

Introduction

This systematic overview was undertaken to evaluate the antiretroviral activity of triple combination therapy as measured by changes in plasma HIV RNA and CD4+ cell count, and to identify factors associated with response. These results provide an update to a similar, previously published systematic overview (Bartlett, et al., AIDS 2001, 15:1369-1377).

Study Selection

- Trials were identified through a search of public domain publications and recent conference presentations (From 1994 to March 2004). Trials meeting the selection criteria are shown in Table 1.
- Triple combination therapy was defined as 2 nucleoside, or a nucleoside and a nucleoside reverse transcriptase inhibitors and either: 1) a protease inhibitor (PI); 2) a non-nucleoside reverse transcriptase inhibitor (NNRTI); 3) a third NRTI (NRTI), or 4) a ritonavir-boosted protease inhibitor regimen (BPI).
- Inclusion Criteria:** Trials at least 24 weeks in duration; at least 30 subjects/treatment arm; only chronically HIV-infected, adult subjects who were ART-naïve or had very limited prior exposure to antiretroviral therapy (<2 weeks prior NRTI exposure), and trials reporting the percentage of patients with undetectable HIV RNA (<400 and <50 copies/mL) using the Roche Amplicor assay in an intent-to-treat analysis. In this intent-to-treat analysis, missing = failure (ITT: M=F).
- Exclusion Criteria:** Induction/maintenance trials, trials with primary infection subject populations (<6 months since seroconversion), and experimental treatments that did not successfully reach US FDA approval were excluded.

Data Collection

- Trial design** – treatment regimen, open-label or blinded; randomization if used; control groups; average daily pill count (defined as the number of tablets or capsules/day including placebo) in the prescribed treatment regimen.
- Baseline characteristics** - number enrolled, % male, race, age, log₁₀ plasma HIV RNA and CD4+ cell count.
- Response rates** – % subjects with plasma HIV RNA <400 and <50 copies/mL at 24 and 48 weeks and change from baseline in CD4+ cell count at 24 and 48 weeks; the ITT:M=F population was used for the virologic analyses, while the as-treated population was used for change from baseline in CD4+ cell counts using all observed data.

Statistical Methods

- Differences in the response rates across drug classes were compared by constructing confidence intervals for the difference in response rates between each drug.
- Estimates for each response outcome are provided along with the number of treatment groups and number of subjects that contributed to the estimate.
- Correlation analyses and weighted least squares multivariate linear regression analysis (MLR) using a backwards stepwise selection procedure were used to assess the variability in treatment group response rates as a function of the following factors: baseline CD4+ cell count, baseline log₁₀ plasma HIV RNA, ART triple drug class, and average daily pill count. For the MLR analyses of categorical virologic endpoints, the natural log of the response rate was used.
- Statistical significance was determined using alpha = 0.05.
- For bubble plots, results for each treatment arm were weighted in direct proportion to the number of subjects enrolled.
- Sensitivity analyses evaluating different factors were conducted, including analyses of dichotomous pill count (≤ 10/day vs. >10/day); analyses of continuous pill count over these ranges (3–10/day and 11–22/day); and pill counts as predictors of response within each drug regimen class.

Studies Included in the Analyses

- Forty-nine clinical trials met the inclusion criteria and are listed in Table 1 (representing the addition of 27 new trials and a new drug class – ritonavir-boosted protease inhibitors (BPI) – since the previous published overview). The selected studies enrolled 13,147 subjects into 85 independent treatment arms.
- For the studies included in this systematic overview, the median baseline HIV RNA levels and CD4+ cell counts were 4.75 log₁₀ copies/ml and 315/mm³, respectively, for all studies combined. Overall, 57% of patients achieved HIV RNA <50 copies/mL at week 48. In contrast, the 2001 analysis found that 45% of patients reached this important threshold, suggesting that more effective regimens have been developed since the first published overview. The overall mean CD4+ cell count increase was +177 cells/mm³ (95% C.I. 169,184) at week 48, compared to +158 (95% C.I. 142, 174) in the previous analysis.

Results

Virologic and Immunologic Results at Weeks 24 and 48

Figure 1 displays virologic responses at week 48 for all treatment arms reporting that data. Virologic and immunologic results at Weeks 24 and 48 for the four drug classes are shown in Table 2.

Figure 1. Proportion of Patients with HIV RNA < 50 copies/mL at Week 48 (ITT: M=F)

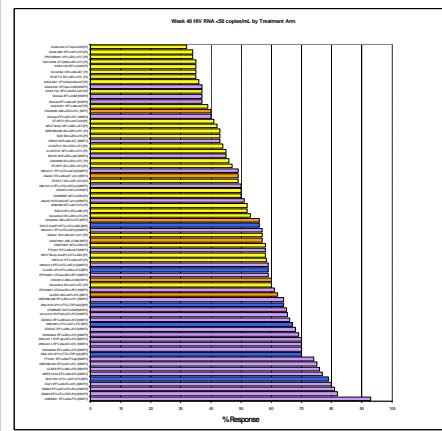


Table 2. Virologic and Immunologic Results at 24 and 48 Weeks All Studies, All Drug Classes

	Week 24 Results			Week 48 Results		
	%RNA <400	%RNA <50	D CD4+	%RNA <400	%RNA <50	D CD4+
PI-Triple						
# Treatment Arms	20	18	16	25	29	28
# Subjects	3162	2551	2219	3697	3898	3712
Weighted ¹ Mean	66	48	131	58	44	178
95% C.I.	63, 69	44, 52	117, 145	55, 61	40, 47	165, 192
BPI-Triple						
# Treatment Arms	4	5	4	4	6	6
# Subjects	805	669	347	812	1002	1002
Weighted ¹ Mean	78	64	130	73	64	209
95% C.I.	71, 85	56, 71	99, 162	66, 80	57, 70	189, 229
NNRTI-Triple						
# Treatment Arms	17	22	19	26	31	34
# Subjects	2593	4167	3242	5287	6355	6516
Weighted ¹ Mean	77	61	131	72	64	174
95% C.I.	73, 81	58, 64	120, 141	70, 75	61, 66	164, 183
NRTI-Triple						
# Treatment Arms	6	4	6	6	6	6
# Subjects	605	549	605	769	811	700
Weighted ¹ Mean	66	56	106	60	51	150
95% C.I.	58, 74	48, 64	91, 121	53, 67	44, 58	122, 178
Overall						
# Treatment Arms	47	49	45	61	72	74
# Subjects	7165	7936	6413	10565	12066	11930
Weighted ¹ Mean	71	57	129	67	57	177
95% C.I.	69, 74	55, 59	121, 136	65, 68	55, 58	169, 184

¹ Mean values are weighted by the sample size for each treatment arm.

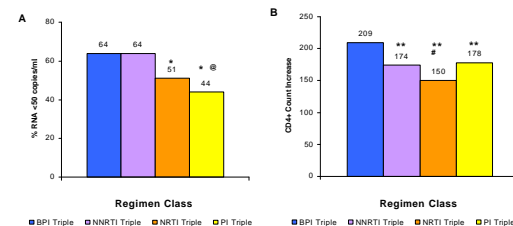
Legend: BPI Triple (blue), NNRTI Triple (purple), NRTI Triple (orange), PI Triple (yellow)

Figure 2 shows the virologic response (% RNA <50 copies/mL, Panel A) and immunologic response (change from baseline in CD4+ cell count, Panel B) at week 48 for the four drug classes.

Table 3 provides the corresponding unadjusted pairwise comparisons of responses for the four drug classes.

- Significantly greater percentages of patients reached HIV RNA < 50 copies/ml at week 48 in the BPI regimens (64%) and NNRTI regimens (64%) compared to the NRTI (51%) or PI (44%) regimens.
- BPI regimens had significantly greater increases in CD4+ cell count (+209 cells/mm³) compared to PI (+178 cells/mm³), NNRTI (+174 cells/mm³), or NRTI (+150 cells/mm³) regimens.

Figure 2. Virologic and Immunologic Results at Week 48 by Drug Class



In Panel A, (*) indicates significant differences from both BPI and NNRTI (p < 0.01) while (⊕) indicates significant differences between NRTI and PI (p < 0.05). In Panel B, (**) indicates significant differences between BPI and the other drug classes (p ≤ 0.003) while (#) indicates significant differences between NNRTI and PI classes vs. NRTI (p < 0.05). See Table 3.

Table 4. Multivariate Linear Regression Analysis Virologic and Immunologic Responses.

FACTOR	Week 24 Results		Week 48 Results	
	%RNA <400	%RNA <50	%RNA <400	%RNA <50
Baseline CD4+ cell count	-0.203	-0.655	NS	-0.353
Baseline HIV RNA level	NS	-0.584	NS	0.510
Pill Count	-0.315	NS	NS	-0.181
Drug Class	-0.188	-0.443	NS	-0.097
Drug Class * Pill Burden	0.083	0.133	NS	NS
Model R-squared	0.514	0.329	0.000	0.479

NS = not statistically significant at 0.05; for significant factors, numbers reported are parameter estimates from multiple regression analysis; - indicates correlation between higher pill count and improved response; + indicates correlation between lower pill count and improved response.

Table 3. Unadjusted Pairwise Comparisons Week 48 Responses by Overall Drug Class

	% RNA < 50 copies/mL		
	NNRTI	PI	NRTI
BPI	0.926	<0.001	0.009
NNRTI		<0.001	0.001
PI			0.045
Change from Baseline in CD4+ Count			
BPI	<0.001	0.003	<0.001
NNRTI		0.577	0.049
PI			0.028

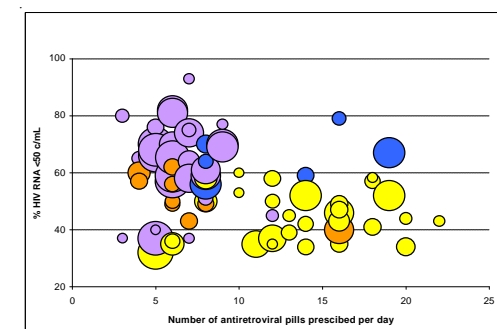


Figure 3. Relationship Between Virologic Response at Week 48 and Pill Count. Bubble size is in direct proportion to the number of subjects enrolled. Univariate analysis indicates a significant correlation between lower pill count and virologic response (p = 0.0053, r = -0.323). However, after adjustment for concomitant factors in the multivariate linear regression analysis, the correlation between pill count and response is not significant (see Table 4 and Table 5).

Factors Affecting Response

Secondary analyses were carried out to further assess the relationship between pill count and virologic responses (Table 5).

Table 5. Sensitivity Analyses Relationship of Pill Count to Week 48 Virologic Response

Population Analyzed	N arms	% patients	% RNA <50 ¹
All Studies, Pill Count as Continuous Variable	72	12,066	NS
By Drug Class			
BPI	6	1,002	NS
NNRTI	31	6,355	NS
NRTI	6	1,111	<0.298
PI	29	3,898	0.213
By Pill Count			
Dichotomous (≤ 10/day vs. > 10/day)	72	12,066	-0.885
Continuous (≤ 10/day)	45	8,409	NS
Continuous (> 10/day)	27	3,657	NS
Excluding AI424-034	70	11,256	NS

¹ NS = not statistically significant at 0.05; for significant factors, numbers reported are parameter estimates from multiple regression analysis; - indicates correlation between higher pill count and improved response; + indicates correlation between lower pill count and improved response.

Outcomes of Sensitivity Analyses

- Pill count was not a significant factor in 6 of the 9 analyses conducted including the primary analysis (all studies, pill count as a continuous variable), the BPI and NNRTI classes, and continuous pill counts (≤ 10 and > 10 pills/day). In an additional analysis, the AI424-034 study was excluded due to low response rates and problems with sample management. When the AI424-034 study was excluded, the effect of pill count was still not significant.
- A correlation between lower pill count and better virologic response was seen only for regimens within the NRTI class and for regimens with ≤ 10 pills compared to regimens with > 10 pills.
- A correlation between higher pill count and better virologic response was seen for regimens in the PI class.

Key Findings

Key findings using all data from all studies for Week 48 Virologic Responses include:

- Drug class is significantly associated with responses; BPI and NNRTI regimens have significantly better virologic responses compared to NRTI and PI regimens.
- Lower pill count was not associated with improved responses in the multivariate regression analysis, but was in some secondary analyses.
- Lower baseline HIV RNA was not significantly associated with improved responses
- Lower baseline CD4+ cell counts were associated with improved response of <50 copies/mL at Week 48. This observation may reflect the more potent regimens used in more recent studies, which enrolled subjects with lower baseline CD4+ cell counts.
- The multiple linear regression model explains 30% of the variability in response rates, reflecting the importance of other variables not included in this analysis in determining virologic responses.

Discussion

The goal of this study is to update and expand upon the systematic overview previously published in 2001. The original analysis included 3,257 patients across 23 trials and 31 independent treatment groups. This updated analysis is significantly larger and now includes 13,147 patients across 49 studies and 85 independent arms.

With the introduction of many new drugs and regimen combinations, the results of this study differ from the results in the 2001 analysis. Specifically,

2001 Results	Current Results
No significant differences were seen in virologic responses by drug class	Boosted PI- and NNRTI- based regimens demonstrate superior virologic response relative to PI and NRTI regimens
No significant differences were seen in Week 48 CD4+ cell count increases by drug class	Boosted PIs demonstrate greater increases in Week 48 CD4+ cell count response compared to the other 3 drug classes
Lower pill count was significantly associated with virologic response in the multivariate linear regression analysis	Lower pill count is not associated with virologic response in the multivariate linear regression analysis

Several factors are likely impacting the changes in results seen in this updated analysis. The larger number of subjects, trials, and regimens allow for a more robust analysis. In addition, many of the newer studies included in the analysis have lower pill counts and include increasingly potent regimens.

Several limitations of this approach should be noted:

- Systematic overview are based on population-level data and not on individual subject data; although the estimation of the overall response rates would be the same, analyses based on individual subject data would allow for more powerful assessment of prognostic factors for response rates.
- Only studies with data reported through week 48 are represented. Trials with poor results may not have been reported, and other trials and study arms that stopped before reaching 48 weeks are not included (e.g., ESS30009).
- The inclusion period for studies spanned 10 years (1994 to March 2004), and it is possible that factors other than treatment regimens may have affected virologic and immunologic responses, such as improved compliance monitoring, adherence education, and subject motivation.

Conclusions

In summary, the results from this systematic overview indicate that:

- Virologic response rates have been improving over time.
- The primary driver of virologic response is regimen potency, and pill count was not consistently associated with virologic responses.
- In pairwise comparisons, BPI and NNRTI regimens were associated with superior virologic suppression at 48 weeks compared to PI and NRTI regimens
- In pairwise comparisons, BPI regimens were associated with greater increases in CD4+ cell counts at 48 weeks compared to NNRTI, PI, and NRTI regimens
- These results support the current DHHS Guidelines for patients starting antiretroviral therapy.

