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Cost-effectiveness of current treatment options in treatment-resistant HIV/AIDS patients in the German setting

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Abstract

Objectives

To perform a comprehensive economic evaluation of all pharmaceutical options in treatment-experienced HIV/AIDS patients in Germany, using the efficiency frontier approach, a method proposed by the German authorities.

Methods

Ten published, randomised, controlled trials were identified for the target population (POWER 1 and 2,[1] RESIST-1 and 2,[2] MOTIVATE 1 and 2,[3] DUET-1 and 2,[4,5] BENCHMRK-1 and 2[6]), from which we extracted: baseline characteristics; percentage of patients with viral load <50 copies/mL at Week 48 (response rates); enfuvirtide (ENF) use as co-medication and its impact on response; and all antiretroviral (ARV) therapies used. Unit drug costs were obtained from Rote Liste©. The results of all treatment arms (average and ± ENF) were plotted on a coordinate system with annual drug costs per patient ('cost') on the horizontal axis and response rates over 1 year ('value') on the vertical axis. The latter was also adjusted for baseline characteristics using logistic regression on pooled data of the DUET trials. Statistical uncertainty analysis was performed using a probability density approach with 1,000 simulations determining the probability that a given option falls on the efficiency frontier, i.e. offers the best value/cost.

Results

Twenty-six value/cost points were created representing all options. Drug costs per year per patient varied between €22,186 and €61,715 and response rates varied between 8.4% and 69.3% in the base case. Etravirine (ETR; TMC125) combinations were most likely to fall on the efficiency frontier (95.2% chance), followed by raltegravir (RAL; 16.6%). The last line segment of the frontier had a slope of €1,796 (95% confidence interval [CI]: €967–€3,072) per extra percentage response.

Conclusions

Constructing an efficiency frontier plot was feasible using adjustment for baseline characteristics. Regimens containing ETR are most likely to be economically efficient. Longer term evaluations including all healthcare costs could add valuable information, but would require many assumptions given the limited available data for the 26 compared strategies.

Data updated since abstract submission.

Background

- Germany has not operated its healthcare system within a fixed national budget
  - the goal of an economic evaluation in Germany is to address the ceiling price at which a superior health technology in a given therapeutic area should continue to be reimbursed
- To answer this question, IQWIG has developed the efficiency frontier concept
- On a graph, the relative value (benefit) and costs of alternatives to treat a single indication are plotted
  - the efficiency frontier is constructed connecting points that deliver the highest value per Euro (€) spent
- The goal of this project is to apply the efficiency frontier method to assess the cost-effectiveness of treatments for patients with treatment-resistant HIV/AIDS

IQWIG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)

Study design

- Patient populations
  - triple-class, ARV-experienced adult patients
  - HIV-1 RNA ≥1,000 copies/mL
  - resistance to three ARV classes by genotype
- Search strategy
  - search terms: 'HIV' AND 'resistan*'‡ OR 'experienced'
  - limits: randomised, controlled trials in humans published in 1998–2008, 48-week follow-up and three-class-experience/resistance
- Ten trials met criteria: POWER 1 and 2,[1] RESIST-1 and 2,[2] MOTIVATE 1 and 2,[3] DUET-1 and 2,[4,5] and BENCHMRK-1 and 2[6]
- Data extracted from all treatment arms
  - baseline characteristics
  - percentage of patients with a viral load <50 HIV-1 RNA copies/mL at Week 48 (response rates)
  - ENF use as co-medication and its impact on response (for data interpretation)

‡The asterisk was used as a wildcard or placeholder for unspecified characters in the search term 'resistan*' to expand the results and include publications with the related terms 'resistance' and 'resistant'

Study design (cont'd)

- HIV-1 RNA viral load <50 copies/mL at Week 48 was selected as parameter for 'value' to assess the cost-effectiveness of treatment
  - recommended parameter by European and US guidelines[7,8]
  - response rate in terms of percentage of patients with viral load <50 HIV-1 RNA copies/mL is expressed on a cardinal scale
- Response rates were adjusted using two independent methods
  - response rates of common treatment arms
  - baseline characteristics, i.e. viral load and resistance
- The use of all ARV therapies was collected and multiplied with their unit costs
- Unit costs were derived from Rote Liste®[9]

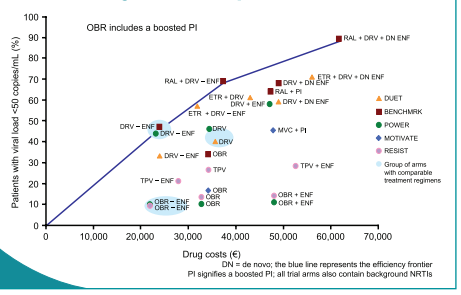
*The list of approved medicines in Germany and throughout Europe

Baseline patient data and treatment characteristics

	POWER[1]		RESIST[2]		MOTIVATE[3]		DUET[4,5]		BENCHMRK[6]	
Intervention	DRV + OBR	PI + OBR	TPV + OBR	PI + OBR	MVC + OBR	PBO + OBR	ETR + OBR	PBO + OBR	RAL + OBR	PBO + OBR
Age, years	44	44	43	42	46	46	46	45	46	45
Male, %	89	88	88	88	90	90	91	89	88	88
CD4 cell count, cells/mm³	153	163	155	155	189	187	99	109	151	158
Viral load, $\log_{10}$ copies/mL	4.60	4.50	4.73	4.73	4.85	4.86	4.80	4.80	4.60	4.60
ENF use, %	46	42	23	18	43	44	52	52	38	38
DRV use, %	100	0	0	0	0	0	100	100	40	42
PSS ≤1 in OBR, %	54	54	43	43	53	53	56	56	46	46

MVC = maraviroc; OBR = optimised background regimen (includes a boosted PI, except in POWER and RESIST); PBO = placebo; TPV = tipranavir; PI = protease inhibitor (boosted) DRV = darunavir; PSS = phenotypic susceptibility score

Efficiency frontier plot: unadjusted response rates



Adjustment for response rates

→ proportional adjustment based on arms with comparable treatment regimens

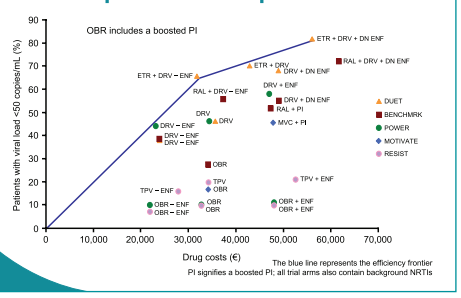
- Example
  - the OBR arm of RESIST shows a response rate of 13.5% vs 10% for the POWER OBR arm
  - this method aligns both arms by applying the factor 13.5/10 = 1.35 to all RESIST arms
- Step 1: adjust RESIST OBR to POWER OBR; adjust DUET DRV to POWER DRV

	DUET	RESIST	POWER	
Arm	DRV	OBR	DRV	OBR
Unadjusted response	40.0	13.5	46.0	10.0
Adjustment factor	0.87	1.35	1.00	1.00
Adjusted response	46.0	10.0	46.0	10.0

- Step 2: adjust BENCHMRK to DUET

	BENCHMRK	DUET
Arm	DRV-ENF	DRV-ENF
Unadjusted response	47.0	38.0
Adjustment factor	1.24	1.00
Adjusted response	38.0	38.0

Efficiency frontier plot: adjusted for response of comparable arms



Adjustment for viral load and resistance level at baseline

Result from multivariate logistic regression on the DUET trial with viral load response as dependent variable

Parameter	Odds ratio
Baseline viral load ($\log_{10}$ copies/mL)	0.35
Percentage of patients with PSS ≤1 in the OBR	2.18

- From the logistic regression several parameters were found to exert an independent impact on response rates
- However, only viral load at baseline and resistance (PSS ≤1) were systematically and transparently reported in all trial reports

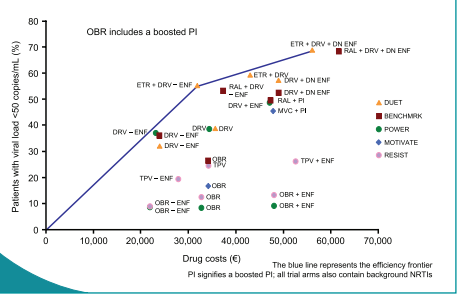
Adjustment for viral load and resistance level at baseline: example

	MOTIVATE		BENCHMRK	
Arm	MVC	OBR	RAL	OBR
Patients with viral load <50 HIV-1 RNA copies/mL at 48 weeks, %	46	17	64	34
MOTIVATE as reference	**MOTIVATE**	**MOTIVATE**	**BENCHMRK**	**BENCHMRK**
Baseline viral load, $\log_{10}$ copies/mL	4.85	4.85	4.60	4.60
Patients with PSS ≤1, %	53	53	46	46
Viral load adjustment factor	0	0	**0.16**	**0.16**
Resistance adjustment factor	0	0	**0.04**	**0.04**
Result adjustment 2				
Patients with viral load <50 HIV-1 RNA copies/mL at 48 weeks, %	46	17	52	27

$\text{Viral load adjustment factor}_{BENCHMRK} = (\text{baseline viral load}_{MOTIVATE} - \text{baseline viral load}_{BENCHMRK})(1-\text{odds ratio}_{\text{baseline viral load}})$
$0.16 = (4.85-4.60)(1-0.35)$

$\text{Adjusted response rate}_{BENCHMRK} = \text{unadjusted response rate}\,(1-\text{viral load adjustment factor})(1-\text{resistance adjustment factor})$
$52\% = 64\%\,(1-0.16)(1-0.04)$

Efficiency frontier plot: adjusted for viral load and resistance level at baseline

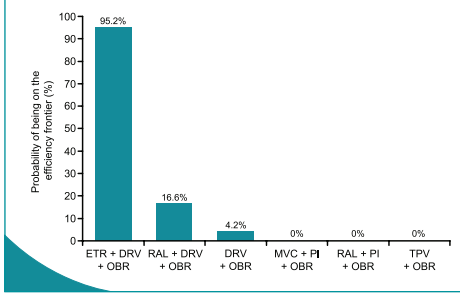


Probabilistic sensitivity analysis

- A probabilistic sensitivity analysis was conducted by applying 1,000 runs of the calculations, using at random possible values of the input data
- All response rates were assumed to be binomially distributed and we therefore generated beta-distributions for probabilistic sensitivity analysis
- For cost data, no SEs were available. We assumed the SE to be 30% of the average cost and applied a gamma distribution to account for possible skewness of the cost data[10]
- The number of times a given combination appeared on the efficiency frontier was counted. Combinations were then grouped according to the main drugs in each combination. The number of appearances of a given drug regimen on the efficiency frontier was then counted

SE = standard error

Probabilistic sensitivity analysis (cont'd)



Discussion

- Strengths
  - feasibility of methodology
  - common endpoint used (viral load <50 HIV-1 RNA copies/mL)
  - endpoint accepted by HIV guidelines
  - in-line with German IQWIG guidance
  - consistent estimates between both independent adjustments (good face validity)
- Limitations
  - only drug costs based on 52 weeks
  - only viral load <50 HIV-1 RNA copies/mL as outcome parameter
  - short time horizon (1 year)
  - not separate de-novo ENF data for POWER and RESIST
  - adjustment on baseline characteristics only possible for viral load and resistance
  - not being able to control for different study baseline characteristics, cross-study comparisons and assumptions
- Longer term evaluation including all healthcare costs is preferable, however, this type of analysis would require many assumptions given the available data for the 26 compared strategies

Conclusions

- Constructing an efficiency frontier plot was feasible using clinical trial results of treatment-resistant HIV/AIDS patients
- However, available trial data limits adjustment possibilities, length of time horizon, and estimation of a wide range of outcomes
- After adjustment, ETR-containing regimens are most likely to be on the efficiency frontier plotting <50 copies/mL endpoint and drug costs, and may therefore represent efficient options for treatment-resistant HIV/AIDS patients on these parameters

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