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Impact of Unplanned Care Interruption on CD4 Response Early After ART Initiation in a Nigerian Cohort

Aimalohi A. Ahonkhai, MD, MPH^{1,2,3}, Juliet Adeola, BSc, MBA⁴, Bolanle Banigbe, MD, MPH⁴, Ifeyinwa Onwuatuelo, BDS, MPH⁴, Abdulkabir B. Adegoke, MD, MPH², Ingrid V. Bassett, MD, MPH^{1,2,3,5}, Elena Losina, PhD^{2,3,5,6,7}, Kenneth A. Freedberg, MD, MSc^{1,2,3,5,8,9,10}, Prosper Okonkwo, MD, FMPCH³, and Susan Regan, PhD^{2,5,8}

¹Division of infectious Disease, Massachusetts General Hospital, Boston, MA, USA

²Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA, USA

³Harvard Medical School, Boston, MA, USA

⁴AIDS Prevention Initiative in Nigeria (APIN), Abuja, Nigeria

⁵Harvard University Center for AIDS Research (CFAR), Boston, MA, USA

⁶Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

⁷Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

⁸Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA

⁹Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

¹⁰Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Abstract

The authors conducted a retrospective cohort study of unplanned care interruption (UCI) among adults initiating antiretroviral therapy (ART) from 2009 to 2011 in a Nigerian clinic. The authors used repeated measures regression to model the impact of UCI on CD4 count upon return to care and rate of CD4 change on ART. Among 2496 patients, 83% had 0, 15% had 1, and 2% had 2 UCIs. Mean baseline CD4 for those with 0, 1, or 2 UCIs was 228/cells/mm³, 355/cells/mm³, and 392/cells/mm³ ($P < .0001$), respectively. The UCI was associated with a 62 CD4 cells/mm³ decrease (95% confidence interval [CI]: -78 to -45) at next measurement. In months 1 to 6 on ART, patients with 0 UCI gained 10 cells/ μ L/mo (95% CI: 7–4). Those with 1 and 2 UCIs lost 2

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Corresponding Author: Aimalohi A. Ahonkhai, Medical Practice Evaluation Center, Massachusetts General Hospital, 9th Floor, 50 Staniford Street, Boston, MA, USA. aahonkhai@mgh.harvard.edu.

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and 5 cells/ μ L/mo (95% CI: -18 to 13 and -26 to 16). Patients with UCI did not recover from early CD4 losses associated with UCI. Preventing UCI is critical to maximize benefits of ART.

Keywords

care interruption; CD4; immunologic recovery; adherence; HIV infection

Introduction

Nigeria, the most populous country in Africa, has an estimated 3.5 million people living with HIV, the second largest number in the world.^{1,2} Patient retention in care remains a major challenge to successful antiretroviral therapy (ART) administration globally as well as in Nigeria.³ With 82% of Nigerians living on less than US\$2 per day, those with HIV face substantial competing demands for basic subsistence and health-care needs.⁴

Retention in HIV care requires commitment to health-related visits, including clinical evaluations and laboratory testing as well as medication adherence. Studies from sub-Saharan Africa demonstrate decreasing average retention rates for people living with HIV after starting ART, from 80% in the first year to 70% in the third year.³ Outcomes among patients not retained in care are often difficult to obtain. Tracking studies suggest that, at one extreme, some have transferred but remained engaged in care and others have died.⁵⁻⁷ Between these extremes, some patients become lost to care, whereas others interrupt but later return to care.⁸⁻¹¹ Whether short- or long-term, care interruptions represent an obstacle to effective care.¹²⁻¹⁴ Multiple studies in the mid-2000s established that planned treatment interruptions increase both morbidity and mortality.^{15,16}

Despite the clear evidence against *planned* care interruption, *unplanned* care interruption (UCI) is common in both resource-limited and resource-rich environments, occurring in 14% to 60% of all patients.^{14,17-19} Like loss to follow-up, the highest UCI rates are in the first year after ART initiation, when the most robust CD4 count response is anticipated.¹⁹⁻²¹ In Nigeria and other resource-limited settings (RLS), high baseline CD4 count may predict subsequent UCI.¹⁹ We sought to determine the immunologic consequence of UCI in the first year after ART initiation in a Nigerian cohort.

Methods

Setting

This study was conducted at the Ahmadu Bello University Teaching Hospital's (ABUTH) HIV clinic in Kaduna, Nigeria, a state in northern Nigeria with a local HIV prevalence of 5.1%. The ABUTH HIV clinic is located in a semiurban community and began providing HIV care in 2006 with President's Emergency Plan for AIDS Relief support. ABUTH offers comprehensive HIV testing and treatment to nearly 4000 patients. During the study period, the clinic was managed by AIDS Prevention Initiative in Nigeria (APIN), one of the largest HIV care and treatment programs in Nigeria.²² Upon clinic enrollment, patients completed clinical evaluation, tuberculosis screening, adherence counseling, and CD4 count and viral load testing. The World Health Organization (WHO) and Nigerian National guidelines

recommended ART initiation for all patients with CD4 <350 cells/ μ L in 2009. After enrollment, patients were scheduled to be seen at 2, 4, 8, and 12 weeks for adherence counseling and clinical examination. Subsequently, they were seen for ART pickup every 4 weeks, clinical examination and adherence counseling every 12 weeks, and laboratory testing (including CD4 count and HIV viral load) every 24 weeks.²³

Care Status Definitions

We conducted a retrospective cohort study of patients ≥ 15 years of age who initiated ART at the ABUTH clinic between January 1, 2009, and December 31, 2011. Data were censored at 1 year of follow-up, and clinical, laboratory, or pharmacy visits were assessed to determine care status. The UCI was defined as a period in which the time between any 2 consecutive visits was >90 days, followed by return to clinic (before the censor date). Patients were defined as having 0, 1, or ≥ 2 UCIs in the first year on ART. Patients known to have transferred care or died during the follow-up period were categorized based on their visit patterns prior to transfer or death.

Data Collection and Analysis

All data were collected in structured data entry forms that were entered into APIN's central electronic clinical database. Patients with an available baseline CD4 count and at least 1 follow-up value within the first 12 months of initiating ART were included in the analysis. We summarized the proportion of patients with 0, 1, or ≥ 2 UCIs in the first year on ART. We used 1-way χ^2 tests (for categorical variables) and Kruskal-Wallis tests (for ordinal variables) to assess whether the baseline characteristics differed by UCI status. We used a locally weighted smoothed scatterplot (LOWESS) curve function to visually assess the relationship between time on ART and observed CD4 count for those with 0, 1, or ≥ 2 UCIs in our aggregate data. The LOWESS curve illustrated the expected sharp, early (phase 1), and blunted later (phase 2) responses to ART, which occurred in this cohort between months 1 to 6 and months 7 to 12 on ART.²¹

To measure the effect of UCI status on CD4 response after ART initiation, we used 2 repeated measures linear regression models. The first allowed us to determine the short-term impact of any UCI on subsequent CD4 count upon return to care, and the second allowed us to estimate the longer-term impact by estimating the rate of CD4 change in the first year on ART for patients with 0, 1, or ≥ 2 UCIs. In the first model, we estimated the effect of having any UCI on the next measured CD4 count upon return to care. In this model, each patient's total observation time during the first 12 months after ART initiation was divided into 1 or more intervals based on the CD4 counts obtained during the period. Each interval was a separate observation in the model, which had the change in CD4 count during the interval as its dependent variable, and included the patient as a random effect. The primary covariate of interest was UCI status, which was assessed as a binary variable indicating whether 0 or any UCI occurred since the previous CD4 count. In the second model, we used aggregate CD4 data to estimate the average rate of CD4 change for patients with 0, 1, or ≥ 2 UCIs in the first year on ART. A spline term was introduced at 6 months after ART initiation to contrast early (1–6 months) versus later (7–12 months) effects of UCIs on CD4 count. We also estimated the marginal mean CD4 count after 1 year on ART for patients with 0, 1, or ≥ 2 UCIs,

holding all other covariates at their mean values. Both multivariate models included potential confounders including age, sex, baseline CD4 count, time since the previous CD4 count, and tuberculosis diagnosis at ART initiation.

Statistical analysis was conducted with Stata Statistical Software (Release 13; StataCorp 2013, College Station, Texas).

Institutional Review Board Approval

Institutional review board approval was obtained from Partners HealthCare (Protocol # 2013P000219), the Harvard T.H. Chan School of Public Health in Boston, Massachusetts, and the Nigerian Institute for Medical Research in Lagos, Nigeria.

Results

Frequency of UCI

The cohort was composed of 2496 patients who initiated ART at the ABUTH clinic during the study period. Among all patients, 83% (n = 2058) had no UCI, 15% (n = 376) had 1 UCI, and 2% (n = 59) had 2 UCIs within the first year on ART. Baseline CD4 count at ART initiation was not available for 467 patients. Follow-up CD4 counts were not available for an additional 380 patients. The remaining 1649 patients who had both a baseline and at least 1 follow-up CD4 count in the first year on ART available in the electronic database were retained for analysis (the analysis cohort, Figure 1).

Baseline Demographics

The majority of patients in the analysis cohort were female (70%; n = 1163), and the mean age was 33 years (standard deviation [SD]: 9.2). Overall, 61% (n = 1004) of patients were married and 63% (n = 1027) were employed. Forty-four percent of patients in the cohort (n = 734) had primary or secondary education and 34% (n = 559) had tertiary-level education (Table 1). The mean baseline CD4 count was 251/ μ L (SD: 193/ μ L). Those with 2 UCIs had a higher mean baseline CD4 of 392/ μ L (SD: 241/ μ L) than those with 1 UCI (355/ μ L; SD: 228/ μ L) or no UCI (228/ μ L; SD: 176/ μ L; $P < .0001$). Sixty-three percent (n = 61) of those with 2 UCIs presented to care with baseline CD4 \geq 350/ μ L compared to 49% of those with 1 UCI (n = 83), and 18% of those with no UCI (n = 254; $P = .0001$).

Twenty-four percent of patients in the cohort enrolled and initiated ART with CD4 $>$ 350 cells/ μ L. We conducted a chart review to determine the reasons for ART initiation in this group. All were documented to have met national guideline criteria for starting ART. The indication for treatment was advanced WHO stage (3 or 4) in 36%, resumption of ART for patients who had discontinued in 20%, concomitant tuberculosis (TB) in 5%, and coinfection with hepatitis B virus in 3% of patients. The indication for ART initiation was not documented in 36% of patients.

The CD4 Count Assessments

The number of CD4 measurements per patient in the first year on ART ranged from 2 to 7. Nineteen percent of patients (n = 314) had 2, 80% (n = 1312) had 3 to 5, and 1% (n = 23)

had 6 or 7 CD4 measurements. The median time between CD4 measurements was 105 days [interquartile range: 88–140].

Impact of UCI on CD4 Count

We plotted CD4 counts over time since ART initiation during the first year on ART using LOWESS smoothing with separate curves for those with 0, 1, and 2 UCIs during the year (Figure 2). Figure 2 illustrates that patients with no UCI had lower baseline CD4 counts but the greatest early rate of CD4 increase in the first 6 months on ART. In contrast, those with 2 UCIs had higher baseline CD4 counts, but early CD4 decrease in the same period.

We assessed the effect of an UCI on the next observed CD4 count in multivariate analysis adjusted for patient age, gender, TB coinfection, baseline CD4 count (before ART initiation), days since ART initiation, previous CD4 count, and the days since the previous CD4 assessment. The CD4 counts increased by an estimated 51 cells/ μ L (95% confidence interval [CI]: 47–55) for each 100 cells/ μ L increase in baseline CD4 count and decreased by 11 cells/ μ L (95% CI: –17 to –5) for each decade increase in patient age. Patients with any UCI had 62 fewer CD4 cells at the next CD4 assessment compared to those with no UCI (95% CI: –78 to –45).

Impact of 0, 1, or 2 UCIs in the First Year on ART on Rate of CD4 Change

In multivariate analysis (adjusted for age, sex, baseline CD4 count, and TB coinfection), statistically significant increases in CD4 count were seen only for those with 0 UCI—10 cells/ μ L/mo (95% CI: 7–14) in the first 6 months on ART and 4 cells/ μ L/mo (95% CI: 2–6) in months 7 to 12. Patients with UCI did not experience statistically significant gains in the first year on ART. Estimated monthly rate of CD4 change in months 1 to 6 was –2 cells/ μ L/mo (95% CI: –18 to 13) and –5 cells/ μ L/mo (95% CI: –26 to 16) for patients with 1 and 2 UCIs, respectively. In months 7 to 12, the estimated rate of CD4 change UCI was 2 cells/ μ L/mo (95% CI: –6 to 11) and 8 cells/ μ L/mo (95% CI: –2 to 7) for patients with 1 and 2 UCIs, respectively (Table 2).

Estimated CD4 Gains After 1 Year on ART

Predicted CD4 count after 1 year on ART was higher for patients with 2 UCIs (435 cells/ μ L, 95% CI: 347–522) than those with 1 UCI (381 cells/ μ L, 95% CI: 298–464) or no UCI (354 cells/ μ L, 95% CI: 334–374). However, a comparison of observed baseline CD4 count to predicted 12-month CD4 count (holding all other variables in the model at their average) showed that patients with no UCI had the greatest CD4 gains at 126 cells/ μ L (from 228 cells/ μ L at baseline). Patients with 1 UCI gained an estimated 26 cells/ μ L (from 355 cells/ μ L at baseline). Patients with 2 UCIs gained 43 CD4 cells/ μ L (from 392 cells/ μ L at baseline).

Discussion

We found that unplanned HIV care interruption is common in a large Nigerian treatment program. Seventeen percent of patients had at least 1 UCI in their first year on ART. Although there is variability in the definition and rates of UCI in the literature, our results are consistent with studies conducted in resource-limited and resource-rich

settings.^{10,18,19,24–27} We used several methods to quantify the impact of UCI on immune response to ART, all of which demonstrated deleterious effects of interruptions from care. The immediate consequence of any UCI was a gain of 62 CD4 cells/ μ L fewer than those who remained in care on the next measured CD4 count. Assessing the longer-term consequence of UCI over the first year on ART allowed us to determine whether patients with UCI were later able to recover from these early CD4 losses; importantly, they were not. Although patients without UCI had substantial CD4 gains, 126 cells/ μ L over the first year on ART, those with 1 or 2 UCIs had only one-third of these gains or less. The UCI was among the strongest predictors of immunologic recovery after ART initiation, along with baseline CD4 count and time on ART.

The first months after starting ART are critical for immune recovery. With effective ART, the CD4 response is biphasic. It is characterized by an initial CD4 increase of 50 to 120 cells/ μ L in the first 3 months and a sustained, gradual increase of 2 to 7 cells/ μ L monthly thereafter, which may continue for years.^{20,28,29} Many factors influence the CD4 response to ART, but baseline CD4 count and time on ART are among the most robust predictors; this was also illustrated in our analysis.^{28–31} Studies of patients with chronic HIV infection coinfecting with TB have shown blunted CD4 responses.³² In our cohort, where only 4% of patients were diagnosed with TB upon presentation, baseline TB diagnosis was not a significant predictor of CD4 response. Studies on the impact of age on CD4 response have been mixed.^{33–35} We found that older patients exhibited poorer immune recovery. Similarly, data on the influence of gender are mixed, and in our cohort, gender did not predict CD4 response.^{30,35–37} Even after adjusting for all of these factors (baseline CD4 count, time on ART, TB, age, and gender), UCI remained a strong, significant, independent predictor of early CD4 response to ART.

We estimated the monthly rate of CD4 increase to be 10 cells/ μ L/mo in months 1 to 6 after starting ART for patients with no UCI. During this period in which patients without UCI were seeing their greatest gains, CD4 counts remained stagnant for those with UCI. Our findings are consistent with reports from 2 large multicenter cohorts in RLS where monthly CD4 increase in the first 6 months on ART ranged from lower estimates of 10 to 16 cells/ μ L to upper estimates of 22 to 23 cells/ μ L.^{30,38} Both studies adjust for baseline CD4 and gender. Of these 2 studies, only 1 aimed to characterize expected immunologic recovery after ART initiation and neither accounted for care interruption.³⁰ Our analysis has allowed us to quantify the critical impact of interruptions from care on immune reconstitution.

Our data suggest that patients with higher baseline CD4 counts exhibited more UCIs after initiating ART. Patients with 2 UCIs started ART with an average of 392 CD4 cells/ μ L, nearly double the average baseline CD4 count of patients with no UCI. However, even when adjusting for baseline CD4 count, patients with any UCI had lower CD4 gains than those without UCI by the end of their first year in care. As a result, patients with any UCI lost the immunologic benefit of both ART and earlier presentation to care. Since patients with UCI are partially but not fully engaged in care, they still require the financial and clinical investment and commitment of care teams. Ensuring that this investment is not lost is crucial not only to individual patients but also for the sustainability of programs as global funding for HIV care levels off in Nigeria and other RLS.^{39,40} Moreover, strategies focusing on

increased adherence and linkage to care among patients initiating ART with higher CD4 counts in Nigeria are even more important considering the recent adoption of WHO guidelines recommending immediate ART diagnosis.⁴¹

The risk of morbidity and mortality is widely appreciated for patients presenting to care with advanced immune suppression and CD4 counts <200 cells/ μ L.^{42,43} But the risk of AIDS and death persist at higher CD4 strata (as high as 500–650 cells/ μ L).^{30,44} This knowledge has driven higher global ART initiation thresholds, which increased first to 350 cells/ μ L then 500 cells/ μ L and now to immediate ART.^{41,45} Furthermore, the absolute risk of AIDS and death is higher in RLS regardless of CD4 count, likely due to the higher burden of TB and invasive bacterial disease.⁴⁶ These findings underscore the importance of maximizing the immune response to ART and adherence to care irrespective of the baseline CD4 counts.

Our study has important limitations. Since it was conducted in an urban environment at 1 university-affiliated clinic, it may not be fully generalizable to other settings. Nonetheless, our estimates of CD4 gains in the first year after starting ART are consistent with those from other RLS. In addition, our analysis of the impact of UCI on CD4 response to ART was restricted to patients who had available baseline and at least 1 follow-up CD4 result. Missing CD4 values could have biased our estimates in either direction, but since more patients excluded from the analysis had UCI than those included, our estimates are likely to be conservative. Finally, our estimates of CD4 recovery may have been biased by the finding that patients with more UCI had higher median CD4 counts at ART initiation and thus had less capacity for immunologic recovery as assessed by CD4 gains on ART. Our models did adjust for baseline CD4 count to address this potential bias.

Despite these limitations, this analysis also has several strengths. Our robust electronic health record allowed us to quantify the frequency of UCI by relying on a range of health-care visits (clinical, laboratory, and pharmacy) over the first year on ART. With nearly one-tenth of the global population of people living with HIV in Nigeria, this setting is critical for assessing the impact of ineffective retention in care. Our analysis is one of the few providing adjusted estimates of the expected immunologic recovery on ART in RLS, where background rates of other infections may affect these estimates. As a result, our analysis allowed us to illustrate and quantify the immunologic impact of UCI for patients initiated on ART. This information can be readily provided at the point of care as a clinical tool to reinforce the importance of adherence to care and to demonstrate the impact of care interruption on CD4 recovery.

This study underscores that UCI from HIV services is common in RLS and is accompanied by a loss in expected therapeutic benefit of ART. Patients with any UCI have both a slower rate of CD4 gain and an early loss of CD4 cells that they do not regain over the first year on ART. Interventions to prevent UCI, and ensure effective retention in care, are critical to optimize clinical outcomes and maximize the health benefit that patients receive from HIV care.

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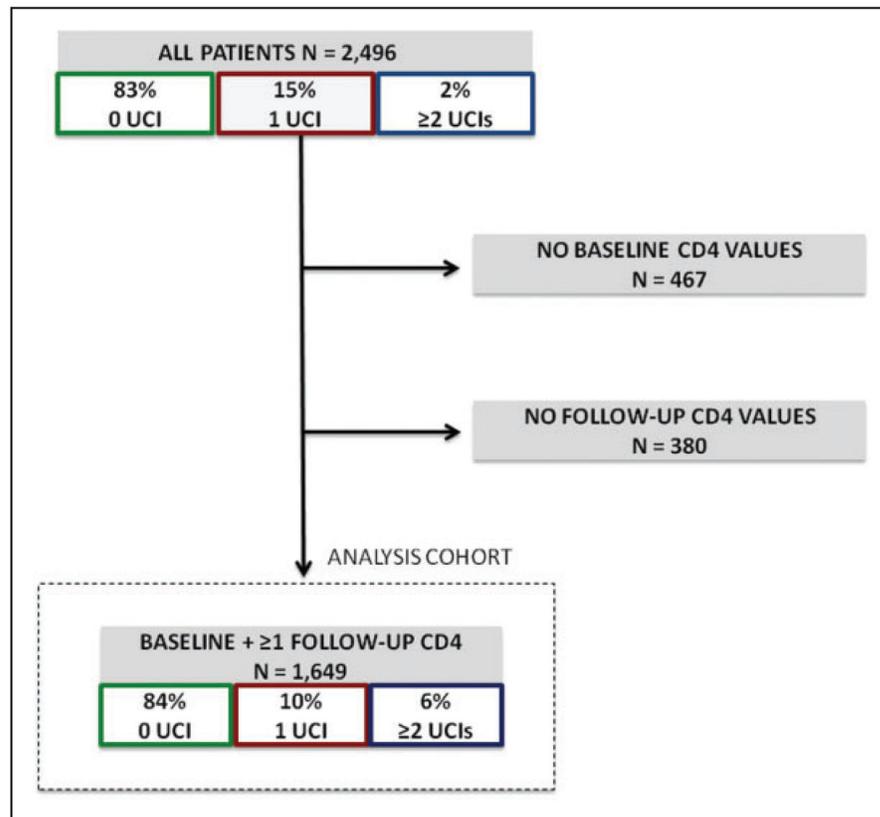


Figure 1. Cohort summary and frequency of unplanned care interruption (UCI) during first year on antiretroviral therapy (ART).

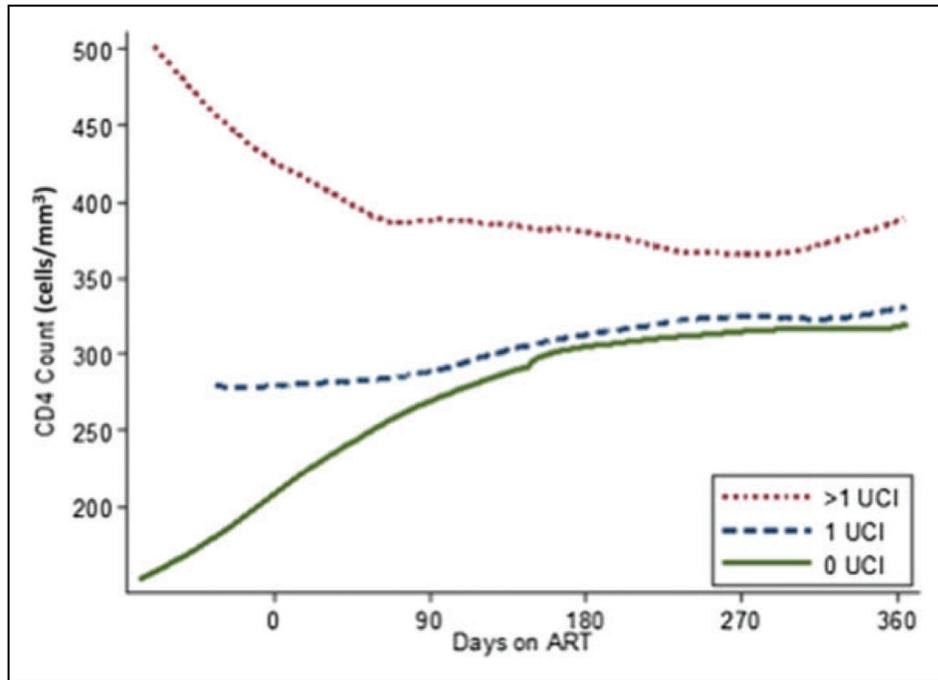


Figure 2. CD4 response by number of unplanned care interruptions in the first year on ART, smoothed LOWESS curve. ART, antiretro-viral therapy; LOWESS, locally weighted smoothed scatterplot; UCI, unplanned care interruption.

Table 1
Demographic and Clinical Parameters in a Cohort of HIV-Infected Persons Initiating ART in Nigeria Between 2009 and 2011.

	All (N = 1649)		No UCI (n = 1384)		1 UCI (n = 168)		2 UCIs (n = 97)		P Value
	%	n	%	n	%	n	%	n	
Sex									
Male	30	486	30	411	26	44	32	31	.5510
Female	70	1163	70	973	74	124	68	66	
Mean age (SD), years		33 (9.2)		34 (9.2)		32 (9.0)		32 (8.5)	.0381
Marital Status									.2605
Married	61	1004	61	840	58	97	68	65	
Single	25	411	25	345	27	45	22	21	
Widowed	14	234	14	199	15	25	10	10	
Employment									.2447
Employed	63	1027	64	873	55	91	65	63	
Unemployed/retired	29	469	29	396	30	49	25	24	
Student	8	137	7	101	16	26	10	10	
Education									.5746
Tertiary	34	559	34	473	35	59	28	27	
Primary/secondary	45	734	44	613	43	73	50	48	
None	22	356	22	298	21	35	23	23	
Baseline CD4, cells/mm ³									
Mean (SD)	251	(193)		228 (176)		355 (228)		392 (240)	<.0001
<50	12	196	13	174	8	14	8	8	.0001
50–100	12	190	13	175	7	11	4	4	
101–200	23	380	25	352	11	19	9	9	
200–350	30	487	31	431	24	41	15	15	
>350	24	396	18	252	49	83	63	61	
Baseline tuberculosis									
Yes	4	65	4	59	3	5	1	1	.2276

Abbreviations: ART, antiretroviral therapy; SD, standard deviation; UCI, unplanned care interruption.

Table 2

Predicted Rate of CD4 Change in the First Year on ART for Patients with 0, 1, or 2 UCIs.^a

No UCI	Months 0–6 on ART		Months 7–12 on ART	
	30-Day CD4 Change	95% CI	30-Day CD4 Change	95% CI
0	10	7 to 14	4	2 to 6
1	-2	-18 to 13	2	-6 to 11
2	-5	-26 to 16	8	-2 to 17

^aModel adjusted for age, gender, baseline CD4 count, and tuberculosis (TB) coinfection.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

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