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Similar efficacy and tolerability of raltegravir-based antiretroviral therapy in HIV-infected patients, irrespective of age group, burden of comorbidities and concomitant medication: Real-life analysis of the German 'WIP' cohort

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Abstract

Only limited efficacy and tolerability data on raltegravir (RAL) use are currently available. Study objectives were to describe the efficacy and tolerability profile of RAL-based antiretroviral therapy (ART) in routine clinical practice in Germany. The WIP study (WIP = "Wirksamkeit von Isentress unter Praxisbedingungen", Efficacy of Isentress under routine clinical conditions) was a prospective, multi-centre cohort study in Germany. Human immunodeficiency virus (HIV)-infected patients aged ≥ 18 years in whom combinational ART with RAL 400 mg BID was indicated were enrolled. The primary endpoint was virologic response (HIV-RNA <50 copies/mL; non-completion equals failure) after 48 weeks. Of 451 patients, 85.1% (n = 384) were still receiving RAL at week 48. At baseline (BL), the prevalence of concomitant diseases was higher in patients of the age group ≥50 years (94.2% vs. 75.7%) as well as concomitant medications (74.8 % vs. 55.4%). Virologic response at week 48 was 74.7% (overall), 75.0% (naïve at BL), 81.5% (suppressed at BL), 47.1% (interrupted previous treatment at BL) and 64.9% (failing at BL), without significant differences by age group. A significant correlation of achievement of HIV-RNA <50 copies/mL was seen with treatment status at BL ($p = 0.004$). In addition, 77.3 % of the patients with a CD4 cell count >200 cells/μL at BL achieved HIV-RNA <50 copies/mL ($p = 0.029$). RAL was well tolerated with 80 adverse events (AEs) in 49 patients (10.9%) and 8 serious AEs (SAEs) in 6 patients (1.3%) reported to be drug related. A total of 22 patients (4.9%) discontinued treatment due to AEs. The WIP study shows that the previously reported efficacy and safety profile of RAL can be achieved in a population with multiple comorbidities and comedications, with no major difference observed in ageing patients (≥50 years) vs. younger patients. RAL is therefore an attractive treatment option in routine medical care in Germany.

Keywords

Antiviral, ART, HIV, integrase

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Background

Raltegravir (RAL)-based antiretroviral therapy (ART) has been shown to be an effective and well-tolerated treatment option for treatment-naïve and -experienced HIV-infected patients in a broad range of major clinical studies. RAL-based therapy has a low potential to induce drug–drug interactions (DDI), due to its beneficial elimination pathway (mainly through UGT1A1-mediated glucuronidation in the liver)[1] and also because

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it does not require pharmacological boosting with ritonavir or cobicistat, in contrast to the boosted integrase inhibitor elvitegravir.[2] The pharmacological profile of the integrase inhibitor dolutegravir (DTG) differs also from RAL as DTG interacts with organic cation transporter 2 and multidrug and toxin extrusion transporter 1.[3]

The antiviral efficacy results observed in the clinical development program after 48 weeks were 86% in ART-naïve (STARTMRK),[4] 89% in virologically suppressed patients who switched to RAL (SPIRAL),[5] and 62% in treatment-experienced individuals (BENCHMRK).[6] However, real-world evidence increasingly influences medical decision making and clinical trial data need to be confirmed in routine clinical practice representing a more heterogeneous population.

Only limited efficacy and tolerability data on RAL use are currently available for routine clinical care of HIV in Germany. The healthcare system in Germany differs somewhat from that of other European countries or the United States. In Germany, HIV care is provided mostly through specialized physicians in office-based private practices, while in other countries it is applied often through outpatient clinics at hospitals.

Cohort analyses conducted in the United States, Brazil, and South Africa reported slightly lower efficacy outcomes than the clinical development program. In the US HIV Outpatient Study cohort with three years of follow-up, 76% of RAL-experienced and 63% of RAL-naïve participants achieved HIV RNA <50 copies/mL with RAL-based regimens.[7] In the REALMRK cohort study conducted in the US, Brazil, Dominican Republic, Jamaica, and South Africa, the antiviral efficacy endpoint at 48 weeks was achieved by 76% of treatment-naïve patients, 64% of patients who had been failing prior therapy, and 76% of patients who were intolerant to prior therapy.[8] Nevertheless, differences in the baseline characteristics (lower mean CD4 cell count, more females, and different ethnic distribution and healthcare situation) compared with the German HIV population make it difficult to apply these efficacy data to a German setting.

The objectives of this study were to describe the efficacy and safety profile of RAL-based ART in routine clinical practice in Germany and discuss this in the context of the findings from the clinical development program of RAL and recent cohort studies. It was of special interest to gather in-depth information about the efficacy of RAL in a cohort representing the growing subpopulation of aging patients also characterized by a high prevalence of comorbidities and concomitant medication and an increased risk of DDIs. This analysis reports data on the 48-week observation period and compares outcomes and tolerability by age strata (<50 and ≥50 years). The proportion of patients above 50 years in Germany has been increasing over the last years and is currently about one third,[9] but expected to grow up to 50% until 2020.

Methods

The WIP study (''Wirksamkeit von Isentress unter Praxisbedingungen'', Efficacy of Isentress under routine clinical conditions) was a prospective, observational, multicentre cohort study in routine clinical care in Germany. A total of 52 sites (comprising of general practitioners, internists, dermatologists, infectious disease specialists, gynaecologists and hospital-based HIV-specialists) participated in this non-interventional study.

Patients were eligible to participate if aged ≥ 18 years (enrolment phase 1 from April 2010 to January 2011) or ≥50 years (enrolment phase 2 from November 2012 to April 2014) with a confirmed HIV-1 infection in whom ART with RAL was indicated according to the RAL product information.[1] Patients were treated with 400 mg RAL BID in combination with other antiretrovirals as prescribed by the treating physician. Patients already treated with RAL were only eligible if treatment with RAL had been started ≤6 months prior to enrolment.

Observation time points were at baseline (BL), weeks 4, 12, 24, 36 and 48. BL was defined as the time point of the start of RAL treatment. The present analysis reports the 48-week results of the combined cohort (enrolment phases 1 and 2).

The primary endpoint was virologic response defined as HIV-RNA <50 copies/mL after 48 weeks using the ''Non-Completer = Failure (NC = F)'' approach. Failure was defined as HIV-RNA ≥50 copies/mL (retest and confirmation of HIV RNA ≥50 copies/mL was not required) or early discontinuation during the observation period for any reason. The analysis did not include the history of viral blips in subjects reaching the endpoint of HIV-RNA <50 copies/mL after 48 weeks. Reasons for early discontinuation were classified as: lack of efficacy, AEs, poor compliance, switch for unknown reasons or reasons unrelated to RAL.

The subgroup analyses concerning efficacy were defined as follows:

- Patient age at start of treatment with RAL (<50 years vs. ≥50 years)
- Patient status before the start of treatment with RAL
  - No previous ART treatment (naïve)
  - Currently treated with virologic suppression (HIV RNA <50 copies/mL) (suppressed at BL)
  - Previously treated but currently interrupted for ≥3 months (interrupted at BL)
  - Currently treated without virologic suppression (HIV RNA ≥50 copies/mL) (failing at BL)

Concerning the evaluation of changes in HIV-1 RNA levels and CD4 cell counts between BL and the subsequent visits, the 'observed failure' (OF) approach was used. For patients who prematurely discontinued the therapy, missing values were replaced by the last available value (last value carried forward). Further endpoints were drug safety and tolerability.

Patient demographics, CD4 cell count, HIV-RNA, treatment history, comorbidities, concomitant medications and laboratory parameters were collected at BL. At weeks 4, 12, 24, 36 and 48, the following parameters were documented: current ART, newly prescribed concomitant medication, HIV-RNA, CD4 cell count and standard laboratory values and abnormalities, AEs and documentation of ongoing observation period, or reasons for discontinuation. Due to the observational nature of the study, data on drug resistance were limited and were not gathered systematically.

Parameters of potential influence on the endpoints were pre-specified as CD4 cell count ($\leq/>200$ cells/μL) at BL, patient status before start of RAL (naïve, suppressed at BL, interrupted at BL or failing at BL), number of antiretroviral substance classes ever used, age, sex and substance classes used in combination with RAL.

A multivariate statistical model was used to analyse the influence of these parameters on the primary endpoint (HIV-1 RNA level <50 copies/mL) at week 48. The logistic regression was calculated by the forward elimination method, eliminating parameters of potential bias stepwise from the model.

For the initial determination of the sample size, the response rates anticipated for this study were based on the response rates of the BENCHMRK-1 and -2 trials. Assuming an actual response rate of 57%, a one-tailed binomial test was used to calculate the minimum sample size required with a statistical significance of 90% to reject H0 in favour of HA at a level of 2.5% (i.e. the confidence interval for the response rate does not include 0.45 but is well above it). This corresponds to 189 patients.

The dropout rate for reasons not associated with medication (number of patients dropping out of the cohort study before the end of the specified follow-up period) was estimated to be 40%. This figure was based on experiences with other HIV studies. The minimum sample size for achieving the study objective was therefore set at 265 patients (189 patients completing treatment and 76 dropouts). No separate sample size calculation was performed for the combined analysis.

The primary patient population for the analysis of efficacy and safety comprised all patients with a signed informed consent form who had been prescribed and had taken at least one dose of RAL (full analysis set (FAS)). The per-protocol set consisted of all patients in the FAS with CD4 cell count and HIV-1 RNA levels available at the start of RAL therapy.

All statistical analyses were performed with the statistical program SAS (Statistical Analysis System, Version 8.2 for Windows).

The study was reviewed and approved by the Ethics Committee of the Bavarian State Medical Board. Written informed consent was obtained from every patient before the beginning of the observation period.

Results

The cohort included 451 patients. At week 48, 85.1% ($n = 384$) of patients were still receiving RAL. The patient disposition is described in Figure 1.

The mean observed duration of therapy was 333.7 ± 64.7 days. The median observed duration of ART with RAL was 344 days (range 25–511 days).

BL characteristics as well as concomitant diseases and concomitant medications at BL in >10% of patients in either age group are described in Table 1. The observational nature of this study and broad inclusion criteria led to a heterogeneous population regarding their ART history. The majority of the cohort was pre-treated with a mean duration of previous ART at BL of 8.6 years. At BL, concomitant diseases and concomitant medications were more frequent in subjects ≥50 years (258, 94.2% vs. 134, 75.7%). Most frequent comorbidities at BL were depression, other psychiatric disorders, hypertension and polyneuropathy.

Reasons for RAL-initiation were mainly intolerance to previous ART (180, 40%), clinical indication as first line ART (96, 21%) and lack of efficacy (81, 18%). RAL was mostly used in combination with NRTIs (289, 64%), followed by a PI/r (73, 16%) across all treatment groups (Figure 2).

Using the ''Non-Completer=Failure'' analysis, the proportion of patients with virologic response was 74.7% (overall), 75.0% (naïve at BL), 81.5% (suppressed at BL), 47.1% (interrupted previous treatment for ≥3 months at BL) and 64.9% (failing at BL), without significant differences by age group (Figure 3(a)). A multivariate statistical model showed that the virologic response at week 48 was significantly correlated with BL patient status (naïve, suppressed, failing or interrupted; $p = 0.004$) and CD4 cell count >200 cells/μL at BL ($p = 0.029$). All other observed parameters had a p-value greater than 10%.

A total of 67 patients (14.9%) discontinued RAL before week 48. Older patients discontinued RAL more often (17.2%, 47/274 vs. 11.3%, 20/177). Patients with a history of ART interruption at BL had the highest rate of discontinuations (4/17, 23.5%), followed by patients failing at BL (19/111, 17.1%). Patients suppressed at BL had the lowest rate

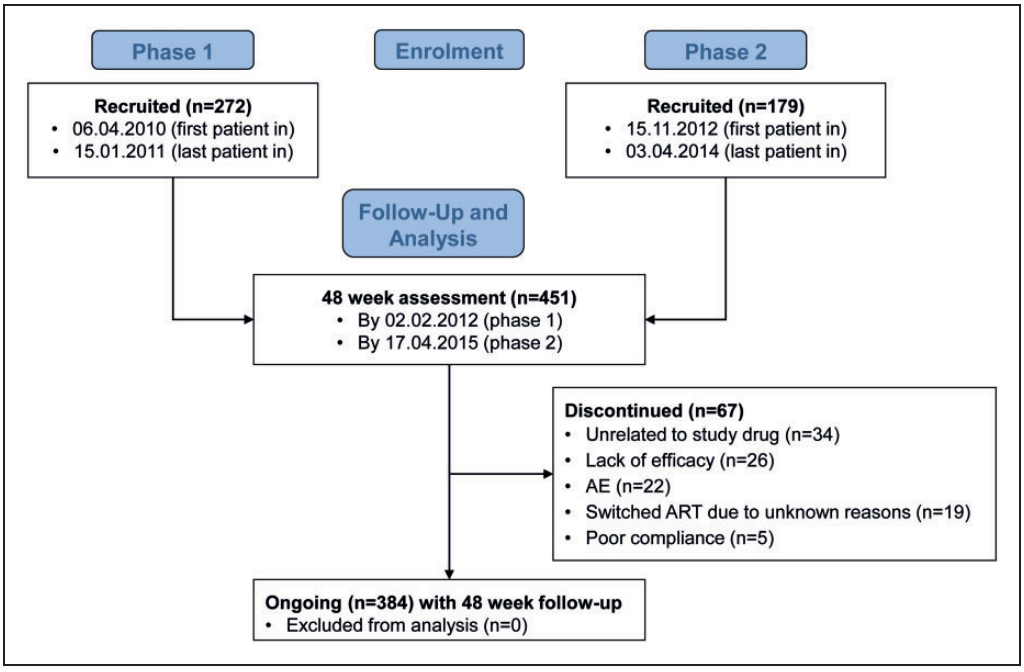


Figure 1. Study disposition.
AE: adverse event; ART: antiretroviral therapy.

Table 1. Baseline characteristics.

Baseline characteristics	<50 Years	≥50 Years	Total
	n = 177 (39.2%)	n = 274 (60.8%)	n = 451 (100%)
Mean age, years (SD)	39.6 (7.0)	58.0 (7.2)	50.8 (11.49)
Male, n (%)	149 (84.2%)	233 (85.0%)	382 (84.7%)
HIV diagnosed since (years), mean (SD)	7.4 (7.2)	12.5 (8.2)	10.5 (8.20)
Treatment-naïve, n (%)	59 (33.3%)	37 (13.5%)	96 (21.3%)
Pre-treated, n (%)			
• Suppressed (VL < 50 copies/mL)	63 (35.6%)	164 (59.9%)	227 (50.3%)
• Failing (VL ≥ 50 copies/mL)	46 (26%)	65 (23.7%)	111 (24.6%)
• Interrupted (paused for ≥3 months before start with RAL)	9 (5.1%)	8 (2.9%)	17 (3.8%)
CD4 cell count, cells/μL (median; range)	372 (8–1375)	476 (23–1668)	433 (8–1668)
• In treatment-naïve, cells/μL (median; range)	310 (8–892)	306 (26–754)	308 (8–892)
• In suppressed, cells/μL (median; range)	557 (40–1375)	538 (57–1668)	552 (40–1668)
• In failing, cells/μL (median; range)	419 (58–769)	465 (23–1582)	423 (23–1582)
• In interrupted, cells/μL (median; range)	310 (34–579)	396 (180–451)	353 (34–579)

Most prominent diseases in >10% of patients in at least one of the age groups

Prevalence of concomitant diseases, *n* (%)	<50 Years	≥50 Years	Total
	n = 134 (75.7%)	*n* = 258 (94.2%)	*n* = 392 (86.9%)
Hypertension	0	87 (31.8%)	87 (19.3%)
Depression	0	75 (27.4%)	75 (16.6%)
Polyneuropathy	12 (6.8%)	60 (21.9%)	72 (16.0%)

(continued)

Table 1. Continued.

Other psychiatric disorder[a]	53 (29.9%)	49 (17.9%)	102 (22.6%)
Other gastrointestinal disorders[b]	0	47 (17.2%)	47 (10.4%)
Hypercholesterolemia	0	46 (16.8%)	46 (10.2%)
Lipoatrophy	15 (8.5%)	45 (16.4%)	60 (13.3%)
Vitamin D deficiency	0	44 (16.1%)	44 (9.8%)
BL diabetes mellitus type 2	5 (2.8%)	43 (15.7%)	48 (10.6%)
Arterial disorder	19 (10.7%)	41 (15.0%)	60 (13.3%)
Sleep disorder	0	38 (13.9%)	38 (8.4%)
Combined hyperlipidaemia	0	34 (12.4%)	34 (7.5%)
Chronic hepatitis C	17 (9.6%)	33 (12.0%)	50 (11.1%)

Concomitant medication in >10% of patients in at least one of the age groups			
Concomitant medication used *n* (%)	<50 Years	≥50 Years	Total
	n = 98 (55.4%)	*n* = 205 (74.8%)	*n* = 303 (67.2%)
Renin-angiotensin system (RAS) acting agents	10 (5.6%)	73 (26.6%)	83 (18.4%)
Antithrombotics	6 (3.4%)	60 (21.9%)	66 (14.6%)
Drugs for acid-related disorders	23 (13.0%)	54 (19.7%)	77 (17.1%)
Lipid-lowering drugs	6 (3.4%)	53 (19.3%)	59 (13.1%)
Beta receptor blockers	6 (3.4%)	51 (18.6%)	57 (12.6%)
Psychoanaleptics	18 (10.2%)	40 (14.6%)	58 (12.9%)
Psycholeptics	8 (4.5%)	38 (13.9%)	46 (10.2%)
Antidiabetics	4 (2.3%)	30 (10.9%)	34 (7.5%)
Vitamins	16 (9.0%)	30 (10.9%)	46 (10.2%)
Antibiotics for systemic use	21 (11.9%)	17 (6.2%)	38 (8.4%)

[a]Excludes depression and sleep disorders, which were uniquely assessed.
[b]Excludes diarrhoea and reflux oesophagitis, which were uniquely assessed.

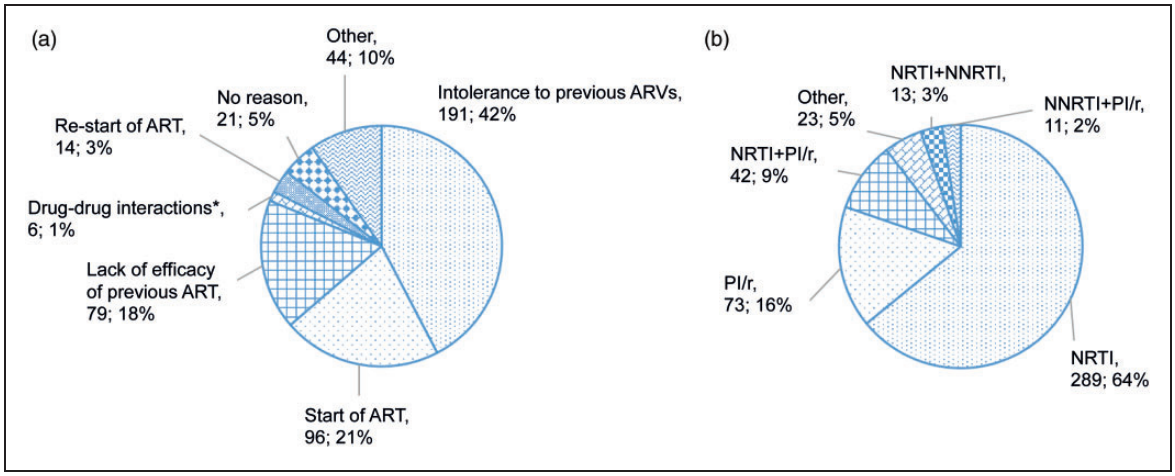
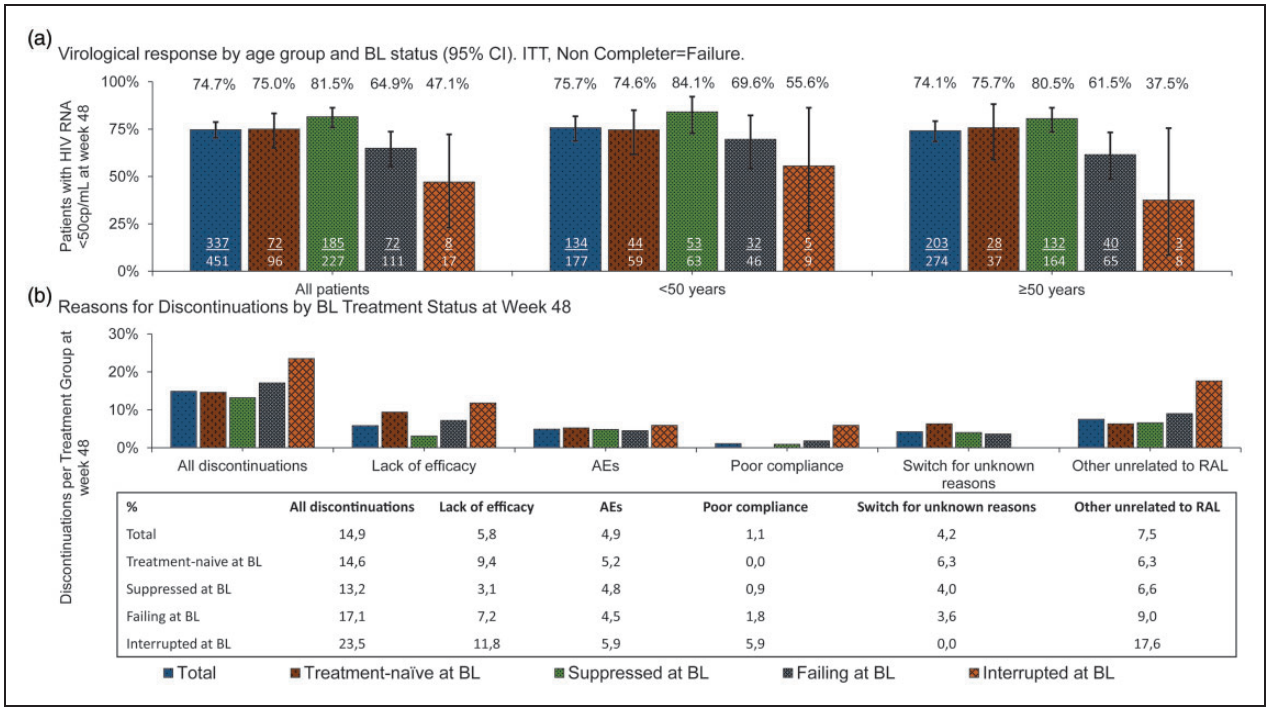


Figure 2. Reasons for RAL initiation (a) and ARVs used in combination with RAL (b); n (%).
RAL: raltegravir; ART; antiretroviral therapy; n: number; ARVs; antiretroviral drugs; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; P*V*r: ritonavir-boosted protease inhibitor.
*Added only during enrolment phase 2 enrichment of the cohort with patients aged ≥50 years).



%	All discontinuations	Lack of efficacy	AEs	Poor compliance	Switch for unknown reasons	Other unrelated to RAL
Total	14,9	5,8	4,9	1,1	4,2	7,5
Treatment-naive at BL	14,6	9,4	5,2	0,0	6,3	6,3
Suppressed at BL	13,2	3,1	4,8	0,9	4,0	6,6
Failing at BL	17,1	7,2	4,5	1,8	3,6	9,0
Interrupted at BL	23,5	11,8	5,9	5,9	0,0	17,6

Figure 3. Virological response by age group and BL status at week 48 (ITT, non-completer =Failure; 95% CI) (a) and discontinuations by BL treatment status at week 48 (b).
BL: baseline; CI: confidence interval; ITT: intent-to-treat; cp: copies; AEs: adverse events; RAL: raltegravir.

of discontinuations (30/227, 13.2%), while 14.6% (14/96) of naïve patients terminated the treatment during the study (Figure 3(b)).

With the possibility to report multiple reasons, the reasons for discontinuations were mostly unrelated to RAL in 34 (7.5%) patients, lack of efficacy in 26 (5.8%) and adverse events in 22 patients (4.9%). A total of 19 patients (4.2%) switched to another ART for unknown reasons, and 5 patients (1.1%) were discontinued due to poor compliance (Figure 3(b)).

The reasons for discontinuation by treatment status at BL were mainly unrelated to RAL (17.6% in interrupted at BL (3/17), 6.6% in suppressed at BL (15/227) and 9.0% in patients failing at BL (10/111)).

In naïve patients, the main reason for discontinuation was lack of efficacy (9/96, 9.4%).

The mean CD4 cell count increased from 482 at BL to 576 cells/μL at week 48.

AEs and SAEs were more frequent in subjects ≥50 years (Table 2). Most AEs were of mild or moderate intensity. Eighty AEs in 49 patients (10.9%) and 8 SAEs in 6 patients (1.3%) were classified as drug related.

Discussion

The results from this cohort study confirm that RAL-based regimens provide a high rate of efficacy with a good tolerability profile in routine clinical practice in Germany in naïve as well as in suppressed patients. Lower virologic efficacy was observed in patients failing prior ART and subjects with previous ART interruption. The major reasons for treatment discontinuations among these groups were unrelated to RAL treatment. This may indicate personal circumstances affecting successful treatment and increasing difficulties of staying on treatment.

There was no difference in efficacy by age strata between patients <50 years and older patients ≥50 years of age, despite a higher rate of concomitant diseases and concomitant medications at BL for patients aged ≥ 50 years.

RAL was well tolerated with low rates of adverse events. Most AEs were of mild or moderate intensity. Surprisingly, the percentage of AEs was only slightly higher for patients aged ≥ 50 years compared with younger subjects, possibly attributable to the low frequency of DDI between RAL and concomitant medications.

The suppression rates observed in previously failing patients were similar to the results from the clinical development program (62.1% BENCHMRK vs. 64.9% WIP). In treatment-naïve patients, the efficacy rates were slightly lower in this cohort analysis (86.1% STARTMRK vs. 75.0% WIP) (Supplementary Table S1).

Table 2. Clinical and laboratory adverse events by age group.

	Patients with AEs, n (%)		
	<50 Years, n = 177	≥50 Years, n = 274	Total, n = 451
Any AE (all grades)	61 (34.5%)	107 (39.1%)	168 (37.3%)
Any clinical AE	51 (28.8%)	81 (29.6%)	132 (29.3%)
Drug-related clinical AEs	14 (7.9%)	22 (8.0%)	36 (8.0%)
Serious clinical AEs	8 (4.5%)	21 (7.7%)	29 (6.4%)
Serious drug-related clinical AEs	1 (0.6%)	3 (1.1%)	4 (0.9%)
Non-serious drug-related clinical AEs	13 (7.3%)	19 (6.9%)	32 (7.1%)
Clinical AEs requiring discontinuations	6 (3.4%)	14 (5.1%)	20 (4.4%)
Deaths due to clinical AEs	2 (1.1%)	2 (0.7%)	4 (0.9%)
Any laboratory AE	16 (9.0%)	42 (15.3%)	58 (12.9%)
Drug-related laboratory AEs	2 (1.1%)	11 (4.0%)	13 (2.9%)
Serious laboratory AEs	2 (1.1%)	4 (1.5%)	6 (1.3%)
Serious drug-related laboratory AEs	0	2 (0.7%)	2 (0.4%)
Non-serious drug-related laboratory AEs	2 (1.1%)	10 (3.6%)	12 (2.7%)
Laboratory AEs requiring discontinuations	1 (0.6%)	3 (1.1%)	4 (0.9%)
Deaths due to laboratory AEs	0	0	0

Drug-related SAEs: Suicide attempt, gastric ulcer haemorrhage, increased triglycerides (n = 2), increased lipase, abnormal ECG, dizziness, depressed mood.
Deaths: Causes of deaths were considered unrelated to treatment and were: recurrent Non-Hodgkin's lymphoma, salivary gland cancer, glioblastoma and hepatic failure.

In a recently published retrospective cohort analysis, Jaeckle et al. reported a slightly lower virological response with HIV-RNA <50 copies/mL at week 48 in treatment-naïve patients compared with the findings in the WIP study (67.7% vs. 75.0%).[10] In addition, the same study reported 80% virologic suppression for 48 weeks using a dual-treatment combination of RAL plus a ritonavir-boosted protease inhibitor.

As expected, discontinuation rates were higher compared with the pivotal 48-week clinical trial data (14.9%, 67/451 WIP vs. 8.5%, 24/282 STARTMRK[11] vs. 5.2%, 24/462 BENCHMRK1+2[6]). A similar rate of discontinuations was recently seen in real-world data for DTG in the Dutch OLVG cohort (16.0%, 62/387[12] vs. 11.4%, 47/411 in SPRING-2[13] vs. 16%, 55/354 in SAILING[14]). Low rates of discontinuations due to intolerance to study drug were reported for RAL (32.8%, 22/67 in WIP), while 90.3% (56/62) were reported for DTG.[12] A cohort analysis of 1467 patients in British Columbia, Canada, reported higher adjusted adverse drug reactions/100 person-years, leading to therapy discontinuation for elvitegravir–cobicistat (4.5, 95% CI 1.7–12.1) and DTG (2.9, 95% CI 1.1–8.0) compared to RAL (1.6, 95% CI 0.6–4.1).[15] These observed tolerability differences in routine practice within the integrase inhibitor drug class might suggest the need for additional studies comparing integrase inhibitors' real-life safety and tolerability profiles.

Taken together, the overall efficacy of 74.7% and good tolerability and safety profile in the WIP study demonstrate high effectiveness of RAL in routine clinical care in Germany.

This is the first prospective observational cohort study that investigated the efficacy and safety of RAL in this context in Germany, with a special focus on patients aged ≥50 years. The results from routine clinical practice demonstrate high efficacy of RAL-based regimens and indicate that these regimens are appropriate for routine clinical care in Germany.

This study has the typical limitations of real-world studies: safety data might not have been as diligently recorded as in randomized clinical trials, the availability of resistance data is limited and the study only recruited patients on RAL-based regimens, which could have introduced some channelling bias and limits the insight into age-related differences in efficacy of other ART combinations. A recent literature analysis by Jourjy et al.[17] reported a slower immune recovery but better virologic suppression responses to ART in patients ≥50 years.[17]

The WIP cohort reflects the general German HIV+ population (male gender: 84.7% in WIP cohort vs. 82% national data of the Robert Koch Institute).[9] About one half of the WIP population is >50 years, which displays the advancing ageing in this setting during the next years.

The study results represent the special German setting of decentralized HIV care and thus may not be

generalizable to other European countries with a hospital-based outpatient HIV care setting. Nevertheless, the overall HIV population is aging, and thus ART regimens compatible with multiple concomitant medications are required.

The extensive studies of the DDI profile of RAL indicate that RAL is an important option for treating individuals with a high potential for DDIs and is thus not restricted to older patients, for example in individuals with malignancies, cardiovascular disease or hyperlipidaemia, metabolic disorders or on hormonal replacement therapies.

Conclusion

These observations show that the efficacy and tolerability profile of RAL as reported from the pivotal development program in naïve and pre-treated subjects is mirrored in routine clinical care in Germany. RAL has similar virologic efficacy in both a younger (<50 years) and an older population (≥50 years) with multiple comorbidities and concomitant medications. Together with the low risk for DDIs and thus the limited need for adjustments of RAL-based regimens and concomitant medication, RAL is an attractive option for treating HIV-infected individuals, regardless of age or concomitant medications.

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Declaration of conflicting interests

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Clinical trial registration

This study is registered at ClinicalTrials.gov: NCT01213316. https://clinicaltrials.gov/show/NCT01213316

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