Comparative Analysis of Three-Drug Versus Two-Drug Regimens in HIV Patients: Impact on Progression-Free and Overall Survival

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Statistical Analysis

Baseline demographics and other relevant variables were summarized across treatment categories; frequencies (%) were calculated for categorical variables and median (IQR) were calculated for continuous variables. Two outcomes were assessed in this study: progression free survival (PFS) and overall survival (OS). PFS is defined as the time from clinical trial randomization until either AIDS diagnosis or any-cause death. OS is measured by the time from clinical randomization to all-cause death.

Kaplan-Meier curves and Log-Rank tests were used to visualize and estimate the distribution of survival times by treatment regimen (three-drug regimen including IDV versus two-drug regimen not including IDV) for both PFS and OS. Cox proportional hazards models were applied to assess the associations between covariates and survival (both OS and PFS) in both univariate and multivariate analyses. Covariates that were significant in the univariate analysis (Wald test) were then incorporated into the initial multivariate models. The log partial likelihood ratio test was used to identify the most parsimonious multivariate model for both PFS and OS outcomes; the indicated models were then tested for confounding and assessed for effect modifiers before the final multivariate model was reached. Sex and age were included in all multivariate models, due to their clinical importance in HIV-patient survival outcomes. All analyses were conducted in R version 4.4.1 utilizing the following packages: survival, ggsurvfit, tibble, dplyr, tableone, officer, and flextable.

Results

A total of 1151 subjects were included in this study, categorized as having the two-drug treatment regimen (n=577) and the three-drug treatment regimen (n=574). **Table 1** shows majority female subjects (82.6%) with an average age of 38 (IQR: 33,44). About half (52.8%) of subjects were White Non-Hispanic and 28.4% were Black Non-Hispanic; most subjects (84.1%) had no history of IV drug use. 3% of patients were hemophiliacs, and 65.6% of patients showed at least some signs of disease (according to Karnofsky Performance Scale). Most patients (61.9%) had CD4 counts above 50 at screening, with a baseline CD4 count of 74.5 (IQR: 23, 137). Patients had around 21 (IQR: 10,42) months of prior ZVD use.

<u>Progression Free Survival (PFS) Outcomes:</u>
Figure 1 provides initial evidence that the three-drug regimen including IDV has better progression free survival outcomes compared to the two-drug regimen without IDV ($p = 0.001$). **Table 2** shows the univariate analysis for progression free survival outcomes between the two-drug and three-drug regimen groups. Significant variables ($p < 0.05$) identified to be associated with PFS outcome included treatment group, Karnofsky performance scale, CD4 stratum at screening, and baseline CD4 count. Patients with CD4 counts above 50 (HR: 0.26, $p = 0.000$), higher baseline CD4 count (HR: 0.98, $p = 0.0020$, better health status (according to Karnofsky scale) (HR: 0.34, $p = 0.000$) (HR: 0.21, $p = 0.000$), and on the three-drug regimen including IDV (HR: 0.50, $p = 0.001$) had lower PFS

failure rates. **Table 4** highlights the multivariate analysis results for progression free survival outcomes between the two treatment groups. Results demonstrate that age, Karnofsky performance scale, treatment, and baseline CD4 count are significant predictors of PFS ($p<0.05$). Patients with better health status (according to Karnofsky scale) (HR: 0.48, p = 0.001) (HR: 0.31, p =0.000), on the three-drug regimen including IDV (HR: 0.52, p = 0.002), and those with higher CD4 counts (HR: 0.99, p = 0.000) have lower failure rate. Higher age is associated with a marginal increase in failure rate (HR: 1.02, p = 0.045).

Overall Survival (OS) Outcomes:

Figure 1 provides initial evidence that the three-drug regimen including IDV has greater overall survival outcomes compared to the two-drug regimen without IDV (p = 0.044). **Table 3** shows the univariate analysis for overall survival outcomes between the two-drug and three-drug regimen groups. Significant variables ($p < 0.05$) identified to be associated with OS outcome included treatment group, age, Karnofsky performance scale, CD4 stratum at screening, and baseline CD4 count, though treatment group was only marginally statistically significant with a p-value of exactly 0.05. Patients with CD4 counts above 50 (HR: 0.29, p = 0.003), higher baseline CD4 count (HR: 0.99, p = 0.004, better health status (according to Karnofsky scale) (HR: 0.23, p = 0.001) (HR: 0.07, p = 0.000), and on the three-drug regimen including IDV (HR: 0.43, p = 0.05) had lower OS failure rates. Higher age is associated with an increase in OS failure rate (HR: 1.07, p = 0.000). **Table 4** highlights the multivariate analysis results for overall survival outcomes between the two treatment groups. Results demonstrate that Karnofsky performance scale, treatment, and CD4 stratum are significant predictors of OS ($p<0.05$).Patients with better health status (according to Karnofsky scale) (HR: 0.45, p = 0.000) (HR: 0.16, p =0.000), on the three-drug regimen including IDV (HR: 0.50, p = 0.001), and with CD4 counts higher than 50 (HR: 0.30, p = 0.000) have lower failure rate.

Discussion

Our analyses revealed significant evidence that the three-drug regimen has better PFS compared to the two-drug regimen, supported by the Kaplan Meier curve / Log-rank test, univariate cox proportional hazards model, and multivariate cox proportional hazards model. Other variables significantly associated with PFS (gathered from the univariate analysis) included: Karnofsky performance scale, CD4 stratum at screening, and baseline CD4 count. No significant effect modifiers for the relationship between treatment and PFS were identified.

Although the univariate analysis showed only marginal significance in the relationship between treatment and overall survival (OS), the multivariable analysis—after adjusting for potential confounders—provided strong evidence that the three-drug regimen significantly improves OS compared to the two-drug regimen, as further supported by Kaplan-Meier curves and the log-rank test. Other variables significantly related with OS included age, Karnofsky performance scale, CD4 stratum at screening, and baseline CD4 count. No significant effect modifiers for the relationship between treatment and OS were found.

Appendix

Table 1. Baseline Characteristics

Characteristic	Overall, N = 1151[1]	Two-drug regimen without IDV[1], N = 577	Three-drug regimen including IDV[1], N = 574
Sex			
Male	951 (82.6%)	483 (83.7%)	468 (81.5%)
Female	200 (17.4%)	94 (16.3%)	106 (18.5%)
Race / Ethnicity			
White Non-Hispanic	596 (51.8%)	294 (51.0%)	302 (52.6%)
Black Non-Hispanic	327 (28.4%)	165 (28.6%)	162 (28.2%)
Other/unknown	228 (19.8%)	118 (20.5%)	110 (19.2%)
Age	38.00 [33, 44]	38.00 [33, 44]	38.00 [33, 44]
Karnofsky Performance Scale			
No evidence of disease	396 (34.4%)	202 (35.0%)	194 (33.8%)
Minor signs/symptoms of disease	541 (47.0%)	267 (46.3%)	274 (47.7%)
Some signs/symptoms of disease or cares for self	214 (18.6%)	108 (18.7%)	106 (18.5%)
CD4 stratum at screening			
CD4 ≤ 50	439 (38.1%)	220 (38.1%)	219 (38.2%)
CD4 > 50	712 (61.9%)	357 (61.9%)	355 (61.8%)
Baseline CD4 count	74.50 [23, 137]	69.50 [23, 135]	79.50 [24, 139]
IV drug use history			
Never	968 (84.1%)	484 (83.9%)	484 (84.3%)
Currently/Previously	183 (15.9%)	93 (16.1%)	90 (15.7%)
Hemophiliac			
Yes	35 (3.0%)	21 (3.6%)	14 (2.4%)
No	1116 (97.0%)	556 (96.4%)	560 (97.6%)
Months of prior ZDV use	21.00 [10, 42]	19.00 [10, 42]	22.00 [11, 42]

[1]Median (IQR); n (%).

Table 2. Univariate analysis for progression-free survival (PFS)

Covariate	HR	95% CI	P Value[1]
Sex			
Female	-	-	-
Male	0.92	[0.53, 1.60]	0.778
Race / Ethnicity			
Other/unknown	-	-	-
White Non-Hispanic	0.77	[0.47, 1.25]	0.292
Black Non-Hispanic	0.61	[0.34, 1.10]	0.104
Age	1.02	[1.00, 1.04]	0.061
Karnofsky Performance Scale			
Some signs/symptoms of disease or cares for self	-	-	-
Minor signs/symptoms of disease	0.34	[0.22, 0.53]	0.000
No evidence of disease	0.21	[0.12, 0.37]	0.000
Treatment			
Two-drug regimen without IDV	-	-	-
Three-drug regiment including IDV	0.50	[0.33,0.77]	0.001
CD4 stratum at screening			
CD4 ≤ 50	-	-	-
CD4 > 50	0.26	[0.17, 0.4]	0.000
Baseline CD4 count	0.98	[0.98, 0.99]	0.000
IV drug use history			
Never	-	-	-
Currently/Previously	0.67	[0.36, 1.25]	0.209
Hemophiliac			
No	-	-	-
Yes	1.02	[0.32, 3.22]	0.972
Months of prior ZDV use	1.00	[0.99, 1.01]	0.511

Statistically significant P-values < 0.05, HR: hazard ratio, 95% CI: 95% confidence interval.
[1]Wald test

Table 3. Univariate analysis for overall survival (OS)

Covariate	HR	95% CI	P Value[1]
Sex			
Female	-	-	-
Male	1.22	[0.46, 3.24]	0.686
Race / Ethnicity			
Other/unknown	-	-	-
White Non-Hispanic	0.67	[0.25, 1.81]	0.429
Black Non-Hispanic	1.12	[0.4, 3.14]	0.836
Age	1.07	[1.03, 1.11]	0.000
Karnofsky Performance Scale			
Some signs/symptoms of disease or cares for self	-	-	-
Minor signs/symptoms of disease	0.23	[0.1, 0.53]	0.001
No evidence of disease	0.07	[0.02, 0.32]	0.000
Treatment			
Two-drug regimen without IDV	-	-	-
Three-drug regiment including IDV	0.43	[0.19, 1]	0.050
CD4 stratum at screening			
CD4 ≤ 50	-	-	-
CD4 > 50	0.29	[0.12, 0.66]	0.003
Baseline CD4 count	0.99	[0.98, 1]	0.004
IV drug use history			
Never	-	-	-
Currently/Previously	1.25	[0.47, 3.32]	0.652
Hemophiliac			
No	-	-	-
Yes	1.29	[0.17, 9.51]	0.804
Months of prior ZDV use	0.99	[0.97, 1.01]	0.211

Statistically significant P-values < 0.05, HR: hazard ratio, 95% CI: 95% confidence interval.
[1]Wald test

Table 4. Multivariate analysis for progression-free survival (PFS)

Characteristic	HR	95% CI	P Value[1]
Sex			
Female	-	-	-
Male	1.09	[0.63, 1.91]	0.751
Age	1.02	[1, 1.05]	0.045
Karnofsky Performance Scale			
Some signs/symptoms of disease or cares for self	-	-	-
Minor signs/symptoms of disease	0.48	[0.3, 0.75]	0.001
No evidence of disease	0.31	[0.17, 0.55]	0.000
Treatment			
Two-drug regimen without IDV	-	-	-
Three-drug regiment including IDV	0.52	[0.34, 0.79]	0.002
Baseline CD4 count	0.99	[0.98, 0.99]	0.000

Statistically significant P-values < 0.05, HR: hazard ratio, 95% CI: 95% confidence interval.
[1]Wald test

Table 5. Multivariate analysis for overall survival (OS)

Covariate	HR	95% CI	P Value[1]
Sex			
Female	-	-	-
Male	0.92	[0.53, 1.60]	0.778
Age	1.02	[1, 1.05]	0.057
Karnofsky Performance Scale			
Some signs/symptoms of disease or cares for self	-	-	-
Minor signs/symptoms of disease	0.45	[0.28, 0.7]	0.000
No evidence of disease	0.29	[0.16, 0.51]	0.000
CD4 stratum at screening			
CD4 ≤ 50	-	-	-
CD4 > 50	0.30	[0.19, 0.47]	0.000
Treatment			
Two-drug regimen without IDV	-	-	-
Three-drug regiment including IDV	0.50	[0.33, 0.77]	0.001

Statistically significant P-values < 0.05, HR: hazard ratio, 95% CI: 95% confidence interval.
[1]Wald test

Figure 1. Comparison of Progression Free Survival (PFS) Probability between Treatment Groups

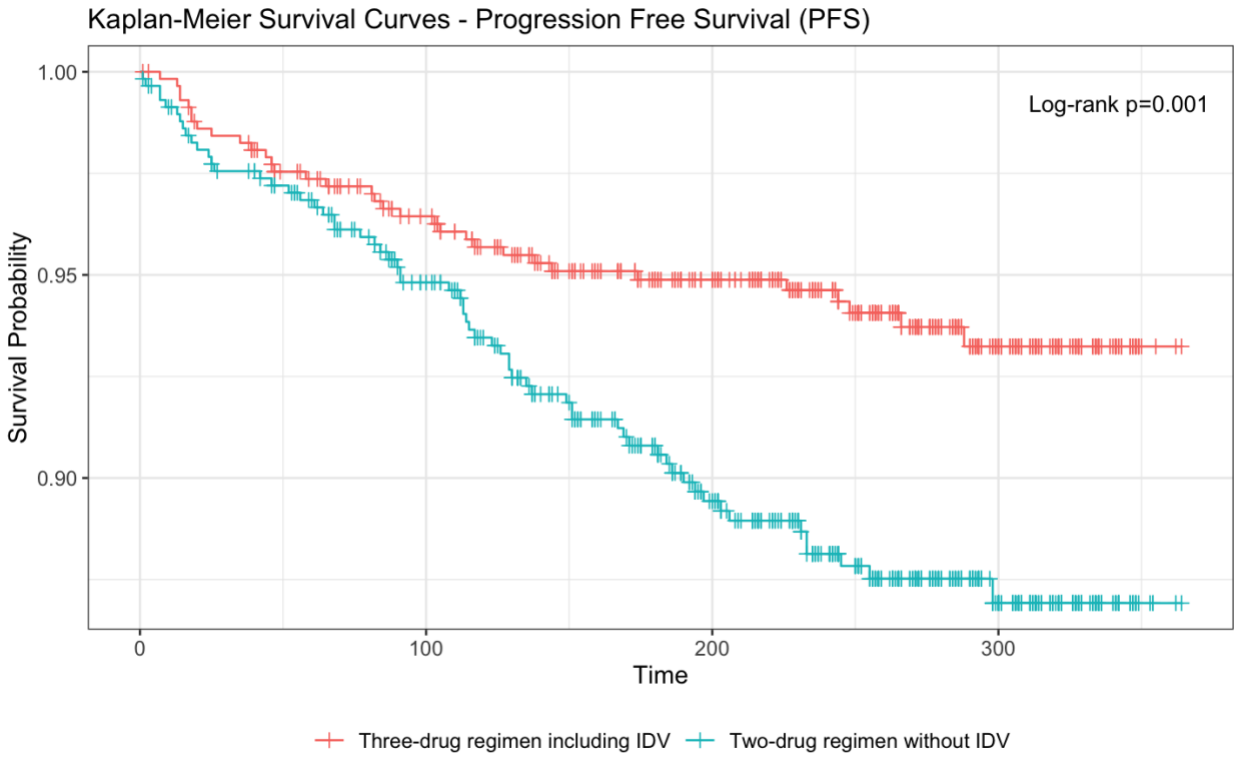

Figure 2. Comparison of Overall Survival (OS) Probability between Treatment Groups