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Darunavir(DRV)/r-based PEP versus Standard of Care (SOC) – the randomized PEPDar Study

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Abstract

Background: Post exposure prophylaxis (PEP) for 4 weeks is state-of-the-art following exposure to HIV with high risk of transmission. None of the recommended regimens has been studied in prospective randomized studies in this indication so far, discontinuations rates due to side effects are high. Darunavir/r has a favorable safety profile and high antiviral potency. It could therefore be an alternative to currently used drugs (mainly lopinavir (LPV)/r). This study was designed to generate data on safety and tolerability of DRV/r-based PEP compared to SOC-PEP.

Methodology: PEPDar was an open-label, randomized multicenter prospective noninferiority study enrolling patients following high risk exposure to HIV in Germany. Recommended SOC as per 2008 National Guidelines included 2 NRTIs plus LPV/r or EFV. Patients were stratified by risk of exposure (occupational [OE] vs. non-occupational [NOE]) to receive DRV/r + 2 NRTIs or SOC-PEP within 72 hours following high risk contact for 28-30 days. Primary endpoint was the early discontinuation rate (% subjects who discontinued HIV-PEP for >2 consecutive days prior to day 28) for any reason except documented negative HIV-status of the index person. The trial had 80% power to show noninferiority (overall significance level 5% [two-sided], non-inferiority margin 12%).

Results: Between 11/2011 and 05/2013 306 patients were enrolled at 22 centers. 82.7% were male (median age 33 years [range: 18-62]); 17.3 % were female (median age 31 years [range 18-55]). Median time between risk contact and start of PEP was 2 hours (range 0.1-22) after OE (n=62 [20.3%]) and 14 hours (range 0-71.9) after NOE (n=244 [79.7%]). 155 patients received DRV/r + 2 NRTIs, 151 patients received SOC (LPV/r-based in all patients) + 2 NRTIs. 97% (n=298) received TDF/FTC as backbone. Early discontinuation rate was 5.8% (n=9) in the DRV/r-arm and 9.4% (n=14) in the SOC-arm showing non-inferiority (CI: -0.148; 0.078). Adverse events (AEs) related to DRV/r or SOC were reported in 106 DRV/r-patients (68.4%) and in 114 SOC-patients (75.5%) (p=0.203). Most common AEs (all grades) were diarrhoea (28 vs. 42 patients [p=0.056]), nausea (16 vs. 26 patients [p=0.097]) and fatigue (17 vs.22 [p=0.393]). SOC-patients experienced more sleep disorders (0 vs. 6 [p=0.014]). Rash was reported in 6 DRV/r-patients and 5 SOC-patients. No seroconversion was documented.

Conclusions: DRV/r showed noninferiority with regard to early discontinuation of PEP when compared to SOC (LPV/r in all SOC-patients). Both regimens were well tolerated. We conclude that DRV/r-based PEP is an alternative to SOC including LPV/r.

Background

Post exposure prophylaxis (PEP) for 4 weeks is state-of-the-art following exposure to HIV with high risk of transmission. None of the recommended regimens has been studied in prospective randomized and stratified studies in this indication so far, discontinuations rates due to side effects are high. Darunavir/Ritonavir (DRV/r) has a favorable safety profile and high antiviral potency. It could therefore be an alternative to currently used drugs (mainly lopinavir/ritonavir (LPV)/r). This study was designed to generate data on safety and tolerability of DRV/r-based PEP compared to SOC-PEP.

Methods

PEPDar was an open-label, randomized multicenter prospective non-inferiority study enrolling patients following high risk exposure to HIV in Germany. Recommended SOC as per 2008 National Guidelines included 2 NRTIs plus LPV/r or EFV (ClinicalTrials.gov Identifier: NCT01516970).

Patients could be included if they met the following major inclusion criteria:

- ≥ 18 years
- Occupational injury or non-occupational exposure with documented or potential for HIV exposure
- Indication for HIV PEP, as determined by the treating physician and/or the investigator
- Initiation of PEP not later than 72 hours after exposure
- HIV antibody test negative
- Informed consent signed

Patients were stratified by risk of exposure (occupational [OE] vs. non-occupational [NOE]) to receive DRV/r + 2 NRTIs or SOC-PEP within 72 hours following high risk contact for 28-30 days. All patients received safer sex counselling, pregnancy tests were performed in all female participants.

Primary endpoint was the early discontinuation rate (% subjects who discontinued HIV-PEP for >2 consecutive days prior to day 28) for any reason except documented negative HIV-status of the index person. The trial had 80% power to show non-inferiority (overall significance level 5% [two-sided], non-inferiority margin 12%).

Additional visits were performed at day 14, day 28 and month 3. At all visits, tolerability and safety were assessed; pregnancy tests were performed in female patients.

Results

Between 11/2011 and 05/2013 305 patients were enrolled at 22 centers in Germany.

Figure 1: Study Population

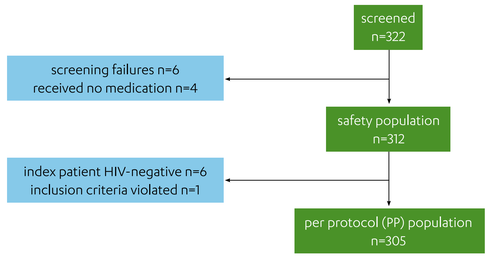


Table 1: Baseline Characteristics (safety population)

	DRV/r (n=159)	SOC-PEP (n=153)	total
male	131 (82%)	125 (82%)	256 (82%)
median age (years)	33.0	31.0	32.0
occupational risk	35 (22%)	30 (20%)	65 (21%)
non-occupational risk	124 (78%)	123 (80%)	247 (79%)
LPV/r as third agent	---	153	
TDF/FTC	159	146	305
AZT/3TC	0	6	6
ABC/3TC		1	1

Table 2: Duration between risk exposure and start of treatment [hours] stratified by exposure type

Type of exposition	Duration between exposure and start of treatment [hours]	Total (n=310)
occupational	Mean	3.40
	SD	3.95
	Median	2.50
	IQR	0.88 / 4.08
non-occupational	Mean	17.64
	SD	14.78
	Median	14.00
	IQR	5.00 / 24.00

IQR: interquartile range

Table 3: Profession of subjects with occupational exposure (n=65)

Profession	n
medical doctor/physician	22 (33.8%)
nurse/care assistant	32 (49.2%)
cleaning staff	2 (3.1%)
medical student	6 (9.2%)
nursing student	1 (1.5%)
other	2 (3.1%)

Table 4: Exposition type in subjects with non-occupational exposure (n=247)

Exposition type	n
receptive anal sex	71 (28.7%)
insertive anal sex	68 (27.5%)
insertive vaginal sex	30 (12.1%)
receptive oral sex	22 (8.9%)
receptive vaginal sex	21 (8.5%)
receptive anal sex/insertive anal sex	9 (3.6%)
insertive oral sex	7 (2.8%)
other	19 (7.7%)

Table 5: Early discontinuation rate by treatment group and overall (PP Population)

HIV PEP discontinuation	DRV/r PEP (n=155) No. (%)	SOC-PEP (n=150) No. (%)	Total (n=305) No. (%)
yes	10 (6.5%)	17 (11.3%)	27 (8.9%)
no	145 (93.5%)	135 (88.7%)	278 (91.1%)
Total	155	150	305

The estimated risk difference DRV/r PEP - SOC-PEP is 3.5% (95 % CI [- 0.148; 0.078]) .
The Cochran-Mantel-Haenszel test was not significant (p = 0.2434) for discontinuation rate comparison, adjusted for exposure type.

Table 6: Adverse Drug Reactions (≥5% and of interest) – all grades (safety population)

	DRV/r PEP (n=159)	SOC-PEP (n=153)	p-value*
Subjects with adverse drug reactions (ADR)	108 (68%)	115 (75%)	0.169
Related severe ADR (Grade 3)	4 (2.5%)	8 (4.6%)	0.250
Gastrointestinal disorders	41 (26%)	51 (33%)	0.172
Abdominal pain	15 (9%)	14 (9%)	1
Diarrhoea	29 (18%)	42 (28%)	0.059
Flatulence	5 (3%)	11 (7%)	0.127
Nausea	17 (11%)	28 (18%)	0.076
Vomiting	9 (6%)	9 (6%)	1
Fatigue	17 (11%)	24 (16%)	0.241
Headache	16 (10%)	8 (5%)	0.138
Sleep disorder	0 (0%)	6 (4%)	0.013
Rash	6 (4%)	4 (3%)	0.750
Rash generalised	0 (0%)	1 (1%)	0.490

* Fisher Exact Probability Test, two-tailed

Figure 2: Overall incidence of ≥ Grade 2 Adverse Drug Reactions judged at least possibly treatment-related

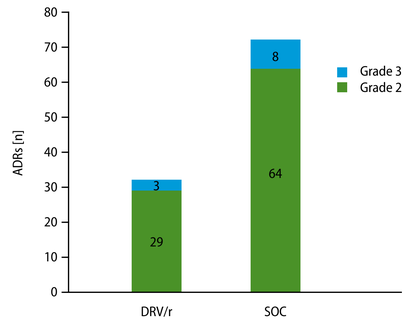
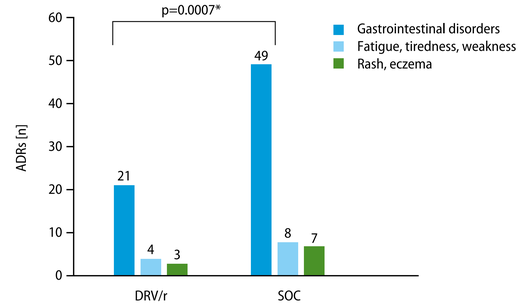


Figure 3: Overview of the most frequently reported Adverse Drug Reactions (≥ Grade 2) judged at least possibly treatment-related (safety population)



* Fisher Exact Probability Test, two-tailed

No serious adverse reactions and no seroconversions were documented.

Conclusions

This is the first randomized trial to compare lopinavir/r as standard of care for PEP with darunavir/r.

- DRV/r showed noninferiority with regard to early discontinuation of PEP when compared to SOC (LPV/r in all SOC-patients).
- Overall, both regimens were well tolerated, no serious adverse reactions were documented.
- The rate of gastrointestinal disorders was significantly lower in the DRV/r group.
- We conclude that DRV/r-based PEP is an alternative to SOC including LPV/r.
- No HIV seroconversions were observed in this trial.

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