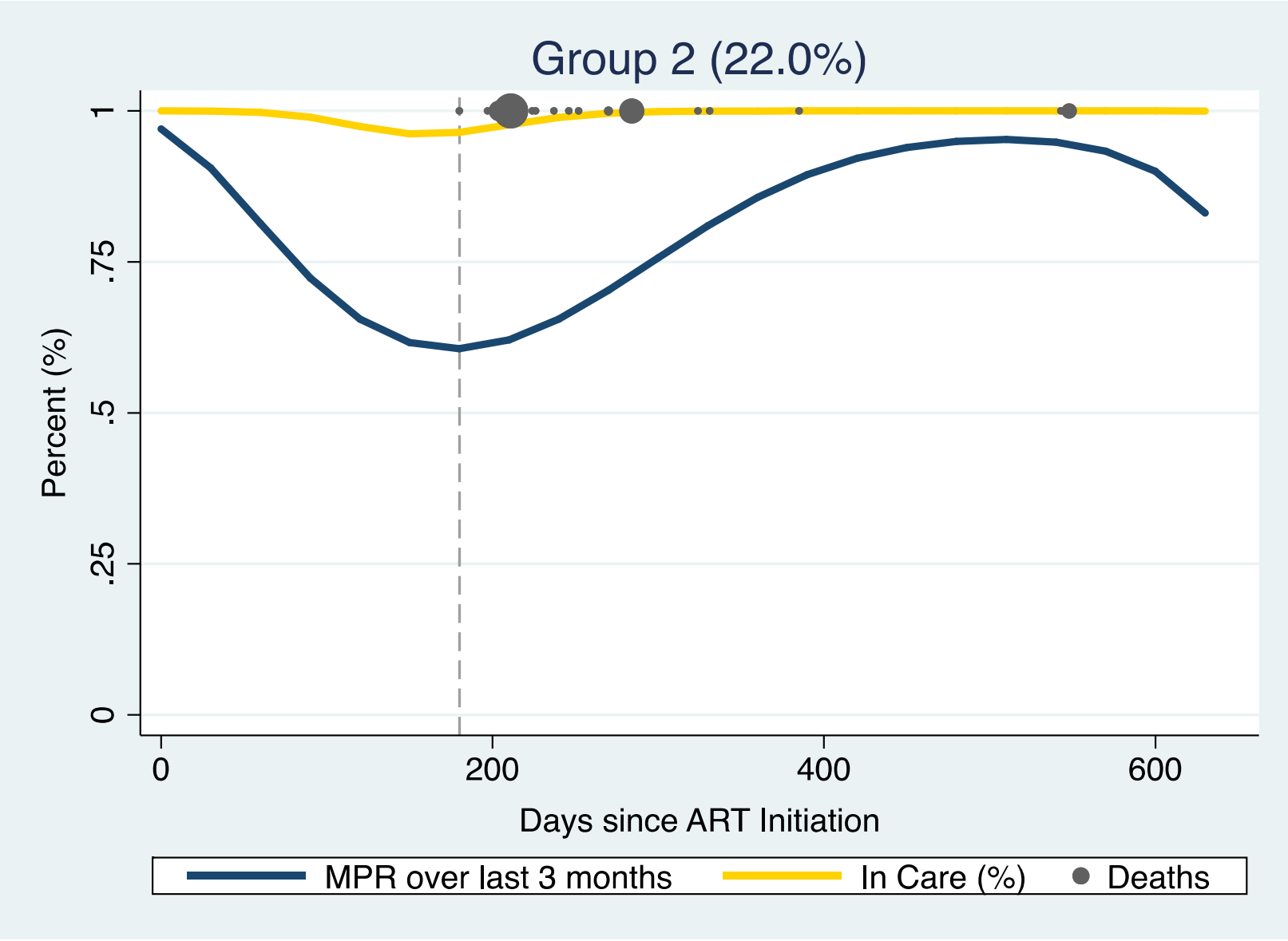
	All Patients (n=38,879)
Sex, n (%)	
Male	14,286 (36.7)
Female	24,593 (63.3)
Median Age, years (IQR)	35 (29, 41)
Median CD4 count, cells/μL (IQR)	280 (146, 431)
WHO Stage, n (%)	
I	18,777 (57.0)
II	6,645 (20.2)
III	6,941 (21.1)
IV	607 (1.8)
TB in past 6m, n (%)	978 (2.5)
Median Time to ART, days (IQR)	35 (14, 225)
Province, n (%)	
Lusaka	20,238 (52.1)
Eastern	7,673 (19.7)
Southern	5,146 (13.2)
Western	5,822 (15.0)

Median time observed, days (IQR): 429 (314, 571)

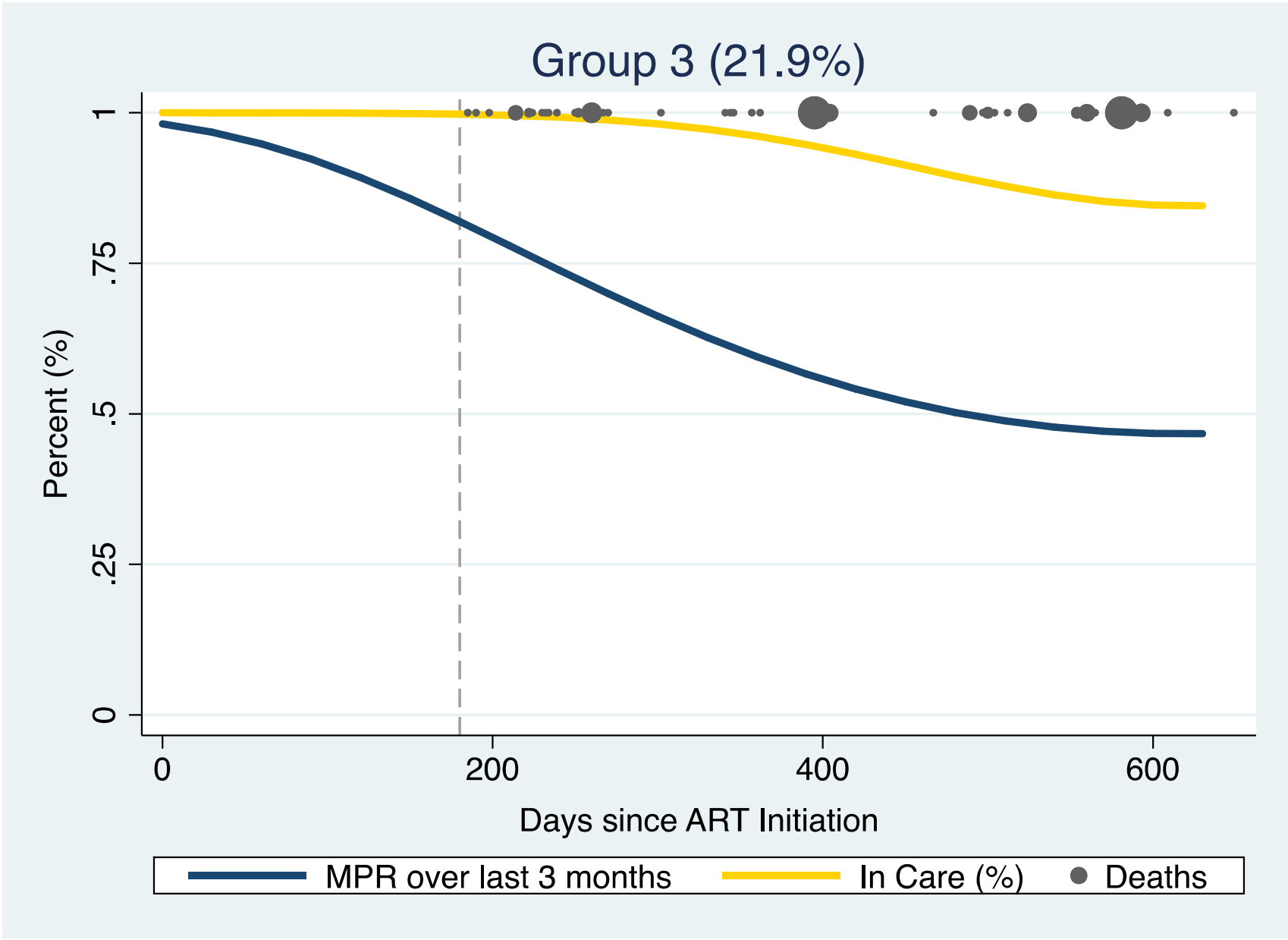
Consistently high MPR and retention (28.9%)



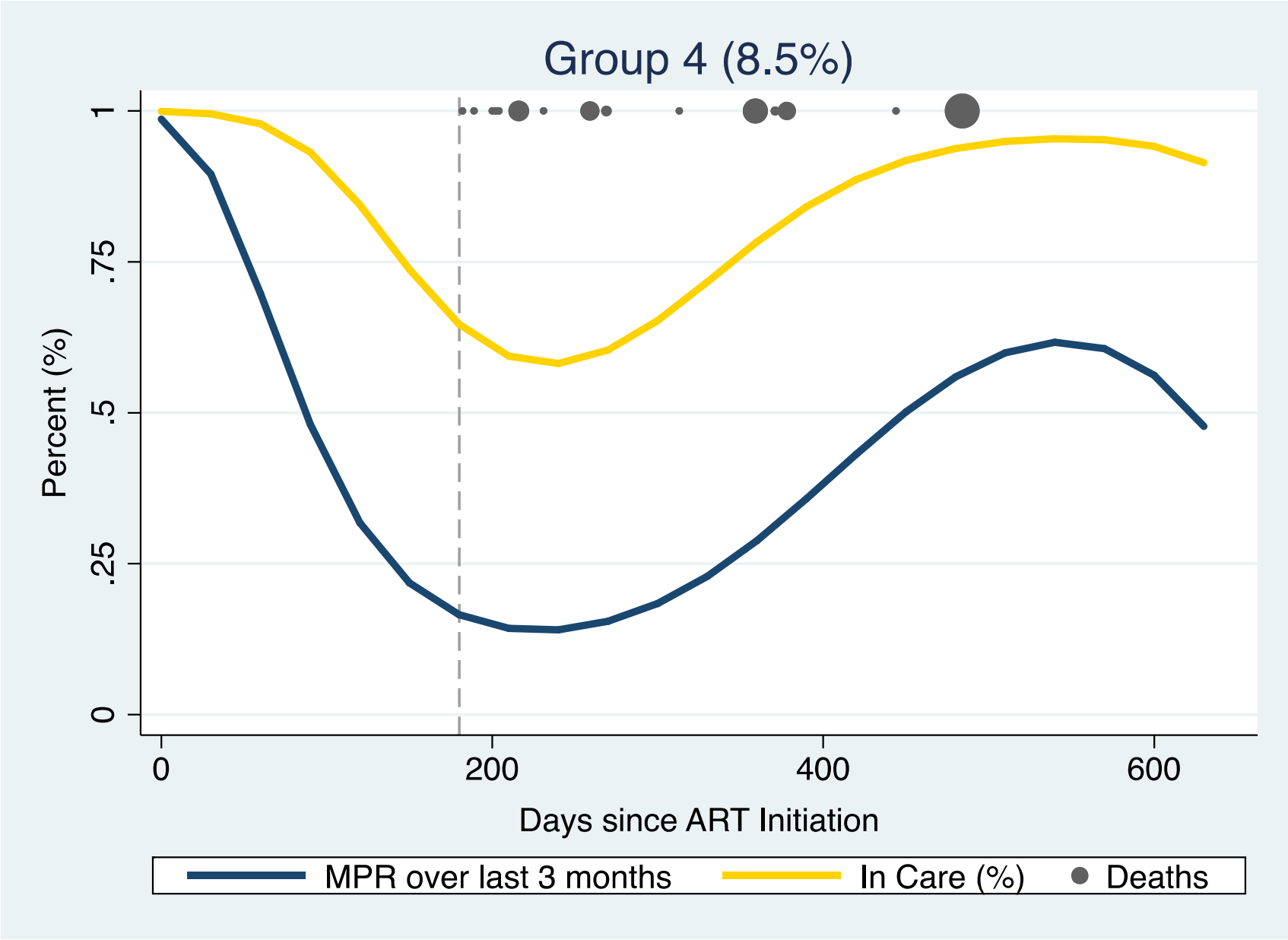
Suboptimal adherence early with late recovery, but consistent retention (22.0%)



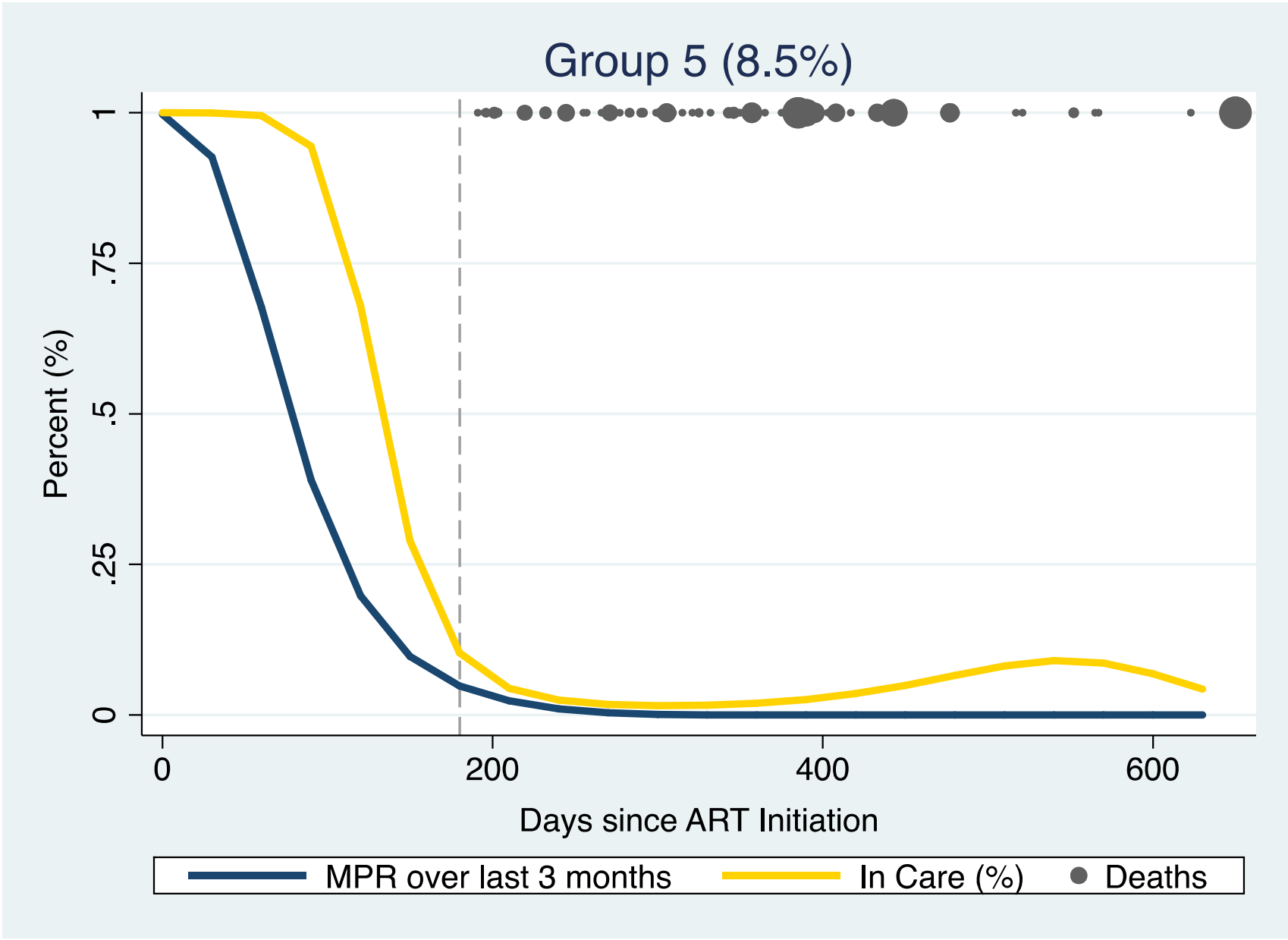
Gradually decreasing MPR and retention (21.9%)



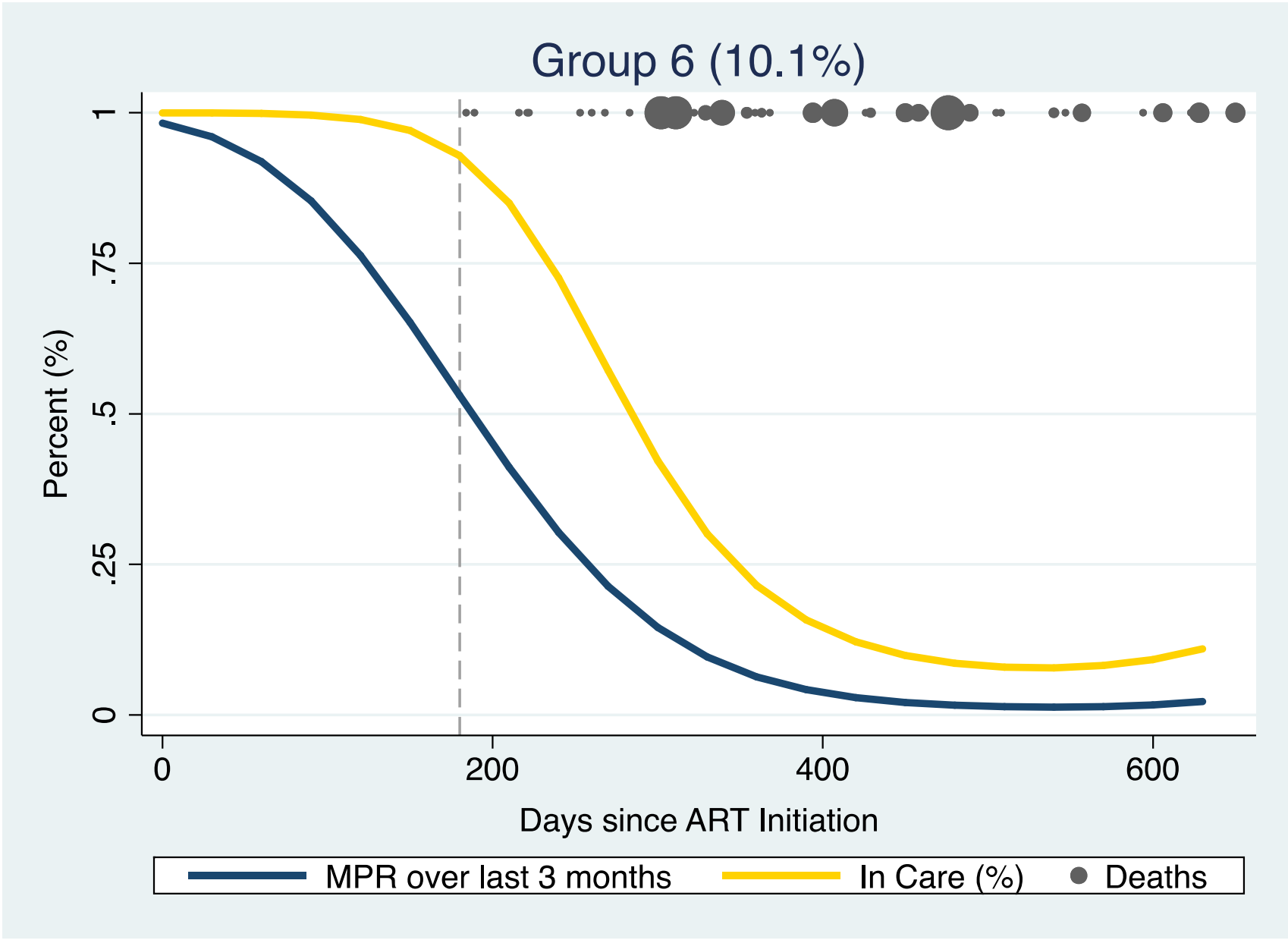
Early nonadherence/LTFU with late recovery (8.5%)



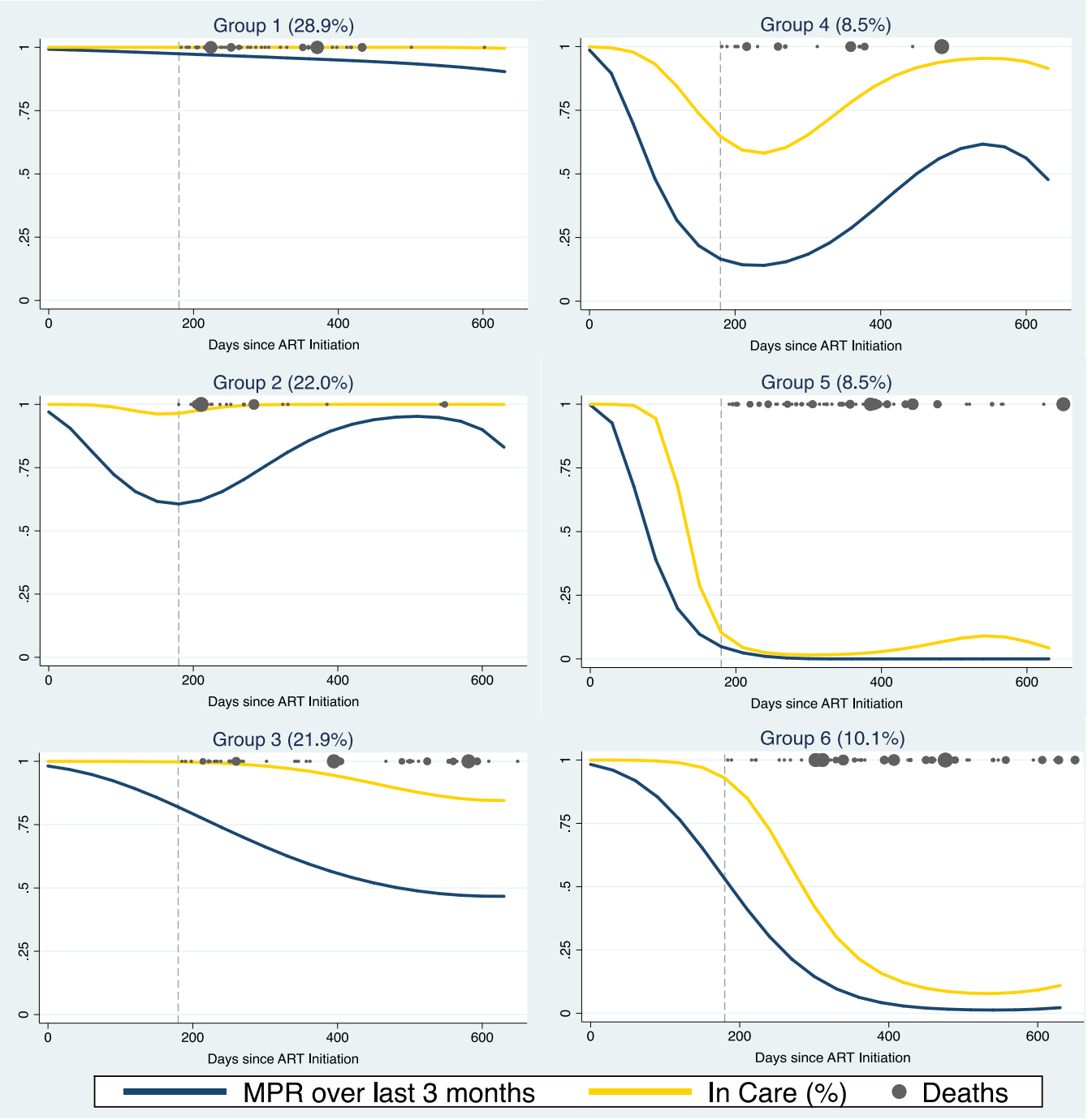
Early nonadherence/LTFU without recovery (8.5%)



Late nonadherence/LTFU without recovery (10.1%)



Trajectory Groups, n=38,879



Model Fit

Classification Error: Probability of being assigned to a particular trajectory group given one's "true" group

		"True" Trajectory Group					
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Predicted Trajectory Group	Group 1	**95.3**	2.4	5.3	<0.1	<0.1	<0.1
	Group 2	1.1	**88.5**	6.2	3.0	<0.1	4.3
	Group 3	3.6	7.0	**87.1**	0.8	<0.1	4.0
	Group 4	<0.1	0.8	0.3	**91.3**	3.2	1.4
	Group 5	0	<0.1	<0.1	1.7	**96.0**	0.6
	Group 6	<0.1	1.2	1.0	3.2	0.8	**89.6**

Entropy for Overall Model: 0.957

- Indicates good separation between trajectory groups

Patient Characteristics by Group, n=38,879

	Group 1 (28.9%)	Group 2 (22.0%)	Group 3 (21.9%)	Group 4 (8.5%)	Group 5 (8.5%)	Group 6 (10.1%)
Male Sex, %	36.2	35.9	37.3	34.8	35.9	41.6
Median Age, years (IQR)	36 (30, 43)	35*** (29, 41)	34*** (29, 41)	34*** (28, 39)	34 (29, 41)	33 (28, 41)
Median CD4 count, cells/μL (IQR)	291 (151, 438)	284 (152, 431)	286 (158, 432)	313 (170, 492)	244 (96, 445)	254 (122, 445)
WHO Stage 3 or 4, %	19.9	20.1	21.3	20.3	28.0	23.8
TB in past 6m, %	2.1	2.1	2.2	3.1*	2.4	3.1
Median Time to ART, days (IQR)	32 (14, 227)	42*** (14, 285)	41 (15, 228)	56*** (15, 455)	42 (14, 190)	44 (14, 191)
Single, (%)	10.8	11.1	13.3	13.4	12.5	24.1***
College/University Education, %	4.3	5.3*	5.1	4.6	7.4	11.7***
Disclosed HIV Status, %	97.7	97.0**	97.7	98.1	98.0	96.0
Lusaka Province, %	39.4	50.5***	52.4***	68.2***	65.9***	57.1***
Proportion of Visits at Clinic Scheduled at 30d, median (IQR)	0.40 (0.31, 0.52)	0.48*** (0.38, 0.55)	0.46*** (0.38, 0.57)	0.53*** (0.39, 0.57)	0.53*** (0.38, 0.65)	0.43*** (0.31, 0.57)
Average Daily Visits at Clinic, median (IQR)	64 (41, 111)	76** (41, 123)	64 (41, 111)	55*** (49,108)	64 (50, 123)	55* (49, 111)

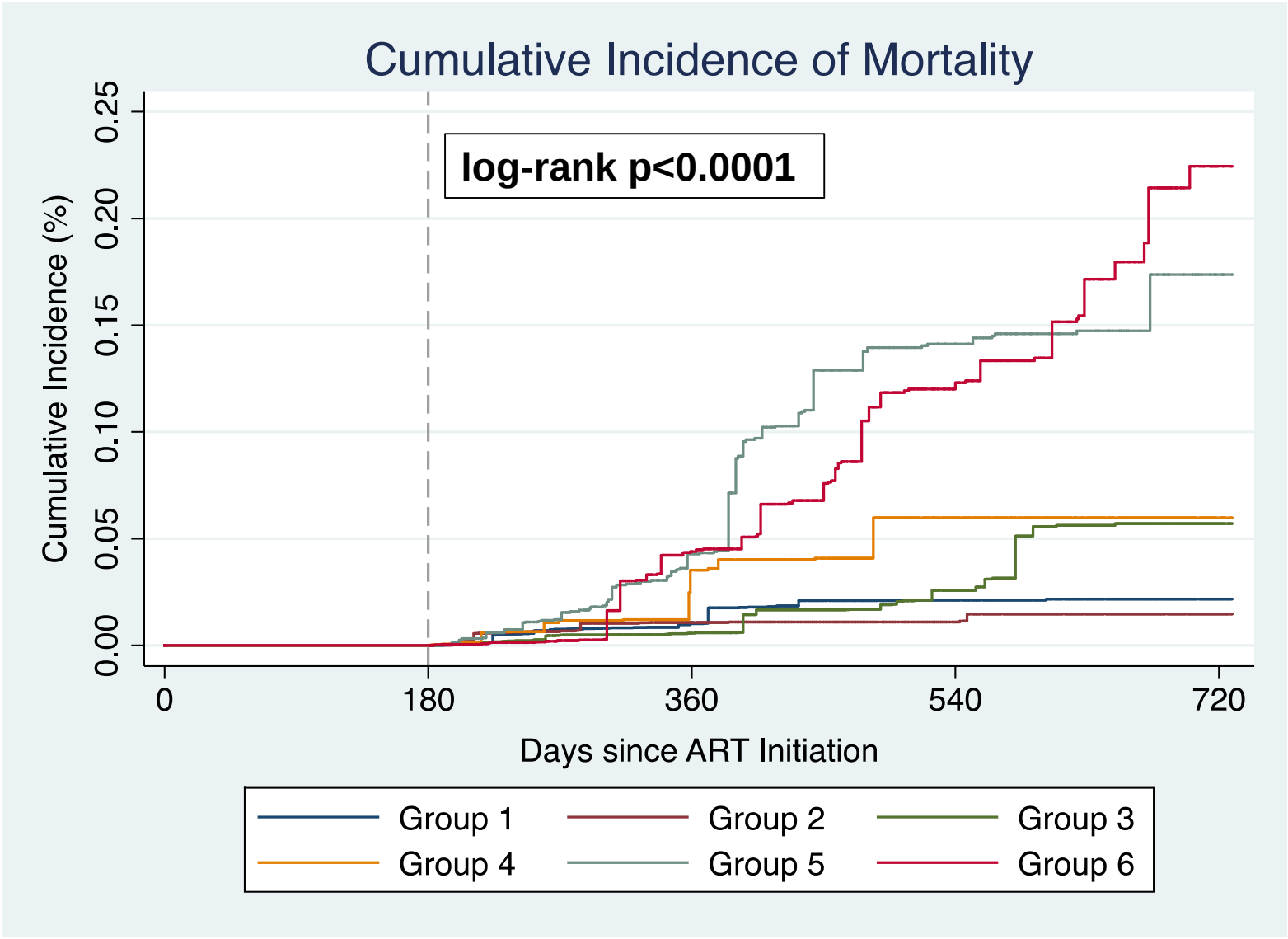
*p<0.1, **p<0.05, ***p<0.01 in adjusted analysis for predictors as compared to Group 1

Patient Characteristics by Group, n=38,879

	Group 1 (28.9%)	Group 2 (22.0%)	Group 3 (21.9%)	Group 4 (8.5%)	Group 5 (8.5%)	Group 6 (10.1%)
Male Sex, %	36.2	35.9	37.3	34.8	35.9	41.6
Median Age, years (IQR)	36 (30, 43)	35*** (29, 41)	34*** (29, 41)	34*** (28, 39)	34 (29, 41)	33 (28, 41)
Median CD4 count, cells/μL (IQR)	291 (151, 438)	284 (152, 431)	286 (158, 432)	313 (170, 492)	244 (96, 445)	254 (122, 445)
WHO Stage 3 or 4, %	19.9	20.1	21.3	20.3	28.0	23.8
TB in past 6m, %	2.1	2.1	2.2	3.1*	2.4	3.1
Median Time to ART, days (IQR)	32 (14, 227)	42*** (14, 285)	41 (15, 228)	56*** (15, 455)	42 (14, 190)	44 (14, 191)
Single, (%)	10.8	11.1	13.3	13.4	12.5	24.1***
College/University Education, %	4.3	5.3*	5.1	4.6	7.4	11.7***
Disclosed HIV Status, %	97.7	97.0**	97.7	98.1	98.0	96.0
Lusaka Province, %	39.4	50.5***	52.4***	68.2***	65.9***	57.1***
Proportion of Visits at Clinic Scheduled at 30d, median (IQR)	0.40 (0.31, 0.52)	0.48*** (0.38, 0.55)	0.46*** (0.38, 0.57)	0.53*** (0.39, 0.57)	0.53*** (0.38, 0.65)	0.43*** (0.31, 0.57)
Average Daily Visits at Clinic, median (IQR)	64 (41, 111)	76** (41, 123)	64 (41, 111)	55*** (49,108)	64 (50, 123)	55* (49, 111)

*p<0.1, **p<0.05, ***p<0.01 in adjusted analysis for predictors as compared to Group 1

Cumulative Incidence of Mortality by Trajectory Group



Cumulative Incidence of Mortality by Trajectory Group

	Cumulative Incidence of Mortality					
	360 days		540 days		720 days	
	%	95% CI	%	95% CI	%	95% CI
Trajectory Group						
Group 1	1.0	0.4 – 1.9	2.1	0.7 – 3.9	2.2	0.8 – 4.0
Group 2	1.1	0.2 – 2.2	1.1	0.2 – 2.2	1.5	0.4 – 2.7
Group 3	0.6	0.3 – 1.0	2.6	0.9 – 4.7	5.7	2.2 – 10.5
Group 4	3.5	0.7 – 7.1	6.0	1.8 – 11.6	6.0	1.8 – 11.6
Group 5	4.3	2.2 – 6.8	14.1	7.4 – 22.6	17.4	9.1 – 28.4
Group 6	4.4	0.8 – 8.4	12.3	6.0 – 19.8	22.4	13.4 – 34.6

Mortality Risk by Trajectory Group - Poisson Regression

	Unadjusted IRR	p-value	Adjusted IRR	p-value
Trajectory Group				
Group 1	REF	-	REF	-
Group 2	0.73	0.61	0.75	0.66
Group 3	1.9	0.25	1.7	0.39
Group 4	2.7	0.084	3.1	0.048
Group 5	6.0	<0.001	6.6	<0.001
Group 6	6.2	<0.001	5.7	0.001
Male Sex	-	-	1.17	0.59
Age, per 10 year increase	-	-	1.44	<0.001
Enrollment CD4 count, per 100 cells/μL increase	-	-	0.68	0.001
WHO Stage 3 or 4	-	-	0.94	0.86
TB in past 6m	-	-	0.49	0.27
Time to ART, per 90 day increase	-	-	1.03	0.40
Single	-	-	0.73	0.52
College/University Education	-	-	0.89	0.86
Disclosed HIV Status	-	-	0.67	0.56
Lusaka Province	-	-	0.72	0.34
Proportion of Visits at Clinic Scheduled at 30d, per 10% increase	-	-	0.98	0.81
Average Daily Visits at Clinic, per 25 visit increase	-	-	0.97	0.74

Limitations

- Unable to assess viral suppression
  - MPR and LTFU are imperfect proxies for virologic outcomes
- Limitations of primary data source
  - Potential for outcome misclassification
- Causal inference may be limited with latent class methodologies

CONCLUSION

Conclusions

- We identified six trajectory groups among new ART starters
  1. Consistently high MPR and retention (28.9%)
  2. Suboptimal adherence early with late recovery/consistent retention (22.0%)
  3. Gradually decreasing MPR and retention (21.9%)
  4. Early nonadherence/LTFU with late recovery (8.5%)
  5. Early nonadherence/LTFU without recovery (8.5%)
  6. Late nonadherence/LTFU without recovery (10.1%)

- Few strong baseline characteristics predictive of trajectory group membership

- Trajectory group strongly associated with risk of mortality

Implications

- Characterizing heterogeneity in longitudinal retention trajectories gives us a richer understanding of retention and patient behavior

- Different retention behaviors are associated with substantially different risk of mortality

- Urgent need to better understand baseline and longitudinal drivers of these engagement behaviors
  - Patients may have baseline behavioral phenotypes, but longitudinal events may also be key drivers

- Improved understanding of drivers of this heterogeneity in patient behaviors could be used to effectively and efficiently target interventions.
  - Patients with different engagement patterns may require different types of interventions

Thank you!

UCSF
- Elvin Geng
- Monika Roy
- Nancy Czaicki (in memorium)

UC Berkeley
- Nancy Padian

Georgetown University
- Charles Holmes

Stellenbosch University
- Ingrid Eshun-Wilson

Johns Hopkins University
- Sheree Schwartz

CIDRZ
- Izukanji Sikazwe
- Carolyn Bolton-Moore
- Thea Savory
- Mwanza wa Mwanza
- Kombatende Sikombe
- Jake Pry
- Sandra Simbeza
- Njekwa Mukamba
- Anjali Sharma

- Zambian Ministry of Health

- Bill and Melinda Gates Foundation