Cost estimates for HIV care and patient characteristics for health resource utilisation from linkage of claims data with the Swiss HIV Cohort Study

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Short summary: Probabilistic record linkage of Swiss HIV Cohort Study data and claim data from the largest health insurer in Switzerland resulted in representative subsample that allowed for patient profiling for high resource use. Antiretroviral therapy was the highest cost factor.

Abstract

Background. Comprehensive and representative data on resource use is critical for health policy decision making but often lacking for HIV infection. Privacy preserving probabilistic record linkage of claim and cohort study data may overcome these limitations.

Methods. Encrypted dates of birth, gender, study center and antiretroviral therapy (ART) of the Swiss HIV Cohort Study (SHCS) from 2012 and 2013 were linked by privacy preserving probabilistic record linkage with claim data from the largest health insurer covering 15% of the Swiss residential population. We modeled predictors for mean annual costs adjusting for censoring and grouped patients by cluster analysis into 3 risk groups for resource use.

Results. The matched subsample of 1196 patients from 9326 SHCS and 2355 claim records was representative for all SHCS patients on ART. Corrected mean total cost (SE) in 2012 and 2013 were USD 30'462 (582) and USD 30'965 (629) and mainly accrued in ambulatory care for ART (70% of mean costs). The low risk group for resource use had mean annual cost of USD 26'772 (536) and USD 26'132 (589) in 2012 and 2013. In the moderate and high risk groups annual costs for 2012 and 2013 were higher by USD 3'526 [1'907; 5'144] (13%) and 4'327 [2'662; 5'992] (17%) and USD 14'026 [8'763; 19'289 (52%) and 13'567[8'844; 18'288] (52%), respectively.

Conclusions. In a representative subsample of patients from linkage of SHCS and claim data, ART was the major cost factor but patient profiling allowed to identify factors related to higher resource use.

Key words: HIV infection, costs, resource, comorbidity, data linkage

Introduction

Accurate data on costs and resource use is critical for health care policy decision making in order to better understanding current and future needs in HIV care as HIV-infected individuals under antiretroviral therapy (ART) get older but suffer from increasing comorbidities [1]. Many studies on costs of HIV are not representative and are based on data from single centers and not across all services or on aggregated data and thus of limited value for health policy decision makers [2].

In the US or Switzerland where reimbursement of health care is not by a unique payer it is even more challenging to acquire representative costs data and different sources must be used. Privacy preserving probabilistic record linkage may be an approach to link anonymized claims data from insurants with anonymized clinical patient data records to gain a merged data set with comprehensive health resource use and clinical information [3]. In this pilot study we matched Swiss HIV Cohort Study (SHCS) and claims data from the largest Swiss health insurer, to study costs for HIV and non-HIV related conditions and their main determinants such as patient characteristics and late presentation.

Methods

Swiss HIV Cohort Study

The SHCS was initiated in 1988 and enrolls all HIV infected individuals, ≥ 18 years [4]. During biannual visits clinical, laboratory and behavioral data is collected. The cohort is representative for the Swiss HIV-epidemic and includes 66% of AIDS cases and estimated 70% of HIV infected individuals on ART [5, 6]. Participants of the SHCS have provided written informed consent for the use of biological and clinical data for SHCS projects. For this project additional ethical approval for privacy preserving probabilistic record linkage was obtained.

Claims data of Swiss health insurer

In Switzerland health insurance by premium and co-payment is mandatory for all residents and provided by several health insurance companies. 98% of claims are electronically processed [7] and may be identified for ambulatory care by unique provider and laboratory codes [8] and by the Anatomical Therapeutic Chemical (ATC) classification system for drugs [9]. They include the dates and reimbursed fees from any health care provider (physicians, paramedical services, and pharmacies), detailed cost on diagnostics (radiology, laboratory, pathology etc.), drugs and devices. Reimbursement of hospitalization costs is by flat charge based on diagnostic related groups (DRGs) [10]. Cost assessments are from the health insurer perspective and represent charges to health insurers that were converted from Swiss Francs (CHF) to US$ using the mean conversion rates for 2012 and 2013 of *1.06 and 1.07*. For this pilot study we merged claims data from Helsana, the largest health insurer in Switzerland with more than 1.9 million insured persons.

Privacy preserving probabilistic record linkage

Privacy preserving probabilistic record linkage guarantees policyholder and patient confidentiality [11]. All policyholders from Helsana with an ART record (2355) and patients from the SHCS on ART

(9326 patients) during 2012 and or 2013 were considered for data linkage based on the matching variables date of birth, gender, SHCS center and ART medication. Each variable was encrypted by data managers from Helsana and the SHCS using Bloom filters. Two sets of link files, each with anonymous identification numbers of Helsana policy holders and SHCS participants were created and sent to an independent biostatistician who performed the record linkage and created the link table (Supplementary Figure 1) [11]. We only considered matched pairs of patients from both data sets with all fully identical variables. That is, we did not allow for a mismatch in any antiretroviral drug. In case of multiple identical pairs we randomly selected one pair. Based on the linked data pairs the final merged dataset was then constructed.

Primary endpoints

The primary endpoints are total health care costs (i.e. ambulatory, hospitalization, HIV and non-HIV related) per year per patient, during years 2012 and 2013 in the HIV infected population of Switzerland, and in relation to patient characteristics and CD4 counts at presentation.

Statistical methods

To account for patients with new HIV infections who entered the SHCS after January 1st, 2012 (or January 1st, 2013, for estimating year 2013 costs), we used the Zhao and Tian semiparametric estimator to obtain the mean total costs, mean differences, standard errors (SE) and 95% confidence intervals (CI) for main cost categories [12, 13]. This estimator utilizes cost history and is suited for estimating mean costs that allow to adjust for censored data. Start times for costs were the later date of the beginning of the year and HIV diagnosis. Survival time was defined as time from the later date of HIV diagnosis and beginning of the year until the earliest date of death, end of the year or loss to follow-up. If the patient was lost to follow-up prior to the end of the year, or was diagnosed with HIV after the beginning of the year but surviving at the end of the year, his/her survival time

was censored. We present analyses for the total costs as well as sub-categories of costs with and without adjusting for censoring.

To elaborate on main factors determining different resource use we aimed in our analysis at patient profiling that would allow us to clearly distinguish patient groups with notable different resource use. For these reasons we classified patients into low, moderate, high and unclassified risk groups for resource use using a Ward hierarchical cluster analysis based on standardized predictors[14]. Details on patient profiling and predictors that constitute the three risk groups are provided in the Web appendix tables 1 and 2. In a sensitivity analysis, the effect of subjects who could not be classified into a risk group due to missing values for one or more risk factors was evaluated using multiple imputation methods [15].

The isolated effect of late presentation on cost was investigated with the use of propensity score matching for patients with CD4 cell count ≤ 350 versus >350 cells/µL at presentation with the Stata *teffects psmatch* procedure [16] [17] and use of multiple imputation methods for missing co-variates [18]. Inverse probability weighting methods were fitted to additionally verify the results of the propensity score matching on late presentation, and on different CD4 cell count categories after adjusting for predictors as specified in table 3 [19]. All analyseswere done with SAS 9.4 (Cary, NC), Stata (version 14, Stata Corp, College Station, TX) and R (R-project.org).

Results

Record matching procedure

In a total of 1196 pairs we found a full match for all matching variables corresponding to a matching performance of 50% of all policyholders with ART; these individuals formed the base for our analysis (Figure 1). At the time of analysis, a total of 9480 HIV patients from the SHCS were on ART or initiated ART between January 1st, 2012 and December 31st, 2013. Of them, a total of 570 (6%) patients were diagnosed with a new HIV infection after January 1st, 2012. The matched sample of 1196 patients was highly representative for the entire cohort of HIV infected ART recipients in regard to key parameters such as CD4 cell count at presentation, time since HIV infection and on ART and further important patient characteristics (n=9480) (Supplementary Table 1). Patients with illicit drug use were slightly overrepresented in the matched group (75%) compared to 69% in the entire SHCS.

Costs per year

In 2012 and 2013, the estimated mean (SE) HIV and non-HIV related total costs with adjustment for censoring were USD 30'462 (582) and USD 30'965(629), respectively and mainly accrued in ambulatory care (Table 1). The observed average costs (SD), that do not account for partial costs from new HIV infections, are smaller and are USD 29'621 (19'841) for 2012 and USD 30'759(21'621) for 2013 (Table 2). The estimated mean (SE) ambulatory costs were USD 28'662 (528) for year 2012 and USD 28'799 (547) for year 2013 and mainly due to ART medications (Table 1). For the year 2012 and 2013, the mean (SE) costs for any HIV related ambulatory procedure (ART or laboratory) were USD 21'489 (257) and USD 21'158 (229). In 2012 and 2013, 294 patients were hospitalized with mean (SE) costs of USD 10'879 (868) and USD 15'071 (1'357). Hospital costs due to AIDS events (HIV related) and other comorbidities (non-HIV related) were similar and amounted in 2012 to USD 10'830 (1'678) and USD 9681 (824)and in 2013 to USD 10044 (1535) and USD 13'988 (1'366), respectively (Table 1). In 2012 and 2013 18 (1.5%) patients died and 33 (2.7%) were lost to follow-up.

Profiling of health resource use

Patients were classified in three patient profiles of low (n=241), moderate (n=673) and high risk (n=69) for increasing resource use. Patients in the low risk group typically were more likely to be of ages ≤59 years (92.1%), males (81.3%), more educated (80.9%), light or non-drinkers (82.6%), not currently using illicit drugs, and of intermediate likelihood to smoke (56%). In addition, these individuals were less likely to have experienced an AIDS event (81.7%) or a cardiovascular event (0%), and to suffer from psychiatric comorbidities (29%). They were also less likely to have experienced virological failure (37%), more likely to adhere to ART medication and the median time with HIV infection and on ART was (6.6 and 5.1 years) and lower than in the remaining groups.

Figure 2 depicts the mean costs and 95% CI obtained for each risk group. Costs in all risk groups differed within each year 2012 and 2013, albeit the cost profiles were similar in both years. The low risk group had adjusted mean (SE) annual cost of USD 26’772 (536) and 26’132 (589) in 2012 and 2013. The moderate and high risk group had additional mean adjusted annual costs of USD 3’526 [1’907; 5’144] (13%) and 14’026 [8’763; 19’289] (52%) in 2012, and USD 4’327 [2’662; 5’992] (17%) and 13’567 [8’844; 18’288] (52%) and in 2013, respectively. When including unclassified patients with missing values by multiple imputation in sensitivity analyses the respective increases in costs of the moderate and high risk groups were 4’587 [1’589, 5’584] (17%) and 10’041 [5’964, 14’119] (38%) in 2012 and 4’060 [1’741, 6’377] (15%) and 8’956[5’508, 12’402] (33%) in 2013.

Costs of late presenters

Mean total costs for late presenters (CD4 cells <350 cells/µL vs non-late presenters) were USD 30'239 vs USD 28'937 in 2012 and USD 30'890 vs 29'678 in 2013, respectively, based on the propensity score matching method. The mean cost difference (late presenter effect) was USD1'303 [-1'113 , 3'718] in 2012 and USD 1'212 [-1'305 , 3'729] in 2013. Results from using inverse probability weighting method showed similar results (Table 3). Costs in relation with CD4 count at presentation by four

levels are shown in Figure 2 in the webappendix. HIV related hospital costs were highest in the lowest CD4 cell strata. After using the IPW method to adjust for patient characteristics, patients with CD4-cell counts between 350-500 cells/µL had somewhat lower costs.

Discussion

This study indicates that privacy preserving probabilistic record linkage of clinical data from the SHCSwith claims data from the largest Swiss Health insurer can successfully match clinical and insurant data. The matched patient sample and resource use data is likely to be representative for the entire SHCS, although the sample compared to the entire cohort had slightly more smokers and patients with suppressed viral load at baseline. Data linkage allowed for a very detailed analysis and characterisation of patients with risk factors for high resource use and the associated costs. This is particular of relevance as comorbidities in this population are increasing and often managed outside the SHCS clinics. Resource use outside of SHCS centers would have been practically impossible to systematically assess without data linkage. Due to the decentralized characteristics of the Swiss health system relating to the federalistic political structure, representative resource use data is lacking. .

Our results show that main costs accumulate in ambulatory HIV care and in particular, for antiretroviral drugs, a finding confirmed in other countries [20-22]. Resource use increases in HIV infected individuals with age, previous AIDS events and in those with directly or indirectly HIV related comorbidities. Patients with suboptimal adherence to ART, illicit drug and higher alcohol use, and psychiatric comorbidities were likely to have higher resource use. Low CD4 cell count at presentation is associated with slightly higher resource use but differences in costs are not excessive compared to individuals who present earlier. Late presentation may lead to higher upfront costs in particular from in-hospital costs as confirmed in this study [23]. In this study with a large proportion of long-term ART recipients with excellent virological control, CD4 cell count at presentation is no longer a major factor for higher costs. A longer observation period would have been needed to study the eventual long-term consequences of late presentation on suboptimal immune recovery and increased resource use. Differences in costs between patients in different CD4 cell categories at first

presentation were small with slightly higher mean costs in those with the lowest CD4 cell counts at presentation.

Overall costs increased from 2012 to 2013 by 1% which is slightly less than the general development of health expenditure (plus 2.5%) in Switzerland while the consumer price index in Switzerland decreased by -0.2%, and by -1.2% from 2013 to 2015 [24].

We identified only few studies providing representative system wide resource use data in HIV infected populations [25, 26]. In a US Veteran Study poor ART adherence was not associated with higher total costs, but patients in long-term care, psychiatric comorbidity, substance use and low CD4 cell count over time incurred higher costs [25]. In a Canadian study from British Columbia, female gender, comorbidity, ever substance abuse, non-suppressed viral load and low CD4 cell count were associated with increased non ART medical use [26].

The strength of this study is the representativeness and comprehensiveness of cost and clinical data on a national level covering ambulatory and in-hospital resource use. Our sample size was big enough (12.5% of all ART recipients in the SHCS) to allow for a detailed study of different cost components. We estimated annual costs over two years. This poses several problems in correctly accounting costs for new HIV infections and individuals lost to follow-up [27]. Excluding incident cases in a fixed sample as done in many studies leads to biased cost estimates [27]. In our cost analysis, we accounted for censoring which lead to higher cost estimates in comparison to unadjusted cost data Loss-of follow-up may also lead to biased cost estimates but this was also taken into account via censoring.

We matched claims data from only one health insurer (covering 15% of the Swiss population) which may be seen as a limitation. It is unlikely that this will have led to bias since health insurers in Switzerland are not allowed to decline applicants or exclude insurants based on their medical records

from basic mandatory insurance products. Given the large population covered by this insurer it is also reasonable to assume that its health care premiums were competitive..

We limited our matching procedure to pairs with fully congruent data for our matching variables and did not release our strict matching criteria. In our modeling we estimated that a 15% increase in sample size would have been possible with the use of less stringent matching criteria. Given the achieved sample size we decided not to enlarge our sample because we anticipated that the increase in the sample size would come at the price of higher variability of costs estimates from eventual mismatches.

Due to the high correlation of patient predictors for high resource use and in order to make interpretation of cost data more intelligible we grouped patients by cluster analysis into patient risk profiles for high resource use. All patient characteristics of interest studied here were highly significant when they were included as covariates in a generalized mixed model for annual costs. The clusters indicated marked differences in patients and comorbidity constellations that are more likely to be associated with higher costs such as age, years with HIV infection and on ART, psychiatric comorbidity or substance use. For a considerable number of patients there were missing values in important co-variates, mainly in those who were newly diagnosed in 2012 and 2013. Results from multiple imputations were similar to the ones of the complete patient data set. However, multiple imputation results are based on Rubin's rule, which requires independent random variables in each imputation, a condition that is not met in the present analysis. Some patients from low and moderate risk profiles were reclassified to different profiles based on newly imputed values. All patients originally classified in the high risk group remained in the same group in all imputations.

For Switzerland and many other countries no representative data for costs and resource use exist for the treatment of HIV infection [28, 29]. Since the completion of this study, costs for ART have changed because integrase inhibitors are now the most widely used antiretrovirals and some

antiretrovirals have come off patent and are now available at lower prices. Previous studies in different European countries show that HIV related costs, and in particular, costs of ART as the major health care cost in HIV patients [20-22]. Annual costs were in a similar range compared to studies from France, (€20,170/year) and Germany (€22,231/year) [20, 21]. Our cost analysis is from the payer's and not from the societal perspective, which may be seen as a limitation. In addition, all public hospitals in Switzerland are subsidized by cantons and costs charged to health insurers generally represent about 50% of the true in-hospital costs.

In conclusion, in this representative subsample of SHCS patient from a pilot linkage study with claims data ART was the major cost factor. Patient profiling allowed to identify multiple factors related to higher resource use, like age, previous AIDS, psychiatric comorbidity, illicit drug and alcohol use, and lower adherence to ART beside others. Repeated matching of SHCS and claims data in a larger sample could provide essential data to model important future costs that will inform health policy making on different levels.

Authors' contribution

HCB, MS, and OR conceived the protocol. SLR conducted the statistical analysis with supervision and additional software configured by HZ. MF and FSA were involved in data provision and data matching with supervision of KS. JS conducted the data matching. CS, MB, MC, BH, EB, AC and MH were responsible for data collection at SHCS centers. HCB wrote the manuscript with assistance of SLE and HZ. All authors provided critical input to the manuscript and approved its final version.

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Competing interest

Heiner C. Bucher has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare and Roche that were not related to this project. He serves as the president of the association contre le HIV et autres infections transmissibles. In this function he has received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, MSD and Abbvie. J. Schäfer is an employee of F. Hoffmann-La Roche Ltd since December 1, 2016. The present study was conducted before J. Schäfer joined F. Hoffmann-La Roche Ltd and had no connection to her employment by the company. Selene Leon Reyes has been employed by Novartis prior to conducting this study. Mathias Früh is an employee of

Helsana. Oliver Reich is a former employee of Helsana. The study was supported by additional grants from the Swiss Ministery of Health, Stiftung Institut für Klinische Epidemiologie and Gilead Sciences. The Swiss Ministery of Health and Gilead Sciences had no role in the collection, analysis, or interpretation of data from this study. Dr. Cavassini reports research grants from Viiv and GIlead paid to his institution, outside the submitted work. Dr. Leon-Reyes reports grants from The Swiss Ministry of Health, grants from Gilead Sciences, during the conduct of the study; and employed by Novartis years prior to this study. Dr. Bernasconi reports other from Gilead Sciences, other from MSD, other from ViiV Healthcare, other from Abbvie, other from Sandoz, other from Pfizer, other from Gilead Sciences, other from ViiV Healthcare, other from Abbvie, personal fees from Pfizer, outside the submitted work.

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Table 1 Estimated mean costs (SE) in years 2012 and 2013 itemized by relevance to HIV disease in 1196 matched patients

Costs in US$ (adjusted for censoring) [a]	2012 (N=1172)	2013 (N=1187)
Total costs		
mean (SE) [a]	30’462 (582)	30’965 (629)
[95% CI]	[29’322, 31’603]	[29’732, 32’197]
Ambulatory costs	28’662 (528)	28’799 (547)
HIV related	21’489 (257)	21’158 (229)
non-HIV related	7’344 (448)	7’679 (488)
Laboratories	1’055 (20)	1’045(25)
any routine lab[b]	91 (2)	98(2)
any HIV lab[c]	719 (11)	739 (12)
Medications	22’504 (349)	22’567 (488)
Anti-retrovirals (ART)	21’108 (248)	20’574 (223)
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)	10’601 (130)	10’317(124)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	5’593 (127)	5’588 (116)
Protease inhibitors (PI)	11’111 (174)	10’400 (168)
Integrase inhibitors[d]	10’710 (308)	10’599 (268)
CCR5 antagonists and fusion blockers	15’915 (3’306)	15’213 (2’388)
Triple combinations of ARTs (as single tablet)[e]	17’380 (294)	15’581 (305)
non-ART medications	1’956 (243)	2’250 (448)
Providers, doctors	2’951 (202)	2’987 (172)
Hospital costs (N= 294)	10’879 (868)	15’071 (1’357)
HIV related	10’830 (1’678)	10’044 (1’535)
non-HIV related	9’681 (824)	13’988 (1’366)
Inhospital stay (days), median (Q1, Q3)	7 (3, 23)	10 (4, 33)
Risk groups(SE)[a]		
Low risk (N=241)	26’772 (536)	26'132 (589)
[95% CI]	[25'721, 27'823]	[24'978, 27’285]
Moderate risk (N=672)	30'298 (629)	30'459 (615)
[95% CI]	[29'066, 31’529]	[29’257, 31’981]
High risk (N=69)	40’797 (2’631)	39’698 (2’337)
[95% CI]	[35’641, 45954]	[35’118, 44’278]
Unclassified risk (N=213)	29’833 (1’465)	32’983 (1’482)
[95% CI]	[26’961, 32’704]	[30’079, 35’887]
First measured CD4 (cells / µL)		
< 100	31'145 (1'430)	31'996 (1'351)
[95% CI]	[28'343, 33'948]	[29'348, 34'646]

Costs in US$ (adjusted for censoring) [a]	2012 (N=1172)	2013 (N=1187)
100 - 350	30'736 (918)	30'539 (819)
[95% CI]	[28'937, 32'535]	[28'934, 32'143]
350 - 500	28'420 (789)	28'480 (796)
[95% CI]	[26’875, 29’963]	[26’919, 30’040]
≥500	30’251 (780)	31’538 (954)
[95% CI]	[28’723, 31’779]	[29’667, 33’410]

[a]Mean (standard error, SE) and 95% confidence intervals are adjusted for censored patients who were diagnosed with HIV after January 1st, 2012 or lost to follow-up before the end of the year and thus, had partial annual cost records.

[b]Routine labs include ALAT, albumin, amylase, calcium, cholesterol (plus lipid profiling), creatinine kinase, hematocrit, hemoglobin, cholesterol, potassium, LDH, sodium, phosphate, urinalysis (including protein differentiation), hepatitis C virus antibody HCV viral load and genotyping, Treponema, FTA/EIA, routine bi-annual screening for syphilis and HCV.

[c]HIV laboratories include HIV-1viral load, geno- and phenotypicresistance testing to antiretrovirals, HVI antibody testing and Western blot, HIV.1 p24 Antigen, DNA amplification, HIV-2 (cultivation and amplification) , HIV-1 tropism, HLA B5701, CD4 and CD8 cell counts, CD4/CD8 ratio, cytomegalovirus, Epstein-Barr, toxoplasmosis, virus, hepatitis A, B, C, D, E, , and Treponema baseline screening.

[d]Integrase inhibitors include all approved compounds by health authorities except dolutegravir which was approved in 2014.

[e]Triple combination of ARTs include ETC+TDF+EFV, ETC+TDF+RPV and ETC+TDF+EVG+COB. ETC=emtricitabine, TDF=tenofovir, EFV= efavirenz, RPV=rilpivirin, EVG=elvitegravir, COB=cobicistat.

Table 2 Average costs (SD) in years 2012 and 2013 itemized by relevance to HIV disease in 1196 matched patients

Costs in US$ (unadjusted for censoring)[a]	2012 (N=1192)	2013 (N=1187)
Total costs	29'621 (19'841)	30'759 (21'621)
Ambulatory costs	27'862 (17'970)	28'573 (18'659)
HIV related	21'149 (8'804)	20'989 7'874)
non-HIV related	7'193 (14'953)	7'637 (16'582)
Laboratories	**1'036 (657)**	**1'039(782)**
any routine lab[b]	89 (67)	98 (71)
any HIV lab[c]	710 (392)	735 (428)
Medications	**21'857 (12'070)**	**22'372 (16'634)**
Anti-retrovirals (ART)	20'832 (8'396)	20'407 (7'658)
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)	10'447 (3'900)	10'236 (3'742)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	5'547 (2'299)	5'580 (2'079)
Protease inhibitors (PI)	10'931 (4'253)	10'294 (4'126)
Integrase inhibitors[d]	10'664 (4'081)	10'482 (3'861)
CCR5 antagonists and fusion blockers	15'915 9'996)	15'213 (7'219)
Triple combinations of ARTs (as single tablet)[e]	17'260 (4'715)	15'436 (5'361)
non-ART medications	1'920 (7'801)	2'232 (14'849)
Providers, doctors	2'895 (5'964)	2'972 5'288)
Hospital costs (N= 294)	**10'489 (11'708)**	**14'913 (18'917)**
HIV related	9'199 (6'636)	8'831 (6'986)
non-HIV related	9'240 (11'222)	14'048 (19'066)
First measured CD4 (cells / µL)		
< 100	29'929 (19'219)	31'743 (18'088)
100 - 350	29'496 (18'524)	30'178 (16'712)
350 - 500	27'956 (13'079)	28'322 (13'070)
≥500	31'050 (25'808)	33'066 (32'329)

[a]Mean (standard deviation, SD) assumes new HIV infections (after January 1st, 2012) or lost to follow-ups had complete all-year cost records.

[b]Routine labs include ALAT, albumin, amylase, calcium, cholesterol, creatinine kinase, hematocrit, hemoglobin, cholesterol, potassium, LDH, sodium, phosphate, urinalysis, hepatitis C virus antibody and viral load and Treponema, FTA/EIA.

[c]HIV laboratories include cytomegalovirus, Epstein-Barr virus, hepatitis A, B, C, D, E, HIV resistance to antiretrovirals, HIV-1, and Treponema, HIV-1 DNA amplification, HIV-2, HIV-1 tropism.

[d]Integrase inhibitors include all approved compounds by health authorities except dolutegravir which was approved in 2014.

[e]Triple combination of ARTs include ETC+TDF+EFV, ETC+TDF+RPV and ETC+TDF+EVG+COB. ETC=emtricitabine, TDF=tenofovir, EFV= efavirenz, RPV=rilpivirin, EVG=elvitegravir, COB=cobicistat.

Table 3 Total costs according to CD4 cell count at presentation (adjusted for patient characteristics)

Method	Cost in 2012 (US$) Potential mean (SE)	Cost in 2013 (US$) Potential mean (SE)
CD4 cell count		
Late presenters vs non-late presenters		
Propensity score matching[#]		
≤ 350 µL	30'239	30'890
> 350 µL *(reference)*	28'937	29'678
difference [95% CI]	1'303 [-1'113 , 3'718]	1'212 [-1'305 , 3'729]
Inverse probability weighting (IPW) [#]		
≤ 350 µL	29'950 (768)	30'377 (690)
> 350 µL	28'875 (566)	29'711 (598)
difference [95% CI]	1'075 [-725 , 2'876]	667 [-1'070 , 2'403]
<100, ≥100 and <350, ≥500 cells/µL vs ≥350 and <500 cells/µL		
IPW[±]		
< 100 µL	31’175 (1’809)	32’542 (1’813)
≥ 350 and < 500 µL *(reference)*	27’887 (755)	27’854 (741)
difference [95% CI]	3’288 [548, 7’125]	4’688 [853, 8’524]*
≥ 100 and < 350 µL	30’502 (965)	30’167 (880)
≥ 350 and < 500 µL	27’887 (755)	27’854 (741)
difference [95% CI]	2'615 [228, 5’001]*	2'313 [65, 4’560]*
≥ 500 µL	29’691 (797)	30’751 (1’053)
≥ 350 and < 500	27’887 (755)	27’854 (741)

difference [95% CI]	1'804 [-342, 3'950]	2'897 [377, 5'416]*

* P < 0.05, ** P < 0.01

[#]All patient characteristics from supplementary table 2 (except first measured CD4 and past AIDS event), ethnicity, sexual transmission risk group and presence of hepatitis C or B were included in the propensity score matching and IPW models for late presentation. Higher order terms such as the second order degree of years with HIV diagnosis and the interaction of years with HIV diagnosis and years on ART (only in propensity score model) were also included.

[±]Age, gender, education, ethnicity, years with HIV diagnosis and on ART were included in the models.

Figures

Figure 1 Flow chart of data matching and analysis of patients and policyholders.

* One hemophiliac patient with annual ambulatory costs of over USD 425’000 with recombinant factor
VIIa treatment was excluded from cost analyses.

Figure 2 Estimated mean total costs (95% confidence intervals) with adjustment for baseline patient characteristics for the low, moderate and high risk groups. Patients in the unknown group were not classified because they had at least one missing baseline variable.

Figure 1.

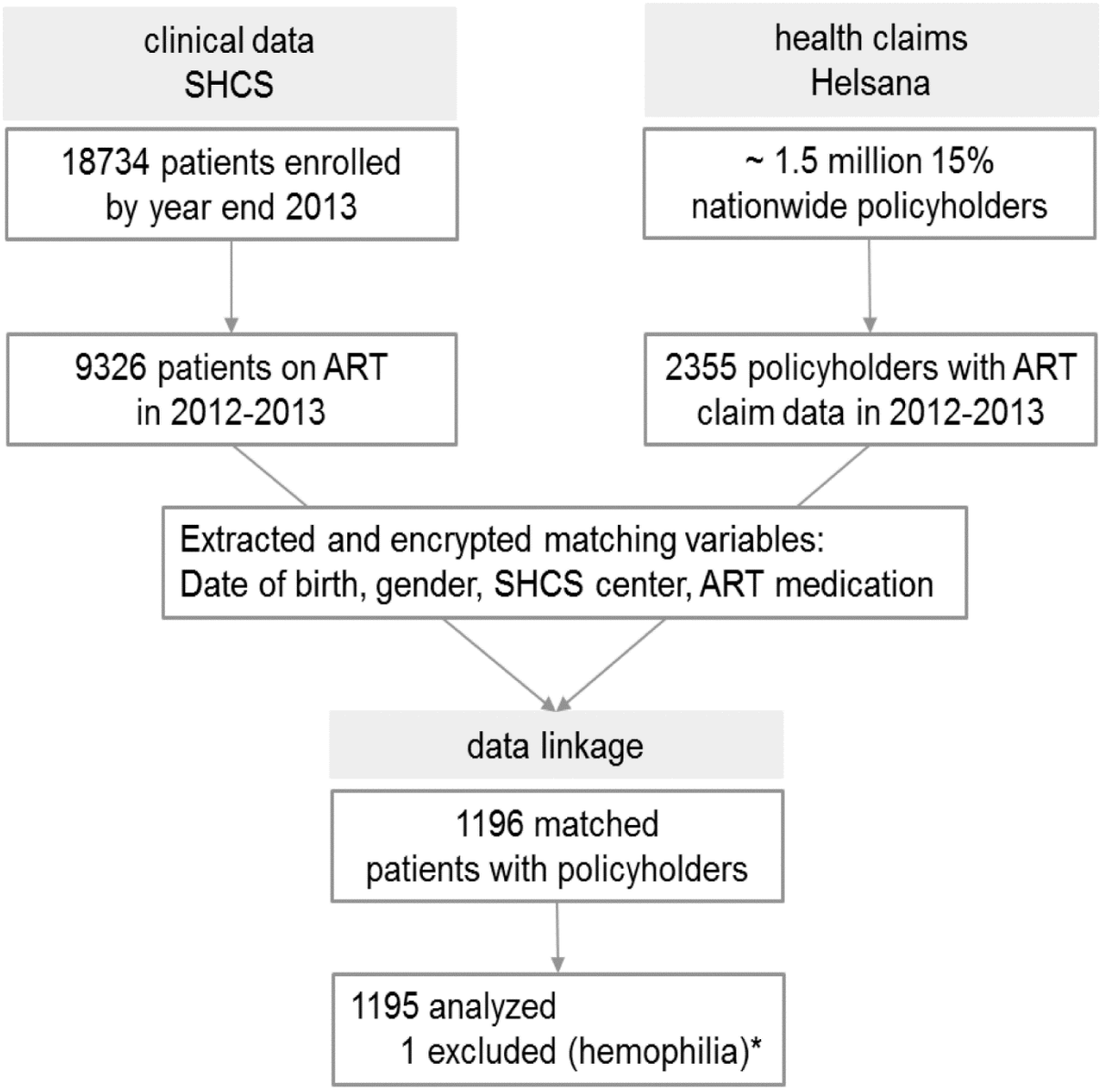

Figure 2.