

A randomized, double-blind trial of half versus standard dose of zidovudine plus zalcitabine in Thai HIV-1-infected patients (study HIV-NAT 001)

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Background: Triple combination antiretroviral therapy, recommended as standard of care, is unaffordable for much of the developing world.

Objectives: To establish whether half doses of zidovudine (AZT) and zalcitabine (ddC) are as effective as standard doses in a Thai population with lower body weight than Western populations and predominantly infected with HIV-1 subtype E.

Methods: A group of 116 antiretroviral naive patients, with CD4 cell counts 100–500 × 10⁶ cells/l, were randomized to: AZT 200 mg three times daily plus ddC 0.75 mg three times daily versus AZT 100 mg three times daily plus ddC 0.375 mg three times daily and followed-up regularly for 48 weeks.

Results: The study enrolled 111 patients: 59 men and 52 women, body weight (mean ± standard deviation) 56.4 ± 12.3 kg, mean CD4 cell count 324 × 10⁶ cells/l, mean HIV RNA 4.7 log₁₀ copies/ml. There were no significant differences between the two groups. Twelve patients discontinued, including two deaths that were unrelated to study medication. No significant differences in adverse events were seen. Week 48 data for the standard dose and half dose arms, respectively, were mean CD4 cell count increases of 52 and 78 × 10⁶ cells/l ($P = 0.34$), mean plasma HIV-1 RNA reduction of 1.4 and 1.1 log₁₀ copies/ml ($P = 0.10$), HIV RNA of < 400 copies/ml in 52 and 20% ($P = 0.001$). Participants with higher than mean baseline CD8 cell counts (mean 1062 × 10⁶ cells/l) showed greater decline in CD8 cells on standard doses. Further analysis showed improved reduction in HIV RNA ($P < 0.0001$) and in the percentage with undetectable HIV RNA ($P = 0.0137$) in the standard dose arm, corrected for baseline HIV RNA, which if < 4.75 log₁₀ copies/ml significantly correlated with HIV RNA < 400 copies/ml at week 48.

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Sponsorship: This work was supported by the Division of AIDS, Department of Communicable Disease Control, Ministry of Public Health, Thailand and Roche (Thailand) Ltd.

Note: These results were presented in part at the Fourth International Conference on AIDS in Asia and the Pacific, Manila, October 1997 (interim analysis week 24); Fifth Conference on Retroviruses and Opportunistic Infections, Chicago, February 1998 (week 36 data); and the XII International Conference on AIDS, Geneva, June 1998 (final analysis).

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Received: 17 February 2000; accepted: 25 February 2000.

Conclusion: At week 48, the proportion with HIV RNA < 400 copies/ml was significantly higher in the standard dose arm; lower baseline HIV RNA correlated with better HIV RNA outcome at 48 weeks. The arms did not differ in CD4 cell response but standard doses correlated with greater CD8 cell decline.

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AIDS 2000, 14:1349–1356

Keywords: clinical trials, Asia, antiretroviral therapy, combination therapy, reverse transcriptase inhibitors, viral load, healthcare/economics

Introduction

There is consensus that combination antiretroviral therapy is the treatment of choice for HIV infection [1,2]. In the developed world, the currently accepted standard of care is to commence therapy with a potent triple antiretroviral regimen consisting of two nucleoside analogues and a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. Such regimens are too costly for the majority of patients and health-care providers in developing countries with a heavy HIV burden and limited resources. In Thailand, most patients must pay for their own health-care expenses. The annual cost of double nucleoside analogue therapy is higher than the mean annual income, while government and third party subsidies for the financially disadvantaged are very limited [3]. Because of the cost of these drugs per milligram dose used, there is a tendency to use lower doses.

The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) was formed in 1996 to design and conduct clinical trials of antiretroviral agents in Thailand according to internationally accepted Good Clinical Practice standards [4] and that were appropriate for the Thai population, who have a lower average body weight and a different HIV subtype pattern than seen in developed countries [5]. Such trials should yield results useful for public health policymakers in Thailand and in other countries with similar resource constraints.

One approach to reduce the cost of antiretroviral therapy in settings with limited resources would be the use of lower doses of drugs. The combination of zidovudine (AZT) and zalcitabine (ddC) has been shown to be effective in decreasing morbidity and mortality [6,7] and decreasing HIV-1 RNA, especially when used in an antiretroviral-naïve population [8–10]. The currently recommended daily doses for AZT and ddC in combination are 600 and 2.25 mg, respectively. Published data suggest that daily doses of AZT as low as 300 mg may be effective in suppressing HIV-1 replication [11–14]. The rationale behind this study was that lower doses of antiretroviral drugs in a Thai HIV-infected study population with lower average body weight (baseline body weight in the study was

56.4 ± 12.3 kg, compared with a mean baseline body weight of 68.0 kg in the Delta study [6]) might lead to similar results to those obtained with standard doses in developed countries. There are no data published on the efficacy of a lower dose of AZT in combination with ddC. Therefore, this study was intended to evaluate whether a half dose of both AZT and ddC used in combination would be equally effective as the standard recommended doses in reducing plasma HIV RNA and in increasing the peripheral CD4 lymphocyte count in a Thai HIV-1-infected study population.

Methods

Study HIV-NAT 001 was a randomized, double-blind comparative trial that compared half dose with the standard dose of the regimen AZT/ddC. Patient inclusion criteria were documented HIV infection; 16 years of age or older; no prior antiretroviral therapy ever; no history of cytotoxic, radiation or investigational therapy 30 days prior to study entry; no active opportunistic infection; and no history of lymphoma, cardiac dysfunction or alcohol/drug abuse. Laboratory inclusion criteria were haemoglobin > 10.5 g/dl, neutrophil count > 1000×10^6 cells/l, platelet count > 75×10^9 cells/l, amylase < 1.5 times upper limit of normal, alanine aminotransferase < 5 times upper limit of normal and a peripheral CD4 lymphocyte count of $100\text{--}500 \times 10^6$ cells/l within 2 weeks prior to study entry. Female patients were required to have a negative pregnancy test within 2 weeks prior to enrolment and utilize adequate contraception for the duration of the study.

Patients were recruited from the Thai Red Cross Society's Anonymous HIV screening clinic and the HIV outpatient clinic of Chulalongkorn Hospital, Bangkok, Thailand. Screening was performed for the presence of tuberculosis by PPD (Siebert purified protein derivative of tuberculin) skin test and chest X-ray. Participants who were positive for the PPD skin test (defined as > 5 mm induration) without symptoms or radiological findings of active tuberculosis were treated with isoniazid prophylaxis 300 mg daily for the

study duration of 48 weeks. Patients with a CD4 lymphocyte count below 200×10^6 cells/l or with HIV-related clinical symptoms received prophylaxis for *Pneumocystis carinii* pneumonia for the duration of the study. The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and written informed consent was obtained from all patients prior to enrolment.

AZT (Government Pharmaceutical Organization of Thailand) was supplied by the Division of AIDS of the Thai Ministry of Public Health; matched placebo capsules, containing starch, were provided by the research pharmacist of Chulalongkorn Hospital. ddC and matched placebo tablets were supplied by Roche Pharmaceuticals (Roche Thailand Ltd, Bangkok 10 900, Thailand).

Patients were equally randomized by a computer-generated scheme, provided by a NATEC statistician, to one of the two double-blind study arms. The half dose arm received three times daily dosing of one capsule of AZT 100 mg plus one tablet of ddC 0.375 mg and a matched placebo of each. The standard dose arm received three times daily dosing of two AZT 100 mg capsules and two ddC 0.375 mg tablets. All participants were asked to take one tablet from each of two bottles of ddC/matched placebo and one capsule from each of two bottles of AZT/matched placebo three times daily. Adherence to the study treatment was estimated by counting the residual amounts of study medication returned by participants at all study visits. Upon randomization, stratification took place for gender, age above or below 35 years, a baseline CD4 lymphocyte count above or below 300×10^6 cells/l and for whether a previous AIDS-defining illness had occurred.

After screening and study entry, patients were followed up at weeks 2, 4, 12, 24, 36 and 48. At each visit, clinical findings, adverse events and haematological, biochemical and immunological parameters were evaluated. Plasma HIV-1 RNA was assessed retrospectively in batches using the Roche Amplicor HIV-1 Monitor assay with added primer set with a lower limit of detection of 400 copies/ml.

A review of adverse events and efficacy data by a data and safety monitoring board occurred in October 1997, after all participants had reached 24 weeks of follow-up.

Statistical analysis

In the efficacy analysis, the two arms were compared with their baseline at each time point for differences in plasma HIV-1 RNA, the percentage of participants with plasma HIV-1 RNA < 400 copies/ml and changes in peripheral CD4 and CD8 lymphocyte

counts. Primary objectives of the interim analysis at 24 weeks were to analyse whether the treatments were safe and whether a statistically significant difference in HIV RNA copy number of at least $0.5 \log_{10}$ copies/ml between the arms at this time point could be demonstrated. Changes were tabulated and significance levels were assessed using the Wilcoxon 2-sample rank sum test and a non-linear mixed effects regression model.

Results

Baseline characteristics

A total of 116 Thai HIV-seropositive patients were randomly assigned to the two treatment arms from December 1996 to March 1997. An additional 31 patients were screened but excluded on the basis of the exclusion criteria: raised amylase in 11 patients, CD4 cell count $> 500 \times 10^6$ cells/l in 10, CD4 cell count $< 100 \times 10^6$ cells/l in six, active tuberculosis in two, prior zidovudine therapy in one and high alanine aminotransferase in one. After randomization, five patients did not commence study medications. Three did not attend their week 0 visit and were subsequently lost to follow-up. The other two were found to be ineligible after randomization as one was subsequently found to have received prior zidovudine therapy and one had developed active tuberculosis. The remaining 111 patients commenced study medications and were included in the analysis. Baseline parameters are shown in Table 1.

Adverse events and premature discontinuations

A total of 502 adverse events were reported: 269 in the half dose arm and 233 in the standard dose arm. Exactly 200 adverse events were judged by the investigators to have a probable or definite relationship to the study medications. Adverse events with a probable relationship to the study medications and that occurred in 10 or more patients were nausea ($n = 56$), anorexia ($n = 25$), headache ($n = 14$) and vomiting ($n = 11$). No statistically significant differences were seen between the two study arms in the number or nature of events observed. Symptoms and signs of peripheral neuropathy, one of the most anticipated adverse events, were elicited at every study visit but reported in only seven participants; all were grade 1 or 2 events, with five instances occurring in patients receiving half dose.

Participants with peripheral neuropathy complained of numbness of both feet only, without pain or involvement of the lower legs. No disturbances of motor function were reported.

A total of 10 laboratory events classified as grade 3 or 4 occurred, equally divided over the two study arms. Two of these events occurred at week 0: one with

Table 1. Baseline patient characteristics.

	Half dose arm	Standard dose arm
Patients randomized [No. (%)]	58 (52%)	53 (48%)
Gender (M/F)	26/32	26/27
Age (years)	31	31
Mean body weight \pm SD (kg) ^a	56.0 \pm 14.1	56.8 \pm 10.0
Mean CD4 cell count \pm SD ($\times 10^6$ cells/l)	321 \pm 114	361 \pm 125
Mean CD8+ count \pm SD ($\times 10^6$ cells/l)	1007 \pm 513	1121 \pm 455
Mean plasma HIV-1 RNA \pm SD (\log_{10} copies/ml)	4.7 \pm 0.7	4.7 \pm 0.8
CDC classification [No. (%)]		
A	42 (38%)	31 (28%)
B	16 (14%)	21 (19%)
C	1 (1%)	0
HIV transmission [No. (%)]		
Heterosexual	55 (50%)	43 (38%)
Homosexual	2 (2%)	10 (9%)
Intravenous drug use	1 (1%)	0

^aMean body weight for female subjects 49.5 kg, male 64.1 kg.

increased alanine aminotransferase (standard dose) and one with increased amylase (half dose). The other eight events occurred during the study after week 0: anaemia in three (one on half dose, two on standard dose), raised liver enzymes in two (standard dose), neutropenia in one (standard dose), raised amylase in one (half dose) and hypoglycaemia in one (half dose). Once again, no statistically significant differences were observed between the two study arms. Besides these grade 3 and 4 laboratory abnormalities, a total of six serious adverse events were reported. A suicide and an unintended overdose occurred in the half dose arm. In the standard dose arm, there was a pregnancy followed by an abortion at 5 weeks of gestation, one patient with dengue hemorrhagic fever, a death from respiratory failure of unknown cause in another hospital, and one patient with acute psychosis.

Premature discontinuation from the study occurred in 12 patients, including the two deaths mentioned as serious adverse events above. Three patients withdrew because of nausea, two of whom were subsequently lost to follow-up. Another three patients discontinued because of anaemia ($n = 1$), patient choice for alternative medication ($n = 1$) and moving out of the area ($n = 1$); all were subsequently lost to follow-up. Another four patients were lost to follow-up for unknown reasons. Of these 12 premature discontinuations, nine occurred in the high dose arm; however, this difference between the arms did not quite reach statistical significance ($P = 0.08$). A total of 99 patients completed 48 weeks of the study.

Table 2 shows deaths and progression to a Centers for Disease Control and Prevention (CDC) HIV classification category B or C event for each dose group. A total of 21 CDC-B events and one CDC-C event (presumptive extrapulmonary tuberculosis) were re-

Table 2. Clinical endpoints for each dose group.

	Half dose arm	Standard dose arm	Total
CDC category B events ^a			
Oropharyngeal candidiasis	0	1	1
Oral hairy leukoplakia	6	6	12
Multidermatomal herpes zoster	3	1	4
Pruritic papular eruption	1	3	4
Total events	10	11	21
CDC category C events	0	1 ^b	1
Deaths	1	1	2
Total endpoints	11	13	24

^a $P = 0.637$ for total group B experiences.

^bExtrapulmonary tuberculosis

ported, with no statistically significant differences observed in frequency or nature of CDC events between the two study arms.

Efficacy analysis: changes in plasma HIV-1RNA concentrations

HIV-1 RNA levels in the two study arms up to 48 weeks were determined in all available plasma samples from all study visits (Fig. 1 and Table 3). At no time point was a difference of greater than 0.5 \log_{10} copies/ml observed between the two study arms. However, a consistently lower HIV-1 RNA copy number was observed in the group on standard dose than in the half dose group, which was of borderline statistical significance at all time points after baseline. Further analysis using a non-linear mixed effects regression model for repeated measurements showed a clear benefit for the standard dose group. By using all time points in the study in a single analysis, this method provides more robust statistical power compared with a t-test at a single time point.

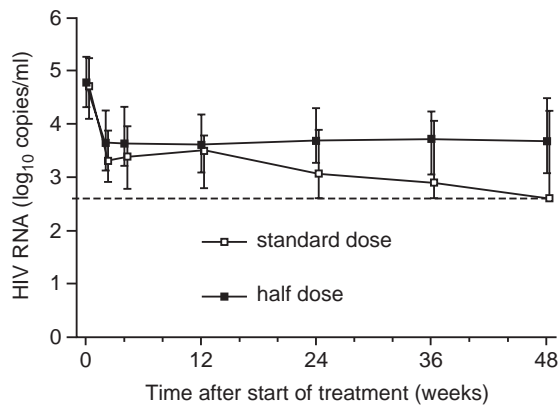


Fig. 1. Mean HIV RNA levels in the study treatment arms using all available samples (uncorrected data as specified in Table 3).

Analysis of the proportion of patients achieving plasma HIV-1 RNA < 400 copies/ml showed a superior effect of the standard dose arm at all time points, with 52 and 20% of participants reaching this level at week 48 in the standard and half dose arms, respectively ($P = 0.001$) (Table 3 and Fig. 2).

To correct for potential bias resulting from the increased drop-out in the standard dose arm compared with the half dose arm, the analysis was re-run assuming that all missing HIV-1 RNA samples would have shown a detectable result (> 400 copies/ml) if the patients had remained in the study (Table 3). Although this method had a negative impact on the percentage of responders, in essence the difference between the study-arms remained unchanged with $P = 0.013$ at week 48 in favour of the standard dose arm.

Additional analyses showed that both the baseline plasma HIV-1 RNA copy number and the AZT/ddC dose received were highly predictive of the ability of the treatment to reduce plasma HIV-1 RNA levels to < 400 copies/ml at week 48. A baseline plasma HIV-1

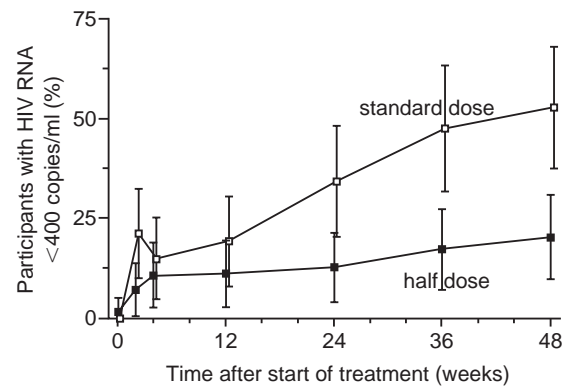


Fig. 2. Percentage of participants with HIV RNA levels < 400 copies/ml in each treatment arms using all available samples (uncorrected data as specified in Table 3).

RNA level < 4.75 log₁₀ copies/ml (the median HIV-1 RNA level at baseline) was associated with an odds ratio of 5.0 to reach < 400 copies/ml HIV-1 RNA at week 48 in both a univariate and multivariate analysis. Receiving AZT/ddC in standard dose was also associated with an odds ratio of 5.0 in achieving an HIV-1 RNA < 400 copies/ml at week 48.

Efficacy analysis: change in CD4 and CD8 cell counts

The half dose group had a lower baseline CD4 cell count (mean 321 × 10⁶ cells/l; SD = 114) than the high dose group (361 × 10⁶ cells/l, SD = 125) (Table 1 and Fig. 3). Despite an initial increase in CD4 cells after the start of therapy, observed in both arms and mostly in patients with low CD4 cell counts ($P = 0.0001$), no further significant CD4 cell increase over time was found in either arm ($P = 0.57$), and no difference was found between the two arms ($P = 0.21$).

The maximum increases in mean peripheral CD4 lymphocyte count from baseline were 73 × 10⁶ cells/l

Table 3. Percentage of patients with HIV-1 RNA of < 400 copies/ml (see also Fig. 2).

Week	Available samples		% HIV RNA < 400 copies/ml (initial analysis) ^a					% HIV RNA < 400 copies/ml (correcting for drop-outs) ^b				
	HD	SD	HD	SD	P	RR	95% CI	HD	SD	P	RR	95% CI
0	58	53	1.7	0				1.7	0			
2	56	52	7.1	21.2	0.05	3.49	1.03–11.76	6.9	20.8		3.54	1.05–11.90
4	56	47	10.7	14.9	0.56	1.46	0.45–4.69	10.3	13.2		1.32	0.41–4.21
12	54	47	11.1	19.1	0.27	1.90	0.62–5.79	10.3	17.0		1.77	0.86–5.37
24	56	44	12.5	34.1	0.01	3.62	1.32–9.92	12.1	28.3		2.88	1.07–7.74
36	53	38	17.0	47.4	0.002	4.40	1.73–11.18	15.5	34.0	0.03	2.80	1.13–6.96
48	55	42	20.0	52.4	0.001	4.40	1.83–10.56	19.0	41.5	0.01	3.03	1.29–7.12

HD, half dose; SD, standard dose; RR, relative risk; CI, confidence interval.

^aIncluding all available samples. Three participants from HD arm and nine from SD arm were lost to follow-up in the course of 48 weeks; HIV-1 RNA repeatedly indeterminate in the remaining missing samples.

^bIncluding all available samples plus drop-outs and indeterminate samples included as presumed failures.

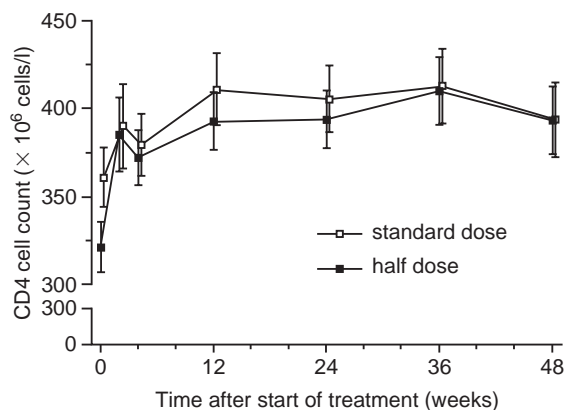


Fig. 3. Mean CD4 cell counts during the study for both treatment arms.

(week 12) in the standard dose arm and 95×10^6 cells/l (week 36) in the half dose arm. The half dose arm had a lower mean baseline CD8 cell count (1007×10^6 cells/l, SD = 513) than the standard dose arm (1121×10^6 cells/l, SD = 455) (Table 1 and Fig. 4). A high baseline CD8 cell count was more likely to decline than a lower (more normal) baseline CD8 cell count upon initiation of therapy ($P = 0.0001$). Overall there was a decline in CD8 cell counts over time ($P = 0.003$) that was not related to receiving half or standard dose ($P = 0.25$).

A subgroup analysis was performed after dividing patients according to CD8 cell count above or below the baseline mean of 1062×10^6 cells/l to investigate whether CD8 cell count decline was related to the treatment dose (Fig. 5). Using the mean baseline CD8 cell count distinguished participants with high baseline counts from those with low baseline counts more accurately than achieved using the median value. For participants with a CD8 cell count $< 1062 \times 10^6$ cells/l at baseline, no relation was found with the treatment dose ($P = 0.88$); however, for participants with

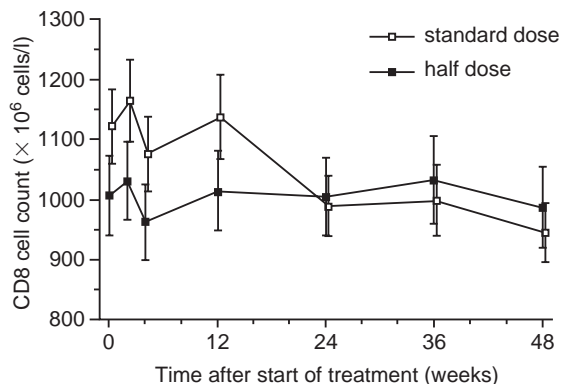


Fig. 4. Mean CD8 cell counts in the study in each treatment arm.

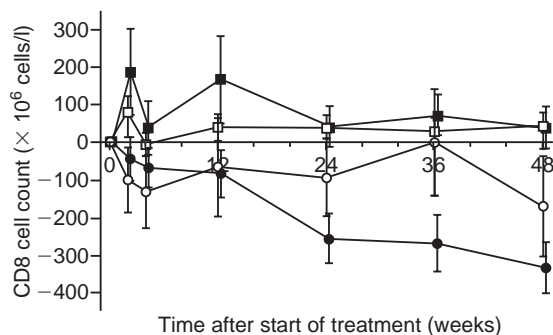


Fig. 5. Mean changes in CD8 cell count from baseline in each treatment arm after dichotomizing patients around the mean baseline CD8 cell count (1062×10^6 cells/l). High CD8 cell count with half dose ($-O-$), standard dose ($-●-$); low CD8 cell count with half dose ($-□-$), standard dose ($-■-$).

$> 1062 \times 10^6$ cells/l at baseline, a positive correlation (i.e., a greater decline in CD8 cell count; $P = 0.03$) was found in those receiving standard dose AZT/ddC.

Discussion

This study showed that the standard dose of AZT/ddC resulted in greater efficacy than half dose in the proportion of patients achieving a plasma HIV-1 RNA level of < 400 copies/ml at week 48 (52.4% versus 20%). In an additional analysis where drop-outs were regarded as treatment failures, this statistically significant difference persisted. The HIV RNA curves (Fig. 1) suggest that the favourable response in the standard dose group results from better inhibition of replication at all time points in the study and not from a higher number of rebounds in the half dose group. Further analysis using a repeated measurements model also showed statistically significant ($P = 0.0017$) superiority of the standard dose arm.

The degree of plasma HIV-1 RNA reduction in the standard dose AZT/ddC arm compares favourably with other studies using this combination. In the Delta trial, where zidovudine-naïve participants were randomized to either AZT alone or AZT combined with either didanosine or ddC, the group randomized to the AZT/ddC arm had median HIV-1 RNA reductions of 1.3, 1.1 and 0.9 \log_{10} copies/ml at 4, 24 and 48 weeks, respectively [8]. In the ACTG 175 study, which was similar to the Delta study but with an additional didanosine monotherapy arm, a mean decrease of 0.87 \log_{10} copies/ml was observed in the AZT/ddC arm, with no significant difference in those antiretroviral naïve or experienced [9]. In both studies, the median baseline HIV-1 RNA level was similar to our study. Schooley *et al.* reported another randomized trial of

180 patients with no more than 4 weeks prior treatment with AZT and identical study arms to Delta; this trial showed 1.0 and 0.6 log₁₀ copies/ml HIV-1 RNA reduction in the AZT/ddC arm at 12 and 48 weeks, respectively [10]. However in these three studies, the percentage of patients reaching undetectable HIV-1 RNA was not reported.

No data have been published on the efficacy of half dose AZT in suppressing HIV-1 RNA, either as monotherapy or in combination, because the trials with reduced dose AZT were performed before standardized assays became routinely available. However, studies by Fischl *et al.* and Collier *et al.* reported no significant differences in the degree of reduction of HIV p24 antigen in patients receiving AZT at daily doses of 300 and 600 mg compared with the standard daily doses at the time of 1200 mg or greater [11,12].

The observed difference in HIV-1 RNA response between the two arms in our study did not translate into a difference in CD4 cell response. This corresponds with similar observations in other cohorts in which 'fully suppressive' and less than fully suppressive highly active antiretroviral regimens are used [15–18]. However, in the standard dose arm, a greater decline in CD8 cell counts in participants with higher baseline CD8 cell counts was shown, probably reflecting improved viral suppression and subsequently improved immune activation.

The maximum mean CD4 cell increases of 73 and 95×10^6 cells/l from baseline for the standard and half dose arms, respectively, are similar to the maximum rises observed in antiretroviral drug-naïve patients receiving AZT/ddC in the Delta study (median rise 67×10^6 cells/l), ACTG 175 (mean rise 41×10^6 cells/l) and the Wellcome study (mean rise 85×10^6 cells/l) [6,7,10]. All of the above large trials used a standard dose of AZT at 600 mg/day in all arms; half dose was only used in the event of toxicity. However, earlier papers report the efficacy of half dose AZT as measured by peripheral CD4 lymphocyte counts. In the study by Collier *et al.*, patients receiving 300, 600 and 1500 mg AZT daily had mean CD4 cell count changes from baseline of +91, -20 and 0×10^6 cells/l, respectively [12]. A Japanese study reported no significant difference in increases in CD4 cell count between daily doses of AZT of 400 and 800 mg, but the increase with the lower dose was sustained for a significantly longer period [13]. A Norwegian clinical endpoint study compared daily doses of AZT of 400, 800 and 1200 mg in 474 patients with symptoms of AIDS or CD4 cell counts of $< 200 \times 10^6$ cells/l at baseline [14]. The monthly decline in CD4 cell count did not differ between the groups.

Since our study showed superiority of the standard dose

of AZT/ddC but the above studies reported at least equal efficacy of half dose AZT when used as monotherapy, we postulate that it is more important to maintain standard dosing of ddC than AZT for efficacy. This hypothesis is supported by another study from our group, which compared didanosine and stavudine in a range of dose combinations in 78 participants [19]. For maximal viral suppression, standard dosing of didanosine was essential, but the stavudine dose showed no significant correlation with virological outcome. This raises the hypothesis that the dose of a thymidine analogue, such as AZT and stavudine, is less critical than the dose of a non-thymidine nucleoside analogue when the drugs are used in combination. A comparison of half versus standard dose of a thymidine analogue in combination with the standard dose of a non-thymidine nucleoside analogue would enable this hypothesis to be studied further.

Overall, the two drug regimens were well tolerated with a low incidence of adverse events other than a slight non-significant decrease in haemoglobin in two patients receiving standard doses. The relationship between zidovudine dose and haematological toxicity has been well documented in other studies [11–14].

The inferiority of dual therapy compared with triple therapy regimens was illustrated by a large retrospective cohort study by Rhone *et al.* where only a minority of patients on dual nucleoside therapy regimens were able to maintain sustained HIV RNA suppression [20]. Given the ever increasing incidence and prevalence of HIV in the resource-poor settings of the developing world, the need for cost-effective anti-HIV therapy is evident [21]. The authors are well aware of the public health risks associated with suboptimal antiretroviral therapies but also recognize a seemingly universal consensus regarding access to treatment for HIV in developing countries [22,23]. As the cost of implementing triple combination antiretroviral therapy in some African countries is estimated to be as high as 84% of the gross national product [24], we feel that effective dual nucleoside therapy is still appropriate for resource-poor settings. This study showed that the standard dose combination of AZT/ddC may be considered in situations where the recommended 'standard of care' regimen of triple combination therapy is unaffordable by either patients themselves or the health care providers, but where adherence monitoring is feasible. When resources are even more constrained, using half dose AZT/ddC can be considered to maintain acceptable efficacy while reducing toxicity, based on the reasonable CD4 cell count rises observed in our study and supported by other studies [12–14] showing equivalent effect on CD4 lymphocyte counts of reduced dose AZT. A moderately reduced dose of AZT of 400 mg/day is currently used routinely in clinical practice in Thailand. The alternative for these patients

would be no antiretroviral therapy at all, with subsequent clinical deterioration and associated increase in health care costs. Based on the predictive value of a lower baseline plasma HIV-1 RNA level in this study in determining the success of the AZT/ddC regimen, a single baseline determination of plasma HIV-1 RNA might help in choosing the appropriate antiretroviral therapy for an individual patient. When resources are available to treat only a limited number of patients with triple combination therapy, consideration could be given to initiation of double nucleoside therapy in antiretroviral-naïve patients with lower baseline plasma HIV-1 RNA, thereby reserving more expensive triple therapy regimens for pretreated patients or those with higher baseline plasma HIV-1 RNA.

Acknowledgements

We would like to thank the week 24 interim analysis Data and Safety Monitoring Board: Dr Scott Hammer, Chief, Division of Infectious Diseases, Columbia University College of Physicians and Surgeons, New York, USA; Mrs Piyalamporn Havanond, Biostatistician, Institute of Health Research, Chulalongkorn University, Bangkok, Thailand and Dr Surapol Suwanagool, Associate Professor of Medicine, Department of Preventive and Social Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

We would also like to thank Dr Guenther Forster and Mrs Pongphaya Choosakulchart of Roche (Thailand) Ltd; Dr Matthew Law and Dr Sean Emery of NCHECR; Dr Gerrit-Jan Weverling, Ms Nadine Pakker and Mr Gerben-Rienk Visser of NATEC; Mrs Somsong Teeratakulpisarn, Ms Nongluk Yimsuan, Ms Joedjan Saetiauw, Mr Chowalit Phadungphon, Mr Johan Schuijtemaker and Mr Radjin Steingrover of HIV-NAT; and Dr Wiput Phoolcharoen of the Division of AIDS, Department of Communicable Disease Control, Ministry of Public Health, Nonthaburi, Thailand.

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