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RANDOMIZED, DOUBLE-BLIND TRIAL COMPARING INDINAVIR ALONE, ZIDOVUDINE ALONE AND INDINAVIR PLUS ZIDOVUDINE IN ANTIRETROVIRAL THERAPY-NAIVE HIV-INFECTED INDIVIDUALS WITH CD4 CELL COUNTS BETWEEN 50 AND 250/MM³

David S. LEWI(1), Jamal M. SULEIMAN(2), David E. UIP(3), Rogerio J. PEDRO(4), Rosa A. SOUZA(5), Grace S. SULEIMAN(2), Conceição ACCETTURI(1), Olavo M. LEITE(3), William B. ABREU(4), Artur O. KALICHMAN(5), Joaquim P.P. MORAES-FILHO(6), Eduardo F. MOTTI(6), Maria Lucia C. PECORARO(6), Mark R. MAKURATH(7), Michael L. NESSLY(7), Randi Y. LEAVITT(7), for the Protocol 028 Study Group

SUMMARY

Treatment with indinavir has been shown to result in marked decreases in viral load and increases in CD4 cell counts in HIV-infected individuals. A randomized double-blind study to evaluate the efficacy of indinavir alone (800 mg q8h), zidovudine alone (200 mg q8h) or the combination was performed to evaluate progression to AIDS. 996 antiretroviral therapy-naive patients with CD4 cell counts of 50-250/mm³ were allocated to treatment. During the trial the protocol was amended to add lamivudine to the zidovudine-containing arms. The primary endpoint was time to development of an AIDS-defining illness or death. The study was terminated after a protocol-defined interim analysis demonstrated highly significant reductions in progression to a clinical event in the indinavir-containing arms, compared to the zidovudine arm ($p < 0.0001$). Over a median follow-up of 52 weeks (up to 99 weeks), percent reductions in hazards for the indinavir plus zidovudine and indinavir groups compared to the zidovudine group were 70% and 61%, respectively. Significant reductions in HIV RNA and increases in CD4 cell counts were also seen in the indinavir-containing groups compared to the zidovudine group. Improvement in both CD4 cell count and HIV RNA were associated with reduced risk of disease progression. All three regimens were generally well tolerated.

KEYWORDS: Randomized study; Double blind clinical trial; HIV; AIDS; Protease inhibitors; Indinavir; Zidovudine; Disease progression; Therapy; Clinical endpoint.

INTRODUCTION

The introduction of protease inhibitors for the therapy of human immunodeficiency virus type 1 (HIV-1) infection has been associated with a marked decrease in morbidity and mortality in HIV-1 infected individuals^{2,14,25,27}. Early studies demonstrated that monotherapy with certain protease inhibitors resulted in marked decreases in HIV RNA and increases in CD4 cell counts^{6,12,18,31}. Subsequently, the use of the protease inhibitor indinavir in combination with zidovudine plus

lamivudine was shown to have superior antiretroviral efficacy compared to zidovudine plus lamivudine in several clinical trials^{12,14}. In a study of zidovudine experienced patients with 50-400 CD4 cells/mm³, the triple combination of indinavir plus zidovudine plus lamivudine suppressed HIV RNA to below 500 copies/mL in more than 80% of patients¹². Recently, therapy with indinavir in combination with zidovudine plus lamivudine was shown to reduce the rate of clinical HIV-1 disease compared to zidovudine plus lamivudine in zidovudine experienced patients with ≥ 200 CD4 cells/mm³¹⁴.

Protocol 028 Study Group, Centers and Investigators -

- (1) Escola Paulista de Medicina / UFESP, São Paulo, Brazil: Gilberto Turcato Jr.; Ana C. Gales; Ana L. Schmidt; Eduardo O. Marliere; Jessé R. Alves; Lucas E. Darrigo; Marcelo Sampaio; Maria Claudia Stockler; Maria Tereza P. Lima; Paulo R.A. Ferreira; Swami C. Oliveira; Greyce B.L. Lewi
- (2) Instituto de Infectologia Emílio Ribas, São Paulo, Brazil: Marcia Y.S. Tomishige; Alexandre Almeida; Gloria L.B.F. Brunetti; Luiz A.B. Barra; Marileide J. Vasconcelos; Tamara N.L. Souza; Ricardo Minkoves; Zarifa K. Gregorio; Paulo D. Garbelotto; Paulo T. Dualiby; Guido C. Levi, Nelly A. Fantini.
- (3) Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil: Ana Marli C. Sartori; Ana Lúcia L.M. Lima; Luis Henrique B. Borges; Luiz G. Martins Filho; Alexandre L.G.P. Lins; Ruth M. Leite; Cristina M.F. Guastini; Maria Luiza P. Brussi; Fátima M. Tengan; Carlos R.V. Kiffer; Marília S. de Oliveira; Juliane G. Paula; Marise O. Fonseca; Francisco Bonasser Filho; Eliana B. Gutierrez; Noemia C. Pereira; Sheila W. Santoro; Bruno Caramelli; Marilena A. Barone.
- (4) Faculdade de Ciências Médicas da UNICAMP, Campinas, Brazil: Francisco H. Aoki; Josué N. Lima; Dináida T. Monteiro; Mariana C.E.S. Carvalho; Ana Lucia Krzesinski; Monica J. Moraes; Carlos M. Sabioni; Claudia C. Santos; Andrea F. Colombo.
- (5) Centro de Referência e Treinamento de AIDS, São Paulo, Brazil: Paulo R. Teixeira; José V. Madruga; Suzana Leme; Fabio Araujo; Leila Peron; Wong K. Kuen; Denize L. Estevam; Eduardo R. Lagonegro; Maria E. Galafassi; Sílvia A. Piedade; Ana Lucia Monteiro; Marcia Roque; Wah W. Wong; Cristina Muccioli; Julio C. Pacca; Maura R. Silveira.
- (6) Merck Research Laboratories - Brazil: Celia T. Wünsch, Sílvia A. Assakawa, Lilian F. Azevedo, Kleber Castilho, Patricia L. Fortner, Neide Lima, Ana Paula Neves, Maria Victoria F. Thompson, Suzana Zamataro, Karina Z. Brito, Adriana Fernandes, Gisela M. Karic, Luciana V. Gimenez.
- (7) Merck Research Laboratories - USA: Jeffrey A. Chodakewitz, Emilio Emini, Pamela M. Fearon, Lucinda R. Gilde, Albert J. Getson, Jorge G. Guerra, Charlotte Harvey, Rand Rhodes, Jacobo Sabbaj, William Schleif.

Correspondence to: Dr. David S. Lewi, Depto de Doenças Infecciosas e Parasitárias, Escola Paulista de Medicina, UFESP, Rua Dr. Bacelar 384, 04026-001 São Paulo, SP, Brazil.

In this study, we compared the clinical efficacy, antiretroviral activity and safety of indinavir to zidovudine or the combination of indinavir plus zidovudine in HIV-1 infected patients who were antiretroviral therapy-naive with CD4 cell counts between 50 and 250 cells/mm³. The study began in April 1995; and at that time, zidovudine monotherapy was the standard of care for antiretroviral therapy-naive patients. As data from other trials became available indicating the superiority of double nucleoside analogue combinations over zidovudine monotherapy^{7,13,28}, the study was amended to add lamivudine to the regimens of patients in either zidovudine containing arm.

The study was conducted entirely in Brazil and represents the first large clinical endpoint trial in HIV-infected patients performed in a developing country. Patients were recruited at four large STD/AIDS clinics in São Paulo, and one in Campinas. From 1980 to 1996, of the 82,852 cases of AIDS reported in Brazil, 55% were reported in this region of the country²⁹. Protease inhibitors were initially licensed in Brazil in January 1996, and were widely distributed to patients by the Brazilian Ministry of Health by November 1996.

METHODS

Patient population

Antiretroviral therapy-naive, HIV-1 seropositive, male or female patients at least 18 years old with a prestudy CD4 cell count of 50-250 cells/mm³ (average of two determinations) were eligible for enrollment. Patients were required to meet a list of prestudy laboratory requirements (hematology, chemistry, coagulation) and to be free of any conditions consistent with the early stages of an opportunistic infection (OI). Major exclusion criteria were: use of chronic therapy for an active opportunistic infection or malignancy; history of OI, and use any other investigational, immunomodulatory or immunosuppressive agents. The protocol was approved by the Brazilian Ministry of Health, and by the ethical review committees of the participating institutions. Each patient provided written informed consent.

Study Design and Endpoints

The study was designed to compare the efficacy and safety of indinavir alone (800 mg q8h) to zidovudine alone (200 mg q8h) or to the combination of both. Patients were stratified according to prestudy CD4 cell count (Stratum I: 50-150 cells/mm³; Stratum II: 151-250 cells/mm³) and randomly allocated in a 1:1:1 ratio to one of the three treatment groups. The study was conducted in a double-blind fashion, including sponsor blinding, and enrolled 996 patients beginning in April 1995.

The primary objective of the study was to compare the efficacy of the three treatment regimens as measured by time to progression to first clinical event (AIDS-defining illness or death). Clinical events and corresponding diagnostic criteria were specified per protocol and based on the 1993 CDC case definition⁴. Histological/microbiological diagnoses were required for most events, but presumptive diagnoses of CMV retinitis, progressive multifocal leukoencephalopathy, and toxoplasmosis of the brain, based on pre-defined criteria, were also accepted. Additional objectives of the study were to compare the three treatment regimens with respect to safety (clinical adverse events, laboratory abnormalities), and changes in surrogate markers (CD4 cell counts, HIV RNA). Laboratory safety tests, CD4 cell counts, and HIV RNA measurements

were performed by central laboratories. The Amplicor HIV-1 Monitor assay (Roche Diagnostics, NJ, USA) was used to measure the level of HIV RNA in serum.

In July 1996 the protocol was amended to modify the zidovudine-containing treatment groups as data from other trials became available demonstrating the superiority of certain double nucleoside analogue combinations over zidovudine monotherapy^{7,13}. In a blinded manner, patients who had not yet experienced a clinical event were offered the option of receiving lamivudine (150 mg, b.i.d.) or placebo in addition to other protocol therapy. Of the 817 eligible patients, 783 (96%) elected to add lamivudine or placebo. Patients who were originally randomized to a zidovudine-containing regimen (zidovudine alone, or indinavir plus zidovudine) added lamivudine, while patients randomized to indinavir monotherapy added lamivudine placebo. Although the treatment groups were modified, treatment allocation remained blinded. All analyses were done according to the original treatment group assignments, as the study was not designed to definitively answer questions regarding the addition of lamivudine. The median study week for addition of lamivudine or placebo was Week 41.

The study was designed with 95% power to detect a 30% reduction in clinical events (AIDS-defining illness or death), assuming a rate of 20% per year for such events in the zidovudine arm. The design was event-based with a fixed sample size and study completion when 300 patients had each experienced at least one confirmed clinical event. To control for increased probabilities of Type I error due to multiple interim analyses, an alpha spending function⁸ was employed to maintain a conservative Type I error at early analyses, to preserve the overall Type I error close to $\alpha=0.025$, and to allow interim assessment at irregular intervals. This alpha spending rate function approximates the boundaries of O'BRIEN & FLEMING²³. A critical overall $\alpha=0.025$ was employed to protect against increased chances of Type I error as there were two pairwise comparisons of the indinavir containing arms versus zidovudine.

Patient Follow-Up

Patients reported for scheduled visits at Weeks 2 and 4, every 4 weeks thereafter, upon discontinuation, and 2 weeks following discontinuation. At each visit, patients underwent a physical examination, and aggressive surveillance for clinical events and other adverse experiences. Laboratory safety testing, CD4 cell counts, and HIV RNA measurements were performed at frequent intervals. Investigators and patients had access to all of their test results except HIV RNA measurements. Toxicity management guidelines were defined per protocol for isolated hyperbilirubinemia, granulocytopenia, anemia, nausea, vomiting, and renal colic.

Blinded documentation (laboratory reports, narrative summary) of all protocol-defined clinical events was promptly forwarded to an independent Data and Safety Monitoring Board (DSMB) responsible for final confirmation of each diagnosis as a clinical event. Upon confirmation of the clinical event, patients were offered the option to permanently discontinue all blinded study therapy, and begin therapy with open-label indinavir, alone or in combination with one or more nucleoside analogues. Patients with presumptive diagnoses of *Pneumocystis carinii* pneumonia, *Mycobacterium tuberculosis* or other diagnoses considered to reflect treatment failure but not defined as clinical events per protocol were offered the option to continue on blinded

indinavir or placebo, plus open-label nucleoside analogue therapy. The protocol allowed a double-blind treatment duration of up to 156 weeks, but included provisions for changes in study design based on planned interim analyses performed at time points determined by the number of clinical events observed, or at the discretion of the DSMB. Charged with the responsibility to periodically review enrollment and safety and efficacy data, the DSMB in March 1997 recommended that the double-blind portion of the study be ended due to the superior clinical efficacy of the indinavir-containing groups over the zidovudine group. The protocol was amended to provide all patients with open-label indinavir, and the study is ongoing for long-term follow-up purposes.

Statistical Methods

Analyses of all efficacy variables were performed on the intention to treat basis that included all patients randomized and all available follow-up (including that obtained after discontinuation of study treatment). Statistical models included the randomization blocking factors of investigative sites and screening CD4 cell count strata as main effects. Nominal two-sided p-values are reported. Estimates of treatment differences and 95 percent confidence intervals are unadjusted for multiplicity.

The distributions of times to clinical events were compared between treatment groups by Kaplan-Meier estimates, stratified log rank tests and Cox proportional hazards models. Patients who did not progress to the primary endpoint had time to event censored at the date of last follow-up.

The primary metric for analysis of surrogate marker changes from baseline was the area under the curve minus baseline (AUCMB)¹⁹. The AUCMB estimated the average change from baseline over the time of follow-up, using all observed data. With respect to HIV RNA, values below assay detection were set equal to 250 copies/mL and detectable values below the assay threshold of quantification (500 copies/mL) were set equal to 500 copies/mL. For the presentations of changes from baseline in HIV RNA and CD4 cell count, data for patients who discontinued from the study or experienced a clinical event were censored at the time of the discontinuation or clinical event, respectively.

Proportions of patients whose HIV RNA levels were below the assay threshold of quantification (500 copies/mL) were determined. This analysis accounts for the virological status of all patients enrolled, including those who were lost to follow-up. All patients who discontinued from the study or experienced a clinical event, and who had HIV RNA levels of at least 500 copies/mL at the time of discontinuation or the clinical event, were considered to be failures at subsequent time points. Patients who discontinued the study due to a drug-related adverse experience were considered to have HIV RNA levels greater than or equal to 500 copies/mL at time points subsequent to their discontinuation, regardless of viral burden at the time of the adverse experience. Patients who discontinued for other reasons (e.g. contraindicated medications, patient request) or who experienced a clinical event, and who had HIV RNA levels less than 500 copies/mL at the time of discontinuation or clinical event, were not included in the analysis of subsequent time points. When a HIV RNA level was missing at a given time point while the patient was still being followed, if the HIV RNA levels immediately preceding and immediately following the missing value were both measured to be less than 500 copies/mL, the missing value was assumed

to be less than 500 copies/mL; otherwise the missing value was assumed to be at least 500 copies/mL. In this analysis, the denominator at any given time point may be comprised both of patients with actual viral load determinations and of patients with imputed values; in this setting, the denominator is referred to as "contributing patients". Exact binomial 95% confidence intervals were calculated based on the proportion of contributing patients with HIV RNA below 500 copies/mL.

Associations between the surrogate marker results and risk of clinical progression were examined using the subset of patients with data for both surrogate markers at study entry and at least one post-randomization result. Four groups were defined by quartiles of the combined surrogate marker AUCMB results: low CD4/high HIV RNA, low CD4/low HIV RNA, high CD4/high HIV RNA, high CD4/low HIV RNA. Estimates of time to first clinical event were compared graphically between these quartiles. The quartiles were divided about the level of no net change from baseline.

Safety was evaluated by tabulation of adverse experiences and treatment-emergent laboratory abnormalities. All adverse experiences reported for patients while on study therapy or within 14 days after discontinuing study therapy were included in the safety analysis. The proportions of patients in each treatment group experiencing a particular adverse experience or laboratory abnormality were compared by the Fisher's exact test.

RESULTS

Accrual and Baseline Characteristics

996 patients were enrolled in the study between April 1995 and October 1996. Baseline characteristics for all patients by treatment group are presented in Table 1. The majority of the patients were male (72%). Two hundred eighty women (28%) were enrolled into the study. The median age of all patients was 33 years, ranged from 18 to 67 years of age at study entry and were Caucasian (88%), in majority. The patients were approximately evenly split between the two CD4 cell count strata, with 46% of the patients in the 50 to 150 cells/mm³ stratum. The median CD4 cell count over all patients was 147.0 cells/mm³. The overall baseline median viral serum viral RNA was 4.49 log₁₀ copies/mL (30,651 copies/mL). The indinavir monotherapy group had a lower HIV RNA at baseline than the other two treatment groups.

Interim analyses; Termination of Double-Blind Period

The study design was based on the assumption that accrual of at least one clinical event in each of 300 patients would be necessary to demonstrate a statistically significant difference between the treatment groups. At the time of the analyses which resulted in the DSMB recommendation to end the double-blind portion of the study, 107 patients had experienced at least one clinical event (approximately 36% of the originally projected 300 clinical events). The critical p-value associated with 100 events was a two-tailed $\alpha = 0.0009$ and provided a conservative stopping guideline.

Patient Accounting and Follow-up

Overall, a total of 165 (17%) patients discontinued their participation in the study: 66 (20%) in the indinavir plus zidovudine group, 42 (13%) in the indinavir group and 57 (17%) in the zidovudine group. Only 9 (0.9%) patients discontinued due to a clinical or laboratory adverse

Table 1
Patient characteristics at baseline by treatment group

Demographic characteristics	Indinavir plus zidovudine (N=332)	Indinavir (N=332)	Zidovudine (N=332)	Total (N=996)
Gender - no. (%)				
Male	242 (73)	238 (71)	239 (72)	719 (72)
Female	90 (27)	94 (29)	93 (28)	277 (28)
Median age at study entry (Q1-Q3; years)	33 (29, 40)	33 (29, 39)	33 (29, 40)	33 (29, 39)
Racial origin – no. (%)				
Caucasian*	297 (89)	288 (87)	290 (87)	874 (88)
Black/Mulatto	32 (10)	40 (12)	40 (12)	112 (11)
Asian	3 (1)	4 (1)	2 (1)	9 (1)
CD4 cell count stratum - no. (%)				
50 to 150 cells/mm ³	153 (46)	150 (45)	158 (48)	461 (46)
151 to 250 cells/mm ³	179 (54)	182 (55)	174 (52)	535 (54)
HIV infection risk factors [†] - no. (%)				
Homosexual/bisexual sexual contact	123 (37)	125 (38)	134 (40)	382 (38)
Heterosexual Sexual contact	139 (42)	140 (42)	136 (41)	415 (42)
Intravenous drug abuse	52 (16)	40 (12)	37 (11)	129 (13)
Hemophilia/blood transfusion	6 (2)	6 (2)	2 (1)	14 (1)
Not known	23 (7)	26 (8)	30 (9)	79 (8)
Median CD4 cell count (Q1-Q3; cells/mm ³)	146 (86, 207)	147 (99, 194)	148 (91, 201)	147 (91, 202)
Median HIV RNA (Q1-Q3; log ₁₀ copies/mL)‡	4.56 (4.13, 4.93)	4.38 (3.94, 4.75)	4.56 (4.12, 4.93)	4.49 (4.07, 4.91)

* Includes 2 patients of Hispanic origin (1 in the indinavir treatment group, and 1 in the zidovudine treatment group).

† Patients could have multiple risk factors.

‡ Values that were below the assay threshold of quantification (<500 copies/mL) were coded as equal to 500 copies/mL (2.70 log₁₀ copies/mL). Nonamplifiable results (those below the assay threshold of detection) were reported as “negative” by the laboratory, but, for purposes of data analysis, these results were coded as equal to 250 copies/mL (2.40 log₁₀ copies/mL).

experience. A total of 25 patients, including 12 patients who died, discontinued from the study after experiencing a clinical event. Four patients discontinued the study at the time of a clinical event.

Since the primary objective of this study was to assess clinical efficacy based on the occurrence of clinical events, the patients who discontinued from the study without experiencing a clinical event are especially important as such discontinuations could potentially impact the results of the primary efficacy analyses. Among the 136 patients who discontinued without experiencing a clinical event, the difference in time to discontinuation between the indinavir plus zidovudine group (57/332, 17%) and the indinavir treatment group (36/332, 11%) was statistically significant (p=0.0175, log rank test, stratified by investigative site and screening CD4 cell strata). The differences between the indinavir plus zidovudine and zidovudine (43/332, 13%) treatment groups (p=0.1434, stratified log rank test) and the indinavir versus zidovudine (p=0.3497, stratified log rank test) were not statistically significant. The follow-up time for clinical progression ranged from 0 to 99 weeks, with a median follow-up time of 52 weeks and was similar for all three treatment groups.

Progression to Clinical Event (AIDS-Defining Illness or Death)

One hundred and twelve patients (11%) experienced a clinical event (AIDS-defining illness or death). Six patients had two different events with the same diagnosis dates; therefore, there were a total of 118 primary clinical events. Twenty patients (6%, or 6.8 events per 100 patient-years) in the indinavir plus zidovudine group had at least one clinical event, compared to 28 patients (8%, or 8.5 events per 100 patient-years) in the indinavir group and 63 patients (19%, or 20.8 events per 100 patient-years) in the zidovudine group. The most common first clinical events were esophageal candidiasis (42 events), *Pneumocystis carinii* pneumonia (12 events), death due to any cause (12 events), and toxoplasmosis of the brain (10 events).

Kaplan-Meier estimates of progression-free survival by treatment group are shown in Figure 1. The comparison of indinavir plus zidovudine to zidovudine was statistically significant (p<0.0001, stratified log rank test) with an estimated hazard ratio of 0.30 (95% confidence interval: 0.18, 0.50). The comparison of indinavir to zidovudine was also statistically significant (p<0.0001, stratified log rank test) with an estimated hazard ratio of 0.39 (95% confidence interval: 0.24, 0.61).

The comparison of indinavir plus zidovudine versus indinavir was not statistically significant ($p=0.2863$, stratified log rank test) with an estimated hazard ratio of 0.77 (95% confidence interval: 0.72, 2.32). The percentage reductions in hazard for the indinavir plus zidovudine and indinavir groups compared to the zidovudine group were 70% and 61%, respectively.

Mortality

A total of 25 (2%) of the 996 patients enrolled died: 8 (3%) from the indinavir plus zidovudine treatment group, 5 (2%) from the indinavir group, and 12 (4%) from the zidovudine group. None of the between-treatment comparisons was statistically significant by the stratified log rank test.

Surrogate Marker Efficacy Follow-Up Period

The median follow-up available for the two measures of surrogate marker efficacy (HIV RNA, CD4) differed because different laboratories and data handling procedures were utilized for CD4 cell counts and HIV RNA measurement. The median follow-up for HIV RNA was 68 weeks (range 0 to 104 weeks) for all 984 patients with baseline and at least one post-randomization HIV RNA measurement. The median follow-up for CD4 cell counts was 48 weeks (range 0 to 96 weeks) for all 996 patients enrolled. For both HIV RNA and CD4 cell counts, a change in trajectory was seen after Week 48 in the zidovudine-containing groups.

Changes in Viral RNA

The adjusted mean change in HIV RNA over available follow-up, as measured by the AUCMB, was statistically significantly greater ($p<0.0001$) for the indinavir plus zidovudine group ($-1.04 \log_{10}$ copies/mL) than for the zidovudine group ($-0.28 \log_{10}$ copies/mL). Likewise, the adjusted mean

change in HIV RNA for the indinavir group ($-0.68 \log_{10}$ copies/mL) was statistically significantly greater than the change for the zidovudine group ($p<0.0001$). The difference between the indinavir plus zidovudine and indinavir groups was statistically significant ($p<0.0001$). At the median follow-up of 68 weeks, 37% of patients on indinavir plus zidovudine, 23% of patients on indinavir, and 6% of patients on zidovudine had HIV RNA levels below 500 copies/mL.

Changes in CD4 Cell Counts

Figure 2 displays observed mean changes in CD4 cell counts by treatment group. The adjusted mean change in CD4 cell count over available follow-up, as measured by the AUCMB, was statistically significantly greater ($p<0.0001$) for the indinavir plus zidovudine group (109.7 cells per cubic millimeter) than for the zidovudine group (20.1 cells per cubic millimeter). Likewise, the adjusted mean change in CD4 cell count for the indinavir group (93.6 cells per cubic millimeter) was statistically significantly greater than the change for the zidovudine group ($p<0.0001$). The difference between the indinavir plus zidovudine and indinavir groups was not statistically significant ($p=0.2552$).

Association Between Surrogate Markers and Progression of Disease

The subgroup of patients with data for both CD4 cell count and HIV RNA at study entry and at least one post-randomization result included 967 patients (97% of total enrollment). There were 107 patients in this subgroup with at least one clinical event.

Low risk of progression was defined primarily by CD4 cell count. The majority of clinical events occurred in patients enrolled into the lower CD4 stratum (50-150 cells/mm³). The last available CD4 cell count

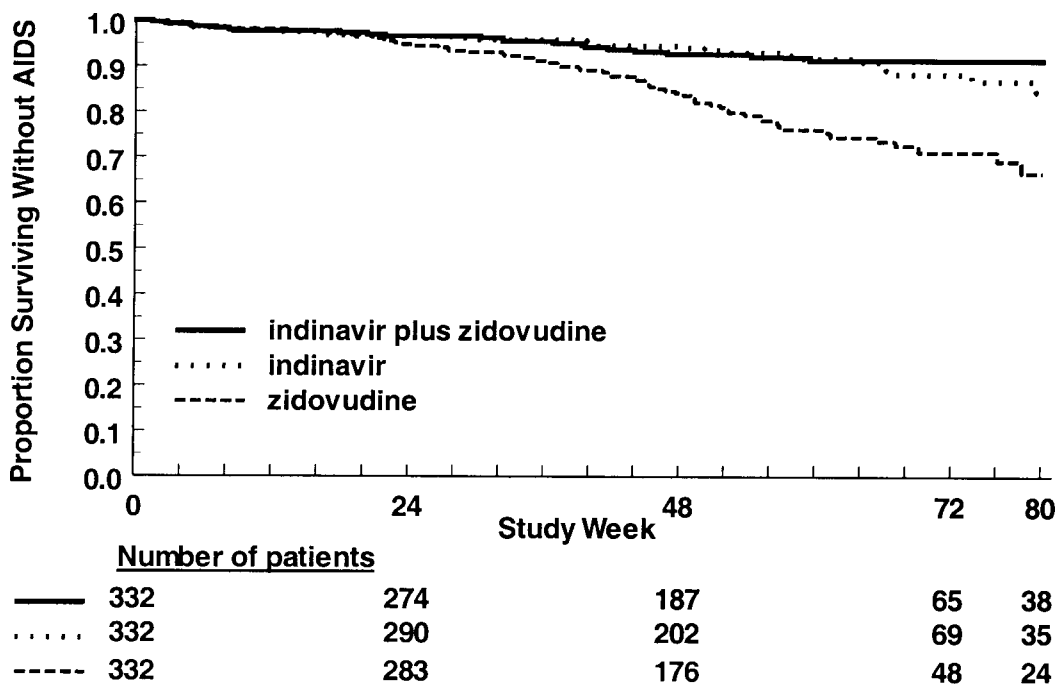


Fig. 1 - Kaplan-Meier estimates of the proportions of patients not reaching the primary study end point of progression to AIDS event or death.

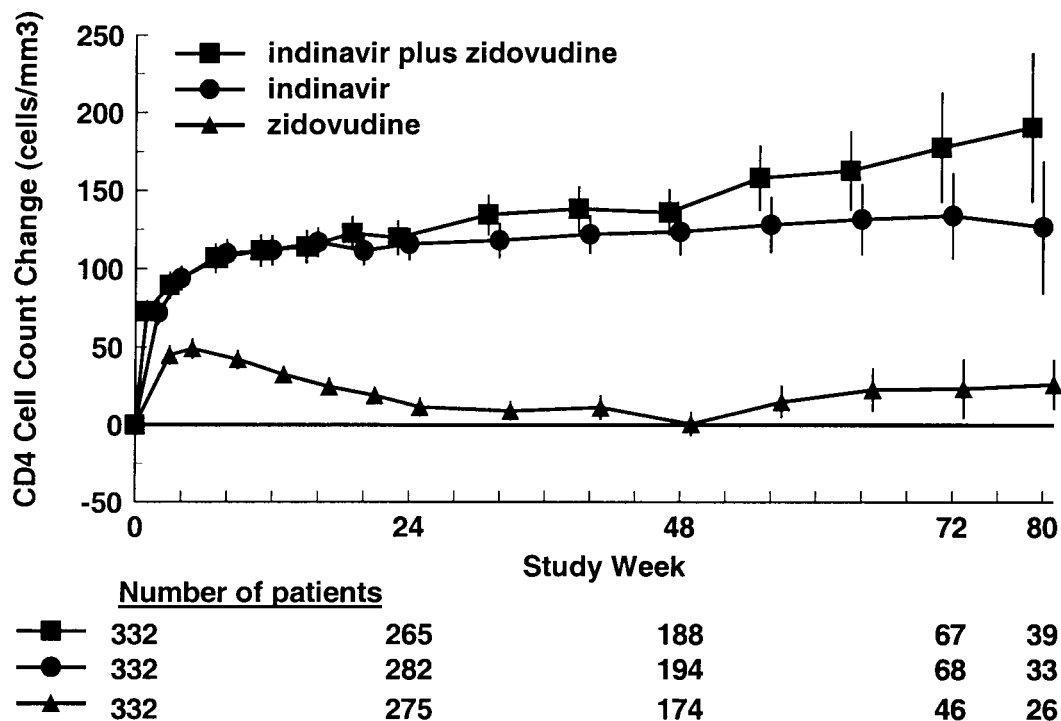


Fig. 2 - Mean (95% CI) change from baseline in CD4 cell counts (cells/mm³) by treatment group.

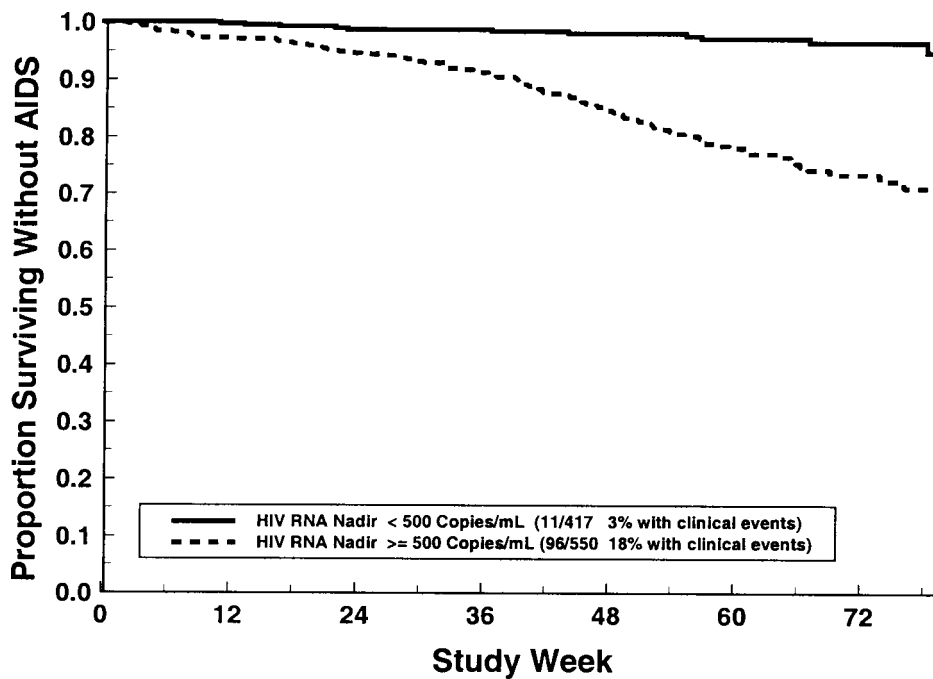


Fig. 3 - Kaplan-Meier estimates of proportions of patients with progression-free survival by viral suppression status (HIV RNA nadir below threshold of quantification versus HIV RNA nadir above 500 copies/mL).

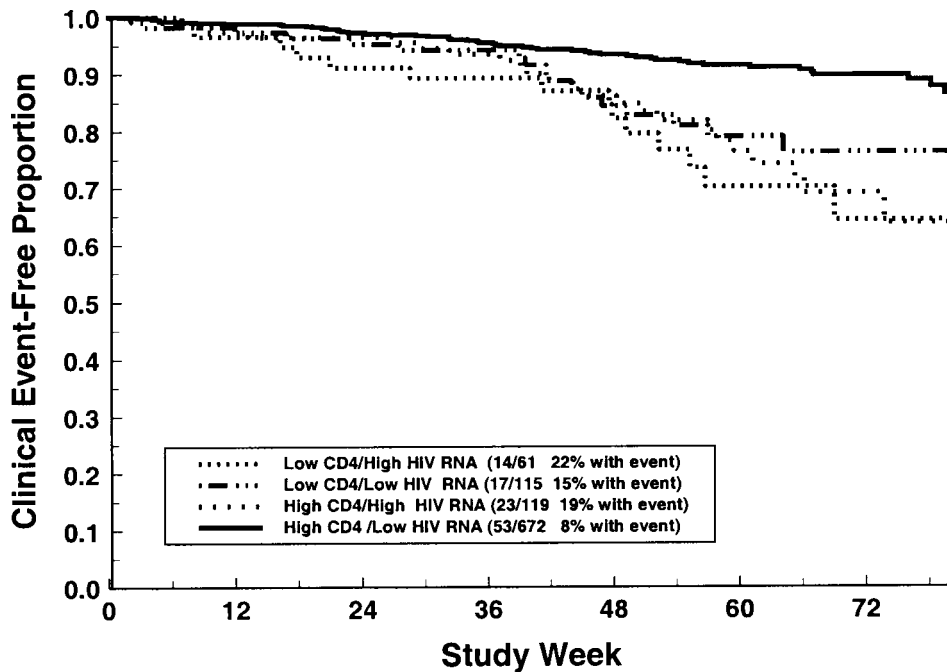


Fig. 4 - Kaplan-Meier estimates of the proportions of patients not reaching the primary study end point of progression to AIDS event or death - by surrogate marker AUCMB quadrants.

was associated with clinical benefit; patients with low CD4 cell counts had the highest risk of disease progression.

Patients who had at least one HIV RNA result below 500 copies/mL had markedly reduced risk of disease progression relative to those whose HIV RNA never was below this threshold (88% risk reduction for all treatments pooled, $p < .0001$, Figure 3). This analysis included all patients who achieved HIV RNA suppression to below 500 copies/mL at any time during the study regardless of treatment group, including 196/319 (61%) of the patients who were randomized to receive indinavir plus zidovudine, 169/323 (52%) of the patients randomized to receive indinavir and 52/325 (16%) of the patients randomized to receive zidovudine. The majority of patients (95%) who had at least one HIV RNA measurement below 500 copies/mL also had at least 2 consecutive measurements showing this degree of HIV RNA suppression. While for all three treatment groups, having HIV RNA nadirs below 500 copies/mL was associated with reduced clinical progression risk, the magnitude of this association was greater for the indinavir containing arms than in the control arm.

However, improvement in both CD4 cell count and HIV RNA are associated with reduced risk of disease progression. Patients were divided into quartiles based on average changes in CD4 cell count and HIV RNA (Figure 4). The patients with increases in CD4 cell count as well as decreases in HIV RNA had a statistically significant increase in progression-free survival compared to the patients in the other three quadrants ($p < 0.006$).

Safety

The proportion of patients with clinical adverse experiences was similar in all treatment groups. The most common clinical adverse experiences were: abdominal pain, fever, asthenia/fatigue, and malaise. The incidence of nephrolithiasis attributable to indinavir was approximately 8%. The proportions of patients with nephrolithiasis were 12% (40/332) in the indinavir plus zidovudine group, 12% (40/332) in the indinavir group and 4% (13/332) in the zidovudine group. Overall, 122 (12%) patients had serious adverse experiences during the trial: 36 (11%) in the indinavir plus zidovudine group, 33 (10%) in the indinavir group and 53 (16%) in the zidovudine group. Many of the serious adverse events were clinical events or adverse experiences associated with clinical events.

Twenty-nine (2.9%) of 996 patients permanently discontinued some or all of their study therapy due to clinical or laboratory adverse experiences prior to a clinical event. The proportion of patients in the indinavir arm (3/332, 0.9%) who discontinued therapy due to adverse experiences was statistically significantly less ($p = 0.0099$, Fishers exact test) than in either the indinavir plus zidovudine arm (13/332, 4%) or the zidovudine arm (13/332, 4%). The proportions of patients who discontinued study therapy in the two zidovudine containing arms were not statistically significantly different.

Five (0.5%) of 996 patients discontinued study due to clinical or laboratory adverse experiences: 2/332 (0.6%) in the indinavir plus zidovudine group (due to headache/nausea/vomiting, and exanthema),

1/332 (0.3%) in the indinavir group (due to extrapulmonary cryptococcosis) and 2/332 (0.3%) in the zidovudine group (due to decreased neutrophils, and nausea/vomiting).

Laboratory results were evaluated using the AIDS Clinical Trials Group Grade 3 definitions for severity⁹. The proportions of patients with hyperbilirubinemia (>2.5 mg/dL) was statistically significantly higher in the indinavir containing groups than in the zidovudine group ($p < 0.0001$, Fishers exact test). The proportions of patients with hematologic abnormalities (decreased hemoglobin [< 7 g/dL], decreased absolute neutrophil count [< 750 ths/mm³]) were statistically significantly higher in the zidovudine group than in the indinavir group ($p = 0.0061$ and $p = 0.0046$, respectively). Hyperglycemia (>250 mg/dL) occurred in 1.2% (4/321), 0.9% (3/329), and 0.6% (2/330) of patients in the indinavir plus zidovudine, indinavir, and zidovudine groups, respectively. Hypertriglyceridemia (>750 mg/dL) occurred in 3.1% (10/321), 3.0% (10/329), and 4.2% (14/330) of patients in the indinavir plus zidovudine, indinavir, and zidovudine groups, respectively. There were no statistically significant differences between treatment groups with respect to hyperglycemia ($p = 0.590$) and hypertriglyceridemia ($p = 0.690$).

DISCUSSION

This study demonstrates the considerable antiretroviral effect of indinavir, alone and in combination with zidovudine, compared to zidovudine alone in HIV-1 seropositive treatment-naïve patients with average CD4 cell counts of 50 to 250 cells/mm³, with respect to progression to an AIDS-defining event or death. In addition, consistent benefit was demonstrated with respect to changes from baseline in CD4 cell counts and HIV RNA.

The percent reductions in hazards for the indinavir plus zidovudine and indinavir groups compared to the zidovudine group were 70% and 61%, respectively. Both indinavir groups were statistically significantly different from zidovudine but not from each other. The overall occurrence of events was similar to available epidemiologic data regarding the occurrence of AIDS-defining events in the state of São Paulo, Brazil²⁹.

The indinavir-treated patients had sustained increases in CD4 cell count during the study. The average changes from baseline in CD4 cell count in the indinavir-containing groups were statistically significantly greater than for the zidovudine group, but the indinavir groups were not statistically different from each other. At Week 48, the median elevation in CD4 cell count was >100 cells/mm³ above baseline in both indinavir-containing groups.

In analyzing the changes in CD4 cell counts and HIV RNA, a change in trajectory was observed after Week 48 in the indinavir plus zidovudine and zidovudine groups. This change may be due to the addition of lamivudine, or due to censoring of surrogate marker follow-up after experiencing a DSMB-confirmed clinical event. The median study time for addition of lamivudine or placebo to lamivudine was Week 41.

A large proportion of indinavir-treated patients had sustained decreases in HIV RNA to <500 copies/mL, which represents the lower limit of quantification of the assay. Recently the proportion of patients achieving maximal HIV RNA suppression has become the standard for evaluating antiretroviral therapies^{1,3}. The indinavir plus zidovudine group

had a greater and more sustained suppression of HIV RNA compared to the other groups as measured by proportions of patients with HIV RNA <500 copies/mL or changes from baseline HIV RNA. Over the duration of the study, the indinavir group had greater HIV RNA suppression than the zidovudine group. However, at later timepoints the change from baseline for HIV RNA is similar between the indinavir and zidovudine groups.

This study provides further confirmation of the clinical benefit of protease inhibitors in treating HIV-infected patients^{2,14,25,27}. The study also provides information on the relationship between changes in CD4 cell counts and HIV RNA and disease progression. The indinavir containing groups both had decreased disease progression compared to the zidovudine control group. The indinavir containing groups showed similar benefit with regard to change from baseline in CD4 cell counts but indinavir plus zidovudine treatment resulted in a statistically significantly greater decline in HIV RNA when compared to indinavir alone. The difference between the HIV RNA suppression in the two indinavir-containing groups appeared to be greater at later timepoints although this observation is complicated by the addition of lamivudine to the indinavir plus zidovudine group. However, suppression of HIV RNA to below 500 copies/mL was clearly associated with a decreased risk of disease progression, supporting the prognostic value of HIV RNA quantification demonstrated previously^{5,15,17,20,22,24,26,32}. Although the study demonstrates clinical benefit from indinavir alone or in combination with zidovudine, recent data suggest that using indinavir in combination with other antiretroviral agents (zidovudine plus lamivudine, stavudine plus didanosine, stavudine plus lamivudine, efavirenz) results in greater and more durable antiviral activity which will likely result in greater longterm clinical benefit^{10,11,14,16,30}.

Overall, 14% of patients discontinued from the study without experiencing a DSMB-confirmed clinical event. In the indinavir plus zidovudine group, 17% of patients discontinued, as compared to 11% of patients in the indinavir arm, and 13% in the zidovudine arm. The highest discontinuation rate occurred in the group with the numerically superior surrogate marker responses. This was of concern because the potential differential loss of patients who were not doing well from a specific treatment group might bias the final study results. Therefore, attempts were made to obtain a follow-up status on those patients who discontinued from the study. Ultimately, survival and progression information was available for 95% of all patients enrolled. Analyses including this additional follow-up information indicated that patient discontinuations did not affect the primary study conclusions.

This study clearly demonstrates the marked clinical efficacy and general tolerability of indinavir, either alone or in combination with zidovudine, in treatment-naïve HIV-infected patients with moderate degrees of immunosuppression. Although the study was initiated prior to the demonstration of the potency of combination therapy, the study was amended to reflect the current standard of care. Profound and durable improvements in CD4 cell counts and viral load were also demonstrated. Because of the large sample size and the long follow-up, this study allows a unique opportunity to explore associations between surrogate marker changes and clinical outcome. This study shows that the combination of favorable CD4 cell count and HIV RNA changes are associated with a decrease in the risk of HIV disease progression. At a time when advances in the treatment of HIV infection and the prevention of opportunistic

infections have complicated the conduct of clinical endpoint trials, the results of this study support the utility of long-term surrogate marker responses in assessing antiretroviral treatment regimens.

RESUMO

Estudo duplo-cego, randômico comparando indinavir, zidovudina e indinavir mais zidovudina na terapia anti-retroviral de indivíduos HIV+ sem tratamento anterior, com contagem de células CD4 entre 50 e 250/mm³

Foi demonstrado que o tratamento com indinavir resulta em importante redução da carga viral e aumentos das células CD4 em pacientes infectados pelo HIV. Foi realizado um estudo duplo-cego, randômico para avaliar a eficácia do indinavir isoladamente (800 mg cada 8h), zidovudina isoladamente (200 mg cada 8h) ou a combinação, para avaliar a progressão para AIDS. Foram distribuídos para tratamento 996 pacientes virgens de tratamento antiretroviral, com contagens de CD4 entre 50 e 250 células/mm³. Durante o estudo, o protocolo foi modificado para adicionar lamivudina aos braços contendo zidovudina. O "endpoint" primário foi o tempo para o desenvolvimento de uma doença-definidora de AIDS ou morte. O estudo foi interrompido após uma análise preliminar definida no protocolo ter demonstrado reduções significativas na progressão para um evento clínico nos grupos contendo indinavir, comparado ao grupo da zidovudina ($p < 0,0001$). Após uma mediana de seguimento de 52 semanas (chegando a 99 semanas), as reduções percentuais nas ocorrências para indinavir+zidovudina e indinavir, comparado com zidovudina foram de 70% e 61%, respectivamente. Reduções significativas na medida do RNA viral e aumentos nas contagens de CD4 também foram observadas nos grupos contendo indinavir, em relação ao da zidovudina. A melhora nas células CD4 e RNA viral foram ambas associadas a risco reduzido de progressão da doença. Os três tratamentos foram geralmente bem tolerados.

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