Long-Term Efficacy, Safety, and Tolerability of Indinavir-Based Therapy in Protease Inhibitor–Naive Adults with Advanced HIV Infection

Martin S. Hirsch,[1] Roy T. Steigbigel,[2] Scholomo Staszewski,[7] Deborah McMahon,[3] Margaret A. Fischl,[5] Bernard Hirschel,[8] Kathleen Squires,[6] Mark J. DiNubile,[4] Charlotte M. Harvey,[4] Joshua Chen,[4] and Randi Y. Leavitt,[4] for the Protocol 039 Study Group

[1]Massachusetts General Hospital, Harvard Medical School, Boston; [2]University Hospital, State University of New York at Stony Brook; [3]University of Pittsburgh Medical Center, Pittsburgh, and [4]Merck Research Laboratories, West Point, Pennsylvania; [5]University of Miami School of Medicine, Florida; [6]University of Alabama at Birmingham; [7]Klinikum der J. W. Goethe University, Frankfurt, Germany; and [8]Hopital Cantonal Universitaire, Geneva, Switzerland

A double-blind, randomized study of zidovudine-experienced, PI- and lamivudine-naive adults with baseline CD4 cell counts of ≤50 cells/mm^3 had demonstrated that the HIV suppression achieved with zidovudine, lamivudine, and indinavir therapy was superior to that achieved with dual-nucleoside or indinavir-only regimens after 24 weeks of therapy. In a 192-week extension of the study, 371 participants received open-label indinavir with or without other antiretroviral drugs. One hundred and eight subjects were originally randomized to receive triple therapy. After 216 weeks, the proportion of subjects with HIV RNA levels of <500 copies/mL were 34%, according to a general estimating equation analysis, 92%, according to an observed data analysis, and 24%, according to an intention-to-treat analysis counting noncompleters as failures; the proportions of subjects with HIV RNA levels of <50 copies/mL were 31%, 85%, and 22%, respectively. Hyperbilirubinemia (experienced by 31% of subjects), nausea (17%), abdominal pain (14%), and nephrolithiasis (13%) were the most common drug-related adverse events during the extension.

Combination antiretroviral therapy including a protease inhibitor (PI) is a standard of care for patients with HIV infection [1]. Treatment with PI-containing regimens has resulted in improved rates of patient survival, decreased rates of morbidity, and reduced health care expenditures [2–9]. Indinavir-based combination therapy can suppress plasma HIV RNA levels below the limit of quantification of standard assays in the majority of PI-naive patients [10, 11]. Viral suppression has been maintained in some patients for >3 years [12, 13]. Less extensive data are available for the subset of patients with far-advanced infection, as indicated by CD4 cell counts of ≤50 cells/mm^3. A double-blind, randomized study of zidovudine-experienced, PI- and lamivudine-naive adults with baseline CD4 cell counts of ≤50 cells/mm^3 had previously demonstrated that the HIV suppression achieved with triple zidovudine, lamivudine, and indinavir therapy was superior to that achieved with dual-nucleoside or indinavir-only regimens after 24 weeks of therapy [14]. Participants completing the initial 24-week study were eligible to enter a noncomparative extension phase of the study to assess the long-term efficacy and tolerability of indinavir-based therapy for advanced HIV infection. In this report, we update the virological and immunological response data of subjects originally randomized to the triple-therapy arm in the double-blind study through 216 weeks. We also describe safety data for all subjects who entered the extension phase of the study.

METHODS

Study design. The original study was a double-blind, randomized, 24-week study to evaluate the efficacy and safety of indinavir, zidovudine, and lamivudine (triple) therapy versus zidovudine and lamivudine (dual nucleoside) therapy versus indinavir monotherapy in PI- and lamivudine-naive adults with baseline CD4 cell counts of ≤50 cells/mm^3 who had been treated with zidovudine for >6 months [14]. There were no exclusion criteria based on viral RNA levels. Individuals meeting the entry criteria but ineligible for randomization could be treated with indinavir-containing regimens in a fourth open-label arm of the study. Participants completing the initial 24-week study were invited to enter an anticipated, noncomparative 48-week extension phase of the study and receive open-label indinavir alone or in combination with other approved non-PI antiretroviral drugs. There were 3 subsequent extensions. Subjects were instructed to take 800 mg of indinavir every 8 h on an empty stomach; adequate fluid intake was stressed. The protocol was approved by the Institutional Review

Received 11 February 2003; accepted 5 June 2003; electronically published 18 September 2003.

Reprints or correspondence: Dr. Mark DiNubile, Merck Research Laboratories, PO Box 4, BL3-4, West Point, PA 19486 (mark_dinubile@merck.com).

Clinical Infectious Diseases 2003; 37:1119–24

1058-4838/2003/3708-0018$15.00

Board at each site, and all participants provided written informed consent.

Participants who were initially randomized to receive triple therapy were observed for 216 weeks for evaluation of efficacy. All subjects entering the open-label extension study were included in the safety evaluation. Only adverse experiences that developed between week 25 and week 216 of the study were included in this analysis. Adverse events were considered drug-related if they were judged by the site investigator as definitely, probably, or possibly related to indinavir therapy.

Virological and immunological studies. Serum viral RNA levels were determined by the standard Amplicor PCR assay (Roche Diagnostics), with a lower limit of quantification of 500 copies/mL. If a signal was detected but the number of copies was <500 copies/mL, a value of 500 copies/mL was recorded for that specimen. A value of 250 copies/mL was assigned to specimens with levels of viral RNA that were undetectable according to the standard assay. During the extension phase, testing with the UltraDirect assay (Roche Diagnostics), with a lower limit of quantification of 50 copies/mL, was performed whenever viral RNA levels were <500 copies/mL according to the standard assay [15]. CD4 cell counts were measured by flow cytometry.

Statistical analysis. The proportions of subjects with viral RNA levels below the limit of quantification at scheduled study visits were analyzed in 3 different ways: first, a "model-based" intention-to-treat analysis derived from generalized estimating equations (GEE) that imputed missing data from treatment-related discontinuations of therapy as failures of treatment subsequent to discontinuation; second, an observed data analysis in which no missing values were imputed; and, third, a worst-case intention-to-treat analysis that counted all non-completed courses of therapy as instances of treatment failure (NCF) [16–18]. For the GEE analysis, viral RNA measurements that were missing because of skipped or mistimed visits were imputed as indicating treatment failure (or success) if the values from visits immediately preceding and following the missing measurement both indicated treatment failure (or success); other intermittently missing values were left as missing. In the NCF calculations, viral RNA measurements missing because of skipped or mistimed visits were imputed as indicating treatment failure unless the values immediately before and after the missing value both indicated treatment success, in which case the absent value was left as missing.

Indinavir was the only protocol-mandated drug administered during the extension phases. Participants were not forced to withdraw from the study if another protease inhibitor or unlicensed antiretroviral agent was added to their indinavir-containing regimen. However, if subjects stopped receiving indinavir, their participation in the study was discontinued. All subjects with viral RNA measurements were counted in the intention-to-treat analyses. Participants no longer taking indinavir, whether alone or in combination with other drugs, were subsequently counted as having experienced treatment failure in the NCF analysis, and they were not included in the observed data thereafter. These participants were also excluded from the GEE model after stopping indinavir unless the discontinuation of indinavir was prompted by virological failure and/or a drug-related adverse event, under which conditions they were counted as having experienced treatment failure.

Changes in baseline viral RNA levels and CD4 cell counts were summarized over time using both observed data and a mixed-effects model for repeated measurements in which participants with treatment-related discontinuations had their missing values imputed by carrying forward the last observed data.

RESULTS

Participant characteristics. The majority of the 465 participants enrolled in the 4 treatment arms of the original study were middle-aged white men with prior AIDS-defining illnesses who had been treated with zidovudine for >2 years before entry into the study [14]. A total of 371 subjects completed the parent study and entered the open-label extension phase. Efficacy was evaluated over the entire 216 weeks of the study in all 108 of the participants who were initially randomized to triple therapy (table 1). Ninety-one (84%) of these 108 subjects completed the randomized phase, entered the extension phase, and continued to receive their original triple combination regimen. Three subjects receiving triple therapy (3%) declined to enter the extension phase after completing the initial 24 weeks.

Table 1. Selected characteristics and baseline laboratory values of 108 subjects initially randomized to triple-combination antiretroviral therapy.

Characteristic	Value
Male	93 (86)
White	81 (75)
Age in years, median (range)	40 (26–62)
CD4 cell count at baseline,[a] cells/mm^3	
Mean ± SD	19 ± 15
Median (range)	15 (5–63)
Serum HIV RNA level, $\log_{10}$ copies/mL	
Mean ± SD	4.83 ± 0.51
Median (range)	4.88 (3.04–6.08)
AIDS-defining illness(es)	62 (57)

NOTE. Data are no. (%) of patients, unless otherwise indicated. These 108 subjects constituted the efficacy cohort for the entire 216 weeks of this study.

[a] Four study participants whose CD4 cell counts were ≤50 cells/mm^3 when screened had CD4 cell counts of >50 cells/mm^3 (range, 57–63 cells/mm^3) on the first day of study therapy.

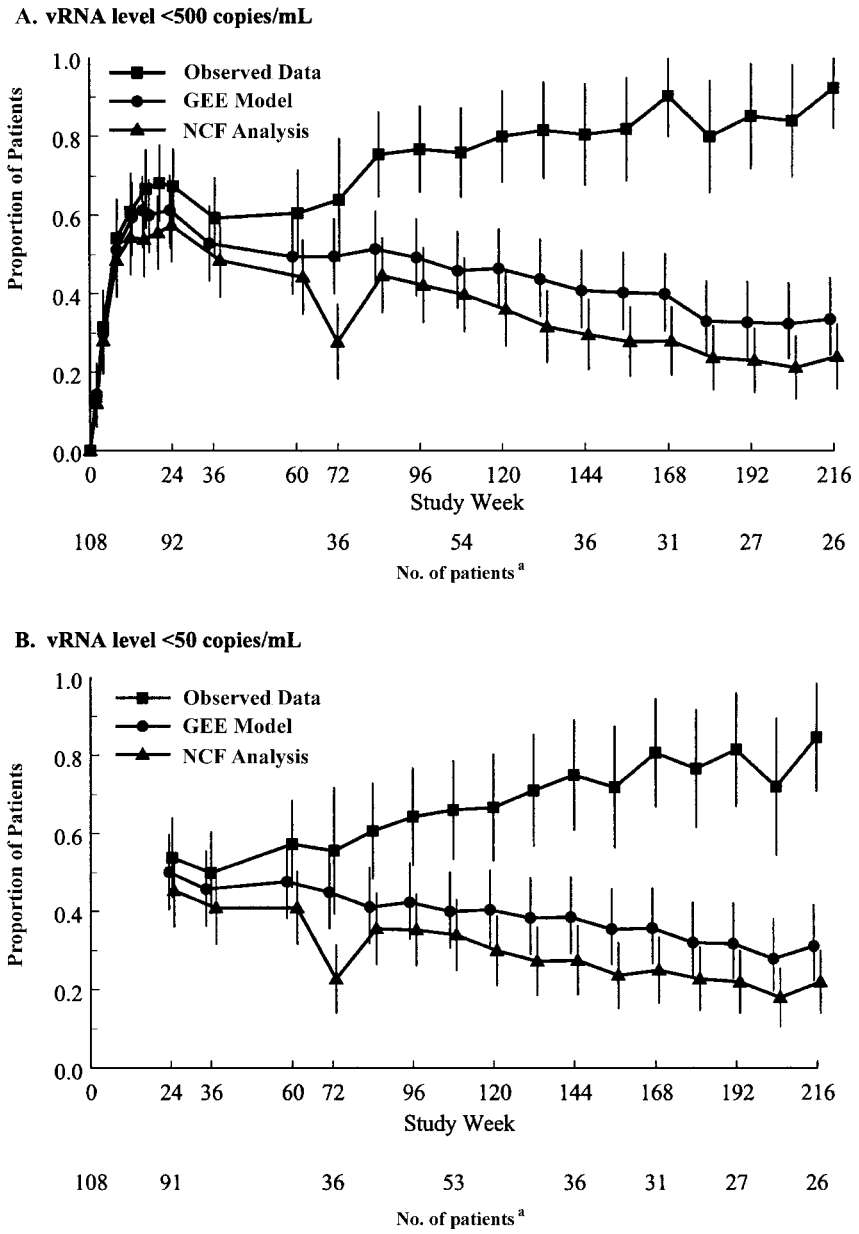

Figure 1. Proportions of subjects with viral RNA (vRNA) levels <500 copies/mL *(A)* and <50 copies/mL *(B)*. The proportions of the 108 subjects initially randomized to triple-therapy whose vRNA levels fell below the limit of quantification for the standard *(A)* and ultrasensitive *(B)* vRNA assays are shown at each scheduled study visit, based on observed data, a general estimating equation model (GEE model), and the analysis counting all noncompleted courses of therapy as instances of treatment failure (NCF) (for definitions, see *Methods)*. Bars represent 95% CIs. [a]No. of patients with observed data at the corresponding time.

Twenty-eight subjects who received triple therapy (26%) completed all 216 weeks of the study.

Seventy-seven subjects receiving triple-therapy did not complete all 216 weeks of the study. Reasons for not completing the entire study included the following: reaching clinical end points, 4 (4%) of 108 subjects; experiencing clinical adverse events, 14 (13%) (9 of whom [8%] experienced drug-related clinical adverse events); experiencing laboratory adverse events, 5 (5%) (4 of whom [4%] experienced drug-related laboratory adverse events); lack of efficacy, 26 (24%); and withdrawal of consent, 18 (17%). Four (4%) of the 108 participants discontinued the study for miscellaneous reasons related to relocation, investigator discretion, or personal preference. Six subjects (6%) were lost to follow-up during the extension period.

A total of 5 subjects, 2 of whom were initially randomized to triple therapy, added ritonavir to their regimens during the

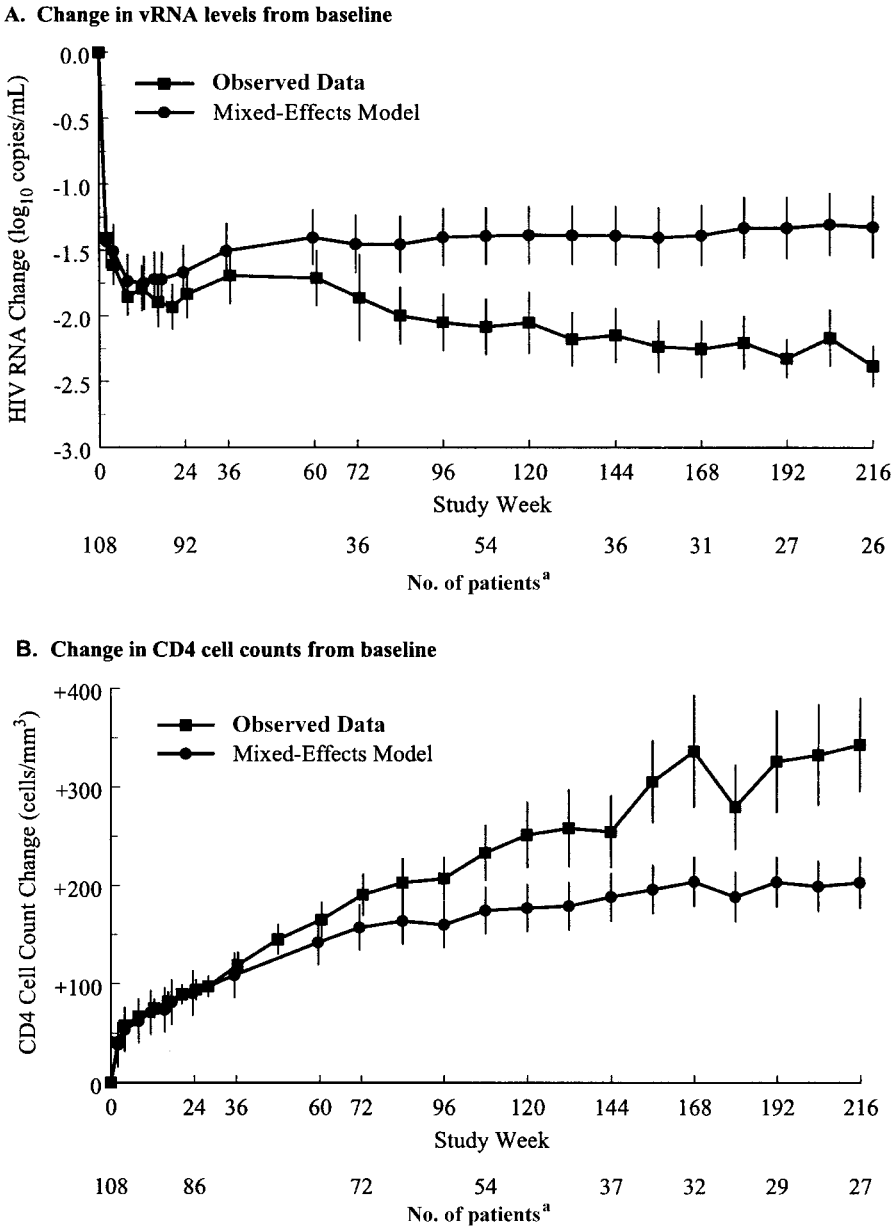

Figure 2. Changes from baseline viral RNA (vRNA) levels *(A)* and CD4 cell counts *(B)* over time. The mean changes from baseline in vRNA levels *(A)* and CD4 cell counts *(B)* at each scheduled study visit are shown for the 108 subjects initially randomized to triple therapy, computed using either the observed data or the mixed-effects model (for definitions, see *Methods).* Bars represent 95% CIs. [a]No. of patients with observed data at the corresponding time.

extension phases. One participant who was randomized to triple therapy developed *Pneumocystis carinii* pneumonia and died during the first 24 weeks of the study, and 3 additional subjects died during the extension periods. In 2 of these cases, death was attributed to infections.

Virological and immunological responses. The proportions of the 108 subjects receiving triple therapy with viral RNA levels of <500 copies/mL and <50 copies/mL over the duration of the study are shown in figure 1, which displays the results of all 3 analyses. At week 216, the GEE analysis showed that 34% of the 108 subjects had viral RNA levels of <500 copies/mL and 31% had <50 copies/mL. According to the NCF analysis, 26 (24%) of the subjects had RNA levels of <500 copies/mL and 24 (22%) of the subjects had RNA levels of <50 copies/mL at week 216. According to the observed data of the 26 participants with viral RNA measurements at week 216, there

were 24 (92%) who had RNA levels of <500 copies/mL and 22 (85%) who had RNA levels of <50 copies/mL. Only 2 participants with viral suppression at the completion of the study had changed antiretroviral therapy from their original triple-drug regimen. Figure 2 displays the mean changes in viral RNA levels (shown in panel A) and CD4 cell counts (shown in panel B) from baseline values. The model-based estimates were a decrease of 1.3 $\log_{10}$ viral RNA copies/mL and an increase of 204 CD4 cells/mm^3 at week 216.

Adverse events. Of the 465 participants enrolled in the original 24-week study, 371 (80%) entered the first extension (weeks 25–72); 251 (54%) entered the next extension (weeks 73–120); 119 (26%) entered the third extension (weeks 121–168); and 80 (17%) entered the final extension (weeks 169–216). Of the 371 subjects (86% men; 84% white; median age [range] in years, 39 [20–66]) who entered any extension phase, 97% experienced ⩾1 clinical adverse event and 73% experienced ⩾1 laboratory adverse event between week 25 and week 216 (table 2). Overall, 68% experienced drug-related clinical adverse events and 63% experienced drug-related laboratory adverse events, which were considered serious in 11% and 1% of cases, respectively. Thirty-four persons (9%) discontinued the extension because of drug-related adverse events, including 5 (1%) with serious drug-related adverse events. Eighteen participants (5%) died during the extension period, but no death was directly attributable to drug toxicity.

The most frequent drug-related clinical adverse events were diarrhea (experienced by 38% of subjects), fatigue (34%), nausea (33%), abdominal pain (32%), and fever (30%). Nephrolithiasis was documented in 13% of subjects; 20 subjects (5%) discontinued the study because of nephrolithiasis. The most common drug-related laboratory adverse events were hyperbilirubinemia (31% of subjects) and abnormal urinalysis results (28%) (including hematuria, pyuria, and proteinuria, each documented in 10% of subjects).

DISCUSSION

This study is unique in 2 respects. Only zidovudine-experienced subjects with advanced HIV infection, characterized by a CD4 lymphocyte count of ⩽50 cells/mm^3, were enrolled. Furthermore, participants with far advanced HIV were observed for up to 4 years. Our results indicate that triple-combination antiretroviral therapy containing indinavir can result in long-term virological and immunological benefits for some PI-naive patients with advanced HIV infection [12, 13].

Marked reductions of viral RNA levels and elevations in CD4 cell counts were maintained in a sizable minority of subjects for up to 216 weeks. According to the GEE analysis, at week 216, 34% of subjects initially randomized to triple-therapy had viral RNA levels that were suppressed to <500 copies/mL, and the viral RNA levels of 31% of subjects were <50 copies/mL. According to a worst-case intention-to-treat analysis in which noncompletion of therapy was regarded as treatment failure, viral RNA levels were suppressed to <50 copies/mL in 22% of subjects. During the 216-week study, lack of efficacy led to study discontinuation by 22% of the subjects receiving triple therapy, and adverse experiences led to study discontinuation by 18% of the subjects receiving triple therapy. In the large majority of participants still under observation at the end of the study, viral RNA levels remained <50 copies/mL.

Adverse experiences observed among subjects receiving prolonged indinavir therapy appeared to be comparable in type and frequency to those observed during the initial 24 weeks of the study [14] and were consistent with the established adverse-event profile for indinavir-containing regimens [10, 11]. The

Table 2. Clinical and laboratory adverse events developing during the 192-week extension phase in all 371 subjects entering the extension phase.

	No. (%) of subjects, by clinical or laboratory adverse experience			
	Clinical		Laboratory[a]	
Type of adverse experience	Developed adverse experience	Discontinued therapy	Developed adverse experience	Discontinued therapy
Any	360 (97.0)	54 (14.6)	272 (73.3)	12 (3.2)
Drug-related	253 (68.2)	33 (8.9)	234 (63.1)	11 (3.0)
Serious	125 (33.7)	21 (5.7)	11 (3.0)	1 (0.3)
Serious and drug-related	39 (10.5)	4 (1.1)	5 (1.3)	1 (0.3)

NOTE. Eighteen (4.8%) of 371 subjects died during the extension phase.

[a] Laboratory test results were available for 369 (99%) of the 371 subjects during the extension phase.

open-label design of the extension phase and the paucity of restrictions on other medications may have affected the reporting and attribution of adverse experiences. Overall, constitutional and gastrointestinal complaints, isolated hyperbilirubinemia, and suspected or documented nephrolithiasis were the most important adverse events. Five percent of subjects left the study during the extension phases as a result of nephrolithiasis.

In summary, we investigated the effects of zidovudine, lamivudine, and indinavir combination therapy in an open-label, noncomparative study of PI-naive subjects at a late stage of HIV infection who had been pretreated with zidovudine. Our results indicate that some patients with advanced HIV infection can benefit from combination antiretroviral therapy for prolonged periods. The frequency and severity of drug-related adverse experiences reported in this study were similar to the established adverse-event profile for indinavir-containing regimens.

Acknowledgments

We thank all the patients and their caregivers who participated in this study. We gratefully recognize the important contributions of the investigators, especially Drs. John Mellors, Paul Berry, Ellen Yetzer, Peter Wolfe, Timothy Babinchak, Kelly Henning, Michael Buckley, Ann Collier, Ernesto Scerpella, James Kahn, Thomas Merigan, Donna Mildvan, Robert Murphy, Kent Sepkowitz, Michael Saag, Melanie Thompson, Willy Rozenbaum, Daniel Vittecoq, Wolfgang Stille, Joep Lange, Stephen Adelstein, and Christos Tsoukas, who enrolled their patients in this trial.

References

1. Panel on Clinical Practices for the Treatment of HIV Infection convened by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at: http://www.aidsinfo.nih.gov. Accessed 14 July, 2003.
2. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. Lancet **1998**; 352: 1725–30.
3. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med **1998**; 338:853–60.
4. Hoggs RS, Health KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA **1998**; 279:450–4.
5. Vittinghoff E, Scheer S, O'Malley P, et al. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. J Infect Dis **1999**; 179:717–20.
6. Li TS, Tubiana R, Katlama C, et al. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet **1998**; 351:1682–6.
7. Gebo KA, Chaisson RE, Folkemer JG, et al. Costs of HIV medical care in the era of highly active antiretroviral therapy. AIDS **1999**; 13:963–9.
8. Casado JL, Perez-Elias MJ, Antela A, et al. Predictors of long-term response to protease inhibitor therapy in a cohort of HIV-infected patients. AIDS **1998**; 12:F131–5.
9. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med **2001**; 344:824–31.
10. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med **1997**; 337:725–33.
11. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med **1997**; 337:734–9.
12. Gulick RM, Mellors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. Ann Intern Med **2000**; 133:35–9.
13. Gulick RM, Meibohm A, Halvir D, et al. Six-year follow-up of HIV-1 infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. AIDS (in press).
14. Hirsch MS, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. J Infect Dis **1999**; 180:659–65.
15. Sun R, Ku J, Jayakar H, et al. Ultrasensitive reverse transcriptase-PCR assay for quantitation of human immunodeficiency virus type 1 RNA in plasma. J Clin Microbiol **1998**; 36:2964–9.
16. Kleinman KP, Ibrahim JG, Laird NM. A Bayesian framework for intent-to-treat analysis with missing data. Biometrics **1998**; 54:265–78.
17. Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics **1996**; 52:1324–33.
18. Tsiatis A. Methodological issues in AIDS clinical trials: intent-to-treat analysis. J Acquir Immune Defic Syndr **1990**; 3:S120–3.