Combined Analysis of Two-Year Follow-Up from Two Open-Label Randomized Trials Comparing Efficacy of Three Nucleoside Reverse Transcriptase Inhibitor Backbones for Previously Untreated HIV-1 Infection: OzCombo 1 and 2

J. Amin,[1] A. Moore,[1] A. Carr,[2] M.A. French,[3] M. Law,[1] S. Emery,[1] and D.A. Cooper,[1,2] on behalf of the OzCombo 1 and 2 investigators*

[1]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW, Australia; [2]HIV Immunology and Infectious Disease Clinical Services Unit, St Vincent's Hospital, Sydney, Australia; [3]Department of Clinical Immunology and Communicable Diseases Services, Royal Perth Hospital, Perth, Australia

Purpose: To compare inhibition of HIV replication, improvements in CD4+ T-cell counts, metabolic parameters, and body shape changes after 2 years of assigned therapy in OzCombo patients. **Method:** Study participants were those who were recruited into the open-label OzCombo 1 (1996/1997) and OzCombo 2 (1997/1998) trials. Patients in OzCombo 1 were randomized to receive indinavir in combination with zidovudine+lamivudine (AZT+3TC; *n* = 35), stavudine (d4T)+3TC (*n* = 34), or d4T+didanosine (ddI) (*n* = 37). OzCombo 2 patients were randomized to the same nucleoside reverse transcriptase inhibitor (NRTI) backbones with nevirapine (*n* = 20, 22, 23, respectively). The mean time-weighted changes from baseline in CD4 T-cell count/mL, HIV RNA (log copies/mL plasma), and proportions with detectable viral load (>500 copies plasma HIV RNA/mL) between NRTI arms over 2 years were compared by formal meta-analysis. A cross-sectional study of metabolic and body shape complications was also undertaken. **Results:** For the comparison of d4T+3TC and d4T+ddI to AZT+3TC, mean differences in time-weighted change from baseline in CD4 T-cell count/μL and log copies HIV RNA/mL adjusted for baseline CD4+ T-cell and HIV RNA counts were: -44 (*p* = .08) and -14 (*p* = .56) cells/μL and -0.1 (*p* = .40) and -0.1 (*p* = .6) copies/mL. Odds ratios for detectable viral load in the last study quarter were 0.6 (*p* = .44) and 1.0 (*p* = .95). The mean percent leg fat was lower in the d4T+3TC and d4T+ddI than the AZT+3TC arm (mean difference 5.1% [*p* = .07] and 7.6% [*p* = .02], respectively). **Conclusion:** For all regimens, virological control and immunological response were maintained over 2 years. Regimens containing d4T and particularly d4T+ddI were significantly associated with increased peripheral fat loss compared with AZT+3TC. **Key words:** *antiretroviral therapy, highly active, HIV-1, lipodystrophy, meta-analysis, virological failure*

The use of highly active antiretroviral therapy (HAART) containing three or more drugs is now recommended treatment for HIV infection.[1,2] Most randomized controlled studies designed to evaluate the efficacy of HAART in terms of virological, immunological, and clinical outcomes have only been conducted over 48 to 52 weeks. Most of these studies have described inhibition of HIV replication to undetectable levels in the majority of patients. However, longer term outcomes have not been well described.

For correspondence or reprints contact: J. Amin, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, 376 Victoria Street, Sydney, NSW Australia 2010. Email: Jamin@nchecr.unsw.edu.au

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*See Appendix for complete list

The OzCombo 1 and OzCombo 2 studies compared dual nucleoside reverse transcriptase inhibitor (NRTI) backbones (zidovudine+lamivudine [AZT+3TC]; stavudine [d4T]+3TC; d4T+didanosine [ddI]), in combination with indinavir (IDV) in OzCombo 1 and nevirapine (NVP) in OzCombo 2. The outcomes of these trials have been reported previously with no difference found in immunological or virological endpoints at 1 year.[3,4] To determine whether the observed impact of treatment on viral suppression and immunological improvement could be sustained, patients participating in these two randomized controlled trials were followed up to 2 years after randomization. During the conduct of these studies, reports were made of adverse metabolic and morphologic effects arising from the use of antiretroviral therapy in individuals with HIV infection.[5–7] Thus, a cross-sectional substudy was also conducted to assess the frequency of these abnormalities.

METHOD

Participants

All 106 participants enrolled in OzCombo 1 and 65 from OzCombo 2 were included in this study.[3,4] The main eligibility criteria of these trials included documented HIV infection, age greater than 18 years, and no prior antiretroviral therapy. OzCombo 1 patients were required to have a CD4+ T-cell count less than 500 cells/μL or HIV RNA load greater than 30,000 copies/mL plasma, whereas OzCombo 2 required CD4+ T-cell count greater than 50 cells/μL with no restriction on viral load.

Interventions and Assessments

Patients in OzCombo 1 were randomized to receive IDV in combination with AZT+3TC (n = 35), d4T+3TC (n = 34), or d4T+ddI (n = 37). OzCombo 2 patients were randomized to the same NRTI backbones with NVP (n = 20, 22, 23, respectively). Drugs were prescribed at the manufacturers' recommended doses: AZT 250 mg, 3TC 150 mg, d4T 40 mg, ddI 200 mg, NVP 200 mg twice daily, and IDV 800 mg three times a day. Dose modifications of ddI and d4T were recommended for patients with body weight <60 kg. Patients received an initial dose of NVP 200 mg daily for 2 weeks increasing to 200 mg bid. Drug substitution within the same class was mandatory for recurrent grade 3 or 4 drug-related adverse events and was optional for persistent drug-related grade 1 to 2 adverse events or for therapeutic failure. No interventions beyond initial randomized treatment were instigated as part of long-term follow up. Real-time plasma HIV RNA load, CD4+ T-cell count, and changes in antiretroviral therapy data were collected on all randomized patients who consented to long-term follow-up at as close to 12 weekly intervals as possible from day of randomization until 31 January 2001 (close of study). Plasma HIV RNA levels were measured using Amplicor Version 1.0 (Roche Diagnostics, Branchburg, New Jersey, USA; lower detection limit of 500 copies/mL plasma). CD4+ T-cell counts were determined by dual-color flow cytometry.

Statistical Analyses

All analyses were conducted to compare the randomized treatment nucleoside backbones AZT+3TC versus d4T+3TC versus d4T+ddI. The primary study endpoints were the time-weighted mean change from randomization in plasma HIV RNA copies and CD4+ T-cell count, the proportions of patients with plasma HIV RNA <500 copies/mL, and the proportion of patients with a new AIDS-defining event (CDC category C) at 2 years.

Changes in plasma HIV RNA copies and CD4+ T-cell count from baseline were summarized by nominal study weeks using a time window approach; the average value was used if there was more than one value in a time window. Time windows for the first 52 weeks of the studies are as used previously.[3,4] Twelve-week time windows were used for the second year of follow-up until Week 104, which included data to the end of 130 weeks.

To account for differences in inclusion criteria between trials and potential confounding variables, analyses were adjusted for baseline CD4+T-cell count and plasma HIV RNA copies using regression techniques. All analyses were conducted on the basis of intention to treat for available data; missing-equals-failure analysis is also presented for proportion of patients with detectable viral load. Data from OzCombo 1 and 2 were combined by fixed effects meta-analysis using STATA™ 7.0

(Stata Corp., College Station, Texas, USA).[8] All analyses were undertaken to compare the randomized NRTI backbones. Comparisons between IDV and NVP were not undertaken, as these assignments were not randomized. An implicit assumption of this analysis is that NRTI backbone effects were qualitatively similar regardless of combination with either IDV or NVP. Tests for heterogeneity between trial and treatment were not statistically significant ($p > .05$ for all endpoints, data not shown).

Metabolic and Morphologic Adverse Affects Substudy

All randomized patients were eligible to participate in this substudy, which was conducted in 1999. The substudy required additional informed consent. Ethics committees of participating sites approved both the protocol and informed consent. The protocol required the collection of HIV history and demographics, antiretroviral therapy, clinician- and patient-diagnosed clinical features of lipodystrophy syndrome, laboratory data (including fasted lipid and glycemic profiles), skin fold thicknesses, abdominal (L4) CT scans, and dual-energy X-ray absorptiometry scans (all data not shown). As far as was possible, all data were to be collected from a single patient within a 3-month window. All data from all patients were collected within a 6-month window. Procedures for collection of DEXA and CT scan data were uniform, and imaging by DEXA was performed using identical equipment (LUNAR) and software. Presence and severity of peripheral (face, arms, legs, lipomatosis, prominent veins, buttocks), central (abdomen, breasts, and buffalo hump), and overall (peripheral and central) lipodystrophy were assessed independently by clinicians and patients. In each region, a score of 0 was assigned for no change and 1 for any fat loss.

Patient characteristics and measures of metabolic abnormality or fat change were summarized and analyzed by *t* test for continuous outcomes and logistic regression for binary outcomes on the basis of originally assigned nucleoside treatment group. Data from both trials were again combined by fixed effects meta-analysis.

RESULTS

Patient Accountability

One hundred and seventy-one patients began assigned treatment in the OzCombo 1 and 2 trials. The median time of follow-up was 152 weeks (interquartile range [IQR], 100–180 weeks). By Week 52, 168 (98%) patients remained in follow-up; this fell to 132 (77%) by Week 104 (**Table 1**). Maintenance in follow-up was greatest in the d4T+3TC arm (86%), followed by the d4T+ddI arm (77%) and then the AZT+3TC arm (69%).

Patient Characteristics

Patient characteristics at baseline were similar across treatment arms (**Table 2**). OzCombo 1 patients comprised 62% of the patient population. This proportion was consistent across study arms. CD4+ T-cell counts were slightly higher in the d4T+3TC arm. The ddI+d4T arm had fewer men. All baseline AIDS-defining conditions (Centers for Disease Control category C) occurred in patients enrolled in OzCombo 1.

Table 1. Patient allocation and follow-up

	Randomized treatment							
	AZT+3TC		d4T+3TC		d4T+ddI		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Week 0	55		56		60		171	
Week 52	55	(100)	54	(96)	58	(97)	168	(98)
Week 104	38	(69)	48	(86)	46	(77)	132	(77)

Note: AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine.

Table 2. Baseline characteristics, pooled from OzCombo 1 and 2

	AZT+3TC *n* = 55		d4T+3TC *n* = 56		d4T+ddI *n*= 60	
OzCombo 1 [*n* (%)][a]	35	(64)	34	(61)	37	(62)
Males [*n* (%)]	52	(95)	54	(96)	52	(87)
AIDS [*n* (%)]	5	(9)	6	(11)	8	(13)
Real time viral load, $\log_{10}$copies/mL [mean (*SD*)]	4.60	(0.70)	4.68	(0.66)	4.67	(0.74)
CD4+ count, cells/μL[mean (*SD*)]	333	(219)	346	(210)	307	(224)
Age, years [mean (*SD*)]	38	(7.9)	40	(10.5)	36	(9.4)
Weight, kg [mean (*SD*)]	75	(17.5)	77	(13.7)	70	(10.9)

Note: AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine.
[a]Patients enrolled in OzCombo 1.

Treatment Outcomes

At Week 52, of those who had ceased an assigned drug, more had ceased one or more of their NRTIs than IDV or NVP (24% vs. 15%, McNemar's p = .0001) (**Figure 1**). This difference was most marked in the d4T+ddI arm in which 30% of participants had ceased an NRTI and 10% had ceased IDV or NVP (McNemar's $p < .0001$).

At Week 104, 85 (64%) patients were still on assigned treatment, with proportions by treatment varying from 82%, 67%, to 46% for the AZT+3TC, d4T+3TC, and d4T+ddI (χ^2 p = .002) arms, respectively. In the d4T+ddI arm, the proportion of participants who had ceased an NRTI (54%) was more than double that in the other arms (AZT+3TC, 16%; d4T+3TC, 21%; χ^2 p = .0001).

By the end of Week 52, there were three AIDS-

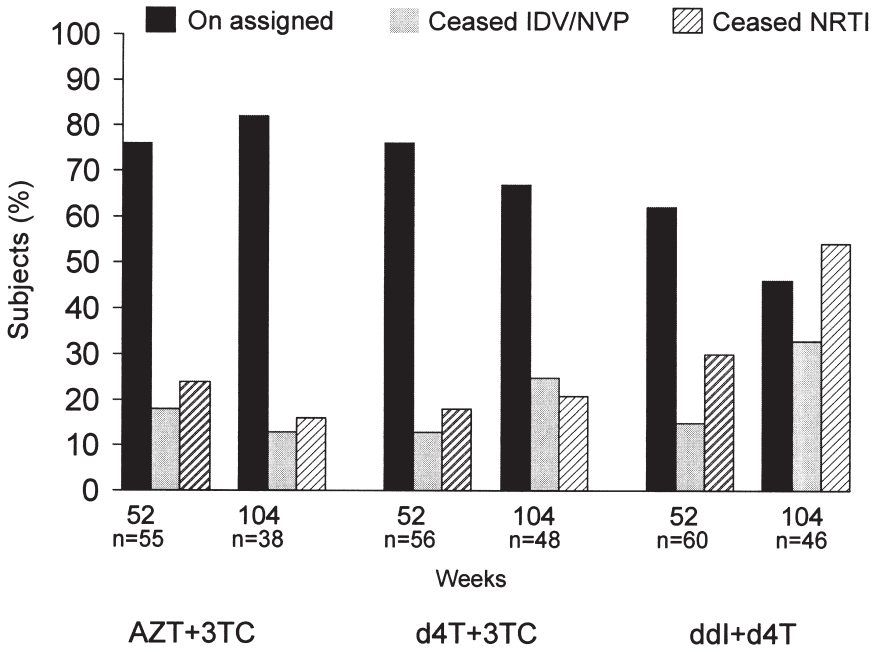

Figure 1. Treatment status of patients by week of follow-up and treatment assignment. AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine, IDV = indinvavir, NVP = nevirapine.

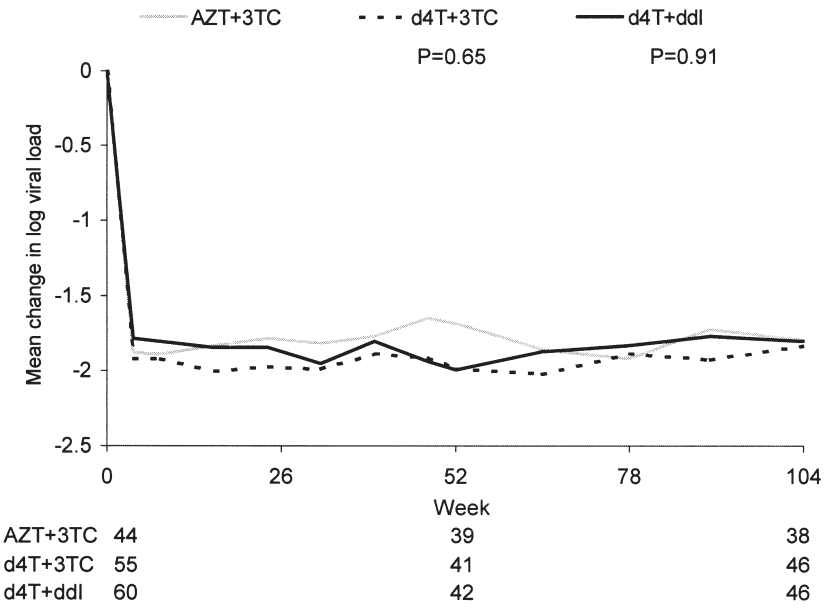

Figure 2. Mean change from baseline in plasma HIV RNA copies/mL. *P* for difference in mean time-weighted change from baseline, AZT+3TC referent group. AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine.

defining (CDC category C) events, all from OzCombo 1 and one in each treatment arm. There were two further events in OzCombo 1 by the end of Week 104, both in patients on d4T+ddI+IDV. There were no AIDS events in OzCombo 2 to Week 104.

Virological Responses

Mean plasma HIV RNA level fell from baseline by almost 2 log copies/mL in all treatment arms within 4 weeks, and at least a 1.6 log copies/mL reduction was maintained through 104 weeks (**Figure 2**). Mean time-weighted changes in log copies plasma HIV RNA per mL from baseline to Week 104, adjusted for baseline CD4+ T-cell count and plasma HIV RNA copies, were -1.6, -1.8, and -1.7 $\log_{10}$ copies/mL in the AZT+3TC, d4T+3TC, and d4T+ddI arms, respectively. The mean differences in time-weighted change HIV RNA copies from baseline relative to the AZT+3TC arm were -0.04 (95% CI -0.12 – 0.19; p = .65) and 0.0 (95% CI -0.07 – 0.08; p = .91) $\log_{10}$ copies/mL for d4T+3TC and d4T+ddI arms, respectively. Overall, 22 (17 %) had a plasma HIV RNA viral load greater than 500 copies/mL at Week 104, with no statistically significant difference in proportions between treatment (**Table 3**). When patients with missing data were allocated as having a detectable HIV RNA, the number of patients with detectable plasma HIV RNA rose to 75 (44%): 49%, 25%, and 57% for the AZT+3TC, d4T+3TC, and d4T+ddI arms, respectively.

Immunological Responses

In all arms, the CD4+ T-cell count increased by at least 100 cells/µL by Week 16 and generally continued to rise to over 200 cells/µL by Week 104 follow-up (**Figure 3**). The mean time-weighted changes from baseline to Week 104 in CD4 T-cell count/mL were 167, 199, and 193 cells/µL in the AZT+3TC, d4T+3TC, and d4T+ddI arms, respectively. The mean differences in time-weighted change from baseline compared with the AZT+3TC arm, adjusted for baseline CD4 T-cell count and plasma HIV RNA copies, were -44 (95% CI -92 – 5; p = .08) and -14 (95% CI -62 – 33; p = .56) cells/µL for the d4T+3TC and d4T+ddI arms, respectively.

Metabolic and Morphologic Adverse Events Substudy

In total, 84 (47%) patients from the original OzCombo 1 and 2 cohorts were recruited into the

Table 3. Meta-analysis of Week 104 outcomes by treatment arm

	AZT+3TC[a]	d4T+3TC			d4T+ddI		
	Mean	Mean	Difference (95% CI)	*p*	Mean	Difference (95% CI)	*p*
CD4 TWAUC (cells/μL)	167	199	−44 (−92 – 5)	.08	193	−14 (−62 – 33)	.56
HIV RNA TWAU (cells/μL)	−1.65	−1.76	−0.04 (−0.12 – 0.19)	.65	−1.72	0.00 (−0.07 – 0.08)	.91
	AZT+3TC[a]	d4T+3TC			d4T+ddI		
	n (%)	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*
HIV RNA >500 copies/mL	7(18)	6(13)	0.60 (0.17 – 2.17)	.44	9 (20)	1.04 (0.33 – 3.21)	.95

Note: Adjusted for baseline CD4 T-cell count and baseline HIV RNA copies. TWAUC = time-weighted change from baseline to Week 104, area under curve.

[a]Reference group

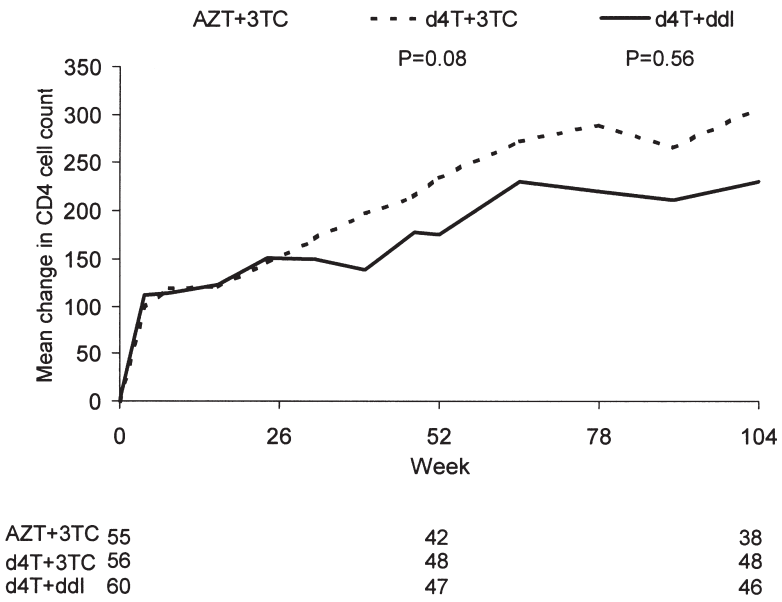

Figure 3. Mean change from baseline in CD4+ T-cell count/mL. *P* for difference in mean time-weighted change from baseline, AZT+3TC referent group. AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine.

substudy. The patient distribution was 21 (59%), 35 (35%), and 28 (35%) for the AZT+3TC, d4T+3TC, and d4T+ddI arms, respectively. Significant differences between nucleoside arms were detected for variables related to peripheral fat changes. Compared to the AZT+3TC referent arm, proportion of fat mass in legs was significantly less in the d4T+3TC (5.1%) and d4T+ddI (7.6%) nucleoside arms (**Table 4**). Patient- and clinician-reported peripheral fat loss also had significantly greater odds of being associated with d4T+3TC (OR 4.0, 95% CI 1.1–14.5, and OR 6.7, 95% CI 1.6–27.6) and d4T+ddI (OR 8.0, 95% CI 2.0–32.0, and OR, 4.1, 95% CI 1.0–16.3) compared with AZT+3TC. The d4T+ddI group had the lowest mean BMI (22.7 kg/m^2, p = .02). There were no significant differences between treatment arms in other metabolic and body composition endpoints (data not shown).

DISCUSSION

Of the 171 patients randomized in OzCombo 1 and 2 to AZT+3TC, d4T+3TC, or d4T+ddI in combination with either IDV or NVP, 77% remained in follow-up and 64% were still on their assigned regimen at Week 104. Virological and immunological responses were maintained over the 2 years of follow-up, with no significant difference between randomized treatment arms. However, peripheral lipoatrophy was significantly increased in patients assigned to treatment with d4T+3TC or d4T+ddI.

The 36% assigned therapy discontinuation rate reported in our study is within the 36%–43% range reported in other long-term follow-up studies of antiretroviral-naïve patients.[9,10] The lower proportion of patients maintaining d4T regimens, particularly in combination with ddI, during the second year of follow-up is consistent with reports of declining use of d4T+3TC- and d4T+ddI-containing regimens since 1999 in the Australian HIV Observational Database.[11] Patients on ddI were also found to have the highest stopping rate in the Royal Free Hospital cohort study, with an incidence of stopping of 41.6% per 10 person-years of follow-up.[12]

Although reasons for stopping antiretroviral therapy were not collected in this study, other studies report the primary reasons for stopping as toxicity (21.1%–42.7%), failure (5%–28%), and nonadherence (7.1%–23%).[9,10] In the d'Armino Monforte study, the median follow-up time was much shorter than in this study at 45 weeks, with most toxicity-related discontinuations occurring earlier (median 84 days) and discontinuations due to failure occurring later (median 270 days).[9] However, the plateau in plasma HIV RNA levels and

Table 4. Body fat distribution and metabolic abnormalities in patients taking part in the morphologic and metabolic adverse effects substudy

	Treatment	Mean	Difference	95% confidence interval	*p*
Lactate (mmol/L)	AZT+3TC	1.42			
	d4T+3TC	1.35	0.10	–0.25 - 0.44	.58
	d4T+ddI	1.66	–0.30	–0.72 - 0.12	.16
Triglyceride (mmol/L)	AZT+3TC	1.58			
	d4T+3TC	2.11	–0.40	–1.13 - 0.34	.29
	d4T+ddI	2.09	–0.42	–1.29 - 0.45	.34
HDL cholesterol (mmol/L)	AZT+3TC	1.20			
	d4T+3TC	1.21	–0.01	–0.19 - 0.18	.96
	d4T+ddI	1.14	0.08	–0.14 - 0.31	.47
Leg fat (%)	AZT+3TC	22.03			
	d4T+3TC	17.28	5.08	–0.50 - 10.66	.07
	d4T+ddI	15.03	7.63	1.15 - 14.12	.02
VAT	AZT+3TC	104.13			
	d4T+3TC	118.66	–20.36	–66.96 - 26.24	.39
	d4T+ddI	90.18	11.39	–31.98 - 54.77	.61
SAT	AZT+3TC	147.61			
	d4T+3TC	146.67	1.31	–48.95 - 51.57	.96
	d4T+ddI	133.28	11.06	–46.86 - 68.99	.71
BMI (kg/m)	AZT+3TC	25.28			
	d4T+3TC	27.71	0.87	–1.36 - 3.10	.43
	d4T+ddI	22.67	2.72	0.44 - 5.00	.02
		Proportion	Odds ratio		
Patient-reported peripheral fat loss[a]	AZT+3TC	19			
	d4T+3TC	49	3.95	1.08 - 14.45	.04
	d4T+ddI	64	7.97	1.98 - 32.06	<.01
Clinician-reported peripheral fat loss[a]	AZT+3TC	19			
	d4T+3TC	57	6.71	1.64 - 27.57	<.01
	d4T+ddI	46	4.09	1.03 - 16.26	<.05

Note: AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine, HDL = high density lipoprotein, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, BMI = body mass index.

[a]See text for method of calculation.

continued increase in CD4+ T-cell counts over 2 years in our study indicate that the higher discontinuation rates in the second year of the study are unlikely to be related to failure overall.

The higher discontinuation and loss to follow-up rates in the d4T-containing arms during the second year, particularly the arm that included ddI, may be due to drug toxicity or awareness of the association between the use of these drugs and lipodystrophy during the late 1990s.[6,7] It is probable that lipodystrophy did occur more often in the d4T+ddI arm as indicated by the significantly increased peripheral fat loss detected in this study arm. However, the mean baseline weight in this study arm was lower than other arms, which may have resulted in these patients being more susceptible to lipodystropy and discontinuation of therapy. Patient- and clinician-assessed peripheral fat loss was also significantly greater in the d4T-containing arms. Stavudine-containing regimens in general have subsequently been found to be associated with an increased risk of fat wasting in both treatment-experienced and -naïve patients.[13,14]

There are limitations to our study. Even though the follow-up rate of 77% was reasonable, loss to follow-up may have led to a bias in study findings.

Reasons for stopping therapy were not routinely collected in the second year of the study. While they may be deduced on the basis of other studies, few studies have follow-up over 2 years and therefore may not be comparable. The metabolic and morphological abnormalities substudy was cross-sectional, a study type with inherent flaws, and the sample size of this study may have been too small to detect other differences between NRTI backbones. The open-label clinician and patient assessment of lipodystrophy was also open to bias. However, objective measures of lipodystrophy by imaging measures were in agreement with the patient and clinician assessments. Comparisons between the IDV and NVP treatments were not made, as assignment to these treatments was not randomized.

In conclusion, 64% of patients were on assigned therapy at the end of 2 years. There was a significantly higher association of lipodystrophy with d4T+3TC and d4T+ddI assignment than with AZT+3TC, and cessation of original treatment was highest in the d4T+ddI arm. Of patients in follow-up at 2 years, 83% had undetectable viral load and achieved a greater than 200 cell/μL mean increase in CD4 T-cell count, with no significant differences between NRTI backbones for either clinical measure.

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