Immune, Virologic and Adherence Measures as Time-Dependent Predictors of Loss to Follow-Up

Seema Thakore Meloni[1], Charlotte Chang[1], Doug Hoi Cheung[1], Beth Chaplin[1], Holly Rawizza[1], Oluwatoyin Jolayemi[2], Bolanle Banigbe[2], Prosper Okonkwo[2], Phyllis Kanki[1]

[1]Harvard School of Public Health, Boston, MA, U.S.A; [2]AIDS Prevention Initiative Nigeria, Ltd./Gte., Abuja, Nigeria

Poster Abstract #1797

ABSTRACT

Background: For programs supporting large numbers of patients on ART, loss to follow-up (LTFU) and inadequate adherence pose major obstacles in achieving successful outcomes. In preliminary analyses examining patterns and predictors of attrition, we found that baseline CD4+ cell counts, baseline viral loads and early adherence patterns were associated with overall LTFU. In this evaluation, we further characterized the association of CD4+ cell counts, viral loads (VL), and treatment gaps on LTFU in a time-dependent fashion.

Methodology: From 2004-2012, Harvard/APIN received PEPFAR funds (HRSA #U51HA02522) to support and develop a sustainable HIV prevention, care and treatment program across multiple clinical centers in Nigeria. All patient ART-related data were collected and stored electronically. LTFU was defined as ≥60 days since the last scheduled refill date. For the analyses on CD4 counts and VL, we examined LTFU in 6-month increments, evaluating the CD4+ cell counts and VL taken at the prior visit as a predictor of loss in a time-dependent fashion. For the evaluation on large early treatment gaps and LTFU, the gap was defined as a contiguous ≥90 days between refill dates during the first 6 months of treatment (i.e., "+90 gap"). Logistic regression methods were used to evaluate the association between +90 gap and LTFU.

Results: Between June 2004-February 2011, the Harvard/APIN PEPFAR program enrolled 57,376 previously ARV-naïve ART patients. Of those, 35% were eventually LTFU. In evaluating the association of CD4+ cell counts and VL suppression rates in a prior visit for months 6, 12, 18, 24, 30, 36, 42, and 48, we found that CD4+ cell counts and VL at prior visits remained significant predictors of attrition (p<0.05; Figure 1). Additionally, patients with the +90 gap were more likely to become LTFU beyond 6 months than those that did not have the gap (p<0.05). Patients with the +90 gap were less likely to have VL suppression and had a lower CD4 count increase by month 12 versus those without the gap (p<0.05).

Conclusions: The majority of analyses on LTFU focus on baseline measures as predictors of attrition. In this evaluation, we were able to show that time-dependent CD4+ cell counts and viral loads are continuous predictors of loss at 6-month time points starting at ART initiation extending to month 48 and that early large gaps in treatment were associated with LTFU within the first year of ART initiation. These data highlight additional indicators that should trigger counseling to ensure low rates of attrition.

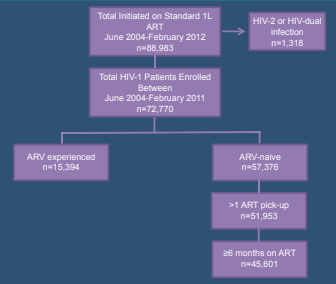
BACKGROUND

- From 2004-2012, Harvard School of Public Health partnered with AIDS Prevention Initiative in Nigeria (APIN) to utilize PEPFAR funds to scale-up HIV services across Nigeria.
  - Scale-up was successful, but the need to retain patients on therapy at a reduced cost was challenging; cost-effective tools for designing targeted interventions are needed
- Rates and predictors of LTFU have been evaluated in multiple HIV programs; the majority focus on baseline measures[1-11]
- The goal of this evaluation was to use additional statistical methods to build upon existing information on baseline predictors to examine time-dependent predictors of LTFU
- Hypothesis: early adherence patterns, CD4+ counts and viral loads (VLs) are strong indicators of risk of loss in a time-dependent manner
- Ultimate goal was to identify easy and inexpensive indicators for health care workers with limited resources and high patient volumes to identify potential future interventions for improving overall retention

METHODS

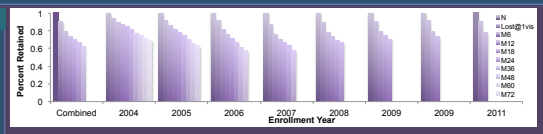
- Patients: HIV-1-infected patients enrolled on ART in Harvard/APIN PEPFAR program
  - Inclusion criteria: enrolled June 2004-February 2011 (to allow for at least 1 year of follow-up time for evaluations), at least 15 years of age
    - Subset analysis on early adherence and LTFU focused on patients with ≥6 months on treatment
  - Exclusion: prior ARV experience, HIV-2 infection
- Loss to follow-up defined as ≥2 months since patient's last scheduled pick-up date at time point of interest/evaluation
- Variables evaluated as predictors of LTFU:
  - Demographic: sex, education level achieved, occupation type, enrollment site, enrollment year, HIV transmission category
  - Clinical: HBV co-infection, HCV co-infection, TB status at entry, baseline WHO stage, CD4+ cell count (baseline and every 6 months), RNA viral load (baseline and every 6 months)
  - Behavioral: adherence pattern in first 6 months of treatment (measured by pill refill)
- Statistical methods (Stata version 13.0):
  - Univariate
    - Normally distributed variables: Chi-square for categorical and Student's t-test for continuous
    - Non-normally distributed variables: Fisher's exact for categorical and Wilcoxon rank sum for continuous
  - Random effects Cox proportional hazards models for examining factors associated with LTFU
    - Models run with both complete cases and following 10 multiple imputations for missing data
    - Models re-run with CD4+ count and viral load as time-varying covariates

Flow diagram for patients included in the evaluations



Baseline characteristics of ARV-inexperienced treatment cohort

Characteristic	Patients Retained after 1st pick-up	Patients LTFU after 2nd pick-up	Patients Retained after 2nd pick-up	p-value
N	51,953	14,626	34,996	-
Median time on ART, months (IQR)	28.6 (14.8-44.9)	9.3 (2.9-21.0)	36.6 (23.9-51.2)	0.0001
Median age, in years (IQR)	35 (29-41)	34 (28-41)	35 (29-41)	<0.0001
Sex, n (%)				
Female	33,676 (64.8)	8,861 (60.6)	23,307 (66.6)	<0.001
Male	18,277 (35.2)	5,765 (39.4)	11,689 (33.4)	
Site type				
Secondary	5,183 (10.0)	1,108 (7.6)	3,705 (10.6)	>0.001
Tertiary	46,770 (90.0)	13,518 (92.4)	31,291 (89.4)	
ART initiation year				
Jun 2004 – Dec 2005	4,428 (8.5)	1,333 (9.1)	2,837 (8.1)	<0.001
2006	4,714 (9.1)	1,756 (12.0)	2,630 (7.5)	
2007	6,945 (13.4)	2,424 (16.6)	4,130 (11.8)	
2008	11,754 (22.6)	3,545 (24.2)	7,706 (22.0)	
2009	11,714 (22.5)	3,034 (20.7)	8,183 (23.4)	
2010-Feb 2011	12,398 (23.9)	2,534 (17.3)	9,510 (27.2)	
Education, n (%)				
None	9,421 (18.5)	3,160 (22.1)	5,811 (16.9)	<0.001
Primary	11,194 (21.9)	3,292 (23.0)	7,422 (21.5)	
Secondary	18,025 (32.3)	4,910 (34.3)	12,344 (35.8)	
Tertiary	12,436 (24.3)	2,966 (20.7)	8,896 (25.8)	
Marital Status, n (%)				
Single	10,084 (19.6)	3,219 (22.3)	6,398 (18.4)	<0.001
Married	29,697 (57.7)	7,814 (54.2)	20,584 (59.2)	
Divorced/Separated	4,559 (8.9)	1,445 (10.0)	2,902 (8.4)	
Widowed	7,142 (13.9)	1,945 (13.5)	4,868 (14.0)	
Occupation				
Non-income-generating	12,612 (24.6)	3,890 (27.0)	8,108 (23.4)	<0.001
Laborer/Service Worker	35,458 (69.0)	9,747 (67.7)	24,178 (69.8)	
Manager/Professional	3,292 (6.4)	757 (5.3)	2,377 (6.9)	
HIV Risk Factor				
Heterosexual Sex	46,273 (95.5)	13,031 (95.8)	31,152 (95.3)	0.028
Other/multiple	2,188 (4.5)	574 (4.2)	1,532 (4.7)	
Baseline CD4+ count, cells/mL				
≤50	7,715 (15.6)	2,718 (19.6)	4,544 (13.6)	<0.001
51-100	8,766 (17.7)	2,685 (19.4)	5,586 (16.7)	
101-200	19,054 (38.5)	5,084 (36.7)	13,193 (39.4)	
>200	14,012 (28.3)	3,359 (24.3)	10,143 (30.3)	
Baseline viral load, copies/mL				
0-999	3,879 (8.6)	1,083 (8.6)	2,633 (8.7)	<0.001
1,000-9,999	6,261 (13.9)	1,653 (13.1)	4,343 (14.3)	
10,000-99,999	15,675 (34.8)	4,229 (33.5)	10,761 (35.4)	
≥100,000	19,221 (42.7)	5,671 (44.9)	12,645 (41.6)	
WHO Stage, n (%)				
1	10,919 (24.3)	2,412 (19.8)	8,046 (26.3)	<0.001
2	12,858 (26.7)	3,150 (25.9)	9,108 (29.7)	
3	15,028 (33.5)	4,321 (35.5)	10,018 (32.7)	
4	6,031 (13.5)	2,300 (18.9)	3,452 (11.3)	
TB at Entry				
Yes	11,492 (22.1)	3,484 (23.8)	27,595 (78.9)	<0.001
No	40,461 (77.9)	11,142 (76.2)	7,401 (21.1)	
HBV Status at Baseline				
Positive	5,575 (15.8)	1,828 (17.5)	3,497 (15.2)	<0.001
Negative	29,624 (84.2)	8,644 (82.5)	19,592 (84.8)	
HCV Status at Baseline				
Positive	1,980 (5.7)	577 (5.6)	1,247 (5.5)	0.54
Negative	32,921 (94.3)	9,805 (94.4)	21,647 (94.5)	
First-line drug regimen				
TDF+XTC+EFV	9,097 (17.5)	2,683 (18.3)	6,045 (17.3)	<0.001
TDF+XTC+NVP	10,265 (19.8)	2,977 (20.4)	6,758 (19.3)	
AZT+3TC+EFV	4,783 (9.2)	1,570 (10.7)	2,989 (8.5)	
AZT+3TC+NVP	24,147 (46.5)	6,230 (42.6)	16,894 (48.3)	
d4T+3TC+EFV	248 (0.5)	93 (0.6)	141 (0.4)	
d4T+3TC+NPV	3,413 (6.6)	1,073 (7.3)	2,169 (6.2)	



The majority of discontinuation typically occurred within the first 12-18 months following initiation of treatment.

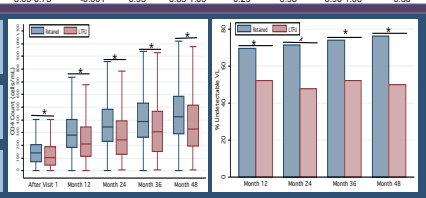
Random effects Cox proportional hazards model of baseline predictors of LTFU

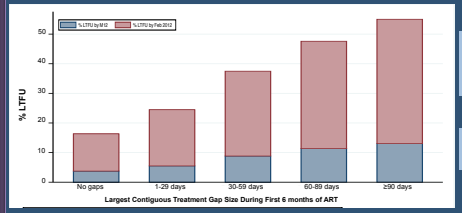
	Unadjusted HR			Adjusted HR (Complete Cases)			Adjusted HR (Multiple Imputations)		
Variable	**HR**	**95%CI**	**p**	**aHR**	**95%CI**	**p**	**aHR**	**95%CI**	**p**
Age ≥35 years	0.91	0.88-0.94	<0.001	0.87	0.83-0.91	<0.001	0.89	0.86-0.92	<0.001
Female sex	0.81	0.79-0.84	<0.001	0.76	0.72-0.90	<0.001	0.76	0.73-0.79	<0.001
ART initiation year ≥2006	1.43	1.35-1.52	<0.001	1.39	1.28-1.52	<0.001	1.36	1.26-1.46	<0.001
Tertiary site	1.10	1.03-1.17	0.003						
Married/Widowed	0.79	0.77-0.82	<0.001	0.78	0.74-0.81	<0.001	0.79	0.76-0.81	<0.001
Occupation									
Non-income generating	Ref	-	-	Ref	-	-	Ref	-	-
Laborer/Svc worker	0.91	0.87-0.94	<0.001	0.92	0.83-0.91	0.001	0.91	0.87-0.95	<0.001
Manager/Professional	0.69	0.64-0.75	<0.001	0.91	0.83-1.01	0.07	0.92	0.84-0.99	0.049
Education									
None	Ref	-	-	Ref	-	-	Ref	-	-
Primary	0.85	0.81-0.89	<0.001	0.92	0.87-0.98	0.011	0.94	0.89-0.99	0.014
Secondary	0.77	0.73-0.81	<0.001	0.79	0.75-0.74	<0.001	0.81	0.77-0.85	<0.001
Tertiary	0.63	0.60-0.66	<0.001	0.63	0.59-0.57	<0.001	0.66	0.62-0.70	<0.001
Non-heterosexual sex as main HIV risk factor	1.09	1.00-1.19	0.04						
WHO Stage									
1	Ref	-	-	Ref	-	-	Ref	-	-
2	1.11	1.05-1.17	<0.001	1.03	0.98-1.10	0.25	1.04	0.98-1.10	0.19
3	1.36	1.29-1.43	<0.001	1.15	1.09-1.22	<0.001	1.16	1.10-1.23	<0.001
4	1.86	1.76-1.97	<0.001	1.36	1.27-1.46	<0.001	1.36	1.28-1.45	<0.001
TB at Entry	1.10	1.06-1.15	<0.001						
HBV at Entry	1.10	1.05-1.16	<0.001						
HCV at Entry	0.93	0.85-1.01	0.08						
Baseline CD4+ count, cells/mL									
≤50	Ref	-	-	Ref	-	-	Ref	-	-
51-100	0.82	0.78-0.87	<0.001	0.84	0.79-0.89	<0.001	0.84	0.79-0.89	<0.001
101-200	0.70	0.67-0.73	<0.001	0.74	0.70-0.78	<0.001	0.74	0.71-0.78	<0.001
>200	0.62	0.59-0.65	<0.001	0.67	0.64-0.72	<0.001	0.67	0.64-0.71	<0.001
Baseline viral load, copies/mL									
<100,00	Ref	-	-	Ref	-	-	Ref	-	-
≥100,000	1.13	1.09-1.17	<0.001	1.06	1.02-1.10	0.004	1.05	1.01-1.09	<0.018
Starting ART regimen									
TDF+FTC/3TC+EFV	Ref	-	-	Ref	-	-	Ref	-	-
TDF+FTC/3TC+NVP	0.90	0.85-0.95	<0.001	1.05	0.98-1.12	0.15	1.07	1.01-1.13	0.026
AZT+3TC+EFV	0.97	0.91-1.03	0.37	0.93	0.87-1.00	0.06	0.92	0.86-0.98	0.007
AZT+3TC+NVP	0.77	0.74-0.80	<0.001	0.88	0.83-0.94	<0.001	0.89	0.85-0.93	<0.001
d4T+3TC+EFV	1.02	0.83-1.25	0.85	0.87	0.64-1.19	0.39	1.06	0.86-1.31	0.57
d4T+3TC+NVP	0.70	0.65-0.75	<0.001	0.95	0.85-1.05	0.29	0.98	0.90-1.06	0.56

Median CD4+ cell counts continually increased over the 4 years for both those that were retained and not retained in the evaluated time period.

At each of the assessed time points, the median CD4+ cell count from the prior 6 months was higher in those retained as compared to those LTFU.

VL suppression rate at prior 6 months was also predictive of LTFU at each measured time point.

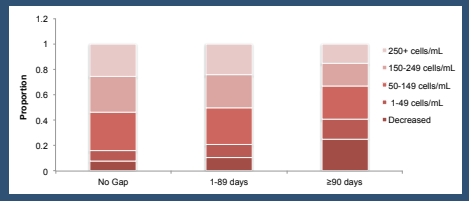


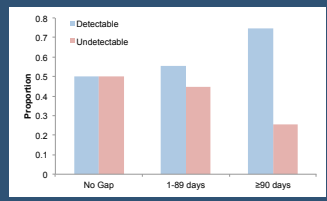


Long (≥90 days) contiguous gaps in pill refill during the first 6 months of treatment were predictive of LTFU by month 12 post-initiation of ART.

Lower likelihood of LTFU as length of longest contiguous gap in pill refill decreased

Patients with +90 gaps had lower CD4+ count increases by month 12 than those with no gaps





Patients with +90 gaps were less likely to have suppressed VL by month 12 than those with no gaps.

RESULTS

- Between June 2004-February 2011, the Harvard/APIN PEPFAR program initiated 57,376 HIV-1 mono-infected ARV-naïve patients on ART
- As of March 2012: 14,626 (28%) were LTFU, 816 (2%) died, and 1,515 (3%) were reported as transferred or withdrawn following the second drug pick-up
- Overall retention rates were 91% following the first pick-up, 79% by month 6, 74% by month 12 and 70% by month 18
- Baseline factors associated with increased risk for LTFU: age less than 35 years, being male, enrollment during or after 2006, having non-income-generating occupations or no education, being single, divorced or separated, higher baseline WHO stage and viral load, and low baseline CD4+ cell counts; patients started on AZT-containing regimens less likely than those on TDF-FTC/3TC-EFV to be LTFU (<0.001)
- Adherence pattern in first 6 months of ART was associated with risk of LTFU by M12 on treatment
- CD4+ cell count and VL were found to be time-dependent predictors of LTFU; associations remained in random effects Cox proportional hazards model that controlled for site variability and baseline predictors of LTFU (data not shown; p<0.001)

CONCLUSIONS

- To our knowledge, this is the first evaluation to examine multiple time-dependent predictors of LTFU using nearly 7 years of electronically maintained patient-level data.
- Retention rates and predictors of LTFU comparable to those reported in other studies[1-11]
- Similar to other studies, majority of loss occurred within the first 12-18 months of treatment[3-6]
- When controlling for baseline predictors, time-dependent adherence, CD4+ cell count and viral load values remained significant predictors of LTFU
- Major study strengths: large sample size, many years of follow-up, patient-level data on number of predictors, data from multiple sites
- Limitations/considerations: did not have patient tracking data to understand what happened to those that were lost
- Ultimately, having more data regarding predictors of patient attrition will be useful for implementers working with limited resources to identify patients on which to focus targeted interventions

REFERENCES

1. Rosen S, *et al.* Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med 2007; 4(10): e298.
2. Ochieng-Ooko V, *et al.* Influence of gender on loss to follow-up in a large HIV treatment programme in western Kenya. Bull WHO 2010; 88(9): 681-8.
3. Ekouevi DK, *et al.* Low retention of HIV-infected patients on antiretroviral therapy in 11 clinical centres in West Africa. Trop Med Int Health 2010; 15 Suppl 1: 34-42.
4. Rasschaert F, *et al.* Short and long term retention in antiretroviral care in health facilities in rural Malawi and Zimbabwe. BMC Health Serv Res 2012; 12: 444.
5. Maru DS, *et al.* Poor follow-up rates at a self-pay northern Indian tertiary AIDS clinic. Int J Equity Health 2007; 6: 14.
6. Cicconi P, *et al.* Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naive patients. HIV Med 2010; 11(2): 104-13.
7. Dalal RP, *et al.* Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. JAIDS 2008; 47(1): 101-7.
8. Ahonkhai AA, *et al.* Not all are lost: interrupted laboratory monitoring, early death, and loss to follow-up (LTFU) in a large South African treatment program. PLoS One 2012; 7(3): e32993
9. Krishnan S, *et al.* Incidence rate of and factors associated with loss to follow-up in a longitudinal cohort of antiretroviral-treated HIV-infected persons: an AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) analysis. HIV Clin Trials 2011; 12(4): 190-200.
10. Mocroft A, *et al.* Loss to follow-up in an international, multicentre observational study. HIV Med 2008; 9(5): 261-9.
11. Mutasa-Apollo T, *et al.* Patient retention, clinical outcomes and attrition-associated factors of HIV-infected patients enrolled in Zimbabwe's National Antiretroviral Therapy Programme, 2007-2010. PLoS One 2014; 9(1): e86305.

ACKNOWLEDGEMENTS

This work was funded, in part, by the U.S. Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with APIN (PS 001058). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors gratefully acknowledge the patients and the incredible work and dedication of the clinical, data, and laboratory staff at all of the Harvard/APIN PEPFAR ART sites. We also want to thank Dr. Eric Tchetgen Tchetgen of the Harvard School of Public Health, Department of Biostatistics, for his feedback on the statistical methods utilized in these evaluations.