THE EFFICACY OF COMBINED ZIDOVUDINE AND LAMIVUDINE COMPARED WITH THAT OF COMBINED ZIDOVUDINE, LAMIVUDINE AND NELFINAVIR IN ASYMPTOMATIC AND EARLY SYMPTOMATIC HIV-INFECTED CHILDREN

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Abstract. In this 6-month prospective study, we compared the efficacy of two treatment regimens: double-drug therapy with zidovudine (ZDV) and lamivudine (3TC) and triple-drug therapy with ZDV plus 3TC plus nelfinavir (NFV), in the treatment of asymptomatic and early symptomatic HIV-infected children. Twenty-five children were enrolled in this study and were divided into 2 groups: group A, consisting of 13 children who were given ZDV+3TC; group B, consisting of 12 children who were given ZDV+3TC+NFV. Serial determinations of weight, CD4-cell count, HIV RNA or plasma viral load (VL) and complete blood counts (CBC), liver function tests (LFT), blood urea nitrogen (BUN) tests, creatinine and serum amylase tests were performed at study entry and at 1, 3 and 6 months. The side-effects of drugs were recorded. Over the 6-month period, the median weight increase in group B (24%) was higher than in group A (2%). The median CD4-cell count increase from baseline in group B (94.5%) was better than in group A (9.4%). The reduction of VL below baseline in group B (1.2 $\log_{10}$; 20.8%) was also better than in group A (0.72 $\log_{10}$; 13.8%). However, these differences were not statistically significant ($p>0.05$). Both combination regimens could not completely suppress HIV RNA below detectable limits (<400 copies/ml). Both groups tolerated the regimens well; no side-effects or toxicities occurred. The efficacy levels of triple-drug therapy (ZDV+3TC+NFV) and double-drug therapy (ZDV+3TC) were not different. There were no side-effects and no deaths during the 6-month study period.

INTRODUCTION

Combination therapy with zidovudine (ZDV) and lamivudine (3TC) has been shown to improve clinical outcomes and survival in HIV-infected patients (Anonymous, 1997; Hammer *et al*, 1996; 1997). Currently, treatment with two nucleoside analogues and a protease inhibitor is one of the recommended initial therapies for most HIV-infected patients (Carpenter *et al*, 1998; CDC, 1998). Triple combination therapy (two nucleoside analogues, such as ZDV and 3TC, together with a protease inhibitor), has been shown to decrease plasma HIV-1 RNA in the peripheral blood to levels below the limit of assay detection in the majority of patients, to improve immune function and to delay the progression of HIV infection (Carpenter *et al*, 1998; Funk *et al*, 1999). Nelfinavir (NFV) is a protease inhibitor which shows good inhibitory activity against HIV-1 (Perry and Benfield, 1997). Former antiretroviral treatment strategies in pediatric HIV-infection were based on the occurrence of clinical symptoms or the loss of CD4 cells. Because of toxicity and dosing concerns, HIV-infected children have often been denied new drugs routinely prescribed to HIV-infected adults. Recently, specialists in pediatric HIV care have developed treatment guidelines that recommend early combination antiretroviral therapies in infants and young children. It is likely that the

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recommendations will change as more evidence becomes available about the effects of different treatment regimens (Jakob-Solder, 1998).

We conducted this study to compare the efficacy of two treatment regimens, double-drug therapy (ZDV+3TC) and triple-drug therapy (ZDV+3TC+NFV), in asymptomatic and early symptomatic HIV-infected children.

MATERIALS AND METHODS

Study design and patients

The study was conducted among babies and children born to HIV-infected mothers who had visited the pediatric outpatient unit of Bamrasnaradura Infectious Disease Hospital, Nonthaburi, Thailand, from January 1999 to June 2001. The major inclusion criteria were: asymptomatic and early symptomatic HIV-infected babies and children in category N or A1 (CDC, 1994); no concomitant treatment with other antiretroviral agents. The exclusion criteria included: being lost to follow-up; a history of chronic diseases. HIV infection was defined according to the CDC/WHO criteria, *ie* for babies under 15 months, by HIV-1 PCR method, and for the children over 15 months, by anti-HIV antibodies (detected by 2 different screening tests over 1 month). The histories of HIV-infected babies and children were also recorded.

Treatment regimens

HIV-infected babies and children were assigned at random to receive treatment with either double-drug therapy (ZDV 360 mg/m^2/ day three times a day before meals plus 3TC 8 mg/kg/day twice a day) or triple-drug therapy (ZDV 360 mg/ m^2/ day three times a day plus 3TC 8 mg/kg/day twice a day plus NFV 60 mg/kg/day three times a day with meals).

This study was approved by the Research Committee and the Ethics Committee, Ministry of Public Health, Thailand. Informed consent was obtained from the parents of subjects.

Evaluation of patients

Patients were examined on entering the study and at 1, 3, and 6 months after starting treatment. Blood samples were collected and tests were performed for CD4-cell counts, HIV RNA (viral load), CBC, LFT, BUN, creatinine, and serum amylase. Side-effects, abnormal laboratory values, and efficacy were recorded at each visit.

Data analysis

Clinical efficacy was defined as the absence of AIDS-related disease or opportunistic infections of categories A, B, and C, according to the 1994 revised classification system for human immunodeficiency virus infection in children (CDC, 1994). Immunological and virological efficacy were defined as the relative changes of CD4-cell counts at each visit above baseline and VL below baseline.

Statistical analysis

To compare baseline characteristics of the two treatment groups, the F-test was used. The relative changes from baseline of median weight, viral load, CD4-cell count and some other laboratory findings of patients at each visit were calculated as percentages. The unpaired *t*-test was used for comparing the differences. All reported p-values were two-sided at the 0.05 significance level.

RESULTS

Patients and baseline characteristics

A total of 25 HIV-infected children were enrolled, of whom 13 were assigned double-drug therapy and 12 were assigned triple-drug therapy. Table 1 shows the baseline characteristics of the study population. The duration of study was 6 months. The two groups were comparable in terms of age, sex, mothers' risks, CD4-cell counts and HIV RNA. The baseline characteristics were broadly similar in the two treatment groups ($p>0.05$), except with regards to gender. The number of male children in group A (38%) was lower than in group B

Table 1
Baseline characteristics of the two treatment groups.

Characteristics	Group A (AZT+3TC) (N = 13)	Group B (AZT+3TC+NFV) (N = 12)	Remarks
Age in years (mean age)	4.2	4.3	F = 0.49 p > 0.05
Age range in years	4/12-7 9/12	6/12-6 4/12	
Males (%)	5 (38.5)	10 (83.3)	
Mothers' risk: heterosexual contact (%)	12/12 (100)	12/12 (100)	
Mean CD4-cell count (x 10^6/l) (range)	839 (8-1,967)	760 (6-2,707)	F = 0.79 p > 0.05
Mean VL level (log_{10} copies/ml) (range)	4.91 (2.94 - >5.87)	5.31 (<2.6 - >5.87)	F = 0.86 p > 0.05
Mean weight (kg) ± SD	15.31±5.6	12.97±3.8	F = 2.17 p > 0.05

Table 2
Side-effects/toxicities and laboratory findings in the two treatment groups.

Characteristics	Group A (AZT+3TC) (N = 13)		Group B (AZT+3TC+NFV) (N = 12)		Remarks
	Baseline	6 months	Baseline	6 months	
Side-effects	-	-	-	-	
Toxicities	-	-	-	-	
Hb in g%	10.6	10.9	9.8	10.2	t = 1.05
Hb change (%)		+0.3 (+2.8)		+0.4 (+4.1)	p > 0.05
Hct in %	31	33	30	32	t = 0.848
Hct change (%)		+2 (+6.5)		+2 (+6.7)	p > 0.05
WBC	7,475	7,557	8,565	8,792	
PMN	8,259	8,514	7,895	10,234	
Lymphocytes	3,785	3,391	3,900	4,580	
Platelets	Adequate	Adequate	Adequate	Adequate	
SGOT	38	33	37.5	34	
SGPT	26	28	15	43	
BUN	10.4	10.6	9.2	0.02	
Creatinine	0.54	0.52	0.50	0.52	
Serum amylase	151	157	174	155	

(83%). All subjects in both groups had become infected by vertical tranmission from mothers who had acquired HIV by heterosexual contacts (100%).

Side-effects/toxicities and laboratory findings of both therapies are shown in Table 2. There were no side-effects in either group. Both combination therapies were well tolerated, not necessitating any drug interruption during the study period. Anemia was found in the children of both groups before the start of treatment (Group A mean Hb 10.6 g%; mean Hct 31%. Group B mean Hb 9.8 g%; mean Hct 30%). Hemoglobin increased by 0.03 g%

Table 3
Clinical efficacy: weight and progression of disease in the two treatment groups.

	Group A (AZT+3TC) (N = 13)		Group B (AZT+3TC+NFV) (N = 12)		Remarks
	Baseline	6 months	Baseline	6 months	
Median weight in kg	15.3	15.6	12.9	16	t = 0
Median weight		+0.3		+ 3.1	p > 0.05
Change (%)		(+2)		(+24)	
Development of opportunistic infection/related diseases	Oral candidiasis	-	Oral candidiasis	-	
Deaths	-	-	-	-	

(2.8%) in the double-drug therapy group and by 0.4 g% (4.1%) in the triple-drug therapy group with no significant difference ($p > 0.05$). There were no instances of leukopenia, neutropenia, lymphopenia, or thrombocytopenia after 6 months of therapy. All children in both groups had no elevations of liver enzymes, BUN or creatinine during the 6 months of therapy. The levels of serum amylase in both groups were twice the normal value in HIV-infected children before the start of treatment but did not deteriorate with 6 months of treatment.

Efficacy

Clinical efficacy: Weight and progression of disease are shown in Table 3. The median weight had increased by 0.3 kg (2%) in the double-drug therapy group and by 3.1 kg (24%) in the triple-drug therapy group after 6 months of therapy with no significant difference ($p>0.05$). One patient in each group had oral candidiasis at study entry: they had recovered by the end of the 6-month therapy. During the study, no opportunistic infections or disease progression occurred in either group. No patients were diagnosed with any AIDS-defining illness and there were no deaths during the 6-month study period.

Immunological efficacy: CD4-cell counts are shown in Table 4. Because the groups comprised patients of different ages, we calculated relative rather than absolute changes as CD4-cell counts are highly dependent on the age of patients. As shown in Table 4, in group A the median CD4-cell count decreased by 14% (66×10^6/l) after 1 month and by 3% (14×10^6/l) after 3 months, whereas the counts increased by 9.4% (44×10^6/l) after 6 months of therapy. In group B, the median CD4-cell count decreased by 11% (44×10^6/l) after 1 month, but it increased by 82% (329×10^6/l) after 3 months and by 94.5% (379×10^6/l) after 6 months of therapy. The immunological efficacy levels based on CD4-cell counts of both groups were not significantly different after 1, 3 and 6 months of therapy ($p>0.05$).

Virological efficacy: The results of HIV RNA (viral load or VL) test (Amplicor, Roche) after treatments with the two regimens are shown in Table 5. In group A, the median VL reduction was 21.5% (1.12 $\log_{10}$) after 1 month, 16.3% (0.85 $\log_{10}$) after 3 months, and 13.8 (0.72 $\log_{10}$) after 6 months of treatment. In group B, the median VL reduction was 35.3% (2.04 $\log_{10}$) after 1 month, 31.3% (1.81 $\log_{10}$) after 3 months, and 20.8% (1.2 $\log_{10}$) after 6 months of treatment. There was no significant difference between the two treatment groups ($p>0.05$). The virological efficacy levels for both groups based on the plasma viral load were not significantly different after 1, 3 and 6 months of therapy ($p>0.05$). One (7.7%) child in group A and three children (25%) in

Table 4
Immunological efficacy: median CD4-cell counts in the two treatment groups.

	Median CD4-cell (1 x 10^6/l) (Range)		Remarks
	Group A (AZT+3TC) (N = 13)	Group B (AZT+3TC+NFV) (N = 12)	
At baseline	470 (8-1,967)	401 (6-2,707)	
At 1st month of treatment	404 (4-2,065)	357 (20-3,803)	t = 0.192
CD4-cell count change (%)	-66 (-14)	-44 (-11)	p > 0.05
At 3rd month of treatment	456 (16-2,641)	730 (120-3,307)	t = 0.192
CD4-cell count change (%)	-14 (-3)	+329 (+82)	p > 0.05
At 6th month of treatment	514 (12-1,867)	780 (32-4,075)	t = 1.35
CD4-cell count change (%)	+44 (+9.4)	+379 (+94.5)	p > 0.05

Table 5
Virological efficacy: comparison of median viral loads (log_{10}) in the two treatment groups

	Viral load (log_{10})		Remarks
	Group A (AZT + 3TC) (N = 13)	Group B (AZT + 3TC + NFV) (N = 12)	
At baseline	5.2 (2.94 - >5.87)	5.78 (<2.6 - >5.87)	
At 1st month of treatment	4.08 (<2.6 - 5.38)	3.74 (<2.6 - 5.72)	t = 0.2
VL decrease (%)	1.12 (21.5)	2.04 (35.3)	p > 0.05
At 3rd month of treatment	4.35 (<2.6 - 5.58)	3.97 (<2.6 - 5.87)	t = 0.192
VL decrease (%)	0.85 (16.3)	1.81 (31.3)	p > 0.05
At 6th month of treatment	4.48 (<2.6 - >5.87)	4.58 (<2.6 - 5.56)	t = 0.507
VL decrease (%)	0.72 (13.8)	1.2 (20.8)	p > 0.05

group B reached and maintained a viral load of <400 copies/ml during the 6-month therapy. Ten children (~ 77%) in group A and nine (75%) in group B did not reach a viral load of <400 copies/ml.

DISCUSSION

Highly active antiretroviral therapy (HAA RT) has become the standard of care for the treatment of HIV infection (Department of Health and Human Services, 1998). In antiretroviral naïve patients with advanced HIV infection, combination therapy with zidovudine, lamivudine and nelfinavir produces a significantly greater mean decrease in viral load than combination therapy with zidovudine and lamivudine (Henry *et al*, 1994). Previous studies suggested three-drug combinations as salvage regimens after failure of their second regimens (Smeaton *et al*, 2001).

This study evaluated the effect of the two treatment regimens, the double-drug therapy (ZDV+3TC) and triple-drug therapy (ZDV+ 3TC+NFV), in asymptomatic and early symptomatic HIV-infected children. Our data sug-

gest that the clinical, immunological and virological efficacy of triple-drug therapy were slightly superior to those of double-drug therapy, although the difference is not significant.

Approximately 90% of HIV-infected children experience wasting and/or nutritional deficiencies during the course of their disease (Miller and Garg, 1998; McKinney *et al*, 1993). The growth rate will be useful for comparing the growth effects of the new therapeutic strategies (Carey *et al*, 1998). Malnutrition manifests itself in poor growth rates through decreases in weight-for-age (Miller and Garg, 1998). In our study, all children before the start of treatment were asymptomatic and early symptomatic, so their weights were mostly borderline or just a little lower than the normal weight-for-age limit for Thai children (group A median age 4-7 years; median weight 13.3 kg; group B median age 3.9 years; median weight 12.9 kg). There were increases in weight in both treatment groups after 6 months of treatment: a higher increase in the triple-drug therapy group (24%) than in the double-drug therapy group (2%). This shows the different efficacy of both regimens although they are not significantly different.

Opportunistic infections (OI) are an important cause of morbidity and mortality among HIV-infected children. Some OI were common in the pre-HAART era (Danker *et al*, 2001). In this study we did not observe any OI or AIDS-related diseases in either study group. We observed a greater CD4-cell increase and VL decrease in the triple-drug therapy group, which is consistent with a previous report (Funk *et al*, 1999). Only 7.7% in the double-drug therapy group and 25% in the triple-drug therapy group could maintain an undetectable VL in the 6-month period of this study. This evidence shows that both regimens have little impact on the complete suppression of viral load below the detectable limit, as shown in one other study (Hoffmann *et al*, 2000). This might be the emergence of resistant HIV strains or due to poor drug compliance. In this study, we did not perform any drug resistance tests because the study was conducted in a short period. Long-term responses may be different (Nadal *et al*, 2000; Precious *et al*, 2000). However, other studies have reported the emergence of resistance mutations (Tremblay *et al*, 1999; Hoffman *et al*, 2000). Resistance to nelfinavir has been observed *in vitro* and in clinical isolates from patients experiencing insufficient or waning viral suppression during treatment (Bardsley-Elliot and Plosder, 2000).

Both regimens were well tolerated in this as in other studies (Henry *et al*, 1994; Mueller *et al*, 1998). Hematological abnormalities are found in many adult and pediatric patients with HIV infection. The etiology of hematological problems in the patient infected with HIV includes the direct effect of HIV-1, opportunistic infections, and drug toxicities (Mueller, 1998). Anemia is the most common hematological disorder observed in children infected with HIV and is related to the severity of HIV infection, the age group, and the use of antiretroviral therapy (Mueller, 1998; Ellaurie *et al*, 1990). In our study, we found anemia in both groups [mean Hb = 10.6 g% (group A), 9.8 g% (group B)] before the start of treatment; hemoglobin had slightly increased after 6 months of therapy, as in another study that reported an improvement in anemia among HIV-infected drug-users receiving HAART (Semba *et al*, 2001). This suggests that there was no effect on hemoglobin in the short-term treatment of both groups. There were no developments of leukopenia, neutropenia, lymphopenia, and thrombocytopenia in either treatment group during the 6-month treatment period, whereas other studies have found that AZT is limited by the associated development of neutropenia and anemia, which frequently necessitate transfusions (Pediatric Branch, National Cancer Institute, Maryland, 1990). A transient form of thrombocytopenia associated with retroviral syndrome has been reported in previous studies (Ellaurie *et al*, 1988; Karpatkin, 1990).

Hepatotoxic medications are often administered to children infected with HIV. An increase in aminotransferases accompanying the administration of any new medication should suggest

potential hepatotoxicity. Asymptomatic elevation of serum aminotransferases with hepatomegaly is the most common clinical presentation. Drugs are also toxic to the pancreas. Serial serum amylase and lipase levels should be obtained to moniter the clinical course (Miller and Garg, 1998). No evidence of drug toxicity was found in this study; there was no elevation of liver enzymes, BUN, creatinine, an amylase after 6 months of treatment. Diarrhea is the most frequent adverse event in patients receiving nelfinavir-based combination therapy, but is generally mild and results in minimal discontinuation of therapy in clinical trials. (Miller and Garg, 1998). Mann *et al* (1999) reported the development of abnormal body fat with protease inhibitors. Side-effects were not seen in this study.

In conclusion, our data show that double-drug therapy (ZDV+3TC) was not significantly different from triple-drug therapy (ZDV+3TC+ NFV), although the efficacy of the triple-drug therapy appears to be slightly superior; a further long-term study may be required to examine the apparent superiority of triple therapy. Triple-drug therapy may be offered as a salvage regimen after failure of a double-drug regimen. However, these drugs remain expensive for developing counties.

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REFERENCES

Anonymous. Randomized trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. *Lancet* 1997; 349: 1413-21.

Bardsley-Elliot A, Plosder GL. Nelfinavir: an update on its use in HIV Infection. *Drugs* 2000; 59: 581-620.

Carey VJ, Yong FH, Frenkel LM, McKinney Jr RE. Pediatric AIDS prognosis using somatic growth velocity. *AIDS* 1998; 12: 1361-9.

Carpenter CC, Fischl MA, Hammer SM, *et al*. Antiretroviral therapy for HIV infection in 1998: Updated recommendations of the International AIDS Society-USA Panel. *JAMA* 1998; 280: 78-86.

Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994; 43: 1-10.

Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral therapy in HIV-infected adults and adolescents. *MMWR* 1998; 47(RR-5): 43-65.

Dankner WM, Lindsey JC, Levin MJ, The Pediatric ACTG Protocol Teams. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J* 2001; 20: 40-8.

Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *MMWR* 1998; 47(RR-5): 43-82.

Ellaurie M, Burns ER, Bernstein LJ, Shah K, Rubinstein A. Thrombocytopenia and human immunodeficiency virus in children. *Pediatrics* 1988; 82: 905-8.

Ellaurie M, Burns ER, Rubinstein A. Hematologic manifestations in pediatric HIV infection: severe anemia as a prognostic factor. *Am J Pediatr Hematol Oncol* 1990; 12: 449-53.

Funk MB, Linde R, Wintergerst U, *et al*. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS* 1999; 13: 1653-8.

Hammer SM, Katzenstein D, Hughes M, *et al*. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med* 1996; 335: 1081-90.

Hammer SM, Squires K, Hughes M, *et al*. A random-

ized, placebo-controlled trial of indinavir in combination with two nucleoside analogs in human immunodeficiency virus infected person with CD4 counts less than or equal to 200 per cubic millimeter. *N Engl J Med* 1997; 337: 725-33.

Henry K, Lamarca A, Myers R, *et al*. The safety of VIRACEPTR (nelfinavir mesylate) in pivotal phase II/III double-blind randomized controlled trials as monotherapy and in combination with d4T or AZT/3TC [Poster]. Atlanta: 4th Conference on Antiviral Research, Apr 6-11, 1994.

Hoffmann F, Notheis G, Wintergerst U, *et al*. Comparison of ritonavir plus saquinavir- and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. *Pediatr Infect Dis J* 2000; 19: 47-51.

Jakob-Solder B. Antiretroviral therapy in children. *Wien Med Wochenschr* 1998; 148: 539-46.

Karpatkin S. HIV-1-related thrombocytopenia. *Hematolol Oncol Clin North Am* 1990; 4: 193-218.

Mann M, Piazza-Hepp T, Koller E, Struble K, Murray J. Unusual distributions of body fat in AIDS patients: a review of adverse events reported to the Food and Drug Administration. *AIDS Patient Care STDS* 1999; 13: 287-95.

McKinney RE, Robertson WR, the Duke Pediatric AIDS Clinical Trials Unit. Effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr* 1993; 123: 579-82.

Miller TL, Garg S. Gastrointestinal and nutritional problems in pediatric HIV disease. In : Pizzo PA, Wilfert CM, eds. Pediatric AIDS : the challenge of HIV infection in Infants, children, and adolescents, 3rd ed. Maryland: Williams & Wilkins, 1998: 363-82.

Mueller BU. Hematologic problems. In : Pizzo PA, Wilfert CM, eds. Pediatric AIDS: the challenge of HIV infection in Infants, children, and adolescents, 3rd ed; Maryland: Williams & Wilkins, 1998: 427-42.

Mueller BU, Sleasman J, Nelson RP Jr, *et al*. A phase I/II study of the protease inhibitors in children with HIV infection. *Pediatrics* 1998; 102: 101-9.

Nadal D, Steiner F, Cheseaux JJ, *et al*. Long-term responses to treatment including ritonavir or nelfinavir in HIV-1-infected children. Pediatric AIDS Group of Switzerland. *Infection* 2000; 28: 287-96.

Pediatric Branch, National Cancer Institute, Bethesda, Maryland 20892. Treatment of human immunodeficiency virus-infected infants and young children with dideoxynucleosides. *Am J Med* 1990; 88: 16S-19S.

Perry CM, Benfield P. Nelfinavir. *Drugs* 1997; 54: 81-7.

Precious HM, Gunthard HF, Wong JK, *et al*. Multiple sites in HIV-1 reverse transcriptase associated with virological response to combination therapy. *AIDS* 2000; 14: 31-6.

Semba RD, Shah N, Vlahov D. Improvement of anemia among HIV-infected injection drug users receiving highly active antiretroviral therapy. *J AIDS* 2001; 26: 315-9.

Smeaton LM, DeGruttola V, Robbins GK, Shafer RW. ACTG (AIDS Clinical Trials Group) 384: a strategy trial comparing consecutive treatment for HIV-1. *Control Clin Trials* 2001; 22: 139-41.

Tremblay C, Merrill DP, Chou TC, Hirsch MS. Interactions among combinations of three protease inhibitors against drug-susceptible and drug-resistant HIV-1 isolates. *J AIDS* 1999; 22: 430-6.