Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults

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Aim: To estimate the effectiveness of triple combination therapy in antiretroviral-naive adults.

Methods: A systematic overview of results from clinical trials involving triple combination therapy with dual nucleoside reverse transcriptase inhibitors (NRTI) and: a protease inhibitor (PI triple); a non-nucleoside reverse transcriptase inhibitor (NNRTI triple); or a third NRTI (triple NUC). Data from 23 clinical trials involving 31 independent treatment groups, 19 unique antiretroviral regimens, and 3257 enrolled patients were included in this study.

Results: Median $\log_{10}$ baseline plasma HIV RNA and CD4 cell count over all trials averaged 4.69 (49 329 copies/ml) and 375×10^6 cells/l, respectively. The overall estimated percentage of patients with plasma HIV RNA $\leqslant$ 400 copies/ml at 24 weeks was 64% [95% confidence interval (CI), 60 to 67%]. The percentages of patients with plasma HIV RNA $\leqslant$ 50 copies/ml at 48 weeks by drug class were: PI triple, 46% (95% CI, 41 to 52%); NNRTI triple, 51% (95% CI, 43 to 59%); triple NUC, 45% (95% CI, 36 to 54%). The CD4 cell count increase over all trials at 24 and 48 weeks averaged $+123 \times 10^6$ cells/l (95% CI, 111×10^6 to 135×10^6 cells/l) and $+160 \times 10^6$ cells/l (95% CI, 146×10^6 to 175×10^6 cells/l), respectively and did not differ between drug classes. In multivariable regression analysis, neither baseline plasma HIV RNA level and CD4 cell count nor treatment regimen predicted plasma HIV RNA $\leqslant$ 50 copies/ml at week 48. However, pill count was significantly negatively associated with plasma HIV RNA $\leqslant$ 50 copies/ml at week 48 ($P = 0.0085$).

Conclusions: The results suggest that three drug regimens containing two NRTI with a PI, a NNRTI, or a third NRTI may provide comparable activity, and practical issues such as daily pill burden should be considered when choosing a treatment regimen.

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Introduction

HIV disease progression, including opportunistic infections and mortality, can be profoundly altered by antiretroviral treatment regimens [1–6]. Whereas increased CD4 cell counts are considered to be important immunological markers of treatment response, plasma HIV RNA levels are the primary assessment used to guide decisions to initiate or change antiretroviral therapy [7]. During antiretroviral therapy, suppressing plasma HIV RNA to undetectable levels greatly limits the selection of drug-resistant viruses associated with treatment failure, and is the goal of treatment interventions [8]. In evaluating drug-related activity, the percentage of patients with undetectable plasma HIV RNA after 24 weeks of therapy has become the

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primary endpoint used for comparisons [9]. Historically, undetectable plasma HIV RNA was defined as < 400 copies/ml, although more sensitive assays can now measure HIV RNA to $< 20–50$ copies/ml. Accumulating evidence suggests that treatments which lower HIV RNA to < 50 copies/ml are associated with more complete and durable viral suppression compared to levels between 50–500 copies/ml [7,10].

Currently 16 antiretroviral drugs are available by prescription in the USA. The most commonly recommended combinations include two nucleoside reverse transcriptase inhibitors (NRTI) with a third drug: either a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a third NRTI. Several trials have compared directly the activity of triple drug regimens in treatment-naive subjects, but their results are not consistent. In addition, there may be differences in study design (e.g. open-label versus double-blind), baseline characteristics of enrolled subjects (e.g. baseline plasma HIV RNA levels, CD4 cell counts or antiretroviral drug experience), the reporting of results (e.g. intent-to-treat versus as-treated analyses), and sample size which confound the interpretation of cross-protocol comparisons [11,12].

This study was undertaken to estimate antiretroviral activity, as measured by changes in plasma HIV RNA and CD4 cell count, and to assess the variability of treatment response across different drug classes. We performed an overview of results from published and/or recently presented clinical trials in antiretroviral treatment-naive HIV-infected adults who received triple combination therapy, representing the first comprehensive synthesis of the activity of antiretroviral regimens across similarly designed clinical trials.

Methods

Inclusion/exclusion criteria

Clinical trials of triple combination regimens for the treatment of HIV-infected, antiretroviral treatment (ART)-naive adults were identified through a search of public domain publications and conference presentations. All clinical trials included were conducted and presented or published between July 1994 and February 2000. A literature search using the MEDLINE database was performed for the years 1994–2000 using the following keywords: clinical trial; plasma HIV-1 RNA; highly active antiretroviral therapy; antiretroviral therapy; and naive. Additionally, all clinical trials presented in the package insert for approved antiretroviral drugs were included. The following conferences were reviewed for relevant trials: Interscience Conference on Antimicrobial Agents and Chemotherapy; Conference on Retroviruses and Opportunistic Infections; International AIDS Conference; European Conference on Clinical Aspects and Treatment of HIV Infection; and the Annual Meeting of the Infectious Disease Society of America. Triple combination therapy was defined as dual NRTI and either: (i) a PI (PI triple); (ii) a NNRTI (NNRTI triple); or (iii) a third NRTI (triple NUC). Only treatment regimens which included at least 30 chronically HIV-infected, adult subjects who were ART-naive or had very limited prior ART exposure ($\leqslant 2$ weeks prior NRTI exposure) were included in the analysis. All studies must have been at least 24 weeks in duration and have either reported the percentage of patients with undetectable HIV RNA using the Roche Amplicor (Branchburg, New Jersey, USA) or Chiron bDNA (Emeryville, California, USA) assays in an intent-to-treat analysis, or provided sufficient data to enable the calculation of intent-to-treat results. Some exceptions to these criteria were noted and are indicated below (for example, for some trials 16 or 28 week data was used in lieu of 24 week data). Several trials were identified which fit one or more inclusion criteria but were not included in this overview for the following reasons: AG-511, plasma HIV-1 RNA not available for the study population; BI-1090, ACTG193A, and ACTG261, plasma HIV-1 RNA data not available for the subset of naive patients.

Data abstraction

After identifying the trial for inclusion in the analysis, all published or presented source documentation for the trial was collected. The following information was then abstracted for each treatment group from the trial source documentation by two independent reviewers. (i) Trial design characteristics: treatment regimen, open-label or blinded design; whether or not randomization was used; whether or not the trial contained a concurrent control group; average daily pill burden, defined as the nominal number of tablets/capsules per day (including placebo) in the prescribed treatment regimen. (ii) Baseline and disease characteristics of the study population: number of patients enrolled, percent male, racial and ethnic distribution, median age, median $\log_{10}$ baseline plasma HIV RNA and median baseline absolute CD4 cell count; (iii) Response rates: percentages of patients with plasma HIV RNA $\leqslant 50$ and $\leqslant 400$ copies/ml at 24 and 48 weeks, where available, and recalculated (if necessary) using the intent-to-treat method as described below; actual change from baseline in CD4 cell count at 24 and 48 weeks was abstracted using the last observation carried forward or on an as-treated basis (typically only patients remaining on randomized treatment at week 24 or week 48). After data abstraction, the results for the two reviewers were compared and differences were reconciled such that there was concordance between the actual results between the two reviewers. If median values were unavailable then the mean was used. In general, most studies reported plasma HIV RNA using

$\leqslant$ 400 copies/ml (Roche Amplicor assay) and $\leqslant$ 50 copies/ml (Roche Ultrasensitive Assay). The exceptions to this were the START I and II trials and the VIRGO I/II trial, where results were reported as the percent $<$ 500 copies/ml using the bDNA assay.

Statistical methods

As described above, the primary analysis method for HIV RNA was intent-to-treat. By definition, this is the percent of enrolled subjects with plasma HIV RNA less than or equal to the limit of detection at the specified time point, which is mathematically equal to $100\% \times (\gamma/\mathrm{N})$, where γ is the number of subjects with plasma HIV RNA less than or equal to the limit of detection and still on assigned therapy at the specified time point and N is the number of subjects enrolled. When the result using the intent-to-treat method was unavailable, but the number of evaluable subjects and number of subjects below the assay detection limit were reported, then the result using the intent-to-treat method was determined by calculating γ in the above formula as $(Z\% \times \mathrm{n})/100$, where Z is the number of subjects with undetectable plasma HIV RNA at the given time point and n is the number of evaluable subjects at that time point. We only included week 24 or week 48 data from studies in which all study participants had the opportunity to reach week 24 or week 48; otherwise, the above calculation would lead to downward-biased estimates as patients would be considered to have detectable plasma HIV RNA by virtue of their later enrollment into the study. To synthesize the data across regimens and trials, we used a fixed effects model whereby each result was weighted in direct proportion to the number of patients contributing data to the analysis. Ninety-five percent confidence intervals (CI) were constructed for the mean response rate using the derived weighted mean and its variance; 95% CI for the pairwise differences between drug classes were also derived analogous to the above weighted estimators. Comparison of response rates across drug classes yielded three contrasts, two of which are unique: NNRTI–PI, NNRTI–NUC, and PI–NUC. The statistical significance of the differences in mean response rates across drug classes was assessed by an asymptotic test based on the normal distribution. Estimates for each response variable are provided along with the number of treatment groups (N_t) and number of patients (N_p) which contributed to the estimate. Simple weighted linear correlation analysis and weighted least-squares regression using a backwards stepwise selection procedure was used to assess the variability in treatment group response rates as a function of the following population baseline and treatment factors: population baseline CD4 cell count, population median baseline $\log_{10}$ plasma HIV RNA, ART triple drug class, and average daily pill burden. These candidate predictors were selected as they have been shown in other studies to correlate with ART response. Logarithmic transformation of the predictor and response variables was used to stabilize the variance of the response variables.

Results

Descriptive characteristics of included trials

All trials included in this overview were conducted and presented or published between July 1994 and February 2000. Baseline patient characteristics and demographic data from the 23 trials that satisfied the inclusion criteria are presented in Table 1. The median $\log_{10}$ baseline HIV RNA across the treatment groups was 4.69 (49 329 copies/ml) and ranged from 4.25 to 5.33, while the mean CD4 cell count was 375×10^6/l and ranged from 185×10^6/l to 473×10^6/l. The mean patient age was 35 years; 83% of patients were male and 63% of patients were Caucasian.

Design characteristics

Design characteristics of the 23 clinical trials were as follows: all but four were randomized designs with a concurrent control arm; 12 were open-label, and 11 were double-blind.

Treatment regimens

A total of 31 independent treatment groups were included in the analysis, of which 19 were unique treatment regimens. The specific treatment regimens by drug class are summarized as follows: PI-triple, of the 15 PI-triple treatment groups included in this analysis, eight contained indinavir, four contained nelfinavir, one contained saquinavir-soft gel capsules, one contained amprenavir, and one contained lopinavir/ritonavir; NNRTI-triple, of the 13 NNRTI-triple regimens included, five contained efavirenz, four contained nevirapine, three contained emivirine, and one contained delavirdine; NUC triple: of the three triple-NUC regimens included in the analysis, two contained zidovudine + lamivudine + abacavir and one contained stavudine + didanosine + lamivudine. The most frequently represented treatment regimen was zidovudine + lamivudine + indinavir (n = 5). The distribution of the nucleoside backbone across the 31 independent treatment groups was: zidovudine + lamivudine [15], stavudine + didanosine [8], stavudine + lamivudine [5], zidovudine + didanosine [1], and didanosine + emtricitabine [1]. One trial (NV-15355) allowed the physician/patient to select the nucleoside backbone; there was no information reported from this trial on the frequency distribution of the chosen background nucleoside regimen.

Summary of virologic and immunologic results

Table 2 presents the results at 24 weeks and at 48 weeks. Estimates by triple therapy drug class and overall

Table 1. Baseline characteristics and demographics.

Trial	Design	Median HIV RNA ($\log_{10}$ copies/ml)	Median CD4 cell count ($\times 10^6$/l)	Female (%)	Median age (years)	Caucasian (%)	References
AI454–148	Open-label	4.69	368	29	35	56	Gathe *et al.* [13]
ANRS-091	Open-label	4.80	396	12	33	NR	Molina *et al.* [14]
Atlantic[a]	Open-label	4.35	424	20	35[b]	NR	Murphy *et al.* [15]
AVANTI-2	Double-blind	4.70	291	25	35	81	AVANTI Study Group [16]
AVANTI-3	Double-blind	5.00	448	11	35	78	Cooper *et al.* [17]
CNA3003	Double-blind	4.50	473	24	34	54	Fischl *et al.* [18]
CNAAB3005[a]	Double-blind	4.87	357	14	NR	NR	Staszewski *et al.* [19]
COMBINE	Open-label	4.80	354	26	36	NR	Podzamczer *et al.* [20]
DMP266–006[a]	Open-label	4.80[b]	343[b]	14	36[b]	60	Staszewski *et al.* [21]
DMP266–005	Double-blind	4.64[b]	386[b]	24	38[b]	68	Manion *et al.* [22],Haas *et al.* [23], Gallant *et al.* [24]
DMP266–043	Open-label	4.85[b]	375[b]	9	37[b]	46	Luskin-Hawk *et al.* [25]
DMP266–044	Open-label	4.89[b]	289[b]	17	38[b]	48	Luskin-Hawk *et al.* [25]
INCAS	Double-blind	4.25	395	8	38	96	Montaner *et al.* [26]
M97–720	Double-blind	4.90	301	3	35	63	Gulick *et al.* [27]
M/3331/0013C	Double-blind	5.33[b]	185[b]	45	36[b]	45	Wood *et al.*. [28]
MKC-202	Open-label	4.47	328	38	33	45	Johnson *et al.* [29]
MKC-301	Double-blind	4.28	456	46	32	50	Sereni *et al.* [30]
MKC-302	Double-blind	4.99	341	45	33	43	Raffi *et al.* [31]
NV15355	Open-label	4.80[b]	449[b]	8	38[b]	68	Tsoukas *et al.* [32]
PROAB3001	Double-blind	4.64	442	11	35	77	Goodgame *et al.* [33]
START I	Open-label	4.53	399	23	37[b]	51	Squires *et al.* [34], Squires *et al.* [35]
START II	Open-label	4.50	422	15	37[b]	61	Eron *et al.* [36]
VIRGO I/II	Open-label	4.70	413	23	34[b]	NR	Raffi *et al.* [37,31]

[a]Values averaged across treatment groups. [b]Denotes mean value. NR, Not reported.

Table 2. Undetectable HIV RNA and CD4 cell count increase from baseline: results at 24 and 48 weeks.

	Week 24			Week 48		
	% < 400 HIV RNA copies/ml (ITT)	% < 50 HIV RNA copies/ml (ITT)	CD4 cell count increase ($\times 10^6$/l)	% < 400 HIV RNA copies/ml (ITT)	% < 50 HIV RNA copies/ml (ITT)	CD4 cell count increase ($\times 10^6$/l)
PI-Triple						
N_t	15	13	14	12	12	11
N_p	1740	1365	1687	1295	1295	1242
Weighted mean (95% CI)	62 (58 to 67)	53 (48 to 58)	130 (111 to 149)	53 (48 to 59)	46 (41 to 52)	168 (145 to 191)
NNRTI-Triple						
N_t	13	13	13	9	7	10
N_p	1063	1063	1063	812	582	886
Weighted mean (95% CI)	66 (60 to 72)	55 (49 to 61)	122 (102 to 143)	57 (50 to 64)	51 (43 to 59)	153 (123 to 183)
Triple-NUC						
N_t	3	3	3	3	3	3
N_p	454	454	454	454	454	454
Weighted mean (95% CI)	64 (55 to 73)	52 (43 to 61)	101 (84 to 119)	54 (45 to 63)	45 (36 to 54)	151 (138 to 164)
Total						
Overall N_t	31	29	30	24	22	24
Overall N_p	3257	2882	3204	2561	2331	2582
Overall Weighted mean (95% CI)	64 (60 to 67)	54 (50 to 57)	123 (111 to 135)	55 (51 to 58)	47 (43 to 51)	160 (146 to 175)

ITT, Intent-to-treat; N_t, number of treatment groups upon which estimate is based; N_p, number of patients upon which estimate is based.

are provided, along with the 95% CI. The number of treatment groups (N_t) and patients (N_p) upon which the grouped estimates were calculated are also provided.

Plasma HIV RNA ⩽ 400 copies/ml

The overall percentage of patients having plasma HIV RNA ⩽ 400 copies/ml at week 24 was 64% (N_t, 31; N_P, 3257; 95% CI, 60–67%). The results by drug class

demonstrated that the NNRTI class had an overall response rate of 66%, followed by the triple NUC (64%) and PI classes (62%) (95% CI for difference of NNRTI versus PI, −4 to 11%, and NNRTI versus NUC, −9 to 13%). This result appears to have been influenced by studies DMP-043, DMP-044, and ANRS-091, as the relatively high response rates in these studies may have resulted in a disproportionately high weight relative to the other studies. The overall mean estimate of the percentage of patients with plasma HIV RNA ⩽ 400 copies/ml at week 48 was 55%, and the difference observed across drug classes at week 24 was not observed at week 48.

Plasma HIV RNA ⩽ 50 copies/ml

The overall percentage of patients having plasma HIV RNA ⩽ 50 copies/ml at week 24 was 54% (N_t, 29; N_P, 2882; 95% CI, 50 to 57%). The results by drug class indicate that the NNRTI group had a similar percentage of patients with plasma HIV RNA ⩽ 50 copies/ml at week 24 (55%) than the triple NUC and PI patients (52% and 53%, respectively). However, the overall mean estimate at week 48 was 47%, with no significant difference among drug classes.

Change from baseline in CD4 cell count

The overall mean increase in CD4 cell count at week 24 was 123×10^6/l (N_t, 30; N_P, 3204; 95% CI, 111 to 135) and at week 48 it was 160×10^6/l (N_t, 24; N_P, 2582; 95% CI, 146 to 175). At week 24 the NNRTI class had an improved CD4 cell count relative to the NUC class (95% CI for difference, 1 to 42; $P < 0.05$) whereas the PI class had an improved CD4 cell count relative to the NUC class (95% CI for difference, 9 to 47; $P < 0.01$). Although there was a trend towards superior CD4 cell responses in the PI drug class at week 48, there was considerable overlap among the 95% CI.

Multivariable linear regression analysis

To examine the variability of the response rates across treatment groups, we fit a multiple linear regression analysis to the response variable including the predictor variables triple drug class, baseline CD4 cell count, baseline $\log_{10}$ plasma HIV RNA, and average daily pill burden. The results of these analyses are shown (Table 3). Population median baseline plasma HIV RNA, population median baseline CD4 cell count, and triple drug class did not predict treatment response at 24 or 48 weeks with the exception of greater CD4 cell increases at 24 and 48 weeks in subjects receiving PI ($P < 0.05$ for week 24; $P < 0.10$ for week 48). In contrast, pill count did predict significantly the percentages of subjects with RNA levels ⩽ 400 and ⩽ 50 copies/ml at weeks 24 and 48, or greater increases in CD4 cell count at week 24. These results were consistent if the trials which utilized bDNA assays for plasma HIV RNA measurement were excluded from the multivariable linear regression analysis, if the trials investigating unapproved agents (emtricitabine or emivirine) were excluded, or if only the results of published trials were included (results not shown). Fig. 1 presents a scatter plot of the antiretroviral response (< 50 copies/ml) at week 48 versus the average number of tablets per day in the treatment regimen. The results indicate that regimens involving a fewer number of pills per day were associated with a superior virologic response (r, −0.57; $P = 0.0085$). The results suggest that daily pill burden was the most significant predictor of the antiretroviral response at 48 weeks. This conclusion was supported by additional sensitivity analyses in which different modeling approaches were employed; i.e., forward versus backwards selection.

Discussion

This overview of 24 and 48 week treatment responses in ART-naive HIV-infected subjects demonstrates similar suppression of plasma HIV RNA levels to < 50

Table 3. Parameter estimates and significance levels from multiple linear regression analysis of virologic and immunologic results[a].

	Week 24			Week 48		
Variable	HIV RNA < 400 copies/ml (%)	HIV RNA < 50 copies/ml (%)	CD4 cell count	HIV RNA < 400 copies/ml (%)	HIV RNA < 50 copies/ml (%)	CD4 cell count
Baseline CD4 cell count	NS	NS	NS	NS	NS	NS
Baseline HIV RNA (copies/ml)	NS	NS	NS	NS	NS	NS
Pill burden	-0.20^{***}	-0.169^{**}	-55.2^{***}	-0.399^{***}	-0.566^{**}	-45.6^{*}
Drug class	NS	NS	20.1^{**}	0.075	0.143	20.1^{*}
Model R^2	0.32	0.10	0.28	0.43	0.34	0.17

[a]Parameter estimates are reported when significant at $\alpha = 0.15$; estimates were calculated from stepwise multiple regression analysis using a backward selection procedure. Estimated regression coefficients were adjusted for all other variables which remained in the final model. NS denotes that the variable met the significance level criterion for elimination from the model at $\alpha = 0.15$, therefore no parameter estimate was obtained. Superscripts on parameter estimates indicate that the variable was significant at the following significance levels (drug class modeled as a linear predictor with three levels: 1, non-nucleoside reverse transcriptase inhibitor; 2, nucleoside reverse transcriptase inhibtor; 3, protease inhibitors): *statistically significantly different from zero, $P < 0.10$; **statistically significantly different from zero, $P < 0.05$; ***statistically significantly different from zero, $P < 0.01$.

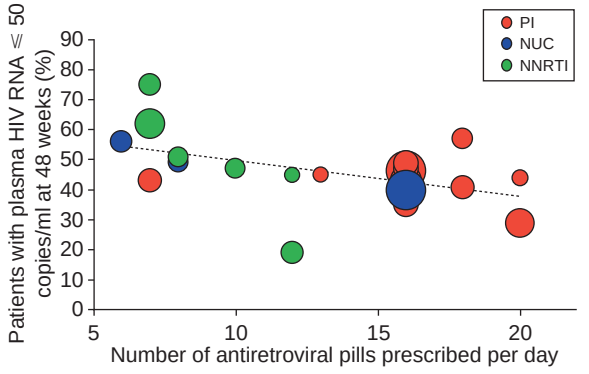

Fig. 1. Virologic response by daily pill burden (*r*, −0.57; $P = 0.0085$). Symbol size is directly proportional to weight of the data point in the analysis.

copies/ml in patients receiving triple therapy containing two NRTI with a PI, a NNRTI, or a third NRTI. This finding was confirmed in a multiple logistic regression model controlling for baseline plasma HIV RNA level, baseline CD4 cell count, and prescribed pill count for each treatment regimen. Interestingly, neither population baseline plasma HIV RNA level nor CD4 cell count was a significant predictor of suppressing HIV RNA to < 50 copies/ml at week 48. However, a significant correlation was established between the percentage of patients with HIV RNA < 50 copies/ml at week 48 and pill count. This correlation carries important implications for the choice of treatment regimens in ART-naive patients.

A potential strength of this study is the large sample size of 3257 subjects across 23 clinical trials. The largest single clinical trial (CNAAB3005) in this overview included 562 subjects (282 and 280 patients per treatment group). An overview was performed of similarly designed treatment trials; all subjects were ART-naive, all received three-drug combination therapy including two NTRI, nearly all plasma HIV RNA results used the Roche Amplicor Monitor assay, and all provided adequate data to calculate plasma HIV RNA results using the intent-to-treat method. By using this large number of patients, significant diversity was achieved in demographics, geographic distribution, and disease stage. Pooling of data across these clinical trials is justified because a common method of assaying plasma HIV RNA was used, there is general consistency of response to each of the three drug class regimens across trials, and one drug does not appear to dominate within a class with the possible exception of efavirenz in the NNRTI class.

The possible limitations of the current study include the inability to reach conclusions about specific drugs and drug regimens as these conclusions should only be reached following the analysis of prospective, randomized trials comparing treatment regimens. Differences in activity within a drug class may also exist and are not addressed by this overview. Secondly, the mean CD4 cell count of the subjects was 375×10^6/l and the median plasma HIV RNA level was 49 329 copies/ml. It may not be possible to extrapolate these results to patient populations with very low CD4 cell counts or very high plasma HIV RNA levels beginning antiretroviral therapy. Third, the follow-up period of this overview is only 48 weeks, and continuing follow-up beyond week 48 will be important. Nevertheless, plasma HIV RNA levels < 50 copies/ml have been identified as an important predictor of durable virologic response and therefore week 48 assessments are likely to have long-term predictive value. Fourth, this overview was not performed with individual subject data because these data were unavailable. Therefore a summary statistic overview was performed, which may introduce some variability. There are additional potential sources of bias in the overview. While most trials were randomized, the majority were open-label, and some of the treatment regimens utilized medication formulations that are different from those commercially available (e.g., indinavir 200 mg capsules in clinical trials versus 400 mg capsules available commercially). In the multivariable linear regression analysis the R^2 values for our models were relatively low, suggesting that our predictor variables can only explain a proportion of the differences in treatment activity. Finally, our results suggesting the importance of pill burden need to be confirmed in additional clinical trials.

Across the three drug classes, the percentages of patients with plasma HIV RNA levels < 50 or < 400 copies/ml at weeks 24 and 48 were not significantly different, although the NNRTI triple had the highest percentage. In one prospective randomized trial, a combination of zidovudine, lamivudine, and efavirenz did achieve a significantly higher percentage of subjects with RNA $\leqslant 50$ copies/ml compared to zidovudine, lamivudine and indinavir, or efavirenz and indinavir. In our review, efavirenz-containing regimens were responsible for the overall success of the NNRTI group. When efavirenz-containing regimens were excluded, only 38% of NNRTI-treated patients had RNA levels < 50 copies/ml at 48 weeks. However, because many of the trials evaluating efavirenz were not blinded, these results may be difficult to compare to the results of well-controlled, double-blind clinical trials.

Absolute CD4 cell responses add predictive value for clinical outcomes beyond the measurement of plasma HIV RNA responses. The overall CD4 cell count increase at 48 weeks was $+160 \times 10^6$/l, and the increases in CD4 cell counts by drug class had overlapping 95% CIs. The multivariable logistic regression analysis favored PI regimens at 24 weeks ($P < 0.05$), but there were more modest significant differences at

48 weeks ($P < 0.10$). If the three drug classes provide similar suppression of plasma HIV RNA and increases in CD4 cell counts in ART-naive HIV-infected subjects, then other factors should guide the choice of initial ART. These factors may include adherence to the regimen, drug-related toxicities, and potential for emergence of cross-resistant HIV in patients who experience failure on their initial ART.

Adherence to antiretroviral medications was not assessed prospectively during many of the trials included in this overview, and therefore no definite conclusions can be reached. The factors influencing adherence are complex and include dosing frequency, food restrictions, drug-related toxicities and pill burden. In the context of this overview, we sought to characterize the variability of treatment response to patient and treatment factors that have been reported to increase the likelihood of virologic failure. Therefore, the nominal pill burden was tabulated for each of the treatment regimens. In the multivariable analysis examining the predictors of plasma HIV RNA levels < 50 copies/ml at weeks 24 and 48, lower pill burden was strongly associated with greater virologic suppression, independent of the assigned treatment regimen. Interestingly, the level of significance increased from week 24 to week 48, raising the possibility that pill count becomes a stronger predictor over time, perhaps due to treatment fatigue. These results suggest that simpler, potent regimens with few pills should be considered in choosing initial ART to achieve durable virologic suppression.

The strong predictive value of pill count for achieving virologic suppression confirms our clinical experience that complex regimens are challenging for patients. This may seem to be a trivial issue; however, this finding poses a serious challenge to clinical trial design. The most robust clinical trial design includes the use of both active and inactive medications to ensure blinding of both study subjects and investigators. Within double-blind comparative treatment trials the high pill burden containing both active and inactive components imposed on study participants may lead to suboptimal treatment responses, presumably due to decreased adherence. The impact on study subjects may be greatest when there is a large discrepancy in active pill number between treatment arms, leading to the disproportionate addition of inactive pills to one arm.

The finding that population baseline plasma HIV RNA levels and CD4 cell counts did not significantly predict virologic and immunologic responses was unexpected. Baseline plasma HIV RNA levels and CD4 cell counts did have marginal significant predictive value for HIV RNA < 400 copies/ml at week 24, but not for HIV RNA < 50 copies/ml at week 24 or either threshold at week 48. Previous studies have suggested that baseline plasma HIV RNA levels, CD4 cell counts, or symptomatic HIV disease may predict virologic responses. Our finding is supported by the large sample size, the inclusion of a relatively homogeneous subject population, and the potency of newer treatment regimens, even in subjects with high baseline plasma HIV RNA, low CD4 cell counts, and symptomatic disease. However, our analysis included only aggregate data from the studies surveyed and the group baseline plasma HIV RNA levels and CD4 cell counts displayed relatively little heterogeneity. Stronger conclusions could be reached if results from individual subject data with a broader range of baseline plasma HIV RNA levels and CD4 cell counts were available. Ultimately, decisions regarding the early versus delayed initiation of ART should be guided by prospective randomized clinical trials.

Recognizing that only 47% of subjects in the overall overview have plasma HIV RNA levels < 50 copies/ml after 48 weeks of treatment, more than half of the patients did not derive full benefit from their initial regimen. This result underscores the need for the continuing development of potent ART and strategies to optimize its use. Of the total percentage of patients who did not have full benefit at 48 weeks, some had virologic rebound. Viral isolates during rebound are likely to be resistant to one or more of the components of the initial regimen, and may compromise the antiretroviral activity of subsequent regimens. Multidrug resistant isolates are a major obstacle to the successful management of the HIV-infected patients, and one of the most effective ways to limit multidrug resistant virus is to optimize initial therapy.

In summary, this overview of 3257 ART-naive subjects initiating triple therapy suggests the comparability of dual NRTI combined with a PI, an NNRTI or a third NRTI as measured by suppression of plasma HIV RNA to < 50 copies/ml and increases in CD4 cell count at 48 weeks.

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