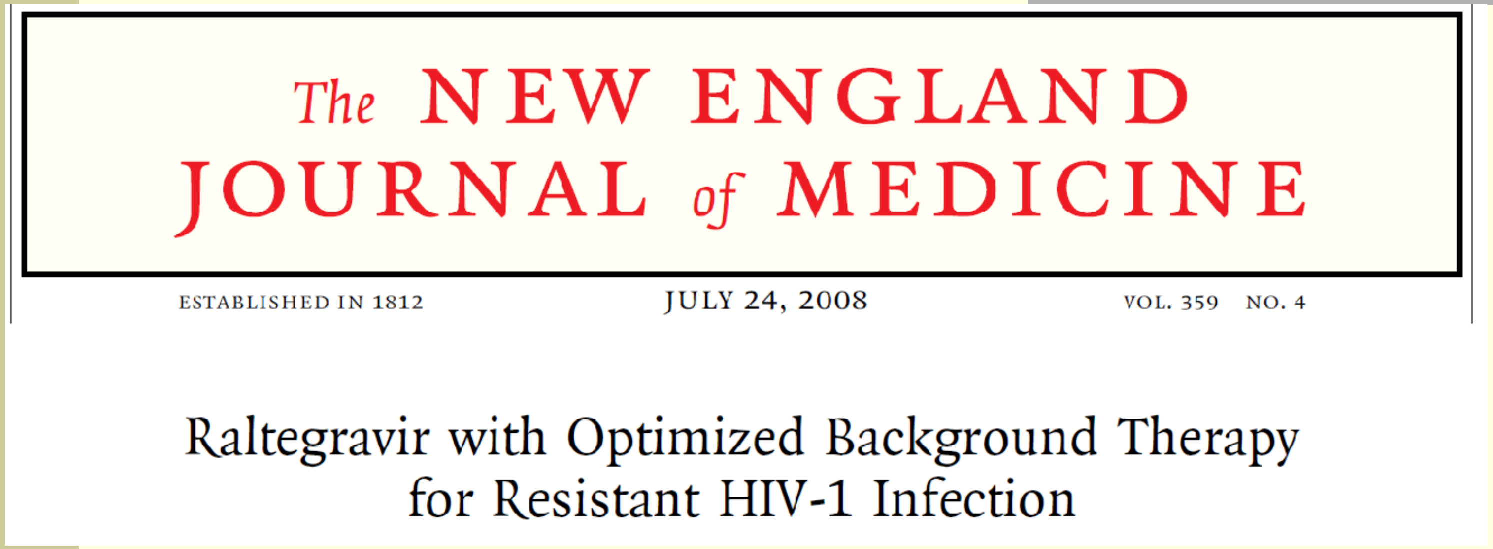

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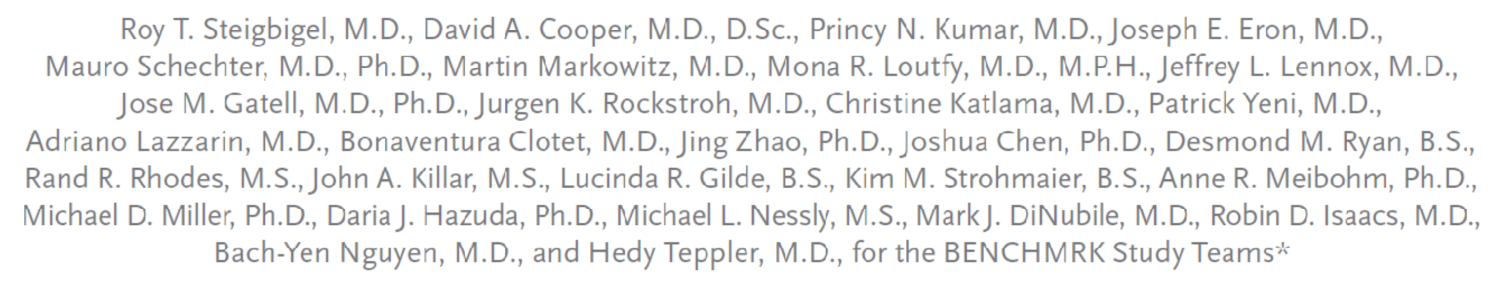
Raltegravir with Optimized Background Therapy for Resistant HIV-1 Infection



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BASE DEL ESTUDIO

- Evaluar la eficacia,seguridad y tolerabilidad de raltegravir en pacientes con infección por el VIH-1 previamente tratados con antirretrovirales.

JUSTIFICACION

- En la actualidad el tratamiento antirerretroviral se basa en la combinación de al menos tres fármacos, utilizando la asociación de medicamentos que actúan en distintas dianas del ciclo de replicación del virus de la inmunodeficiencia humana (VIH).
- A pesar de contar con un número importante de fármacos, en ocasiones los tratamientos no son eficaces por la aparición de resistencias o de efectos secundarios.
- Resulta muy interesante el desarrollo de nuevos fármacos que intervengan en fases del ciclo de replicación aún no inhibidas.

METODOS: Pacientes

- **Criterios de inclusión:**
  - **Edad >16 años**
  - **Resistencia documentada (por prueba fenotípica/genotípica) a 3 de las 4 clases de antirretrovirales (nucleósidos, no nucleósidos e inhibidores de la proteasa)**
  - **Carga viral >1.000 copias/ml**

METODOS: Pacientes

- Criterios de exclusión:
  - Insuficiencia renal
  - Descompensación aguda de una hepatopatía crónica
  - Uso de drogas

METODOS

- **BENCHMRK-1 se realizó en Europa, Asia, Australia y Perú**
- **BENCHMRK-2 en Norteamérica y Sudamérica**
- **Ambos con idéntico diseño. Estudios de fase 3, aleatorizados, doblemente enmascarados y multicéntricos**
- **Los pacientes se aleatorizaron a recibir raltegravir 400 mg/12 horas o placebo, más una combinación de un tratamiento optimizado**
- **Presenta los resultados de eficacia y seguridad a las 48 semanas**

RESULTADOS

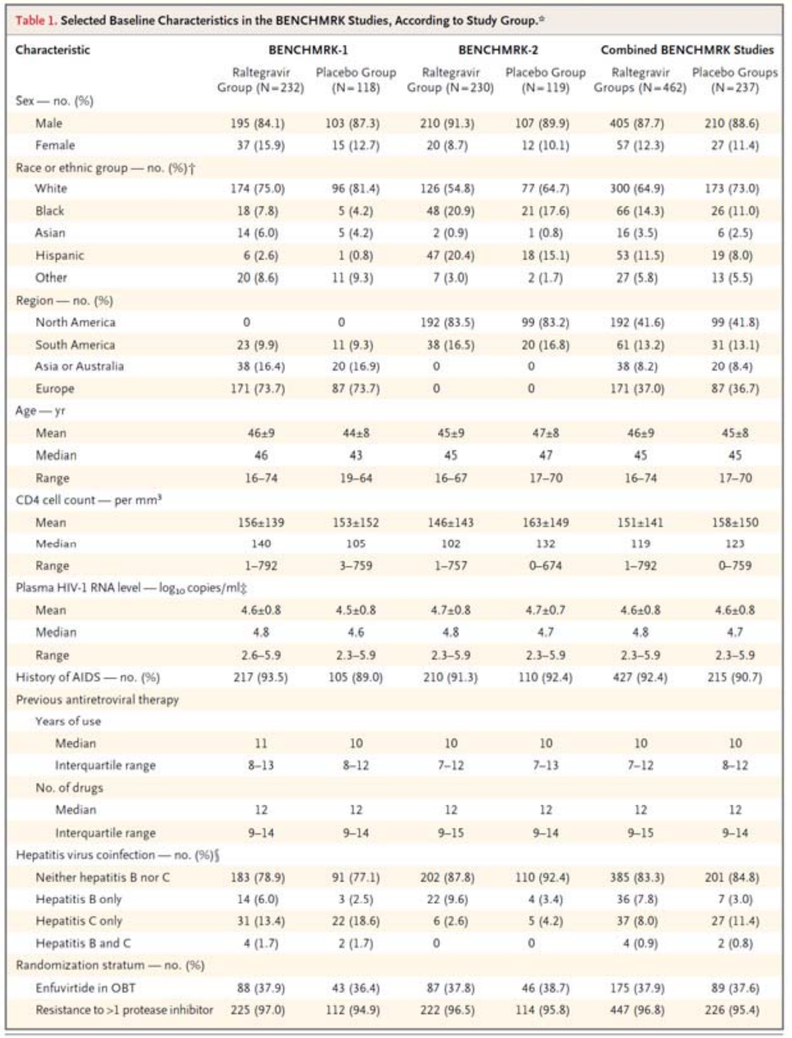


Table 1. Selected Baseline Characteristics in the BENCHMRK Studies, According to Study Group.[*]

Characteristic	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
Sex — no. (%)						
Male	195 (84.1)	103 (87.3)	210 (91.3)	107 (89.9)	405 (87.7)	210 (88.6)
Female	37 (15.9)	15 (12.7)	20 (8.7)	12 (10.1)	57 (12.3)	27 (11.4)
Race or ethnic group — no. (%)[†]						
White	174 (75.0)	96 (81.4)	126 (54.8)	77 (64.7)	300 (64.9)	173 (73.0)
Black	18 (7.8)	5 (4.2)	48 (20.9)	21 (17.6)	66 (14.3)	26 (11.0)
Asian	14 (6.0)	5 (4.2)	2 (0.9)	1 (0.8)	16 (3.5)	6 (2.5)
Hispanic	6 (2.6)	1 (0.8)	47 (20.4)	18 (15.1)	53 (11.5)	19 (8.0)
Other	20 (8.6)	11 (9.3)	7 (3.0)	2 (1.7)	27 (5.8)	13 (5.5)
Region — no. (%)						
North America	0	0	192 (83.5)	99 (83.2)	192 (41.6)	99 (41.8)
South America	23 (9.9)	11 (9.3)	38 (16.5)	20 (16.8)	61 (13.2)	31 (13.1)
Asia or Australia	38 (16.4)	20 (16.9)	0	0	38 (8.2)	20 (8.4)
Europe	171 (73.7)	87 (73.7)	0	0	171 (37.0)	87 (36.7)
Age — yr						
Mean	46±9	44±8	45±9	47±8	46±9	45±8
Median	46	43	45	47	45	45
Range	16–74	19–64	16–67	17–70	16–74	17–70
CD4 cell count — per mm^3						
Mean	156±139	153±152	146±143	163±149	151±141	158±150
Median	140	105	102	132	119	123
Range	1–792	3–759	1–757	0–674	1–792	0–759
Plasma HIV-1 RNA level — $\log_{10}$ copies/ml[‡]						
Mean	4.6±0.8	4.5±0.8	4.7±0.8	4.7±0.7	4.6±0.8	4.6±0.8
Median	4.8	4.6	4.8	4.7	4.8	4.7
Range	2.6–5.9	2.3–5.9	2.3–5.9	2.3–5.9	2.3–5.9	2.3–5.9
History of AIDS — no. (%)	217 (93.5)	105 (89.0)	210 (91.3)	110 (92.4)	427 (92.4)	215 (90.7)
Previous antiretroviral therapy						
Years of use						
Median	11	10	10	10	10	10
Interquartile range	8–13	8–12	7–12	7–13	7–12	8–12
No. of drugs						
Median	12	12	12	12	12	12
Interquartile range	9–14	9–14	9–15	9–14	9–15	9–14
Hepatitis virus coinfection — no. (%)[§]						
Neither hepatitis B nor C	183 (78.9)	91 (77.1)	202 (87.8)	110 (92.4)	385 (83.3)	201 (84.8)
Hepatitis B only	14 (6.0)	3 (2.5)	22 (9.6)	4 (3.4)	36 (7.8)	7 (3.0)
Hepatitis C only	31 (13.4)	22 (18.6)	6 (2.6)	5 (4.2)	37 (8.0)	27 (11.4)
Hepatitis B and C	4 (1.7)	2 (1.7)	0	0	4 (0.9)	2 (0.8)
Randomization stratum — no. (%)						
Enfuvirtide in OBT	88 (37.9)	43 (36.4)	87 (37.8)	46 (38.7)	175 (37.9)	89 (37.6)
Resistance to >1 protease inhibitor	225 (97.0)	112 (94.9)	222 (96.5)	114 (95.8)	447 (96.8)	226 (95.4)

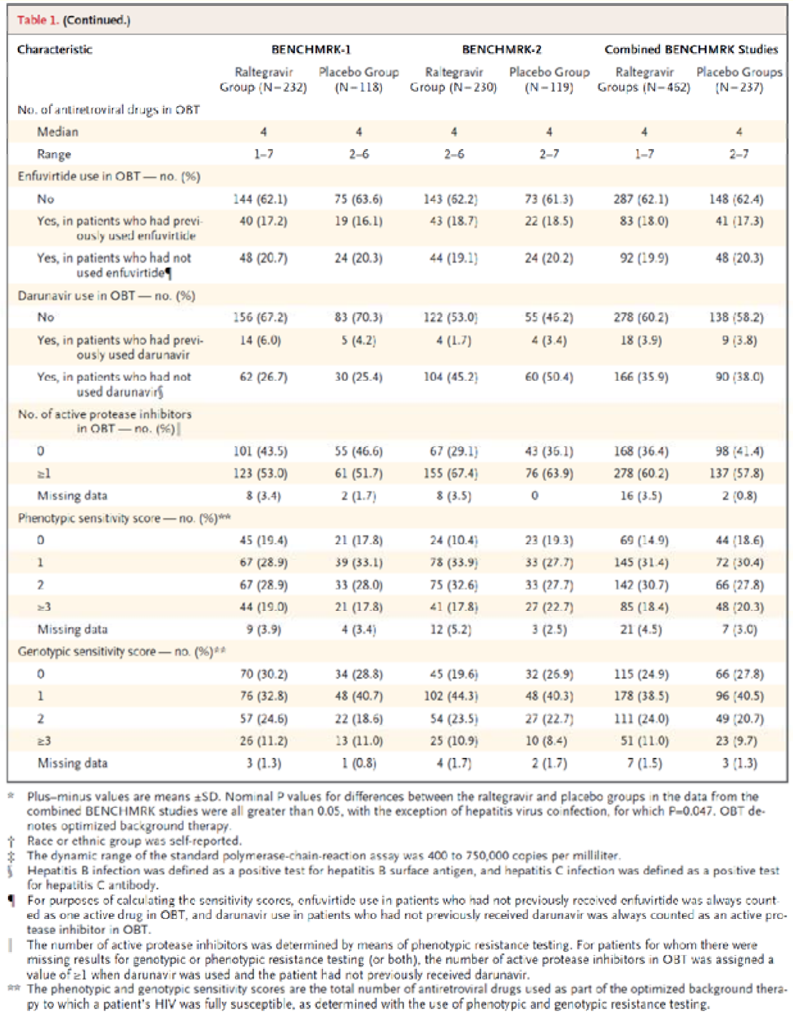


Table 1. (Continued.)

Characteristic	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
No. of antiretroviral drugs in OBT						
Median	4	4	4	4	4	4
Range	1–7	2–6	2–6	2–7	1–7	2–7
Enfuvirtide use in OBT — no. (%)						
No	144 (62.1)	75 (63.6)	143 (62.2)	73 (61.3)	287 (62.1)	148 (62.4)
Yes, in patients who had previously used enfuvirtide	40 (17.2)	19 (16.1)	43 (18.7)	22 (18.5)	83 (18.0)	41 (17.3)
Yes, in patients who had not used enfuvirtide[¶]	48 (20.7)	24 (20.3)	44 (19.1)	24 (20.2)	92 (19.9)	48 (20.3)
Darunavir use in OBT — no. (%)						
No	156 (67.2)	83 (70.3)	122 (53.0)	55 (46.2)	278 (60.2)	138 (58.2)
Yes, in patients who had previously used darunavir	14 (6.0)	5 (4.2)	4 (1.7)	4 (3.4)	18 (3.9)	9 (3.8)
Yes, in patients who had not used darunavir[§]	62 (26.7)	30 (25.4)	104 (45.2)	60 (50.4)	166 (35.9)	90 (38.0)
No. of active protease inhibitors in OBT — no. (%)[‖]						
0	101 (43.5)	55 (46.6)	67 (29.1)	43 (36.1)	168 (36.4)	98 (41.4)
≥1	123 (53.0)	61 (51.7)	155 (67.4)	76 (63.9)	278 (60.2)	137 (57.8)
Missing data	8 (3.4)	2 (1.7)	8 (3.5)	0	16 (3.5)	2 (0.8)
Phenotypic sensitivity score — no. (%)[**]						
0	45 (19.4)	21 (17.8)	24 (10.4)	23 (19.3)	69 (14.9)	44 (18.6)
1	67 (28.9)	39 (33.1)	78 (33.9)	33 (27.7)	145 (31.4)	72 (30.4)
2	67 (28.9)	33 (28.0)	75 (32.6)	33 (27.7)	142 (30.7)	66 (27.8)
≥3	44 (19.0)	21 (17.8)	41 (17.8)	27 (22.7)	85 (18.4)	48 (20.3)
Missing data	9 (3.9)	4 (3.4)	12 (5.2)	3 (2.5)	21 (4.5)	7 (3.0)
Genotypic sensitivity score — no. (%)[**]						
0	70 (30.2)	34 (28.8)	45 (19.6)	32 (26.9)	115 (24.9)	66 (27.8)
1	76 (32.8)	48 (40.7)	102 (44.3)	48 (40.3)	178 (38.5)	96 (40.5)
2	57 (24.6)	22 (18.6)	54 (23.5)	27 (22.7)	111 (24.0)	49 (20.7)
≥3	26 (11.2)	13 (11.0)	25 (10.9)	10 (8.4)	51 (11.0)	23 (9.7)
Missing data	3 (1.3)	1 (0.8)	4 (1.7)	2 (1.7)	7 (1.5)	3 (1.3)

[*] Plus–minus values are means ±SD. Nominal P values for differences between the raltegravir and placebo groups in the data from the combined BENCHMRK studies were all greater than 0.05, with the exception of hepatitis virus coinfection, for which P=0.047. OBT denotes optimized background therapy.

[†] Race or ethnic group was self-reported.

[‡] The dynamic range of the standard polymerase-chain-reaction assay was 400 to 750,000 copies per milliliter.

[§] Hepatitis B infection was defined as a positive test for hepatitis B surface antigen, and hepatitis C infection was defined as a positive test for hepatitis C antibody.

[¶] For purposes of calculating the sensitivity scores, enfuvirtide use in patients who had not previously received enfuvirtide was always counted as one active drug in OBT, and darunavir use in patients who had not previously received darunavir was always counted as an active protease inhibitor in OBT.

[‖] The number of active protease inhibitors was determined by means of phenotypic resistance testing. For patients for whom there were missing results for genotypic or phenotypic resistance testing (or both), the number of active protease inhibitors in OBT was assigned a value of ≥1 when darunavir was used and the patient had not previously received darunavir.

[**] The phenotypic and genotypic sensitivity scores are the total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined with the use of phenotypic and genotypic resistance testing.

RESULTADOS

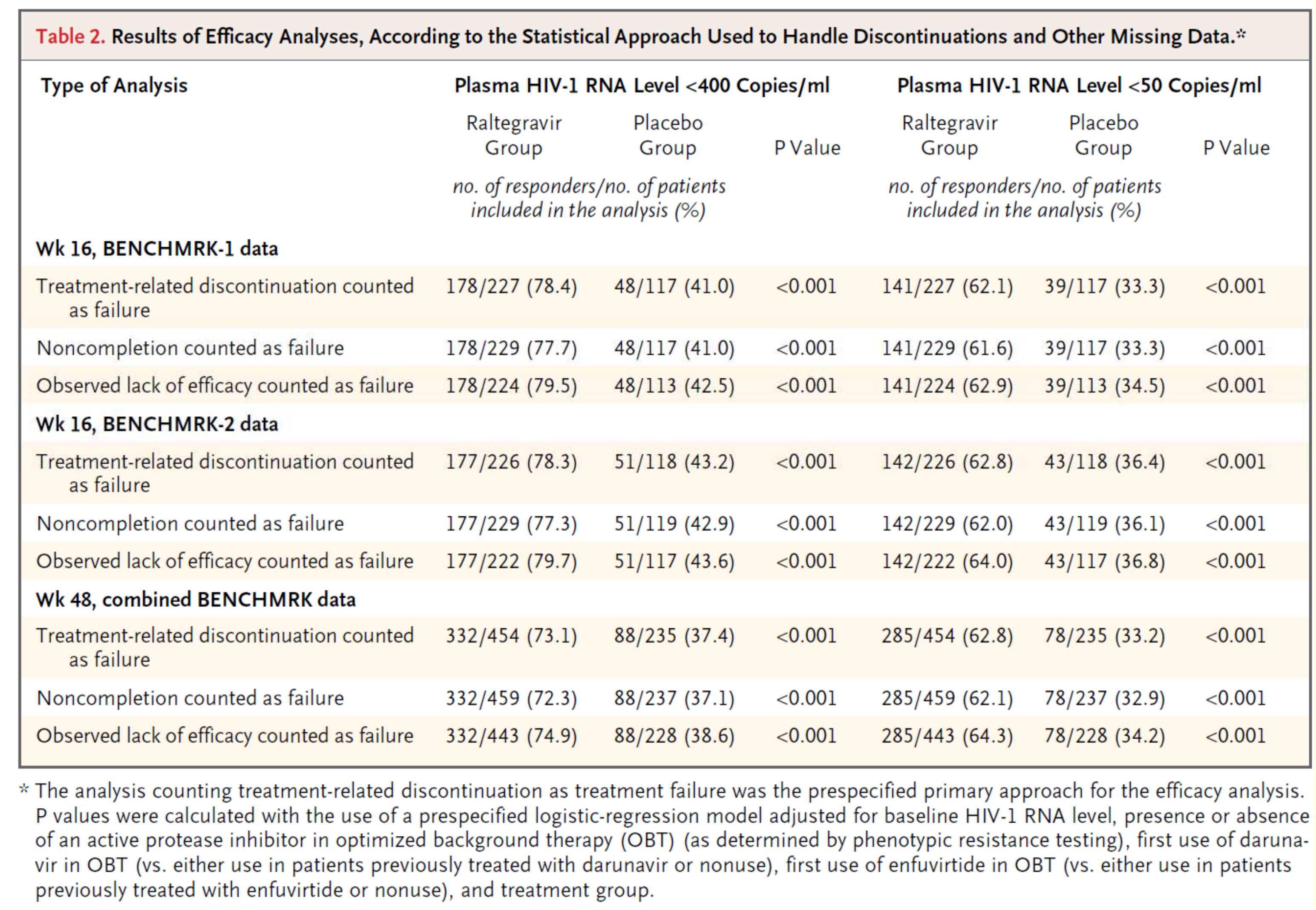
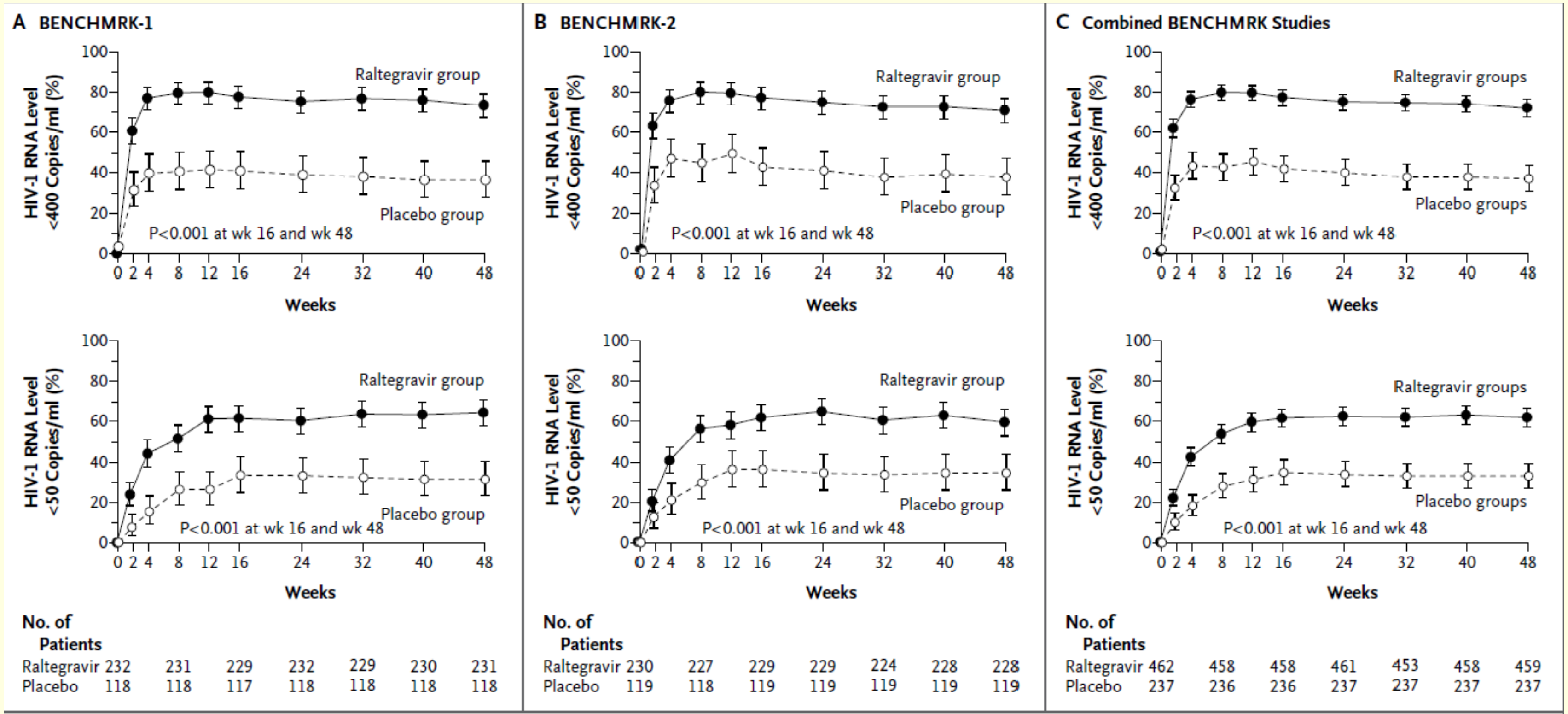


Table 2. **Results of Efficacy Analyses, According to the Statistical Approach Used to Handle Discontinuations and Other Missing Data.***

Type of Analysis	Plasma HIV-1 RNA Level <400 Copies/ml			Plasma HIV-1 RNA Level <50 Copies/ml		
	Raltegravir Group	Placebo Group	P Value	Raltegravir Group	Placebo Group	P Value
	no. of responders/no. of patients included in the analysis (%)			*no. of responders/no. of patients included in the analysis (%)*		
Wk 16, BENCHMRK-1 data						
Treatment-related discontinuation counted as failure	178/227 (78.4)	48/117 (41.0)	<0.001	141/227 (62.1)	39/117 (33.3)	<0.001
Noncompletion counted as failure	178/229 (77.7)	48/117 (41.0)	<0.001	141/229 (61.6)	39/117 (33.3)	<0.001
Observed lack of efficacy counted as failure	178/224 (79.5)	48/113 (42.5)	<0.001	141/224 (62.9)	39/113 (34.5)	<0.001
Wk 16, BENCHMRK-2 data						
Treatment-related discontinuation counted as failure	177/226 (78.3)	51/118 (43.2)	<0.001	142/226 (62.8)	43/118 (36.4)	<0.001
Noncompletion counted as failure	177/229 (77.3)	51/119 (42.9)	<0.001	142/229 (62.0)	43/119 (36.1)	<0.001
Observed lack of efficacy counted as failure	177/222 (79.7)	51/117 (43.6)	<0.001	142/222 (64.0)	43/117 (36.8)	<0.001
Wk 48, combined BENCHMRK data						
Treatment-related discontinuation counted as failure	332/454 (73.1)	88/235 (37.4)	<0.001	285/454 (62.8)	78/235 (33.2)	<0.001
Noncompletion counted as failure	332/459 (72.3)	88/237 (37.1)	<0.001	285/459 (62.1)	78/237 (32.9)	<0.001
Observed lack of efficacy counted as failure	332/443 (74.9)	88/228 (38.6)	<0.001	285/443 (64.3)	78/228 (34.2)	<0.001

* The analysis counting treatment-related discontinuation as treatment failure was the prespecified primary approach for the efficacy analysis. P values were calculated with the use of a prespecified logistic-regression model adjusted for baseline HIV-1 RNA level, presence or absence of an active protease inhibitor in optimized background therapy (OBT) (as determined by phenotypic resistance testing), first use of darunavir in OBT (vs. either use in patients previously treated with darunavir or nonuse), first use of enfuvirtide in OBT (vs. either use in patients previously treated with enfuvirtide or nonuse), and treatment group.

RESULTADOS


A BENCHMRK-1

B BENCHMRK-2

C Combined BENCHMRK Studies

No. of Patients

A

Raltegravir	232	231	229	232	229	230	231
Placebo	118	118	117	118	118	118	118

B

Raltegravir	230	227	229	229	224	228	228
Placebo	119	118	119	119	119	119	119

C

Raltegravir	462	458	458	461	453	458	459
Placebo	237	236	236	237	237	237	237

Figure 1. Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than 400 or Less Than 50 Copies per Milliliter during the BENCHMRK Studies, According to Study Group.
Percentages are shown for patients in the BENCHMRK-1 study (Panel A), patients in the BENCHMRK-2 study (Panel B), and patients in the combined studies (Panel C). The data, based on standard and ultrasensitive assays, are for the patients included in the analysis counting noncompletion as treatment failure. I bars represent 95% confidence intervals.

RESULTADOS

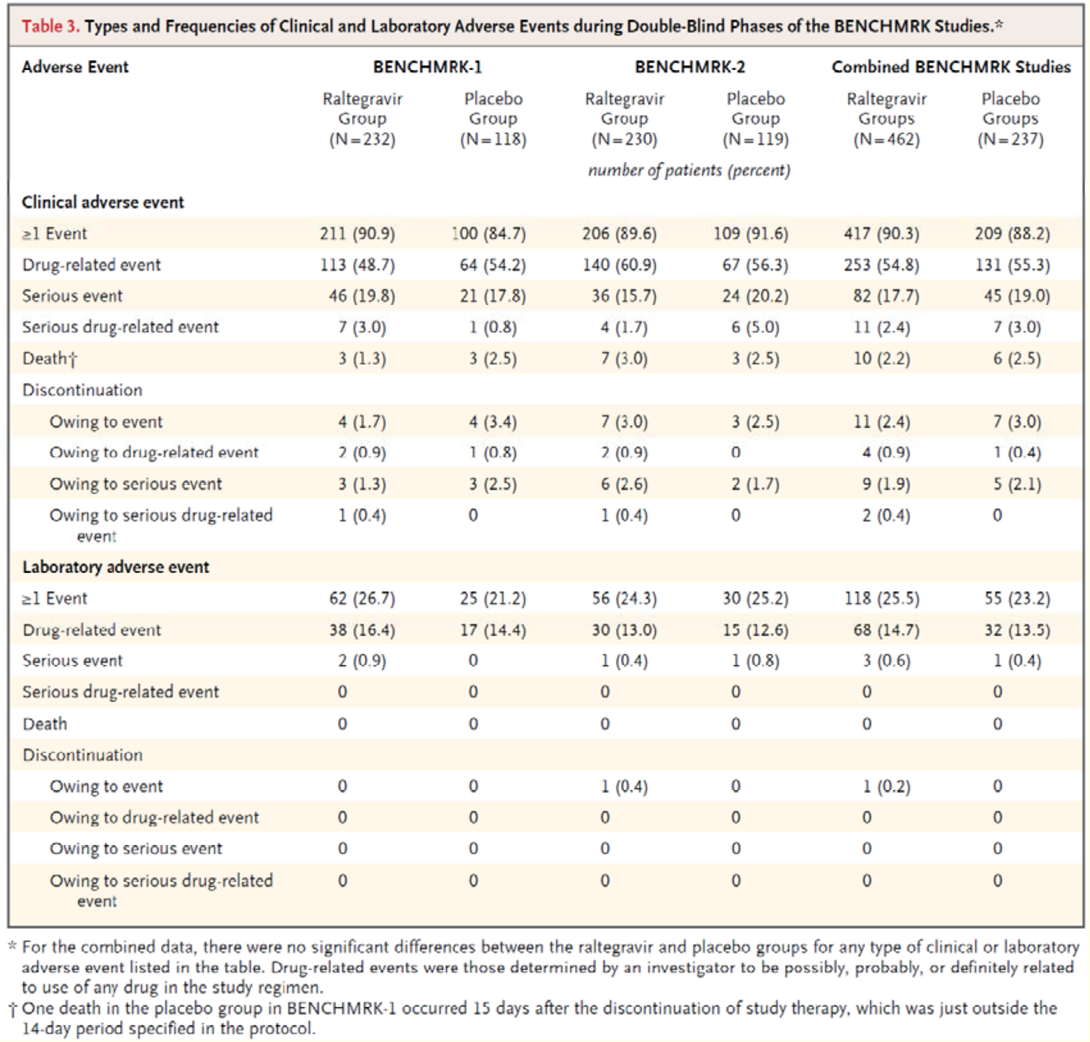


Table 3. Types and Frequencies of Clinical and Laboratory Adverse Events during Double-Blind Phases of the BENCHMRK Studies.*

Adverse Event	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
	number of patients (percent)					
Clinical adverse event						
≥1 Event	211 (90.9)	100 (84.7)	206 (89.6)	109 (91.6)	417 (90.3)	209 (88.2)
Drug-related event	113 (48.7)	64 (54.2)	140 (60.9)	67 (56.3)	253 (54.8)	131 (55.3)
Serious event	46 (19.8)	21 (17.8)	36 (15.7)	24 (20.2)	82 (17.7)	45 (19.0)
Serious drug-related event	7 (3.0)	1 (0.8)	4 (1.7)	6 (5.0)	11 (2.4)	7 (3.0)
Death†	3 (1.3)	3 (2.5)	7 (3.0)	3 (2.5)	10 (2.2)	6 (2.5)
Discontinuation						
Owing to event	4 (1.7)	4 (3.4)	7 (3.0)	3 (2.5)	11 (2.4)	7 (3.0)
Owing to drug-related event	2 (0.9)	1 (0.8)	2 (0.9)	0	4 (0.9)	1 (0.4)
Owing to serious event	3 (1.3)	3 (2.5)	6 (2.6)	2 (1.7)	9 (1.9)	5 (2.1)
Owing to serious drug-related event	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Laboratory adverse event						
≥1 Event	62 (26.7)	25 (21.2)	56 (24.3)	30 (25.2)	118 (25.5)	55 (23.2)
Drug-related event	38 (16.4)	17 (14.4)	30 (13.0)	15 (12.6)	68 (14.7)	32 (13.5)
Serious event	2 (0.9)	0	1 (0.4)	1 (0.8)	3 (0.6)	1 (0.4)
Serious drug-related event	0	0	0	0	0	0
Death	0	0	0	0	0	0
Discontinuation						
Owing to event	0	0	1 (0.4)	0	1 (0.2)	0
Owing to drug-related event	0	0	0	0	0	0
Owing to serious event	0	0	0	0	0	0
Owing to serious drug-related event	0	0	0	0	0	0

* For the combined data, there were no significant differences between the raltegravir and placebo groups for any type of clinical or laboratory adverse event listed in the table. Drug-related events were those determined by an investigator to be possibly, probably, or definitely related to use of any drug in the study regimen.

† One death in the placebo group in BENCHMRK-1 occurred 15 days after the discontinuation of study therapy, which was just outside the 14-day period specified in the protocol.

RESULTADOS

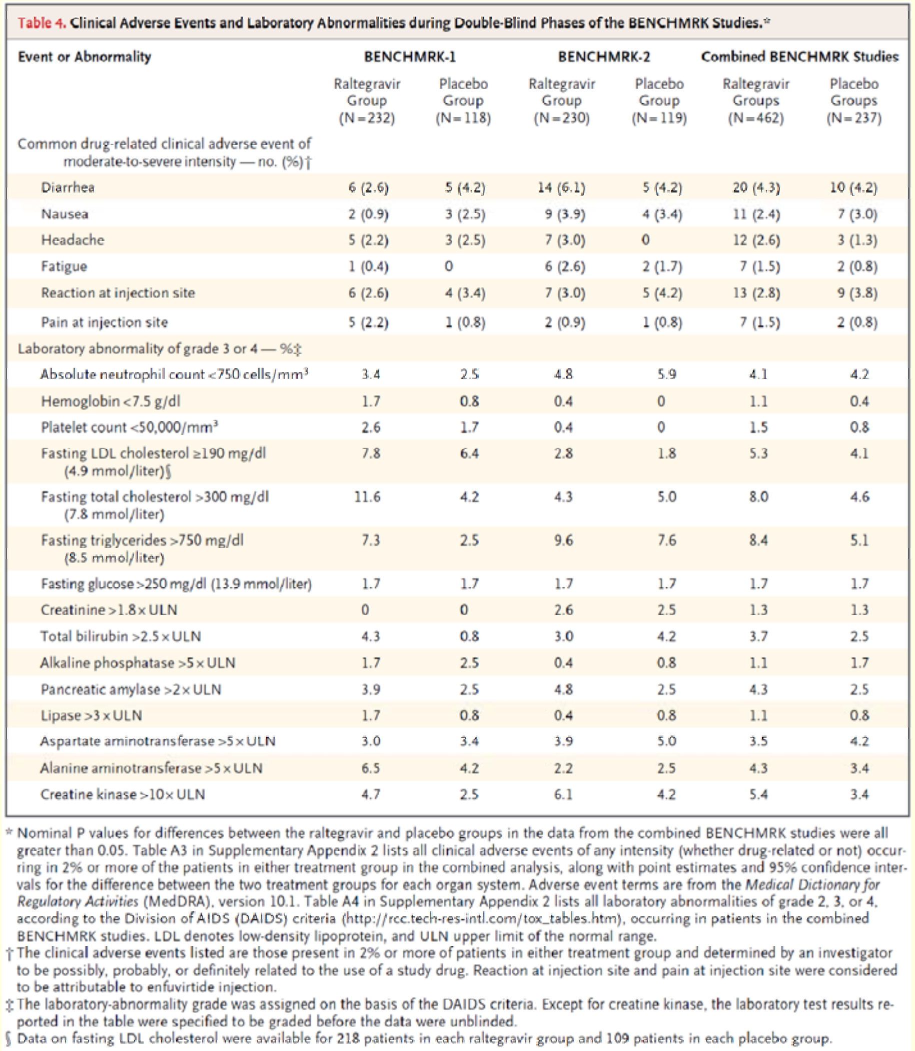


Table 4. Clinical Adverse Events and Laboratory Abnormalities during Double-Blind Phases of the BENCHMRK Studies.*

Event or Abnormality	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
Common drug-related clinical adverse event of moderate-to-severe intensity — no. (%)†						
Diarrhea	6 (2.6)	5 (4.2)	14 (6.1)	5 (4.2)	20 (4.3)	10 (4.2)
Nausea	2 (0.9)	3 (2.5)	9 (3.9)	4 (3.4)	11 (2.4)	7 (3.0)
Headache	5 (2.2)	3 (2.5)	7 (3.0)	0	12 (2.6)	3 (1.3)
Fatigue	1 (0.4)	0	6 (2.6)	2 (1.7)	7 (1.5)	2 (0.8)
Reaction at injection site	6 (2.6)	4 (3.4)	7 (3.0)	5 (4.2)	13 (2.8)	9 (3.8)
Pain at injection site	5 (2.2)	1 (0.8)	2 (0.9)	1 (0.8)	7 (1.5)	2 (0.8)
Laboratory abnormality of grade 3 or 4 — %‡						
Absolute neutrophil count <750 cells/mm^3	3.4	2.5	4.8	5.9	4.1	4.2
Hemoglobin <7.5 g/dl	1.7	0.8	0.4	0	1.1	0.4
Platelet count <50,000/mm^3	2.6	1.7	0.4	0	1.5	0.8
Fasting LDL cholesterol ≥190 mg/dl (4.9 mmol/liter)§	7.8	6.4	2.8	1.8	5.3	4.1
Fasting total cholesterol >300 mg/dl (7.8 mmol/liter)	11.6	4.2	4.3	5.0	8.0	4.6
Fasting triglycerides >750 mg/dl (8.5 mmol/liter)	7.3	2.5	9.6	7.6	8.4	5.1
Fasting glucose >250 mg/dl (13.9 mmol/liter)	1.7	1.7	1.7	1.7	1.7	1.7
Creatinine >1.8 × ULN	0	0	2.6	2.5	1.3	1.3
Total bilirubin >2.5 × ULN	4.3	0.8	3.0	4.2	3.7	2.5
Alkaline phosphatase >5 × ULN	1.7	2.5	0.4	0.8	1.1	1.7
Pancreatic amylase >2 × ULN	3.9	2.5	4.8	2.5	4.3	2.5
Lipase >3 × ULN	1.7	0.8	0.4	0.8	1.1	0.8
Aspartate aminotransferase >5 × ULN	3.0	3.4	3.9	5.0	3.5	4.2
Alanine aminotransferase >5 × ULN	6.5	4.2	2.2	2.5	4.3	3.4
Creatine kinase >10 × ULN	4.7	2.5	6.1	4.2	5.4	3.4

* Nominal P values for differences between the raltegravir and placebo groups in the data from the combined BENCHMRK studies were all greater than 0.05. Table A3 in Supplementary Appendix 2 lists all clinical adverse events of any intensity (whether drug-related or not) occurring in 2% or more of the patients in either treatment group in the combined analysis, along with point estimates and 95% confidence intervals for the difference between the two treatment groups for each organ system. Adverse event terms are from the *Medical Dictionary for Regulatory Activities* (MedDRA), version 10.1. Table A4 in Supplementary Appendix 2 lists all laboratory abnormalities of grade 2, 3, or 4, according to the Division of AIDS (DAIDS) criteria (http://rcc.tech-res-intl.com/tox_tables.htm), occurring in patients in the combined BENCHMRK studies. LDL denotes low-density lipoprotein, and ULN upper limit of the normal range.

† The clinical adverse events listed are those present in 2% or more of patients in either treatment group and determined by an investigator to be possibly, probably, or definitely related to the use of a study drug. Reaction at injection site and pain at injection site were considered to be attributable to enfuvirtide injection.

‡ The laboratory-abnormality grade was assigned on the basis of the DAIDS criteria. Except for creatine kinase, the laboratory test results reported in the table were specified to be graded before the data were unblinded.

§ Data on fasting LDL cholesterol were available for 218 patients in each raltegravir group and 109 patients in each placebo group.

CONCLUSIONES

- En la semana 48 se observó un porcentaje mayor de pacientes con carga viral indetectable en los que recibieron raltegravir dos veces al día frente a los que recibieron placebo.
- Los efectos secundarios fueron escasos sin diferencias significativas en ambos grupos