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Cost-effectiveness of rilpivirine- or efavirenz-based regimens for treatment-naïve, HIV-1-infected patients: NHS England perspective

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Introduction

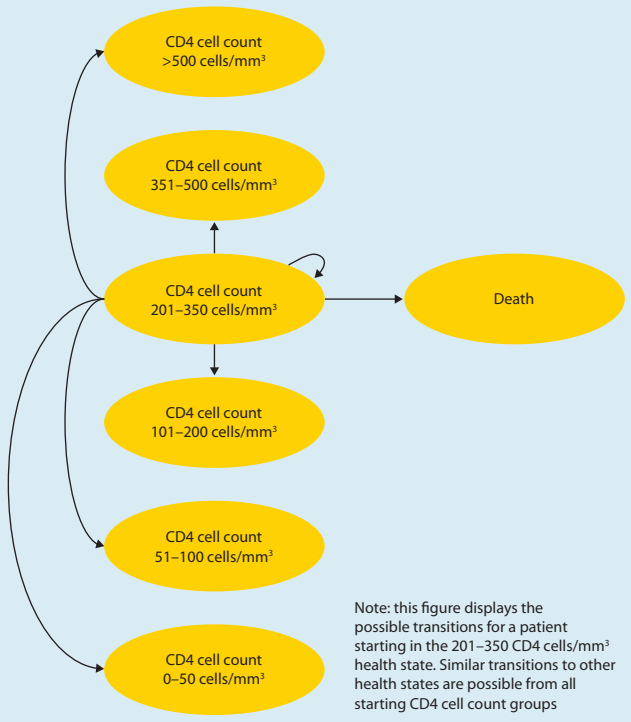
- Rilpivirine (RPV; EDURANT®), a new NNRTI, is approved for use in combination with other antiretroviral (ARV) drugs in HIV-1-infected, treatment-naïve adults, in the USA and Canada.[1] In the UK, as in the rest of the EU, RPV is approved for patients with a baseline viral load of ≤100,000 copies/mL.[2]
- Two Phase III, randomised, double-blind, double-dummy trials, ECHO (TMC278-C209, NCT00540449)[3] and THRIVE (TMC278-C215, NCT00543725)[4] demonstrated
  - Non-inferior efficacy of RPV 25 mg qd + background regimen (BR) of two N(t)RTIs to efavirenz (EFV) 600 mg qd + BR at 48 weeks
  - Lower rates of grade 2–4 treatment-related adverse events (rash, dizziness, abnormal dreams/nightmares), and statistically significantly smaller lipid elevations for RPV 25 mg qd + BR compared with EFV 600 mg qd+ BR.[3,4]
- The aim of the present analyses was to assess the cost-effectiveness of RPV 25 mg qd + BR in England, where RPV is used as a first-line regimen in multi-drug ARV therapy in HIV-1-infected patients
  - EFV 600 mg qd + BR was used as the active comparator in these analyses, as clinical guidelines recommend this regimen for HIV-1-infected, treatment-naïve adults.[5]

Methods

Model overview

- These analyses were based on a Markov model, with a 3-month cycle length typical of other Markov models in HIV.[6]
- In this Markov model, HIV-1-infected patients can transition between six possible CD4 cell count health states and death as the absorbing health state (**Figure 1**). The CD4 cell count ranges were based on clinical relevance (risk of disease progression) and reflected differences in treatment of patients at different CD4 cell count ranges.[7]

Figure 1. Markov model illustrating possible transitions between health states.



- The model assumes an NHS costing perspective in England and a lifetime horizon, which is appropriate for evaluating costs and effectiveness of treatments in a life-long condition such as HIV.
- As required by UK health technology assessment agencies, the annual discount rate is 3.5% for both outcomes and costs.[8]
- The patient population included in this economic model is reflective of the licensed patient population for RPV 25 mg qd, treatment-naïve patients who present with a baseline viral load ≤100,000 copies/mL, and who start treatment with RPV (25 mg qd + BR) or EFV (600 mg qd + BR) (as per the clinical trials ECHO[3] and THRIVE[4]).
- The model allows for three treatment switches after first-line therapy (**Figure 2**). Subsequent treatments are based on those optimised for treatment-experienced HIV-1-infected patients according to the latest BHIVA guidelines and expert opinion (**Table 1**).[5]
- Transition between health states of the model were defined according to the change in CD4 cell count over time and virologic response
  - The model assumed that, for every new treatment, each patient would experience up to three phases of CD4 cell count changes: a rapid increase initially; a slow increase or no change (stable); a decline (treatment is switched, or if fourth-line continued until death).[9]
  - The model also defined three levels of virologic response for every treatment based on HIV viral load: undetectable with <50 copies/mL; partially suppressed with >50 copies/mL but achieving ≥1 $\log_{10}$ drop in viral load; unsuppressed with <1 $\log_{10}$ drop in viral load, including those discontinuing treatment for any reason.

Model efficacy input parameters

- For the first-line regimens, pooled Week 48 data from the ECHO[3], and THRIVE[4], trials for patients with a baseline viral load of ≤100,000 copies/mL, were used to estimate the percentage of patients with undetectable viral load, considering the magnitude and duration of CD4 cell count changes in each response category.

Table 1. Subsequent treatment options.

Switch regimens considered	Weight, %
Second-line regimens	
Darunavir/r 800/100 mg qd + BR	80.0
Lopinavir/r + BR	10.0
Atazanavir/r + BR	10.0
Third-line regimens	
Etravirine + darunavir/r 600/100 mg bid + BR	25.0
Maraviroc + PIs (excluding darunavir/r 600/100 mg bid) + BR	25.0
Raltegravir + PIs + BR	50.0
Fourth-line regimens	
Etravirine + darunavir/r 600/100 mg bid + BR	12.5
Darunavir 600/100 mg bid + BR	25.0
PIs	12.5
Tipranavir + BR	12.5
Maraviroc + PIs (excluding darunavir/r 600/100 mg bid) + BR	12.5
PIs + BR	25.0

PI = protease inhibitor; /r = boosted with ritonavir; qd = once daily; bid = twice daily; BR = background regimen of two N(t)RTIs

- For subsequent regimens, efficacy estimates of the magnitude of virologic and immunologic responses were calculated as a weighted average of the relevant treatment options using data from randomised, controlled trials.[10–16]
- Base-case values for the duration of CD4 cell count changes in each virologic response category for subsequent regimens were based on published data[17] (**Table 2**).

Table 2. Duration (years) of CD4 cell count time periods by virologic response categories.

CD4 cell count change	Virologic response: Undetectable	Virologic response: Partially suppressed	Virologic response: Unsuppressed
First-line regimens			
Initial CD4 cell count rapid increase	0.5	0.5	0.5
Slowly increasing CD4 cell count	3	1	0.5
Stable CD4 cell count	9.75	0	0
Second-line regimens			
Initial CD4 cell count rapid increase	0.5	0.5	0.5
Slowly increasing CD4 cell count	2	0.5	0
Stable CD4 cell count	2	0	0
Third- and fourth-line regimens			
Initial CD4 cell count rapid increase	0.5	0.5	0.5
Slowly increasing CD4 cell count	2	0.5	0
Stable CD4 cell count	0	0	0
Declining CD4 cell count*	Until death	Until death	Until death

*Only relevant for fourth-line regimen
Viral load categories: undetectable with <50 copies/mL; partially suppressed with >50 copies/mL but achieving ≥1 $\log_{10}$ drop in viral load; unsuppressed with <1 $\log_{10}$ drop in viral load/discontinued

- Declining CD4 cell counts were only considered for fourth-line regimens. The model assumed that the rate of decrease (estimated from published data in highly treatment-experienced patients with virologic failure[18]) was constant until death, and that the transition probabilities were independent of treatment pathway, therapy line, and previous virologic response.

Other input parameters

- HIV-related mortality rates and utility weights for each of the model health states were obtained from published data[19,20] (**Table 3**).

Table 3. HIV-related mortality rates and utility values by model health state (CD4 cell count ranges).

CD4 cell count range (cells/mm³)	HIV-related mortality (annual rate)[19]	Utility values[20]
0–50	0.176	0.742
51–100	0.055	0.742
101–200	0.022	0.750
201–350	0.008	0.778
351–500	0.004	0.784
>500	0.004	0.798

- Non-HIV-related mortality was assumed to be similar to the general UK population[21] with an applied relative-risk value of 2.5 times the age-specific rate of death in a comparable non-HIV population.[22]
- The model also incorporated utility decrements for various adverse events based on the differences in adverse events between the RPV + BR and EFV + BR arms of the ECHO and THRIVE trials.[20] It was assumed that adverse events either resolved without intervention or were treated successfully within the first 3-month cycle. Only disutilities due to adverse events occurring in the first line of treatment were considered.
- ARV regimen costs (mean daily and 3-month costs; **Figure 3**) were derived via a micro-costing approach, based on
  - BR usage associated with RPV and EFV (consistent with the pooled ECHO/THRIVE data in patients with a baseline viral load of ≤100,000 copies/mL)
  - Costs applied to the distribution of drugs used first line and in the selection of subsequent regimens
  - The listed daily recommended dosages and costs/unit of dosing were obtained from the British National Formulary.[23] The cost of RPV used in the model was its NHS list price of £6.68/day (one 25 mg tablet).[23]
- Non-ARV drug costs (mean 3-monthly/patient costs, **Figure 4**) were based on a UK-based retrospective database analysis of overall resource use, direct medical costs of HIV infection (for varying degrees of treatment experience, immune deficiency and viral inhibition), management costs of adverse events, and costs of non-terminal and terminal care for patients with HIV/AIDS between 2000 and 2006[23]
  - Costs were inflated to 2010 prices using the Hospital and Community Health Service inflation index[24]
  - Analyses were conducted by CD4 cell count range.

Figure 2. Model treatment pathways.

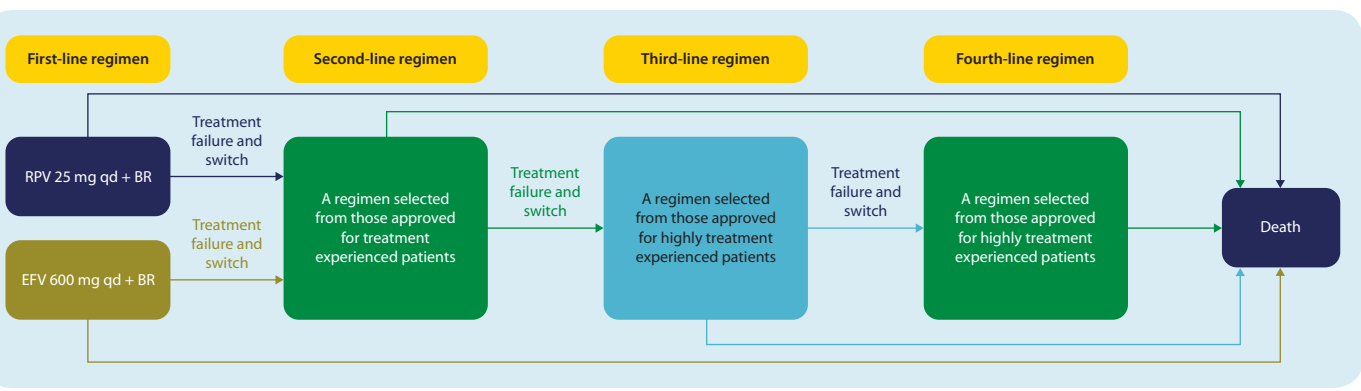


Figure 3. Mean ARV drug costs by regimen.[23]

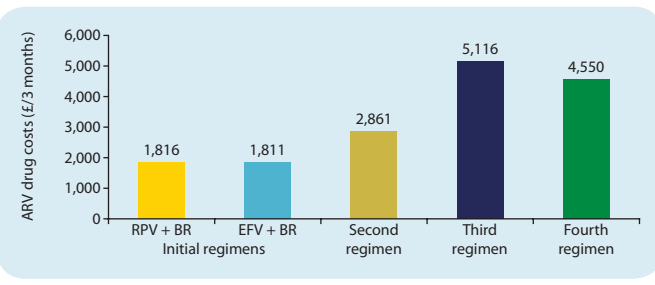
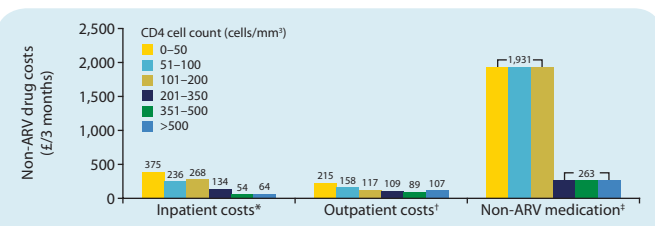


Figure 4. Mean non-ARV drug costs by CD4 cell count (cells/mm³) range.[24,25]



*Includes hospitalisation episodes and laboratory tests; †Includes HIV and non-HIV physician visits, laboratory tests and ambulatory procedures; ‡Patients with CD4 cell count <200 cells/mm³ are defined as AIDS patients, so all non-ARV medications used in these groups were averaged, and this average cost estimate was applied for all CD4 cell count groups below 200 cells/mm³

Results

- The main outcomes of this cost-effectiveness analysis included an estimation of the lifetime costs and quality-adjusted life-years (QALY) for newly diagnosed HIV-1-infected patients with a baseline viral load of ≤100,000 copies/mL
  - The incremental cost-effectiveness ratio (ICER) calculated was expressed in terms of costs per QALY
  - One-way (involving all key parameters) and probabilistic sensitivity analyses were also conducted.

Base-case cost-effectiveness results

- Over a patient lifetime, the cost of the RPV-based regimen was less than the EFV-based treatment
  - The incremental results were –£2,991 (–1.40%) over a lifetime (**Table 4**)
  - The RPV-based regimen dominated the EFV-based regimen and generated 0.068 (+0.5%) additional QALYs (**Table 4**).

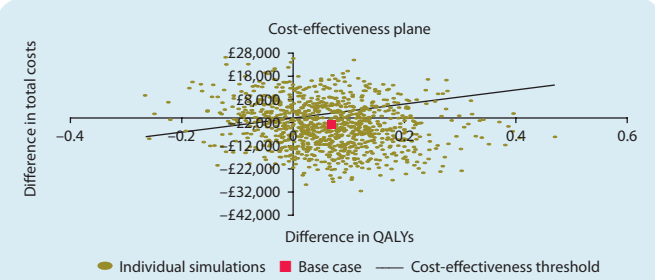
Table 4. Cost-effectiveness results for RPV 25 mg qd + BR versus EFV 600 mg qd + BR – lifetime horizon.

	Total costs, £	QALYs	Cost per QALY gained (RPV versus EFV)
RPV (25 mg qd + BR)	214,869	13.650	
EFV (600 mg qd + BR)	217,860	13.582	
Incremental results	–2,991	0.068	RPV dominates EFV

Sensitivity analyses

- One-way sensitivity analyses concluded that the rates of CD4 cell count changes and the first-line response rates were the main parameters that influenced ICER the most.
- Probabilistic sensitivity analyses were also conducted on the base case with 1,000 individual simulations (**Figure 5**), and indicated that the likelihood of an incremental cost-utility ratio below £20,000 and £30,000 per QALY gained was 65% and 66%, respectively.

Figure 5. Cost-effectiveness plane – base-case probabilistic sensitivity analysis.



Conclusions

- This economic evaluation shows that RPV 25 mg qd + BR costs £2,991 less than EFV 600 mg qd + BR and yields 0.068 additional QALYs.
- One-way and probabilistic analyses demonstrates that RPV 25 mg qd as part of an ARV drug regimen dominates EFV 600 mg qd when used in treatment-naïve HIV-1-infected patients.
- Differences between these treatments are very small over the lifetime of the model and the cost-effectiveness analyses should be interpreted with caution.
- One of the strengths of this model is that it uses strongly established, independent surrogate markers of HIV disease progression, the plasma HIV RNA and CD4 cell count, to project the efficacy findings of randomised trials over a longer time period.
- One of the limitations of this model is that the consequences of resistance upon first-line regimen failure were not taken into account.

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This poster is available on request to Isabelle Girod (igirod@ITS.JNJ.com)