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Pharmacokinetics and pharmacodynamics of the nucleoside sparing dual regimen containing rilpivirine plus darunavir/ritonavir in treatment-naïve HIV-1-infected individuals

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Background: We aimed at investigating the antiviral activity and the pharmacokinetics of the dual antiretroviral (ARV) combination of rilpivirine plus darunavir/ritonavir 25/800/100 mg once-daily in naïve HIV-1-infected individuals (NHII) with different baseline viral loads.
Settings: Pharmacokinetic/pharmacodynamics study in ARV-naïve HIV-infected individuals.
Methods: The primary endpoint was the number of NHII with HIV-RNA < 40 copies/mL at week 48. Secondary endpoints included rilpivirine/darunavir/ritonavir pharmacokinetics, HIV-RNA decay, and changes in ECG QT interval.
Results: Thirty-six individuals were enrolled, 18 with a baseline viral load < 100,000 copies/mL (group A) and 18 with a baseline viral load > 100,000 copies/mL (group B). All but 1 (HIV-RNA = 63 copies/mL) subjects achieved viral load < 50 copies/mL by week 36, and all at week 48. Median (range) HIV-RNA reduction (Log10 copies/mL) was 1.3 (0.6–1.9) over the first week, with no differences between groups A and B. Geometric mean and 95%CI rilpivirine C_{max}, C_{trough}, AUC were 183 (165–239), 114 (104–109) ng/mL, 2966 (2704–3820) ng h/mL. No QTcF interval changes were recorded.
Conclusions: rilpivirine/darunavir/ritonavir could be efficacious, with limited short-term toxicity in ARV-naïve patients. Although rilpivirine was co-administered with ritonavir, its exposure was within ranges measured during phase III trials.

Keywords: Dual antiretroviral therapy, Pharmacokinetics, HIV antiviral pharmacology, Rilpivirine, Darunavir

Background

Triple drug antiretroviral combination therapy (cART, containing two nucleoside analogs, NRTIs, and a third agent) is recommended by international guidelines for the treatment of HIV infection.[1] However, drug-sparing strategies, such as dual therapies, have been explored lately in numerous studies aiming at improving tolerability, adherence, and reducing toxicity and cost.[2–5]

Additionally, (i) the possible transmission of virus already containing resistance mutations, such that patients may have a viral genotype with less than optimal susceptibility to the commonly used NRTIs[1] (ii) the low genetic barrier of certain NRTIs like lamivudine (3TC) and the likelihood of some patients to harbor resistance to this or other NRTIs if they have a history of poor adherence,[6] and (iii) the rapidly increasing use of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based pre-exposure prophylaxis (PrEP) for HIV that may increase the development of resistance in individuals who seroconvert on PrEP,[7] are other important factors to consider when investigating optimal alternative cART.

Rilpivirine, is a HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) approved in Europe and the USA for treatment of therapy-naïve HIV-1 infected adult patients (with a viral load </= 100,000 copies/mL) in combination with other agents.[8,9] It primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system, therefore drugs that induce or inhibit CYP3A may affect its clearance.[10] The recommended dose of rilpivirine is 25 mg given once-daily, taken with a meal of at least 390 kcal.[8]

Darunavir, is a member of the protease inhibitor class. In treatment-naïve patients, the recommended darunavir dose is 800 mg with ritonavir (a potent inhibitor of CYP3A4) 100 mg once-daily taken with food.[11]

A phase I study investigating the drug interaction between rilpivirine dosed at 150 mg once-daily and

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darunavir/ritonavir in HIV-negative healthy volunteers showed an increase in rilpivirine pharmacokinetic parameters ranging between 80 and 180% with no changes in darunavir or ritonavir concentrations.[12]

However, data in adult antiretroviral-naïve patients living with HIV (PLWH) on the currently approved rilpivirine dose of 25 mg once-daily are lacking. Yet, a combination of rilpivirine and ritonavir-boosted darunavir could potentially form a once-daily NRTI-sparing treatment, as shown in a switch study by Maggiolo et al.[13] and in a study in adolescents by Foca et al.[14] Hence, this study investigated the antiviral activity, steady-state pharmacokinetics and safety of rilpivirine plus darunavir/ritonavir in therapy-naïve HIV-infected adults.

Methods

Participants

Written informed consent was obtained from PLWH (between December 2012 and February 2014), aged 18 to 65 years old, naïve to cART with a VL > 1000 copies/mL and a CD4 count > 50 cells/mm^3. As this was a pilot investigational study (where 15–20 patients per group were assumed to draw for relevant conclusions because of the intense pharmacokinetic/pharmacodynamics assessments), patients with CD4 counts < 200 cells/mm3 and viral loads above 100,000 copies/mL (see below) were included despite treatment guidelines recommendations.[1] Participants were excluded if they had significant acute or chronic psychiatric/medical illnesses that could have interfered with the ability of taking part in the study, anomalies and risk factors for QTc prolongation (QTc interval was calculated with the Fridericia's equation, QTcF) or clinical laboratory determinations; positive screens for hepatitis B/C; baseline transmitted resistance compromising rilpivirine (K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C, M230I, M230L) and darunavir (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) efficacy; use of other drugs known to interact with the study drugs (this was also checked throughout the 48-week study duration period).

Study design

This was a single-arm, open-label study approved by the City and East Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA), UK (EUdraCT – 2012-002663-10; Clinicaltrials.gov NCT01736761). Because of the pilot nature of the study, a sample size calculation was not performed.

Following recruitment of the first 10 participants with baseline viral loads below 100,000 copies/mL (group A), a protocol steering committee convened to review viral load responses over the first four weeks of therapy and to advise on whether to proceed with recruitment of participants with baseline viral loads above 100,000 copies/mL (group B).

After successful screening, participants were administered rilpivirine 25 mg plus darunavir/ritonavir 800/100 mg once-daily, and given weekly appointments until week 4 for drug concentration measurement (trough concentration, C_{trough}), HIV-RNA testing and resting ECG monitoring. At week 4, they were admitted to the research unit for 24 h pharmacokinetic sampling, blood was taken pre-dose, 1, 2, 4, 6, 8, 12, and 24 h post-dose. Follow-up appointments for safety laboratory test, viral load measurement and ECG monitoring were at weeks 6, 8, 10, 12, 24, 36, and 48 post-cART initiation.

On the pharmacokinetic day, the study medication was taken with a standardized breakfast (534 kcal) and 240 mL of water. Compliance with study drug administration was assessed by pill counting by the study staff throughout the study period.

Bioanalysis (drug plasma concentration measurement)

Blood samples were collected for the measurement of rilpivirine, darunavir, ritonavir concentrations into lithium heparin-containing blood tubes (6 mL) at each time point, protected from light and immediately inverted several times and then kept on ice or refrigerated until centrifugation. Within 30 min of blood collection, each blood sample was centrifuged for 10 min at 1200 g at 4 °C. Plasma was then aliquoted equally into three 2.0 mL tubes (light protected) and stored at –20 °C. Samples were shipped on dry ice to the Liverpool Bioanalytical Facility for analysis.

Plasma drug concentrations were determined using protein precipitation of analyte and stable isotope labeled internal standard using validated high-pressure liquid chromatography tandem mass spectrometry methods, as previously described.[15,16] The assay was validated over a calibration range of 15–15000 ng/mL (darunavir), 5–5000 ng/mL (ritonavir), and 0.5–400 ng/mL (rilpivirine). The accuracy (percentage bias) and precision (% coefficient of variation) were less than 15%.

Data analysis

All HIV-RNA for the studied subjects were transformed to the Log_{10} scale and a linear mixed model fitted, with the trend estimated using a cubic spline.

The calculated pharmacokinetic parameters for rilpivirine, darunavir, and ritonavir were the plasma concentration measured 24 h after the observed dose (C_{trough}), the maximum observed plasma concentration (C_{max}) and the area under the plasma concentration curve from 0 to

24 h ($AUC_{0\text{-}24}$). All pharmacokinetic parameters were calculated using actual blood sampling time and non-compartmental modeling techniques (WinNonlin Phoenix, version 6.1; Pharsight Corp., Mountain View, CA). Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (95% CI) were calculated for all pharmacokinetic parameters. Inter individual variability in drug pharmacokinetic parameters was expressed as a percentage coefficient of variation [CV, (standard deviation/mean) × 100].

Pearson correlation was used to investigate the presence of a relationship between rilpivirine exposure and QTc interval four weeks after drug initiation.

Results

Fifty-two PLWH and naïve to cART were screened for the study and 37 were enrolled. One subject withdrew for personal reasons, therefore 36 completed the study (Table 1). Thirty-five were males and 33 were Caucasian (two Indians and one Pakistani); median (range) age was 35 (21–58) years. Baseline median (range) CD4 count was 388 (170–1375) cells/mm^3. Pre-cART resistance testing showed that no patient had any resistance to NNRTIs or protease inhibitors, while four had baseline resistance to NRTIs expressed as a single thymidine analog mutation (TAM).

Viral load dynamics

Eighteen subjects had a baseline viral load below 100,000 copies/mL (group A) and 18 with a baseline viral load above 100,000 copies/mL (group B) at screening (Table 2). Viral load decay curve is illustrated in Figure 1. All but one (viral load = 63 copies/mL at week 36, baseline 36,769 copies/mL, baseline CD4 count 345 cells/mm^3) study subjects achieved viral load < 50 copies/mL by week 36 and all by week 48 (Table 1). Overall median (range) viral load reduction (Log_{10} copies/mL) was 1.3 (0.6–1.9) over the first week of treatment, with no major differences between group A and B (Table 2).

Pharmacokinetics

GM plasma concentration vs. time curves for rilpivirine, darunavir, and ritonavir are shown in Figure 2 and their pharmacokinetic parameters summarized in Table 3.

Although approximately 45% higher, rilpivirine AUC measured in this study was within the range of those reported from Phase III pharmacokinetic substudies that showed an inter-individual variability in rilpivirine exposure of 45%.[10]

All subjects had darunavir C_{trough} values above the protein binding adjusted IC_{50} of 550 ng/mL, and the darunavir pharmacokinetic parameters measured were similar to those reported from Phase III studies (Table 3).[11]

Safety and tolerability

Study drugs were well tolerated with no subjects discontinuing rilpivirine and darunavir/ritonavir because of drug-related toxicity.

Three serious adverse events were recorded during the study, none of which were deemed by the investigator to be related to study medication: (i) admission to hospital for treatment of prostatitis complicated by peri-urethral abscess; (ii) overnight admission to hospital to treat dehydration and confusion caused by recreational drug intoxication; (iii) laparotomy and bowel resection with temporary stoma to repair rectal trauma.

Table 1 Baseline demographic and clinical characteristics of the 36 subjects who completed the study

	Group A (*n* = 18)	Group B (*n* = 18)	All subjects (*n* = 36)
Gender (male:female)	17:1	18:0	35:1
Age (years)	36	35	34
Median (range)	(21–58)	(21–54)	(21–58)
Mode of HIV transmission			
MSM	16	17	33
Heterosexual	1	–	1
Unknown	1	1	2
HIV-RNA (copies/mL)	91,999	24,403	215,120
Median (range)	(807–5,595,624)	(807–78,113)	(105,885–5,595,624)
HIV Subtype			
B (N)	15	13	28
Non-B (N)	3	5	8*
CD4 count (cells/mm^3)	388	450	370
Median (range)	(170–1375)	(204–1375)	(170–787)
N with CD4 count < 200	1	None	1
QTc m/sec	360	358	360
Median (range)	(308–404)	(308–404)	(324–404)
BMI (kg/m^2)	23	22	23
Median (range)	(16–35)	(20–28)	(16–35)

*Non-B subtypes were AG, D, C, and AE.
Note: *N* = number, MSM = men who have sex with men, BMI = body mass index

Table 2 Viral load (VL) decay in the 36 subjects who completed the study, and in group A (VL < 100,000 copies/mL) and group B (VL > 100,000 copies/mL) over the study period

			Subgroup of HIV RNA at baseline			
			A = Under 100,000		*B* = At least 100,000	
	Overall *n* = 36		*n* = 18		*n* = 18	
Visit time points	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Viral load at baseline (copies/ml)	376,746.8 *n* = 36	1,026,153.2	28,621.7 *n* = 18	21,687.4	724,871.8 *n* = 18	1,382,320.9
Viral load at week 1 (copies/ml)	9663.3 *n* = 36	13,423.7	1630.8 *n* = 18	2001.7	17,695.8 *n* = 18	15,177.3
Viral load at week 2 (copies/ml)	4177.3 *n* = 34	8177.9	864.0 *n* = 17	1513.5	7490.6 *n* = 17	10,597.9
Viral load at week 3 (copies/ml)	2915.7 *n* = 35	4650.8	419.6 *n* = 17	415.0	5273.1 *n* = 18	5566.3
Viral load at week 4 (copies/ml)	2242.1 *n* = 32	3416.2	349.7 *n* = 15	215.4	3911.8 *n* = 17	4031.3
Viral load at week 6 (copies/ml)	1200.4 *n* = 32	1690.7	205.5 *n* = 14	184.3	1974.2 *n* = 18	1933.2
Viral load at week 8 (copies/ml)	752.9 *n* = 30	951.2	236.9 *n* = 12	228.6	1096.8 *n* = 18	1093.8
Viral load at week 10 (copies/ml)	500.4 *n* = 27	541.4	165.8 *n* = 9	158.3	667.7 *n* = 18	589.6
Viral load at week 12 (copies/ml)	292.6 *n* = 27	347.5	87.8 *n* = 10	42.4	413.1 *n* = 17	391.8
Viral load at week 24 (copies/ml)	68.6 *n* = 8	25.1	77.0 *n* = 1	NA	67.4 *n* = 7	26.9
Viral load at week 36 (copies/ml)	53.5 *n* = 2	13.4	63.0 *n* = 1	–	<50 –	
Viral load at week 48 (copies/ml)	<50	–	<50	–	<50	

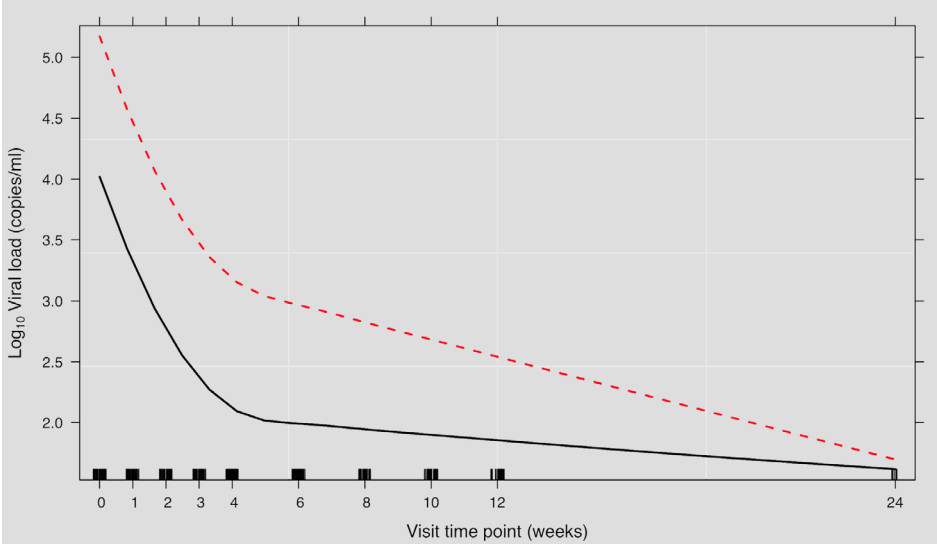

Figure 1 Geometric mean viral load decay over 24 weeks of rilpivirine/darunavir/ritonavir treatment in Group A (straight line) and Group B dotted line, predicted by cubic spine model fit

There were no other adverse events higher than Grade 2 of severity. Two patients experienced a transient self-limiting generalized rash (without mucosal involvement) following cART initiation, which resolved with continued dosing.

No significant change from baseline, no QTcF interval greater than 450 ms were recorded during the study and no relationship between riplvirine C_{max} and QTcF interval were observed 9p = 0.26). No laboratory parameter changes higher than Grade 2 were measured.

Discussion

In this pharmacokinetic/pharmacodynamic study in HIV-1-infected treatment-naive participants, the NRTI-free

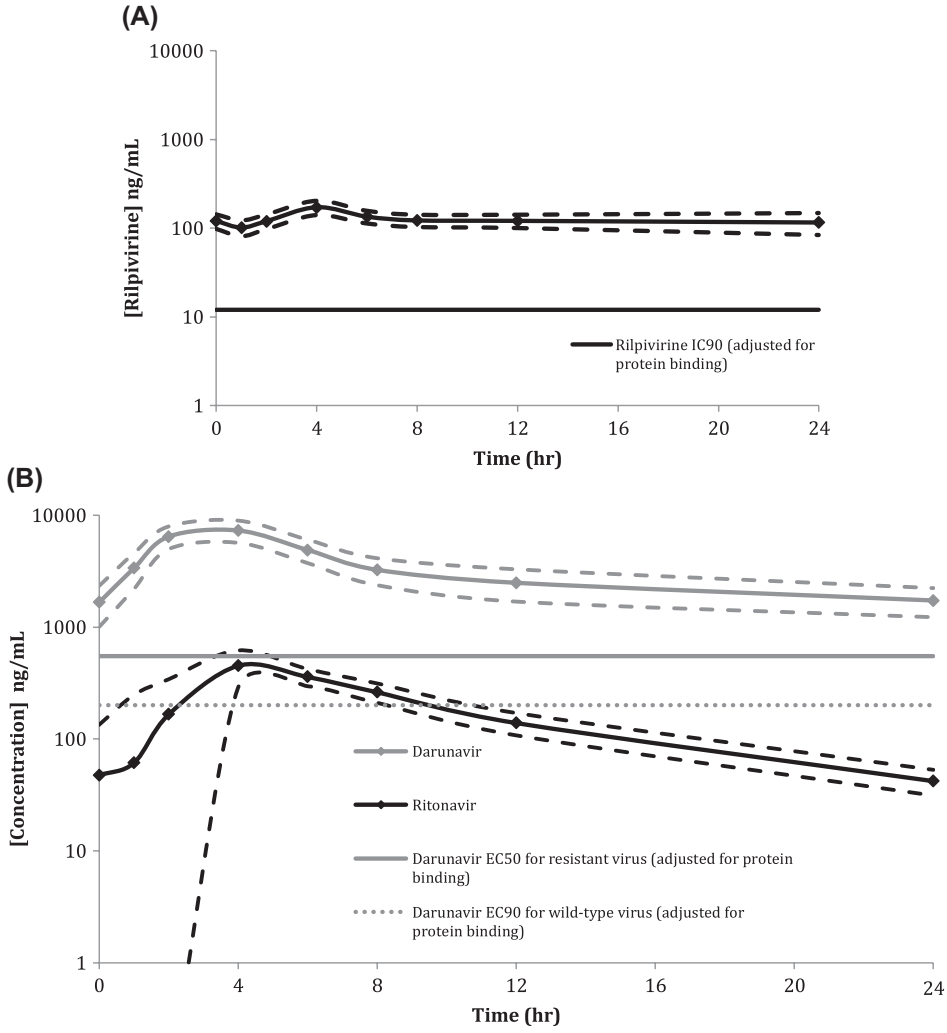

Figure 2 Geometric mean (GM, solid line) and 95% confidence interval (95% CI, dotted lines) plasma concentrations of rilpivirine (A), and darunavir/ritonavir (B). *Y*-axes are illustrated as logarithmic scales, and straight lines indicate: (A) rilpivirine concentration associated with a 90% reduction in viral replication (inhibitory concentration, IC_{90}) of 12 ng/mL and (B) solid line darunavir half-maximal effective concentration (EC_{50}) (resistant, protein adjusted = 550 ng/mL) and dotted line darunavir 90% of maximal EC (EC_{90}) (WT, protein adjusted = 200 ng/mL)

Table 3 Rilpivirine (RPV), darunavir (DRV) and ritonavir (RTV) pharmacokinetic (PK) parameters at steady state in 36 patients living with HIV (PLWH) expressed as geometric mean (GM) and 95% confidence intervals (95%CI). Rilpivirine concentration associated with a 90% reduction in viral replication (inhibitory concentration, IC_{90}) for wild type virus and protein binding adjusted is 12 ng/mL and darunavir 90% of maximal EC (EC_{90}) for wild-type virus and protein binding adjusted is 200 ng/mL

PK parameter	RPV	DRV	RTV
N = 36		GM (95% CI)	
$AUC_{0-24\ h}$ ng h/mL	3036 (2876–3969)	82,598 (76,508–113,143)	4455 (4098–6475)
CV%	49	59	68
C_{max} (ng/mL)	188 (175–248)	8381 (7802–11,279)	503 (463–845)
CV%	53	56	90
C_{trough} (ng/mL)	116 (106–171)	1728 (1661–2669)	42 (38–60)
CV%	72	71	68

combination containing rilpivirine and darunavir/ritonavir led to achievement of an undetectable viral load in all subjects at week 48 (and in all but one who had a viral load of 63 copies/mL, by week 36). A secondary objective was to investigate whether baseline viral load (higher or lower than 100, 000 copies/mL) would influence virologic

response and no differences in viral load decrease or achievement of an undetectable viral load were observed between patients with a baseline viral load above and below 100,000 copies/mL.

Rilpivirine exposure was slightly increased by ritonavir co-administration via CYP3A4 inhibition; however, its AUC was still within the range observed in historical controls.[9,10] Importantly, no changes in ECG QTcF were seen during the study. The study drugs were well tolerated with no drug-related adverse events or laboratory parameters higher than Grade 2.

While an association between efficacy and baseline viral load has been demonstrated with other cARTs containing two or three active drugs,[2,17,18] this small but intensive study showed that rilpivirine plus darunavir/ritonavir is efficacious independently of baseline viral load. A potential explanation of this finding could be (i) the slightly higher concentrations that were measured for rilpivirine in the presence of darunavir/ritonavir, however this would be difficult to prove as pharmacokinetic/pharmacodynamic data from Phase III clinical trials with higher rilpivirine dose are unavailable; or (ii) the fact that being this a pharmacokinetic/pharmacodynamic study, participants were followed closely and adherence monitored frequently, especially during the first four weeks of treatment.

Although rilpivirine can prolong the QTc interval in a dose-dependent manner[8] and increases in its concentrations were expected because of ritonavir co-administration and CYP3A4 inhibition, ECG recordings throughout the study were available and showed no change in QTcF from baseline and no correlation between QTc change and rilpivirine C_{max}.

Dual antiretroviral treatments containing a boosted protease inhibitor-based therapy, (e.g. a boosted protease inhibitor plus one agent from another class) is not the preferred strategy recommended by most recent guidelines. However, over the past 15 years numerous studies have been published showing how dual antiretroviral therapies may be beneficial in clinical practice. Importantly, a recent meta-analysis showed minor differences in terms of virological efficacy when comparing dual to triple cART.[19] Furthermore, it was observed that although a similar risk of serious adverse events in patients on dual and triple therapies, the former had a lower risk of adverse events leading to discontinuation, suggesting that dual therapies may be better tolerated.[19]

Interpretation of these data should take into account its single-arm design, the pilot nature of the study, and the small number of patients studied. A larger randomized trial comparing rilpivirine plus darunavir/ritonavir to standard of care is warranted to draw definite conclusions. However, interestingly in the past, single-arm Phase IIb trials have predicted more definitive findings from Phase III clinical trials: the ACTG A5262 study was followed by NEAT001 that showed that the dual regimen containing raltegravir plus darunavir/ritonavir did not achieve non-inferiority in individuals with high baseline viral loads and low CD4 counts.[2,17] Furthermore, the efficacy of RPV/DRV/r in maintaining an undetectable viral load in suppressed patients as a switch strategy and in adolescents has also been confirmed.[13,14]

Interest in reducing the number of drugs in a standard antiretroviral regimens is growing and different innovative boosted protease inhibitor-free combinations are being studied with drugs with a high genetic barrier like dolutegravir, in combination with a NRTI (e.g. lamivudine, 3TC)[4] or an NNRTI (e.g. rilpivirine).[5] The outcome of these studies is important because new dual combinations may limit short- and long-term antiretroviral drugs toxic effects. Importantly, however, dual regimens need to be carefully selected and to date large randomized clinical trial data on dual therapy are available only for boosted protease inhibitor-containing combinations.[3,4,20]

In conclusion, our study has demonstrated that the combination of rilpivirine and darunavir/ritonavir could be efficacious, with limited short-term toxicity in ARV-naïve patients. Therefore, it is potentially useful as an alternative strategy in patients for whom standard cART is not an option due to resistance or toxicity.

Contributors

AJ had contributed in study design, protocol writing, recruitment of patients, data analysis, and manuscript writing. LE had contributed in bioanalysis, data analysis, and manuscript writing. CH had contributed in recruitment of patients, and manuscript revision. ZK had contributed in recruitment of patients and manuscript revision. SK had contributed in bioanalysis, data analysis, manuscript writing. DB had involved in bioanalysis, data analysis, and manuscript writing. ED had involved in recruitment of patients and manuscript revision. AP had contributed in study design, recruitment of patients, and manuscript revision. MB had involved in study design, protocol writing, principal investigator, recruitment of patients, data analysis and manuscript writing.

Declaration of interest

AJ following the completion of the study became an employee of Gilead Sciences, SK has received support from ViiV Healthcare, Merck, Janssen, Gilead, and Bristol Myers Squibb for the HIV drug interactions website, and research grants from Merck, Janssen, and ViiV Healthcare, DB received honoraria for speaking and advising, travel grants and research grants (to the institution) from Bristol-Myers Squibb, Janssen, Viiv, Gilead, and Merck, AP received honoraria for speaking and advising, travel grants and research grants (to the institution)

from Bristol-Myers Squibb, Janssen, ViiV, Gilead, and Merck, MB received honoraria for speaking and advising, travel grants and research grants (to the institution) from Bristol-Myers Squibb, Janssen, ViiV, Gilead, Teva, Mylan, Cipla, LE, CH, ZK, ED have no conflicts.

Some of the results of this study were presented at 20th Conference on Retroviruses and Opportunistic Infections (CROI), 3–6 March 2013, Atlanta: Jackson et al. Rilpivirine with Darunavir/Ritonavir; Pharmacokinetics & Safety in HIV Therapy-Naïve Patients. Poster 507.

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