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Clinical and Immunologic Predictors of Death After an Acute Opportunistic Infection: Results from ACTG A5164

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Abstract

Background—In the pre-ART era, markers of increased disease severity during an acute opportunistic infection (OI) were associated with mortality. Even with ART, mortality remains high during the first year after an OI in persons with advanced HIV infection, but it is unclear whether previous predictors of mortality remain valid in the current era.

Objective—Determine clinical and immunological predictors of death after an OI.

Methods—We used clinical data and stored plasma from ACTG A5164, a multi-center study evaluating the optimal timing of ART during a non-tuberculous OI. We developed Cox models evaluating associations between clinical parameters and plasma marker levels at entry and time to death over the first 48 weeks after the diagnosis of OI. We developed multivariable models incorporating only clinical parameters, only plasma marker levels, or both.

Results—The median CD4⁺ T-cell count in study participants at baseline was 29 cells/uL. 64% had *Pneumocystis jirovecii* pneumonia (PCP). Twenty-three of 282 (8.2%) subjects died. In univariate analyses, entry mycobacterial infection, OI number, hospitalization, low albumin, low hemoglobin, lower CD4, and higher IL-8 and sTNFrII levels and lower IL-17 levels were associated with mortality. In the combined model using both clinical and immunologic parameters, the presence of an entry mycobacterial infection and higher sTNFrII levels were significantly associated with death.

Conclusions—In the ART era, clinical risk factors for death previously identified in the pre-ART era remain predictive. Additionally, activation of the innate immune system is associated with an increased risk of death following an acute OI.

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Conflict of Interest Statement

The authors report no conflicts related to this work.

Keywords

HIV Infections/complications; mortality; opportunistic infections

INTRODUCTION

Despite the availability of antiretroviral therapy (ART), a substantial proportion of individuals with HIV access medical care with advanced immunosuppression and develop opportunistic infections (OIs)¹. Studies in the pre-ART era evaluated clinical factors associated with death during OIs^{2–4}; similar studies have been conducted more recently in resource-limited settings^{5–8}. However, there are few risk factor analyses for death after an acute OI in developed world settings in the ART era. Given the potency of current regimens, it is unclear whether previously identified clinical predictors remain relevant today. In addition to clinical factors, soluble inflammatory markers have been independently associated with mortality and other adverse outcomes in both treated and untreated populations^{8–11}, reflecting that host responses to HIV may also contribute to the pathogenesis of disease progression.

AIDS Clinical Trials Group (ACTG) Study A5164 evaluated the optimal timing of ART during an acute OI and found that early ART lead to a reduction in the composite outcome of death/AIDS progression in the ensuing year¹². Here, we investigate the clinical and immunologic predictors of death during this study

METHODS

ACTG A5164 Study Design

ACTG A5164 was a 48-week randomized study of early versus deferred ART that enrolled 282 HIV-1 infected participants (262 from the United States or Puerto Rico; 20 from South Africa) with an AIDS-related OI, excluding tuberculosis (TB). Subjects were randomized 1:1 within 14 days of starting antimicrobial therapy for the entry OI to receive ART immediately upon study entry or to have ART deferred for at least 4 weeks after randomization. Participants in the early arm initiated ART after a median of 12 days of treatment for their acute OI, while participants in the deferred arm initiated ART at a median of 45 days after initiation of OI treatment.

Statistics

Using univariate Cox models, we evaluated the following entry clinical parameters and entry plasma marker levels as predictors of time to death: age, sex, race/ethnicity, hospitalization at entry, OI number and type, early vs. deferred ART, hemoglobin, albumin, white blood cell (WBC) count, total lymphocyte count, CD4+ T-cell count, HIV-1 RNA level, IL-1, IL-2, IL-6, IL-8, IL-10, IL-15, IL-17, shed tumor necrosis factor receptor II (sTNFrII), TNF, and IFN γ . Participants who were alive at last contact were censored at that contact date, with one exception; one study participant died of a cocaine overdose after week 48 of the study, but before his final study visit, and was categorized as "alive" and censored at week 48. Biomarker levels in cryopreserved plasma were assessed using a Bioplex system (Bio-Rad,

Hercules, CA). The choice of plasma markers was based on their inclusion in this off-the-shelf multiplex assay that assessed multiple immunologic pathways potentially implicated in the pathogenesis of HIV disease. We $\log_{10}$ transformed the values of plasma markers to approximate normal distributions.

Variables identified in univariate analyses as being associated with mortality, using a liberal screening criterion of $p < 0.20$, were considered potential candidate variables in multivariable modeling. We used forward and backward selection and limited our models to no more than two dependent variables to avoid overfitting. We created models with only clinical parameters, only plasma markers, and combining one of each. We used log likelihood chi-square tests to compare the models' fit. For the above analyses, we evaluated significance at $p < 0.05$ and did not correct for multiple comparisons.

Ethics

CTG A5164 study participants provided written informed consent for future testing of their stored samples. The Institutional Review Board at the Keck School of Medicine approved the analysis plan of the stored samples.

RESULTS

Baseline Characteristics

Participants enrolled in the primary study had a median age of 38 years, were primarily men (85%) with a median CD4+ T-cell count of 29 cells/uL and HIV RNA level of 5.1 $\log_{10}$ copies/mL (Table 1). The most common OI at study entry was *Pneumocystis jirovecii* pneumonia (PCP) (64%). The median number of OIs per study participant at entry was 2 (IQR 1,3) with 52% of participants having 2 or more entry OIs. Median baseline plasma marker levels are reported in Table 1.

Mortality

Twenty-three of 282 (8.2%) study subjects died at a median of 9.1 weeks (IQR: 3.3, 32.3) after study entry. The listed causes of death were primarily HIV-related opportunistic infections or malignancies including PCP ($n=4$), mycobacterial infection (4), lymphoma (4), sepsis (3), cryptococcal meningitis (2), histoplasmosis (1), invasive aspergillosis (1), and cirrhosis (1). The cause of death in three individuals was not determined.

In univariate analyses, subjects hospitalized at entry (HR=3.7; 95% CI: 1.6–8.5; $p=0.002$), with multiple OIs (HR=2.2 per additional OI; 95% CI: 1.4–3.5; $p=0.001$), and with an entry mycobacterial infection (HR=5.9; 95% CI: 2.3–14.9; $p<0.001$) had shorter survival times, while those with entry PCP had a lower risk of mortality (HR=0.42; 95% CI=0.19–0.97; $p=0.041$). The presence of anemia, low albumin, low lymphocyte count, and low CD4+ T-cell count were also associated with mortality (Table 2). Age, sex, and race/ethnicity were not associated with time to death.

For plasma inflammatory markers, baseline elevated levels of IL-8 and sTNFrII and low IL-17 levels were associated with mortality in univariate analyses (Table 2). There was no association between IL-6 levels and death.

In multivariable modeling using only clinical characteristics, mycobacterial infection at entry and low CD4+ T-cell count were associated with time to death ($p<0.001$ and $p=0.037$, respectively; Table 3). Inclusion of low CD4+ T-cell count as an independent variable in this model provided a statistically significant improvement over the model that only included mycobacterial infection ($p<0.001$). In a model that included only plasma markers, higher sTNFrII and lower IL-17 levels were associated with death ($p=0.006$ and $p=0.035$, respectively). In a combined model, the presence of an entry mycobacterial infection and higher sTNFrII levels were strongly associated with death ($p<0.001$ and $p=0.006$, respectively).

DISCUSSION

In this secondary analysis of a large randomized study of the timing of ART during an OI, we found in univariate analyses that clinical markers of advanced HIV including the presence of mycobacterial disease, hospitalization, anemia, and low CD4+ T-cell count are associated with an increased risk of death over the ensuing 48 weeks. In multivariable analysis, the presence of mycobacterial disease and a lower CD4+ T-cell count at entry were strong risk factors for death in the ensuing year after the acute OI. Additionally, we found higher levels of IL-8 and sTNFrII and lower levels of IL-17 were associated with an increased risk for death during a non-TB OI.

There are few recent data evaluating clinical risk factors for death during an acute OI in the developed world and recently published studies still often include patients treated in the pre-ART era^{13,14}. Our results are consistent with earlier studies in PCP and cryptococcal meningitis that showed that markers of more advanced HIV disease such as low albumin¹⁵, hemoglobin^{16,17}, and total lymphocyte count¹⁸ predicted mortality. In the ART era, a recent study in HIV/TB did not show a relationship between lower CD4+ T-cell count and death⁸. However, CAMELIA, a randomized study of the timing of ART in HIV-TB co-infection conducted in Cambodia, did find that markers of more advanced HIV disease predicted death over 48 weeks¹⁹. Other studies have also reported increased mortality in older individuals, in women, and in patients of color^{19–21}. We did not find evidence of these health outcome disparities during ACTG A5164, potentially related to similar access to ART and medical care among study participants.

Biomarkers are increasingly used to better understand the pathophysiology of HIV infection^{9,22–25}. We found lower IL-17 levels predicted death. On the other hand, we and others have reported that higher IL-17 levels predicted the development of Immune Reconstitution Inflammatory Syndrome (IRIS) during an OI^{10,26}, suggesting that there are distinct biomarker profiles that can characterize those at higher risk for dying versus for the development of IRIS. In normal immune homeostasis, pro-inflammatory Th17 responses (i.e., IL-17) are counterbalanced by regulatory T-cell activity²⁷. The lack of a pro-inflammatory Th17 response appears to place individuals at greater risk for death during an acute OI. Boulware and colleagues reported that a rising level of IL-17 predicted death in a cohort of individuals with cryptococcal meningitis²⁶. Given that many of the deaths during ACTG A5164 occurred early, we were not able to investigate the predictive value of the IL-17 trajectory within our cohort.

Our findings that baseline elevated IL-8 and sTNFrII predicted death provide further support for the role of an activated innate immune system in HIV disease progression^{24,28–30}. IL-8 is a chemokine produced by macrophages and epithelial cells that induces neutrophil chemotaxis. TNF is a cytokine secreted primarily by activated macrophages that stimulates the acute phase reaction. The more stable sTNFrII is an indicator of the biological effects of the TNF system.

In individuals with advanced HIV but free of diagnosed OIs at baseline, Boulware and colleagues found higher IL-8 levels one month post-ART were associated with death and AIDS progression⁹. Other investigators have reported an association between higher IL-8 levels and death in a cohort of patients with HIV and hepatitis B or C co-infection³¹. A study in PCP in the pre-ART era reported an association between higher IL-8 levels in bronchoalveolar lavage fluid and death³².

Multiple biomarker studies have identified a higher IL-6 level as a predictor of subsequent mortality^{9,22,23}. A number of explanations could account for the lack of association between IL-6 levels and death found in our study. We may have been underpowered to find an effect. IL-6 was marginally increased in individuals who died compared to those who did not but the difference did not reach statistical significance. Additionally, others have reported that ELISA and single platform assays may be superior to multiplex bead assays when evaluating the significance of IL-6 levels³³. Many studies that reported a relationship between IL-6 and death were in individuals asymptomatic at baseline^{9,22–25}, and the presence of elevated levels of IL-6 may reflect the presence of an undiagnosed OI or vascular disease in these patients. In this study, baseline elevated IL-6 was not associated with a higher risk for death, perhaps because all participants had an active OI at baseline. Similarly, in a recent study of patients with HIV-TB co-infection, baseline IL-6 level was also not associated with death⁸.

There are several limitations to our study that deserve highlighting. Our findings may only apply to death in those individuals presenting with an acute non-TB OI, and it may not be appropriate to extrapolate these results to the prediction of death in patients initiating ART who have TB or who are asymptomatic. Additionally, as this data was derived from a clinical trial population, the generalizability of our results to other settings is unknown. Due to the relatively few deaths, we may have been underpowered to detect some important associations. By including a heterogeneous sample of patients, factors underlying death from specific pathogens may not have been elucidated. Study data were not collected on hepatitis C status or active injection drug use, and it is possible that these factors may also have been associated with death if the data were available and analyzed in our study.

Corticosteroids inhibit cytokine production and were not assigned randomly within ACTG A5164, being generally given to those participants with severe PCP. Thus, our biomarker results could have been confounded by corticosteroid usage. There was substantial collinearity in both the clinical and immunologic data within this study, and clinical and immunologic variables other than those that we presented were also found to be significantly associated with death in multivariable analysis. We selected the models with the strongest correlations that we felt could best be applied clinically and best captured the underlying

pathophysiology but without specifically comparing the strength of fit of each model. We limited our multivariable models to two dependent variables to avoid overfitting. However, it is possible that in doing so we failed to identify variables that were masked in univariable analyses that would have been unmasked after co-adjustment for other factors. Finally, since this was an analysis with multiple comparisons, marginally significant associations should be interpreted cautiously.

CONCLUSION

In summary, we found that mortality among participants who presented with an OI in developed-world settings was still substantial. Despite the provision of ART and the availability of advanced medical care, previously identified markers of HIV disease severity remain predictors of death, and individuals with these characteristics should be closely monitored for clinical deterioration. Additionally, increased levels of innate immune activation place individuals at higher risk of death during an acute OI.

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References

1. Mocroft A, Lundgren JD, Sabin ML, et al. Risk Factors and Outcomes for Late Presentation for HIV-Positive Persons in Europe: Results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). *PLoS medicine*. 2013 Sep.10(9):e1001510. [PubMed: 24137103]
2. Harris JE. Improved short-term survival of AIDS patients initially diagnosed with *Pneumocystis carinii* pneumonia, 1984 through 1987. *JAMA : the journal of the American Medical Association*. 1990 Jan 19; 263(3):397–401. [PubMed: 2294306]
3. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *The New England journal of medicine*. 1997 Jul 3; 337(1):15–21. [PubMed: 9203426]
4. Jabs DA, Gilpin AM, Min YI, Erice A, Kempen JH, Quinn TC. HIV and cytomegalovirus viral load and clinical outcomes in AIDS and cytomegalovirus retinitis patients: Monoclonal Antibody Cytomegalovirus Retinitis Trial. *AIDS (London, England)*. 2002 Apr 12; 16(6):877–887.
5. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS (London, England)*. 2009 Mar 27; 23(6):701–706.
6. Varma JK, Nateniyom S, Akksilp S, et al. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. *BMC infectious diseases*. 2009; 9:42. [PubMed: 19364398]
7. Croda J, Croda MG, Neves A, De Sousa dos Santos S. Benefit of antiretroviral therapy on survival of human immunodeficiency virus-infected patients admitted to an intensive care unit. *Critical care medicine*. 2009 May; 37(5):1605–1611. [PubMed: 19325488]
8. Ravimohan S, Tamuhla N, Steenhoff AP, et al. Early Immunologic Failure is Associated With Early Mortality Among Advanced HIV-Infected Adults Initiating Antiretroviral Therapy With Active

- Tuberculosis. *The Journal of infectious diseases*. 2013 Dec; 208(11):1784–1793. [PubMed: 23908475]
9. Boulware DR, Hullsiek KH, Puroon CE, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. *The Journal of infectious diseases*. 2011 Jun 1; 203(11):1637–1646. [PubMed: 21592994]
 10. Grant PM, Komarow L, Lederman MM, et al. Elevated Interleukin 8 and T-Helper 1 and THelper 17 Cytokine Levels Prior to Antiretroviral Therapy in Participants Who Developed Immune Reconstitution Inflammatory Syndrome During ACTG A5164. *The Journal of infectious diseases*. 2012 Dec; 206(11):1715–1723. [PubMed: 23002445]
 11. Kalayjian RC, Machekano RN, Rizk N, et al. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV disease progression in subjects treated with highly active antiretroviral therapy. *The Journal of infectious diseases*. 2010 Jun 15; 201(12):1796–1805. [PubMed: 20446847]
 12. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS one*. 2009; 4(5):e5575. [PubMed: 19440326]
 13. Armstrong-James D, Copas AJ, Walzer PD, Edwards SG, Miller RF. A prognostic scoring tool for identification of patients at high and low risk of death from HIV-associated *Pneumocystis jirovecii* pneumonia. *International journal of STD & AIDS*. 2011 Nov; 22(11):628–634. [PubMed: 22096046]
 14. Fanjul F, Riveiro-Barciela M, Gonzalez J, et al. Evaluation of progressive multifocal leukoencephalopathy treatments in a Spanish cohort of HIV-infected patients: do protease inhibitors improve survival regardless of central nervous system penetration-effectiveness (CPE) score? *HIV medicine*. 2013 May; 14(5):321–325. [PubMed: 23217049]
 15. Wachter RM, Russi MB, Bloch DA, Hopewell PC, Luce JM. *Pneumocystis carinii* pneumonia and respiratory failure in AIDS. Improved outcomes and increased use of intensive care units. *The American review of respiratory disease*. 1991 Feb; 143(2):251–256. [PubMed: 1990936]
 16. Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985–2006. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2008 Feb 15; 46(4):625–633. [PubMed: 18190281]
 17. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014 Mar; 58(5):736–745. [PubMed: 24319084]
 18. Bennett CL, Weinstein RA, Shapiro MF, et al. A rapid preadmission method for predicting inpatient course of disease for patients with HIV-related *Pneumocystis carinii* pneumonia. *American journal of respiratory and critical care medicine*. 1994 Dec; 150(6 Pt 1):1503–1507. [PubMed: 7952607]
 19. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIVinfected adults with tuberculosis. *The New England journal of medicine*. 2011 Oct 20; 365(16):1471–1481. [PubMed: 22010913]
 20. Levine RS, Briggs NC, Kilbourne BS, et al. Black-White mortality from HIV in the United States before and after introduction of highly active antiretroviral therapy in 1996. *American journal of public health*. 2007 Oct; 97(10):1884–1892. [PubMed: 17761583]
 21. Lemly DC, Shepherd BE, Hulgán T, et al. Race and sex differences in antiretroviral therapy use and mortality among HIV-infected persons in care. *The Journal of infectious diseases*. 2009 Apr 1; 199(7):991–998. [PubMed: 19220139]
 22. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS medicine*. 2008 Oct 21; 5(10):e203. [PubMed: 18942885]
 23. McDonald B, Moyo S, Gabaitiri L, et al. Persistently elevated serum interleukin-6 predicts mortality among adults receiving combination antiretroviral therapy in Botswana: results from a clinical trial. *AIDS research and human retroviruses*. 2013 Jul; 29(7):993–999. [PubMed: 23590237]

24. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *The Journal of infectious diseases*. 2011 Mar 15; 203(6):780–790. [PubMed: 21252259]
25. Erlandson KM, Allshouse AA, Jankowski CM, et al. Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. *The Journal of infectious diseases*. 2013 Jul 15; 208(2):249–259. [PubMed: 23559466]
26. Boulware DR, Meya DB, Bergemann TL, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS medicine*. 2010; 7(12):e1000384. [PubMed: 21253011]
27. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature*. 2006 May 11; 441(7090):235–238. [PubMed: 16648838]
28. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. *JAMA : the journal of the American Medical Association*. 2012 Jul 25; 308(4):379–386. [PubMed: 22820791]
29. Barber DL, Andrade BB, Sereti I, Sher A. Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none. *Nature reviews. Microbiology*. 2012 Feb; 10(2):150–156.
30. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature medicine*. 2006 Dec; 12(12):1365–1371.
31. Andrade BB, Hullsiek KH, Boulware DR, et al. Biomarkers of inflammation and coagulation are associated with mortality and hepatitis flares in persons coinfecting with HIV and hepatitis viruses. *The Journal of infectious diseases*. 2013 May 1; 207(9):1379–1388. [PubMed: 23335804]
32. Benfield TL, Vestbo J, Junge J, Nielsen TL, Jensen AB, Lundgren JD. Prognostic value of interleukin-8 in AIDS-associated *Pneumocystis carinii* pneumonia. *American journal of respiratory and critical care medicine*. 1995; 151(4):1058–1062. 1995/04/01. [PubMed: 7697231]
33. Cozzi-Lepri A, French MA, Baxter J, et al. Resumption of HIV replication is associated with monocyte/macrophage derived cytokine and chemokine changes: results from a large international clinical trial. *AIDS (London, England)*. 2011 Jun 1; 25(9):1207–1217.

Table 1

Baseline Clinical Characteristics and Plasma Marker Levels in A5164 Study Subjects (n=282 for clinical characteristics; n=278 for plasma markers)

Characteristics	
Median Age (IQR)	38 (32, 44) years
Sex	85% (241/282)
Male	15% (41/282)
Female	
Race/Ethnicity	37% (103/282)
Black	36% (101/282)
Latino	23% (64/282)
White	5% (14/282)
Other	
Entry Opportunistic Infection	64% (181/282)
Pneumocystis Pneumonia	15% (41/282)
Cryptococcosis	15% (41/282)
Bacterial Infection	6% (18/282)
Mycobacterial infection	5% (15/282)
Toxoplasmosis	4% (10/282)
Histoplasmosis	2% (6/282)
Cytomegalovirus	52% (148/282)
Multiple Opportunistic Infections	
Median CD4+ T cells -cells/ μ L (IQR)	29 (10–55)
Median HIV-1 RNA -log ₁₀ copies/mL (IQR)	5.1 (4.7–5.6)
Median IL-1 Level -pg/mL (IQR)	0.61 (0.25–2.3)
Median IL-2 Level -pg/mL (IQR)	1.8 (0.89–5.3)
Median IL-6 Level -pg/mL (IQR)	9.1 (2.4–30.6)
Median IL-8 Level -pg/mL (IQR)	9.8 (5.7–19.7)
Median IL-10 Level -pg/mL (IQR)	15.1 (6.7–33.0)
Median IL-15 Level -pg/mL (IQR)	3.2 (1.6–6.9)
Median IL-17 Level -pg/mL (IQR)	2.1 (0.75–6.0)
Median TNF Level -pg/mL (IQR)	8.1 (4.2–16.2)
Median sTNFrII Level -pg/mL (IQR)	4.5 (2.9–6.6)
Median IFN γ Level -pg/mL (IQR)	5.1 (1.6–20.1)

Table 2

Univariate Cox Models of Baseline Clinical Characteristics and Selected Plasma Markers and Their Association with Death

Clinical Characteristic/ Plasma Marker	Hazard Ratio (95% CI)	p-value
Age (≥ 40 year vs. <40 years)	1.6 (0.67, 3.7)	0.30
Male vs. Female	1.8 (0.42, 7.6)	0.44
White vs. Other	0.95 (0.37, 2.4)	0.91
Hospitalized at entry	3.7 (1.6, 8.5)	0.002
Number of Opportunistic Infections at entry	2.2 (1.4, 3.5)	0.001
Entry Mycobacterial infection	5.9 (2.3, 14.9)	<0.001
<i>Pneumocystis jirovecii</i> pneumonia	0.42 (0.19, 0.97)	0.041
Randomized Treatment Assignment (Early vs. Deferred)	0.66 (0.29, 1.5)	0.33
Hemoglobin <10 g/dL	2.8 (1.1, 6.7)	0.025
Albumin <2.5 mg/dL	3.6 (1.3, 10.1)	0.015
Lymphocytes <600 cell/μL	4.8 (1.7, 13.3)	0.002
CD4+ T-cell count (per 10 cell/μL decrement)	1.3 (1.0, 1.5)	0.025
Entry HIV RNA > 5 log ₁₀ copies/mL	2.6 (0.97, 7.0)	0.06
IL-6 Level (per 1 log pg/mL higher)	1.2 (0.70, 2.1)	0.51
IL-8 Level (per 1 log ₁₀ pg/mL higher)	3.0 (1.3, 6.8)	0.011
IL-10 Level (per 1 log ₁₀ pg/mL higher)	1.7 (0.83, 3.3)	0.15
IL-15 Level (per 1 log ₁₀ pg/mL higher)	1.3 (0.59, 3.0)	0.49
IL-17 Level (per 1 log ₁₀ pg/mL higher)	0.52 (0.28, 0.96)	0.035
TNFα Level (per 1 log ₁₀ pg/mL higher)	2.1 (0.92, 5.0)	0.08
sTNFrII Level (per 1 log ₁₀ pg/mL higher)	9.2 (1.9, 44.4)	0.006
IFNγ Level (per 1 log ₁₀ pg/mL higher)	0.69 (0.38, 1.2)	0.21

Table 3

Multivariate Cox Models Predicting Mortality with Models using Only Clinical Parameters, Only Immune Markers, or a Combination of Bot

	Parameter	Hazard Ratio (95% CI)	p-value
With Clinical Parameters	Mycobacterial infection	5.1 (2.0, 13.1)	<0.001
	Entry CD4+ T-cell count (per 10 cell/ μ L decrement)	1.2 (1.0, 1.5)	0.037
With Immune Markers	sTNFrII Level (per 1 log pg/mL higher)	9.6 (1.9, 47.9)	0.006
	IL-17 Level (per 1 log ₁₀ pg/mL higher)	0.52 (0.28, 0.96)	0.035
Combined	Mycobacterial infection	6.0 (2.3, 15.6)	<0.001
	sTNFrII Level (per 1 log ₁₀ pg/mL higher)	7.3 (1.8, 30.2)	0.006