An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults

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Objective: To compare the effectiveness of three drug combination antiretroviral therapy (ART) in treatment-naive HIV-infected persons, and identify the predictors of responses.

Design and methods: Overview of trials identified by searching public domain publications and conference presentations. The three-drug combination therapy was defined as two nucleoside reverse transcriptase inhibitors (NRTI) or nucleotide and NRTI, and either: (1) a protease inhibitor (PI); (2) a non-nucleoside RTI (NNRTI); (3) a third NRTI; or (4) a ritonavir-boosted PI (BPI). Week 24 and 48 results for the proportions of patients with plasma HIV RNA levels < 400 and < 50 copies/ml, and change in CD4+ cell counts were recorded.

Results: Fifty-three trials met the entry criteria, and enrolled 14 264 patients into 90 treatment arms. Overall 55% of patients had plasma HIV RNA levels < 50 copies/ml at week 48 and this percentage increased with later publication dates. In unadjusted pairwise comparisons at week 48, significantly greater percentages of patients receiving NNRTI (64%) and BPI (64%) had RNA < 50 copies/ml than NRTI (54%) or PI (43%), and CD4+ cell count increases were significantly greater in the BPI group (+200 cells/μl) than the PI (+179), NNRTI (+173), or NRTI (+161) groups. Pill count and percentage of patients with week 48 plasma HIV RNA levels < 50 copies/ml were correlated in the univariate analysis ($P = 0.0053$; $r = -0.323$), but pill count was not a significant predictor in the multivariate analyses. Drug class and baseline CD4+ cell counts were significant predictors, but explained only a modest amount of the treatment effect, ($R^2 = 0.355$).

Conclusions: NNRTI and BPI-containing regimens offer superior virologic suppression over 48 weeks, supporting existing guidelines for the choice of initial ART. Pill count was not a consistent predictor of virologic suppression.

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Introduction

Antiretroviral therapy with three agents provides potent suppression of plasma HIV RNA levels below detectable limits in many treated persons, with resulting immunologic improvements, decreases in HIV-related complications, and prolonged survival. Twenty individual antiretroviral drugs, four fixed dose two-drug combinations, and two fixed dose three-drug combinations are currently available, resulting in 364 potential three-drug combinations for treatment. The ideal drug combinations will maximize antiretroviral potency, immunologic reconstitution, and quality of life while minimizing medication-related toxicities and the potential for drug resistance. Published guidelines utilize the currently available evidence base to make specific

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recommendations regarding treatment [1,2], but obviously not all three-drug combinations can be compared directly in clinical trials.

Although prospective, randomized trials provide the most robust evidence for regimen comparisons, systematic overviews may assist in assessing the relative attributes of alternative initial treatment regimens. A previous systematic overview identified the need for improved potency in initial treatment regimens, a lack of differences in virologic suppression and CD4+ cell count increases between treatment regimens using unboosted protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and a third nucleoside reverse transcriptase inhibitor (NRTI) with two NRTI in three-drug regimens, and the predictive value of pill count for virologic responses [3]. However, since the publication of this systematic overview additional clinical trials have been completed evaluating novel classes of antiretroviral agents [boosted protease inhibitors (BPI), nucleotide reverse transcriptase inhibitors and fusion inhibitors], and simpler treatment regimens with lower pill counts due to improved formulations and fixed dose combinations.

This systematic overview was performed to re-examine the activity of initial three-drug combinations in antiretroviral-naive persons with contemporary agents, the predictors of activity, and the temporal changes in activity over time.

Methods

Study selection

A search of public domain and recent conference presentations was conducted for the period from 1994 to July 2004. A MEDLINE search was undertaken with the following keywords: clinical trial, plasma HIV-1 RNA, HAART, antiretroviral therapy, and naive. In addition, the package inserts for US Food and Drug Administration (FDA)-approved antiretroviral drugs were examined and listed trials were reviewed. Proceedings from the following conferences were reviewed: Conference on Retroviruses and Opportunistic Infections (CROI), the World AIDS Conference, the International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, the European Conference on Clinical Aspects and Treatment of HIV Infection, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the International Conference on Drug Therapy in HIV Infection (ICDT), and the Annual Meeting of the Infectious Diseases Society of America (IDSA). Triple combination therapy was defined as either two nucleoside or a nucleoside and a nucleotide reverse transcriptase inhibitor and either: (1) a protease inhibitor (PI); (2) a non-nucleoside reverse transcriptase inhibitor (NNRTI); (3) a third nucleoside reverse transcriptase inhibitor (NRTI); or (4) a ritonavir-boosted protease inhibitor (BPI). Regimens were assigned to these four categories based upon the class of the third agent in the regimen, (PI, NNRTI, NRTI and BPI; the inclusion of BPI-containing regimens represents an addition since the previous overview). Trials were included if they were at least 24 weeks in duration, had at least 30 patients per treatment arm, included chronically HIV-infected patients who were treatment-naive or had very limited prior exposure to antiretroviral therapy (< 2 weeks prior NRTI exposure), and reported the percentages of patients with undetectable plasma HIV RNA levels (< 400 and < 50 copies/ml) using an intent-to-treat missing equals failure analysis, (ITT:M = F). Trials were excluded if they studied induction/maintenance strategies, acutely or recently infected patient populations (< 6 months since seroconversion), or experimental treatments which did not successfully receive US FDA approval.

Data collection

Following inclusion of a trial in the overview, all published or presented source documentation was reviewed for each trial, (journal citations, conference abstract books, posters, slides, package inserts, etc.). Information on each trial was abstracted on the following trial characteristics and results: (1) trial design: treatment regimens, open-label or blinded, randomization if used, control groups, and average daily pill count (defined as the number of pills or tablets/day including placebo) in the treatment regimen; (2) baseline characteristics: number of individuals enrolled, percentage male, race, age, $\log_{10}$ plasma HIV RNA, and CD4+ cell counts; and (3) response rates: percentages of patients with plasma HIV RNA < 400 and < 50 copies/ml at 24 and 48 weeks in the ITT:M = F populations, and change in CD4+ cell counts at 24 and 48 weeks in the as-treated populations. The date of a study's first presentation or publication was defined as the 'publication date'. Publication dates were divided into the following intervals; prior to 1998, 1999–2000, 2001–2002 and 2003–2004. Abstractions were performed by one reviewer and were confirmed by a second; any discrepancies were reconciled by conference with the study team. If median values were unavailable then the mean was used. All trials reported plasma HIV RNA results with the Roche Amplicor assay (< 400 copies/ml) and the Roche Ultrasensitive assay (< 50 copies/ml) (Roche Diagnostics, Indianapolis, Indiana, USA) with the exception of the START I and II trials and the VIRGO I/II trials, where the results were reported as the percentage < 500 copies/ml with the Chiron bDNA assay (Chiron Corporation, Emeryville, California, USA).

Statistical methods

For plasma HIV RNA responses, the primary analysis utilized reported results for ITT:M = F population, and for changes in CD4+ cell counts, the primary analysis used reported results for the as-treated population. When

ITT:M = F results were unavailable, the ITT:M = F results were calculated using the number of patients with plasma HIV RNA undetectable at weeks 24 or 48 divided by the number of enrolled patients. Response rates for each of the four drug classes (PI, NNRTI, NRTI and BPI) were estimated with the number of treatment groups and patients contributing to the estimate. These resulting estimates were then compared by constructing confidence intervals (CI) for the differences in response rates between drug classes. Correlation analyses and weighted least squares multivariate linear regression analyses (MLR) using backwards stepwise selection procedures were used to assess the variability in treatment group response rates as a function of the following factors; baseline $\log_{10}$ plasma HIV RNA level and CD4+ cell count, drug class, and average daily pill count. For the MLR analysis of categorical virologic endpoints, the natural log of the response rate was used. Statistical significance was determined using alpha = 0.05. Bubble plots were constructed, and the results for each treatment arm were weighted in direct proportion to the numbers of patients enrolled. Sensitivity analyses were conducted to evaluate different factors including dichotomous pill counts ($\leq$ 10/day versus $>$ 10/day), analyses of continuous pill counts over these ranges (3–10/day and 11–22/day), and pill counts as predictors of response within each regimen category.

Results

Descriptive characteristics of included trials

Fifty-three trials met the inclusion criteria and are listed in Table 1, (representing the addition of 30 trials since the previously published overview). These 53 trials enrolled 14 264 patients into 90 independent treatment arms. The median baseline plasma HIV RNA level was 4.75 $\log_{10}$ copies/ml and the median baseline CD4+ cell count was 315/μl. Seventy-six percent of patients were male.

Design characteristics and regimens studied

Thirty-four trials were randomized and 19 included only one treatment arm. Thirty-two trials were open-label, 19 were double-blinded, and two were partially blinded. A total of 90 treatment arms were included in these 53 trials with 40 unique treatment regimens. NNRTI-containing regimens were most commonly studied (n = 38), followed by PI-containing (n = 32), NRTI-containing (n = 12) and BPI-containing regimens (n = 8). Efavirenz-containing regimens were most commonly studied; they were included in 20 different trials and 29 treatment regimens in 5798 individuals. In addition, efavirenz-containing regimens were combined with more NRTI combinations than any other drug, (nine stavudine and lamivudine, eight zidovudine and lamivudine, four abacavir and lamivudine, three stavudine and didanosine, two didanosine and lamivudine, two didanosine and emtricitabine, one tenofovir and lamivudine). In comparison with the previous overview, there was a slight decrease in the representation of PI-containing regimens [15/31 regimens in 2001 (48%) versus 32/90 in 2005 (36%)], no difference in the representation of NNRTI-containing regimens [13/31 regimens in 2001 (41%) versus 38/90 in 2005 (42%)], a substantial increase in the number of efavirenz-containing regimens (five in 2001 versus 29 in 2005), and the addition of BPI-containing regimens. The median pill count was 10/day, with a range of 3–22/day.

Temporal trends in baseline characteristics and responses by publication date

In the previous overview, the median baseline plasma HIV RNA levels and CD4+ cell counts were 4.69 $\log_{10}$ copies/ml and 375/μl. In the current update, the values were 4.75 $\log_{10}$ copies/ml (P = 0.10) and 315/μl (P = 0.001). Over the period of observation, the weighted mean responses for the percentage of patients with plasma HIV RNA levels $<$ 50 copies/ml at week 48 steadily improved, (prior to 1998, 41%; 1999–2000, 50%; 2001–2002, 56%; 2003–2004, 64%), (Fig. 1). During the same periods of time the weighted mean responses for increases in CD4+ cell counts at week 48 were similar, (prior to 1998, +173 cells/μl; 1999–2000, +174 cells/μl; 2001–2002, +180 cells/μl; 2003–2004, +169 cells/μl) (Fig. 1).

Virologic and immunologic responses

The virologic and immunologic responses at weeks 24 and 48 are shown in Table 2 with the number of treatment arms and patients, the weighted means, and the 95% CI. These responses are unadjusted for baseline characteristics, and are presented as the percentages with plasma HIV RNA levels below 400 and 50 copies/ml and the change from baseline in CD4+ cell counts by drug class. Overall, 55% of patients had plasma HIV RNA levels below 50 copies/ml at week 48 with a CD4+ cell count change from baseline of +176 cells/μl. In unadjusted pairwise comparisons of the proportions of patients with plasma HIV RNA $<$ 50 copies/ml at week 48, the BPI and NNRTI groups were each superior to the PI and NRTI groups (BPI versus PI, $P < 0.001$; BPI versus NRTI, P = 0.017; NNRTI versus PI, $P < 0.001$; NNRTI versus NRTI, P = 0.001), but were not significantly different from each other, (BPI versus NNRTI, P = 0.945). The NRTI group was also superior to the PI group in pairwise comparisons (P = 0.001). In pairwise comparisons of the unadjusted changes from baseline in CD4+ cell counts, the BPI group was superior to NNRTI, PI and NRTI groups (BPI versus NNRTI, $P < 0.001$; BPI versus PI, P = 0.004; BPI versus NRTI, $P < 0.001$). The PI and NNRTI groups did not have significantly greater increases in CD4+ cell counts than the NRTI group, and were not significantly different from each other.

Figure 2 displays a bubble plot of the relationship between pill count and plasma HIV RNA levels $<$ 50 copies/ml at

Table 1. Studies included in the analysis.

Study name/number	Class	Regimens	No patients	BL RNA	BL CD4
Study 096 Brett-Smith, 2002 [4]; Pollard, 2002 [6]; Brett-Smith, 2003 [5]	NNRTI	EFV + 3TC + d4T(ir)	76	4.65	285
	NNRTI	EFV + 3TC + d4T(xr)	74	4.65	285
Study 099 Brett-Smith, 2002 [4]; Pollard, 2002 [6]; Brett-Smith, 2003 [5]	NNRTI	EFV + 3TC + d4T(ir)	391	4.8	277
	NNRTI	EFV + 3TC + d4T(xr)	392	4.8	277
2NN van Leth, 2003 [8]; Van Leeuwen, [7] 2002; van Leth, [9] 2004	NNRTI	NVP qd + d4T + 3TC	220	4.7	200
	NNRTI	NVP bid + d4T + 3TC	387	4.7	170
	NNRTI	EFV qd + d4T + 3TC	400	4.7	190
ACTG 384 Shafer, 2003 [12]; Robbins, 2002 [10]; Robbins, 2002 [11]	NNRTI	EFV + ZDV + 3TC	155	4.9	278
ACTG 5095 Gulick, 2004 [14]; Gulick, 2003 [13]; NIAID, 2003 [15]; NIAID; 2003 [15]	NRTI	ZDV + 3TC + ABC	382	4.9	234
AI424-007 Sanne, 2003 [17]; Squires, 2001 [18]; Gatell, 2001 [16]	PI	ZDV (400) + ddI + d4T	78	4.65	357
	PI	NFV + ddI + d4T	82	4.79	341
AI424-008 Sanne, 2001 [24]; Cahn, 2001 [20]; Murphy, 2003 [21]; Pantaleo, 2001 [23]; Wood, 2004 [25]; Bristol-Myers Squibb Company, 2004 [19]; Murphy, 2003 [22]	PI	ZDV (400) + d4T + 3TC	181	4.74	294
	PI	NFV + d4T + 3TC	91	4.73	283
AI424-034 Squires, 2002 [28]; Delfraissy, 2002 [27]; Bristol-Myers Squibb Company, 2004 [26]	NNRTI	EFV qd + COM	405	4.8	321
	PI	ZDV qd + COM	405	4.8	321
AI454-148 Gathe, 1999 [29]; Bristol Myers Squibb, 2004 [26]	PI	NFV + ZDV + 3TC	253	4.69	340
	PI	NFV + ddI + d4T	503	4.69	340
AI454-152 Badaro, 2001 [30]; Gathe, 2001 [31]; Bristol Myers Squibb, 2004 [26]	PI	NFV + COM	253	4.71	411
	PI	NFV + ddI-EC + d4T	258	4.71	411
ANRS 091 (MONTANA) Molina, 2000 [32]; Molina, 2001 [33]; Molina, 2000 [34]; Molina, 2003 [36]; Molina, 2000 [35]	NNRTI	EFV + ddI + FTC	40	4.8	396
ANRS 12-04 Landman, 2002 [37]; Landman, 2003 [38]	NNRTI	EFV + ddI + 3TC	40	5.4	164
Atlantic Murphy, 1999 [39]; van Leeuwen, 2003 [40]	NNRTI	NVP + ddI + d4T arm 3	89	4.33	394
	NRTI	3TC + ddI + d4T arm 2	109	4.2	396
	PI	IDV + ddI + d4T arm 1	100	4.3	417
AVANTI 2 Avanti Study Group, 2000 [41]; Hill, 1998 [43]; Goebel, 1997 [42]	PI	IDV + ZDV + 3TC	52	4.7	281
AVANTI 3 Gartland, 2001 [45]; Clumeck, 1998 [44]	PI	NFV + ZDV + 3TC	53	5	295
CLASS Bartlett, 2002 [46]; Bartlett, 2004 [132]	BPI	APV/RTV + ABC + 3TC	96	4.8	296
	NNRTI	EFV + ABC + 3TC	97	4.9	307
	NRTI	ABC + d4T + 3TC	98	4.9	299
CNA 30021(ZODIAC) Gazzard, 2003 [47]; Glaxo-Smith-Kline, 2005 [48]; Piliero, 2003 [49]	NNRTI	EFV + ABC qd + 3TC	384	4.89	264
	NNRTI	EFV + ABC + 3TC	386	4.89	259
CNA 3003 (CNAA3003/CNAB3003) Fischl, 1999 [50]; Fischl, 1998 [51]	NRTI	ABC + ZDV + 3TC	87	4.5	473
CNA30024 Dejesus, 2003 [52]; Glaxo-Smith-Kline, 2005 [48]	NNRTI	EFV + ABC + 3TC	324	4.79	267
	NNRTI	EFV + ZDV + 3TC	325	4.79	258

Table 1 (*continued*)

Study name/number	Class	Regimens	No patients	BL RNA	BL CD4
CNA3005 (CNAB3005) Staszewski, 1999 [53]; Staszewski, 1999 [54]; Staszewski, 1999 [55]; Staszewski, 2001 [56]	NRTI	ABC + ZDV + 3TC	282	4.85	359
	PI	IDV + ZDV + 3TC	280	4.82	360
CNA3014 Vibhagool, 2001 [58]; Jordan J, [57] 2002; Vibhagool, [59] 2004	NRTI	ABC + COM	164	4.78	331
	PI	IDV + COM	165	4.82	299
CNAF3007 Matheron, [60] 2003	NRTI	ABC + COM	95	4.2	387
	PI	NFV + COM	91	4.1	449
COMBINE Podzamczer, 2002 [129]; Podzamczer, 2000 [62]; Podzamczer, 2001 [61]	NNRTI	NVP + COM	72	4.77	361
	PI	NFV + COM	70	4.81	351
Dart I Dejesus, 2003 [63]; Ward, 2004 [64]	NNRTI	EFV + ddI-EC + 3TC	65	4.8	311
DART II Brett-Smith, 2003 [5]; Ward, 2004 [64]; Jayaweera, 2004 [66]; Felizarta, 2004 [65]	NNRTI	d4T-XR + 3TC + EFV	70	4.54	351
DMP 266-005 Manion, 1999 [69]; Manion, 1999 [70]; Hicks, 1998 [68]; Haas, 1998 [67]	NNRTI	EFV + ZDV + 3TC	34	4.64	386
DMP266-006 Staszewski, 1999 [69]	NNRTI	EFV + ZDV + 3TC	154	4.77	345
	PI	IDV + ZDV + 3TC	148	4.79	341
DMP266-043 Luskin-Hawk, 1999 [72]; Cohen, 2000 [71]	NNRTI	EFV + d4T + 3TC	68	4.85	375
DMP266-044 Luskin-Hawk, 1999 [72]; Cohen, 2000 [71]	NNRTI	EFV + ddI + d4T	65	4.89	289
Domula Domula, 2002 [73]	NNRTI	EFV + COM	35	4.9	275
	NNRTI	EFV + d4T + 3TC	35	4.9	163
	NNRTI	EFV + ddI + d4T	38	4.9	165
Earth-2 Garcia, 1999 [74]; Garcia, 2000 [75]	PI	IDV + d4t + 3TC	32	4.38	708
EPV 20001 DeJesus, 2004 [76]	NNRTI	3TC qd + ZDV + EFV	278	4.64	340
	NNRTI	3TC bd + ZDV + EFV	276	4.69	386
EPV 40001 Bowonwatanuwong, 2001 [77]	NRTI	ZDV + 3TC 300 qd + ABC 300 bid	50	4.8	380
	NRTI	ZDV + 3TC 150 bid + ABC 600 qd	51	4.8	380
	NRTI	ZDV + 3TC 150 bid + ABC 300 bid	50	4.8	380
FTC 301A Saag, 2002 [80]; Raffi, 2003 [79]; Cahn, 2003 [78]; Saag, 2002 [80]	NNRTI	EVF + ddI + FTC qd	286	4.9	282
	NNRTI	EFV + ddI + d4T	285	4.9	300
Gerstoft, Danish study Katzenstein, 2000 [81]; Gerstoft, 2003 [82]; Hill, 2004 [83]	NRTI	ABC + d4T + ddI	60	5.00	190
	PI	3TC + ZDV + SQV/r (400/400 bid)	60	5.00	152
GPO Bangkok Anekthananon, 2004 [84]	NNRTI	d4T + 3TC + NVP	101	5.40	59
GS 903 Gallant, 2002 [85]; Staszewski, 2003 [86]	NNRTI	EFV + 3TC + TDF + PLA	299	4.9	276
	NNRTI	EFV + d4T + 3TC + PLA	301	4.9	283
ICC-002 Skowron, 1997 [87]	NNRTI	NVP + ZDV + ddI	53		
	NRTI	ZDV + ddI + 3TC	53		
IMEA-01 Saimot, 1998 [88]	PI	RTV + ddI + d4T	36	4.86	236
INCAS Myers, 1996 [91]; Montaner, 1998 [89]; Montaner, 1998 [90]	NNRTI	NVP + ZDV + ddI	51	4.25	395
M/3331/0013C Wood, 1999 [92]; Wood, 2004 [25]	NNRTI	DLV + ZDV + 3TC	74	5.33	185
M02-418 Gathe, 2004 [93]; Podzamczer, 2003 [94]	BPI	LPV/RTV + FTC + TDF (qd)	115	4.8	214
	BPI	LPV/RTV + FTC + TDF (bid)	75	4.6	232
M97-720 (ABT 378/R) Murphy, 2001 [100]; Murphy, 2002 [99]; Eron, 1999 [95]; Hicks, 1999 [97]; White, 2001 [101]; Landay, 2002 [98]; Gulick, 2000 [96]	BPI	LPV/RTV + d4T + 3TC	68	4.9	301

Table 1 (*continued*)

Study name/number	Class	Regimens	No patients	BL RNA	BL CD4
M98-863 Walmsley, 2002 [134]; Luo, 2002 [104]; Cernohous, 2002 [102]; King, 2002 [103]	BPI	LPV/RTV + d4T + 3TC	326	5.01	232
	PI	NFV + d4T + 3TC	327	4.98	232
Merck Study Schranz, 2001 [105]	BPI	IDV-RTV + d4T + 3TC	89	5.03	238
NEAT (APV 30001) Nadler, 2003 [106]; Rodriguez-French, 2002 [107]; Rodriguez-French, 2004 [108]; Vertex Pharmaceuticals, 2004 [109]	PI	fosAPV + 3TC + ABC	166	4.82	214
	PI	NFV + ABC + 3TC	83	4.85	212
Ozcombo I Carr, 1999 [110]	PI	IDV + ZDV + 3TC	35	5.01	267
	PI	IDV + d4T + 3TC	34	5.21	313
	PI	IDV + ddI + d4T	37	5	277
PROAB 3001, 141W94 Goodgame, [111] 1999; Goodgame, [112] 2000	PI	APV + ZDV + 3TC	116	4.64	442
SOLO (APV 30002, GW433908) Schurmann, 2002 [113]; Gathe, 2004 [93]	BPI	fosAPV/RTV + 3TC + ABC	322	4.78	166
	PI	NFV + 3TC + ABC	327	4.83	177
START I Squires, 1999 [114]; Squires, 2000 [115]	PI	IDV + d4T + 3TC	101	4.59	408
	PI	IDV + ZDV + 3TC	103	4.47	391
START II Eron, 1998 [116]; Murphy, 2003 [21]; Eron, 2000 [117]	PI	IDV + ZDV + 3TC	103	4.59	409
	PI	IDV + d4T + ddI	102	4.47	433
SUN Sension, 2001 [118]	PI	SQV + ZDV + 3TC	42	4.8	419
VIRGO Raffi, 1999 [119]; Reliquet, 2001 [120]	NNRTI	NVP + ddI + d4T	100	4.7	413

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; BPI, boosted PI; ir, immediate release; xr, extended release; qd, once daily; bid, twice daily; 3TC, lamivudine; d4T, stavudine; d4T-XR, extended release stavudine; ddI, didanosine; ddI-EC, enteric coated didanosine; ABC, abacavir; APV, amprenavir; COM, fixed dose combination zidovudine and lamivudine; EFV, efavirenz; fosAPV, fos-amprenavir; FTC, emtricitabine; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; PLA, placebo; RTV, ritonavir; TDF tenofovir; ZDV, zidovudine.

week 48. In a univariate analysis this relationship was significant ($P = 0.0053$, $r = -0.323$). However, when evaluated using multivariable linear regression analysis, this relationship was no longer significant. Additional analyses were performed to adjust for baseline differences and identify predictors of virologic and immunologic responses (Table 3). Lower baseline CD4+ cell counts were associated with increased percentages of plasma HIV RNA < 50 copies/ml at weeks 24 and 48, and greater CD4+ cell count increases at week 48. Baseline plasma HIV RNA levels were not consistently associated with plasma HIV RNA responses or CD4+ cell count increases. Drug class was significantly associated with plasma HIV RNA levels < 400 copies/ml at week 24, plasma HIV RNA levels < 50 copies/ml at weeks 24 and 48, and with increases in CD4+ cell counts at week 48. Lower pill count was associated with higher percentages of plasma HIV RNA levels < 50 copies/ml at week 24 but not with plasma HIV RNA < 50 copies/ml at week 48. Higher pill counts were associated with a greater percentage of patients having plasma HIV RNA < 400 copies/ml at week 48. Publication interval was only predictive of plasma HIV RNA levels < 400 copies/ml at week 24. The modeling of all factors had limited predictive value with a maximum R^2 value of 0.436 for plasma HIV RNA levels < 400 copies/ml at week 48, and an R^2 value of 0.355 for plasma HIV RNA levels < 50 copies/ml at week 48.

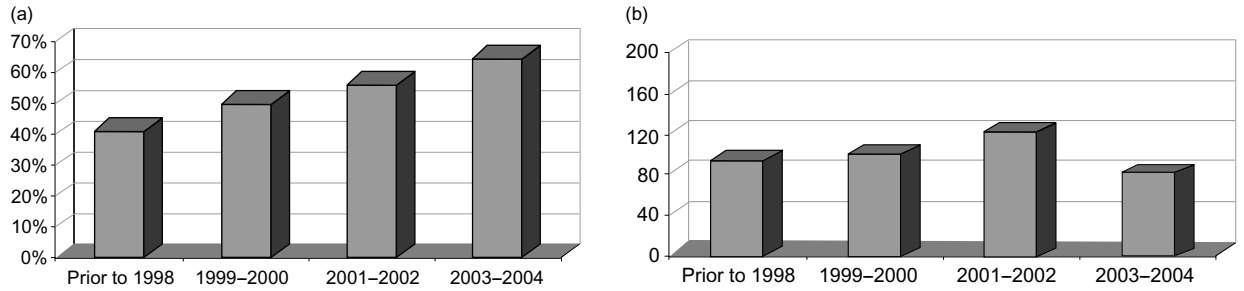

Fig. 1. Week 48 virologic and immunologic responses by publication date. Weighted mean responses of (a) percentages of patients with plasma HIV RNA levels < 50 copies/ml and (b) increases in CD4+ cell counts/μl from baseline at week 48, analyzed by publication date, (defined as the date when a study was first presented or published).

Table 2. Virologic and immunologic results at 24 and 48 weeks.

		Week 24 results			Week 48 results		
Drug class	Variable	Percentage of subjects with RNA < 400	Percentage of subjects with RNA < 50	Change in CD4 cell count	Percentage of subjects with RNA < 400	Percentage of subjects with RNA < 50	Change in CD4 cell count
PI	No. treatment arms	20	18	17	27	32	32
	No. subjects	3564	2572	2674	4474	4735	4602
	Weighted mean	66	49	136	57	43	179
	(95% CI)	62, 69	45, 52	121, 150	54, 60	40, 46	167, 191
BPI	No. treatment arms	4	5	4	4	6	6
	No. subjects	8.5	559	347	812	1002	1002
	Weighted mean	78	64	103	73	64	200
	(95% CI)	71, 85	56, 71	99, 162	66, 80	57, 70	189, 211
NNRTI	No. treatment arms	18	23	20	28	33	36
	No. subjects	2712	4286	3361	5476	6544	6705
	Weighted mean	77	62	130	73	64	173
	(95% CI)	74, 81	59, 65	119, 140	70, 75	61, 66	164, 183
NRTI	No. treatment arms	6	4	6	7	8	8
	No. subjects	629	573	629	1175	1277	1166
	Weighted mean	66	56	106	64	54	161
	(95% CI)	59, 74	48, 64	91, 121	58, 69	48, 59	141, 181
Overall	No. treatment arms	48	50	47	66	79	82
	No. subjects	7710	8100	7011	11937	13558	13475
	Weighted mean	71	57	130	66	55	176
	(95% CI)	69, 73	55, 60	123, 137	64, 68	54, 57	170, 183

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; BPI, boosted PI; CI, confidence interval.

Further analyses were undertaken to explore the relationship between pill count and the weighted mean response of week 48 plasma HIV RNA levels < 50 copies/ml. When pill count was analyzed as a continuous variable in all patients with week 48 results (79 treatment arms and 13 558 participants), no significant overall relationship was identified. Pill counts were next analyzed by drug class dichotomously (≤ 10 pills/day and > 10 pills/day), continuously within these two categories ≤ 10 or > 10 pills/day), when one study with disproportionately low response rates (AI424–034) was excluded in a sensitivity analysis, and as a continuous variable within each drug class. In six of nine secondary analyses no significant association was identified; in the analyses examining dichotomous categories (≤ 10 versus > 10) and within the NRTI

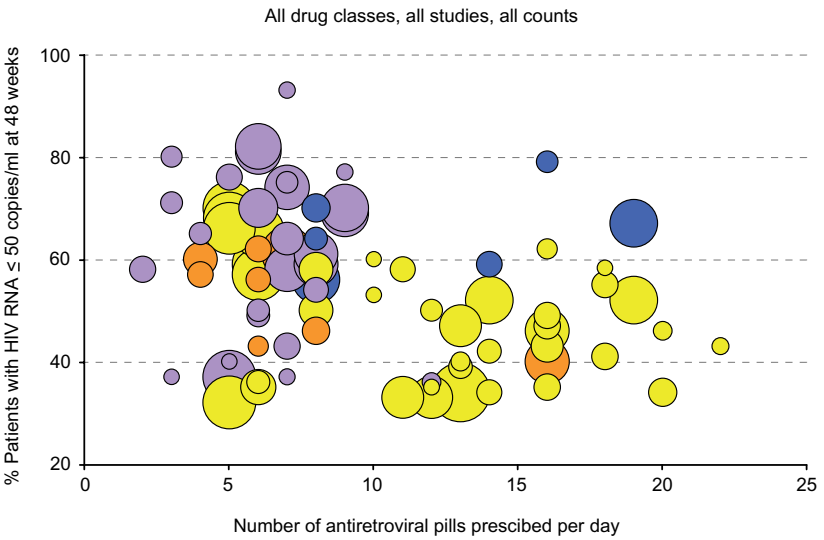

Fig. 2. Bubble plot displaying the relationship between the percentages of subjects with plasma HIV RNA levels < 50 copies/ml at week 48 and pill counts. The size of the bubble reflects the numbers of subjects, and the bubbles are color-coded by regimen type. Univariate analysis demonstrated a significant relationship between lower pill counts and virologic responses, ($P = 0.0053$; $r = -0.323$). However, after adjustment in the multivariate linear regression, the correlation between pill count and response was no longer significant. ●, nucleoside reverse transcriptase inhibitor; ●, non-nucleoside reverse transcriptase inhibitor; ●, protease inhibitor; ●, boosted protease inhibitor.

Table 3. Multivariate linear regression analysis: results at 24 and 48 weeks.

	Week 24 results			Week 48 results		
Factor	Percentage of subjects with RNA < 400	Percentage of subjects with RNA < 50	Change in CD4 cell count	Percentage of subjects with RNA < 400	Percentage of subjects with RNA < 50	Change in CD4
Baseline CD4+ Cell count	NS	−0.617	NS	NS	−0.335	−25.785
Baseline HIV RNA level	NS	−0.584	NS	+0.382	NS	NS
Pill count	NS	+0.294	NS	−0.182	NS	NS
Drug class	−0.031	−0.158	NS	NS	−0.115	5.879
Publication interval	0.126	NS	NS	NS	NS	NS
Model R^2	0.445	0.334	0.000	0.436	0.355	0.108

NS, not statistically significant at $\alpha = 0.05$; for significant factors, numbers reported are parameter estimates from multiple regression analyses. Note that a (+) indicates a positive correlation between the variable and improved response, while (−) indicates a negative correlation between the variable and improved response.

class results favored lower pill counts, and in the PI class the results favored higher pill counts.

Discussion

The results of this expanded overview offer important new observations on the success of contemporary antiretroviral treatment regimens in trials studying ART-naive populations. The percentages of patients achieving plasma HIV RNA levels < 50 copies/ml at 48 weeks is increasing over time, and in reports from most recent trials, more than 80% of patients may reach this threshold [121–123]. The improving virologic responses were seen despite the enrollment of patient populations with lower CD4+ cell counts at entry, and surprisingly, lower entry CD4+ cell counts were associated with improved responses in some analyses. Drug class was the most significant predictor of regimen potency, with the best responses achieved by NNRTI and BPI-containing regimens. Pill count was not consistently identified as a predictor of virologic response, in contrast to our previously published overview.

The improving response rates over time are encouraging evidence for the identification of new treatment regimens and their strategic use in ART-naive patients. Similar observations have been reported in numerous observational cohorts [124–127] and a portion of the declining risk of virologic failure over time could be attributed to the choice of starting regimen [127]. The multivariable linear regression in our study offered the opportunity to assess the predictive value of publication date for plasma HIV RNA levels < 50 copies/ml in comparison with other factors such as drug class. The results demonstrate that improving virologic success is due to the use of more potent drug classes, and not simply a function of publication date. The superiority of NNRTI and BPI-containing regimens over PI and NRTI-containing regimens in suppressing plasma HIV RNA levels below 50 copies/ml observed in this overview is supported by the results of smaller randomized clinical trials [128–131] and provides an additional evidence base consistent with current therapeutic guidelines. Greater CD4+cell count increases were seen in patients receiving BPI-containing than NNRTI, PI and NRTI-containing regimens after 48 weeks. Importantly, the superior CD4+ cell count increases were seen in both the unadjusted analyses and were associated with drug class in the multivariable linear regression analyses. The potential mechanisms for the greater CD4+cell count increases on BPI-containing regimens are uncertain, and must be confirmed in additional randomized studies, especially those directly comparing BPI and NNRTI-containing regimens given the apparent lack of differences between them in observed antiretroviral potency.

Additional factors such as drug-related toxicities and the resistance consequences of first regimen failure may also influence the choice of first line treatment regimens. This analysis considered drug-related toxicities only to the extent that toxicities resulted in treatment discontinuation, and therefore affected the ITT:M = F results. Certainly, many of the toxicities of NNRTI and BPI-containing regimens [132–134] may be non-overlapping, thus allowing for individualization of treatment choices. Nonetheless, the most robust recommendations on drug-related toxicities should come from directly comparative, randomized clinical trials. Drug resistance appears to be less commonly reported from randomized clinical trials among patients receiving BPI-containing regimens, interestingly in both the protease and reverse transcriptase genes. A recent systematic overview identified a lower resistance cost associated with the use of BPI versus NNRTI-containing regimens [135]. However, once again these analyses cannot substitute for resistance results generated from randomized clinical trials comparing the two approaches.

In contrast to our previously published overview, pill count was not identified as a significant predictor of plasma HIV RNA levels below 50 copies/ml at week 48 in the multivariable analysis. However, pill count should not be forgotten as a potential factor influencing the outcome of treatment interventions; pill count was predictive in the current univariable and dichotomous

(≤ 10 versus > 10) analyses. Why did the current analysis not duplicate the results from the previous overview? A number of factors must be considered in assessing the contrasting results. The current overview is much larger with more participants, more trials, more unique treatment regimens, and a broader range of pill counts, and as a result, findings from the current overview are more robust. The current overview included a greatly expanded number of patients receiving NNRTI-containing regimens and BPI-containing regimens, identified as the most potent drug classes and therefore diminishing the impact of pill counts.

There are a number of important limitations to the current overview. Overviews cannot replace randomized clinical trials, which provide the most robust evidence to guide clinical practice. The data used for this overview were generated from population-based results and not individual patients, and therefore the overview may lack the ability to discern some predictors of treatment response, especially baseline characteristics. Analyses focused on the contribution of a third agent to regimen success, and it is possible that the nucleoside or nucleotide reverse transcriptase inhibitor component may affect these results. A recently completed trial highlighted the potential importance of these agents [123]. In the multivariable logistic regression analysis, the R^2 value for the model predicting plasma HIV RNA levels < 50 copies/ml at week 48 was 0.355, reflecting the importance of other unmeasured factors in contributing to treatment responses. In addition, some trials which prematurely closed such as ESS 30009 are not analyzed in this overview [136]. Finally, the time span of included trials now exceeds 10 years, and during this period substantial improvements in care have been implemented beyond the choice of treatment regimen such as improved care access and delivery, monitoring, adherence education, and support for co-morbidities.

Efavirenz was studied in the greatest number of trials, in the largest number of patients, and in more diverse regimens than any other single agent. Efavirenz-containing regimens have provided impressive results in recent trials with suppression of plasma HIV RNA levels below 50 copies/ml in approximately 80% of patients in ITT:M = F analysis, [121–123]. However, NNRTI-containing regimens have been associated with higher resistance costs when virologic failure occurs [135], which may compromise response to subsequent treatment regimens. Important results will be generated from randomized trials which are currently underway comparing directly NNRTI-containing versus BPI-containing regimens (ACTG 5142, 5202).

In summary, this overview has identified improving temporal trends in virologic responses, superior virologic responses for NNRTI and BPI-containing regimens, and an inconsistent and less pivotal role for lowered pill counts.

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