CLINICAL STUDY REPORT (CSR)

Name of Sponsor/Company	**Janssen Research & Development*** **JANSSEN-CILAG GmbH**
Name of Finished Product	**Prezista® and/or Intelence®**
Name of Active Ingredient(s)	**Darunavir and/or Etravirine**

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Status: Approved

Date: 16 January 2014

Prepared by: MUC Research GmbH, Munich, Germany

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Compliance

The study was carried out in accordance with the "Recommendations for the planning and implementation of observational studies" published by BfArM on November 12th 1998 and the VFA´s recommendation for the improvement of quality and transparency of non-interventional studies ("VFA-Empfehlungen zur Verbesserung der Qualität und Transparenz von nicht-interventionellen Studien"; 2007).

Confidentiality Statement

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Protocol No.: TMC114HIV4035 (A non-interventional study, NIS)

Title of Study:

Cost and resource utilization study in antiretroviral treated patients (Corsar) study - a health economic evaluation of costs associated with the HIV infection within the German health care system

Study Name: Corsar

Annotation:

This CSR refers to the evaluation of HIV-related variables (efficacy and safety evaluation) of Corsar. The cost and resource analyses are described elsewhere.

EudraCT Number: N.A.

NCT No.: The study is listed in the register of non-interventional studies of research-based pharmaceutical companies (*vfa, Verband forschender Arzneimittelhersteller*). (http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/nisdb/nis-details/_249)

Clinical Registry No.: N.A.

Coordinating Investigator(s): Prof. Dr. med. Matthias Stoll, Medizinische Hochschule Hannover, Zentrum Innere Medizin, Klin. Immunologie und Rheumatologie, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Study Center(s):

The study was contacted in 10 German sites. The participating study centers were:

- Private Practice Gute, Locher, Lutz (Dr. Klauke)
- ICH Grindel (Prof. H.-J. Stellbrink)
- UK Hamburg-Eppendorf (Dr. O. Degen)
- Klinikum Dortmund (Dr. M. Hower)
- Praxis Georgstrasse (Dr. B. Kuhlmann)
- LMU München (Prof. J. Bogner)
- Praxis Hartl, Gorriahn (Dr. D. Gorriahn)
- MHH (Prof. M. Stoll)
- Ärzteforum Seestrasse (Dr. W. Schmidt)
- Praxis City Ost (Dr. C. Cordes)

Publications (References):

Presentation of preliminary data:

- M. Stoll, et al. CORSAR (Cost and Resource utilization Study in Antiretroviral treated patients): a prospective multicenter cohort study focusing on the financial burden of HIV infection in people living with HIV (PLHIV) receiving antir. 19th International AIDS Conference, Washington D.C.: Abstract no. THPE660.
- M. Stoll et al. CORSAR-Studie: Eine prospektive, multizentrische Kohortenstudie zu den Krankheitskosten der HIV-Infektion unter antiretroviraler Therapie (ART) im deutschen Gesundheitssystem: 96 Wochen Analyse: DÖAK, Innsbruck 2013: Abstract 153.

Study Period: 07 JAN 2009 – 27 JUN 2012

The first patient was enrolled on 07 JAN 2009. The last observation recorded in the data base was 27 JUN 2012.

Phase of Development: N.A.

OBJECTIVES:

- The primary objective of this study was
    - o   to evaluate direct and indirect costs associated with the HIV infection itself as well as the antiretroviral treatment and its effects in HIV-infected patients in Germany

- Secondary objectives were

  o to prescribe habits in terms of antiretroviral therapy and drug combinations used in first, -second or further-line therapy (definition see Protocol)

  o to evaluate efficacy/effectiveness (% of patients with HIV-1-RNA <50 copies/mL at week 24, 48 and 96
  and % of "responders", "non-responders (>50)", "non-responders(>200)"; see CRITERIA FOR EVALUATION)

  o to evaluate the drug safety, particularly with regard to adverse events and serious adverse events in particular in patients receiving Darunavir and/or Etravirine.

  o to describe aspects of quality of life aspects (using the EQ-5D , incl. VAS)

Annotation:

This CSR includes the evaluation of efficacy and drug safety in patients of the Corsar study. Cost and resource analyses and the evaluation of quality of life aspects – all performed by the Institut für Versicherungsbetriebslehre Forschungsstelle für Gesundheitsökonomie, Hannover) – are described elsewhere.

METHODS:

Design

Corsar was a non-interventional prospective cohort study. Physicians and subjects did not follow a defined schedule of diagnostic or therapeutic measures. Documentation of clinical data, direct and indirect costs was based on routine care of HIV infected patients not being influenced by the sponsor.

Quality assurance

Data monitoring was provided by the sponsor. Monitoring included online data checks concerning the intrinsic validity of the saved therapy data and possible gaps in the documentation. On-site monitoring visits were performed as frequently as necessary and included checks of signed informed patient consent forms, AEs/SAEs recorded in the case record forms and data verification (year of birth, gender, data related to the disease, primary objectives and laboratory results) regarding completeness and plausibility. Source data verification was performed in accordance with the data protection laws.

Number of Subjects (planned and analyzed):

The planned sample size was 1114 subjects. The sample size calculation was based on the primary hypothesis that treatment with HAART (highly active antiretroviral therapy) is cost-saving, i.e. due to lower hospitalization rates on HAART (40.7% vs. 52.0%; Medical School of Hannover 1997, see Protocol 11.1).

Analysis data sets

Different analysis sets - the full analysis set, the efficacy and safety sets - were used for the description of the study population, the evaluation of efficacy and the evaluation of drug safety, respectively.

o FULL ANALYSIS SET (FAS)
  ▪ Full Analysis Set (FAS): All patients included in the study
    - Baseline demographics and HIV-related variables were described for the Full Analysis Set

o EFFICACY SET
- Efficacy Set: All patients with at least one-follow-up visit.

o SAFETY SETS
- Safety Set: All patients included in the study (=FAS)

Data Sets Analyzed: All Subjects Analysis Set	Total
Planned	1114
Enrolled	1149
Full Analysis Set	1149
Efficacy Set	1112
Safety Set	1149

Diagnosis and Main Criteria for Inclusion:

Subjects' selection is based on the following criteria:

- Male or female person of 18 years (or older) of age
- Positive HIV antibody-test
- Any CDC stage and any duration of HIV infection
- Patients treated in-hospital or out-hospital
- Subject is in care of one of the approx. 10 HIV-specialized centers that will participate in this study
- Existence of subject data in an electronic patient record
- Subject is treated currently with ARVs (antiretroviral drugs) for at least 6 months or has been treated in the past for at least 3 months with ARVs but is currently not treated with ARVs
- Signed informed consent regarding source data verification is available at the beginning of documentation
- Communication is possible in German language
- Life expectancy more than 6 months•   Male or female Patients with Human Immunodeficiency (HIV-1) virus infection

Test Product, Dose and Mode of Administration, Batch No.:

Darunavir (Prezista®) and/or Etravirine®; Dose and mode of administration were based on the corresponding summary of product characteristics (SPC).

Reference Therapy, Dose and Mode of Administration, Batch No.:

All antiretroviral drugs and combinations were used for treatment of HIV infection in Germany.

Annotation:

Since this is an observational study in routine clinical practice, all antiretroviral drugs were given at the discretion of the treating physician. Assignment of a patient to a particular antiretroviral regimen was part of routine clinical care and was independent from the conduct of Corsar.

Duration of Treatment:

Due to the observational design of Corsar, treatment duration was not specified in the protocol. All subjects fulfilling the inclusion criteria should be followed for 96 weeks with respect to antiretroviral therapy and other variables defined in the protocol.

Duration of treatment was based standard criteria such as virological and/or immunological success, drug safety, individual tolerability and other patient relevant factors.

CRITERIA FOR EVALUATION:

Efficacy measures

 a) Proportion of the cohort with HIV-1 RNA <50 copies/mL at week 24, 48 and 96 (missing data excluded) stratified by 1st-, 2nd/3rd and >3rd-line therapy.
 b) Proportion of "responders", "non-responders (>50)", "non-responders(>200)"*
 c) Absolute CD4 cell counts and change from baseline stratified by 1st-, 2nd/3rd and >3rd-line therapy
 d) Percentage of patients with absolute CD4 cell counts <350, 350-500; >500/µL at week 24, 48 and 96 stratified by 1st-, 2nd/3rd and >3rd-line therapy.
 e) Time on drug stratified by 1st-, 2nd/3rd and >3rd-line therapy and for the most frequent treatment classes; baseline is not the time of inclusion but the time of initiation of the regimen.

 *   *"responder" = HIV-1 RNA <50 copies/mL with and without HAART change*
       "non-responder(>50)" = HIV-1 RNA ≥50 copies/mL in two consecutive test results with change of HAART
       "non-responder(>200)" = multiple peak-HIV-1 RNA >200 copies/mL without change of HAART

Safety measures

 • Laboratory safety parameters were described for the Safety Set (missing data were excluded).
 • Listing of all AEs and SAEs occurring during the course of the study
 • Listing of all AEs and SAEs (including MedDRA Codes) occurring during antiretroviral treatment based on Darunavir and/or Etravirine and causal relationship (unless not reported).

STATISTICAL METHODS:

Sample size

The sample size calculation was based on the primary hypothesis that treatment with HAART is cost-saving, i.e. due to lower hospitalization rates on HAART. (40.7% vs. 52.0%; Medical School of Hannover 1997 (see Protocol 11.1).

Statistical analyses

Primary analyses

The statistical analyses for pharma economic evaluation (direct and indirect costs associated with HIV infection) are based on the methods described elsewhere by the *Institut für Versicherungsbetriebslehre Forschungsstelle für Gesundheitsökonomie, Hannover*.

Version 1.03 Date: 16 January 2014

Secondary analyses

The methods for secondary analyses (efficacy and safety) are described in the statistical analysis plan, version 1.1., of MUC Research. All analyses were performed after cleanup of the database (implausible values were set as missing; all changes and the reasons for changing were documented, see Appendix A. ***Documentation cleanup Corsar database***).

Data were analyzed using descriptive and explorative methods.

- All statistical analyses were carried out by means of the STATA® package (version 10.1) and Excel 2010.
- As this is an observational study, only descriptive statistical methods were used. There was no data imputation. Qualitative data (e.g. categorical variables) were presented by means of frequency distributions. Analyses were based on valid (or observed) data per parameter (resulting in different sample sizes for efficacy and safety laboratory parameters).
- Quantitative variables were summarized using statistical parameters such as valid (or observed) N, mean, standard deviation, minimum, maximum, and selected quantiles (lower quartile (25%), upper quartile (75%), and median (50%)).
- Kruskal-Wallis and Mann-Whitney U test (pairwise) were used to test for significance when comparing continuous variables.
- Wilcoxon signed-rank test was used to test for significance when comparing repeated measurements on a single sample.
- Chi-square-test and Fisher exact test (pairwise) were used to test for significance when comparing frequencies.
- The p-level for significance is $p < 0.05$.

Analysis populations

- o FULL ANALYSIS SET (FAS)

  - ▪ Full Analysis Set (FAS): All patients included in the study
    - - Baseline demographics and HIV-related variables were described for the full analysis set

- o EFFICACY SET

  - ▪ Efficacy Set: All patients with at least one-follow-up visit.

- o SAFETY SETS

  - ▪ Safety Set: All patients included in the study (=FAS)
    - - Laboratory safety parameters were described for all patients of the FAS (missing data were excluded).

    - - All reported AEs and SAEs were listed for the safety set.

    DRV/ETR Subset: All patients receiving Darunavir (Prezista®) and/or Etravirine (Intelence®) as part of their antiretroviral combination regimen.
    - - All reported AEs and SAEs were listed for the DRV/ETR subset; including MedDRA Coding and causal relationship (unless not reported).

RESULTS:

List off Abbreviations:

AE	Adverse Event
ALT (SGPT)	Alanine Transaminase (Glutamic-Pyruvic Transaminase
AST (SGOT)	Aspartat-Aminotransferase (Glutamat-Oxalacetat-Transaminase)
BMI	Body mass index
CDC	Classification System for HIV Infection
FAS	Full Analysis Set
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency virus
IQR	Interquartile range
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NRTI	Nucleoside analog reverse-transcriptase inhibitors
PI	Protease Inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

List of all tables:

STUDY POPULATION

CORSAR started recruitment during 2009 and ended after the last patient had reached week 96 in July 2012.

1149 patients from 8 outpatient and 4 inpatient centers in Germany were included in the study. 40% of patients were on 1st-line HAART at the time of enrolment (baseline), 16% of patients were on 2nd- or 3rd-line HAART and 26% of patients on 4th- or further-line HAART. In 18% of patients this information was not available ("Therapy not classified")

The study visit "week 24" was documented in 812 patients, the visit "weeks 48" in 964 patients and the visit "week 96" in 904 patients.

Baseline demographics and HIV-related variables of the Full Analysis Set and of the Efficacy Set are shown in Tables 1-2.

BASELINE DEMOGRAPHICS AND HIV-RELATED VARIABLES

Socio-demographic data and HIV-related variables including age, gender, CDC status, duration of HIV diagnosis, CD4 cell counts and HIV-1 RNA<50 copies/mL at study start are shown in Tables 1 and 2.

All patients (N= 1149; FAS)

The median age of the patients at time of enrolment was 46 years (IQR: 40-53 years). Patients on 1st-line HAART were younger (44 years) than patients on 2nd- or 3rd-line HAART (48 years) or patients on 4th- or further-line HAART (48 years) (*P*<0.001; Kruskal-Wallis).
The majority of the patients were men (88.7%).

The CDC classification of HIV disease (most recently revised in 1993) was assessed at study start. Overall, about one fourth of patients met the criteria for CDC stage C (28%). Distribution of CDC C stages differed across the therapy lines. CDC stage C was reached in 22% of patients on 1st-line HAART, in 26% on 2nd- or 3rd-line HAART (48 years) and in 40% of patients on 4th- or further-line HAART (*P*<0.001, Chi²).
The median duration of HIV diagnosis was 10 years (1st-line HAART: 5 years; 2nd- or 3rd-line HAART: 12 years; 4th- or further-line HAART: 15 years).

The absolute median CD4+ cell count was 529 cells/µL; the interquartile range (IQR) was 369 – 709 cell/µL years (1st-line HAART: 494/µL; 2nd- or 3rd-line HAART: 580/µL; 4th- or further-line HAART: 538/µL) (*P*=0.02, Kruskal-Wallis).

In 89% of patients HIV-1 RNA was <50 copies/mL at baseline (1st-line HAART: 90%; 2nd- or 3rd-line HAART: 92%; 4th- or further-line HAART: 92%). Most patients received a NRTI+PI (41%) based regimen or a NRTI+NNRTI (41%) based regimen (see Table 2).

The overall observation time was 96 weeks and did not differ within the different therapy lines.
During the observation time, 91 patients (8%) were "lost to follow up" (after a median time of 50 weeks (IQR: 13-79 weeks), see Table 3).

Efficacy set (N= 1112; all patients with at least one-follow-up visit)

The socio-demographic data and HIV-related variables of the Efficacy Set and the FAS were comparable (see Tables 4 and 5).

- ## FAS (=SAFETY SET)

Table 1: Baseline characteristics for FAS; overall and stratified by therapy line

Baseline characteristics		1st-line therapy	2nd/3rd-line therapy	>3rd-line therapy	Therapy not classified	Total
N		458	180	304	207	1149
Gender (N, %)	Male	411 (89.7%)	158 (87.8%)	260 (85.5%)	190 (91.8%)	1019 (88.7%)
	Female	45 (9.8%)	21 (11.7%)	41 (13.5%)	16 (7.7%)	123 (10.7%)
	Trans-sexual	2 (0.4%)	1 (0.6%)	3 (1.0%)	1 (0.5%)	7 (0.6%)
Age [years], (Median, IQR)		44 (38 – 50)	48 (41 – 56)	48 (44 – 58)	46 (40 – 51)	46 (40 – 53)
CDC C (N, %)		102/456 (22.4%)	46/180 (25.6%)	121/303 (39.9%)	42/185 (22.7%)	311 (27.7%)
Duration of HIV diagnosis [years], (Median, IQR)		5.3 (2.6 – 10.0)	11.5 (7.0 – 16.7)	14.5 (10.8 – 19.0)	9.3 (4.0 – 14.1)	9.6 (4.5 – 15.5)
CD4 cell count [cells/µL], (Median, IQR)		494 (356 – 685)	580 (418 – 756)	538 (367 – 770)	532 (369 – 709)	529 (369 – 709)
HIV-1 RNA <50 copies/mL, (n/N, %)		412/456 (90.4)	165/180 (91.7)	278/304 (91.5)	164/201 (81.6)	1019/1141 (89.3)
Observation time [weeks], (Median, IQR)		96.8 (92 – 101.4)	96.0 (91.3 – 101.4)	95.9 (91.7 – 101.4)	92.4 (49.2 – 98.1)	95.9 (91.3 – 101.3)

Table 2: HAART - Treatment classes at baseline, overall and stratified by therapy line

Treatment classes at BL [N, %]	1st-line therapy (N=458)	2nd/3rd-line therapy (N=180)	>3rd-line therapy (N=304)	Therapy not classified (N=207)	Total (N=1149)
NRTI+PI	215 (46.9)	65 (36.1)	137 (45.1)	51 (24.6)	468 (40.7)
NRTI+PI+x	0 (0.0)	1 (0.6)	10 (3.3)	2 (1.0)	13 (1.1)
NRTI+NNRTI	205 (44.8)	92 (51.1)	102 (33.6)	74 (35.7)	473 (41.2)
NRTI+NNRTI+x	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.5)	3 (0.3)
NRTIs	18 (3.9)	19 (10.6)	8 (2.6)	24 (11.6)	69 (6.0)
Other	11 (2.4)	3 (1.7)	44 (14.5)	17 (8.2)	75 (6.5)

Comment: Patients on treatment interruption were excluded.

Table 3: Percentage and time to "lost to follow up", overall and stratified by therapy line

Lost to follow up	n/N (%)	Observation time [weeks], (Median, IQR)
1st-line therapy	32/458 (7.0)	42.9 (13.1 - 54.6)
2nd/3rd-line therapy	15/180 (8.3)	59.1 (44.7 - 78.1)
>3rd-line therapy	29/304 (9.5)	50.0 (28.3 - 70.0)
Therapy not classified	15/207 (7.2)	33.3 (13.0 - 79.0)
Total	91/1149 (7.9)	49.7 (21.7 - 71.4)

- **EFFICACY SET (AT LEAST ONE FOLLOW UP)**

Table 4: Baseline characteristics for Efficacy Set; overall and stratified by therapy line

Baseline characteristics		1st-line therapy	2nd/3rd-line therapy	>3rd-line therapy	Therapy not classified	Total
N		452	180	301	179	1112
Gender (N, %)	Male	408 (90.3)	158 (87.8)	258 (85.7)	162 (90.5)	986 (88.7)
	Female	42 (9.3)	21 (11.7)	40 (13.3)	16 (8.9)	119 (10.7)
	Trans-sexual	2 (0.4)	1 (0.6)	3 (1.0)	1 (0.6)	7 (0.6)
Age [years], (Median, IQR)		44 (38 – 50)	48 (41 – 56)	48 (44 – 58)	46 (40 – 52)	46 (40 – 53)
CDC C (N, %)		102/450 (22.7)	46/180 (25.6)	120/301 (39.9)	35/159 (22)	303/1090 (27.8)
Duration of HIV diagnosis [years], (Median, IQR)		5.3 (2.6 – 10.0)	11.5 (7.0 - 16.7)	14.5 (10.8 - 19.1)	9.3 (4.0 - 14.2)	9.8 (4.5 - 15.5)
CD4 cell count [cells/µL], (Median, IQR)		495 (357 - 685)	580 (418 - 756)	538 (367 - 763)	544 (376 - 717)	532 (373 - 720)
HIV-1 RNA <50 copies/mL, (n/N, %)		408/451 (90.5)	165/180 (91.7)	277/301 (92.0)	144/176 (81.8)	994 /1108 (89.7)
Observation time [weeks], (Median, IQR)		96.9 (92.1 - 101.4)	96.0 (91.3 - 101.4)	95.9 (91.9 - 101.4)	94.0 (83.4 - 100.1)	96.0 (91.7 - 101.4)

Table 5: HAART - Treatment classes at baseline, overall and stratified by therapy line (Efficacy Set)

Treatment classes at BL [N, %]	1st-line therapy (N=452)	2nd/3rd-line therapy (N=180)	>3rd-line therapy (N=301)	Therapy not classified (N=179)	Total (N=1112)
NRTI+PI	215 (47.6)	65 (36.1)	137 (45.5)	51 (28.5)	468 (42.1)
NRTI+PI+x	0 (0.0)	1 (0.6)	10 (3.3)	2 (1.1)	13 (1.2)
NRTI+NNRTI	205 (45.4)	92 (51.1)	102 (33.9)	74 (41.3)	473 (42.5)
NRTI+NNRTI+x	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.6)	3 (0.3)
NRTIs	18 (4.0)	19 (10.6)	8 (2.7)	24 (13.4)	69 (6.2)
Other	11 (2.4)	3 (1.7)	44 (14.6)	17 (9.5)	75 (6.7)

EFFICACY RESULTS

The following analyses are based on data of the Efficacy Set.

HAART changes and treatment interruption (Tables 6 and 7)
Overall, in 211 patients (23%) HAART was different from baseline at week 96 (at week 24: in 86 patients (11%); at week 48: in 163 patients (17%)). Patients on 1st line HAART were more frequently on their baseline HAART (80%) than patients on 2nd- or 3rd-line HAART (75%) and on 4th- or further-line HAART (75%) at week 96. Most common reasons for HAART changes were side effects, patient's wish and virological failure.

At baseline, 3.5% of patients did not receive any HAART, at week 24 1.7%, at week 48 2.1% and at week 96 0.9%. There were no treatment interruptions in patients on 2nd- or 3rd-line HAART or on 4th- or further-line HAART.

Time on drug (Tables 8 and 9)
Overall time on drug until enrolment was 3.3 years (IQR: 2.4-5.0 years). Patients on 2nd- or 3rd-line HAART stayed longer on their baseline regimen as patients on 1st-line HAART or patients on 4th- or further-line HAART (*P*<0.01; Kruskal-Wallis).

HIV-1 RNA
Table 10 shows the percentage of patients with HIV-1 RNA<50 copies/mL at baseline, week 24, 48 and 96; overall and stratified by therapy line.

All patients: At baseline, 90% of patients had an HIV-1 RNA level <50 copies/mL, at week 24, 91% of patients had HIV-1 RNA levels <50 copies/mL, at week 48, 94% of patients had HIV-1 RNA levels <50 copies/mL and at week 96, 94% of patients had HIV-1 RNA levels <50 copies/mL.

Patients on 1st-line HAART: At baseline, 91% of patients had an HIV-1 RNA level <50 copies/mL, at week 24, 92% of patients had HIV-1 RNA levels <50 copies/mL, at week 48, 95% of patients had HIV-1 RNA levels <50 copies/mL and at week 96, 92% of patients had HIV-1 RNA levels <50 copies/mL.

Patients on 2nd- or 3rd-line HAART: At baseline, 92% of patients had an HIV-1 RNA level <50 copies/mL, at week 24, 94% of patients had HIV-1 RNA levels <50 copies/mL, at week 48, 96% of patients had HIV-1 RNA levels <50 copies/mL and at week 96, 95% of patients had HIV-1 RNA levels <50 copies/mL.

Patients on 4th- or further-line HAART: At baseline, 92% of patients had an HIV-1 RNA level <50 copies/mL. , at week 24, 92% of patients had HIV-1 RNA levels <50 copies/mL, at week 48, 95% of patients had HIV-1 RNA levels <50 copies/mL and at week 96, 95% of patients had HIV-1 RNA levels <50 copies/mL.

Proportion of "responders", "non-responders (>50)", "non-responders (>200)"*
Tables 11 and 12 show the percentage of patient "responders", "non-responders (>50)", "non-responders (>200)" at baseline, week 24, 48 and 96; overall and stratified by therapy line and treatment classes.

Most patients were "responders" (76.3%), only 1.4% were "non-responders (>50)", and 1.6% "non-responders (>200)". In 15% of patients HIV-1 RNA was one time >200 copies/mL and/or between 50-200 copies/mL without any HAART change.
There were no significant differences within therapy lines or treatment classes.

Definition: "responder" = HIV-1 RNA <50 copies/mL with or without HAART change;
        "non-responder(>50)" = HIV-1 RNA ≥50 copies/mL in two consecutive test results with change of HAART;
        "non-responder(>200)" = multiple peak-HIV-1 RNA >200 copies/mL without any change of HAART

CD4 cell count
Absolute CD4 cell counts and change in absolute CD4 cell counts are shown in tables 13 and 14.
Overall, the median baseline absolute CD4 cell count was 532/µL (IQR: 373/µL-720/µL). Median follow-up levels were 544/µL (IQR: 393/µL-755/µL), 579/µL (IQR: 410/µL-769/µL) and 599/µL (IQR: 430/µL-785/µL) at weeks 24, 48 and 96, respectively. The median changes from baseline were +24/µL, +30/µL and +56/µL at weeks 24, 48 and 96 (P<0.001, respectively, Wilcoxon).

In patients on 1st-line HAART, the median baseline absolute CD4 cell count was 495/µL (IQR: 357/µL-685/µL). Median follow-up levels were 535/µL (IQR: 397/µL-737/µL), 560/µL (IQR: 408/µL-747/µL) and 580/µL (IQR: 426/µL-784/µL) at weeks 24, 48 and 96, respectively. The median changes from baseline were +33/µL, +53/µL and +73/µL at weeks 24, 48 and 96 (P<0.001, respectively, Wilcoxon).

In patients on 2nd- or 3rd-line HAART, the median baseline absolute CD4 cell count was 580/µL (IQR: 418/µL-756/µL). Median follow-up levels were 580/µL (IQR: 431/µL-771/µL), 596/µL (IQR: 458/µL-780/µL) and 609/µL (IQR: 445/µL-783/µL) at weeks 24, 48 and 96, respectively. The median changes from baseline were +16/µL, +28/µL and +42/µL at weeks 24, 48 and 96 (P<0.001, at week 96, Wilcoxon).

In patients on 4th- or further-line HAART, the median baseline absolute CD4 cell count was 538/µL (IQR: 367/µL-763/µL). Median follow-up levels were 567/µL (IQR: 365/µL-805/µL), 566/µL (IQR: 386/µL-797/µL) and 616/µL (IQR: 407/µL-802/µL) at weeks 24, 48 and 96, respectively. The median changes from baseline were +13/µL, +12/µL and +44/µL at weeks 24, 48 and 96 (P<0.001, at week 96, Wilcoxon).

All patients: At baseline, in 22% CD4 cell count was <350/µL, in 24% CD4 cell count was between 350-500/µL and in 54% CD4 cell count was >500/µL. At week 96, in 15% CD4 cell count was <350/µL, in 21% CD4 cell count was between 350-500/µL and in 64% CD4 cell count was >500/µL.

Patients on 1st-line HAART: At baseline, in 23% CD4 cell count was <350/µL, in 27% CD4 cell count was between 350-500/µL and in 49% CD4 cell count was >500/µL. At week 96, in 14% CD4 cell count was <350/µL, in 23% CD4 cell count was between 350-500/µL and in 64% CD4 cell count was >500/µL.

Patients on 2nd- or 3rd-line HAART: At baseline, in 15% CD4 cell count was <350/μL, in 22% CD4 cell count was between 350-500/μL and in 63% CD4 cell count was >500/μL. At week 96, in 14% CD4 cell count was <350/μL, in 20% CD4 cell count was between 350-500/μL and in 66% CD4 cell count was >500/μL.

Patients on 4th- or further-line HAART: At baseline, in 24% CD4 cell count was <350/μL, in 20% CD4 cell count was between 350-500/μL and in 56% CD4 cell count was >500/μL. At week 96, in 18% CD4 cell count was <350/μL, in 20% CD4 cell count was between 350-500/μL and in 62% CD4 cell count was >500/μL.

Table 6: Patients with or without HAART change after baseline [BL] at baseline, week 24, 48 and 96; overall and stratified by therapy line

	Without HAART change after BL N (%)	HAART change after BL N (%)	Therapy interruption N (%)	Total
1st-line therapy				
Baseline	444 (98.2)	0 (0.0)	8 (1.8)	452 (100.0)
Week 24	312 (91.0)	26 (7.6)	5 (1.5)	343 (100.0)
Week 48	340 (85.9)	51 (12.9)	5 (1.3)	396 (100.0)
Week 96	301 (79.8)	70 (18.6)	6 (1.6)	377 (100.0)
2nd/3rd-line therapy				
Baseline	180 (100.0)	0 (0.0)	0 (0.0)	180 (100.0)
Week 24	115 (89.8)	13 (10.2)	0 (0.0)	128 (100.0)
Week 48	134 (81.7)	30 (18.3)	0 (0.0)	164 (100.0)
Week 96	115 (75.2)	38 (24.8)	0 (0.0)	153 (100.0)
>3rd-line therapy				
Baseline	301 (100.0)	0 (0.0)	0 (0.0)	301 (100.0)
Week 24	195 (88.2)	26 (11.8)	0 (0.0)	221 (100.0)
Week 48	214 (82.3)	46 (17.7)	0 (0.0)	260 (100.0)
Week 96	187 (74.8)	63 (25.2)	0 (0.0)	250 (100.0)
Therapy not classified				
Baseline	148 (82.7)	0 (0.0)	31 (17.3)	179 (100.0)
Week 24	90 (75.0)	21 (17.5)	9 (7.5)	120 (100.0)
Week 48	93 (64.6)	36 (25.0)	15 (10.4)	144 (100.0)
Week 96	82 (66.1)	40 (32.3)	2 (1.6)	124 (100.0)
Total				
Baseline	1073 (96.5)	0 (0.0)	39 (3.5)	1112 (100.0)
Week 24	712 (87.7)	86 (10.6)	14 (1.7)	812 (100.0)
Week 48	781 (81.0)	163 (16.9)	20 (2.1)	964 (100.0)
Week 96	685 (75.8)	211 (23.3)	8 (0.9)	904 (100.0)

Table 7: Any documented reasons for HAART change after Baseline until week 96, overall and stratified by therapy line

Reason for HAART change after BL [N, %]	1st-line therapy	2nd/3rd-line therapy	>3rd-line therapy	Therapy not classified	Total
Side effects	12 (13.2)	9 (19.1)	8 (9.8)	10 (19.2)	39 (14.3)
Patient´s wish	2 (2.2)	2 (4.3)	8 (9.8)	1 (1.9)	13 (4.8)
Virological failure	1 (1.1)	1 (2.1)	5 (6.1)	4 (7.7)	11 (4.0)
Immunological failure	0 (0.0)	0 (0.0)	1 (1.2)	2 (3.8)	3 (1.1)
Noncompliance	1 (1.1)	1 (2.1)	0 (0.0)	0 (0.0)	2 (0.7)
Simplification	6 (6.6)	1 (2.1)	2 (2.4)	0 (0.0)	9 (3.3)
Therapy intensification	1 (1.1)	1 (2.1)	1 (1.2)	1 (1.9)	4 (1.5)
Therapy interruption	1 (1.1)	0 (0.0)	1 (1.2)	1 (1.9)	3 (1.1)
Resistance	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	2 (0.7)
Comorbidites	1 (1.1)	1 (2.1)	3 (3.7)	0 (0.0)	5 (1.8)
Clinical study start	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.9)	2 (0.7)
Unknown	65 (71.4)	31 (66.0)	51 (62.2)	32 (61.5)	179 (65.8)
Total	88 (100.0)	42 (100.0)	72 (100.0)	48 (100.0)	250 (100.0)

Comment: Table includes all HAART changes; there are patients with more than one HAART changes

Table 8: Time on drug at baseline, overall and stratified by therapy line

Time on drug – Therapy lines [years]	N	Median (IQR)
1st-line therapy	444	3.2 (2.4 - 4.5)
2nd/3rd-line therapy	180	3.8 (2.6 - 5.7)
>3rd-line therapy	301	3.3 (2.3 - 4.9)
Therapy not classified	148	3.8 (2.4 - 5.8)
Total	1073	3.3 (2.4 - 5.0)

Comment: P=0.0014; Kruskal-Wallis

Table 9: Time on drug at baseline, overall and stratified by treatment classes

Time on drug – Treatment Classes [years]	N	Median (IQR)
NRTI+PI	459	3.2 (2.3 – 4.8)
NRTI+PI+x	13	2.6 (1.9 – 3.3)
NRTI+NNRTI	460	3.4 (2.5 – 5.2)
NRTI+NNRTI+x	3	3.1 (1.0 – 3.7)
NRTIs	67	4.8 (2.9 – 8.0)
Other	70	3.0 (2.0 – 5.0)

Table 10: Percentage of patients with HIV-1 RNA<50 copies/mL at baseline, week 24, 48 and 96, overall and stratified by therapy line

HIV-1 RNA <50 copies/mL	Baseline n/N (%)	Week 24 n/N (%)	Week 48 n/N (%)	Week 96 n/N (%)
1st-line therapy	408/451 (90.5)	315/343 (91.8)	376/396 (94.9)	348/377 (92.3)
2nd/3rd-line therapy	165/180 (91.7)	120/128 (93.8)	158/164 (96.3)	146/153 (95.4)
>3rd-line therapy	277/301 (92.0)	203/221 (91.9)	246/260 (94.6)	237/250 (94.8)
Therapy not classified	144/176 (81.8)	100/116 (86.2)	123/137 (89.8)	114/124 (91.9)
Total	994/1108 (89.7)	738/808 (91.3)	903/957 (94.4)	845/904 (93.5)

Table 11: Percentage of "responder", "non-responder(>50)" and "non-responder(>200)" overall and stratified by therapy line

Responders and Non-responders [N, %]	1st-line therapy	2nd/3rd-line therapy	>3rd-line therapy	Therapy not classified	Total
"responder"	347/449 (77.3)	144/178 (80.9)	234/296 (79.1)	124/177 (70.1)	849/1112 (76.3)
"non-responder(>50)"	4/449 (0.9)	2/178 (1.1)	6/296 (2.0)	4/177 (2.3)	16/1112 (1.4)
"non-responder(>200)"	6/449 (1.3)	6/178 (3.4)	4/296 (1.4)	2/177 (1.1)	18/1112 (1.6)
1 time HIV-1 RNA ≥50 copies/mL and HAART change	12/449 (2.7)	2/178 (1.1)	9/296 (3.0)	4/177 (2.3)	27/1112 (2.4)
1 time HIV-1 RNA >200 copies/mL and/or HIV-1 RNA between 50-200 copies/mL without HAART change	79/449 (17.6)	24/178 (13.5)	43/296 (14.5)	25/177 (14.1)	171/1112 (15.4)
without any HAART	1/449 (0.2)	0/178 (0.0)	0/296 (0.0)	18/177 (10.2)	19/1112 (1.7)

Definition: "responder" = HIV-1 RNA <50 copies/mL with or without HAART change; "non-responder(>50)" = HIV-1 RNA ≥50 copies/mL in two consecutive test results with change of HAART; "non-responder(>200)" = multiple peak-HIV-1 RNA >200 copies/mL without any change of HAART

Table 12: Percentage of "responder", "non-responder(>50)" and "non-responder(>200)", stratified by treatment classes

Responders and Non-responders [N, %]	NRTI+PI	NRTI+PI+x	NRTI+NNRTI	NRTI+NNRTI+x	NRTIs	Other
"responder"	328/452 (72.6)	7/13 (53.8)	386/457 (84.5)	3/3 (100.0)	52/66 (78.8)	56/69 (81.2)
"non-responder(>50)"	6/452 (1.3)	1/13 (7.7)	2/457 (0.4)	0/3 (0.0)	0/66 (0.0)	4/69 (5.8)
"non-responder(>200)"	14/452 (3.1)	1/13 (7.7)	1/457 (0.2)	0/3 (0.0)	1/66 (1.5)	1/69 (1.4)
1 time HIV-1 RNA ≥50 copies/mL and HAART change	12/452 (2.7)	0/13 (0.0)	10/457 (2.2)	0/3 (0.0)	2/66 (3.0)	3/69 (4.3)
1 time HIV-1 RNA >200 copies/mL and/or HIV-1 RNA between 50-200 copies/mL without HAART change	92/452 (20.4)	4/13 (30.8)	58/457 (12.7)	0/3 (0.0)	11/66 (16.7)	5/69 (7.2)

Definition: "responder" = HIV-1 RNA <50 copies/mL with or without HAART change; "non-responder(>50)" = HIV-1 RNA ≥50 copies/mL in two consecutive test results with change of HAART; "non-responder(>200)" = multiple peak-HIV-1 RNA >200 copies/mL without any change of HAART

Table 13: Absolute CD4 cell count [cells/μL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

CD4 cell count [cells/μL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	452	537.2	254.1	16	1770	357	685	495
Week 24	343	577.0	258.8	66	1730	397	737	535
Week 48	396	602.9	264.1	100	1677	408	747	560
Week 96	375	626.5	280.3	13	1793	426	784	580
2nd/3rd-line therapy								
Baseline	180	610.5	281.1	24	1464	418	756	580
Week 24	128	621.6	277.7	78	1742	431	771	580
Week 48	164	638.2	285.0	0	1599	458	780	596
Week 96	152	648.7	290.4	150	1712	445	783	609
>3rd-line therapy								
Baseline	301	578.9	295.8	2	1994	367	763	538
Week 24	221	600.8	300.3	83	1449	365	805	567
Week 48	260	597.5	280.0	52	1459	386	797	566
Week 96	250	626.4	295.8	57	1600	407	802	616
Therapy not classified								
Baseline	176	575.3	298.2	44	1670	376	717	544
Week 24	116	563.9	268.5	131	1875	387	711	513
Week 48	137	609.2	275.6	121	1770	411	751	581
Week 96	124	629.7	278.2	109	1844	445	760	612
Total								
Baseline	1109	566.4	278.4	2	1994	373	720	532
Week 24	808	588.7	275.2	66	1875	393	755	544
Week 48	957	608.4	273.7	0	1770	410	769	579
Week 96	901	630.7	285.7	13	1844	430	785	599

Table 14: Change in CD4 cell count [cells/µL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in CD4 cell count [cells/µL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	452	0.0	0.0	0	0	0	0	0
Week 24	343	29.2	142.8	-595	522	-41	104	33
Week 48	396	57.0	170.6	-700	1091	-30	131	53
Week 96	375	85.6	192.6	-696	818	-15	171	73
2nd/3rd-line therapy								
Baseline	180	0.0	0.0	0	0	0	0	0
Week 24	128	15.5	147.8	-353	556	-84	80	16
Week 48	164	34.4	172.6	-894	752	-51	110	28
Week 96	152	40.6	169.2	-420	597	-56	122	42
>3rd-line therapy								
Baseline	301	0.0	0.0	0	0	0	0	0
Week 24	221	18.2	158.8	-582	734	-55	76	13
Week 48	260	2.4	159.4	-781	594	-64	85	12
Week 96	250	40.3	178.2	-797	689	-46	119	44
Therapy not classified								
Baseline	176	0.0	0.0	0	0	0	0	0
Week 24	116	11.4	173.1	-800	668	-49	93	17
Week 48	137	24.4	174.0	-612	476	-46	95	15
Week 96	124	38.4	206.5	-987	581	-48	150	46
Total								
Baseline	1109	0.0	0.0	0	0	0	0	0
Week 24	808	21.5	152.6	-800	734	-50	94	24
Week 48	957	33.6	169.7	-894	1091	-47	113	30
Week 96	901	59.0	188.0	-987	818	-36	152	56

Table 15: Percentage of patients with CD4 cell count <350/µL, 350-500/µL and >500/µL at baseline, week 24, 48 and 96, overall and stratified by therapy line

CD4 cell count categories	Baseline n/N (%)	Week 24 n/N (%)	Week 48 n/N (%)	Week 96 n/N (%)
1st-line therapy				
CD4 cell count<350/µL	105/452 (23.2)	62/343 (18.1)	70/396 (17.7)	51/375 (13.6)
CD4 cell count 350-500/µL	124/452 (27.4)	89/343 (25.9)	91/396 (23.0)	86/375 (22.9)
CD4 cell count>500/µL	223/452 (49.3)	192/343 (56.0)	235/396 (59.3)	238/375 (63.5)
2nd/3rd-line therapy				
CD4 cell count<350/µL	27/180 (15.0)	18/128 (14.1)	21/164 (12.8)	21/152 (13.8)
CD4 cell count 350-500/µL	39/180 (21.7)	30/128 (23.4)	32/164 (19.5)	30/152 (19.7)
CD4 cell count>500/µL	114/180 (63.3)	80/128 (62.5)	111/164 (67.7)	101/152 (66.4)
>3rd-line therapy				
CD4 cell count<350/µL	73/301 (24.3)	50/221 (22.6)	46/260 (17.7)	44/250 (17.6)
CD4 cell count 350-500/µL	60/301 (19.9)	43/221 (19.5)	65/260 (25.0)	51/250 (20.4)
CD4 cell count>500/µL	168/301 (55.8)	128/221 (57.9)	149/260 (57.3)	155/250 (62.0)
Therapy not classified				
CD4 cell count<350/µL	39/176 (22.2)	22/116 (19.0)	23/137 (16.8)	20/124 (16.1)
CD4 cell count 350-500/µL	40/176 (22.7)	32/116 (27.6)	30/137 (21.9)	19/124 (15.3)
CD4 cell count>500/µL	97/176 (55.1)	62/116 (53.4)	84/137 (61.3)	85/124 (68.5)
Total				
CD4 cell count<350/µL	244/1109 (22.0)	152/808 (18.8)	160/957 (16.7)	136/901 (15.1)
CD4 cell count 350-500/µL	263/1109 (23.7)	194/808 (24.0)	218/957 (22.8)	186/901 (20.6)
CD4 cell count>500/µL	602/1109 (54.3)	462/808 (57.2)	579/957 (60.5)	579/901 (64.3)

PHARMACOKINETIC [AND PHARMACODYNAMIC] RESULTS:

N.A.

PHARMACOGENOMIC RESULTS:

N.A.

PATIENT-REPORTED OUTCOMES RESULTS:

N.A.

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS RESULTS:

The results concerning the pharma economic evaluation are presented elsewhere.

SAFETY RESULTS

The safety results include

- a listing of all AEs and SAEs reported during the course of the Corsar study **(**see Appendix B and C. *Listing of AEs Corsar Study; Listing of SAEs Corsar Study)**

- and, in particular, all AEs and SAEs occurring in patients who received Darunavir (DRV; Prezista®) and/or Etravirine (ETR; Intelence®) as part of their antiretroviral combination regimen (see Appendix D. *Corsar Drug Safety Report DRV and ETR; MUC Research GmbH, V01.03, 16 Jan 2014*). **

* Of 1149 patients in the Safety Set, 591 patients (51.4%) experienced at least one AE (2183 notifications including follow-up reports), and 230 patients (20.0%) experienced at least one SAE (440 notifications including follow-up reports). Overall, there were 14 deaths.

** Of 197 patients receiving DRV and/or ETR, 76 patients (38.6%) experienced at least one AE, and 44 patients (22.3%) experienced at least one SAE. In total, 79 SAEs were documented in 44 patients. The reported SAEs belong to 65 SAE episodes (60 hospitalizations and 5 deaths) involving one or several diagnoses classified as SAE. The most commonly affected SOC was 'infections and infestations' with 6.1%. All other SOCs were affected in less than 5% of patients. In 77/79 (97.8%) cases the relationship with DRV or ETR was documented by the treating physician as 'not related', in once case relationship was 'doubtful' (femur fracture, drug: Darunavir, SAE category: hospitalization), and in one case relationship was not provided. Only two patients stopped DRV due to adverse (n=1) or serious adverse events (n=2).

VITAL SIGNS

BMI, blood pressure and pulse are shown in table 16-19. The median BMI was 24 kg/m^2 in each group, the median diast. /syst. blood pressure was 80/128 mmHg and the median pulse was 76 beats/minute.

Table 16: BMI [kg/m²] at baseline, week 24, 48 and 96, overall and stratified by therapy line

BMI [kg/m²]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	449	23.9	3.3	16	44	22	26	24
Week 24	260	24.6	3.6	16	45	22	26	24
Week 48	304	24.3	3.4	16	44	22	26	24
Week 96	281	24.5	3.7	16	45	22	27	24
2nd/3rd-line therapy								
Baseline	179	24.7	3.7	15	36	22	27	24
Week 24	104	25.0	3.7	15	34	23	28	24
Week 48	133	25.3	3.9	15	38	22	28	24
Week 96	115	25.1	4.0	15	39	22	27	24
>3rd-line therapy								
Baseline	302	24.1	4.0	15	48	21	26	24
Week 24	154	24.3	3.8	17	39	22	26	24
Week 48	197	24.2	3.7	16	37	22	26	24
Week 96	178	24.4	4.0	17	41	22	26	24
Therapy not classified								
Baseline	182	24.1	3.7	17	39	21	26	24
Week 24	80	24.1	3.8	18	34	21	27	24
Week 48	92	24.2	3.4	18	34	22	27	24
Week 96	90	24.3	3.1	18	32	22	26	24
Total								
Baseline	1112	24.1	3.6	15	48	22	26	24
Week 24	598	24.5	3.7	15	45	22	26	24
Week 48	726	24.4	3.6	15	44	22	27	24
Week 96	664	24.6	3.8	15	45	22	27	24

Table 17: Blood pressure systolic [mmHg] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Blood pressure, systolic [mmHg]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	372	126.1	15.9	90	200	118	135	125
Week 24	255	130.3	16.8	90	190	120	140	130
Week 48	302	130.8	15.9	86	180	120	140	130
Week 96	265	130.1	14.4	92	168	120	140	130
2nd/3rd-line therapy								
Baseline	144	130.0	18.1	90	180	120	141	130
Week 24	102	129.4	14.3	100	170	120	140	130
Week 48	128	131.5	16.8	89	180	120	140	130
Week 96	116	134.1	18.2	100	200	120	140	131
>3rd-line therapy								
Baseline	237	129.2	15.3	84	180	120	140	130
Week 24	157	128.3	15.6	90	180	120	140	129
Week 48	190	130.0	16.1	92	170	120	140	130
Week 96	169	130.7	16.4	90	180	120	140	130
Therapy not classified								
Baseline	141	126.8	15.1	90	185	120	135	125
Week 24	77	126.3	14.4	99	161	120	137	123
Week 48	89	130.8	16.6	100	180	120	140	130
Week 96	81	130.6	18.7	90	185	120	140	130
Total								
Baseline	894	127.7	16.0	84	200	120	140	128
Week 24	591	129.1	15.8	90	190	120	140	130
Week 48	709	130.7	16.2	86	180	120	140	130
Week 96	631	131.0	16.3	90	200	120	140	130

Table 18: Blood pressure diastolic [mmHg] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Blood pressure, diastolic [mmHg]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	372	80.9	10.7	60	130	72	90	80
Week 24	257	82.8	11.7	53	120	74	90	81
Week 48	302	82.0	11.5	48	150	73	90	80
Week 96	264	82.1	9.9	43	105	75	90	80
2nd/3rd-line therapy								
Baseline	144	82.7	11.2	50	112	75	90	80
Week 24	102	82.5	9.4	69	120	77	90	80
Week 48	128	83.4	11.1	49	111	79	90	80
Week 96	116	83.1	10.4	59	110	77	90	80
>3rd-line therapy								
Baseline	237	81.8	10.0	56	110	75	90	80
Week 24	157	80.9	9.8	53	117	75	88	80
Week 48	190	82.4	10.2	60	118	75	90	80
Week 96	169	81.8	11.4	60	110	72	90	80
Therapy not classified								
Baseline	138	80.5	10.0	50	110	75	85	80
Week 24	76	81.1	11.2	60	105	70	90	80
Week 48	89	81.2	10.3	50	110	75	89	80
Week 96	81	81.4	11.0	56	108	70	90	80
Total								
Baseline	891	81.4	10.5	50	130	75	90	80
Week 24	592	82.0	10.8	53	120	75	90	80
Week 48	709	82.3	10.9	48	150	75	90	80
Week 96	630	82.1	10.6	43	110	75	90	80

Table 19: Pulse [beats/minute] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Pulse [beats/minute]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	358	76.3	11.1	40	117	68	82	76
Week 24	249	78.5	11.4	50	117	72	84	79
Week 48	294	77.9	12.3	50	125	69	85	77
Week 96	262	79.0	12.5	54	130	71	86	78
2nd/3rd-line therapy								
Baseline	138	76.5	9.9	52	120	70	82	76
Week 24	99	76.1	10.0	51	113	70	80	75
Week 48	121	79.1	11.9	44	112	72	85	79
Week 96	113	77.9	11.8	54	116	70	84	76
>3rd-line therapy								
Baseline	229	76.0	10.4	55	111	68	82	75
Week 24	149	75.6	10.8	52	108	68	83	75
Week 48	183	76.4	11.4	53	115	68	83	76
Week 96	163	76.0	12.4	50	112	67	84	74
Therapy not classified								
Baseline	135	76.5	10.2	54	114	70	80	78
Week 24	75	75.6	11.4	48	122	68	82	78
Week 48	89	76.4	13.4	50	120	68	84	76
Week 96	81	74.6	11.0	53	108	67	81	74
Total								
Baseline	860	76.3	10.6	40	120	68	82	76
Week 24	572	77.0	11.1	48	122	70	84	76
Week 48	687	77.5	12.2	44	125	69	84	76
Week 96	619	77.5	12.3	50	130	68	84	76

SAFETY LABORATORY

Triglyceride (see table 20-21)
Overall, the median baseline triglyceride level was 159 mg/dL. Median follow-up levels were 164 mg/dL, 154 mg/dL and 157 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, -5 mg/dL and -3 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline triglyceride level was 149 mg/dL. Median follow-up levels were 153 mg/dL, 145 mg/dL and 143 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +3 mg/dL, +2 mg/dL and -2 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline triglyceride level was 142 mg/dL. Median follow-up levels were 153 mg/dL, 145 mg/dL and 152 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +3 mg/dL, -8 mg/dL and +1 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline triglyceride level was 181 mg/dL. Median follow-up levels were 185 mg/dL, 169 mg/dL and 173 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were -5 mg/dL, -9 mg/dL and -3 mg/dL at weeks 24, 48 and 96.

Total cholesterol (see table 22-23)
Overall, the median baseline total cholesterol was 205 mg/dL. Median follow-up levels were 203 mg/dL, 206 mg/dL and 208 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/- 0 mg/dL, +2 mg/dL and +3 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline total cholesterol was 202 mg/dL. Median follow-up levels were 203 mg/dL, 205 mg/dL and 205 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, +4 mg/dL and +3 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline total cholesterol was 211 mg/dL. Median follow-up levels were 211 mg/dL, 212 mg/dL and 209 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were -3 mg/dL, -2 mg/dL and +1 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline total cholesterol was 209 mg/dL. Median follow-up levels were 201 mg/dL, 207 mg/dL and 213 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +3 mg/dL, +/-0 mg/dL and +4 mg/dL at weeks 24, 48 and 96.

LDL cholesterol (see table 24-25)
Overall, the median baseline LDL cholesterol was 121 mg/dL. Median follow-up levels were 121 mg/dL, 125 mg/dL and 124 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +2 mg/dL, +2 mg/dL and +4 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline LDL cholesterol was 121 mg/dL. Median follow-up levels were 121 mg/dL, 125 mg/dL and 123 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were -1 mg/dL, +4 mg/dL and +2 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline LDL cholesterol was 127 mg/dL. Median follow-up levels were 128 mg/dL, 131 mg/dL and 124 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, -1 mg/dL and +4 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline LDL cholesterol was 120 mg/dL. Median follow-up levels were 117 mg/dL, 121 mg/dL and 126 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +6 mg/dL, +2 mg/dL and +5 mg/dL at weeks 24, 48 and 96.

HDL cholesterol (see table 26-27)
Overall, the median baseline HDL cholesterol was 46 mg/dL. Median follow-up levels were 45 mg/dL, 47 mg/dL and 47 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, +1 mg/dL and +1 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline HDL cholesterol was 45 mg/dL. Median follow-up levels were 46 mg/dL, 47 mg/dL and 48 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, +2 mg/dL and +2 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline HDL cholesterol was 48 mg/dL. Median follow-up levels were 46 mg/dL, 49 mg/dL and 48 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were -1 mg/dL, +/-0 mg/dL and +/-0 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline HDL cholesterol was 45 mg/dL. Median follow-up levels were 44 mg/dL, 44 mg/dL and 46 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, +/-0 mg/dL and -1 mg/dL at weeks 24, 48 and 96.

AST (SGOT) (see table 28-29)
Overall, the median baseline AST was 29 U/L. Median follow-up levels were 30 U/L, 29 U/L and 28 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 U/L, +/-0 U/L and -2 U/L at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline AST was 28 U/L. Median follow-up levels were 28 U/L, 28 U/L and 27 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 U/L, +/-0 U/L and -2 U/L at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline AST was 29 U/L. Median follow-up levels were 31 U/L, 30 U/L and 28 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 U/L, +1 U/L and -2 U/L at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline AST was 31 U/L. Median follow-up levels were 31 U/L, 30 U/L and 28 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 U/L, +/-0 U/L and -2 U/L at weeks 24, 48 and 96.

ALT (SGPT) (see table 30-31)
Overall, the median baseline ALT was 29 U/L. Median follow-up levels were 30 U/L, 30 U/L and 30 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 U/L, +/-0 U/L and +/-0 U/L at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline ALT was 27 U/L. Median follow-up levels were 28 U/L, 29 U/L and 29 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 U/L, +/-0 U/L and +/-0 U/L at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline ALT was 29 U/L. Median follow-up levels were 31 U/L, 31 U/L and 31 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 U/L, +2 U/L and +/-0 U/L at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline ALT was 32 U/L. Median follow-up levels were 31 U/L, 32 U/L and 33 U/L at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 U/L, -1 U/L and -2 U/L at weeks 24, 48 and 96.

Glucose (see table 32-33)
Overall, the median baseline glucose was 90 mg/dL. Median follow-up levels were 91 mg/dL, 90 mg/dL and 88 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, +/-0 mg/dL and -2 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline glucose was 90 mg/dL. Median follow-up levels were 90 mg/dL, 88 mg/dL and 88 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, -1 mg/dL and -1 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline glucose was 90 mg/dL. Median follow-up levels were 90 mg/dL, 90 mg/dL and 90 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were -1 mg/dL, +/-0 mg/dL and -2 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline glucose was 90 mg/dL. Median follow-up levels were 91 mg/dL, 92 mg/dL and 89 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +1 mg/dL, +2 mg/dL and +/-0 mg/dL at weeks 24, 48 and 96.

Creatinine (see table 34-35)
Overall, the median baseline creatinine was 0.9 mg/dL. Median follow-up levels were 0.9 mg/dL, 0.9 mg/dL and 0.9 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, +/-0 mg/dL and +0.01 mg/dL at weeks 24, 48 and 96.

In patients on 1st-line HAART, the median baseline creatinine was 0.9 mg/dL. Median follow-up levels were 0.9 mg/dL, 0.9 mg/dL and 0.9 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, +/-0 mg/dL and +0.02 mg/dL at weeks 24, 48 and 96.

In patients on 2nd- or 3rd-line HAART, the median baseline creatinine was 0.9 mg/dL. Median follow-up levels were 0.9 mg/dL, 0.9 mg/dL and 0.9 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, -0.01 mg/dL and +/-0 mg/dL at weeks 24, 48 and 96.

In patients on 4th- or further-line HAART, the median baseline creatinine was 0.9 mg/dL. Median follow-up levels were 1.0 mg/dL, 1.0 mg/dL and 1.0 mg/dL at weeks 24, 48 and 96, respectively. The median changes from baseline were +/-0 mg/dL, +/-0 mg/dL and +/-0 mg/dL at weeks 24, 48 and 96.

LIPIDS

Table 20: Triglyceride [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Triglyceride [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	413	187.3	140.0	39	1404	103	225	149
Week 24	293	190.1	132.4	36	908	103	235	153
Week 48	352	183.3	122.8	31	696	101	223	145
Week 96	329	178.5	118.6	36	855	101	222	143
2nd/3rd-line therapy								
Baseline	166	196.5	134.9	32	871	106	273	142
Week 24	118	199.7	150.8	33	1163	110	260	153
Week 48	152	181.1	117.2	44	969	108	224	145
Week 96	136	201.1	145.7	40	802	109	252	152
>3rd-line therapy								
Baseline	292	242.1	269.2	37	3609	117	285	181
Week 24	204	232.7	218.5	51	2417	117	292	185
Week 48	241	226.6	173.2	48	1182	115	279	169
Week 96	215	242.2	243.9	45	2486	117	279	173
Therapy not classified								
Baseline	177	192.5	114.6	47	839	107	246	168
Week 24	105	183.3	119.1	42	712	101	229	159
Week 48	127	182.4	123.9	48	1000	99	230	151
Week 96	111	211.3	167.2	49	1229	114	262	169
Total								
Baseline	1048	204.9	183.0	32	3609	107	248	159
Week 24	720	202.7	163.5	33	2417	108	249	164
Week 48	872	194.8	139.0	31	1182	105	237	154
Week 96	791	204.3	173.6	36	2486	109	247	157

Table 21: Change in Triglyceride [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in Triglyceride [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	413	0.0	0.0	0	0	0	0	0
Week 24	286	3.3	122.3	-1178	480	-36	39	3
Week 48	340	-2.9	123.5	-1151	550	-42	42	2
Week 96	314	-8.4	131.3	-1252	527	-51	38	-2
2nd/3rd-line therapy								
Baseline	166	0.0	0.0	0	0	0	0	0
Week 24	113	4.1	113.4	-304	625	-39	45	3
Week 48	145	-13.6	112.6	-528	604	-58	38	-8
Week 96	129	4.1	125.5	-433	546	-38	43	1
>3rd-line therapy								
Baseline	292	0.0	0.0	0	0	0	0	0
Week 24	199	-28.1	241.3	-2353	1338	-64	38	-5
Week 48	234	-22.0	257.8	-3149	687	-50	34	-9
Week 96	209	-1.0	189.0	-1123	954	-44	53	-3
Therapy not classified								
Baseline	177	0.0	0.0	0	0	0	0	0
Week 24	103	-0.9	113.1	-495	457	-50	32	0
Week 48	121	-14.9	109.6	-419	690	-56	20	-20
Week 96	105	16.5	151.6	-274	1033	-50	56	-13
Total								
Baseline	1048	0.0	0.0	0	0	0	0	0
Week 24	701	-6.1	163.3	-2353	1338	-45	39	1
Week 48	840	-11.8	169.1	-3149	690	-49	39	-5
Week 96	757	-0.8	151.2	-1252	1033	-47	44	-3

Table 22: Total cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Total cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	410	204.6	45.0	92	385	174	233	202
Week 24	294	210.0	45.4	113	367	180	239	203
Week 48	350	208.2	40.8	93	352	181	231	205
Week 96	330	208.0	43.0	103	407	180	234	205
2nd/3rd-line therapy								
Baseline	166	214.0	47.5	110	491	186	239	211
Week 24	118	209.5	46.4	104	462	179	234	211
Week 48	152	212.4	43.0	100	321	183	242	212
Week 96	138	213.0	45.0	111	388	188	243	209
>3rd-line therapy								
Baseline	290	209.1	51.9	108	572	174	240	209
Week 24	203	209.4	51.0	120	441	174	235	201
Week 48	242	207.4	43.0	119	353	175	233	207
Week 96	216	214.0	47.3	113	446	183	243	213
Therapy not classified								
Baseline	179	204.8	44.1	106	385	174	232	201
Week 24	105	203.8	47.2	108	419	174	231	201
Week 48	127	207.4	40.1	126	330	175	237	203
Week 96	111	212.6	50.2	123	494	182	239	205
Total								
Baseline	1045	207.4	47.3	92	572	176	236	205
Week 24	720	208.8	47.4	104	462	178	236	203
Week 48	871	208.6	41.7	93	353	180	236	206
Week 96	795	211.1	45.6	103	494	182	238	208

Table 23: Change in total cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in Total cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	410	0.0	0.0	0	0	0	0	0
Week 24	284	2.5	30.4	-155	125	-16	21	1
Week 48	337	3.1	30.4	-159	109	-12	21	4
Week 96	313	3.4	33.5	-143	191	-13	23	3
2nd/3rd-line therapy								
Baseline	166	0.0	0.0	0	0	0	0	0
Week 24	112	0.6	26.8	-54	78	-20	21	-3
Week 48	145	-1.4	31.6	-170	87	-19	16	-2
Week 96	131	-0.7	38.2	-222	119	-21	20	1
>3rd-line therapy								
Baseline	290	0.0	0.0	0	0	0	0	0
Week 24	198	1.5	41.4	-195	231	-17	17	3
Week 48	234	-2.8	39.4	-284	111	-18	17	0
Week 96	209	3.9	36.4	-124	109	-17	25	4
Therapy not classified								
Baseline	179	0.0	0.0	0	0	0	0	0
Week 24	103	0.3	31.1	-82	175	-15	11	-3
Week 48	122	0.4	30.2	-101	85	-14	19	0
Week 96	106	6.2	41.3	-94	275	-12	24	2
Total								
Baseline	1045	0.0	0.0	0	0	0	0	0
Week 24	697	1.6	33.4	-195	231	-17	19	0
Week 48	838	0.3	33.4	-284	111	-16	19	2
Week 96	759	3.2	36.3	-222	275	-16	23	3

Table 24: LDL cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

LDL cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	358	122.6	38.6	21	300	96	146	121
Week 24	257	125.3	39.7	31	259	100	148	121
Week 48	302	125.8	35.1	28	253	100	146	125
Week 96	282	126.9	38.6	35	315	101	150	123
2nd/3rd-line therapy								
Baseline	144	127.8	37.3	32	254	105	147	127
Week 24	99	125.7	35.9	43	221	99	155	128
Week 48	125	130.8	36.5	43	223	110	155	131
Week 96	114	131.0	43.1	34	303	103	156	124
>3rd-line therapy								
Baseline	249	118.7	36.1	36	263	94	141	120
Week 24	166	123.6	41.9	27	250	95	154	117
Week 48	189	123.4	37.3	50	211	97	147	121
Week 96	179	130.0	40.8	36	241	103	154	126
Therapy not classified								
Baseline	133	119.5	33.2	50	204	91	146	119
Week 24	68	121.8	38.7	51	223	96	147	117
Week 48	92	122.8	33.1	57	237	97	147	124
Week 96	76	125.8	35.1	51	217	100	147	123
Total								
Baseline	884	121.9	37.0	21	300	97	145	121
Week 24	590	124.5	39.5	27	259	97	150	121
Week 48	708	125.7	35.7	28	253	100	148	125
Week 96	651	128.4	39.6	34	315	102	152	124

Table 25: Change in LDL cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in LDL cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	358	0.0	0.0	0	0	0	0	0
Week 24	244	0.9	24.6	-118	96	-13	15	-1
Week 48	284	2.0	27.6	-129	81	-14	17	4
Week 96	262	3.5	28.5	-91	188	-13	21	2
2nd/3rd-line therapy								
Baseline	144	0.0	0.0	0	0	0	0	0
Week 24	91	2.3	26.2	-91	113	-12	17	0
Week 48	117	1.1	27.8	-72	137	-14	15	-1
Week 96	105	2.8	31.5	-127	90	-12	21	4
>3rd-line therapy								
Baseline	249	0.0	0.0	0	0	0	0	0
Week 24	159	6.5	28.1	-89	111	-10	18	6
Week 48	179	2.6	26.2	-100	88	-11	18	2
Week 96	170	7.4	31.6	-134	96	-9	23	5
Therapy not classified								
Baseline	133	0.0	0.0	0	0	0	0	0
Week 24	63	2.1	25.9	-65	103	-13	19	0
Week 48	83	1.9	27.4	-90	67	-9	15	2
Week 96	67	6.5	26.4	-48	95	-10	23	4
Total								
Baseline	884	0.0	0.0	0	0	0	0	0
Week 24	557	2.9	26.1	-118	113	-12	16	2
Week 48	663	2.0	27.2	-129	137	-13	16	2
Week 96	604	4.8	29.7	-134	188	-11	21	4

Table 26: HDL cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

HDL cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	361	48.3	15.3	10	119	38	56	45
Week 24	258	50.0	15.7	20	125	39	57	46
Week 48	302	50.2	16.0	12	121	40	58	47
Week 96	286	49.9	15.1	15	117	39	58	48
2nd/3rd-line therapy								
Baseline	146	51.2	18.7	22	146	38	61	48
Week 24	101	49.1	16.8	20	102	38	56	46
Week 48	128	51.7	18.9	22	143	39	59	49
Week 96	115	50.7	18.7	12	150	40	57	48
>3rd-line therapy								
Baseline	254	46.8	14.5	21	132	36	54	45
Week 24	166	46.7	15.6	17	140	36	54	44
Week 48	194	46.2	14.8	19	138	36	54	44
Week 96	183	46.7	13.6	21	117	36	56	46
Therapy not classified								
Baseline	136	49.1	15.0	22	101	40	59	46
Week 24	68	49.3	16.5	18	109	40	56	47
Week 48	92	51.3	15.0	27	91	40	62	49
Week 96	77	49.6	16.0	13	86	37	60	48
Total								
Baseline	897	48.5	15.7	10	146	38	57	46
Week 24	593	48.8	16.0	17	140	38	56	45
Week 48	716	49.5	16.2	12	143	38	58	47
Week 96	661	49.1	15.6	12	150	38	58	47

Table 27: Change in HDL cholesterol [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in HDL cholesterol [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	361	0.0	0.0	0	0	0	0	0
Week 24	246	1.3	9.1	-38	58	-3	5	1
Week 48	285	2.3	10.1	-56	49	-3	7	2
Week 96	266	2.6	11.9	-74	58	-3	8	2
2nd/3rd-line therapy								
Baseline	146	0.0	0.0	0	0	0	0	0
Week 24	93	-0.9	9.6	-53	30	-5	3	-1
Week 48	120	1.2	11.1	-59	51	-3	6	0
Week 96	106	0.0	12.1	-51	32	-6	6	0
>3rd-line therapy								
Baseline	254	0.0	0.0	0	0	0	0	0
Week 24	161	0.0	7.6	-19	33	-4	3	0
Week 48	185	-0.6	8.0	-26	21	-5	4	0
Week 96	175	-0.1	10.1	-26	51	-5	3	-1
Therapy not classified								
Baseline	136	0.0	0.0	0	0	0	0	0
Week 24	65	-0.7	13.7	-51	61	-6	6	1
Week 48	84	1.7	10.2	-36	43	-5	8	1
Week 96	70	1.0	11.5	-54	26	-5	8	2
Total								
Baseline	897	0.0	0.0	0	0	0	0	0
Week 24	565	0.4	9.5	-53	61	-4	5	0
Week 48	674	1.2	9.8	-59	51	-4	6	1
Week 96	617	1.2	11.4	-74	58	-4	6	1

LIVER

Table 28: AST (SGOT) [U/L] at baseline, week 24, 48 and 96, overall and stratified by therapy line

AST (SGOT) [U/L]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	443	32.5	18.0	12	172	24	35	28
Week 24	325	34.9	42.2	13	688	24	35	28
Week 48	378	32.3	19.5	11	179	24	33	28
Week 96	353	29.8	15.9	2	182	23	31	27
2nd/3rd-line therapy								
Baseline	172	32.5	13.2	13	110	25	36	29
Week 24	122	33.2	11.8	14	82	26	38	31
Week 48	156	34.5	16.6	15	143	26	38	30
Week 96	145	33.2	17.2	10	113	24	36	28
>3rd-line therapy								
Baseline	302	34.6	16.5	11	176	25	38	31
Week 24	210	35.0	19.4	11	238	26	39	31
Week 48	254	34.1	15.5	9	130	25	38	30
Week 96	230	32.8	25.1	13	325	23	35	28
Therapy not classified								
Baseline	194	33.1	17.6	15	155	24	35	29
Week 24	111	32.3	13.2	14	93	25	35	31
Week 48	134	31.3	10.8	14	76	24	34	29
Week 96	120	30.7	18.0	8	201	24	34	28
Total								
Baseline	1111	33.2	16.9	11	176	24	36	29
Week 24	768	34.3	30.1	11	688	25	36	30
Week 48	922	33.0	16.9	9	179	24	35	29
Week 96	848	31.3	19.3	2	325	23	34	28

Table 29: Change in AST (SGOT) [U/L] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in AST (SGOT) [U/L]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	443	0.0	0.0	0	0	0	0	0
Week 24	323	2.7	33.5	-94	525	-4	4	1
Week 48	373	0.9	17.2	-94	146	-4	3	0
Week 96	351	-1.8	16.4	-98	127	-6	2	-2
2nd/3rd-line therapy								
Baseline	172	0.0	0.0	0	0	0	0	0
Week 24	119	1.1	8.5	-47	32	-3	4	1
Week 48	151	1.2	12.0	-57	79	-4	4	1
Week 96	141	0.2	14.0	-39	73	-6	4	-2
>3rd-line therapy								
Baseline	302	0.0	0.0	0	0	0	0	0
Week 24	210	0.4	20.9	-139	206	-4	5	0
Week 48	252	-0.8	15.4	-142	75	-4	4	0
Week 96	229	-1.7	25.3	-150	270	-8	2	-2
Therapy not classified								
Baseline	194	0.0	0.0	0	0	0	0	0
Week 24	110	-1.4	18.6	-123	40	-4	4	0
Week 48	132	-1.7	17.7	-132	30	-3	3	0
Week 96	118	-2.8	22.8	-133	140	-6	4	-1
Total								
Baseline	1111	0.0	0.0	0	0	0	0	0
Week 24	762	1.2	25.6	-139	525	-4	4	1
Week 48	908	0.1	16.0	-142	146	-4	4	0
Week 96	839	-1.6	19.8	-150	270	-7	3	-2

Table 30: ALT (SGPT) [U/L] at baseline, week 24, 48 and 96, overall and stratified by therapy line

ALT (SGPT) [U/L]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	446	36.0	29.2	8	270	20	41	27
Week 24	329	41.3	71.0	8	1137	21	43	28
Week 48	383	38.0	46.7	8	610	21	40	29
Week 96	361	35.2	27.4	9	270	21	39	29
2nd/3rd-line therapy								
Baseline	172	35.9	24.1	11	164	22	40	29
Week 24	124	38.7	24.3	10	131	23	47	31
Week 48	159	40.5	33.6	9	318	22	46	31
Week 96	147	37.9	24.4	10	171	22	44	31
>3rd-line therapy								
Baseline	297	40.0	26.3	6	187	24	49	32
Week 24	209	39.8	28.6	13	266	22	49	31
Week 48	254	39.3	27.2	10	232	24	45	32
Week 96	232	39.9	39.6	10	524	24	43	33
Therapy not classified								
Baseline	194	38.0	43.5	10	425	21	39	30
Week 24	111	33.8	17.0	10	126	21	40	31
Week 48	135	32.6	16.1	8	115	21	39	30
Week 96	121	33.3	20.9	5	209	22	40	30
Total								
Baseline	1109	37.4	30.8	6	425	22	42	29
Week 24	773	39.4	50.1	8	1137	22	45	30
Week 48	931	38.0	36.5	8	610	22	41	30
Week 96	861	36.6	30.1	5	524	22	41	30

Table 31: Change in ALT (SGPT) [U/L] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in ALT (SGPT) [U/L]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	446	0.0	0.0	0	0	0	0	0
Week 24	326	4.5	57.1	-173	867	-5	7	1
Week 48	377	3.5	46.2	-199	591	-5	6	0
Week 96	358	0.1	27.0	-200	195	-6	7	0
2nd/3rd-line therapy								
Baseline	172	0.0	0.0	0	0	0	0	0
Week 24	120	4.2	16.8	-52	82	-3	9	1
Week 48	151	3.7	27.2	-125	248	-3	8	2
Week 96	140	1.1	24.8	-122	128	-6	8	0
>3rd-line therapy								
Baseline	297	0.0	0.0	0	0	0	0	0
Week 24	205	-1.5	23.0	-139	138	-7	5	0
Week 48	247	-2.2	21.6	-152	116	-7	6	-1
Week 96	226	-1.0	35.5	-152	396	-10	6	-2
Therapy not classified								
Baseline	194	0.0	0.0	0	0	0	0	0
Week 24	110	-5.9	48.2	-351	61	-6	6	1
Week 48	132	-6.3	46.8	-390	53	-6	5	0
Week 96	118	-6.4	52.2	-380	167	-7	7	-1
Total								
Baseline	1109	0.0	0.0	0	0	0	0	0
Week 24	761	1.3	43.9	-351	867	-5	6	0
Week 48	907	0.5	38.3	-390	591	-5	6	0
Week 96	842	-0.9	33.7	-380	396	-7	7	0

GLUCOSE

Table 32: Glucose [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Glucose [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	430	91.6	20.0	50	292	82	96	90
Week 24	309	90.9	15.3	46	168	83	97	90
Week 48	365	91.4	21.6	56	301	81	97	88
Week 96	342	89.1	16.1	49	189	80	96	88
2nd/3rd-line therapy								
Baseline	172	94.0	20.1	55	178	83	100	90
Week 24	119	92.5	22.5	53	238	83	99	90
Week 48	156	95.9	21.8	47	184	83	103	90
Week 96	141	93.9	24.7	52	271	81	101	90
>3rd-line therapy								
Baseline	295	96.2	31.0	45	336	81	100	90
Week 24	205	98.9	33.6	59	295	82	105	91
Week 48	249	97.6	25.9	44	219	83	104	92
Week 96	216	95.2	29.9	42	309	80	102	89
Therapy not classified								
Baseline	179	94.1	20.2	52	170	83	101	91
Week 24	110	97.0	29.0	53	246	83	101	90
Week 48	131	92.7	20.3	59	189	80	99	90
Week 96	116	92.2	38.7	43	426	79	97	86
Total								
Baseline	1076	93.7	23.6	45	336	82	99	90
Week 24	743	94.3	25.0	46	295	83	100	91
Week 48	901	94.1	22.8	44	301	82	100	90
Week 96	815	92.0	25.8	42	426	80	98	88

Table 33: Change in glucose [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in Glucose [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	430	0.0	0.0	0	0	0	0	0
Week 24	302	-0.2	18.5	-176	57	-8	8	1
Week 48	353	-0.5	18.9	-88	173	-9	7	-1
Week 96	332	-1.9	17.5	-127	48	-11	8	-1
2nd/3rd-line therapy								
Baseline	172	0.0	0.0	0	0	0	0	0
Week 24	116	-0.3	22.9	-100	81	-9	9	-1
Week 48	150	1.4	20.6	-88	72	-9	12	0
Week 96	136	-0.7	26.0	-85	179	-11	7	-2
>3rd-line therapy								
Baseline	295	0.0	0.0	0	0	0	0	0
Week 24	202	0.9	19.9	-101	80	-6	10	1
Week 48	242	1.4	25.2	-244	95	-8	13	2
Week 96	212	-0.9	20.2	-115	126	-9	8	0
Therapy not classified								
Baseline	179	0.0	0.0	0	0	0	0	0
Week 24	105	2.5	23.2	-70	116	-8	13	1
Week 48	123	-2.0	19.0	-63	67	-11	9	0
Week 96	109	-1.5	36.8	-68	317	-14	7	-4
Total								
Baseline	1076	0.0	0.0	0	0	0	0	0
Week 24	725	0.5	20.4	-176	116	-8	10	1
Week 48	868	0.2	21.2	-244	173	-9	9	0
Week 96	789	-1.3	23.2	-127	317	-11	7	-2

CREATININE

Table 34: Creatinine [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Creatinine [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	441	0.9	0.2	0.5	2.1	0.8	1.0	0.9
Week 24	329	0.9	0.2	0.5	2.0	0.8	1.0	0.9
Week 48	382	0.9	0.2	0.4	2.2	0.8	1.0	0.9
Week 96	360	1.0	0.2	0.5	2.3	0.8	1.1	0.9
2nd/3rd-line therapy								
Baseline	175	0.9	0.2	0.5	1.6	0.8	1.0	0.9
Week 24	124	0.9	0.2	0.5	1.5	0.8	1.0	0.9
Week 48	157	0.9	0.2	0.5	1.7	0.8	1.0	0.9
Week 96	145	0.9	0.2	0.4	1.6	0.8	1.0	0.9
>3rd-line therapy								
Baseline	301	1.0	0.2	0.5	2.2	0.8	1.1	0.9
Week 24	211	1.0	0.2	0.5	1.9	0.8	1.1	1.0
Week 48	252	1.0	0.3	0.5	2.8	0.8	1.1	1.0
Week 96	229	1.0	0.3	0.5	2.9	0.8	1.1	1.0
Therapy not classified								
Baseline	189	1.0	0.4	0.5	4.1	0.8	1.0	0.9
Week 24	112	1.0	0.8	0.6	7.7	0.8	1.1	0.9
Week 48	135	1.0	0.7	0.6	8.3	0.8	1.1	1.0
Week 96	121	1.0	0.3	0.6	3.5	0.8	1.1	0.9
Total								
Baseline	1106	0.9	0.2	0.5	4.1	0.8	1.0	0.9
Week 24	776	0.9	0.3	0.5	7.7	0.8	1.1	0.9
Week 48	926	1.0	0.3	0.4	8.3	0.8	1.1	0.9
Week 96	855	1.0	0.2	0.4	3.5	0.8	1.1	0.9

Table 35: Change in creatinine [mg/dL] at baseline, week 24, 48 and 96, overall and stratified by therapy line

Change in Creatinine [mg/dL]	N	Mean	SD	Min	Max	25th Percentile	75th Percentile	Median
1st-line therapy								
Baseline	441	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week 24	325	-0.01	0.10	-0.40	0.30	-0.08	0.04	0.00
Week 48	373	0.01	0.13	-0.43	1.19	-0.06	0.09	0.00
Week 96	353	0.03	0.15	-0.50	1.29	-0.06	0.10	0.02
2nd/3rd-line therapy								
Baseline	175	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week 24	121	-0.02	0.12	-0.27	0.50	-0.10	0.06	-0.01
Week 48	153	0.01	0.11	-0.36	0.33	-0.06	0.10	0.00
Week 96	141	0.02	0.14	-0.33	0.67	-0.08	0.10	0.00
>3rd-line therapy								
Baseline	301	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week 24	210	0.01	0.11	-0.44	0.44	-0.04	0.07	0.00
Week 48	249	0.02	0.13	-0.30	0.61	-0.07	0.10	0.00
Week 96	227	0.04	0.14	-0.30	0.71	-0.07	0.10	0.00
Therapy not classified								
Baseline	189	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week 24	107	0.03	0.54	-0.74	5.30	-0.10	0.06	0.00
Week 48	130	0.05	0.53	-0.40	5.90	-0.08	0.10	0.01
Week 96	117	0.01	0.19	-1.24	0.48	-0.05	0.10	0.03
Total								
Baseline	1106	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week 24	763	0.00	0.22	-0.74	5.30	-0.08	0.06	0.00
Week 48	905	0.02	0.23	-0.43	5.90	-0.06	0.10	0.00
Week 96	838	0.03	0.15	-1.24	1.29	-0.07	0.10	0.01

Study Limitations:

The observational, non-interventional design of the study was mandatory to meet the primary study objective, i.e. evaluation of direct and indirect costs associated with routine clinical care of HIV patients in Germany. In contrast to randomized clinical trials, assignment of a patient to a particular antiretroviral regimen was at the discretion of the treating physician. Therefore evaluation of efficacy and safety could only be descriptive for the different treatment strata.

CONCLUSION(S):

CORSAR started recruitment during 2009 and ended after the last patient had reached week 96 in July 2012. This large observational cohort included 1149 patients from 8 outpatient and 4 inpatient centers in Germany.

40% of patients were on 1st-line HAART at the time of enrolment, 16% of patients were on 2nd- or 3rd-line HAART and 26% of patients on 4th- or further-line HAART. Most patients received a NRTI+PI (41%) based regimen or a NRTI+NNRTI (41%) based regimen. Patients on 1st-line HAART were younger (44 years) than patients on 2nd- or 3rd-line HAART (48 years) or patients on 4th- or further-line HAART (48 years). The majority of the patients were men (88.7%).

Overall, 23% of patients changed HAART regimen at least once during follow–up. Most common reasons for HAART changes were side effects, patient's wish and virological failure. Treatment interruptions were only in patients on 1st-line HAART.

More than 90% of patients had a HIV-a RNA <50 copies/mL at the various time points during follow-up reflecting a good virological control in patients treated in HIV-specialized centers in Germany.

Most patients were "responders" (76.3%), only 1.4% were "non-responders (>50)", and 1.6% "non-responders (>200)", but in 15% of patients HIV-1 RNA was at one time >200 copies/mL and/or between 50-200 copies/mL without any HAART change.

In addition to a good virological response, immunological control was very successful. CD4 cell counts were >500/µL in 54% of patients at enrollment and in 64% of patients at week 96.

Overall, the laboratory safety parameters were stable and did not shown any deterioration. 51% of patients experienced at least one AE, and 20% of patients at least one SAE.

The safety of DRV or ETR in patients of the Corsar study was within expected ranges. No new unexpected adverse events were observed which could affect the safety profile of DRV or ETR.