

# Comparison of Prognostic Importance of Latest CD4+ Cell Count and HIV RNA Levels in Patients with Advanced HIV Infection on Highly Active Antiretroviral Therapy

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The comparative prognostic importance of latest plasma HIV RNA levels (viral loads) and CD4+ cell counts among patients prescribed highly active antiretroviral therapy (HAART) has not been well characterized. **Method:** We assessed the prognostic value of latest CD4+ cell counts and latest viral loads for progression to AIDS or death and explored their interaction among 432 HIV-infected persons with advanced HIV who were prescribed a protease inhibitor (PI) as their first HAART regimen. **Results:** Pre-HAART median CD4+ cell count and viral load were 41 cells/mm<sup>3</sup> and 126,331 copies/mL, respectively. After 12 months of HAART, the median CD4+ cell count was 154 cells/mm<sup>3</sup>; 39% of patients had a viral load of 400 copies/mL or lower. Over a median follow-up of 33 months, 109 (25%) of the 432 patients experienced an AIDS event or died. The hazard ratio for AIDS or death for those with latest CD4+ cell count <50 cells/mm<sup>3</sup> versus ≥200 cells/mm<sup>3</sup> was 13.9 (95% CI 6.5 to 29.7) without adjustment for latest viral load measurements and 9.5 (95% CI 4.0 to 22.5) after adjustment for latest viral load. In contrast, the hazard ratio for AIDS or death for those with viral load ≥100,000 versus <400 copies/mL was 4.2 (95% CI 2.3 to 7.7) without adjustment for latest CD4+ level and 1.2 (95% CI 0.6 to 2.4) with adjustment for latest CD4+ cell count. **Conclusion:** We conclude that when latest CD4+ cell count and viral load are considered separately, both are significantly related to AIDS or death; when these markers are jointly considered, the association of viral load with AIDS or death is substantially diminished. Latest CD4+ levels are more strongly related to AIDS or death than latest viral load levels in patients on HAART. **Key words:** advanced HIV, AIDS risk, CD4+ cell count, HAART

CD4+ cell count and plasma viral load are used commonly to assess risk of disease progression and to monitor the effects of treatment. The prognostic importance of both markers has been evaluated in cohorts that vary by use of treatment regimens and stage of disease. In 1996, the Multicenter AIDS Cohort Study (MACS) quantified the prognostic importance of plasma HIV RNA levels (viral loads) and CD4+ cell counts, measured prior to the initiation of antiretroviral treatment, and concluded that viral load was a better predictor of progression to AIDS and death than CD4+ cell count.<sup>1</sup> Over the median follow-up

of 10 to 11 years, few members of this cohort had been treated with antiretroviral regimens that would be considered "highly active" by today's standards. More recently, the CASCADE

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Collaboration quantified the short-term risk of AIDS associated with latest values of CD4+ cell counts and viral loads among individuals who were antiretroviral naïve or had taken zidovudine monotherapy. They found that latest CD4+ cell counts and viral loads were both significant predictors of the development of AIDS over the next 6 months.<sup>2</sup>

The relative importance of CD4+ cell counts and viral loads for predicting progression to AIDS or death also has been investigated when these markers were measured immediately prior to initiation of highly active antiretroviral therapy (HAART). In an overview that involved 13 cohorts from around the world, CD4+ cell count at the initiation of HAART was found to be a stronger predictor of AIDS or death than viral load.<sup>3</sup> A graded relationship with CD4+ cell count was observed; there was an increasingly greater risk of AIDS or death with lower CD4+ cell count. A corresponding relationship with viral loads was not observed. Similar findings have been reported by smaller cohort studies, some of which were included in the previously mentioned overview.<sup>4-9</sup>

The comparative prognostic importance of CD4+ cell count and viral load measured after initiating HAART has been explored only to a limited extent.<sup>9-15</sup> One report involving several prospective studies found that 6 months after starting HAART current CD4+ cell counts and viral loads, but not baseline values, were strongly associated with subsequent progression of disease.<sup>15</sup> Both CD4+ cell counts and viral loads at 6 months were associated with AIDS or death in a graded relationship. For death, there was no difference in risk among persons with viral loads <100,000 copies/mL. In a similar investigation involving a smaller cohort, Lewden et al. reported a significant association between CD4+ cell counts measured 4 months after initiating HAART and mortality, but no association between 4-month viral loads and mortality.<sup>12</sup>

Four studies have used latest values of CD4+ count and viral load instead of only those within 4 to 6 months after initiating HAART for studying future risk of clinical AIDS and death.<sup>10,13,14,16</sup> In each of these studies, both latest CD4+ cell counts and viral loads predicted disease progression. The study by Miller and colleagues,<sup>10</sup> in particular, suggested that the highest risk of disease progression occurred among those individuals with CD4+ cell counts <50 cells/mm<sup>3</sup> whose viral load level was >1,000,000

copies/mL. However, in none of the studies was the relative strength of the associations quantified (e.g., comparison of hazard ratios associated with specific percentiles of the latest CD4+ cell count and viral load level distributions, with and without adjustment for the other variable). Furthermore, the possibility of an interaction (e.g., a stronger association of latest CD4+ cell counts with disease progression among those with low versus high viral loads) was not fully explored.

The purpose of our study is to assess the prognostic importance of latest CD4+ cell counts to latest viral loads and to determine whether the prognostic value of latest CD4+ cell counts is similar in persons who are viremic versus those who are not in a cohort of HIV-infected persons with CD4+ cell counts  $\leq$ 200 cells/mm<sup>3</sup> at the time of initiation of HAART.

## METHOD

### Study Design

In January 1997, the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the Canadian HIV Trials Network (CTN) initiated a randomized trial of two protease inhibitor (PI)-based regimens, one including nelfinavir (NFV) and one including zidovudine (ZDV) and zalcitabine (ZCZD), among HIV-infected patients with advanced HIV disease (CPCRA 042/045; the NvR study). The choice of other antiretroviral (AR) agents used in the NFV- and ZDV/ZCZD-based regimens was not specified. To be eligible for the study, persons had to have CD4+ cell counts <200 cells/mm<sup>3</sup>. Persons who previously had taken PIs, other than zalcitabine, were not eligible. During the study, patients could switch to other ARs as clinically indicated. The primary endpoint of the trial was AIDS or death. Participants were allowed to change or discontinue therapy at any time throughout the trial. The main trial results have been described.<sup>17</sup>

Of the 775 patients randomized, 610 enrolled in a virologic substudy and had regular viral load measurements during follow-up (see later discussion). Eight of these patients were missing a baseline viral load or CD4+ cell count; 7 patients did not have any follow-up measurements of CD4+ cell count and viral load; 30 patients had previously been prescribed a nonnucleoside reverse transcriptase inhibitor (NNRTI), and 133 patients had taken zalcitabine. These patients have been excluded, leav-

ing 432 patients who are the subject of this report. Median follow-up of this cohort was 33 months.

### Measurements

For patients in the virologic substudy, plasma HIV RNA levels (viral loads) and CD4+ cell counts were measured prior to randomization (baseline), at 1 and 4 months following randomization, and every 4 months thereafter through August 2000. Viral loads were centrally measured by quantitative RT-PCR (Roche Molecular Systems, Alameda, California, and Branchburg, New Jersey, USA). The lower limit of detection for the assay used was 400 copies/mL.<sup>18</sup> CD4+ cell counts were measured locally. For this study, follow-up for progression to AIDS or death was censored on October 1, 2000. Clinical events were reviewed by a committee, blinded to treatment group, using previously described procedures.<sup>19</sup>

### Statistical Methods

Proportional hazards regression models with strata corresponding to trial network (CTN or CPCRA) were used to assess the relationships of latest viral load and CD4+ cell count with two endpoints: (1) progression to AIDS or death, and (2) death.<sup>20</sup> The two randomly assigned treatment groups were pooled for this analysis as the findings did not vary by treatment group. Hazard ratios for each endpoint are given for four categories of latest CD4+ cell counts (<50, 50–99, 100–199, and  $\geq 200$ + cells/mm<sup>3</sup>) and four categories of latest viral loads ( $\leq 400$ , 401–9,999, 10,000–99,999, and  $\geq 100,000$ + copies/mL). To obtain event rate estimates, person-years for each CD4+ and viral load category were accumulated during follow-up. In addition, to standardize the scale for comparing latest CD4+ cell counts and latest viral loads, an analysis was performed to obtain hazard ratios for the third (highest) versus first (lowest) tertile of latest viral loads and for the first (lowest) versus third (highest) tertile of latest CD4+ cell counts. These hazard ratios and the corresponding two-degrees of freedom (*df*) chi-square statistics are compared. Tertiles for latest viral loads and CD4+ cell counts were determined by considering all follow-up readings beginning with the 1-month follow-up visit for each patient. For analyses based on continuous measurements, viral loads were log<sub>10</sub> transformed and levels <400 cop-

ies/mL were set at 400 copies/mL; CD4+ cell counts were square-root transformed. For the latest viral loads and CD4+ cell counts, measurements were updated every 4 months and considered as time-dependent covariates. Two models were fit for each marker: (1) a model in which latest CD4+ cell counts and latest viral loads were entered separately in the model along with baseline predictors—baseline CD4+ cell counts after square-root transformation, baseline viral loads after log<sub>10</sub> transformation, age, gender, race, risk group (injection drug use versus other or missing [5 patients], prior AIDS, and prior use of antiretroviral treatment); and (2) a model in which latest values of both markers were included as well all of the baseline covariates. Models investigating the association of baseline levels of these markers with progression to AIDS or death are also considered.

To assess whether the relationship of latest CD4+ cell count and each endpoint varied by level of latest viral load, interaction terms were included in the proportional hazards regression model. Specifically, we assessed whether the hazard ratios associated with different CD4+ cell count levels were consistent for patients with latest viral load levels  $\leq 400$ , 401–9,999, and  $\geq 10,000$ + copies/mL. *P* values corresponding to whether hazard ratios differ from 1.00 and 95% confidence intervals (CIs) are cited. Rates cited are per 100 person-years.

## RESULTS

### Baseline Characteristics

Thirty-three percent of the 432 patients considered in the report were antiretroviral naïve. Of the remaining 67%, many added the PI (NFV or RTV) to ongoing therapy, without modifying background ARs. Nineteen percent were female; 62% were Black or Latino/Latina. Median baseline CD4+ cell count and viral load were 51 cells/mm<sup>3</sup> and 126,331 copies/mL (5.1 log<sub>10</sub> copies/mL), respectively. Forty-nine percent of patients had experienced an AIDS-defining opportunistic infection or malignancy prior to entering the study (see Table 1).

### Follow-up Values of Viral Load and CD4+ Cell Count

Figure 1 gives median CD4+ cell counts and percent of patients with viral loads <400 copies/mL

Table 1. Baseline characteristic, progression to AIDS or death, and death

	No. of patients	AIDS or death			Death		
		No. of events	Rate <sup>a</sup>	HR <sup>b</sup> (95% CI)	No. of deaths	Rate <sup>a</sup>	HR <sup>b</sup> (95% CI)
Age (years)							
<35	141	39	11.7	1.00	19	4.9	1.00
35-44	198	50	10.8	0.84 (0.54-1.31)	29	5.6	1.10 (0.59-2.08)
≥45	93	20	9.1	0.81 (0.46-1.42)	9	3.7	0.84 (0.37-1.94)
Gender							
Men	352	86	10.3	1.00	44	4.7	1.00
Women	80	23	12.4	1.24 (0.77-1.98)	13	6.1	1.42 (0.75-2.69)
Race							
White	147	26	7.2	1.00	12	3.0	1.00
Non-white	285	83	12.6	1.83 (1.12-2.99)	45	6.0	2.23 (1.07-4.63)
Risk group							
Injection-drug use	90	35	18.6	2.16 (1.40-3.34)	20	8.9	2.33 (1.28-4.25)
Other	342	74	8.9	1.00	36	4.0	1.00
Prior AIDS							
Yes	213	68	14.4	1.75 (1.18-2.61)	37	6.6	2.03 (1.15-3.59)
No	219	41	7.5	1.00	20	3.4	1.00
Baseline CD4+ cell count (cells/mm <sup>3</sup> )							
<25	154	53	15.6	1.00	25	6.1	1.00
25-49	86	24	11.8	0.83 (0.51-1.36)	13	5.6	0.94 (0.47-1.88)
50-99	123	17	5.4	0.40 (0.23-0.70)	10	2.9	0.52 (0.24-1.10)
≥100	69	15	9.6	0.65 (0.36-1.18)	9	5.4	0.85 (0.38-1.89)
Baseline viral load (copies/mL)							
<10,000	85	18	8.7	1.00	11	4.9	1.00
10,000-99,999	109	28	11.0	1.23 (0.66-2.26)	15	5.1	1.05 (0.46-2.36)
≥100,000	238	63	11.3	1.41 (0.80-2.48)	31	4.9	1.40 (0.67-2.93)
Prior nucleoside therapy							
Yes	288	86	12.4	1.84 (1.12-3.05)	53	6.8	6.27 (2.19-17.97)
No (treatment naïve)	144	23	7.1	1.00	4	1.1	1.00

<sup>a</sup>Per 100 person-years. <sup>b</sup>HR = hazard ratio adjusted for all baseline characteristics in the table.



### Risk of Progression to AIDS or Death and Risk of Death Associated with Latest CD4+ Cell Count and Viral Load

All of the baseline variables cited previously and shown in Table 1 were considered as covariates in the analyses carried out investigating the prognostic importance of latest values of CD4+ cell counts and viral loads. The association of progression to AIDS or death with latest values of CD4+ cell counts and viral loads are summarized in Table 2.

A strong association of CD4+ cell count with AIDS or death was evident after adjustment for baseline covariates (first, second, and third columns) and after adjustment for baseline covariates and latest value of viral load (last two columns). Adjustment for viral load had a modest effect on the estimated hazard ratios for different CD4+ cell count categories. In contrast, adjustment for latest values of CD4+ cell count had a more pronounced effect on the association of latest values of viral load with AIDS or death. In the analysis adjusting for latest levels of CD4+ cell count, none of the hazard ratios for the viral load categories differed significantly from one.

The stronger association of CD4+ cell count than viral load with AIDS or death was also evident when tertiles were compared. In separate models that included follow-up and CD4+ cell count and viral load levels, the hazard ratio for AIDS or death for the lowest (<91 cells/mm<sup>3</sup>) versus highest (≥203 cells/mm<sup>3</sup>) tertile of latest CD4+ cell count was 10.5 (95% CI 4.8 to 22.7;  $\chi^2_2 = 69.4$ ) after adjustment for baseline covariates. The corresponding hazard ratio for highest (19,128 copies/mL) versus lowest (≤400 copies/mL) tertile of viral load was 3.7 (95% CI 2.1 to 6.5;  $\chi^2_2 = 34.8$ ). When indicators for CD4+ tertiles were added to the model with viral load tertiles, the model fit was substantially improved ( $\chi^2_2 = 42.6$ ); in contrast with the addition of viral load tertiles to the model with CD4+ tertiles, the corresponding  $\chi^2_2$  was only 8.0. When continuous CD4+ cell count, square-root transformed, and viral load, log<sub>10</sub> transformed, were included in the model, both were significantly associated with progression to AIDS or death ( $p < .001$  and  $p = .008$ , respectively), but the strength of the association was stronger for CD4+ count than viral load.

Of the 109 patients who developed an AIDS event or died, only 4 (3.7%) had CD4+ cell counts ≥ 250 cells/mm<sup>3</sup> immediately before the event, 5 (4.6%)

had CD4+ cell counts between 200–249 cells/mm<sup>3</sup>, and 14 (12.8%) had CD4+ cell counts between 100–199 cells/mm<sup>3</sup>. The remaining patients had CD4+ counts below 100 cells/mm<sup>3</sup>. The average of the latest viral loads for the nine patients with CD4+ cell counts ≥200 cells/mm<sup>3</sup> was 4.0 log<sub>10</sub> copies/mL. Of the nine patients who experienced an AIDS-related event or died with a count ≥200 cells/mm<sup>3</sup>, three developed lymphoma, two developed esophageal candidiasis, one developed *Pneumocystis carinii* pneumonia (PCP), and three patients died from kidney failure/septicemia, septicemia/diabetes, and Kaposi's sarcoma, respectively.

There were 17 patients with undetectable viral loads (<400 copies/mL) preceding an event signaling disease progression. Death occurred in eight of these patients from various causes, including lung cancer, cardiopulmonary arrest, *Mycobacterium avium* complex, Kaposi's sarcoma, septicemia/diabetes, or ventricular arrhythmia/liver failure. The other nine patients experienced AIDS dementia (one patient), wasting syndrome (one patient), and six different opportunistic infections (PCP occurred in two cases). Eight of the 17 patients had latest CD4+ cell counts <100 cells/mm<sup>3</sup>; the average of the latest CD4+ cell count for these patients was 121 cells/mm<sup>3</sup>.

Findings for latest CD4+ and viral load levels were similar for the outcome of death: latest levels of CD4+ cell counts as compared to latest levels of viral loads were more strongly related to death. When included as continuous variables, square root of latest CD4+ cell count was significantly associated with death ( $p < .001$ ) while log<sub>10</sub> of latest viral load was not ( $p = .22$ ).

### DISCUSSION

Our principal findings are: (1) latest values of both CD4+ cell counts and viral loads are significant predictors of short-term risk of AIDS and death; (2) latest CD4+ cell count is a stronger predictor of progression to AIDS or death than latest viral load; (3) latest values of both CD4+ cell count and viral load are stronger predictors of progression to AIDS or death than baseline values; and (4) risk of progression to AIDS or death is low among patients with latest CD4+ cell counts of 200 cells/mm<sup>3</sup> or higher.

While data from the MACS study<sup>1</sup> indicate that viral load is superior to CD4+ cell count in defining long-term prognosis of progression to AIDS or

**Table 2.** Association of latest CD4+ cell count and latest viral load with progression to AIDS or death

	No. of events	Rate <sup>a</sup>	Adjusted for baseline characteristics <sup>b</sup>		Adjusted for baseline characteristics <sup>b</sup> and latest viral load	
			HR	95% CI	HR	95% CI
<b>Latest CD4+ cell count (cells/mm<sup>3</sup>)</b>						
<50	66	26.2	13.9	6.5–29.7	9.5	4.0–22.5
50–99	20	10.1	4.7	2.1–10.6	3.7	1.6–8.8
100–199	14	4.2	1.7	0.7–4.0	1.5	0.6–3.5
≥200	9	2.3	1.0	(reference)	1.0	(reference)
<b>Latest viral load (copies/mL)</b>						
			Adjusted for baseline characteristics <sup>b</sup>		Adjusted for baseline characteristics <sup>b</sup> and CD4+ cell count	
			HR	95% CI	HR	95% CI
≥100,000	48	19.1	4.2	2.3–7.7	1.2	0.6–2.4
10,000–99,999	29	11.6	2.5	1.3–4.6	1.1	0.6–2.2
401–9,999	15	5.7	1.1	0.5–2.3	0.7	0.4–1.5
≤400	17	4.2	1.0	(reference)	1.0	(reference)

<sup>a</sup>Per 100 person-years. <sup>b</sup>Baseline characteristics considered as covariates: age, gender, race, HIV risk category, prior AIDS diagnosis, and prior NRTI therapy.

death among patients not taking antiretroviral therapy, our study indicates that among patients with CD4+ cells <200 cells/mm<sup>3</sup> about to begin HAART and while on HAART, CD4+ cell count is a stronger predictor of progression to AIDS or death than viral load.

For both CD4+ cell count and viral load, the latest values are more important prognostically than baseline levels. Our data are consistent with the findings of the Antiretroviral Therapy (ART) Cohort Collaboration,<sup>15</sup> which reported that hazard ratios (compared to those with a 6-month CD4+ cell count of <25 cells/mm<sup>3</sup>) were 0.55, 0.62, 0.42, 0.25, and 0.18 for those with 25–49, 50–99, 100–199, 200–349, and ≥350 cells/mm<sup>3</sup>, respectively. In that study, compared to patients with 6-month viral loads ≥100,000 copies/mL, hazard ratios were 0.59, 0.42, and 0.29 for viral loads 10,000–99,999, 500–9999, and ≤500 copies/mL, respectively. It is im-

portant to note that neither baseline CD4+ cell count nor viral load was associated with disease progression after controlling for 6-month levels. Mocroft et al.<sup>21</sup> described the substantially reduced risk of AIDS-defining illnesses among patients prescribed HAART with latest values of CD4+ cell counts >200 cells/mm<sup>3</sup> but did not consider latest values of viral load. In that study, the incidence of AIDS illnesses for patients with latest CD4+ cell counts >200 cells/mm<sup>3</sup> was 1.4 per 100 patient-years compared to 29.2 (21 times greater) for those with latest values <50 cells/mm<sup>3</sup> and 6.2 per 100 patient-years (4.4 times greater) for those with latest CD4+ cell counts of 51–200 cells/mm<sup>3</sup>. Recently, the PLATO Collaboration<sup>22</sup> reported a 15.8-fold increased 3-year mortality risk in HIV-infected persons failing three-class therapy with CD4+ cell counts <50 cells/mm<sup>3</sup> compared to those with CD4+ cell counts >200 cells/mm<sup>3</sup>. In that 13-cohort

analysis, with a median entry CD4+ cell count of 199 cells/mm<sup>3</sup>, latest viral load did not independently predict death.

Our findings also show a significant risk gradient between latest CD4+ cell count and progression to AIDS or death. Risk of progression to AIDS or death (adjusted for baseline characteristics and latest viral load) was 9.5 times greater for those with CD4+ cell counts <50 cells/mm<sup>3</sup> compared to those with CD4+ cell counts ≥200 cells/mm<sup>3</sup>. The stronger relationship between latest values of CD4+ cell count with progression to AIDS or death than between viral load and progression to AIDS or death is consistent with a meta-analysis of 16 randomized trials of nucleoside analogue reverse transcriptase inhibitors.<sup>23</sup> In that overview, latest levels of CD4+ cell counts (after 6 months of treatment) were significantly related to risk of progression to AIDS or death after adjustment for viral loads, but 6-month changes in viral load were not significantly related to progression to AIDS or death after adjustment for CD4+ cell count changes. Taken together, these results indicate that while both markers are valuable in predicting future risk, short-term risk of progression to AIDS or death is best assessed with the CD4+ cell count.

Our study also showed, as did Phillips et al.,<sup>24</sup> that persons with low CD4+ cell counts at baseline could achieve substantial immunologic benefit and disease reduction. In our study, few patients with high CD4+ cell counts developed AIDS or death; for the 10 who did, viral load averaged only 4.0 log<sub>10</sub> copies/mL. In the pre-HAART era, Hennessey et al. found that patients who developed events with CD4+ cell counts ≥300 cells/mm<sup>3</sup> at the time of AIDS diagnosis had higher viral loads than CD4+ cell count matched controls who did not experience AIDS.<sup>25</sup> Our findings suggest that this relationship may not be the case in the era of HAART. There may be other factors associated with progression that are more important than viral load in these patients. In a review, Lederman and Valdez<sup>26</sup> noted that immune restoration is often incomplete and that it is not clear that immune deficiency as measured by current markers is the critical determinant of risk of progression to AIDS or death. Additional research on patients who develop opportunistic illnesses with high CD4+ cell counts in the era of HAART is needed.

A limitation of our study is that only patients with advanced HIV disease were included. It is

important that similar analyses among patients starting therapy with higher CD4+ cell counts be conducted to examine more carefully the determinants of short-term risk of progression to AIDS or death, particularly among patients who experience an AIDS-defining illness at higher CD4+ cell counts.

In conclusion, we found that both proximal CD4+ cell count and viral load provided relevant information about disease prognosis in HAART recipients with advanced HIV infection at the time of initiation of a PI-containing ART regimen, with proximal CD4+ cell count being the better predictor of clinical outcome in these patients. These findings have relevance for risk stratification for determining changes in antiretroviral therapy and for the re-initiation of opportunistic infection prophylaxis; they also suggest that novel treatment strategies are needed for patients with low CD4+ cell counts who are at high risk of progression to AIDS or death, irrespective of their viral load.

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