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Analysis of contemporary HIV/AIDS health care costs in Germany

Driving factors and distribution across antiretroviral therapy lines

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Abstract

To analyze contemporary costs of HIV health care and the cost distribution across lines of combination antiretroviral therapy (cART). To identify variations in expenditures with patient characteristics and to identify main cost determinants. To compute cost ratios between patients with varying characteristics.

Empirical data on costs are collected in Germany within a 2-year prospective observational noninterventional multicenter study. The database contains information for 1154 HIV-infected patients from 8 medical centers.

Means and standard deviations of the total costs are estimated for each cost fraction and across cART lines and regimens. The costs are regressed against various patient characteristics using a generalized linear model. Relative costs are calculated using the resultant coefficients.

The average annual total costs (SD) per patient are €22,231.03 (8786.13) with a maximum of €83,970. cART medication is the major cost fraction (83.8%) with a mean of €18,688.62 (5289.48). The major cost-driving factors are cART regimen, CD4-T cell count, cART drug resistance, and concomitant diseases. Viral load, pathology tests, and demographics have no significant impact. Standard non-nucleoside reverse transcriptase inhibitor-based regimens induce 28% lower total costs compared with standard PI/r regimens. Resistance to 3 or more antiretroviral classes induces a significant increase in costs.

HIV treatment in Germany continues to be expensive. Majority of costs are attributable to cART. Main cost determinants are CD4-T cells count, comorbidity, genotypic antiviral resistance, and therapy regimen. Combinations of characteristics associated with higher expenditures enhance the increasing effect on the costs and induce high cost cases.

Abbreviations: ALT = alanine aminotransferase, ARV = antiretroviral, cART = combination antiretroviral therapy, CCR5 = C-C chemokine receptor type 5, CDC = Centers for Disease Control and Prevention classification system, CORSAR = Cost and

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Resource Utilization Study in Antiretroviral Therapy, GLM = a generalized linear model, HIV = the human immunodeficiency virus, LDL= low-density lipoprotein cholesterol, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PLWHIV = people living with HIV, SD = standard deviation.

Keywords: combination antiretroviral therapy, cost determinants, cost ratios, costs, HIV, prospective cohort survey, utilization

1. Introduction

The introduction of combined antiretroviral (ARV) therapy and its successful scale-up have resulted in major reductions in HIV-associated morbidity and mortality,[1–3] and transformed HIV into a chronic and manageable condition.[4] cART regimens have been proven effective and well tolerated, and have become the standard in HIV-related health care[4–6]; however, cART is expensive and together with the growing number of people living with HIV, who receive cART and their prolonged life expectancy, it poses an increasing financial burden on public health systems. Continuous accurate estimations of the related costs have become important for decision-making in management of HIV infection.[7] Estimates of annual total expenditures per patient have been obtained worldwide[8–13]; however, in Germany relatively few studies have investigated costs of HIV treatment since the advent of cart.[8,14–16] For the period from 2006 to 2009, mean average costs for Germany were estimated as € 23,298 per patient.[14] It has been determined that patient characteristics, such as CD4-T cell count are good predictors of annual costs; however, the authors point to a need for further research in this field.[7,14]

The objective of the present study is to explore links between costs and a wide set of patient characteristics using data, which were collected within a 96 weeks noninterventional, multicenter prospective cohort study: Cost and Resource Utilization Study in Antiretroviral Therapy (CORSAR).[16] Previously, we conducted a descriptive analysis of the cost data obtained over the first 48 weeks of this survey.[16]

In this analysis, we examine composition of the annual costs, determine major cost drivers,[17] and estimate relative cost ratios[18] between patients with varying characteristics. The relative cost ratios, in comparison to point estimates, have the advantage of possible stability across various populations, and therefore, they may be applicable to populations other than the German case.[18]

2. Methods

2.1. Setting and study design

The multicenter CORSAR study recruited patients in 8 regionally and structurally different health care providers from different areas in Germany for a prospective noninterventional survey from 2009 to 2012: 4 specialized private practices (outpatient centers) and 4 hospitals offering both HIV-related inpatient and outpatient services. The multicenter design and absence of preselection minimized a risk of bias.

Major criteria for enrolment of the patients to the survey were HIV-positive status, age older than 18 years, and ongoing cART. At the beginning of the survey, the participating sites recorded full patient data as at the date of individual entry to the study; thereafter, the observation and recording of the data were documented every 3 months on an individual schedule. The resultant database provided information on (i) demographics: age, gender, education, and income status; (ii) clinical conditions: diagnosis, time after initial diagnosis of HIV infection, CD4-T cell count, Centers for Disease Control and Prevention classification system (CDC) class, viral load, pathology tests, disability, and comorbidities; (iii) therapy: therapeutic regimen (dosage, substances, and treatment periods), line of ARV regimen at start of the study, genotypic resistance testing, and details of concomitant medications.

The following classifying parameters were assigned to the patients at the date of entry and were not changed during the follow-up period: age, CDC classification, time since the initial diagnosis of HIV before entering the study, assigned therapy regimen, and cART therapy line.

For the analysis, ARV regimens were classified according to the classes of the ARV substances (further references to the defined here ARV regimens are highlighted in Italic format and used for the purpose of the present analysis only):

1. *"NNRTI"* (non-nucleoside reverse transcriptase inhibitor): NNRTI-based regimen, consisting of 1 NNRTI in addition to nucleos(t)ide analogues;
2. "*PI-standardized*": PI-based regimen, consisting of 1 ritonavir-boosted PI (Protease inhibitor, PI/r) in addition to nucleos (t)ide analogues;
3. *"PI-individualized"*: individualized PI/r-based cART regimens consisting of elements of more than 2 different ARV classes and more than 3 different ARV substances including boosted PIs (predominantly used as a salvage regimen in multiple pretreated patients);
4. *"Other"*: other cART regimens that do not meet the criteria of the 3 previous regimen classes, that is, regimens that consist neither of PI nor NNRTI elements, that is, those based on the INSTI (integrase strand transfer inhibitor) raltegravir or the CCR5 (C-C chemokine receptor type 5) inhibitor maraviroc, nor nuke-sparing regimens, for example, boosted double PI/r therapy;
5. *"Mixed"*: if patients spent less than 95% of the year on one of the aforementioned regimen classes, their therapy classes were classified as "Mixed."

2.2. Ethical review

The CORSAR survey was approved by the national regulatory authorities and local ethics committees of all participating centers. All patients were given thorough information on the survey. Before the participation in the interviews, the patients gave a written consent. No incentive was offered for the participation in the survey.

2.3. Cost calculations

The collected data contained detailed information on utilization of various resources, including (i) cART medication and non-HIV medication; (ii) outpatient care (physicians' services, outpatient rehabilitation, nutritional, and psychological support); (iii)

inpatient care (hospital stay, inpatient costs, rehabilitation, physiotherapy, and overhead expenses); (iv) indirect costs; and (v) out-of-pocket costs.

The expenditures were calculated by taking the volume of resource utilization for inpatient days, outpatient specialist visits, lab tests, usage of in- and outpatient rehabilitation, and services of nutritionists and psychologists, and multiplying these by the respective unit cost in accordance with the current German recommendations for the assessment of health care resource consumption.[19,20] Following these recommendations,[20] we calculated drug costs taking pharmacy retail prices and subtracting manufacturer and pharmacy discounts paid to the statutory health insurance.

We estimated the unit cost of an inpatient stay based on German hospital statistics.[21] The calculation of in- and outpatient rehabilitation unit cost was performed using data from the statutory health insurance fund, retirement insurance, and the Federal Association for Rehabilitation.[22–24] Data on the unit cost for a specialist visit were retrieved from the salary report provided by the German Association of Statutory Health Insurance Doctors.[25] Publically available reports on supportive medical care were used in estimating the unit cost for massages and physiotherapy services.[26–28] Indirect costs were calculated as the product of number of days of absence from work and work compensation per day. To avoid overestimation of the indirect costs of early retirements or permanent occupational disability, we put an upper limit to the days of absence from work equal to the vacancy time of jobs in Germany in 2012 (77 days).[20] This approach is a simplification of the friction costs approach.[29]

Cumulative annual costs were calculated prospectively by annualization. Total costs were computed as the sum of the cost fractions following a bottom-up method.

2.4. Analysis

Total costs were analyzed separately for each year of the observational period. We excluded from the obtained data all individuals on treatment break, all patients who had abandoned the survey during the first year, and those patients who incurred extremely high expenditures on non-HIV medication (over €100,000/year). We defined proportions for each of the cost components and analyzed the variation of the total costs across the patient variables. We calculated means and standard deviations of the total costs as well as the costs in each fraction.

In order to estimate mean annual costs as a function of various patient characteristics, we employed different multiple regression models. We developed the models based on distributional characteristics of the cost data and selected the best-fitting model using McFadden's pseudo-R^2 and measures of prediction ability.[30] We used the obtained estimates to calculate cost ratios[18] that allowed the comparison of cost projections for patients with varying indicative characteristics while holding others unchanged. Detailed description of the model development and estimation of the cost ratios are given in Appendix A (see Appendix A and to that related Table 9, Table 10, and Figures 2–5, Supplemental Content, http://links.lww.com/MD/B55, which describe the applied methods in greater detail).

3. Results

Overall, CORSAR enrolled 1154 adult patients. In total, we excluded 132 patients: 63 people with treatment interruptions, 65 people who abandoned the survey during the first year and 4 patients who incurred extremely high expenditures on non–HIV-related medications. Eighty patients did not follow the survey into the second year. The resulting sample was of 1022 patients who had completed the first year and 942 who had completed both years of the survey, totally resulting in 1964 patient years.

Table 1 reports details on the patient data and estimates of the average annualized total costs stratified across clinical and demographic variables.

The patient data for subjects lost to follow-up during the first year of the study are given in supplement (see Table 6, Supplemental Content, http://links.lww.com/MD/B55) and show no particular differences from the rest sample. Results of the descriptive analysis of the costs do not show a considerable difference between the estimates obtained for the first and the second year as well as there were no significant differences in the cost of HIV care across the 8 health care provider sites in the survey. For the first and the second year, the mean annual total costs (SD) per patient were €22,477.57 (8809.45) with a maximum of €87,920, and €22,231.03 (8786.13) with a maximum of €83,970, respectively. cART medication was found to be the major contributor (83.8%) to the total costs with mean (SD) of €18,852.53 (5297.44) in the first and €18,688.62 (5289.48) in the second year. The second largest fraction was medication costs on treatment of comorbidities with mean values of €1499.36 (3718.50) and €1805.05 (5034.45) and for the first (6.6%) and second (8.1%) years, respectively. Expenditures on inpatient care were estimated as €1246.98 (3850.15) and €984.53 (2894.06) and contributed 5.6% and 4.4% into the total costs, respectively. Further data on costs stratified by therapy line and therapy class are given in Table 2 for both years.

Tables presenting the cost data across the 8 health care providers stratified by cost categories (see Table 7, Supplemental Content, http://links.lww.com/MD/B55) and annualized costs of HIV care by cost category for both years of CORSAR(see Table 8, Supplemental Content, http://links.lww.com/MD/B55) are given in the supplemental content.

The regression analysis was performed using the full patient data collected at the beginning of the survey and data on expenditures obtained over the following 1-year period of the CORSAR survey (n = 1022; Table 1). Patients with CD4-T count below 200 cells/mm^3 incur the highest total costs, cART medication costs, and inpatient costs compared with those for patients with less advanced cellular immunodeficiency. Table 3 reports mean (SD) total costs for each therapy line and therapy class stratified by CD4-T cell count showing the same pattern of variability of the costs for different disease stages across therapy classes and cART lines.

As assessed by 1-way analyses of variance, overall differences in mean total costs were statistically significant across the categories of the following variables: CD4-T cell count, plasma viral load of HIV, genotypic antiviral resistance, comorbidity, ARV therapy line, and therapy class.

We regressed the annual total costs against 14 explanatory variables using a generalized linear model (GLM) with a log link function and inverse Gaussian distribution of the error term.[31] The estimates with 95% confidence intervals resulting from fitting the model are given on a log scale in Table 4. Exponentiating the value of the intercept gives an estimate of the mean total costs for a hypothetical patient with the reference characteristics as €22,959.80. All estimates represent the mean differences in total costs relative to these control categories.

Table 1

Description of the CORSAR patients' data (independent variables) and respective mean annualized total costs (outcome variable; n = 1022).

Variable	Description	Categories	Percentage of observations, %	Mean total costs (SD), Euro
Patient sociodemographics				
Age group	Age group of a patient in years	20–29	2.45	20433.52 (5832.53)
		30–44	35.03	21204.40 (7139.14)
		45–59	48.43	23293.55 (9619.25)
		60+	13.99	23146.07 (9955.26)
		n.a.*	0.10	
Gender	Gender	Female	11.15	21135.21 (7313.19)
		Male	88.16	22631.30 (9001.27)
		n.a.	0.68	
Education	The highest educational level achieved	Graduated	17.22	22899.59 (9874.76)
		Neither nor	69.57	22593.78 (8792.30)
		No school certificate	1.86	22257.89 (5689.44)
		n.a.	11.35	
Income	Stable or nonstable income	Full-time employment	36.89	22109.67 (9331.49)
		Pensioner	26.22	24353.18 (9792.38)
		Other	23.48	21553.61 (7067.69)
		n.a.	13.41	
HIV-related variables				
Time since diagnosis of HIV	Time after initial diagnosis of HIV infection before entering the survey (in years)	0–10	45.89	20887.23 (6546.21)
		10–20	33.37	22856.04 (9426.28)
		>20	10.96	26947.46 (12355.37)
		n.a.	9.78	
CDC class	Class according to the CDC classification system for HIV infection	Category A: Mildly symptomatic	29.26	20444.96 (6887.97)
		Category B: Moderately symptomatic	43.25	23013.70 (8742.01)
		Category C: Severely symptomatic	27.50	23759.40 (10400.28)
		n.a.	0.00	
Viral load	HIV viral load (RNA copies/mL)	<50	85.23	22114.38 (8523.27)
		50–500	6.36	24674.51 (10423.58)
		>500	2.05	26808.55 (16209.45)
		n.a.	6.36	
CD4-T	CD4-T cell count (cells/mm^3)	>500	55.09	22014.91 (8559.18)
		200–500	38.36	22203.99 (8151.42)
		<200	6.46	27960.86 (12774.61)
		n.a.	0.10	
Treatment-related variables				
Therapy class	Assigned antiretroviral drugs classes	PI-ind	5.58	38333.72 (13250.53)
		PI-standard	40.90	25057.94 (6769.53)
		NNRTI	26.52	18221.90 (5457.26)
		Mixed	7.63	22575.21 (9796.56)
		Other	19.37	18295.04 (7014.85)
		n.a.	0.00	
Therapy line	Combination antiretroviral therapy (cART) line	First line	42.27	21182.04 (7193.05)
		Second and third line	17.03	21259.52 (7562.71)
		Beyond the third line	27.89	25285.13 (10824.55)
		n.a.	12.82	
Resistance	Genotypic resistance against antiretroviral medication	No resistance	82.58	21737.98 (8164.37)
		Three classes (PI, NNRTI, and NRTI) and more	4.31	16546.00 (4625.89)
		NNRTI	0.20	27411.45 (11468.56)
		NRTI	1.08	27876.00 (10467.59)
		NRTI and NNRTI	0.49	23194.37 (9335.68)
		PI	7.63	23491.32 (9016.87)
		PI and NRTI	3.72	32670.73 (12439.09)
		n.a.	0.00	
General health-related variables				
ALT test	Alanine aminotransferase test (U/L)	<110	94.81	22454.79 (8787.94)
		≥110	2.64	24926.26 (11215.06)
		n.a.	2.54	
LDL test	Low-density lipoprotein cholesterol test (mg/dL)	<200	76.91	22645.74 (8996.35)
		≥200	1.96	22207.95 (4438.80)

Variable	Description	Categories	Percentage of observations, %	Mean total costs (SD), Euro
		n.a.	21.14	
Creatinine test	Serum creatinine level test (mg/dL)	< 0.9	49.12	21853.01 (8385.95)
		0.9–1.5	46.67	23165.05 (8911.07)
		>1.5	1.66	28518.82 (17065.95)
		n.a.	2.54	
Comorbidity	Number of concomitant diseases and degree the severity of the severest among the diseases	≤2non-severe	33.46	21153.69 (8564.13)
		≤2 severe	8.61	24335.64 (9100.47)
		>2 nonsevere	25.05	21886.39 (7486.47)
		>2 severe	4.01	28704.37 (14693.85)
		None	28.86	21004.24 (8180.29)
		n.a.	0.00	
Disability	Disability index according to the German the Disabled Persons Act†	0—No disability	50.39	21206.26 (7834.82)
		<50—Intermediate/moderate disability	11.35	22169.72 (8152.56)
		≥50—Severe disability in activities of daily living	28.96	24762.82 (10245.40)
		n.a.	9.30	

ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention classification system; HIV = human immunodeficiency virus; LDL = low-density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

* Not available observations.

† Grad der Behinderung (GdB), Deutsches Schwerbehindertenrecht.

The results of the regression revealed that low CD4-T cell count, genotypic resistance against ARV medication, and a greater number and severity of concomitant diseases were strong predictors of more intensive health care utilization and increased treatment costs. Higher costs were induced by the following levels of the predictors: evidence of cellular immunodeficiency at entry to CORSAR ("CD4-T cell count between 200 and 500/mm^3" or "less than 200/mm^3") vs. nonimpaired immune status ("more than 500/mm^3"), disability with index ">50" versus index "0," comorbidity classified as more than 2 nonsevere concomitant diseases and more than 2 severe concomitant diseases versus control category of fewer than 2 nonsevere concomitant diseases, therapy class defined as *"PI-individualized"* versus *"PI-standardized*," drug resistance to *PI*-based regimens or to 3 or more ARV classes versus no genotypic resistance.

The following categories of the predictors were associated with lower costs relative to the control categories: female gender, "10–20 years" versus "0–10 years" after the first positive diagnosis of HIV infection, a laboratory test of blood creatinine with level of ">1.5" versus "<0.9," therapy class of *"NNRTI," "Mixed,"* and *"Other"* category versus *"PI-standardized"* category. Age, CDC-class, laboratory tests low-density lipoprotein (LDL) and alanine aminotransferase (ALT), and viral load did not appear to have a significant effect on the total costs within the study.

Using the obtained estimates, we calculated cost ratios between patients with different characteristics.[18] Assuming all other patient characteristics being held constant, cost ratios were estimated relative to the following comparison group: "male" gender, *"PI-standardized"* therapy class, "<500" CD4-T cell count, comorbidity of fewer than 2 nonsevere diseases, no drug resistance. The ratios were calculated across genders, all CD4-T cell strata, all therapy classes, and 2 categories of drug resistance: resistance to at least 3 therapy classes and no resistance. Figure 1 illustrates calculated cost ratios. The values of the ratios and respective confidence intervals are given in Table 5.

The relative costs show either increasing or decreasing effects of the selected categories of the patients characteristics on the costs in terms of factors relative to the reference case, and can be used to explore interactions among groups of the patient characteristics.

The cost ratios show an enhanced increasing effect of a combination of the patient characteristics associated with higher costs. For instance, for those with resistance to 3 or more ARV classes the costs increase by a factor of 1.266. For those with combination of this resistance with a complex individualized cART regimen, the costs increase by a factor of 1.818. Adding to this combination a low CD4-T cell count and severe comorbidity increases the costs by more significant factors: of 2.202 and 2.722, respectively.

4. Discussion

The strength of CORSAR is that it provides recent cost-of-disease data of HIV infection in a prospective, multicenter study design within a large national cohort in Germany, representing different structures of the German health care providers. It reflects the actual state of cART for patients in different stages of HIV disease and on different ARV treatment lines, including more recently approved ARVs, complies with current treatment guidelines, and takes into account actual price changes in the cART medication during the observation period. Additionally, the present work gains an advantage with estimating the cost ratios that can be applicable for other populations.

The estimated average annual total costs per patient (€22,231.03) are slightly lower comparing with the results of Mostardt et al (€23,298)[14] who conducted their study in Germany, using 2008 as the price reference year. As well as, our estimates fall into ranges of estimates provided in different studies conducted in the United States[7,32,33] and European countries.[8] Overall, comparison of the results between the studies should be done cautiously due to considerable differences in the design of the observational surveys and the resultant population samples.

The proportion of cART costs in total costs has risen from about 67% to about 84% and the fraction of inpatient care costs has decreased from the level estimated in 2001,[34] suggesting a shift of cost out of the inpatient sector to cART medication.

Table 2

Data on annual costs for patients who completed both years of the CORSAR survey (n = 942).

Cost category	Mean value (SD), Euro	Mean of total costs (SD) stratified by cARV classes (Euro)					Mean of total costs (SD) stratified by therapy line (Euro)		
		PI-ind	PI-stand	NNRTI	Mixed	Other	The first	The second and the third	Beyond the third
First year									
Total	22477.57 (8809.45)	38807.37 (13347.77)	25021.43 (6773.17)	18305.38 (5526.97)	22318.67 (9320.46)	18350.06 (7136.07)	21226.70 (7317.71)	21561.67 (7784.97)	25111.35 (10721.43)
cART drugs	18852.53 (5297.44)	31652.08 (8806.35)	21363.35 (2377.22)	15290.10 (2105.68)	17490.97 (5055.32)	15352.91 (2557.63)	18124.78 (3529.85)	17722.98 (4408.11)	21002.50 (7066.84)
non-ARV medication	1499.36 (3718.50)	2631.13 (4025.93)	1440.57 (3631.37)	1187.56 (2774.55)	1679.84 (3405.73)	1658.48 (4849.21)	1437.29 (3915.39)	1235.37 (2844.53)	1507.77 (2637.36)
Inpatient	1246.98 (3850.15)	807.01 (2465.48)	1547.97 (3917.44)	1767.41 (5269.66)	2848.24 (6271.08)	1335.85 (4034.88)	807.01 (2465.48)	1547.97 (3917.44)	1767.41 (5269.66)
Outpatient	237.04 (365.61)	411.53 (435.21)	237.66 (423.93)	221.47 (305.75)	340.76 (444.53)	174.23 (204.52)	203.80 (344.77)	292.88 (481.83)	256.26 (301.55)
Out-of-pocket	212.23 (588.61)	305.64 (402.85)	177.47 (402.19)	256.43 (847.86)	265.75 (392.49)	187.67 (611.58)	159.72 (322.66)	292.83 (821.54)	227.21 (748.75)
Indirect	1462.79 (3997.91)	3298.73 (6981.94)	1783.14 (5087.58)	922.70 (1818.29)	2072.96 (3530.65)	1063.23 (3200.57)	1502.04 (4454.53)	1575.45 (4754.07)	1414.07 (2998.35)
Second year									
Total	22231.03 (8786.13)	37160.13 (12910.61)	24996.83 (7557.19)	18473.63 (5270.54)	21371.81 (9912.31)	17720.64 (6222.37)	21375.84 (8317.12)	21530.47 (8521.24)	24142.63 (9427.27)
cART drugs	18688.62 (5289.48)	30261.38 (9128.45)	21118.57 (2857.45)	15242.47 (2075.62)	17639.52 (6054.55)	15427.86 (2778.26)	17999.36 (3822.80)	17437.05 (4467.77)	20615.94 (6863.31)
Non-ARV medication	1805.05 (5034.45)	4481.83 (8921.18)	1797.47 (5359.98)	1499.81 (3248.62)	1859.79 (5037.11)	1432.97 (4589.33)	1704.13 (5592.51)	1548.70 (4512.54)	1945.12 (4058.64)
Inpatient	984.53 (2894.06)	1205.02 (2835.33)	1257.06 (3436.72)	927.38 (2631.36)	938.43 (2913.44)	455.77 (1723.47)	969.09 (2829.57)	1530.18 (3728.38)	843.41 (2586.54)
Outpatient	240.06 (391.10)	469.14 (585.54)	239.97 (410.57)	234.36 (355.41)	350.59 (505.19)	148.92 (218.48)	200.08 (352.24)	289.60 (504.87)	287.30 (398.81)
Out-of-pocket	200.87 (605.36)	295.43 (353.03)	233.58 (820.15)	165.88 (335.26)	252.55 (546.88)	133.94 (364.22)	184.13 (776.05)	196.67 (474.20)	231.80 (449.92)
Indirect	1779.37 (4175.84)	665.39 (1004.72)	1691.89 (4897.11)	2054.83 (3487.30)	3116.64 (6525.48)	1487.30 (3175.83)	1898.57 (4975.25)	2498.60 (3682.13)	633.71 (880.17)

ARV = antiretroviral; cART = combination antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

*The estimates of the annualized total costs presented in Table 2 include also negligible cost fractions, for example, massages, psychological support, nutrition consulting.

Table 3

Mean annualized total costs (SD) by CD4-T cells count stratum, the therapy line, and the therapy class.

Mean of total costs (SD) across combination antiretroviral therapy lines stratified by CD4-Tcell count (n = 1022; Euro)			
CD4–T cells/mm^3	The first	The second and the third	Beyond the third
>500	21551.78 (8152.84)	20739.94 (7130.33)	23911.55 (10345.39)
200–500	20609.06 (5824.29)	21056.82 (7239.24)	26060.39 (10305.20)
<200	22592.92 (7701.60)	27489.64 (10824.19)	32418.55 (14193.73)

Mean of total costs (SD) across antiretroviral drugs classes stratified by CD4-T-cell count (n = 1022; Euro)					
CD4–T cells/mm^3	PI-ind	PI-stand	NNRTI	Mixed	Other
>500	37762.54 (13829.54)	25234.02 (7661.74)	17569.25 (4773.33)	20696.30 (6837.91)	17445.12 (4510.64)
200–500	37407.90 (12499.68)	24476.15 (5203.15)	18993.48 (6276.20)	21702.12 (9941.09)	18020.45 (6544.42)
<200	42763.12 (13935.73)	27503.20 (5701.21)	20455.50 (5685.62)	28441.08 (15167.92)	26177.79 (15844.88)

NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Mean cART costs are higher for first-line therapy compared with second- and third-line therapies. The difference is a consequence of the applied ARV regimens: PI/r or INSTI-based regimens were commonly used in first-line therapy and were more expensive than NNRTI-based cART regimens, which were widely applied in second- or third-line cART in Germany before 2013. The predominance of PI/r-based cART in first-line therapy has been previously described in the German Clin-Surv cohort and explained by the assumption of an elevated risk of virologic failures and selection for viral resistance by NNRTIs in cART-naïve patients with a high viral load.[34]

Table 4

Summary of the regression analysis for annualized total costs (GLM with inverse Gaussian distribution of the error term and log link function; n = 1022).

Predictor/reference category	Comparative category	Estimate	Upper CI 95%	Lower CI 95%	$P>\|t\|$
Intercept		10.0415***	10.1278	9.9553	<0.001
Age group/45–59	20–29	−0.0925	0.0716	−0.2567	0.2698
	30–44	−0.0012	0.0510	−0.0533	0.9647
	60+	0.0140	0.0898	−0.0618	0.7177
Gender/male	Female	−0.0891*	−0.0170	−0.1611	0.0157
Disability/none (index "0")	"< 50"	0.0517	0.1216	−0.0182	0.1479
	"≥ 50"	0.0795**	0.1351	0.0239	0.0053
CDC class/B	A	−0.0398	0.0149	−0.0945	0.1540
	C	−0.0545	0.0053	−0.1143	0.0747
Therapy line/the first line	Beyond the third	0.0334	0.0954	−0.0287	0.2926
	The second and the third	0.0555	0.1212	−0.0102	0.0984
Lab ALT/< 110	≥110	−0.0712	0.0683	−0.2107	0.3178
Lab CREAT/<0.9	> 1.5	−0.2205*	−0.0435	−0.3975	0.0150
	0.9–1.5	−0.0119	0.0370	−0.0609	0.6335
Lab LDL/<200	≥ 200	−0.0150	0.1517	−0.1818	0.8598
Comorbidity/≤2 nonsevere	≤2 severe	0.0364	0.1194	−0.0466	0.3902
	>2 nonsevere	0.0785*	0.1404	0.0165	0.0134
	>2 severe	0.2119***	0.3345	0.0892	0.0008
	None	0.0381	0.0990	−0.0228	0.2204
Viral load/<50	> 500	0.0995	0.2895	−0.0905	0.3051
	50–500	−0.0196	0.0810	−0.1203	0.7023
CD4-T cells count/>500	200	0.1917***	0.3017	0.0816	0.0007
	200–500	0.0474	0.0969	−0.0022	0.0615
Time since diagnosis/0–10 years	10–20 years	−0.0573*	−0.0004	−0.1143	0.0491
	>20 years	0.0816	0.1706	−0.0073	0.0728
Drug resistance/none	Three classes (NNRTI, PI, NRTI)	0.2359***	0.3743	0.0975	0.0009
	NNRTI	−0.0711	0.4326	−0.5748	0.7820
	NRTI	0.0523	0.3056	−0.2009	0.6855
	NRTI and NNRTI	0.2837	0.7547	−0.1873	0.2383
	PI	0.0742	0.1546	−0.0062	0.0710
	PI and NRTI	0.0048	0.1186	−0.1089	0.9335
Therapy class/PI-stand	PI-indiv	0.3620***	0.5019	0.2220	<0.001
	NNRTI	−0.3239***	−0.2643	−0.3835	<0.001
	Mixed	−0.1849***	−0.0857	−0.2841	<0.001
	Other	−0.3079***	−0.2462	−0.3695	<0.001

ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention classification system; LDL = low-density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
Signif. codes: 0; "***", 0.001; "**", 0.01; "*", 0.05; ".", 0.1; " ", 1.

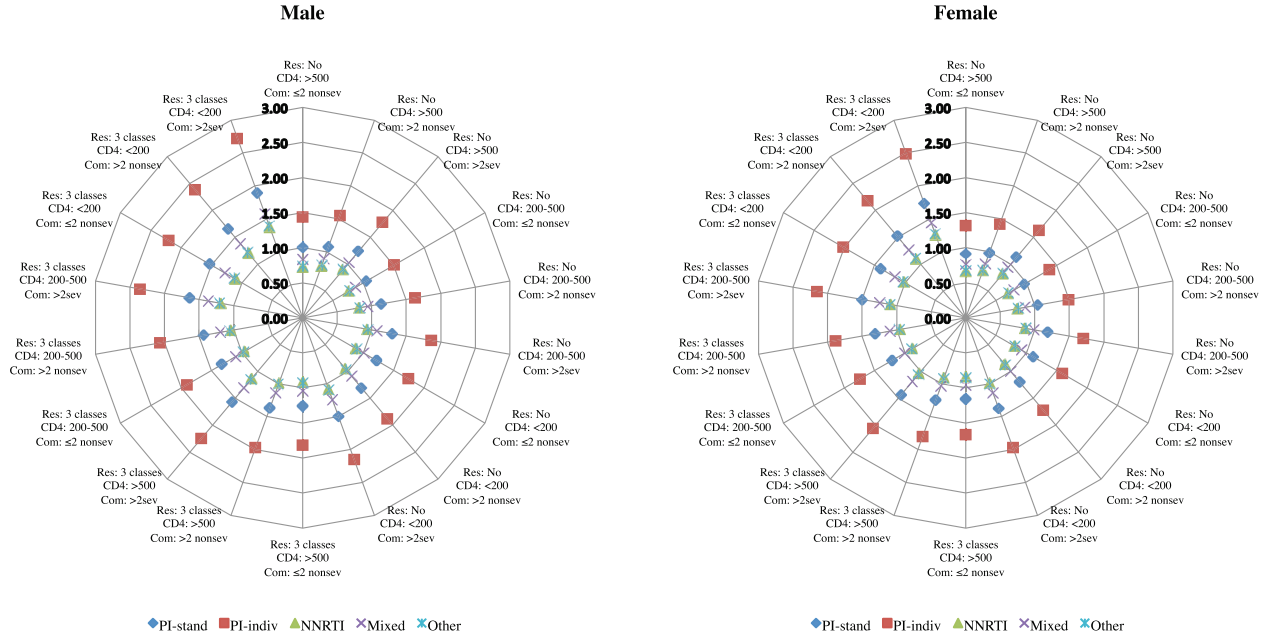

Figure 1. Spider web plot of cost ratios between patients with varying characteristics. Points on the axis give either increasing or decreasing effects of the presented groups of patient characteristics relative to the reference case for men (left) and women (right). Point types represent the respective therapy classes. The blue rhombus in the middle of the plot (left) gives the reference case, which corresponds to a cost ratio of 1 and the following characteristics: male, therapy class = "PI-stand," CD4 = ">500," comorbidity = "≤2 nonsevere," drug resistance = "no resistance." All other ratios (including those given on the plot for women) are presented relative to the reference case. *Res*, drug resistance; *CD4*, CD4-T cells count group; *Com*, comorbidity (categories are described in Table 1).

The second- and third-line therapies, however, are associated with higher utilization of nonmedication HIV care: hospital stays, outpatient care, and rehabilitation. Higher health care services consumption is mainly caused by occurrence of intercurrent diseases or immune reconstitution inflammatory diseases among late-presenting patients with HIV in the first years after initiation of cart.[35,36] Patients under therapy beyond the third-line report the highest direct costs for cART medication, these being driven by more complex ARV treatment regimens: a higher amount of used substances and increased doses of certain ARVs. Although it was not documented in CORSAR, it is reasonable to suggest that switching to a beyond the third-line therapy might be induced either by treatment failures or strategic aspects of ARV treatment or by an intention to overcome adverse long-term effects or individual intolerances against certain ARVs.

The modeling methods applied in this study reveal possible determinants of the average annual costs per patient. Mean total costs increase with a decline in CD4-T cell count. This result is consistent with findings of other studies[7,14]; however, when considering the clinical stage, CDC classification variable, particularly class C, which defines the AIDS stage, shows an absence of statistically significant estimates. It suggests that long-term surviving the AIDS stage does not impact on annual costs; thus, only actual CD4-T cell count below 200/mm^3 is a strong predictor of higher costs due to the higher risk of related infections and diseases. This observation might be relevant to 3 different patient subgroups in the CORSAR cohort: (i) late presenters with advanced cellular immunodeficiency who recently started cART, (ii) patients with an immunological or clinical failing of cART, and (iii) immunological long-term nonresponders, usually late presenters, who started cART with a profound cellular immunodeficiency with a CD4-T cell count below 50/mm^3. All 3 subgroups have a higher risk of receiving a more advanced cART treatment line or to have intercurrent or concomitant diseases or both. In contrast to these subgroups, those late presenters who have been receiving cART for more than 1 or 2 decades and belong to the CDC-C class, but have actual CD4-T cell counts within the normal range, are more likely to receive less complex cART or to have no active concomitant diseases. Female patients incur fewer costs than male patients. These differences have been previously reported elsewhere.[14,37–39] One might hypothesize a number of reasons for gender-specific differences in costs[14]; in our study, considerable differences lie in expenditures on non–HIV-related medication and indirect costs.

We also found an association between costs and the presence of concomitant diseases and disability. The source of these increasing total costs is expenditures on non-HIV medication and additional care. According to the estimated cost ratios, worsening of comorbidity, in terms of number of diseases and their severity, induces a considerable rise in annual total costs. In the CORSAR database, the reported concomitant diseases are grouped into: cardiovascular, respiratory, gastrointestinal, endocrine, neurological, psychiatric, dermatological, hematological, and allergological diseases. Defining cost variation across types of concomitant diseases requires additional data and further analysis.

With regard to the therapy-related predictors, the total costs are linked to the cART regimens, costs of which are directly related to drug prices and the number of ARVs used; when holding all other factors constant, variation of the therapy class from *PI/r*-based cART to *NNRTI*-based treatment which is available as a less expensive alternative in Germany[40] decreases annual costs in the CORSAR cohort. However, individual risks of treatment failure, development of drug resistance or occurrence of toxicity are not modeled in this study; therefore, the impact of these events on the resulting costs in long term cannot be defined. Additionally, the total costs increase when drug

Table 5

Estimated cost ratios relative to the comparison group (male individuals with therapy class "PI-stand," CD4="$>$500," comorbidity="$\leq$2 nonsevere," and drug resistance="no resistance"), 95% confidence intervals in parentheses.

Patient characteristics	Comorbidity	PI-stand	PI-indiv	NNRTI	Mixed	Other
Male. No resistance. CD4: $>$500	$\leq$2 nonsevere	1.000*	1.436 (1.249,1.652)	0.723 (0.681,0.767)	0.831 (0.753,0.918)	0.735 (0.691,0.781)
	$>$2 nonsevere	1.082 (1.016,1.151)	1.553 (1.330,1.814)	0.782 (0.471,1.230)	0.899 (0.798,1.012)	0.795 (0.730,0.865)
	$>$2 severe	1.236 (1.093,1.397)	1.775 (1.466,2.148)	0.894 (0.778,1.027)	1.027 (0.874,1.207)	0.908 (0.793,1.034)
Male. No resistance. CD4: 200–500	$\leq$2 nonsevere	1.049 (0.998,1.102)	1.506 (1.301,1.743)	0.758 (0.703,0.817)	0.871 (0.781,0.972)	0.771 (0.713,0.833)
	$>$2 nonsevere	1.134 (1.045,1.231)	1.629 (1.384,1.916)	0.820 (0.742,0.907)	0.943 (0.829,1.072)	0.834 (0.754,0.921)
	$>$2 severe	1.296 (1.133,1.482)	1.861 (1.528,2.267)	0.937 (0.808,1.087)	1.077 (0.909,1.276)	0.953 (0.824,1.102)
Male. No resistance. CD4: $<$ 200	$\leq$2 nonsevere	1.211 (1.085,1.350)	1.740 (1.461,2.071)	0.876 (0.772,0.994)	1.007 (0.872,1.162)	0.890 (0.788,1.006)
	$>$2 nonsevere	1.310 (1.151,1.491)	1.882 (1.557,2.273)	0.948 (0.821,1.094)	1.089 (0.928,1.278)	0.963 (0.838,1.106)
	$>$2 severe	1.497 (1.273,1.760)	2.150 (1.734,2.665)	1.083 (0.909,1.290)	1.244 (1.032,1.501)	1.100 (0.930,1.302)
Male. Resistance: Three classes. CD4: $>$500	$\leq$2 nonsevere	1.266 (1.102,1.454)	1.818 (1.130,2.926)	0.916 (0.574,1.461)	1.052 (0.656,1.687)	0.931 (0.583,1.485)
	$>$2 nonsevere	1.369 (1.176,1.594)	1.967 (1.624,2.382)	0.991 (0.838,1.171)	1.138 (0.951,1.363)	1.007 (0.853,1.188)
	$>$2 severe	1.565 (1.304,1.877)	2.247 (1.806,2.796)	1.132 (0.930,1.377)	1.301 (1.056,1.601)	1.150 (0.867,1.276)
Male. Resistance: Three classes. CD4:200–500	$\leq$2 nonsevere	1.327 (1.148,1.535)	1.906 (1.588,2.289)	0.960 (0.818,1.126)	1.103 (0.928,1.311)	0.976 (0.831,1.145)
	$>$2 nonsevere	1.436 (1.224,1.685)	2.062 (1.694,2.509)	1.039 (0.873,1.235)	1.193 (0.991,1.437)	1.055 (0.888,1.254)
	$>$2 severe	1.641 (1.358,1.982)	2.356 (1.885,2.945)	1.187 (0.970,1.452)	1.364 (1.102,1.687)	1.206 (0.988,1.472)
Male. Resistance: Three classes. CD4: $<$200	$\leq$2 nonsevere	1.533 (1.284,1.831)	2.202 (1.790,2.709)	1.109 (0.917,1.342)	1.275 (1.046,1.553)	1.127 (0.935,1.359)
	$>$2 nonsevere	1.659 (1.371,2.006)	2.382 (1.912,2.968)	1.200 (0.979,1.470)	1.379 (1.117,1.701)	1.219 (0.999,1.487)
	$>$2 severe	1.895 (1.535,2.340)	2.722 (2.141,3.461)	1.371 (1.096,1.714)	1.575 (1.243,1.997)	1.393 (1.120,1.732)
Female. No resistance. CD4: $>$500	$\leq$2 nonsevere	0.915 (0.851,0.983)	1.314 (1.123,1.537)	0.662 (0.601,0.729)	0.760 (0.674,0.858)	0.672 (0.609,0.741)
	$>$2 nonsevere	0.989 (0.901,1.086)	1.421 (1.199,1.684)	0.716 (0.638,0.803)	0.822 (0.718,0.942)	0.727 (0.649,0.814)
	$>$2 severe	1.131 (0.984,1.298)	1.624 (1.328,1.985)	0.818 (0.700,0.955)	0.940 (0.791,1.116)	0.831 (0.714,0.967)
Female. No resistance. CD4: 200–500	$\leq$2 nonsevere	0.959 (0.877,1.048)	1.377 (1.169,1.622)	0.694 (0.622,0.773)	0.797 (0.670,0.908)	0.705 (0.631,0.787)
	$>$2 nonsevere	1.037 (0.930,1.157)	1.490 (1.248,1.779)	0.750 (0.661,0.851)	0.862 (0.745,0.998)	0.763 (0.673,0.864)
	$>$2 severe	1.185 (1.020,1.377)	1.703 (1.381,2.096)	0.857 (0.727,1.011)	0.985 (0.822,1.180)	0.871 (0.741,1.024)
Female. No resistance. CD4: $<$200	$\leq$2 nonsevere	1.108 (0.973,1.262)	1.591 (1.319,1.919)	0.801 (0.692,0.928)	0.921 (0.786,1.078)	0.814 (0.706,0.939)
	$>$2 nonsevere	1.199 (1.035,1.386)	1.721 (1.409,2.103)	0.867 (0.738,1.018)	0.996 (0.838,1.183)	0.881 (0.754,1.029)
	$>$2 severe	1.370 (1.152,1.628)	1.967 (1.573,2.458)	0.991 (0.821,1.194)	1.138 (0.934,1.387)	1.007 (0.840,1.206)
Female. Resistance: Three classes. CD4: $>$500	$\leq$2 nonsevere	1.158 (0.990,1.354)	1.663 (1.372,2.016)	0.838 (0.705,0.995)	0.963 (0.803,1.154)	0.851 (0.716,1.011)
	$>$2 nonsevere	1.253 (1.059,1.481)	1.799 (1.467,2.205)	0.906 (0.754,1.088)	1.041 (0.858,1.262)	0.921 (0.768,1.104)
	$>$2 severe	1.431 (1.180,1.736)	2.056 (1.637,2.581)	1.035 (0.841,1.275)	1.190 (0.958,1.477)	1.052 (0.857,1.291)
Female. Resistance: Three classes. CD4: 200–500	$\leq$2 nonsevere	1.214 (1.031,1.429)	1.744 (1.432,2.123)	0.878 (0.735,1.049)	1.009 (0.837,1.216)	0.893 (0.747,1.066)
	$>$2 nonsevere	1.313 (1.102,1.565)	1.886 (1.531,2.324)	0.950 (0.786,1.148)	1.092 (0.895,1.331)	0.965 (0.799,1.165)
	$>$2 severe	1.501 (1.228,1.834)	2.155 (1.708,2.719)	1.086 (0.876,1.344)	1.247 (0.998,1.557)	1.103 (0.893,1.362)
Female. Resistance: Three classes. CD4: $<$200	$\leq$2 nonsevere	1.403 (1.117,1.761)	2.015 (1.566,2.591)	1.015 (0.798,1.289)	1.166 (0.914,1.486)	1.031 (0.813,1.306)
	$>$2 nonsevere	1.517 (1.196,1.924)	2.179 (1.677, 2.831)	1.098 (0.966, 1.246)	1.261 (0.977,1.627)	1.115 (0.872,1.425)
	$>$2 severe	1.734 (1.346,2.232)	2.490 (1.886,3.286)	1.254 (0.962,1.634)	1.441 (1.101,1.885)	1.274 (0.982,1.653)

NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

* The cell with a cost ratio of 1 indicates reference categories: all other ratios are estimated relative to them.

resistance occurs; average total costs are particularly responsive to genotypic *PI*-resistance and resistance to 3 or more ARV classes, respectively. One of the results of the regression is that kidney insufficiency (creatinine $>$1.5 vs. $<$0.9) decreases total costs, which is opposite to our expectations; however, the small number of observations in this category (1.66%) prevents a possibility to provide this inference for the whole population.

Viral load is not identified as a cost determinant. Although a link between occurrence of detectable viremia and an increase of annual costs would be suggestive, the design of the CORSAR might not be capable of observing such an effect: (i) the 2-year observation period of the survey might be too short, (ii) the proportion of viremic patients is rather small, and (iii) most cases have either a singular viremic "blip," low viremia, or both, which are associated with a low risk for subsequent virological failure or short-term progression of HIV infection. Further studies with a longer observational period and a rather more restrictive definition of viremic patients will be necessary to investigate the long-term effects of HIV viremia in cART-treated patients on the costs of HIV therapy.

The calculated cost ratios can be interpreted in a similar way as the odd ratios estimated from proportional hazard models.[18] Using relative costs, one can explore interactions among the patients, for example, compare relative costs between patients with varying characteristics. Particularly, combination of a low CD4-T cell count, multiple resistance against *PI* or more than 1 ARV class, severe comorbidity leads to high cost cases. Table 5 and Figure 1 bring additional information and could be useful particularly to health care payers. Some of these cases might be prevented with improvement of ARV adherence, that is by a

patient's ability to follow a prescribed cART plan in accordance with the time lines.[41,42,43]

Our study has certain limitations. First, as a consequence of the selection criteria, ARV-naïve patients were excluded from the study and costs were calculated exclusively for patients under ARV therapy. Therefore, we cannot provide inferences on the costs of ARV-naïve patients or those without cART. Second, information on transmission risks is not available in all participating centers and, therefore, not analyzed. In conclusion, the annual total costs per patient of HIV-related health care in Germany continue to be high and vary greatly depending on severity of the infection, comorbidity, and treatment attributes of patients. The cost ratios and respective confidence intervals show considerable variation within the stratum of CD4-T cell count, genotypic resistance, and ARV classes. The high-cost cases are induced by combinations of low CD4-T cell counts, resistance to at least 3 ARVs and *individualized PI*-based therapy. Improvement of adherence as well as development of cART regimens with enhanced forgiveness (the ability of ARV to sustain viral suppression, despite insufficient adherence) may prevent occurrence of a part of high cost cases of HIV treatment and, therefore, they should be seen as major objectives in management of HIV infection.

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