# The Impact Of Physician Experience, Adherence, And Cd4+ T Cell Count On Rates Of Disease Progression Among Hiv-1 Infected Patients Initiating Triple Drug Antiretroviral Therapy

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## Introduction

We have recently described rates of disease progression stratified by baseline CD4 T cell count and HIV-1 RNA levels among patients initiating antiretroviral therapy in the province of British Columbia (1). In these analyses, we found that patients initiating therapy when CD4 T cell count had declined below 200 cells/mm3 were at heightened risk of disease progression, whereas we were unable to identify a survival benefit of starting therapy at any point above this threshold.

These observations, and similar findings reported elsewhere (2-4), have led to an emerging consensus that 200 CD4 T cells/mm3 represents a threshold beyond which response to therapy is progressively compromised.

Prior to the advent of HAART, it was observed that patients treated by physicians who were more experienced in treating HIV disease had improved survival over patients treated by less experienced physicians (5). Although a role of physician experience in the HAART era has been speculated upon (6), its impact on survival has not been demonstrated since the advent of triple drug therapy.

In addition, several recent studies have demonstrated an association between adherence to antiretroviral therapy and improved survival (7-9), although the impact of adherence has not been considered in evaluations of baseline CD4 cell count and treatment initiation. Therefore, we undertook the present study to evaluate the impact of physician experience and adherence upon rates of disease progression among HIV-infected patients initiating antiretroviral therapy at various CD4 cell count strata.

## Methods

Population-based analysis of 1416 antiretroviral naïve HIV-infected men and women aged 18 years or older in British Columbia who initiated triple drug therapy between August 1, 1996 and July 31, 2000.

Cumulative mortality rates from the initiation of triple drug antiretroviral therapy to July 31, 2001, stratified by CD4 cell count.

Persons whose primary care physician had previously enrolled >5 patients into the HIV treatment program were defined as having an HIV experienced physician, whereas patients whose enrolling physician had enrolled <5 patients were defined as having a non-experienced physician.

Patients who received medication >75% of the time during their first year on therapy were defined as adherent whereas persons who acquired <75% of their prescribed medications were defined as non-adherent.

## Results

A total of 1,416 patients were eligible. As of Sept 30, 2000, 110 patients had died of HIV-related causes, for a crude mortality rate of 7.8%.

Among patients with experienced physicians, the cumulative mortality rates at 12 months were 2.9%, 4.6%, and 0.7% for those with baseline CD4 cell counts <50, 50 – 199, and >200 cells/mm3 respectively. Conversely, among patients with non-experienced physicians the cumulative mortality rates at 12 months were 17.6%, 9.2%, and 1.1% for those with baseline CD4 cell counts <50, 50 – 199, and >200 cells/mm3 respectively.

Among patients who received >75% of their prescribed medications during the first year on therapy, the cumulative mortality rates at 12 months were 7.7%, 5.6%, and 0.6% for those with baseline CD4 cell counts of <50, 50-200, and >200 CD4 cells/mm3 respectively. In contrast, among patients who received < 75% of their medications, the cumulative mortality rates at 12 months were 13.3%, 6.3%, and 1.3% for those with baseline CD4 cell counts of <50, 50-200, and >200 CD4 cells/mm3 respectively.

In a multivariate model, after adjusting for AIDS at baseline, Age, baseline plasma viral load, and CD4 cell count, those whose physicians were more experienced were 0.67 (95% CI, 0.45 – 0.99) times less likely to die, and persons who received >75% of their prescribed medications were 0.30 (95% CI, 0.20 – 0.45) times less likely to die.

**Figure 1:** Kaplan-Meier product limit estimates of cumulative progression to death among 1,416 HIV-infected subjects who started naive on antiretroviral therapy between August 1, 1996 and July 1, 2000, stratified by CD4 cell count groupings (<50, 50 – 200, >200).

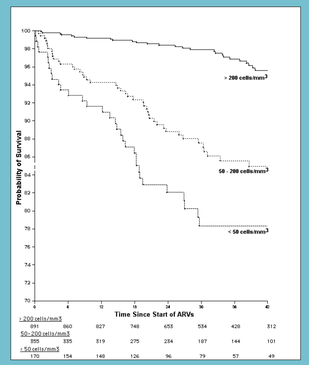


**Figure 2:** Kaplan-Meier product limit estimates of cumulative progression to death among 1,416 HIV-infected subjects who started naive on antiretroviral therapy between August 1, 1996 and July 1, 2000, stratified by CD4 cell count groupings (<50, 50 – 200, >200), and HIV-experienced (Panel A) and non-experienced (Panel B) categories.

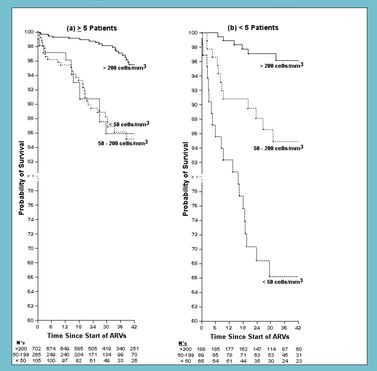


**Figure 3:** Kaplan-Meier product limit estimates of cumulative progression to death among 1,416 HIV-infected subjects who started naive on antiretroviral therapy between August 1, 1996 and July 1, 2000, stratified by CD4 cell count groupings (<50, 50 – 200, >200) and adherent (Panel A) and non-adherent (Panel B) categories.

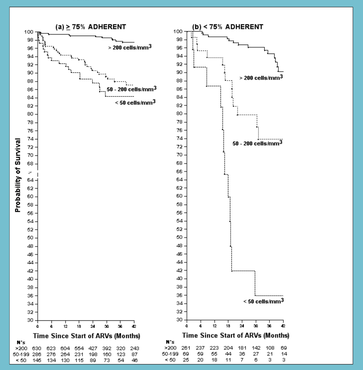


**Table 1:** Univariate and multivariate analysis of factors associated with death among 1416 persons first prescribed triple combination antiretroviral therapy between August 1, 1996 and July 1, 2000.

| Variable | Risk Ratios (RR) Crude (RR, (95% CI)) | Risk Ratios (RR) Adjusted* (RR, (95% CI)) |
|---|---|---|
| **Gender** | | |
| (Male versus female) | 1.37 (0.75 – 2.50) | — |
| **Start of 3-drug therapy** | | |
| (after July 1997 vs before) | 0.71 (0.47 – 1.05) | — |
| **Injection Drug Use** | | |
| (Yes versus No) | 1.03 (0.67 - 1.57) | — |
| **Protease Inhibitor Use** | | |
| (Yes versus No) | 1.48 (0.91 – 2.42) | — |
| **Prior AIDS Diagnosis** | | |
| (Yes versus No) | 2.07 (1.33 – 3.21) | 1.04 (0.64 – 1.67) |
| **Age** | | |
| (per year) | 1.03 (1.01 - 1.05) | 1.02 (1.00 – 1.04) |
| **Physician Experience** | | |
| (>5 versus < 5) | 0.56 (0.38 – 0.83) | 0.67 (0.45 – 0.99) |
| **Adherence** | | |
| (>75% versus <75%) | 0.47 (0.32 – 0.69) | 0.30 (0.20 – 0.45) |
| **Baseline CD4+ count (cells X $10^9$/L)** | | |
| >200 | 1.00 | 1.00 |
| 50 – 199 | 2.16 (1.48 – 3.16) | 3.82 (2.33 – 6.24) |
| <50 | 3.85 (2.58 – 5.75) | 7.10 (4.10 – 12.28) |
| **Baseline HIV-1 RNA (copies/ml)** | | |
| (Per Log10 increase) | 1.99 (1.41 – 2.80) | 1.32 (0.95 – 1.82) |

* Among 1414 persons first prescribed any triple-combination anitretroviral therapy between August 1, 1996 and July 1, 2001. Fixed model excludes all variables that were non-significant in univariate analyses.

**Table 2:** Adjusted Risk Ratios* for the Risk of Death for Baseline CD4 Cell Count and Physician Experience Categories.

| Number HIV+ Patients Previously Treated | CD4 Cell Count | Adjusted Risk Ratio | (95% CI) | p-value |
|---|---|---|---|---|
| ≥6 | ≥200 | 1.00 | ---- | ---- |
| ≤5 | ≥200 | 1.30 | (0.58 – 2.90) | 0.526 |
| ≥6 | 50 - 199 | 3.89 | (2.24 – 6.79) | <0.001 |
| ≤5 | 50 - 199 | 3.07 | (1.96 – 8.46) | <0.001 |
| ≥6 | <50 | 5.07 | (2.50 – 10.26) | <0.001 |
| ≤5 | <50 | 11.99 | (6.33 – 22.74) | <0.001 |

*Model was adjusted for adherence, history of injection drug use, baseline plasma viral load, age, and AIDS at baseline. The number of patients in each strata is shown on Figure 2.

**Table 3:** Adjusted Risk Ratios* for the Risk of Death for Baseline CD4 Cell Count and Adherence Categories

| Number HIV+ Patients Previously Treated | CD4 Cell Count | Adjusted Risk Ratio | (95% CI) | p-value |
|---|---|---|---|---|
| ≥75% | ≥200 | 1.00 | ---- | ---- |
| <75% | ≥200 | 3.55 | (1.72 – 7.35) | <0.001 |
| ≥75% | 50 - 199 | 3.54 | (2.37 – 8.70) | <0.001 |
| <75% | 50 - 199 | 9.78 | (4.48 – 21.31) | <0.001 |
| ≥75% | <50 | 5.19 | (3.03 – 12.65) | <0.001 |
| <75% | <50 | 35.71 | (16.17 – 78.85) | <0.001 |

*Model was adjusted for physician experience, history of injection drug use, baseline plasma viral load, age, and AIDS at baseline. The number of patients in each strata is shown on Figure 2.

## Conclusion

The impact of physician experience on survival was substantial, especially among severely immuno-compromised patients. In addition, despite the conservative nature of our adherence estimate, its impact on rates of survival were large amongst all strata of CD4 cell count.

## References

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