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Relationship between CD4+ T-cell counts/HIV-1 RNA plasma viral load and AIDS defining events among persons followed in the ACTG Longitudinal Linked Randomized Trials (ALLRT) study

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Abstract

Background—AIDS-defining events (ADEs) decreased in the era of highly active antiretroviral therapy but still lead to hospitalizations and deaths. Understanding factors related to ADEs is important to mitigate events.

Methods—We examined the relationship between demographics, behaviors, co-morbidities, laboratory, clinical measurements and ADEs diagnosed among subjects randomized to antiretroviral treatments (ART)/strategies and followed prospectively. Logistic regression models using generalized estimating equations generated odds ratios (ORs) focusing on the relationship between current CD4+ T-cell count (CD4)/HIV-1 RNA viral load (VL) and ADEs in the subsequent 16-week study period.

Results—Among the 2,948 subjects in the analysis, overall incidence of ADEs was 1.53 per 100 person-years. Multivariate regression models adjusted for demographics, BMI and ADE history. A 6-level time-varying variable examined VL (>100,000 copies/mL, ≤ 100,000) at CD4 levels (0–50, 51–200, >200 cells/μl); reference level was CD4>200/VL≤100,000. Among ART-naïves, odds of having an ADE in the subsequent 16-week interval were greater among subjects with lower CD4 counts; this relationship was modified by VL level (CD4≤50/VL>100,000: OR 37.2; CD4≤50/VL≤100,000: OR 30.5; CD4 51–200/VL>100,000: OR 13.0; CD4 51–200/VL≤100,000: OR 4.5; all p-values <0.001). Similar results were seen among ART-experienced subjects.

Conclusions—Recent CD4 and VL values are closely associated with development of ADEs even after examining a multitude of potential factors.

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Keywords

HIV; opportunistic infections; CD4 cell counts; viral load

Introduction

Since the advent of HAART, AIDS defining events (ADEs) and ADEs leading to mortality have been declining among HIV-infected individuals who tolerate and continue their antiretroviral therapies [1](Brodt HR, AIDS, 1997); [2](Palella, JR. FJ, NEJM, 1998); [3](Gebo et al JAIDS 2005); [4](CASCADE AIDS 2006); [5](Buchacz et al AIDS 2008); [6](Neuhaus J, AIDS 2010); [7](Crum-Cianflone N, AIDS 2009). However, ADEs still play a major role in hospitalizations and deaths, and can occur even among patients with elevated CD4+ T-cell counts (CD4) and those on effective ART [8](Koletar, CID, 2004); [9](Baker, 2008, AIDS); [10](Brooks JT, CID, 2009). It remains important to understand risk factors associated with ADEs.

Among ART-naïve individuals, low pre-treatment CD4 has been seen as one of the primary factors influencing increased risk of ADEs after ART initiation [11](Egger, 2002); [12](Torti CHIV Clin Trials. 2007). However, with further investigation, CD4 and viral load, as time-updated factors, are now known to also play a central role in the prediction of AIDS and death [13](Lapadula, 2007); [14](Chene G, Lancet, 2003); [15](MacArthur RD, 2005 HIV clin trials). Pre-treatment and nadir CD4 may be associated with early-onset ADEs among ART-naïve subjects starting ART, and may be more closely associated with immune reconstitution inflammatory syndrome (IRIS) while time-updated CD4 and viral load may be related to ADEs that occur as a consequence of immunologic and virologic changes occurring throughout HIV disease progression and ART treatment. Therefore, we sought to examine both pre-treatment factors and time-updated factors, and their relationship to ADEs, among individuals randomized to their first ARV regimen, as well as among ART-experienced individuals starting new randomized regimens and strategies. Both groups were followed under the same protocol, the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study [16](Smurzynski, 2008). ALLRT is an established cohort of HIV-infected subjects prospectively randomized to receive ART, immune-based therapies or treatment strategies in the context of ACTG parent protocols, and who agree to be followed longitudinally to determine long-term virologic, immunologic, and clinical outcomes and complications associated with ARTs. In this analysis, we describe the occurrence of diagnosed ADEs and examine factors potentially related to ADE diagnoses.

Methods

Study Population

ALLRT subjects are prospectively recruited and enrolled from 26 United States-based ACTG clinical trials and are followed long-term in an observational study [16](Smurzynski, 2008). ALLRT is unique compared to other large observational cohorts in that all subjects received randomized treatment interventions at initial enrollment. When entering their parent clinical trial (baseline) subjects are either ART-treatment-naïve or treatment-experienced. In total, subjects from 18 ALLRT parent clinical trials, the first of which began enrollment in 1997, are included in the analysis; six of these parent trials enrolled ART-naïve subjects. ALLRT subjects excluded from the analysis were from three studies that required virologic suppression on ART at entry, three studies where subjects were randomized to receive immune-based therapies and subjects from two ART-naïve studies where initial ARV-regimens are still blinded. Follow-up time was determined from the time

when a subject entered his/her parent clinical trial (baseline) and continued until a subject left the ALLRT study, was lost-to-follow-up (missed 3 consecutive visits) or died. Data for this analysis were collected on subjects starting with the first parent trial baseline enrollment March 5, 1997 through June 30, 2008. Institutional Review Boards at ACTG sites approved the ALLRT protocol; all subjects provided signed written informed consent.

Demographic (sex, age, race/ethnicity) and behavioral data (injection drug use, smoking) are collected at either baseline or ALLRT entry; clinical, immunologic and virologic data, and co-morbidities, are obtained at baseline and routinely measured every 16 weeks. Hepatitis B (HBV surface antigen and/or HBV core antibody positive tests, or documented hepatitis B diagnosis) and Hepatitis C (HCV antibody positive or a hepatitis C diagnosis) are assessed. Subjects self-report smoking and injection drug use (IDU) (current or previous). First on-study ART regimen was recorded by drug class (protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)). Subjects were considered to be on *Mycobacterium avium* complex (MAC) and/or *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis if one of the following medications was reported for at least 21 days duration over the prior 8 weeks: clarithromycin, azithromycin, and/or trimethoprim-sulfamethoxazole, dapsone, atovaquone, and aerosolized pentamidine. For subjects diagnosed with PCP or MAC, a more strict prophylaxis use definition of at least 4 weeks of continuous use up to and including the date of diagnosis was employed.

ADEs were defined as one of the conditions included in the 1993 Centers for Disease Control and Prevention AIDS surveillance case definition of AIDS (category C) [17](CDC, 1992) and were classified into 7 categories: fungal, bacterial, parasitic, viral, malignancy, metabolic, neurologic. [Table 1] ADEs diagnosed since the previous ACTG study visit, including date of diagnosis, are recorded on ACTG case report forms by site clinical personnel at each subsequent ACTG study visit; medical record data related to ADEs are reviewed by site physicians to ensure they meet pre-established ACTG diagnosis criteria. Diagnosis appendices, created by clinical working groups within the ACTG and reviewed by the Scientific Agenda Steering Committee, specify criteria necessary to make an ADE diagnosis. These appendices are used across study sites for all ACTG clinical trials. Diagnoses are defined as either probable (consistent clinical signs and symptoms, supporting ancillary studies and response to therapy) or confirmed, (requiring either isolation of the pathogen in culture or histopathologic evidence of infection). All ADEs meeting the probable and confirmed ACTG standard definitions were included in these analyses.

Data Analysis

Demographic and behavioral information, co-morbidities, laboratory and clinical measurements, baseline antiretroviral class, PCP and MAC prophylaxis use and information on ADEs (incident and history) were examined among 2,181 ART-naïve and 767 ART-experienced ALLRT subjects (N=2,948). Subjects who were ART-naïve and ART-experienced at baseline were analyzed separately. Incidence rate was calculated as the number of subjects who developed an ADE divided by total person-years at risk; person-years was measured from baseline to the first ADE, last known clinic visit or June 30, 2008. For a subset of ART-naïve subjects with available data (n=968), an additional analysis was done to explore the role of pre-treatment immune activation defined as the percentage of CD8 cells that were CD38+ or CD38+/HLA-DR+.

To investigate the relationship between both baseline and time-varying variables, and first ADE diagnosed on study, we modeled the conditional odds of an ADE diagnosis using logistic regression models and generalized estimating equations (GEE) [18](D'Agostino, Stat Med 1990); [19](Diggle, Liang and Zeger, Oxford Press, 1994). Logit link function and

independent working correlation with robust standard errors were specified. ADE was recorded as a binary variable at each 16-week visit; subjects were no longer included in the analysis after diagnosis of a first ADE. To examine more closely the relationship of CD4 and viral load with ADEs, a 6-level combination variable was created to examine high (>100,000 copies/mL) versus lower ($\leq$ 100,000 copies/mL) viral load at each CD4 level (0–50, 51–200, >200 cells/ μ L); the reference level for this variable is CD4>200 cells/ μ L/VL $\leq$ 100,000 copies/mL. At each 16-week visit (including baseline) there is a CD4/VL combination variable. Time-varying variables were used to examine the relationship between the CD4/VL and ADE diagnosis in the subsequent 16-week visit period. Thus, odds ratios for the time-updated CD4/VL represent the odds of having an ADE diagnosed in the subsequent 16-week visit period, given the subject's current CD4/VL. For time-varying covariate values unavailable at a 16-week visit, we applied a last-value-carry-forward method.

Univariate models were used to determine the unadjusted relationship between observed variables and ADEs while multivariate models were used to control for variables in a final model. The final multivariable model for ARV-naïve subjects was obtained by backward selection, where variables with $p>0.05$ were removed from the model. If any level of a multilevel variable had a $p\leq 0.05$, all levels were retained. Demographic variables were included regardless of p -value. For comparison, the same variables included in the ARV-naïve final model were used in the final model for the ARV-experienced subjects. Data were analyzed using SAS version 9.13 (SAS Institute Inc, Cary, NC).

Results

Characteristics of the Study Population

Demographics, behavioral factors and co-morbidities were not different among subjects diagnosed with an ADE (ART-naïve: $n=147$; ART-experienced: $n=94$) and those without (ART-naïve: $n=2,034$; ART-experienced: $n=673$). (Table 2) Duration of observation, by baseline ART-status, was similar (median years [1st, 3rd quartile]; ART-naïve: 5.3 [3.8, 7.1]; ART-experienced: 5.1 [3.1, 9.5]; the ART-naïve group had more person-years of follow-up when compared to the ART-experienced group (11,466 years of follow-up versus 4,285). The percentage of 16-week visits with CD4 cell counts above 200 cells/ μ L:350 cells/ μ L were slightly higher among the ART-naïves (87%:68%) than among the ART-experienced (83%:59%). A greater proportion of subjects with a diagnosed ADE had baseline CD4 of less than or equal to 50 cells/ μ L when compared to subjects without ADEs (ART-naïve: 55% v. 20%; ARV-experienced: 24% v. 6%); the same was true for percentage with baseline HIV RNA above 100,000 copies/mL (ART-naïve: 74% v. 44%; ARV-experienced: 40% v. 18%). There was no difference in follow-up time between the two groups (median years [1st, 3rd quartile]; ADE: 5.2 [3.5, 7.9]; no ADE: 5.3 [3.6,8.0]); 97% of all subjects were followed for at least 48 weeks.

AIDS Defining Events

Among the ART-naïve subjects, 147 out of 2,181 (7%) were diagnosed with a total of 206 ADEs after starting ART; a slightly higher percentage of the 767 ART-experienced subjects had an ADE ($n=94$ (12%) diagnosed; 145 total diagnoses). The overall incidence rate for ART-naïve subjects was 1.28 per 100 person-years (95% CI: 1.08, 1.51) and among ART-experienced subjects was 2.19 per 100 person-years (95% CI: 1.77, 2.68). Diagnosis with more than one ADE occurred during follow-up among 29% of the ART-naïve subjects and 27% of the ART-experienced subjects.

Analyses focus on first post-baseline ADE; for ART-naïve subjects follow-up time started when they initiated ARTs, while for the ART-experienced group, follow-up time begins when they were randomized to receive new ART treatments or strategies. More than 50% of ADEs were diagnosed in the first 48 weeks on study; incidence rates for these time periods greatly exceed those noted above. Among the ART-naïve population, the incidence rate in the first 24 weeks on study was 6.58 per 100 person-years (95% CI: 5.07, 8.40) and 4.33 per 100 person-years (95% CI: 3.45, 5.37) within the first 48 weeks after starting ART. Among the ART-experienced subjects, in the same time periods, the incidence rate was lower than among the ART-naïves; in the first 24 weeks on study incidence of ADE diagnosis was 4.02 per 100 person-years (95% CI: 2.20, 6.74) and 3.79 per 100 person-years (95% CI: 2.47, 5.55) through week 48.

Among the ART-naïve population, fungal infections (36%) comprised the most common type of first ADEs diagnosed post ART initiation; bacterial infections (24%), parasitic, viral and malignancies followed (all 11%) (Figure 1). Incident MAC and PCP diagnoses comprised the largest percentage of ADEs in the first 24 weeks after starting treatment (44%). Two subjects were diagnosed with more than one 'first' ADE on the same day. Median CD4 counts in the 16-week period prior to an ADE diagnosis were below 100 cells/ μ L for subjects diagnosed with MAI/MAC or *M. kansasii* (15 cells/ μ L), toxoplasmosis of the brain (17 cells/ μ L), CMV retinitis (17 cells/ μ L), HIV Dementia (32 cells/ μ L), cryptococcosis (46 cells/ μ L), histoplasmosis (47 cells/ μ L), KS (48 cells/ μ L), *M. genovensis*/*M. scrofulaceum* (50 cells/ μ L) and TB (65 cells/ μ L). Median CD4 for PCP was just slightly higher at 105 cells/ μ L.

Among the treatment-experienced subjects, fungal infections were also the most common (46%) first ADE diagnoses on study but there was a shift in the distribution of other opportunistic complications, i.e., malignancies (15%), viral (13%) and bacterial (11%); the remaining 15% were metabolic, parasitic and neurologic (Figure 2). One ART-experienced subject had four ADEs diagnosed on the same 'first' date. In the 16-weeks prior to diagnosis, median CD4 counts were below 100 cells/ μ L among subjects diagnosed with cryptococcosis (11 cells/ μ L), CMV retinitis (11 cells/ μ L), other CMV disease (19 cells/ μ L), MAI/MAC or *M. kansasii* (27 cells/ μ L), PCP (61 cells/ μ L), KS (62 cells/ μ L) and herpes simplex (64 cells/ μ L). Subjects with esophageal candidiasis and HIV wasting had similar median CD4 counts of 107 cells/ μ L.

Among the ART-naïve group, when examining overall trends, ADEs were occurring while CD4s were on the rise (CD4 count 16 weeks prior: 69 cells/ μ L [Q1:22, Q3:241]; CD4 count week of event: 128 [62, 266]) while among the ART-experienced group they were declining (CD4 count 16 weeks prior: 108 [Q1:25, Q3:276]; CD4 count week of event: 77 [18, 301]).

Overall, among both groups, PCP and MAC prophylaxis use at baseline was reported more often among subjects with lower CD4 counts at baseline (PCP prophylaxis: subjects with CD4<200 (63% using PCP prophylaxis); CD4 $\geq$ 200 (14%); MAC prophylaxis: subjects with CD4< 50 (39% using MAC prophylaxis); CD4 $\geq$ 50 (4%); Chi-Square, $p<0.001$). Throughout the study, median CD4 count at the time subjects started taking PCP(MAC) prophylaxis was 34 cells/ μ L (15 cells/ μ L) among those diagnosed with PCP(MAC), 45 cells/ μ L (35 cells/ μ L) among those diagnosed with another ADE, and 151 cells/ μ L (137 cells/ μ L) among those who were never diagnosed with an ADE.

Of the 10 subjects with a PCP diagnosis that occurred when CD4 $\geq$ 200, 3 (30%) were on PCP prophylaxis at the time of diagnosis. Only 4 subjects had a MAC diagnosis at CD4 $\geq$ 50; none of these subjects were on MAC prophylaxis at the time of diagnosis. A large

percentage of subjects were not on prophylaxis at the time of their diagnosis (PCP: 29 of 45 subjects (64%) not on prophylaxis; MAC: 22 of 27 (81%) not on prophylaxis).

ART-treatment naïve subjects: Factors associated with ADEs

In unadjusted analyses, baseline demographics, behavioral factors, co-morbidities and initial ART regimen were not statistically ($p>0.05$) associated with the occurrence of a first ADE among subjects who were ART-naïve at baseline. [Table 3]

When evaluated individually, lower baseline CD4 (0 to 50, 51 to 200, versus >200 cells/ μ L) and higher viral load ($>100,000$ versus $\leq 100,000$ copies/mL) were significantly associated with higher odds of having a post-randomization ADE ($p<0.001$). With the baseline 6-level CD4/viral load combination variable the unadjusted odds of having an ADE in subjects with $CD4\leq 50$ and either viral load level was increased compared to the reference group level of $CD4>200$ cells/ μ L/ $VL<100,000$ copies/mL ($p<0.001$).

Associations between time-varying 16-week CD4/VL and ADEs, among the two lower CD4 levels of the combination variable CD4 (0 to 50, 51 to 200 cells/ μ L), were significantly associated with increased odds of ADE diagnosis when compared to the referent group of $CD4>200$ cells/ μ L/ $VL\leq 100,000$ copies/mL; at CD4 above 200 cells/ μ L there was no difference ($p>0.9$). These findings were observed in univariate and multivariate models. (Table 3)

In a separate analysis, among the 968 ART-naïve subjects who had available data on immune activation markers, higher pre-treatment CD8 activation was significantly associated with an ADE diagnosis during follow-up in a univariate model (OR=6.5, comparing highest to lowest quartile of CD38 percentage; $p<0.001$, trend test across quartiles). However, this effect was attenuated in an adjusted model which also included pre-treatment HIV RNA viral load, CD4 cell count, and history of ADE (OR=2.2; $p=0.09$, trend test); a similar effect was seen for the CD38/HLA-DR+ percentages (OR=2.1; $p=0.04$, trend test).

ART-treatment experienced subjects: Factors associated with ADEs

ART-experienced subjects were similar to naïve subjects in the effects seen in univariate analyses. However, in univariate analyses, assigned ARV drug classes PI only/NRTI only and PI+NRTI/PI+NNRTI were statistically associated ($p<0.05$) with first ADE diagnosis on study, but were not included in the multivariate model. (Table 4) History of an ADE increased the risk for the development of a subsequent ADE (univariate OR 1.6; $p=0.03$), but not in the adjusted model ($p>0.9$).

In univariate analyses, odds of ADE diagnosis were significantly increased among subjects with lower baseline CD4 (0 to 50, 50 to 200, versus >200 cells/ μ L) and higher viral load ($>100,000$ versus $\leq 100,000$ copies/mL). The same relationship was observed for time-updated CD4/VL, and in multivariate analyses when adjusting for baseline demographics, BMI and history of ADEs. (Table 4)

Discussion

In our longitudinal, observational study, approximately 10% of the population developed an ADE over a median follow-up time of more than five years for an incidence rate of 1.53 per 100 person-years; this incidence rate is substantially lower than the 13.8 per 100 person-years reported for persons in care in the early HAART era [20](Sullivan, PS; AIDS research and Therapy, 2007). Among ART-naïve subjects who were observed after starting their first ART-regimen, half of the first ADEs occurred within 24 weeks of initiating ART. After

examining the relationship between demographic, immunologic, virologic, and clinical factors and ADE diagnosis, lower proximal CD4 count and higher proximal viral load remained the factors most strongly associated with ADEs diagnosed during the subsequent 16 week period. ADEs continue to occur among both ART-naïve and ART-experienced individuals after they enter their clinical trial, despite treatment with potent combination antiretroviral therapies.

Several factors make this analysis unique. First, we were able to examine both a group of subjects initiating therapy and subjects initiating salvage therapy, who were followed and analyzed using the same research methods. This provides an opportunity to clearly examine the differences between these two groups without having to scrutinize differences in methodology. Second, we used a time-updated proximal CD4/VL combination variable to predict an ADE diagnosis in the next 16-week period. Findings from these analyses can help clinicians determine when it is important to take action in order to decrease the likelihood of a patient getting an ADE within the next few months. In addition, we were able to conduct a subset analysis examining baseline immune activation; these are findings which have not been previously described.

In our multivariate models which included time-varying CD4/VL, the relationship between baseline CD4 and ADEs was not statistically significant, suggesting that the CD4 count at the time a patient begins a new treatment regimen or strategy is not as important as their most recent CD4 count. Although others did not examine a proximal relationship to ADE diagnoses using a time-varying variable, these findings are similar to others who found CD4 counts in the six months after initiating HAART were strongly associated with disease progression whereas baseline values were not [14](Chene G., Lancet 2003); findings from the Swiss HIV Cohort study also demonstrated that six month CD4 counts were associated with events independent of baseline CD4 counts [21](Ledergerber B, JAMA, 1999). In addition, current CD4 count and HIV RNA were found to be strong predictors of ADEs among subjects with CD4 count thresholds higher than expected for usual opportunistic infections [22](Podlekareva D, JID, 2006). This reflects, in part, that patients with similar CD4 pre-treatment can have differential CD4 responses after initiating treatment and provides clinical support for investigation into the heterogeneity of those responses [23] (Schacker, 2005).

To our knowledge, the effect of CD8 activation on ADE among individuals initiating therapy has not previously been published, although an association with lesser CD4 increases on treatment has been reported [24](Hunt, 2003). In addition to CD4 count and viral load, CD8 activation has been shown to be an important predictor of ADEs in untreated HIV infection [25](Giorgi JV, 2002). Our analyses have revealed an association between higher CD8 activation at the time of treatment initiation and risk of subsequent ADE. This effect, however, was attenuated after adjusting for pre-treatment HIV RNA and CD4 levels.

The majority of on-study diagnoses among ART-naïve subjects occurred during the first 48 weeks after antiretroviral treatment initiation while CD4 counts were on the rise, while the ART-experienced group tended to have events spread over a longer time frame after starting a new ARV regimen or strategy, when CD4 counts were declining. In the first 24 weeks after starting ART, treatment-naïve subjects typically have lower CD4 counts than they do after being on ART for a longer period of time, inherently elevating their vulnerability to an ADE, and potentially increasing the likelihood of ADEs manifesting as IRIS while their CD4s are on the rise due to HAART [26](Shelburne SA, Antimicrobial Therapy, 2006); [27] (CDC, MMWR 2009). ADE clustering in close proximity to ARV initiation has been seen in other studies [12](Torti, C 2007, Clinical Trials). PCP and esophageal candidiasis were the most common ADEs in both analysis groups. Mycobacterial infections, primarily MAC,

were more common in subjects who had not previously received ART, with the majority being diagnosed in the first 24 weeks after starting treatment. This pattern suggests these subjects could have been experiencing immune reconstitution inflammatory syndrome (IRIS), since these ADEs have been linked to IRIS [27](CDC, MMWR 2009); [28](Lawn, 2005, Lancet). Of note, many subjects were diagnosed with PCP or MAC just as they started antiretroviral treatment suggesting that prophylaxis, in these cases, might just have been provided too late to halt disease progression. Additionally, non-adherence to PCP prophylaxis could also be a factor [29](Heffelfinger JD. 2009 PLoS ONE).

An interesting difference noted between the ART-naïve and ART-experienced groups is that history of an ADE prior to study initiation was not a statistically significant risk factor among the ART-experienced subjects in the adjusted model. Incomplete immune reconstitution has been observed in subjects who were severely immunosuppressed ($CD4 < 50$ cells/ μ L) prior to receiving HAART [30](Lederman, 2003); [31](Robbins, CID, 2009) and this may in part explain this association in the ART-naïve group. Whether the lesser impact of prior history of ADE in the treatment-experienced group is related to the degree of the functional immune restoration or some other factor such as survival selection bias is not clear from these data.

In our analysis, higher viral loads in any subset that has a CD4 level of 200 or less indicates greater risk for being diagnosed with an ADE. In an attempt to examine the relationship between viral replication and risk for ADEs, supplemental analyses examined plasma HIV-1 RNA thresholds of 50 copies/mL and 1,000 copies/mL, at each of the three CD4 ranges that were evaluated in this analysis (0 to 50, 51 to 200, >200 cells/ μ L). None of the ART-experienced subjects had $CD4 \leq 50$ & $VL \leq 1,000$ in their first 96 weeks on study making this impossible to examine. A four-level variable: $VL \leq 1,000$ and $VL > 1,000$ copies/mL at two CD4 levels: $CD4 \leq 200$ cells/ μ L or $CD4 > 200$ resulted in findings similar to those seen when the viral load cut-off was set at 100,000 copies/mL, thus confirming that lower CD4 counts (<200 cells/ μ L) coupled with a 'higher' viral load (be it 1,000 or 100,000 copies/mL) indicate greater risk of being diagnosed with an ADE.

A limitation of this analysis is that subjects enrolled in the ALLRT cohort are research study participants rather than clinic patients. In other clinical cohorts, such as the Swiss HIV Cohort, data are extracted on participants regardless of their inclusion in a study, although patients can move in and out of care. In ALLRT, subjects may leave the study if/when they are too debilitated to continue, thus they may be censored prior to an event. This could result in a reduction in total number of observed ADEs and may be a reason why we see more ADEs in the first 48 weeks with a reduction in events as the study progresses. Subjects in better health may choose to stay enrolled and come to study visits every 16-weeks while subjects in declining health, experiencing toxicities related to ART, trouble with ART adherence, or drug resistance, may choose to not continue being followed. Although ALLRT makes allowances for subjects who are too sick to continue coming in by offering the option of phone contact rather than a clinic visit, some subjects may still choose to drop out of follow-up. Overall, however, the lost to follow-up rate in ALLRT is 5.1 per 100-person years (excluding deaths and site closures) indicating that study sites have ongoing contact with the majority of enrolled subjects and capture events as they occur. Another limitation of the analysis is that some covariates, such as smoking status, injection drug use, and history of ADEs, are self-reported. Misclassification may be an issue for these data elements and the resulting findings.

While AIDS-defining events are less common among HIV-infected individuals receiving modern antiretroviral therapies, the need for continued follow-up remains an important component of management. Our finding that the combination variable of CD4/viral load

shows the strongest association between potential risk factors and diagnosis with an ADE in the next 16-week visit window underscores the importance of CD4 reconstitution and suppressed viral load in response to ART to maintain health in persons with HIV-1 infection. The clinical implication is that vigilant monitoring provides an opportunity for interventions, such as use of opportunistic infection prophylaxis or modifications of antiretroviral regimens to regain virologic suppression and optimize CD4 responses. Both of these interventions may help prevent ADEs.

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Figure 1.

Total number of first post-baseline ADEs among subjects ARV-naïve at baseline. Clear portions of the bars indicate the number of ADEs diagnosed in the first 24 weeks after study entry and the striped bars represent those ADEs diagnosed at 24 weeks or later.

Figure 2.

Total number of first post-baseline ADEs among subjects ARV-experienced at baseline. Clear portions of the bars indicate the number of ADEs diagnosed in the first 24 weeks after study entry and the striped bars represent those ADEs diagnosed at 24 weeks or later.

Table 1

List of AIDS defining events by category and related CDC Category C conditions.

Category	CDC Category C case conditions
Fungal	Candidiasis of bronchi/trachea/lungs; Candidiasis/esophageal; Coccidioidomycosis/disseminated or extrapulmonary; Cryptococcosis/extrapulmonary; Histoplasmosis/disseminated or extrapulmonary; <i>Pneumocystis jirovecii</i> pneumonia.
Bacterial	<i>Mycobacterium avium</i> complex or <i>M. kansasii</i> /disseminated or extrapulmonary; <i>Mycobacterium tuberculosis</i> /any site, extrapulmonary or pulmonary; Mycobacterium/other species disseminated or extrapulmonary; Pneumonia/recurrent; Salmonella septicemia/recurrent).
Parasitic	Cryptosporidiosis/chronic intestinal (>1 month's duration); Isosporiasis/chronic intestinal (> 1 month's duration); Toxoplasmosis of brain.
Viral	Cytomegalovirus disease other than liver, spleen or nodes; Cytomegalovirus retinitis with loss of vision; Herpes Simplex/chronic ulcers (>1 month's duration) or bronchitis, pneumonitis or esophagitis; Progressive multifocal leukoencephalopathy.
Malignancy	Cervical cancer/invasive; Kaposi's sarcoma; Lymphoma/Burkitt's or equivalent term; Lymphoma/immunoblastic or equivalent term; Lymphoma/primary, of brain.
Metabolic	Wasting syndrome due to HIV.
Neurologic	Encephalopathy/HIV-related Dementia.

Table 2

Baseline factors and covariates by first post-baseline ADE status, N=2,948.

		Naïve (N=2,181)		Experienced (N=767)	
		ADE (N=147)	No ADE (N=2034)	ADE (N=94)	No ADE (N=673)
Sex	Female	30 (20%)	380 (19%)	15 (16%)	83 (12%)
Race/Ethnicity	White	68 (46%)	899 (44%)	52 (55%)	378 (56%)
	Black	45 (31%)	663 (33%)	23 (24%)	147 (22%)
	Hispanic + other	34 (23%)	472 (23%)	19 (20%)	148 (22%)
Baseline age	Min, Max	21, 62	17, 74	21, 60	18, 73
	Median	38	37	43	42
Injection drug use at baseline	Reported (currently or previously)	12 (8%)	175 (9%)	14 (15%)	82 (12%)
Baseline CD4 (cells/ul) ⁽¹⁾	Median	44	220	146	266
	<= 50	81 (55%)	411 (20%)	23 (24%)	42 (6%)
	51–200	38 (26%)	538 (26%)	36 (38%)	196 (29%)
	>200	28 (19%)	1084 (53%)	34 (36%)	435 (65%)
	Median	323,608	69,711	60,128	18,687
Baseline HIV RNA (copy/ml) ⁽²⁾	> 100,000	109 (74%)	885 (44%)	38 (40%)	120 (18%)
	Median	23	25	25	25
	<18.5	11 (7%)	64 (3%)	1 (1%)	20 (3%)
	18.5–24.9	92 (63%)	1028 (51%)	51 (54%)	334 (50%)
	25–29.9	29 (20%)	652 (32%)	38 (40%)	225 (33%)
History of ADE at Baseline	>=30	15 (10%)	281 (14%)	4 (4%)	80 (12%)
		71 (48%)	331 (16%)	33 (35%)	204 (30%)
		15 (10%)	207 (10%)	15 (16%)	83 (12%)
		56 (38%)	760 (37%)	53 (56%)	324 (48%)
		99 (67%)	1242 (61%)	60 (64%)	418 (62%)
Assigned ART drug classes⁽⁴⁾	PI only or NRTI only	23 (16%)	261 (13%)	3 (3%)	49 (7%)
	PI+NRTI or PI+NNRTI	51 (35%)	659 (32%)	41 (44%)	302 (45%)
	NRTI+NNRTI	52 (35%)	855 (42%)	4 (4%)	67 (10%)
	PI+NRTI+NNRTI	21 (14%)	259 (13%)	46 (49%)	255 (38%)

		Naïve (N=2,181)		Experienced (N=767)	
		ADE (N=147)	No ADE (N=2034)	ADE (N=94)	No ADE (N=673)
Calendar year of initial ART regimens in parent study	1997–1999	61 (41%)	746 (37%)	55 (59%)	381 (57%)
	2000–2002	52 (35%)	768 (38%)	5 (5%)	70 (10%)
	2003–2006	34 (23%)	520 (26%)	34 (36%)	222 (33%)
PCP prophylaxis use at baseline	Yes	77 (52%)	592 (29%)	70 (74%)	336 (50%)
MAC prophylaxis use at baseline	Yes	34 (23%)	185 (9%)	25 (27%)	79 (12%)

(1) 1 naïve subject and 1 experienced subject had a missing baseline CD4.

(2) 1 experienced subject had a missing baseline HIV RNA.

(3) 9 naïve subjects and 14 experienced subjects had a missing baseline BMI.

(4) Among those who initially received single class therapy, 27 were 'PI only'-26 amprenavir monotherapy (ACTG 347) and 1 ritonavir-boosted saquinavir and fosamprenavir (ACTG A5146).

Table 3

Unadjusted and adjusted odds ratios (OR) and 95 percent confidence intervals (95% CI) for the association between baseline factors and time-updated 16-week immunologic and virologic risk factors and ADEs, among subjects ARV-naïve at baseline [Unadjusted: N=2181, number of events =147; Adjusted: N=2170, number of events =147].

Variables	Unadjusted		Adjusted **	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (vs Male)				
Female	1.09 (0.72,1.65)	0.68	1.41 (0.91,2.19)	0.13
Race/Ethnicity (vs Black)				
White	1.06 (0.73,1.56)	0.75	1.42 (0.95,2.11)	0.09
Hispanic +other	1.01 (0.64,1.58)	0.98	1.24 (0.79,1.95)	0.36
Age at baseline				
10 year increase in age	1.09 (0.93,1.29)	0.29	1.03 (0.85,1.24)	0.77
Injection drug use at baseline				
Reported (currently or previously)	1.12 (0.61,2.04)	0.72		
CD4 cell count at baseline (vs >200)				
0-50	7.08 (4.57,10.96)	<0.001		
51-200	2.68 (1.64,4.39)	<0.001		
>100,000	3.28 (2.25,4.77)	<0.001		
Baseline viral load vs (<=100,000)				
<18.5	2.05 (1.06,3.97)	0.03	1.18 (0.62,2.21)	0.62
25-29.9	0.49 (0.32,0.75)	0.001	0.65 (0.42,1.00)	0.05
>=30	0.63 (0.36,1.09)	0.10	0.77 (0.43,1.37)	0.37
History of ADE at baseline (vs Not reported)				
Reported	4.66 (3.32,6.54)	<0.001	2.10 (1.47,3.01)	<0.001
HCV infected				
Ever positive	1.05 (0.61,1.80)	0.87		
HBV infected				
Ever positive	0.93 (0.66,1.31)	0.67		
Smoker				
Ever smoker	1.36 (0.95,1.93)	0.09		
Assigned ARV drug class (vs NRTI+NNRTI)				
PI only or NRTI only	1.47 (0.89,2.43)	0.13		
PI+NNRTI or PI+NNRTI	1.20 (0.81,1.78)	0.36		
PI+NNRTI+NNRTI	1.01 (0.60,1.70)	0.97		
Baseline PCP prophylaxis				
Yes	2.42 (1.74,3.37)	<0.001		
Baseline MAC prophylaxis				
Yes	2.84 (1.90,4.25)	<0.001		
Baseline CD4 and viral load (vs CD4:>200 & VL:<=100,000)				
CD4:<=50 & VL:<=100,000	5.69 (2.63,12.32)	<0.001		
CD4:<=50 & VL:>100,000	8.66 (5.11,14.66)	<0.001		
CD4:51-200 & VL:<=100,000	1.76 (0.79,3.94)	0.17		
CD4:51-200 & VL:>100,000	3.97 (2.19,7.20)	<0.001		

	Variables	Unadjusted		Adjusted **	
		OR (95% CI)	p-value	OR (95% CI)	p-value
	CD4:>200 & VL:>100,000	1.54 (0.71,3.34)	0.28		
Time-updated CD4 cell count and viral load (vs CD4:>200 & VL:<=100,000)	CD4:<=50 & VL:<=100,000	35.48 (20.44,61.60)	<0.001	30.49 (16.89,55.05)	<0.001
	CD4:<=50 & VL:>100,000	48.96 (32.26,74.30)	<0.001	37.23 (23.64,58.63)	<0.001
	CD4:51-200 & VL:<=100,000	5.08 (3.04,8.48)	<0.001	4.48 (2.62,7.63)	<0.001
	CD4:51-200 & VL:>100,000	15.48 (8.56,27.97)	<0.001	13.04 (7.11,23.94)	<0.001
	CD4:>200 & VL:>100,000	1.12 (0.15,8.15)	0.91	1.16 (0.16,8.46)	0.88

** Also adjusting for parent study.

Table 4

Unadjusted and adjusted odds ratios (OR) and 95 percent confidence intervals (95% CI) for the association between baseline factors and time-updated 16-week immunologic and virologic risk factors and ADEs, among subjects ARV-experienced at baseline [Unadjusted: N=767, number of events =94; Adjusted: N=752, number of events =93].

	Variables	Unadjusted		Adjusted	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (vs Female)	Female	1.30 (0.73,2.30)	0.37	1.36 (0.74,2.48)	0.32
Race/Ethnicity (vs Black)	White	0.75 (0.45,1.25)	0.27	1.04 (0.62,1.76)	0.88
	Hispanic +other	0.77 (0.41,1.43)	0.41	0.89 (0.48,1.62)	0.70
Age at baseline	10 year increase in age	1.06 (0.84,1.35)	0.62	1.17 (0.91,1.51)	0.22
Injection drug use at baseline	Reported (currently or previously)	1.49 (0.83,2.67)	0.19		
CD4 cell count at baseline (vs >200)	0-50	10.59 (5.89,19.03)	<0.001		
	51-200	2.79 (1.73,4.49)	<0.001		
	>100,000	3.24 (2.10,5.01)	<0.001		
Baseline viral load (vs <=100,000)					
Baseline BMI (vs 18.5-24.9)	<18.5	0.40 (0.05,2.97)	0.37	0.20 (0.02,1.81)	0.15
	25-29.9	1.09 (0.71,1.69)	0.69	1.32 (0.86,2.03)	0.21
	>=30	0.41 (0.15,1.16)	0.09	0.49 (0.18,1.32)	0.16
History of ADE at baseline (vs Not reported)	Reported	1.62 (1.04,2.51)	0.03	0.99 (0.63,1.54)	0.96
HCV infected	Ever positive	1.33 (0.76,2.33)	0.32		
HBV infected	Ever positive	1.19 (0.78,1.81)	0.42		
Smoker	Ever smoker	1.12 (0.73,1.74)	0.60		
Assigned ARV drug class (vs NRTI+NNRTI)	PI only or NRTI only	0.97 (0.22,4.32)	0.97		
	PI+NRTI or PI+NNRTI	3.94 (1.42,10.95)	<0.01		
	PI+NNRTI+NNRTI	3.31 (1.20,9.13)	0.02		
Baseline PCP prophylaxis	Yes	3.19 (1.99,5.13)	<0.001		
Baseline MAC prophylaxis	Yes	3.51 (2.16,5.68)	<0.001		
Baseline CD4 and viral load (vs CD4:>200 & VL:<=100,000)	CD4:<=50 & VL:<=100,000	12.77 (4.98,32.70)	<0.001		
	CD4:<=50 & VL:>100,000	14.02 (6.94,28.32)	<0.001		
	CD4:51-200 & VL:<=100,000	3.59 (2.04,6.34)	<0.001		
	CD4:51-200 & VL:>100,000	3.61 (1.73,7.52)	<0.001		

	Variables	Unadjusted		Adjusted	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Time-updated CD4 cell count and viral load (vs CD4:>200 & VL:<=100,000)	CD4:>200 & VL:>100,000	4.32 (2.02,9.22)	<0.001		
	CD4:<=50 & VL:<=100,000	21.21 (11.43,39.33)	<0.001	21.37 (10.91,41.87)	<0.001
	CD4:<=50 & VL:>100,000	33.96 (18.71,61.63)	<0.001	37.99 (20.61,70.04)	<0.001
	CD4:51–200 & VL:<=100,000	3.36 (1.79,6.31)	<0.001	3.49 (1.81,6.72)	<0.001
	CD4:51–200 & VL:>100,000	11.76 (5.71,24.22)	<0.001	12.96 (6.15,27.30)	<0.001
	CD4:>200 & VL:>100,000	9.75 (3.78,25.16)	<0.001	9.99 (3.85,25.96)	<0.001