HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2015 May 10.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2015 March ; 24(3): 297–300. doi:10.1002/pds.3705.

Evaluating the incident-user design in the HIV population: incident-use vs. naive?

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Abstract

Introduction—The incident-user design is the preferred study design in comparative effectiveness (CER) research. Usually 180–365 days of exposure free time is adequate to remove biases associated with inclusion of prevalent users. In HIV research, the use of antiretrovirals at any time in the past may influence future treatment choices and CER results; thus identifying naïve as opposed to incident users is of importance. We examined misclassification of antiretroviral naïve status based on Medicaid administrative data through linkage to the UNC CFAR HIV Clinical Cohort (UCHCC).

Methods—We identified Medicaid patients with incident exposure to common first-line ARV regimens between 2002 and 2008 that were also patients enrolled in the UCHCC. We calculated the proportion of antiretroviral naïve patients based on the UCHCC, among patients identified as having incident exposure in Medicaid and examined factors associated with being antiretroviral naive in both data sources using logistic regression to generate prevalence odds ratios and associated 95% confidence intervals.

Results—Of the 3,500 Medicaid patients with incident antiretroviral exposure, 1,344 were also enrolled in the UCHCC. In this sample, 34% were antiretroviral naïve at the time of first exposure in the Medicaid data based on the UCHCC. In multivariable models, higher CD4 cell counts and log HIV RNA values were associated with being antiretroviral naïve in both data sources.

Conclusions—Administrative data are an important source of information related to HIV treatment. As the construction of a durable and long-lasting HIV treatment plan involves knowledge of current and past ART, augmentation of this data with comprehensive clinical cohort information is necessary.

Introduction

In comparative effectiveness research (CER), the new- or incident -user, design is preferred over prevalent-user study designs. [1, 2] By including only patients initiating a medication or intervention at a given point of time, it is possible to avoid potential biases related to adjustment of covariates that lie on the causal pathway as well as depletion of patients susceptible to an outcome early in treatment.[1–3] [1–3] When conducting CER using administrative databases, incident-users are identifiable because of documentation of insurance/healthcare eligibility as well as the availability of medical claims data for those

who receive treatment. Currently there is no consensus for the amount of exposure free time (e.g. wash-out, run-in) that is required prior to the identification of incident use and it is usually determined arbitrarily and often constrained by sample size and availability of data. [4] Strict definitions result in increased internal validity but at the cost of statistical power. [4]

Most CER studies use 180–365 days of medication exposure free time directly preceding the initiation of treatment to remove most biases associated with the inclusion of prevalent users. However, with conditions like HIV, the use of antiretrovirals at any time, and not just the previous six months to a year, must also be a consideration. Incident-users of antiretrovirals, as defined using administrative data, may not be antiretroviral naïve. The construction of a durable and long-lasting HIV treatment regimen is complicated and involves attention to past and current antiretroviral regimens. Patients receiving antiretroviral treatment in the past may have discontinued treatment due to side effects or potentially due to the development of resistant virus. Therefore, through the linkage to a comprehensive HIV clinical cohort we aimed to quantify and describe the truly naïve patients in an incident use population identified in Medicaid administrative claims.

Methods

Our sample included incident-users of common first line antiretroviral regimens identified in the North Carolina Medicaid administrative data between 2002 and 2008 that were also patients enrolled in the UNC CFAR HIV Clinical Cohort (UCHCC). The UCHCC, described elsewhere [5], is a clinical cohort initiated in the year 2000 that includes all HIV infected patients seen at the UNC Infectious Diseases clinic that are 18 years of age or older and have provided written informed consent. The Medicaid program is a joint state and federally funded program that provides healthcare benefits to individuals of low income. The data from each source were linked by social security number, first name and last name. In the UCHCC, detailed medication histories including start and stop dates as well as clinical and sociodemographic characteristics are manually abstracted from the electronic medical record. Antiretroviral medications were identified in the Medicaid administrative data through national drug codes. Incident-users of antiretroviral medications were defined as Medicaid beneficiaries who met the following: (1) had a claim for one of the FDA approved antiretrovirals (2) had at least 180 days of continuous Medicaid eligibility prior to the antiretroviral claim, and (3) had no claim for any of the FDA approved antiretrovirals in the Medicaid administrative data during this 180 days period. Patients were classified as naïve if they did not have documented antiretroviral use in the UCHCC before the first Medicaid claim.

Using the incident-user sample described above, we calculated the proportion of incident-users defined using the Medicaid data source who were also naïve based on recorded UCHCC medication history. Among the incident-users who had documented prior antiretroviral exposure based on the UCHCC, we calculated the difference between the two dates. A medication start date identified in the UCHCC that was within 7 days of the start date identified in the claims was considered to be an equivalent start date in the UCHCC. Among the incident-users who had documented prior antiretroviral exposure based on the

UCHCC, we calculated the difference between the two dates. We also evaluated differences in socio-demographic (age, race, sex), HIV infection risk factors (men who have sex with men, injection drug use) and clinical factors (CD4 cell count and log HIV RNA) among patients identified as naïve to those who were not-naïve (experienced). Time-varying factors (i.e., age, CD4 cell count and HIV RNA) were evaluated at the time antiretrovirals were initiated as defined by Medicaid claims. To evaluate factors independently associated with incident and naïve status, we estimated adjusted prevalence odds (POR) ratios using logistic regression with a backwards elimination strategy. This study was approved by the University of North Carolina Institutional Review Board.

Results

Of the 3,500 incident-users identified using the Medicaid administrative data, 1,344 were also enrolled in the UCHCC cohort. In this overlapping sample, 34% of the Medicaid incident users were naïve based on medical record abstraction of antiretroviral use documented in the UCHCC. The average time between antiretroviral initiation in the cohort and documented incident use in the Medicaid claims was 6.3 years (Range: 9 days-19.5 years). Two and a half percent of patients initiated antiretrovirals within the 6 months prior to documentation of incident use in the Medicaid claims (e.g. during the run-in period). Fifty-four percent of patients initiated antiretrovirals more than five years prior to the first documented Medicaid claim.

Unadjusted results demonstrate that patients identified as incident-users in the Medicaid data and also naïve in the UCHCC were younger [Median: 42 (IQR: 25, 48) vs 43 years (IQR: 38, 50)], less likely to use injection drugs (19% vs. 23%), and had similar CD4 cell count and HIV RNA lab values. In general the patient characteristics for the Medicaid sample were similar to the UCHCC with exception of HIV RNA; the overall UCHCC population had higher HIV RNA at entry into the cohort. (Table 1) Age, CD4 cell count and HIV RNA were all independently associated with naivety in adjusted logistic regression models. Higher CD4 cell counts and HIV RNA were associated with naivety in the UCHCC (POR: 1.31/200 μ increase) [95% Confidence Interval (CI): 1.20, 1.43] and POR: 1.76/1 log increase (95% CI: 1.54, 2.01)]. Older patients were less likely to be naïve [POR: 0.14/10 year increase in age (95% CI: 0.04, 0.48)]. (Table 2)

Discussion

By linking comprehensive clinical cohort data to administrative claims, we found that a large proportion of Medicaid patients that were identified as incident-users had documentation of past antiretroviral use based on comprehensive medical chart reviews documented in the UCHCC. As would be expected, age, HIV RNA and CD4 count were all predictors of naivety among the Medicaid incident use sample. Our results are in concordance with another recent study using Veteran's Administration data that also found that HIV RNA was associated with naivety at the time of enrollment in a large clinical cohort.[6]

There are several explanations for our observed results. First, current and past medication history is recorded in the UCHCC based on the medical record regardless of payer. Administrative claims only capture medications that the patient received and were paid for by insurance. It is possible that patients may have received free samples prior to initiating treatment, a likely scenario for patients that had documentation of first antiretroviral use in the UCHCC during the 6 month run-in period prior to incident use in the Medicaid data.

Switching of health insurance coverage in the HIV-infected population has been documented.[7,8] Patients that initiated treatment many years prior to documentation of incident use may have received their medications through a different insurance source earlier in their course of therapy and qualify and subsequently switch to Medicaid years after diagnosis. Another likely explanation is that patients fall out of care and reinitiate treatment at a later date at which point they qualify for Medicaid.[9] It has been shown that patients qualifying for Medicaid are more likely to be on antiretroviral medications and/or have an AIDS diagnosis, suggesting that patients become covered by Medicaid later in disease progression.[10]

A few options are available to increase the proportion of naïve patients included in the Medicaid incident-user sample. Restricting the Medicaid claims defined incident use population to common first line therapies would remove some of the patients who were lost and reentered care. Further, by increasing the wash-out period to 365 days, the proportion of incident-users that are also naïve would increase to greater than 50%.

Clinical cohorts provide a very comprehensive picture of HIV patients in clinical care, however, sample size often limits the ability to conduct CER of specific antiretroviral therapies. Administrative data provides increased power to conduct these studies but at the expense of potential exposure misclassification as well as absence of important clinical variables. The linkage of these two data sources provides valuable insight for future CER using administrative databases.

Acknowledgments

This project was supported, in part, by grants M01RR00046 and UL1RR025747 from the National Center of Research Resources, National Institutes of Health (NIH). The project was also supported by NIH grants P30 AI590410, AHRQ R01 HS018731. This project was also supported by grant number K12 DA035150 from the Office of Women's Health Research and the National Institute on Drug Abuse at the NIH. JJE is a consultant to Merck, BristolMyersSquibb, GlaxoSmithKline and ViiV Healthcare.

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Key Points

- In comparative effectiveness research using administrative claims data, incident users of antiretroviral medications may not be naïve to antiretroviral medications
- Restricting inclusion criteria to patients initiating common first-line regimens or increasing the wash-out period would increase the number of incident users included in the study that are truly naïve to HIV treatment.
- Augmentation of administrative data with comprehensive clinical cohort information is a critical resource when conducting comparative effectiveness research of antiretroviral medications.

Table 1

Clinical and socio-demographic characteristics of the UNC CFAR HIV Clinical Cohort (UCHCC) as well as Medicaid incident users that are antiretroviral naïve and not naïve in the UCHCC

	Naïve N=454 n (%)	Not Naïve n=890 n (%)	UCHCC n=4356 n (%)
Gender			
Female	204 (45)	347 (39)	1280 (29)
Age at antiretroviral start in Medicaid, Median (IQR)	42 (25, 48)	43 (38, 50)	37 (30, 44)*
Race			
White	90 (20)	192 (22)	1355 (31)
Black	326 (72)	637 (72)	2612 (60)
Other Race	38 (8)	61 (7)	389 (9)
Men who have sex with Men (MSM)			
Yes	107 (24)	226 (25.3)	1605 (39)
Intravenous Drug User (IDU)			
Yes	87 (19)	207 (23)	573 (14)
CD4 count (cells/μL) most proximal to Medicaid antiretroviral start (median, IQR)	325 (112, 583)	307 (137, 508)	300 (102, 500)*
Log_{10} HIV RNA (copies/mL) most proximal to Medicaid antiretroviral start (median, IQR)	2.8 (1.8, 4.2)	2.8 (1.7, 4.5)	4.4 (3.3, 5.1)*

*Most proximal to entry into UCHCC

Table 2

Predictors of naïve status in the UNC CFAR HIV Clinical Cohort Study (UCHCC) among patients identified as incident-users through Medicaid claims

	Full Model		Final Model	
	POR*	**95% CI****	**POR***	**95% CI****
Age per 10 year increase	0.14	0.04, 0.54	0.14	0.04, 0.48
Sex (Female)	1.16	0.87, 1.54	--	--
Race (Black vs. White and other race)	1.00	0.77, 1.32	--	--
IV Drug Use (yes)	0.93	0.68, 1.27	--	--
Men who have sex with men	0.96	0.69, 1.35	--	--
HIV RNA (log copies/mL)/1 log increase	1.64	1.48, 1.82	1.65	1.49, 1.63
CD4 Cell Count (cells/uL) per 200 cell increase	1.30	1.19, 1.42	1.31	1.20, 1.43

* POR: Prevalence Odds Ratio

** CI: Confidence Interval