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CD8+ T cells and Risk for Bacterial Pneumonia and All-Cause Mortality Among HIV-infected Women

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Abstract

Background—Bacterial pneumonia risk is disproportionately high among those infected with Human Immunodeficiency Virus (HIV). This risk is present across all $CD4^+$ T cell levels (TCL), suggesting additional factors govern susceptibility. This study examines $CD8^+$ TCL and risk for HIV-associated bacterial pneumonia and all-cause mortality.

Methods—Demographic, clinical, and laboratory data were obtained for 885 HIV-infected (HIV^+) women enrolled in the HIV Epidemiologic Research Study (HERS). Bacterial pneumonia cases were identified using clinical, microbiologic, and radiographic criteria. $CD8^+$ TCLs were assessed at 6-month intervals. Statistical methods included Cox proportional hazards regression modeling and covariate-adjusted survival estimates.

Results—Relative to a referent $CD8^+$ TCL 401–800 cells/mm^3, risk for bacterial pneumonia was significantly higher when $CD8^+$ TCLs were ≤ 400 (hazard ratio 1.65, p=0.017, 95% CI 1.10–2.49), after adjusting for age, $CD4^+$ TCL, viral load, and antiretroviral use. There was also a significantly higher risk of death when $CD8^+$ TCLs were ≤ 400 cells/mm^3 (hazard ratio 1.45, p=0.04, 95% CI 1.02–2.06). Covariate-adjusted survival estimates revealed shorter time to pneumonia and death in this $CD8^+$ TCL category and the overall association of the categorized $CD8^+$TCL with bacterial pneumonia and all-cause mortality were each statistically significant (p=0.017 and p<0.0001, respectively).

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Conclusions—$CD8^+$ TCL ≤ 400 cells/mm^3 was associated with increased risk for pneumonia and all-cause mortality in HIV-infected women in the HERS Cohort, suggesting that $CD8^+$ TCL could serve as an adjunctive biomarker of pneumonia risk and mortality in HIV-infected individuals.

Keywords

Pneumonia; $CD8^+$ T cell; Human Immunodeficiency Virus (HIV); Mortality

Introduction

Patients infected with Human Immunodeficiency Virus (HIV) are 25 times more likely to develop bacterial pneumonia and 100 times more likely to develop invasive disease with *Streptococcus pneumoniae*, the leading cause of bacterial pneumonia worldwide [1,2]. Although this risk is associated with reduced $CD4^+$ T cell levels (TCL), almost half of all HIV-associated bacterial pneumonias occur at $CD4^+$ TCLs above 200 cells/mm^3 [2,3]. Hence, additional host factors must contribute to susceptibility. Among candidate immunologic factors, $CD8^+$ T cells are of particular interest in the pathogenesis of HIV, bacterial pneumonia, and lung disease. HIV controllers have elevated levels of functional HIV-specific $CD8^+$ T cells [4,5]. Murine data suggest a beneficial immunoregulatory role for $CD8^+$ T cells in innate and acquired immunity to pneumococcal and other pneumonias [6–10]. $CD8^+$ T cells have also been implicated in the pathophysiology of chronic obstructive pulmonary disease (COPD) as well as smoking-related lung injury [11–13]. However, to our knowledge, the importance of $CD8^+$ TCL in resistance to HIV-associated pneumonia has not been examined previously.

High rates of bacterial pneumonia, higher hospitalization rates, and recurrent bacterial pneumonias have been reported in HIV-infected women in the pre- as well as post-HAART eras [14–16]. Additionally, despite having higher baseline $CD4^+$ TCLs, HIV-infected women have a higher risk for bacterial pneumonia than HIV-infectedmen [17]. In this study, we examine the relationship between $CD8^+$ TCL, bacterial pneumonia, and all-cause mortality in HIV-infected women.

Methods

Study population

We studied HIV-infected participants in the HIV Epidemiologic Research Study (HERS), a multicenter prospective study that enrolled 885 HIV-infected and 425 HIV-uninfected women aged 16–55 from April 1993 to January 1995, concluding in April 2000[18]. Enrollment criteria are detailed elsewhere[16,18]. Briefly, women with clinical AIDS were excluded, but women with $CD4^+$ TCLs <200 cells/mm^3 were included if they had no prior clinical AIDS-defining illness. Participants underwent semi-annual research visits with standardized interviews to obtain information on sociodemographic status, substance use, medical history, intercurrent hospitalizations, and antiretroviral (ARV) use. All patients underwent blood collection for immunologic analysis, including $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocyte subset quantification. Viral load (VL) was measured prospectively starting in 1997 using version 3.0 ultrasensitive branched-DNA signal amplification assay (Bayer Diagnostics); for samples collected prior to that point, VL was measured retrospectively [19]. Medical records were obtained for all hospitalizations and reviewed per standardized protocol. Episodes meeting predetermined criteria for bacterial pneumonia as defined by Kohli, et. al [16] were included in this analysis. A national death index search was used to assess mortality; death certificates and medical records were reviewed for all deaths identified.

Definition of Bacterial Pneumonia

Pneumonia cases were identified as per the definitions of bacterial pneumonia previously reported by Kohli, et. al [16]. "Definitive" cases were defined by presence of a new or progressive infiltrate on chest radiograph and a positive sputum, blood, or pleural fluid culture with no identifiable primary source other than lung, and clinical findings suggestive of bacterial pneumonia, including response to antibacterial therapy, positive sputum Gram stain, cough, shortness of breath, or respirations >20 breaths/minute. "Probable" cases included a new or progressive infiltrate on chest radiograph with no diagnosis of *Pneumocystis jiroveci* pneumonia (PJP), and either a clinical response to antibacterials or positive sputum Gram stain and temperature >37.8°C. Gram stains were deemed positive if granulocytes and organisms were reported >/=2+, negative if there were no organisms, and inadequate if there were <2+ granulocytes. Probable cases also required clinical criteria, including cough, shortness of breath, or respiratory rate >20 breaths/minute. "Presumed" cases were defined as those with a physician discharge diagnosis of bacterial pneumonia, infiltrate on admission chest radiograph, and no criteria consistent with PJP. We included all HIV-infected pneumonia cases (HIV^+PNA^+) identified by Kohli, et al., except 7 cases for whom records were not identifiable by our group. For all pneumonia cases, diagnostic chest radiographs used for infiltrate determination were dated within 48 hours of admission. We excluded participants whose radiographs demonstrated bilateral interstitial infiltrates or whose test results were positive for PJP, mycobacteria, endocarditis, or malignancy. HIV-infected, pneumonia negative (HIV^+PNA^-) participants were defined as those who never developed pneumonia throughout the duration of the HERS.

Statistical Analysis

Based on the above criteria, 200 cases of bacterial pneumonia were identified among HIV-infected HERS participants from 1993–2000. $CD8^+$ TCLs obtained at 6-month intervals were assessed for all participants. Baseline characteristics were compared between participant groups using student's t-test or Wilcoxon rank-sum test for continuous variables and Chi-squared tests for categorical variables. For HIV^+PNA^+ participants, $CD8^+$ TCLs were assessed until the time closest to, but antedating the pneumonia event or death, depending on the outcome. The mean (SD) time interval between the last $CD8^+$ TCL and the time of pneumonia was 136 (110) days ranging from 5 days to 836 days. Both the mean and median (110 days) time intervals were within 6 months of the pneumonia event. For those with recurrent pneumonia, $CD8^+$ TCLs until the first event were used. For HIV^+PNA^- participants, $CD8^+$ TCLs until the last time available were assessed. Risk for bacterial pneumonia (primary endpoint) and all-cause mortality (secondary endpoint) for HIV^+ subjects was determined as a function of $CD8^+$ TCLs by Cox proportional hazards regression modeling, from which covariate-adjusted survival curves were estimated. Time-dependent covariates included time of enrollment, $CD4^+$ TCL, $\log_{10}$ viral load, and antiretroviral duration. Baseline age at enrollment and smoking status were included as time-independent covariates. Smoking status was considered positive if participants reported any or ever cigarette use and negative if reported never having smoked. Twelve participants whose pneumonia event antedated the first HERS visit were excluded from the analyses. To quantify within-subject variations in $CD8^+$ TCL, we computed variance, standard deviation, and range of biannually measured $CD8^+$ TCL for those subjects who had more than one $CD8^+$ TCL available. We applied t-tests weighted (after removal of one outlier) by the square root of number of observations minus one to compare within-subject variations between cohorts. Analyses were performed using SAS software, version 9.1 (SAS Institute).

RESULTS

Baseline characteristics for each cohort are displayed in Table 1. There were 200 bacterial pneumonias among 885 HIV-infected subjects. Mean age was 36.3 years among HIV-infected patients who developed pneumonia (HIV^+PNA^+), older than HIV-infected patients who did not (HIV^+PNA^-), p= 0.024. Compared to HIV^+PNA^- participants, HIV^+PNA^+ participants were more likely to have ever smoked (p<0.0004), be of African American ethnicity (p=0.019), and report fewer years spent in school (p=0.052). There were no differences in ARV duration, reported alcohol use, or injection drug use between the HIV^+PNA^+ and HIV^+PNA^- participants. Additional data and subgroup analyses of bacterial pneumonia risk were reported previously [16]. $CD4^+$ TCL was significantly lower (366 cells/mm^3) and log_{10}VL significantly higher (3.5) in HIV^+PNA^+ than in HIV^+PNA^- participants (p<0.0001 for each parameter). Mean baseline $CD8^+$ TCLs were significantly higher among HIV-infected than HIV-uninfected participants (941 vs 684 cells/mm^3, respectively, p<0.001). There was no significant difference in baseline $CD8^+$ TCL between HIV^+PNA^+ and HIV^+PNA^- participants.

There was significantly more variation in absolute $CD8^+$ TCLs (p=0.0016), standard deviation (p=0.0064), and range of $CD8^+$ TCLs (p=0.0134) in the HIV^+PNA^+ cohort compared to the HIV^+PNA^- cohort when weighted t-tests were applied, Figure 1a. Thus, there was more within-subject and within-cohort variation in $CD8^+$ TCL among HIV^+PNA^+ than HIV^+PNA^- participants. We also observed an increase in mean $CD8^+$ TCL around visit 10 in the HIV^+PNA^+ cohort. The percentage of HIV^+PNA^+ participants on potent ARVs increased from 36% prior to visit 10, to 100% after that visit. Potent ARV use also increased before and after visit 10 from 30% to 100% for HIV^+PNA^- participants. To account for possible effects of ARV use on $CD8^+$ TCL, we determined log_{10}viral load as a function of time; this did not show significant variation between the PNA^+ and PNA^- cohorts, Figure 1b.

The overall incidences of pneumonia and mortality were 12.9 and 15.9 per 100 person-years, respectively, among HIV-infected participants with $CD8^+$ TCL ≤ 400 cells/mm^3 (Table 2a). At the time closest to but antedating the pneumonia event within 6 months, the mean $CD4^+$ TCL was 267 cells/mm^3, log_{10} viral load was 3.75, with 13.5% of subjects reported having started potent ARVs. To determine a threshold of $CD8^+$ TCL at which bacterial pneumonia rates were highest, we examined $CD8^+$ TCL in the HIV^+PNA^+ cohort by multiple increments across all visits. The most common $CD8^+$ TCL was between 401–800 cell/mm^3, Figure 2(a). The distribution of HIV^+PNA^+ participants by $CD8^+$ TCL category using values within 6 months antedating the pneumonia event was similar to that seen in all participants, Figure 2(b). The percentage of HIV^+PNA^+ participants among the total number of participants in each CD8 category, using the $CD8^+$ TCL antedating the pneumonia event for cases and the baseline level for all participants, is shown in Figure 2(c). The lowest percentage of participants had $CD8^+$ TCLs between 401–800 cells/mm^3 and the highest percentage had $CD8^+$ TCLs either ≤ 400 or between 1201–1600 cells/mm^3.

Cox proportional hazards models for pneumonia and all-cause mortality among HIV^+PNA^+ participants are shown in Table 2. The overall associations of the five $CD8^+$TCL categories with bacterial pneumonia and all-cause mortality were statistically significant (p=0.017 and p<0.0001, respectively), even after adjustment for $CD4^+$ TCL, VL, age, ARV duration. We defined our referent category as $CD8^+$ TCL of 401–800 cells/mm3 as it was the most common $CD8^+$ TCL range among all groups. Relative to this referent, risk for pneumonia was highest when $CD8^+$ TCL was ≤ 400 cells/mm^3 (HR 1.65, p=0.017, 95% CI 1.10–2.49). The highest all-cause mortality was also observed when $CD8^+$ TCLs were ≤ 400 compared to the referent range of 401–800 cell/mm^3 (HR=1.45, p=0.04, 95% CI 1.02–2.06). Both of

these results reflect adjustment for $CD4^+$ TCL, log_{10}VL, age, and ARV duration, and remained statistically significant when further adjusted for smoking (HR 1.61, p=0.024, and 1.49, p=0.035, for pneumonia and mortality, respectively). Upon further adjustment for African American ethnicity, pneumonia and mortality risk also remained significant and borderline significant, respectively, (HR 1.58, p=0.03, and 1.44, p=0.054, respectively). Hence, our data indicate that compared to a referent of 401–800 cells/mm^3, a $CD8^+$ TCL < 400 was associated with a higher risk for pneumonia and all-cause mortality, adjusting for $CD4^+$ TCL, VL, age, ARV duration, smoking, and African-American ethnicity. The results were similar when the model was repeated using the ≤ 400 cells/mm^3 category as the referent. $CD8^+$ TCL categories of 801–1200, 1201–1600, and >1600 were not significantly different from the referent in either the pneumonia or mortality model. Although the Cox proportional hazards model included $CD4^+$ TCL as a time-varying variable and thereby adjusted for the nadir $CD4^+$ TCL, we computed nadir $CD4^+$ TCL for each subject and replaced the time-varying $CD4^+$ TCL by the time-independent nadir $CD4^+$ TCL in the Cox model. Nadir $CD4^+$ TCL was significantly associated with pneumonia but not significantly associated with all-cause mortality. The overall results concerning $CD8^+$ TCL categories remained unchanged in the nadir $CD4^+$ TCL model.

Covariate-adjusted survival estimates based on the fitted Cox models for time to pneumonia and death are shown in Figure 3 for participants aged 50, $CD4^+$ TCL of 200 cells/mm^3, log_{10}VL of 4, and ARV duration of 500 days. These parameters were chosen to reflect a high risk group for both pneumonia and mortality. Among HIV^+PNA^+ participants, 65% of those with $CD8^+$ TCLs 401–800 were estimated to be pneumonia-free five years from study entry, compared to 50% of those with $CD8^+$ TCLs ≤ 400 cells/mm^3. Analysis of time to death revealed 16% more participants were estimated to be alive at five years in the 401–800 than in the ≤ 400 cells/mm^3 $CD8^+$ TCL category. Similar, though less dramatic, differences were observed for non-smokers. The covariate survival estimate model was computed several times, with changes in age, $CD4^+$ TCL, log_{10}VL, smoking status, and race. Neither time to pneumonia nor mortality differences were observed between the cohorts when age was decreased to 35 years, $CD4^+$ TCL was increased to 400, log_{10}VL was decreased to 1.7, or when including only non-African American participants.

A sensitivity analysis conducted by Kohli, et al. established that their results were similar when either all definitive, probable, and presumed cases or only definitive and probable cases were included [16]. However, when we repeated our analyses separately for definitive versus probable and possible pneumonia, none of the $CD8^+$ TCL categories were significant compared to the referent $CD8^+$ TCL category 400–800, while $CD4^+$ TCL counts were significant in both analyses.

A total of 69 participants had more than one pneumonia event. $CD8^+$ TCLs of participants in this subgroup were similar to those in Figure 2 (data not shown). Cox proportional hazards model for those with recurrent pneumonia revealed no significant difference by $CD8^+$ TCL category, perhaps owing to a smaller sample size. However, 49% of those with recurrent pneumonia had $CD8^+$ TCLs > 800 cells/mm^3 within 6 months of their first pneumonia event. Mean $CD8^+$ TCL was 1420 cells/mm^3 for 8 participants with >5 pneumonia events and <200 cells/mm^3 for two such participants.

DISCUSSION

$CD8^+$ T cell levels increase early in HIV infection and remain persistently elevated during the early chronic phase of HIV disease [20,21]. The mean baseline $CD8^+$ TCL of HIV-infected participants in our study was similar to that reported by other groups [22,23]. Baseline $CD8^+$ TCLs were not significantly different between HIV^+PNA^+ and HIV^+PNA^- participants in

our study, but there was a statistically significant association between $CD8^+$ TCL antedating the pneumonia event and bacterial pneumonia whereby a $CD8^+$ TCL ≤ 400 was associated with a 1.7 times higher risk of pneumonia and 1.5 times higher risk for death compared to a referent $CD8^+$ TCL of 401–800 cells/mm^3. These findings remained statistically significant after adjusting for $CD4^+$ TCL, VL, age, ARV use, smoking, and ethnicity.

The possibility that low total $CD8^+$ TCL could increase the risk for an HIV-associated complication like pneumonia is not surprising given that HIV controllers have an expanded and more functional $CD8^+$ T cell compartment and a reduction in $CD8^+$ TCL has been linked to HIV disease progression [4,5,23,24]. The possible impact of $CD8^+$ TCL loss and the risk for pneumonia is further underscored by pre-clinical models demonstrating the importance of $CD8^+$ T cells in host defense against pulmonary pathogens. For example, in mice, $CD8^+$ T cells can compensate for $CD4^+$ T cells in resistance to pulmonary mycobacterial and fungal pathogens, including HIV-associated pathogens such as *Pneumocystis jiroveci* and *Cryptococcus neoformans* [9,25–27]. Of relevance to the risk for bacterial pneumonia, $CD8^+$ T cells were required for protection against *S. pneumoniae* in immunized and naive mice [6,7] and recruited to the lungs in surviving mice [28]. Similar results have been reported for *Klebsiella pneumoniae* [29]. Our findings suggest that the possibility that $CD8^+$ T cells contribute to resistance to HIV-associated bacterial pneumonia deserves further study.

Our data reveal a peak in the percentage of pneumonias (19%) in the $CD8^+$ TCL category of 1201–1600 cells/mm^3, although risk for pneumonia and all-cause mortality in $CD8^+$ TCL categories >800 was not statistically different from the referent group (401–800 cells/mm^3) in the Cox proportional hazards analysis. Nonetheless, among 69 participants with recurrent pneumonias, almost half (34 participants or 49%) had $CD8^+$ TCL >800 cells/mm^3, with the mean level among those with >5 episodes being 1420 cells/mm^3. This is intriguing in light of the Damage-response framework [30], which highlights that host damage can occur in the setting of either an insufficient or a vigorous immune response. Given ample evidence for $CD8^+$ T cell mediated inflammation, we wonder whether higher $CD8^+$ TCLs could be associated with increased disease risk by inducing excessive inflammation. Along these lines, high $CD8^+$ TCLs were inversely correlated with FEV1 and implicated as mediators of smoking-associated lung injury and COPD [31,32] and among HIV-infected smokers, $CD8^+$ TCLs were significantly higher in bronchoalveolar lavage (BAL) from those with than without COPD [33]. In mice with PJP, CD4-depletion led to death due to respiratory compromise with $CD8^+$ T cell mediated lung injury [34] and HIV-infected patients with *Pneumocystis* after starting ARVs had high quantities of rapidly proliferating $CD8^+$ T cells in their BAL fluid [35]. Several studies have implicated $CD8^+$ T cells in lung inflammation in *Pneumocystis* colonization and progressive pulmonary decline in HIV patients [34,36]. Hence, our data raise the possibility that, as per the Damage-response framework [30], either low or high $CD8^+$ TCLs could contribute to susceptibility to HIV-associated bacterial pneumonia.

HIV^+PNA^+ participants had significantly more variability in their $CD8^+$ TCLs than HIV^+PNA^- participants. At present, the significance of this finding is unclear. Further studies are required to evaluate the activation status and antigen specificity of $CD8^+$ T cells in patients with pneumonia as these parameters were not evaluated in the HERS cohort. Nonetheless, our data show that $CD8^+$ T cell levels are not uniform and that greater fluctuation could be associated with risk for HIV-associated pneumonia. The rise in mean $CD8^+$ TCL that was observed at later times in both the HIV^+PNA^+ and HIV^+PNA^- cohorts could reflect an effect of ARV introduction, as the percentage of those having started ARV increased from approximately 36% to nearly 100% with time.

At present, our data are most relevant for HIV-infected individuals with $CD4^+$ TCL in lower ranges who are not on ARVs, such as those in resource-limited settings. As measurement of $CD8^+$ TCL is performed on the same sample as $CD4^+$ TCL and both measurements are commonly obtained even in resource-limited settings[37,38], our results suggest that $CD8^+$ TCL could serve as an adjunctive biomarker for HIV-associated pneumonia risk, in addition to other known risk factors. Our findings may also be important in non-HIV associated and/or non-bacterial pneumonia, as $CD8^+$ T cells can contribute to the pathogenesis of influenza[39]. In light of growing recognition that influenza morbidity and mortality is driven by secondary bacterial pneumonia [40,41], it is logical to hypothesize that $CD8^+$ T cell involvement in host defense against influenza could alter the inflammatory milieu and predispose the host to bacterial pneumonia. This area requires further investigation.

Our study has several limitations. First, most of the pneumonias did not meet definitive criteria for bacterial pneumonia, with the caveat that the definitive category required culture-proven bacterial pneumonia, which is very difficult to obtain. Although a sensitivity analysis conducted by Kohli, et al. found similar results when all definitive, probable, and presumed cases were included and when limited to definitive and probable cases [16], this was not the case in our study. The most likely explanation for this is that the effect of $CD4^+$ TCL on pneumonia and all-cause mortality is substantially greater than that of $CD8^+$ TCL; however, our study was not designed to address this question. Based on our findings, future studies should endeavor to examine $CD8^+$ TCLs among patients with pre-defined $CD4^+$ TCLs and pneumonia definitions. Second, HERS included only women; hence, studies are needed in men. Third, we were not able to account for certain comorbid illnesses that could have confounded our findings, such as viral infections and history of lung disease (e.g., COPD). Fourth, although our data suggest that $CD8^+$ TCLs ≤ 400 cells/mm^3 may be a useful adjunct to $CD4^+$ TCLs for identifying patients at risk for bacterial pneumonias and death, the HERS spanned a period during which potent ARVs first became available. Thus, most participants in the pneumonia cohort were not on potent antiretroviral therapy. While ARV therapy is now widely available in the U.S. and other resourced countries, there are many HIV-infected individuals living in areas where ARVs are not readily or consistently available. Our findings are most relevant to the latter, as well as for patients who do not adhere to their ARV regimens. Finally, the scope of our study and conclusions are limited by our inability to assess $CD8^+$ T cell activation status, effector, or memory $CD8^+$ T cells, as such data was not collected in the HERS.

In summary, we evaluated $CD8^+$ TCL and pneumonia risk in a large, prospective cohort of HIV-infected women and identified an association between $CD8^+$ TCLs ≤ 400 cells/mm^3 and risk for bacterial pneumonia and all-cause mortality relative to a referent range of 401–800 cells/mm^3. These findings suggest that $CD8^+$ TCLs ≤ 400 cells/mm^3 may be a useful adjunct to $CD4^+$ TCLs for identifying patients at risk for pneumonias and death, particularly in individuals with low $CD4^+$ TCLs and/or who are not on ARVs. Furthermore, our finding that $CD8^+$ TCLs were more variable in HIV-infected participants who developed pneumonia and tended to be higher in those who had highly recurrent pneumonia suggest that the role of $CD8^+$ T cells in the pathogenesis of pneumonia is complex and requires further study.

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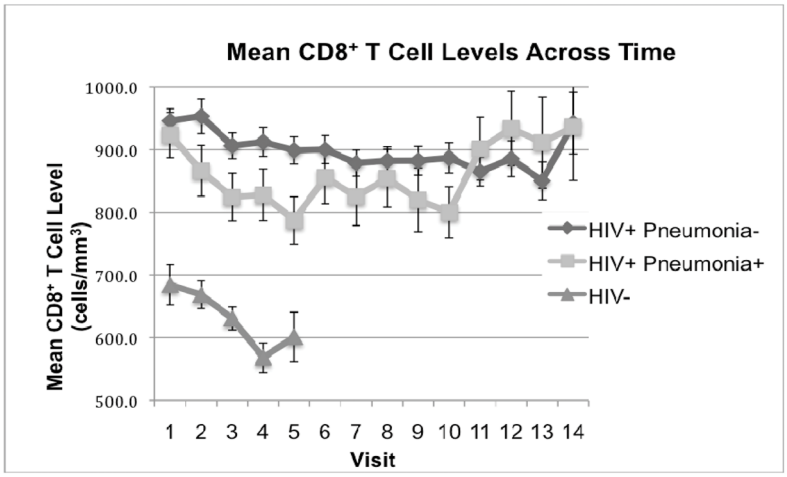
(a)



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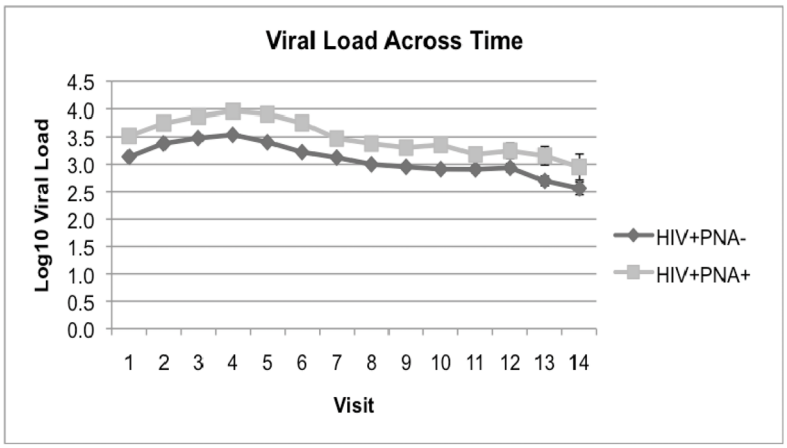
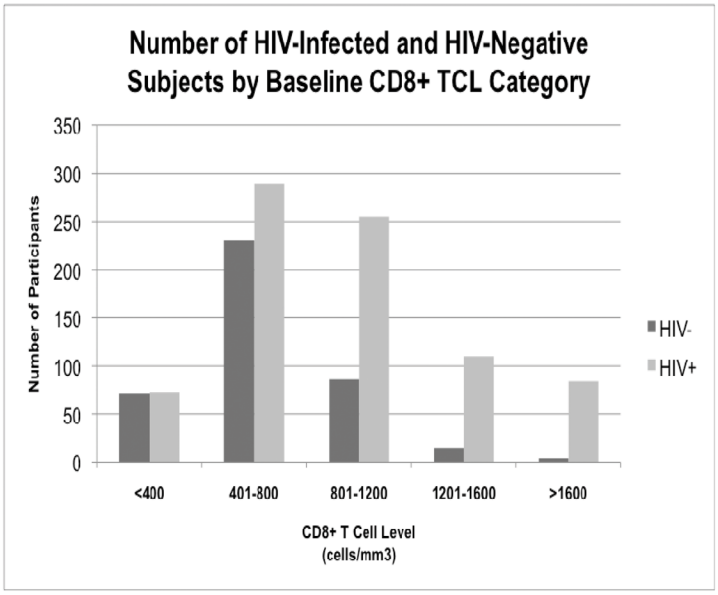


Figure 1. Mean CD8$^+$ T Cell Level and Viral Load Across Time

(a) CD8$^+$ T cell levels (TCLs) among HIV-infected participants who developed pneumonia (HIV$^+$PNA$^+$) exhibited more variation in absolute CD8$^+$ TCLs (p=0.0016), as well as standard deviation (p=0.0064) and range of mean CD8$^+$ TCLs (p=0.0134) compared to HIV-infected participants who never developed pneumonia (HIV$^+$PNA$^-$). (b) Log_{10}viral load in the HIV$^+$PNA$^+$ cohort closely paralleled that of the HIV$^+$PNA$^-$ cohort.

(a)



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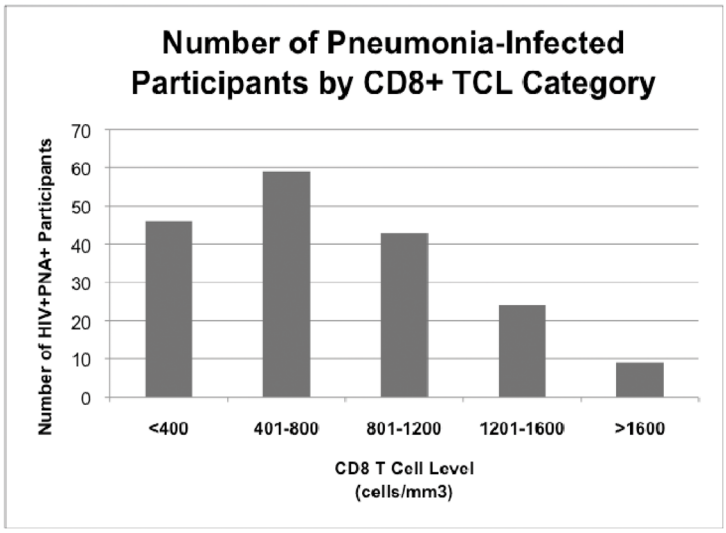

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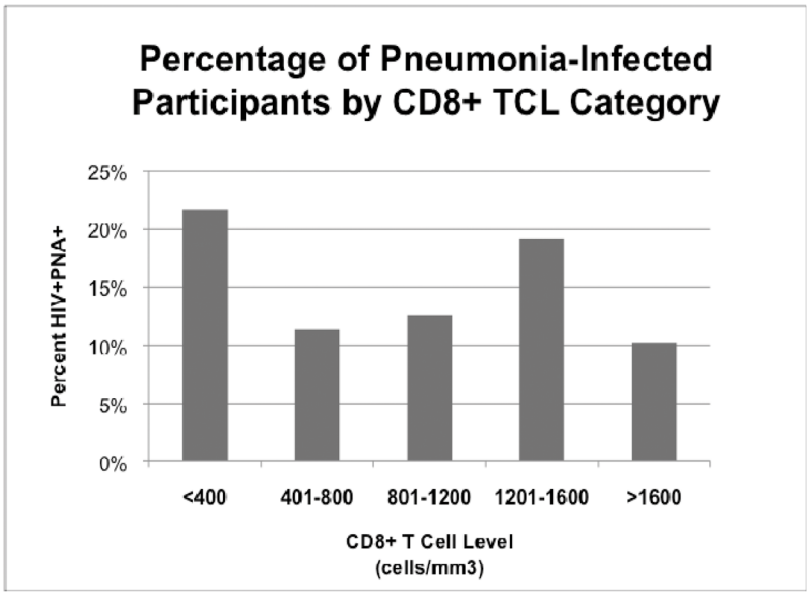
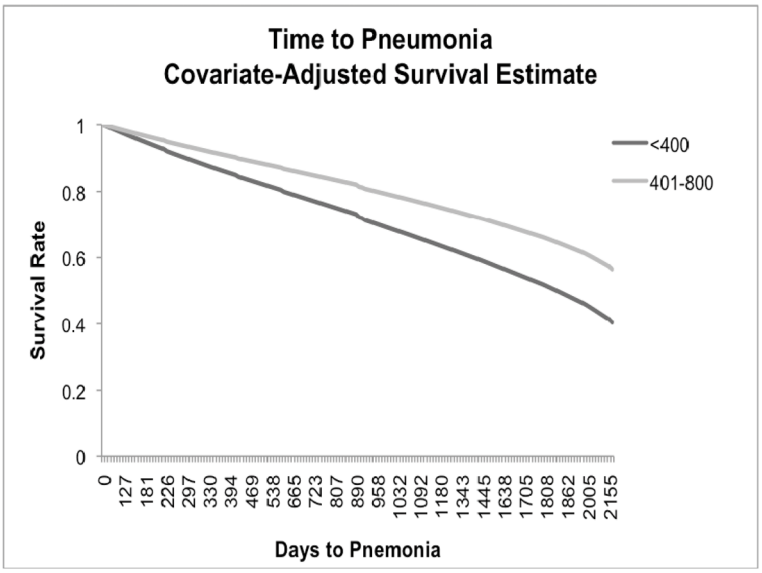


Figure 2. Distribution of HIV-infected participants with pneumonia by $CD8^+$ T cell level (TCL) and as percentage of total number of patients within each CD8 category

(a, b) The most common $CD8^+$ TCL among all participants at baseline as well as HIV^+PNA^+ participants within 6 months of pneumonia diagnosis was between 401–800 cells/mm^3. (c) The percentage of HIV^+PNA^+ participants among the total number of participants in each CD8 category using the $CD8^+$ TCL antedating the pneumonia event for cases and the baseline level for all participants reveals that the highest percentage of pneumonias occurred when $CD8^+$ TCL was ≤ 400 cells/mm^3.

(a)



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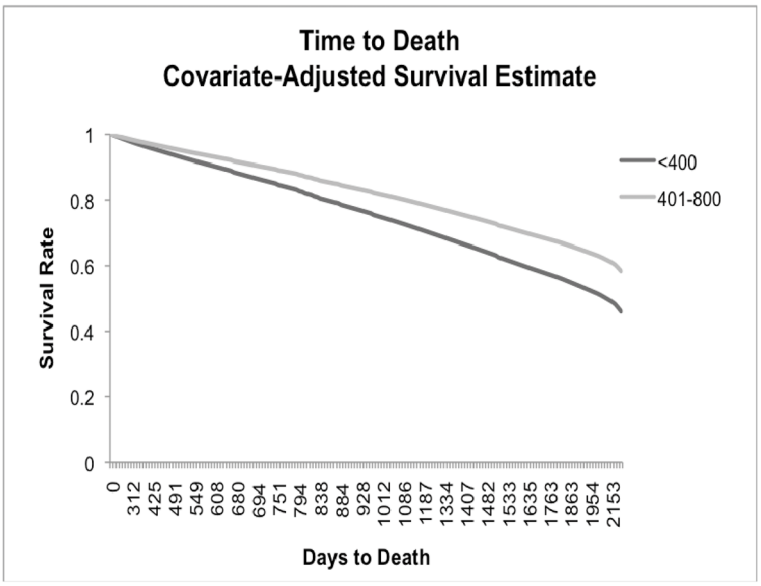

Figure 3. Covariate-Adjusted Survival Estimates for (a) Time to Pneumonia and (b) Death

65% of participants with $CD8^+$ T cell levels (TCL) between 401–800 cells/mm^3 were pneumonia-free and 69% were alive five years from study entry, compared to 50% pneumonia-free and 53% alive among participants with $CD8^+$ TCL ≤ 400 cells/mm^3. This estimate assumed age of 50 years, $CD4^+$ TCL of 200 cells/mm^3, $\log_{10}$VL of 4, and antiretroviral duration of 500 days.

Table 1
Baseline Characteristics of HERS Participants

Baseline age was higher (p=0.024), $CD4^+$ T cell level (TCL) significantly lower (p<0.0001) and viral load significantly higher (p<0.0001) in HIV-infected participants who developed pneumonia (HIV^+PNA^+) than HIV-infected participants who did not (HIV^+PNA^-), however no differences were seen in $CD8^+$ TCL or antiretroviral (ARV) duration. HIV^+PNA^+ patients were significantly more likely to have smoked (p<0.0004), report African American ethnicity (p=0.0186), and have spent fewer years in school (p=0.052). There was no difference in reported alcohol use, IVDU, or high-risk behaviors between the HIV cohorts.

Variable	HIV-Infected No Pneumonia (HIV^+ PNA^-)	HIV-Infected With Pneumonia (HIV^+ PNA^+)
Sample size, N	685	200
Age (Mean)	35.1	36.3
Baseline $CD4^+$TCL (Mean Absolute Count, cells/mm^3)	468	364
Baseline $CD8^+$TCL (Mean Absolute Count, cells/mm^3)	945	925
Baseline $\log_{10}$ Viral Load (Mean)	3.1	3.5
Antiretroviral duration (Mean, in Days)	270	270
Ever smoked	76%	88%
Race		
African American	59%	70%
Latina	19%	14%
White	22%	16%
Education Level (Years)	11.4	11.1

Table 2

Pneumonia and Mortality Incidence (a) and Cox Proportional Hazards Models (b)

Estimated likelihood of pneumonia and death was significantly higher when $CD8^+$ T Cell Level was ≤400. The overall p values for the association of $CD8^+$TCL with bacterial pneumonia and all-cause mortality were p=0.017 and p<0.0001, respectively. Adjusted for age, $CD4^+$ TCL, viral load, and ARV duration.

(a)

CD8 T Cell Category (cells/mm^3)	Pneumonia Incidence (100 persons/year)	Mortality Incidence (100 persons/year)
≤400	12.9	15.9
401–800	4.8	5.0
801–1200	4.4	3.4
1201–1600	5.2	2.8
>1600	3.4	4.5

(b)

CD8 T Cell Category (cells/mm^3)	p value	Hazard Ratio	95% Confidence Interval
Pneumonia Model			
≤400	0.017*	1.65	1.10–2.49
401–800	---	1.00	---
801–1200	0.713	1.08	0.72–1.61
1201–1600	0.158	1.42	0.87–2.32
>1600	0.531	0.79	0.37–1.67
Mortality Model			
≤400	0.04*	1.45	1.02–2.06
401–800	---	1.00	---
801–1200	0.468	.86	0.57–1.29
1201–1600	0.559	.84	0.48–1.49
>1600	0.475	1.25	0.68–2.29

* Two-tailed significance, p < 0.05.