South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: HIV and AIDs

MEDICINE MOTIVATION:

1. Executive Summary

Date: 25 July 2016
Medicine (INN): Rilpivirine
Medicine (ATC): J05AG05
Indication (ICD10 code): B24
Patient population: HIV-infected patients on first-line antiretroviral therapy (ART**)**
Level of Care: Primary
Prescriber Level: Nursing practitioner or medical doctor
Current standard of Care: Efavirenz (EFV), with nevirapine (NVP) or the lopinavir/ritonavir co-formulation (LPV/r) as alternative where efavirenz is contra-indicated or not tolerated.
Motivator/reviewer name(s): Dr Michelle Moorhouse; Dr Karen Cohen
PTC affiliation: NA

2. Name of author(s)/motivator(s)

Dr Michelle Moorhouse *
Dr Karen Cohen**

3. Author affiliation and conflict of interest details

* Wits Reproductive Health and HIV Institute. Dr Moorhouse has received speaker fees and honoraria from Gilead Sciences and HIV Virology, and has previously received conference sponsorship from Gilead, Merck, Dr Reddy, Cipla and Mylan. Wits RHI is part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care and has received drug donations for studies.

** Division of Clinical Pharmacology, Department of Medicine; no conflicts of interest declared.

4. Introduction/ Background

As from September 2016, antiretroviral therapy (ART) will be initiated in all individuals diagnosed with HIV infection, regardless of CD4 count in South Africa. This aligns current World Health Organization (WHO) recommendations which were recently released (1).

Initiation of antiretroviral therapy in adults with a CD4 count of more than 500 cells/mm^3 is supported by observational data and by two randomised controlled trials (RCTs) (2)(3), START and TEMPRANO studies.

START showed a more than 50% decrease in primary outcomes (any serious event [AIDS related or non-AIDS related] or death) in the group of patients who initiated ART as soon as they were diagnosed (1.8%) vs the group who delayed ART initiation (4.8%) (2). TEMPRANO showed a substantially lower hazard of death or serious HIV-related disease with early ART initiation compared with deferred ART (HR = 0.56; 95% CI: 0.41-0.76) (3).

While there is evidence of benefit of ART, even at high baseline CD4 counts as has been outlined above, for those with earlier stage disease, benefits are modest, and need to be weighed up against the potential harms, including side effects and toxicity from ART when initiated in asymptomatic patients initiated at high viral loads, which may result in poor adherence and resistance, with wider public health consequences (4). Current first-line ART in SA is a fixed dose combination (FDC) of efavirenz (EFV) with two nucleoside reverse transcriptase inhibitors (NRTIs), usually tenofovir with lamivudine (3TC) or emtricitabine (FTC). For those patients in whom EFV is contra-indicated or poorly tolerated, nevirapine (NVP) or boosted lopinavir (LPV/r) are alternatives, depending on the CD4 count of the patient if initiating ART. A systematic review including 42 randomised control trials showed a statistically significant increased risk of discontinuation of NVP due to adverse events compared to EFV (5), and that the relative risk for discontinuations due to adverse effects was higher for EFV compared with most other first-line options (low-dose EFV, rilpivirine (RPV), tenofovir (TDF), atazanavir (ATV) and maraviroc (MVC)).

The systematic review demonstrated that neuropsychiatric adverse events were common with EFV, affecting close to 30% of patients (29.6%; 95% CI: 21.9% to 37.3%), of which 6.1% (95% CI: 4.3% to 7.9%) were severe. Dizziness and abnormal dreams were the most commonly reported neuropsychiatric adverse events experienced by patients treated with EFV (5). Notably, most of the studies included were conducted among predominantly white populations and therefore would not account for differences in metabolism of EFV in African populations, which may result in more frequent neuropsychiatric adverse effects. There is a high prevalence of EFV slow metaboliser genotypes in South Africa (17% versus 3% in Caucasian groups) (6).

There are no recent data describing the prevalence of neuropsychiatric adverse effects among patients using EFV-based regimens in SA. Boulle *et al* showed that in the first three years of ART, substitutions due to EFV toxicity were low (2%) compared to NVP (8%). However, this was based on data collected from 2001/2 until 2004/5, when CD4 counts were significantly lower at ART initiation based on guidelines (median 85 cells/mm^3) and use of NVP was higher as EFV use during pregnancy was contra-indicated at that time. More substitutions were seen with NVP (7.6%), usually relating to hypersensitivity. Of note, baseline weight below 60 kg was associated with a higher risk of NNRTI substitution in this cohort, while higher clinical stage was associated with EFV substitutions specifically (7).

While EFV continues to be the recommended third drug on a backbone of two NRTIs in WHO and SA guidelines, many other guidelines now recommend other agents as the preferred third drug, including integrase inhibitors and newer protease inhibitors. The good virological efficacy, availability as FDC, ability to use in pregnant patients and those with TB support the continued use of EFV in first-line ART. However, with the move to starting ART irrespective of WHO clinical stage or CD4 count, additional options for patients in whom EFV is poorly tolerated need to be considered. EFV has a low genetic barrier to resistance, and is therefore dependent on high levels of adherence to maintain virological suppression and prevent the emergence of resistance. Individuals initiating ART at higher

CD4 counts may need additional adherence support, as well as access to better tolerated first-line regimens where intolerance to EFV-based ART develops. In addition, the continued role of NVP in first-line ART also needs to be reconsidered. CD4 count restrictions make NVP less suitable as an alternative to EFV in patients with higher CD4 counts, as well as the fact that it has been shown in a systematic review that NVP is associated with a higher frequency of severe adverse events, particularly treatment discontinuations, than EFV (8).

There are no studies which compare NVP to RPV directly. The major reason for this is that for many years, EFV was considered the gold standard third drug and consequently most studies would have compared new ARV agents to EFV. The 2NN study (9), an open-label RCT, compared four regimens (NVP once daily, NVP twice daily, EFV, EFV plus NVP; all on a backbone of stavudine and lamivudine) and was unable to demonstrate equivalence within 10%, despite being adequately powered to do so. 2NN showed similar rates of treatment failure between twice daily NVP 169/387 (43·7%) and EFV 151/400 (37·8%) with a difference of 5·9% (95% CI –0·9 to 12·8). However there were differences in terms of the safety profiles among the four regimens, with two deaths occurring on NVP. Discontinuations due to adverse events of HIV events were higher on twice daily NVP 83/387 (21·5%) than EFV 63/400 (15·8%) Nevirapine is associated with severe hepatotoxicity and Stevens-Johnson syndrome, especially when administered at higher CD4 counts (9). On account of the lack of studies comparing RPV and NVP directly, it is necessary to make use of indirect comparisons to infer that EFV has demonstrated better tolerability than NVP, while RPV has demonstrated better tolerability than EFV, therefore it is likely RPV is better tolerated than NVP.

5. **Purpose/Objective i.e. PICO question**]:
   -P *(patient/population):* Adult patients on first-line ART
   -I *(intervention):* Rilpivirine
   -C *(comparator):* Efavirenz
   -O *(outcome):* 1. Efficacy (virological suppression) 2. Adverse effects 3. Neuropsychiatric adverse effects

   (P) Amongst adult patients on first-line antiretroviral therapy (ART), is **(I)** the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) compared to **(C)** efavirenz **(O)** an efficacious and better tolerated alternative to efavirenz in an ART regimen comprising an NNRTI and two nucleoside reverse transcriptase inhibitors (NRTI)?

6. **Methods:**
   a. **Data sources**
      Pubmed

   b. **Search strategy**
      ("rilpivirine"[MeSH Terms] OR "rilpivirine"[All Fields]) AND ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]).

A search was performed on August 1 2016 using the search terms above. We identified 174 abstracts, from which we selected 26 for further review.
These 26 abstracts describe the following:

- Systematic reviews (5,10–12)
- The phase 2b study (13,14)

- The ECHO and THRIVE phase 3 RCTs 48 week data, and multiple analyses pooling data from these two phase 3 studies (15–29)
- STaR study (30,31)

In addition, one randomised switch study was identified, presented at AIDS 2016 (32). Several other switch studies were identified in the search but were excluded as they were not RCTs.

Study inclusion criteria:
Type of studies: RCTs and systematic reviews
Participants: Adults on first-line ART
Intervention: Rilpivirine
Control: Efavirenz
Outcomes: Virological efficacy; adverse effects; neuropsychiatric adverse effects

c. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
Ford N, 2011 (10)	SR	Narrative review. No meta-analysis.
Li S, 2014 (11)	Meta-analysis	Only abstract available therefore we have only scant detail of methodology. Only looks at outcomes to 48 weeks.
Schafer JJ, 2012 (33)	SR	Narrative review. No meta-analysis.
Gupta S, 2015 (34)	RCT	Healthy volunteer study.

d. Evidence synthesis

Author, date	*Type of study*	*n*	*Population*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
Ford N, 2015 (5)	Systematic review of randomised controlled trials (RCTS) and quasi randomised trials	8466 patients on EFV and 9631 on comparator drug	ARV- naïve HIV infected adults (children included in theory but no paed studies met inclusion criteria)	EFV-based ART versus non-EFV based ART (NVP in 9; ritonavir-boosted lopinavir in 7, rilpivirine in 4	Drug discontinuation as a result of an adverse event (AE)	Discontinuation greater for EFV versus RPV; RR 2.0 (95% CI 1.0 to 3.8) and RD 4.1 (95% CI 1.3 to 6.8) Lower risk of discontinuations EFV vs NVP. RR 0.7 (95% CI 0.5 to 0.9) and RD -3.6 (95% CI -6.6 to -0.6).	No significant difference in neuropsychiatric AEs between EFV and RPV or NVP; small risk differences: RPV RR 2.9 (95% CI 0.9 to 10.0); RD 1.0 (-0.3 to 2.4) NVP RR 1.7 (95% CI 0.9 to 3.0); RD 1.1 (95% CI -0.2 to 2.5)
Kryst J, 2015 (12)	Systematic review of RCTS published as peer-reviewed papers	777 patients on EFV and 779 on comparator drug at licensed dose	ARV- naïve HIV infected adults	Patients commencing EFV- based ART versus any other "commonly used treatment schedule. Included 3 EFV vs RPV studies (ECHO, THRIVE and the 25mg dose data from the Phase 2b)	Death; disease progression or death; VL < 50 copies/mL at weeks 48-52; discontinuation of therapy due to adverse events	No statistically significant difference between EFV and RPV in terms of death; disease progression or death; VL < 50 copies/mL at weeks 48-52.	Risk of discontinuation due to intolerance comparable in the meta-analysis for all NNRTIs. Forest plot: ECHO study increased risk of discontinuation for intolerance for EFV compared to RPV M-H, fixed 3.39 (95% CI 1.56 to 7.37). However THRIVE and Phase 2 b no significant difference, did not show pooled result for RPV versus EFV
TMC278-C204 study Pozniak A *et al* (14), Wilkin A *et al* (13)	RCT (phase 2b)	368	Treatment-naïve HIV-1 infected adults	RPV 25 mg vs RPV 75 mg vs RPV 150 mg vs EFV 600 mg, in combination	Proportion of patients with confirmed VL < 50 copies/mL at 48 weeks	Proportion of patients with confirmed VL < 50 copies/mL	At week 96, 71.4–76.3% of patients in RPV groups and 70.8% in EFV group had a VL < 50 copies/mL. No clear RPV

				with AZT/3TC FDC or TDF/FTC FDC (1:1:1:1). All RPV doses blinded; EFV open-label	(responders) according to the time to loss of virological response (TLOVR) algorithm	(TLOVR) after 48 weeks was similar across RPV groups (76.9–80.0%) and comparable with that of EFV (80.9%).	dose–response relationships observed. The logistic regression model showed no statistically significant differences among groups at weeks 48 or 96.
ECHO study: Molina *et al* 2011 (28)	RCT (phase 3)	690	Treatment-naïve HIV-1 infected adults	RPV + TDF + FTC vs EFV + TDF + FTC	Percentage of patients with confirmed response (viral load <50 copies /mL Intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48	At week 48, 83% of patients from both groups had confirmed response (ITT-TLOVR algorithm). There were proportionally more virological failures in the rilpivirine group than in the efavirenz group. 45/346 (13%) versus 19/344 (6%).	
THRIVE study: Cohen C *et al* 2011 (29)	RCT (phase 3)	678	Treatment-naïve HIV-1 infected adults	RPV vs EFV combined with TDF/FTC or AZT/3TC or ABC/3TC	Percentage of patients with confirmed response (viral load <50 copies /mL intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48	86% of patients on RPV had a confirmed VL < 50 copies/ mL at 48 weeks, compared with 82% for EFV.	The lower 95% CI of estimated difference in confirmed response at 48 weeks in the logistic regression model was greater than –12% and –10%, confirming non-inferiority at 12% (primary endpoint) and 10% margins ($p<0.0001$).

STaR study Porter *et al* (30), Cohen *et al* (31)	RCT (phase 3b)	798	Treatment-naïve HIV-1 infected adults	RPV + TDF + FTC (FDC) vs EFV + TDF + FTC (FDC)	Efficacy: proportion of participants with HIV-1 RNA < 50 copies/mL at 48 weeks	RPV/FTC/TDF demonstrated non-inferior efficacy to EFV/FTC/TDF (85.8 vs. 81.6%, respectively) based on Snapshot analysis of virologic suppression (VL < 50 copies/mL) at week 48 (difference 4.1%, 95% CI -1.1 to 9.2%, p=0.12).	TLOVR analysis showed virologic response of 85.3% in RPV/FTC/TDF arm and 79.6% in the EFV/FTC/TDF arm (difference 5.9%, 95% CI 0.6–11.2%, p=0.03).
Munderi P et al 2016 (SALIF study)(32)	RCT	426	HIV-1 infected adults on NNRTI based ART for ≥1 year, CD4>200 cells/microL; no resistance mutations, VL<50 copies/mL	Randomized to switch to TDF/FTC/RPV versus TDF/FTC/EFV (both given as a fixed dose combination)	proportions of participants with HIV-1 RNA < 50 copies/mL at 48 weeks	Difference at week 48: -2.3%; 95% CI (-6.4% to 1.8%) i.e. non-inferiority demonstrated	Treatment limiting AEs: 8(3.8%) in the rilpivirine arm and 1 (0.5%) in the efavirenz arm. Similar numbers with 1 or more neuropsychiatric event of interest; 28.2% for rilpivirine versus 29.9% for efavirenz.

TMC278-C204 study
This is a phase 2b dose-ranging RCT which compared 3 different doses of RPV to EFV 600 mg, all with 2 NRTIs in 368 ARV-naïve subjects (14). This 96-week study was extended to investigate long term safety and efficacy, with all RPV arms' participants being switched to RPV 75 mg at week 96 and then 25 mg at week 144 (the 25mg dose was selected for development), while the control participants continued on EFV-based therapy. Patients were followed up to week 192. By week 192, 59% of RPV- and 61% of EFV-treated participants had sustained virological suppression at < 50 copies/mL. Overall, RPV was associated with fewer grade 2-4 AEs than EFV, including rash ($p<0.001$) and neurologic AEs ($p<0.05$ Fisher's exact test, *post hoc* analyses). Serious AEs, grade 3/4 AEs and discontinuations due to AEs were similar across the groups (13).

ECHO
Phase 3 96-week non-inferiority study EFV vs RPV, non-inferiority margin 12%. EFV vs RPV in combination with TDF and FTC.

THRIVE
Phase 3 96-week non-inferiority study EFV vs RPV, non-inferiority margin 12%. See table above for NRTI backbones.

Data from ECHO and THRIVE were pooled for analyses at 48 and 96 weeks (n=1368).

- Rate of virological failure higher (9% versus 4.8%) at 48 weeks on RPV versus EFV (26); 14% versus 8% at 96 weeks (21).
- More treatment-limiting adverse events with EFV.
- By week 48, 17% of RPV vs. 38% of EFV patients had neurological AEs of interest that were attributed to EFV (22). Six patients permanently discontinued treatment because of neurological AEs of interest– one RPV patient (grade 3 dizziness and headache) and five EFV patients (grade 2 somnolence in two patients, and grade 3 irritability, grade 2 dizziness and grade 2 headache, each in one patient) (22). Psychiatric AES tended to occur in first 4 weeks. 15% of patients on RPV vs. 23% patients on EFV developed psychiatric AEs of interest by week 48 and 10 patients on RPV (1%) vs 15 on EFV (2%) permanently discontinued study medication because of psychiatric AEs of interest (22).
- More dyslipidaemia in EFV treated patients versus RPV. At baseline few patients on lipid-modifying therapy 11 patients on RPV (1.6%) and 8 on EFV (1.2%). At week 96, significantly fewer RPV-treated patients (18; 2.6%) were receiving lipid-modifying drugs compared with the EFV group (38 patients; 6%; P = 0.006) (18). No data on cardiovascular events presented.

STaR study
EFV vs RPV in combination with TDF and FTC as a fixed dose combination. Randomisation stratified by VL>100,000 copies/mL. Non-inferiority if difference in response rates > -12%. Discontinuation for adverse events 10/394 (2.5%) in RPV arm and 34/392 (8.7%) in EFV arm (31).

SALIF
The SALIF trial is a 48 week, randomized, open-label clinical non-inferiority study. Adult participants currently on first-line NNRTI-based (EFV or nevirapine) ART, with HIV-1 RNA < 50copies/mL at study entry, on ART for at least 1 year (n=426) were randomized to switch to TDF/FTC/RPV versus TDF/FTC/EFV (both given as a fixed dose combination). The primary endpoint was maintaining HIV-1 RNA suppression (VL< 400copies/mL), with a non-inferiority margin of -10% for the 97.5% lower confidence limit for the

difference in proportion suppressed at 48 weeks between the 2 arms. Study sites were in Cameroon, Kenya, Senegal, South Africa and Thailand.

The intention to treat analysis included 424 participants (1 was randomized in error, 1 withdrew consent). Virological suppression (< 400copies/mL) after 48 weeks was maintained in 200/213 (93.9%) individuals switched to TDF/FTC/RPV and in 203/211 (96.2%) on TDF/FTC/EFV. Difference at week 48: -2.3%; 95% CI (-6.4% to 1.8%) i.e. non-inferiority demonstrated. Discontinuation rates: 17 (8%) in rilpivirine arm and 10 (4.7%) in the efavirenz arm. Treatment limiting AEs: 8(3.8%) in the rilpivirine arm and 1 (0.5%) in the efavirenz arm. Similar numbers with 1 or more neuropsychiatric event of interest; 28.2% for rilpivirine versus 29.9% for efavirenz.

Concerns

1. **Interaction with rifampicin-containing TB treatment:** Rilpivirine AUC, Cmax and Cmin decreased by 80%, 69% and 89% respectively. (Presented by Van Heeswijk *et al* at Seventh International Workshop of Clinical Pharmacology, Lisbon, 2006. Never published). This clinically significant interaction means that patients developing TB would either:
   - Need to be switched to alternative ART; either double dose ritonavir-boosted lopinavir, or NVP. With the move to Test and Treat, we may see less incident TB as patients initiate ART at higher CD4 counts, which would mean that the number of patients needing such a switch which would relatively low.
   - Require rifabutin - this is not a feasible option for primary care.
2. **Higher rate of virological failure and viral resistance emergence than EFV:** Cohen *et al* 2012 pooled analysis of ECHO and THRIVE (n=1368) at week 48. Although non-inferior efficacy, rate of virological failure higher (9% versus 4.8%). However, the incidence of AEs resulting in treatment discontinuation was higher in EFV group; confirmed in Ford *et al*'s systematic review (5). Difference in virological response particularly in those with baseline VL > 100,000 copies/mL. Most failures occurred in first 48 weeks, at week 96 78% VL<50 in both arms.

7. **Alternative agents:** NA

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: x Not confident: Uncertain:	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: x Harms outweigh benefits: Benefits = harms or Uncertain:	**Only for limited use as recommended:** 1. For patients intolerant of EFV. 2. As an alternative for those with neuropsychiatric contraindication

<table>
<tr>
<td>THERAPEUTIC INTERCHANGE</td>
<td>Therapeutic alternatives available:
Yes [ ] No [x]

List the members of the group.
n/a

List specific exclusion from the group:
n/a</td>
<td>Rationale for therapeutic alternatives included:
n/a

Rationale for exclusion from the group:
n/a</td>
</tr>
<tr>
<td>VALUES & PREFERENCES / ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [ ]</td>
<td></td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?

More intensive [ ] Less intensive [x] Uncertain [ ]</td>
<td>Cost of medicines/ month:
<table>
<tr><th>Medicine</th><th>Cost (ZAR)</th></tr>
<tr><td>EFV/TDF/FTC FDC</td><td>R133.52*</td></tr>
<tr><td>RPV + TDF/FTC FDC</td><td>R45.99** + R78.89* = R124.88</td></tr>
<tr><td>NVP + TDF/FTC FDC</td><td>R33.93* + R 78.89* = R112.82</td></tr>
</table>
*Weighted average prices from contract circular HP132015.
** SEP database: 5 July 2016 (Edurant® 25 mg, 30 tablets).</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?

Yes [ ] No [x] Uncertain [ ]</td>
<td></td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td>
<td></td>
</tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	☐

Recommendation: Based on this evidence review, the PHC Expert Review committee suggests that rilpivirine be made available:

- For patients intolerant of efavirenz - these patients will likely be partially or completely virologically suppressed at the time of switching.
- As an alternative for those with neuropsychiatric contraindication - RPV would in such cases be used at treatment initiation as an alternative to nevirapine. Nevirapine is associated with severe AEs, with rates of discontinuation due to AES higher than EFV, therefore considerably higher than RPV [5]. Small increase in risk of failure needs to be weighed up against increased risk of AEs for this patient group.

Rationale: See above.

Level of Evidence: I RCTs

NEMLC MEETING OF 15 SEPTEMBER 2016:

The NEMLC did not accept the PHC Expert Review Committee's recommendation.

Discussion:

Nevirapine: The proposed recommendation of RPV was to replace nevirapine (NVP) which is considered a toxic medicine, was reviewed in the above-mentioned medicine review. However, there is no available head-to-head safety data comparing NVP to RPV. The medicine review used the available data and extrapolated the evidence.

Efavirenz (EFV): RPV is better tolerated than EFV, but RPV is less efficacious than EFV in patients with a viral load (VL)>100 000 copies/mL, which is the VL of about half of South African patients at baseline.

Recommendation: Rilpivirine not be recommended to replace NVP as part of the firstline ART regimen.

Rationale: RPV is less effective than EFV at high viral loads.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x	x	

VEN status:

Vital	Essential	Necessary
	x	

Monitoring and evaluation considerations

Research priorities

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