Title	**Observational Cohort Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC** **Amendment 1 to the Final Study Report (dated 18 June 2019)** **This Study Report Amendment is confidential and is prepared according to the Terms stated in the agreement signed by EuroSIDA Study and the sponsor (Janssen Research & Development Ireland). No part of this data may be released to any third party except Gilead Sciences without prior acceptance by the EuroSIDA coordination office.**
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EU PAS register number	*EUPAS5766*
Active substance	Rilpivirine Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitor (J05AG05)
Medicinal product	*EDURANT, Eviplera*
Product reference	*EMEA/H/C/002264 (EDURANT)* *EMEA/H/C/002312 (Eviplera)*
Procedure number	*EMEA/H/C/002264/II/XXXX (EDURANT)* *EMEA/H/C/002312/II/XXXX (Eviplera)*
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Joint PASS	*Yes*
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1. RATIONALE

The final study report (dated 18 June 2019) of the Observational Cohort Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC has been submitted to the European Medicines Agency (EMA) by the Marketing Authorisation Holders of EDURANT and Eviplera on 28 June 2019 (procedures EMEA/H/C/002264/II/0037 and EMEA/H/C/002312/II/0100). During the preparation of the responses to the questions received from EMA for these procedures, EuroSIDA noticed that the final study report of this Drug Utilisation Study (DUS) contains a few inconsistencies. The corrected sections and tables have been provided in this study report amendment together with the results from an additional analysis performed by EuroSIDA on the existing study data on request of EMA. Overall, the conclusions as stated in the final study report dated 18 June 2019 remain valid after correction of the errata.

2. SUMMARY OF CHANGES

The following sections of the final study report have been updated.

Bold and underlined is used to indicate addition of text; ~~strikethrough~~ is used to indicate deletion of text.

7. RESEARCH QUESTION AND OBJECTIVES

One of the secondary study objectives of the DUS (as described in protocol amendment 1, dated 30 Aug 2013), was "to describe concomitant medications (only those contraindicated for RPV as per the SmPC) of patients initiating RPV-containing regimens and changes over the course of RPV treatment". The study protocol mentioned that "information on concomitant medication (secondary study objective) is collected every 6 months" but this secondary study objective should have been removed from the protocol via a protocol amendment as information on concomitant medications that are contraindicated for RPV in patients initiating RPV-containing regimens is not routinely collected in the EuroSIDA database. This was explained already in the final study protocol section 10.4.6 but was not yet explained in section 7. Section 7 has therefore been updated to include this explanation.

Updated text for section 7 (p. 17)

Secondary objectives

- ….
- To describe concomitant medications (only those contraindicated for RPV as per the approved SmPC) of patients initiating RPV-containing regimens and changes over the course of RPV *****
- ….

  *** as information on concomitant medications that are contraindicated for RPV in patients initiating RPV-containing regimens are not routinely collected in the EuroSIDA database, it has not been possible to collect data for this secondary study objective (see also section 10.4.6)**

10.3 Main Results: Primary Objectives

10.3.1 Use of RPV according to EU SmPC (Table 2)

In the final study report EuroSIDA indicated that, because of the way data are collected by EuroSIDA, it was not possible to distinguish the exact number of patients initiating treatment with EDURANT from those initiating treatment with Eviplera. However, as explained in the updated text below, for most of the patients, it is possible to make a distinction, while this remains unclear only for a minority of participants. Based on an additional analysis of the data that were described in Table 8 of the final study report, the text in section 10.3.1 has been updated.

Updated text for section 10.3.1 (p 30)

Table 2 summarizes the patients who initiated RPV-containing regimens. Of the 1,355 patients, 1,184 patients (87.4%) had a viral load measurement in the 6 months prior to baseline; of these, 1,173/1,184 (99.1%) had HIV-RNA viral load ≤100,000 copies/ml. Among those with HIV-RNA viral load ≤100,000 copies/ml, 938/1,173 (80.0%) also had HIV-RNA viral load ≤50 copies/ml at baseline (all in the ART-experienced group). 144 (10.6%) were completely ART-naive and 172 (12.7%) patients were naïve to cART (i.e. they had never previously received a regimen including ≥3 ARVs); overall 1,211 individuals (89.4%) had previously taken at least one ARV drug. As mentioned in Section 6 of the final study report, while EDURANT is only approved in treatment-naïve patients (since November 2011), the indication for Eviplera was extended in October 2013 to include ART-experienced adults who are virologically suppressed with no history of virologic failure. However, because of the way data are collected by EuroSIDA it is not possible to distinguish the exact number of patients initiating treatment with EDURANT from those initiating treatment with Eviplera. **For patients where the use of Eviplera was explicitly reported using the corresponding ATC code, EuroSIDA could be sure that the single tablet combination was used. As indicated in Tables 8b and 8c of the study report amendment, this is the case for 894 patients. In contrast, if use of TDF/FTC/RPV as individual drugs is indicated, it is impossible to reliably distinguish between the use of EDURANT and Eviplera. For 300 patients who started rilpivirine, no concomitant use of TDF/FTC was reported, so these patients likely started EDURANT. For the remaining 161 patients for which the use of TDF/FTC/RPV as individual drugs was indicated, it was not possible to determine whether they started on Eviplera or EDURANT. From the 300 patients who started treatment with EDURANT, 274 (91%) were not ARV-naïve, which is not consistent with the EDURANT prescribing information. Of the 894 patients being treated with Eviplera, 133 (15%) patients were ART naive, and 761 (85%) patients were ART-experienced.**

Of the 172 cART-naïve patients, 147 (85.5%) had available viral load data in the 6 months prior to baseline; for 140 of these (95.2%), HIV viral load was ≤100,000 copies/ml. Overall, 103/1,355 (7.6%) patients had screening for ARV RAMs performed within 5 years prior to baseline recorded in the database; 27 (26.2%) of these patients were cART-naïve and 76 (73.8%) were cART-experienced. Among the 76 treatment-experienced patients with available genotypic resistance data, 43 (56.6%) had their screening for ARV RAMs performed pre-ARV treatment initiation.

Overall, 87/894 (10%) participants initiating Eviplera were screened for ARV RAMs within 5 years prior to baseline. This proportion was 14/300 (5%) in the EDURANT group and 2/161 (1%) in the unknown group, suggesting that participants starting Eviplera might have been more frequently screened for drug resistance. Of the 133-ART naïve who started Eviplera, 25(19%) vs. 1 (4%) out 26 who started EDURANT were screened for drug resistance. As

EuroSIDA is an observational cohort that only includes data collected from locally performed laboratory testing at the participating clinics, the completeness of the screening for ARV RAMs prior to initiating Eviplera may be under-reported (only subset of clinics had routinely sent resistance testing results of resistence tests to the central database and only prior to March 2016) which may explain the low proportion of participants initiating Eviplera with screening for ARV RAMs within 5 years prior to baseline.

10.4.4 HIV treatment regimens of patients initiating RPV or EFV-containing regimens (Table 8)

In the final study report EuroSIDA indicated that, because of the way data are collected by EuroSIDA it was not possible to distinguish the exact number of patients initiating treatment with EDURANT from those initiating treatment with Eviplera. As explained in the updated text below, for most of the patients however, it is possible to make a distinction, while this remains unclear for a minority of patients. The data described in Table 8 of the final study report for patients initiating RPV-based regimens have been split now by ART status (ART-naïve vs. ART-experienced) in Tables 8b and 8c (see below). Regimens have been colour-coded so that it is possible to further split the regimens into 3 groups: patients who started Eviplera (n=894 color coded as blue), patients who probably started EDURANT as no concomitant use of TDF/FTC was reported (n=300, no shading) and patients for whom it was not possible to determine whether they started on Eviplera or EDURANT (n=161, color coded as grey).

Updated text for section 10.4.4 (p49)

The data described in Table 8 for patients initiating RPV- based regimens have been further split by ART status (ART-naïve vs. ART-experienced) in Tables 8b and 8c. Regimens have been colour-coded so that it is possible to further split the regimes into 3 groups: participants who started Eviplera (n=894 color coded as blue), patients who probably started EDURANT as no concomitant use of TDF/FTC was reported (n=300, no shading) and patients for whom it was not possible to determine whether they were started on Eviplera or EDURANT (n=161, color coded as grey).

Table 8b

cART-naïve patients initiating RPV (n=172)	
Regimen	***Number***
Eviplera (TDF/FTC/RPV)	**132**
Abacavir/Rilpivirine/Lamivudine	**16**
Rilpivirine/TDF/Emtricitabine	**13**
Rilpivirine/TDF/Lamivudine	**5**
Abacavir/Rilpivirine/Etravirine/Lamivudine	**1**
Eviplera (TDF/FTC/RPV)/Dolutegravir	**1**
Rilpivirine/Dolutegravir	**1**
Rilpivirine/Raltegravir/Lamivudine	**1**
Rilpivirine/Raltegravir/TDF	**1**
Rilpivirine/Zidovudine/Lamivudine	**1**
Total	**172**

Table 8c

cART-experienced patients initiating RPV (n=1183)	
Regimen	***Number***
Eviplera (TDF/FTC/RPV)	**714**
Rilpivirine/TDF/Emtricitabine	**111**
Abacavir/Rilpivirine/Lamivudine	**96**
Rilpivirine/Dolutegravir	**54**
Rilpivirine/Dolutegravir/TDF	**9**
Rilpivirine/Raltegravir	**9**
Ritonavir/Rilpivirine/Darunavir	**9**
Raltegravir/Eviplera(TDF/FTC/RPV)	**8**
Rilpivirine/Dolutegravir/TDF/Emtricitabine	**8**
Abacavir/Rilpivirine/Dolutegravir/Lamivudine	**7**
Rilpivirine/Raltegravir/Lamivudine	**7**
Ritonavir/Eviplera(TDF/FTC/RPV)/Darunavir	**6**
Eviplera(TDF/FTC/RPV)/Atazanavir	**5**
Rilpivirine/Darunavir	**5**
Rilpivirine/Dolutegravir/Emtricitabine	**5**
Rilpivirine/Dolutegravir/Lamivudine	**5**
Ritonavir/Rilpivirine/Raltegravir/Darunavir	**4**
Eviplera(TDF/FTC/RPV)/Dolutegravir	**3**
Eviplera(TDF/FTC/RPV)/Nevirapine	**3**
Rilpivirine/Raltegravir/TDF	**3**
Ritonavir/Rilpivirine/Darunavir/Lamivudine	**3**
Abacavir/Rilpivirine/Lamivudine/Nevirapine	**2**
Abacavir/Rilpivirine/Lopinavir/Lamivudine	**2**
Abacavir/Rilpivirine/Raltegravir/Lamivudine	**2**
Abacavir/Rilpivirine/TDF/Lamivudine/Emtricitabine	**2**
Abacavir/Ritonavir/Eviplera(TDF/FTC/RPV)/Darunavir/Lamivudine	**2**
Eviplera(TDF/FTC/RPV)/Darunavir	**2**
Eviplera(TDF/FTC/RPV)/Lamivudine	**2**
Maraviroc/Rilpivirine/Dolutegravir	**2**
Maraviroc/Rilpivirine/Raltegravir	**2**
Maraviroc/Rilpivirine/Raltegravir/TDF/Emtricitabine	**2**
Rilpivirine/Dolutegravir/TDF/Nevirapine/Emtricitabine	**2**

Rilpivirine/Elvitegravir/TDF/Emtricitabine	**2**
Rilpivirine/Raltegravir/TDF/Emtricitabine	**2**
Rilpivirine/TDF/Lamivudine	**2**
Ritonavir/Eviplera(TDF/FTC/RPV)/Atazanavir	**2**
Ritonavir/Rilpivirine/Dolutegravir/Darunavir	**2**
Ritonavir/Rilpivirine/Dolutegravir/TDF/Darunavir/Emtricitabine	**2**
Ritonavir/Rilpivirine/Raltegravir/Atazanavir	**2**
Ritonavir/Rilpivirine/TDF/Darunavir/Emtricitabine	**2**
Abacavir/Eviplera(TDF/FTC/RPV)	**1**
Abacavir/Eviplera(TDF/FTC/RPV)/Dolutegravir/Lamivudine	**1**
Abacavir/Eviplera(TDF/FTC/RPV)/Lamivudine	**1**
Abacavir/Rilpivirine	**1**
Abacavir/Rilpivirine/Dolutegravir	**1**
Abacavir/Rilpivirine/Dolutegravir/Atazanavir/Lamivudine	**1**
Abacavir/Rilpivirine/Dolutegravir/TAF/Lamivudine/Emtricitabine	**1**
Abacavir/Rilpivirine/Dolutegravir/TDF/Emtricitabine	**1**
Abacavir/Rilpivirine/Dolutegravir/TDF/Lamivudine	**1**
Abacavir/Rilpivirine/Dolutegravir/TDF/Lamivudine/Emtricitabine	**1**
Abacavir/Rilpivirine/Etravirine/Lamivudine	**1**
Abacavir/Rilpivirine/Raltegravir	**1**
Abacavir/Rilpivirine/Raltegravir/Dolutegravir/Lamivudine	**1**
Abacavir/Rilpivirine/Raltegravir/Etravirine	**1**
Abacavir/Rilpivirine/Raltegravir/Etravirine/Lamivudine	**1**
Abacavir/Rilpivirine/TDF	**1**
Abacavir/Rilpivirine/TDF/Lamivudine	**1**
Abacavir/Ritonavir/Rilpivirine/Atazanavir/Lamivudine	**1**
Abacavir/Ritonavir/Rilpivirine/Darunavir/Lamivudine	**1**
Abacavir/Ritonavir/Rilpivirine/Dolutegravir/Lamivudine	**1**
Abacavir/Ritonavir/Rilpivirine/Raltegravir/Saquinavir/Darunavir/Lamivudine	**1**
Eviplera(TDF/FTC/RPV)/Atazanavir/Lamivudine	**1**
Eviplera(TDF/FTC/RPV)/Dolutegravir/Etravirine	**1**
Eviplera(TDF/FTC/RPV)/Dolutegravir/Lamivudine	**1**
Eviplera(TDF/FTC/RPV)/Etravirine/Lamivudine	**1**
Eviplera(TDF/FTC/RPV)/Lopinavir	**1**
Eviplera(TDF/FTC/RPV)/Saquinavir	**1**

Maraviroc/Rilpivirine/Dolutegravir/TDF	**1**
Maraviroc/Rilpivirine/Dolutegravir/TDF/Saquinavir	**1**
Maraviroc/Rilpivirine/Raltegravir/Dolutegravir/Emtricitabine	**1**
Maraviroc/Rilpivirine/Raltegravir/Dolutegravir/Lamivudine	**1**
Raltegravir/Eviplera(TDF/FTC/RPV)/Lamivudine	**1**
Rilpivirine/Cabotegravir	**1**
Rilpivirine/Cobicistat/TDF/Darunavir/Emtricitabine	**1**
Rilpivirine/Dolutegravir/Atazanavir	**1**
Rilpivirine/Dolutegravir/Lopinavir/Lamivudine	**1**
Rilpivirine/Elvitegravir/TAF/Darunavir/Emtricitabine	**1**
Rilpivirine/Raltegravir/Didanosine/Etravirine	**1**
Rilpivirine/Raltegravir/Dolutegravir	**1**
Rilpivirine/Raltegravir/Dolutegravir/TDF/Etravirine/Emtricitabine	**1**
Rilpivirine/Raltegravir/Lopinavir/Darunavir	**1**
Rilpivirine/Raltegravir/TDF/Etravirine/Emtricitabine	**1**
Rilpivirine/TDF/Atazanavir/Emtricitabine	**1**
Rilpivirine/TDF/Darunavir	**1**
Rilpivirine/TDF/Lamivudine/Emtricitabine	**1**
Rilpivirine/TDF/Lopinavir/Emtricitabine	**1**
Rilpivirine/Zidovudine/Lopinavir/Lamivudine	**1**
Rilpivirine/Zidovudine/TDF/Lamivudine/Emtricitabine	**1**
Ritonavir/Eviplera(TDF/FTC/RPV)	**1**
Ritonavir/Eviplera(TDF/FTC/RPV)/Saquinavir	**1**
Ritonavir/Maraviroc/Rilpivirine/Darunavir	**1**
Ritonavir/Raltegravir/Eviplera(TDF/FTC/RPV)/Darunavir	**1**
Ritonavir/Rilpivirine/Amprenavir(Fos-)/Didanosine	**1**
Ritonavir/Rilpivirine/Amprenavir(Fos-)/Dolutegravir/Lopinavir/Darunavir	**1**
Ritonavir/Rilpivirine/Amprenavir(Fos-)/Lamivudine	**1**
Ritonavir/Rilpivirine/Dolutegravir	**1**
Ritonavir/Rilpivirine/Dolutegravir/Atazanavir	**1**
Ritonavir/Rilpivirine/Dolutegravir/Atazanavir/Etravirine	**1**
Ritonavir/Rilpivirine/Dolutegravir/Emtricitabine	**1**
Ritonavir/Rilpivirine/Dolutegravir/Lopinavir/Darunavir	**1**
Ritonavir/Rilpivirine/Dolutegravir/TDF/Atazanavir/Nevirapine/Emtricitabine	**1**
Ritonavir/Rilpivirine/Elvitegravir/TDF/Darunavir/Emtricitabine	**1**

Ritonavir/Rilpivirine/Raltegravir	**1**
Ritonavir/Rilpivirine/Raltegravir/Dolutegravir/TDF/Darunavir/Etravirine	**1**
Ritonavir/Rilpivirine/Raltegravir/Dolutegravir/TDF/Darunavir/Etravirine/Emtricitabine	**1**
Ritonavir/Rilpivirine/Raltegravir/Dolutegravir/TDF/Darunavir/Lamivudine/Emtricitabine	**1**
Ritonavir/Rilpivirine/Raltegravir/Elvitegravir/Cobicistat/Darunavir/Lamivudine/Nevirapine	**1**
Ritonavir/Rilpivirine/TDF/Atazanavir/Lamivudine/Emtricitabine	**1**
Ritonavir/Rilpivirine/TDF/Emtricitabine	**1**
Ritonavir/Rilpivirine/TDF/Saquinavir	**1**
Zidovudine/Eviplera(TDF/FTC/RPV)/Lamivudine/Nevirapine	**1**
Total	**1,183**

Blue shading indicates patients who started the STR Eviplera
Grey shading indicates patients staring TDF/Emticitabine/RPV for whom it is not possible to distinguish Between Eviplera and EDURANT use
No shading indicates patients for whom no concomitant use of TDF/FTC was reported, so these patients are probably patients who started started EDURANT

10.5 Other analyses

10.5.2. Patient characteristics that are likely to influence health care providers to channel patients to RPV over EFV-containing regimens (Table 10)

As requested by EMA, a reanalysis of the data described in Table 10, was done. The Multivariable model now includes all variables selected by backward selection that were retained with a p-value less than 0.3 level. The new analysis shows broadly the same associations as those reported in the original study report with similar estimates of the magnitude of the effect with no implications for the conclusions.

Updated text for Section 10.5.2 (p 54)

Because rates of virological failures over prospective follow-up could not be compared, a cross-sectional analysis comparing patients' characteristics at the time of starting RPV- or EFV-based regimens was performed. Table 10 displays the results obtained from fitting a logistic regression model and the factors identified as independently associated with the probability of initiating RPV over EFV, after adjusting for all variables included in Table 10. ~~The multivariable model was built taking account of factors that were significant in univariable models (p <0.1) and for categorical variables the type III p-value was used.~~ **The multivariable model was constructed using a backward selection with variables being removed one by one from the initial saturated model if the F statistic was significant at the 0.3 level (the models selected using the level of 0.1 or a forward procedure were similar).**

There appeared to be significant regional differences between those initiating RPV- and EFV-based regimens in EuroSIDA. After mutual adjustment for all variables as shown in the table, patients

treated with RPV were less likely to reside in East Europe (adjusted Odds Ratio [aOR]: 0.1~~3~~ **0.11;**(95% confidence interval [C.I]. ~~0.05 – 0.32~~ **0.04 – 0.28**; p<0.001) compared with West Central Europe. Those with higher HIV viral loads were also less likely to be treated with RPV (aOR: ~~0.69~~ **0.72;** 95% C.I.: ~~0.57 - 0.84~~ **0.61 - 0.84**; p<0.001, per log_{10} copies/ml), while those with higher CD4 cell counts were more likely to be treated with RPV (aOR: ~~1.10~~ **1.37** ; 95% C.I.: ~~1.00 – 1.20; p=0.04~~ **1.15 – 1.63; p<0.001**, per doubling of the count). Patients who started RPV-based regimens were followed for a longer duration of time in the cohort (aOR:1.17 per year longer of follow-up; 95% C.I.:1.11-1.2~~2~~**3**; p<0001). None of the other factors considered showed an association with the probability of starting RPV instead of EFV, including ART-status prior to baseline.

***Updated Table 10*:**

	Table 10					
	Logistic regression estimates of factors associated with initiating RPV vs EFV					
	Based on 1355 initiations of RPV and 333 initiations of EFV					
		Univariable estimates		**Multivariable estimates**		
Factor		**Odds ratio (95% CI)**	**p-value**	**Adjusted Odds ratio (95% CI)**	**p-value**	**Type III p-value**
Age/Sex/Race/Weight						
Age	per 5 years older	1.42 (1.33, 1.52)	<.001	~~1.01 (0.89, 1.15)~~	~~0.869~~	
Male	vs. Female	0.68 (0.50, 0.94)	0.020	**0.63 (0.34, 1.16)**	**0.137**	
White	vs. Non-white	0.99 (0.71, 1.37)	0.936	**1.68 (0.87, 3.22)**	**0.119**	
Underweight (BMI<19)	vs. (19<=BMI<25)	0.85 (0.48, 1.51)	0.588	~~0.86 (0.41, 1.82)~~	~~0.700~~	~~<.001~~
Overweight (25<=BMI<30)	vs. (19<=BMI<25)	1.36 (0.82, 2.26)	0.240	~~1.13 (0.58, 2.20)~~	~~0.720~~	
Obese (BMI>=30)	vs. (19<=BMI<25)	1.27 (0.55, 2.92)	0.572	~~1.13 (0.39, 3.25)~~	~~0.820~~	
BMI unknown	vs. (19<=BMI<25)	0.46 (0.34, 0.63)	<.001	~~0.92 (0.53, 1.59)~~	~~0.757~~	
Geographical region						<.001
South	vs. West Central	0.92 (0.64, 1.34)	0.679	0.72 (0.38, 1.37)**0.64 (0.33, 1.24)**	**0.189**~~0.317~~	
North	vs. West Central	0.58 (0.39, 0.84)	0.005	**0.45 (0.23, 0.91)**~~0.57 (0.29, 1.11)~~	**0.025**~~0.100~~	
East Central	vs. West Central	0.52 (0.35, 0.77)	0.001	**0.43 (0.21, 0.91)**~~0.54 (0.27, 1.08)~~	**0.026**~~0.082~~	
East	vs. West Central	0.05 (0.03, 0.09)	<.001	**0.11 (0.04, 0.28)**~~0.13 (0.05, 0.32)~~	<.001	
HIV Parameters						
CD4 Cell count	per doubling	1.19 (1.13, 1.25)	<.001	**1.37 (1.15, 1.63)**~~1.10 (1.00, 1.20)~~	**<.001**~~0.044~~	
CD4 Cell count nadir	per doubling	0.96 (0.91, 1.01)	0.119	**0.79 (0.67, 0.92)**	**0.003**	
HIV viral load	per log10 higher	0.46 (0.42, 0.51)	<.001	~~0.69 (0.57~~, **0.72 (0.61,** 0.84)	<.001	
HIV Transmission Route						<.001
PWID	vs. MSM	0.52 (0.38, 0.69)	<.001	**0.79 (0.43, 1.46)**~~0.68 (0.34, 1.37)~~	**0.458** 0.277	
Heterosexuals	vs. MSM	0.72 (0.53, 0.99)	0.041	**0.46 (0.26, 0.81)**~~0.50 (0.30, 0.83)~~	**0.007** ~~0.008~~	
Other	vs. MSM	0.78 (0.47, 1.29)	0.337	**0.56 (0.24, 1.29)**~~0.66 (0.30, 1.41)~~	**0.173**~~0.282~~	
Hepatitis virus						

coinfection						
HBsAg positive	vs. Negative	0.63 (0.37, 1.08)	0.095	**0.84 (0.27, 2.59)**	**0.766**	<.001
HBsAg unknown	vs. Negative	0.43 (0.32, 0.58)	<.001	**1.49 (0.79, 2.78)**	**0.214**	
HCVAb positive	vs. Negative	0.58 (0.45, 0.75)	<.001	~~1.37 (0.76, 2.49)~~	~~0.294~~	~~<.001~~
HCVAb unknown	vs. Negative	0.30 (0.20, 0.45)	<.001	~~1.10 (0.48, 2.50)~~	~~0.829~~	
Hypertension/Diabetes/ eGFR						
Previous hypertension	vs. None	1.07 (0.74, 1.53)	0.726	**1.19 (0.70, 2.03)**~~1.06 (0.62, 1.80)~~	**0.519**~~0.831~~	<.001
Unknown hypertension	vs. None	0.20 (0.15, 0.27)	<.001	**0.59 (0.31, 1.11)**~~0.58 (0.30, 1.10)~~	**0.100**~~0.096~~	
Previous diabetes	vs. None	2.95 (1.26, 6.88)	0.012	**1.04 (0.33, 3.27)**~~0.92 (0.28, 2.99)~~	**0.942**~~0.893~~	<.001
Unknown diabetes	vs. None	0.60 (0.47, 0.77)	<.001	**1.40 (0.88, 2.23)**~~1.26 (0.80, 1.98)~~	**0.155**~~0.327~~	
eGFR	per 5 mL/1.73m^2	0.85 (0.81, 0.89)	<.001	**0.94 (0.88, 1.00)**~~0.94 (0.88, 1.02)~~	**0.046**~~0.130~~	
Prior AIDS diagnoses						
Previous AIDS		1.22 (0.91, 1.64)	0.183	**0.62 (0.34, 1.14)**	**0.125**	
Prior non-AIDS diagnoses						
Cardiovascular disease		3.74 (1.35, 10.38)	0.011	~~1.52 (0.25, 9.11)~~	~~0.647~~	
Non-AIDS defining malignancies		2.53 (1.08, 5.90)	0.032	~~1.58 (0.35, 7.14)~~	~~0.550~~	
Smoking Status						<.001
Never smoked	vs. Curr smoker	1.26 (0.88, 1.81)	0.216	**1.30 (0.78, 2.17)**~~1.38 (0.83, 2.30)~~	**0.322**~~0.212~~	
Former smoker	vs. Curr smoker	1.82 (1.02, 3.27)	0.044	**0.87 (0.40, 1.93)**~~0.90 (0.41, 1.97)~~	**0.739**~~0.794~~	
Unknown smoking status	vs. Curr smoker	0.27 (0.20, 0.36)	<.001	**1.24 (0.61, 2.50)**~~1.11 (0.54, 2.29)~~	**0.551**~~0.767~~	
Time Controllers						
Time Enrolled in EuroSIDA	per year longer	1.18 (1.15, 1.21)	<.001	1.17 ~~(1.11, 1.22)~~ **(1.12, 1.23)**	<.001	
ART-status						
ART-naive	vs. ART-experienced	0.10 (0.08, 0.14)	<.001	~~0.86 (0.46, 1.61)~~	~~0.634~~	

BMI Body mass index; MSM Men who have sex with men; IDU Injecting Drug User; HBsAg Hepatitis B surface antigen; HCVAb Hepatitis C antibody; eGFR estimated glomerular filtration rate; PWID person who injects drugs

Multivariable model includes all **variables selected by backward selection that were retained with a p-value less than 0.3 level** ~~univariable factors significant at the p-value less than 0.1 level~~

10.6 Adverse events/adverse reactions

10.6.2 Laboratory abnormalities over the course of RPV or EFV treatment (Table 12)

Table 12 of the final study report has been updated in order to include the normal ranges that were missing in the original Table. Compared to the original study report, the Chi-square values have been corrected and the Fisher exact test p-values were added. Some of the differences between the drugs (i.e. for haemoglobin and ALP) are now significant but in favour of RPV so conclusions of the report remain unchanged.

Updated Text for Section 10.6.2 (page 74):

Table 12 summarises laboratory abnormalities, defined as deviations from the normal range, in the lab parameters haemoglobin, ALT, AST, ALP, bilirubin and platelets. Of note, only patients with available data for these markers were included in this table (those with available data are the denominator for the percentages which are shown in brackets in the header of the Table). For 149/691 (21.6%) RPV patients and 41/108 (38.0%) EFV patients, haemoglobin was reported to be below the normal range. For 445/1111 (40.1%) RPV patients and 89/183 (48.6%) EFV patients, ALT was reported to be above the normal range; and for 401/997 (40.2%) RPV patients and 71/156 (45.5%) EFV patients, AST was reported to be above the normal range. ~~There was no evidence for a difference in ALT or AST between treatment groups (p=0.81, p=0.82, respectively).~~ **There was no difference in AST between treatment groups. Compared to the group with results within normal range there was no difference by treatment group of those with either values above normal range (p=0.21) or >3 times higher than normal range (p=0.32). In contrast, fewer patients on RPV reported ALT values above the normal range (p=0.03). More patients on RPV had hemoglobin and ALP levels within normal range compared to the EFV treated patients.**

Updated Table12: Frequency of laboratory abnormalities during the course of RPV or EFV treatment

Parameter Adverse event	RPV N (%)	EFV N (%)	P-value*
Haemoglobin[a] (N with data: RPV=691; EFV=108)			
Below normal range	149 (21.6%)	41 (38.0%)	**0.001**
Normal range	**488 (70.6%)**	**63 (58.3%)**	
Above normal range	54 (7.8%)	4 (3.7%)	
ALT[b] (N with data: RPV=1111; EFV=183)			
Normal range	**666**	**94**	
Above normal range	445 (40.1%)	89 (48.6%)	~~0.81~~**0.03**
Above 3 times the normal range	85 (11.3%)	18 (16.1%)	**0.15**
AST[c] (N with data: RPV=997; EFV=156)			
Normal range	**596**	**85**	

Parameter **Adverse event**	**RPV N (%)**	**EFV N (%)**	**P-value***
Above normal range	401 (40.2%)	71 (45.5%)	**0.21** ~~0.82~~
Above 3 times the normal range	69 (10.4%)	13 (13.3%)	**0.39**
ALP[d] (N with data: RPV=718; EFV=127)			
Normal range	**603**	**79**	
Above normal range	115 (16.0%)	48 (37.8%)	**<0.0001**
Above 3 times the normal range	2 (0.3%)	4 (**4.8**~~3.1~~%)	**0.003**
Bilirubin[e] (N with data: RPV=1014; EFV=156)			
Normal range	**913**	**150**	
Above normal range	101 (10.0%)	6 (3.**9**~~8~~%)	**0.01**
Above 2 times the normal range	29 (**3.1** ~~2.9~~%)	3 (**2** ~~1.9~~%)	**0.61**
Platelets[f] (N with data: RPV=880; EFV=127)			
Normal range	**731**	**112**	
Below normal range	149 (**17.0**~~16.9~~%)	15 (11.8%)	**0.16**
Below 100 10^9/L	58 (**7.4** ~~6.6~~%)	3 (2.**6**~~4~~%)	**0.07**

[&]**Considering all values after baseline and while the person was still receiving the drug**

*Chi-square p-value or Fisher exact test when <5 events in the EFV group

***When two p-values are shown, they refer to separate 2x2 tables with the 'Normal range' category used as common comparator**

[a]Haemoglobin normal range: (Men: 14.0 < g/dl < 18.0; Women: 12.0 < g/dl < 16.0)

[b]ALT normal range: (Men: U/L < 50; Women: U/L < 40)

[c]AST normal range: (Men: U/L < 40; Women: U/L < 34)

[d]ALP normal range: (Men: U/L < 128; Women: U/L < 98)

[e]Bilirubin normal range: (mg/dL < 1.4; µmol/L < 25.0)

[f]Platelets normal range: (140 < 10^9/L < 400)