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Assessment of risk in longitudinal observational studies with time-varying drug exposures for treatment of a chronic disease

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Abstract

Background: Drug exposures can be continuous or intermittent with several competing exposures which can influence the analysis of exposure-response relationships in longitudinal observational data.

Purpose: We report the in-depth application of research methods employed in a nested case-control study to assess risk for fracture among persons with human immunodeficiency virus (HIV) infection treated with antiretroviral (ARV) therapy. These pharmacoepidemiological research methods, extrapolated from occupational epidemiology, permitted detailed exposure-response analysis in longitudinal observational data sources.

Methods: Multidrug administrative prescription claims data were reformatted to create time-varying, non-overlapping drug exposure histories that preserved the information in the original prescriptions. We applied research methods from occupational health to estimate drug-class (N=5) and drug-specific (N=29) exposure summary measures associated with fracture events.

Results: Using pharmacy claims from the Clinformatics™ DataMart Multiplan (IMPACT) database, a product of OptumInsight Life Sciences, Inc., 1,929,067 prescription histories from 30,405 ARV-treated HIV subjects were restructured retaining gaps and removing overlaps and encompassments in the prescription histories. Most subjects were dispensed at least three different ARV drugs; over 75% had prescription histories with at least one gap in prescriptions and 23.5% had over 65 prescription claims. Drug exposure summary metrics were computed from the restructured claims to determine time-varying exposure-response relationships for individual ARV drug exposures and fractures.

Conclusions: We report a research method to assess drug exposure using administrative prescription claims in observational data that goes beyond dichotomous or cumulative exposures measurements of HIV drug classes and specific ARV drugs. The time-varying measures derived here are easily applicable to other observational data sources such as drug exposures for other chronic diseases where prescription histories are complex and evolve over time.

Keywords: Pharmacovigilance, pharmacoepidemiology, antiretroviral (ARV), prescription claims data, benefit-risk analysis

Introduction

Advancing age, comorbid conditions, and cumulative drug exposures contribute to long-term health outcomes among persons with chronic diseases [1-3]. Historically, observational studies using administrative pharmacy claims characterize drug exposure as either dichotomized variables or as cumulative

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exposure for drug class, combination regimens, or specific drugs [4]. Measurement bias in prescribed drug exposures measured in administrative claims data may under- or over-estimate risk identified in exposure-response relationships of health outcomes and in pharmacovigilance, and is of concern in this era of comparative effectiveness research [5,6]. While randomized trials provide enhanced understanding of treatment efficacy, often well-designed studies with adequate person-years of observation in epidemiology studies are needed for longer-term assessments of health outcomes, drug safety, and benefit-risk balance [7,8].

Recently, we used time-varying exposure metrics using data from an administrative claims database and reported the differential low-impact fracture risk of 22 antiretroviral (ARV) drug exposures among persons treated for human immunodeficiency virus (HIV) infection [9]. The research methodology for this nested case-control study was used because of the time-varying and complex ARV exposures in our observational data source [9]. The analytical process included the reformat of the administrative drug prescription claims data to drug-exposure histories for computation of time-varying summary measures of exposure utilizing the Occupational Mortality Analysis Program (OCMAP-Plus® -http://www.ibridgenetwork.org/university-of-pittsburgh/ocmap-software). This structured approach permitted the extrapolation of exposures and risks, as defined in occupational epidemiology, to our assessment of drug exposures and event risk in pharmacoepidemiology [10-14]. The detailed prescription histories for longitudinal drug exposures are often as complex as occupational exposure histories [10-14]. We computed typical occupational exposure metrics (duration of exposure, cumulative exposure, and average intensity of exposure) in our nested case-control study, along with the assessment of drug lag periods and latency, defined as time since first drug exposure [10-14]. By reformatting prescription claims data and using these metrics, we explored drug-exposure relationships in HIV treatment and risk of fracture. The methods, however, are applicable to any disease where partitioning the disease and complex treatment exposures are needed to further inform drug exposure response relationships. In this report, we illustrate in detail the application of these occupational exposure methods for a nested case-control study of ARV treatment exposure and response defined as risk for fracture. This framework offers application in other pharmacoepidemiology settings, comparative effective research methods, and in-depth assessments of treatment benefit-risk balance.

Materials and methods

Study population

The case-control study population was selected from a health-insured cohort of 59,584 adults with HIV infection enrolled in the Clinformatics™ DataMart Multiplan (IMPACT) database, a product of OptumInsight Life Sciences, Inc, between January 1, 1997 and March 31, 2008. The database was Health Insurance Portability and Accountability Act (HIPAA) compliant; HIV infection was identified by ICD-9-CM codes 042 or v08 and other enrollment criteria, definitions of cases and controls, and other study methodology were previously reported [9].

Initial assessment of exposure-response relationships: ARV drug class prescription histories utilized as dichotomous exposures

We performed an initial feasibility assessment of the source data using years 1997-2006 to explore ARV prescription histories and their relationship to risk of fracture. By class, there were 29 nucleoside reverse transcriptase inhibitors (NRTI), nine non-nucleoside reverse transcriptase inhibitors (NNRTI), 27 protease inhibitors (PI), and one fusion inhibitor (FI). Given the broad distribution of ARV exposures, the exposures were grouped by a two-step categorization for each ARV drug class. First, subject-level exposure to each of the four drug classes was categorized as a dichotomous exposure (exposed or not exposed across the whole prescription history). We further partitioned the NRTI drugs as either nucleoside reverse transcriptase inhibitors (NsRTI) or nucleotide reverse transcriptase inhibitors, (NtRTI). Then, the subjects' were grouped by cumulative combinations of ARV drug exposures based on national treatment guidelines for the entire observation period (**Table 1**). Fracture incidence rate ratios were computed but did not include time-varying exposure measures and were strictly static measures of exposure computed across the total prescription history.

Assessment of exposure-response relationships using a time-varying strategy

Step 1: Convert claims into prescription history records

The final drug dataset contained 1,929,067 single drug ARV prescription history records after the 435,319 original combination ARV drug claims were converted to 958,509 single ARV drug claims and combined with the 970,558 original single drug claims for years 1997 quarter 1 through 2008 quarter 2. The standard components of each claim included sales date, drug name, strength, days supplied, and metric quantity dispensed. Initially, there were 40,105 ARV claims (2.1%) with one or more missing standard components of the prescription. In addition, 16,379 prescriptions (0.8%) had zero for days supplied, and 107,348 prescriptions (5.6%) had a cost-driven vendor-derived imputation for metric quantity. For the 56,484 (2.9%) prescription claims with missing, or zero, for days supplied, we imputed the mode of the frequency distribution for days supplied for each specific ARV drug-strength.

Step 2: Deriving the daily-dose estimates of drug exposure

To quantify the time-varying drug exposures for the 68 different drug and drug strength combinations, estimates of daily dose were needed. We calculated the drug-specific daily doses as drug strength and a multiple of pills per day (PPD) which is a function of metric quantity. For those drugs

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Table 1. Initial assessment of antiretroviral drug prescription claims among 23,207 subjects with HIV infection during calendar years 1997-2006: Groupings of exposures based on National treatment guidelines.

Antiretroviral drug combinations	No. (%)
Common NsRTI/NtRTI and PI combinations (N=3,923)	
NsRTI, PI	2,958 (75.4)
NsRTI, NtRTI, PI	869 (22.2)
NtRTI, PI	51 (1.3)
NsRTI, NtRTI, PI, FI	45 (1.1)
Common NsRTI/NtRTI and NNRTI combinations (N=3,629)	
NsRTI, NNRTI	2,691 (74.1)
NsRTI, NtRTI, NNRTI	845 (23.3)
NtRTI, NNRTI	93 (2.6)
Common NsRTI/NtRTI, PI and NNRTI combinations (N=3,226)	
NsRTI, NNRTI, PI	1,867 (57.9)
NsRTI, NtRTI, NNRTI, PI	1,247 (38.7)
NsRTI, NtRTI, NNRTI, PI, FI	72 (2.2)
NtRTI, PI, NNRTI	40 (1.2)
Else (N=1,068)	
NsRTI	763 (71.4)
NsRTI, NtRTI	138 (12.9)
PI	68 (6.4)
NNRTI, PI	34 (3.2)
NNRTI	20 (1.9)
NtRTI	17 (1.6)
NsRTI, NNRTI, PI, FI	9 (0.8)
Other[1]	19 (1.8)

NsRTI: Nucleoside reverse transcriptase inhibitor
NtRTI: Nucleotide reverse transcriptase inhibitor
NNRTI: Non-nucleoside reverse transcriptase inhibitor
PI: Protease inhibitor
FI: Fusion inhibitor
[1]Other: NsRTI, PI, FI (6); FI only (4); PI, FI (3); NNRTI, PI, FI (1); NsRTI, NNRTI, FI (1); NsRTI, FI (1); NsRTI, NtRTI, FI (1); NtRTI, PI, FI (2)

that were missing metric quantity, we assessed the vendor supplied cost-derived imputations from the prescription claims. The estimated values of metric quantity were not equivalent with either clinically-derived values or data-driven estimates for metric quantity. Therefore, we used an alternative method to assign daily-dose estimates for those drug-strengths with missing metric quantity that combined the prescription claims data and standard dosing practices. When the calculated daily dose for >80% of the prescription claims for an ARV drug-strength was equivalent to the standard adult daily dose defined from the drug label, that daily dose was assigned to all of the prescription claims for that ARV drug-strength. The ARV drug-strength claims that met this >80% threshold for daily-dose assignment primarily included drugs that were either once-daily regimens or single-strength formulations. For drug-strengths that did not meet the >80% equivalency threshold for assigning a daily dose, we assessed the drug-strength prescriptions by formulation (elixir, power, tablets, etc.) and created groupings of daily-dose estimates for imputation. Daily-dose estimates were assigned to 22 drug-strength combinations that did not meet the >80% threshold (**Appendix 1**).

Step 3: Restructure the prescription claims data

To utilize the OCMAP-Plus® program for computing the ARV drug exposure metrics, it was necessary to restructure the pharmacy history records to remove encompassed and overlapping prescriptions with the same drug-strength. While dispensed drugs most likely overlapped as real time prescription sales, the assumption was that drug ingestion did not overlap. An overlapped record occurred when the prescription start date of the current prescription was before the previous prescription end date and the current prescription end date was after the previous prescription's end date. An encompassed record occurred when the current prescription start and stop dates were before the previous prescription end date. An ARV drug gap in the prescription record was one or more days' interval with no drug claim for the same ARV drug-strength exposure. A continuous exposure record had the same ARV drug-strength prescriptions with no overlaps or encompassments. When a prescription for an ARV drug was overlapping with another prescription of the same drug-strength, the overlap was removed by taking the days of supply that constituted the overlap and adding the days to the end of the first prescription, pushing out the second prescription the same number of days as the overlap; this removed the overlap but preserved the days of supply. When a prescription for an ARV drug was totally encompassed by another prescription of the same drug-strength, the last date of the first prescription was extended forward in time the same amount of days as the encompassed prescription to ensure the correct number of days supplied was retained. Gaps between prescription claims were retained when they occurred in the prescription history.

A systematic, quality-control check of the restructured data was performed by stratifying the subset of the cohort exposed to ARV drugs into approximate quartiles of number of prescriptions per subject (<15, 15-34, 35-64, >65 prescriptions). Within each quartile a random sample of 25 subjects was selected for a manual review of the restructure process. Each of these 100 records were manually restructured and then compared to the computerized restructured record to check for accuracy. No errors were found during this quality-control assessment. We used PERL language in a MySQL database to perform the computerized restructure of the pharmacy claims.

Step 4a: Construct risk sets for exposure-response modeling

Traditional analyses of exposure-response typically include the use of Poisson regression of the internal cohort rates. Relative risk regression (RRR) is an alternative to the traditional analyses and was used in our nested case-control study of ARV drug use and bone fracture risk [**9**]. For each case, a risk

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set was defined as the case plus all cohort members alive and at risk for fracture but not yet having had a fracture (non-cases) who were the same age of the case. We used age as the time dimension to construct these full risk sets (using the RISKSET module in OCMAP-Plus®) [10] from the HIV cohort. Risk sets were further matched on gender and year of birth (within five years) to control for birth cohort effects because individuals of the same age were not necessarily born in the same year. We randomly selected four non-case subjects (controls) from each risk set. For each non-case in each risk set, each exposure variable was evaluated as of the age of the corresponding case with fracture.

Relative risk regression (RRR) was used to investigate the dependence of internal cohort fracture rates (modeled as time to diagnosis) on the duration of time exposed to a drug and separately to the cumulative exposure of the drug with adjustment for the potential confounding factors. Multiplicative RRR models of the form $\lambda(t)=\lambda_0(t)\exp\{x(t)\beta\}$ were fit to the internal cohort rates using stratified conditional logistic regression [15-17]. In this model, $\lambda_0(t)$ is the hazard of an event at time t for an individual with baseline levels of all covariates, x(t) is a vector of covariates (exposures and potential confounding variables evaluated as of each event time t), and β is the corresponding parameter vector estimated by partial likelihood [15-17]. The RRR modeling was performed using the conditional logistic regression module in Stata [18]. The risk sets were explicitly constructed for the objectives of the nested case-control study of ARV exposures and fracture events, and the conditional logistic regression algorithm to compute the estimates of relative risk was equivalent to fitting a Cox model. When there were multiple time-varying covariates (i.e., ARV drug exposures), the most feasible way to fit these models was to explicitly construct risk sets and to estimate parameters using a conditional logistic regression [15-17].

Step 4b: Summary measures of ARV drug exposure

The restructured prescription data were used for the computation of time-varying summary measures of drug exposure using the RISKSET program module in OCMAP-Plus® [10]. An ARV drug exposure period was the entire time period of exposure to the specific ARV drug in the person's prescription history. The cumulative measure of exposure for a drug ($Drug\_Cum_j$) computed over N_j prescriptions during drug exposure period j was given by:

$$Drug\_Cum_j = \sum_{i=1}^{N_j} Time_i \cdot Exp\_dose_i \quad (1)$$

where $Time_i$ and Exp_dose_i represented the duration of the prescription (in days) and daily dose of the drug (in milligrams), respectively, of the i^{th} prescription during drug exposure period j.

The duration of exposure for a drug ($Drug\_Dur_j$) computed over N_j prescriptions during drug exposure period j was given by:

$$Drug\_Dur_j = \sum_{i=1}^{N_j} Time_i \cdot Exp\_YN_i \quad (2)$$

where $Time_i$ represented the duration of prescription (in days) and Exp_YN_i was equal to 1 if exposed to that drug and 0 otherwise. These quantities were specific for the i^{th} prescription during drug exposure period j.

The average intensity of exposure for a drug (Drug_AIE) computed over N_j prescriptions during drug exposure period j was:

$$Drug\_AIE_j = Drug\_Cum_j / Drug\_Dur_j \quad (3)$$

Step 4c (if warranted): Assess drug exposure lags and latency

The internal event rates relative to cumulative drug exposures in the regression models assumed that an event during an observation period was related to the cumulative drug exposure from study entry up to the event. The actual exposure-response relationship may change over time and may be negligible during parts of the drug history. To explore for this possible changing exposure-response relationship, alternative characterizations of the above summary measures were computed by incorporating a lag period [10,19]. Lag is the period of time before the event during which drug exposures are not counted. This is based on the assumption that a latent period exists between when an individual is exposed and when the exposure may possibly impact the disease [19]. In occupational epidemiology, the choice of the lag period depends on a known or hypothesized exposure-response and latency (time since first exposure). For the assessment of ARV drug latency and fracture, latency (defined as the time from first exposure to development of fracture) remained exploratory so we used lag periods of 3, 6, and 12 months.

Results

Initial assessment of exposure-response relationships: ARV drug class prescription histories utilized as dichotomous exposures

The initial analysis of the cohort was based on 23,207 subjects with HIV infection from calendar years 1997-2006. In this feasibility assessment, the ARV prescription claims were grouped into four categorical combination regimens (**Table 1**). The majority of the claims were for NsRTI/PI, NsRTI/NNRTI, and NsRTI/NNRTI/PI respectively. There were 1,096 subjects with fracture, for a fracture incidence rate of 2.68 per 100 person years (95% CI: 2.46-2.91) for subjects without ARV exposure (reference group). When comparing the subjects with ARV exposure to those no ARV exposure, we estimated incidence rate ratios that ranged from 0.46-1.19 for subjects with various combinations of drug class exposures (data not shown). When comparing those with no ARV exposure to regimens with and without tenofovir, we estimated an incidence rate ratio of 2.57 (95% CI: 2.32-2.83) among subjects on combination regimens without tenofovir, 1.16 (95% CI: 0.94-1.38)

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among subjects on combination regimens with tenofovir, and 3.19 (2.34-4.04) among subjects on other ARV regimens (data not shown). The structure of the prescription histories did not permit ARV-class or ARV-drug specific assessments of risk for fracture.

Assessment of exposure-response relationship

An example of the time-varying drug exposure restructuring and computation of summary measures of ARV drugs

The prescription data for one study participant showing the original overlapped and encompassed ARV prescriptions, as well as gaps, are displayed in **Figure 1a**. The dispensed drugs were a combination regimen of stavudine, lamivudine, and ritonavir. The 1st ritonavir prescription was filled on October 27, with the 1st stavudine and lamivudine prescriptions filled on November 9. The 2nd stavudine and lamivudine prescriptions on December 4 overlapped with the 3rd stavudine and lamivudine prescriptions filled on December 29, while the 2nd and 3rd ritonavir prescriptions occurred one day apart with the 3rd totally encompassed within the 2nd, after a gap of 20 days from the 1st prescription of ritonavir. The restructure of the original pharmacy claims, inclusive of the prescribed dose, resulted in daily, multidrug exposure intervals while preserving the original number of days supplied and drug strength for each prescription (**Figure 1b**).

The details for the computation of the summary exposure measures for this subject are displayed as the original prescription claims data (**Table 2a**) restructured to create non-overlapping daily, drug-specific exposures (**Table 2b**). Using the drug's metric quantity and days supplied from the original pharmacy claim (**Table 2a**) and the derived daily-dose estimates (**Appendix 1**), **Table 2b** shows the daily-dose was 1200 mg (prescriptions 1, 2, 6-10 and 15-17) or 800 mg for ritonavir, 80 mg for stavudine, and 300 mg for lamivudine (prescription 12). As noted in **Table 2b**, the subject received 100 days of ritonavir (90 days at 1200 mg and 10 days at 800 mg), 90 days of stavudine (80 mg), and 90 days of lamivudine (300 mg). The ARV drug exposure summary measures of duration of exposure, cumulative exposure, and average intensity of exposure were computed across the total prescription history (**Table 2c**).

ARV-exposed HIV study cohort and their prescription claims

There were 30,405 subjects with HIV infection and one or more ARV drug prescription claims. The median age was 41.9 years, 15.5% of the subjects were women, 41.4% were from the northeastern United States (US) census region, the median duration of observation was 2.0 years, and the majority (91.2%) was dispensed three or more different ARV drugs (**Table 3**). Most subjects (98.9%) were dispensed one or more NRTI, 58.1% were dispensed one or more NNRTI, 55.8% were dispensed one or more PI, and few subjects were dispensed an FI or EI. Over 75% of the subjects had a prescription history with at least one gap, 25.3% of subjects had less than 15 prescription claims, and 23.5% had 65 or more prescription claims. Gaps in the prescription history were evident after the restructure of the original claims. In the restructure of 1,929,067 ARV prescription history records, 144,258 (13%) prescription history records had one or more days in prescription gaps.

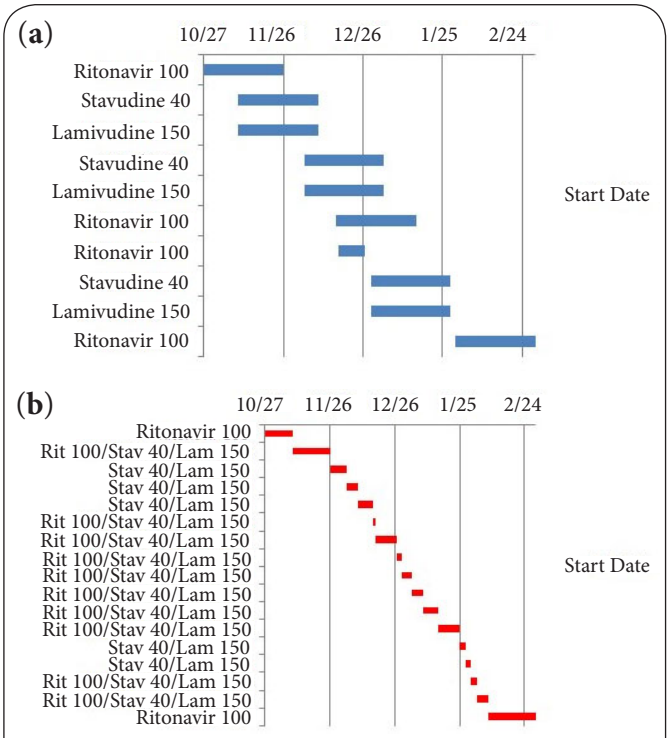

Figure 1. Antiretroviral administrative prescription claims data from original pharmacy file by date prescribed and number of days supplied (**a**) and as a restructured pharmacy history (**b**) for assessment of risk in the Occupational Mortality Analysis Program (OCMAP-Plus®).

Within each drug class, most subjects had prescriptions with no overlap or encompassed records (**Table 3**). For subjects with NRTIs, 32.3% had at least one prescription that overlapped, less than 1% had at least one prescription encompassed within another, and 3% had NRTIs that both overlapped and encompassed other prescriptions. For subjects with NNRTIs, 3.5% had records that overlapped or encompassed another NNRTI. For subjects with PIs, 28.1% had overlap, less than 1% had encompassed prescriptions, and 4.4% had prescriptions which overlapped and encompassed other PIs. All subjects with FI and EI exposures had no prescriptions with overlap or encompassment.

Summarizing ARV drug prescriptions

Each of the 1,929,067 ARV prescription history records were for a single ARV drug and associated strength as well as a start and end date. By class, 62.1% of the records were for NRTIs, 14.3% were for NNRTIs, 23.2% were for PIs, and less than 1% were for FIs or EIs. Subjects' single drug prescription history records were combined into intervals containing multiple drugs when

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Table 2. Original pharmacy prescription claims data from the Clinformatics™ DataMart Multiplan (IMPACT) database for a single study subject (Table 2a), restructured as non-overlapping prescriptions of daily ARV drug-specific exposure (Table 2b), and as summary measures of drug exposures computed across the subject's total prescription history (Table 2c).

Table 2a

Prescription No.	Drug Strength	Generic Drug Name	ARV drug class	Days Supplied	Metric Quantity	Prescription Start Date	Prescription End Date	Computed Pills Per Day (PPD)
1	100	Ritonavir	PI	30	360	27OCT2000	26NOV2000	12
2	40	Stavudine	NRTI	30	60	09NOV2000	09DEC2000	2
3	150	Lamivudine	NRTI	30	60	09NOV2000	09DEC2000	2
4	40	Stavudine	NRTI	30	60	04DEC2000	03JAN2001	2
5	150	Lamivudine	NRTI	30	60	04DEC2000	03JAN2001	2
6	100	Ritonavir	PI	30	360	16DEC2000	15JAN2001	12
7	100	Ritonavir	PI	10	100	17DEC2000	27DEC2000	10
8	40	Stavudine	NRTI	30	60	29DEC2000	28JAN2001	2
9	150	Lamivudine	NRTI	30	60	29DEC2000	28JAN2001	2
10	100	Ritonavir	PI	30	360	30JAN2001	01MAR2001	12

Table 2b

Prescription	Start date	End date[#]	Ritonavir	Stavudine	Lamivudine	Span of Days
1	10/27/2000	11/09/2000	1200 mg	0	0	13
2	11/09/2000	11/26/2000	1200 mg	80 mg	300 mg	17
3	11/26/2000	12/04/2000	0	80 mg	300 mg	8
4	12/04/2000	12/09/2000	0	80 mg	300 mg	5
5	12/09/2000	12/16/2000	0	80 mg	300 mg	7
6	12/16/2000	12/17/2000	1200 mg	80 mg	300 mg	1
7	12/17/2000	12/27/2000	1200 mg	80 mg	300 mg	10
8	12/27/2000	12/29/2000	1200 mg	80 mg	300 mg	2
9	12/29/2000	01/03/2001	1200 mg	80 mg	300 mg	5
10	01/03/2001	01/08/2001	1200 mg	80 mg	300 mg	5
11	01/08/2001	01/15/2001	1200 mg	80 mg	300 mg	7
12	01/15/2001	01/25/2001	800 mg	80 mg	300 mg	10
13	01/25/2001	01/28/2001	0	80 mg	300 mg	3
14	01/28/2001	01/30/2001	0	80 mg	300 mg	2
15	01/30/2001	02/02/2001	1200 mg	80 mg	300 mg	3
16	02/02/2001	02/07/2001	1200 mg	80 mg	300 mg	5
17	02/07/2001	03/01/2001	1200 mg	0	0	22

Table 2c

Summary Measure	Ritonavir	Stavudine	Lamivudine
Duration of Exposure	(1*13)+(1*17)+(0*8)+(0*5)+(0*7)+(1*1)+(1*10)+(1*2)+(1*5)+(1*5)+(1*7)+(1*10)+(0*3)+(0*2)+(1*3)+(1*5)+(1*22)=100 days	(0*13)+(1*17)+(1*8)+(1*5)+(1*7)+(1*1)+(1*10)+(1*2)+(1*5)+(1*5)+(1*7)+(1*10)+(1*3)+(1*2)+(1*3)+(1*5)+(0*22)=90 days	(0*13)+(1*17)+(1*8)+(1*5)+(1*7)+(1*1)+(1*10)+(1*2)+(1*5)+(1*5)+(1*7)+(1*10)+(1*3)+(1*2)+(1*3)+(1*5)+(0*22)=90 days
Cumulative Exposure	(1200*13)+(1200*17)+(0*8)+(0*5)+(0*7)+(1200*1)+(1200*10)+(1200*2)+(1200*5)+(1200*5)+(1200*7)+(800*10)+ (0*3)+(0*2)+(1*3)+(1200*5)+(1200*22)=116,000 mg-days	(0*13)+(80*17)+(80*8)+(80*5)+(80*7)+(80*1)+(80*10)+(80*2)+(80*5)+(80*5)+(80*7)+(80*10)+(80*3)+(80*2)+(80*3)+(80*5)+(0*22)=7200 mg-days	(0*13)+(300*17)+(300*8)+(300*5)+(300*7)+(300*1)+(300*10)+(300*2)+(300*5)+(300*5)+(300*7)+(300*10)+(300*3)+(300*2)+(300*3)+(300*5)+(0*22)=27,000 mg-days
Average Intensity	116,000 mg-days/100 days=1160 mg per day	7200 mg-days/90 days=80 mg per day	27,000 mg-days/90 days=300 mg per day

[#]End date calculated from start date+number of days supplied

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Table 3. Demographic and prescription-level data for 30,405 subjects with human immunodeficiency virus (HIV) infection prescribed antiretroviral (ARV) therapy between January 1, 1997 and March 31, 2008.

Variables	N=30,405 No. (%)
Demographic descriptive data	
Age (years)	
<37	8,170 (26.9)
37-41	7,262 (23.9)
42-47	7,613 (25.0)
48+	7,360 (24.2)
Gender	
Male	25,689 (84.5)
Female	4,716 (15.5)
Geographic region of United States	
Northeast	12,595 (41.4)
Other continental	17,810 (58.6)
Number of ARV drugs	
<3	854 (2.8)
3-5	22,801 (75.0)
6-8	5,641 (18.6)
9-12	1,046 (3.4)
>12	63 (0.2)
Number of prescriptions	
<15	7,696 (25.3)
15-34	8,154 (26.8)
35-64	7,414 (24.4)
65+	7,141 (23.5)
Prescription gaps	
No gaps	7,078 (23.3)
Gaps	23,327 (76.7)
ARV drug class	
Nucleoside reverse transcriptase inhibitor (NRTI)	30,080 (98.9)
Continuous	19,370 (64.4)
Overlap only	9,724 (32.3)
Encompassed only	87 (0.3)
Overlap and encompassed	899 (3.0)
Non-NRTI (NNRTI)	17,673 (58.1)
Continuous	17,045 (96.4)
Overlap only	583 (3.3)
Encompassed only	30 (0.2)
Overlap and encompassed	15 (0.1)
Protease inhibitor (PI)	16,951 (55.8)
Continuous	11,384 (67.2)
Overlap only	4,763 (28.1)
Encompassed only	52 (0.3)
Overlap and encompassed	752 (4.4)
Fusion inhibitor (FI)	598 (2.0)
Continuous	598 (100)
Overlap only	0 (0.0)
Encompassed only	0 (0.0)
Overlap and encompassed	0 (0.0)
Entry inhibitor (EI)	68 (0.2)
Continuous	68 (100)
Overlap only	0 (0)
Encompassed only	0 (0)
Overlap and encompassed	0 (0)

Gap: one or more day interval with no drug claim for the same drug
Continuous: no overlaps or encompassments; Overlap: prescription start date of the current prescription was before the previous prescription end date and the current prescription end date was after the previous prescription's end date; Encompassed: current prescription start and stop date were before the previous prescription end date

prescription start and end dates were the same for separate single-agent prescription history records. This compilation of prescription records resulted in 914,821 different, time-varying prescription history records, with 542,418 (59.3%) overlapped and 9,379 (1.0%) encompassed prescriptions (**Table 4**). Among these time-varying multidrug prescription history records, 72.9% contained the NRTIs, 30.1% NNRTIs, 34.5% PIs, and less than 1% FIs or EIs. Within drug classes, prescription gaps for one or more days occurred 17-31% of the time. From the restructured prescription history records, we calculated

Table 4. Description of original antiretroviral (ARV) single drug prescriptions (N=1,929,067) and time-varying multiple ARV drug prescriptions (N=914,821) among 30,405 persons with human immunodeficiency virus (HIV) infection.

ARV drug class	Single drug prescription records N=1,929,067 No. (%)
Nucleoside reverse transcriptase inhibitor (NRTI)	1,198,354 (62.12)
Non-NRTI (NNRTI)	276,380 (14.33)
Protease inhibitor (PI)	446,640 (23.15)
Fusion Inhibitor (FI)	7,512 (0.39)
Entry Inhibitor (EI)	181 (0.01)
Record Status by ARV Class	**Time-varying multiple drug prescriptions N=914,821 No. (%)**
NRTI	666,734 (72.9)
Continuous	467,542 (70.1)
Overlap	197,264 (29.6)
Encompassed	1,928 (0.3)
NNRTI	275,548 (30.1)
Continuous	274,480 (99.6)
Overlap	1,021 (0.4)
Encompassed	47 (0.0)
PI	315,906 (34.5)
Continuous	235,900 (74.7)
Overlap	78,234 (24.8)
Encompassed	1,772 (0.5)
FI	7,463 (0.8)
Continuous	7,463 (100.0)
Overlap	0 (0.0)
Encompassed	0 (0.0)
EI	179 (0.02)
Continuous	179 (100)
Overlap	0 (0.0)
Encompassed	0 (0.0)
Number of gaps by ARV drug class	
NRTI	172,734 (25.9)
NNRTI	85,475 (31.1)
PI	93,332 (29.5)
FI	2,301 (30.8)
EI	31 (17.3)

Gap: one or more day interval with no drug claim for the same drug
Continuous: no overlaps or encompassments
Overlap: prescription start date of the current prescription was before the previous prescription end date and the current prescription end date was after the previous prescription's end date; Encompassed: current prescription start and stop date were before the previous prescription end date

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the summary ARV exposure metrics for the entire exposed cohort. Distributions of the ARV drug and class-specific summary measures are summarized in **Appendix 2**.

Using the summary measures for ARV drug exposure

The use of the cumulative exposure metric (in milligrams months) for fracture risk is illustrated for ritonavir, stavudine, and lamivudine (**Table 5**). There were no increased risks for fracture with ritonavir or stavudine with increasing levels of cumulative exposure in unadjusted and adjusted models. In contrast, lamivudine showed statistically significant reduced risk with increasing levels of cumulative exposure in both unadjusted and adjusted models.

Assessment of risk by drug class using lagged exposures

The use of lagging with ARV drug class duration of exposure is illustrated in **Table 6**. Duration of exposure (in months) for each drug class was categorized into approximate quartiles using the unlagged exposures (zero lag). Risk estimates were minimally different across lag periods and NRTI and NNRTI showed reductions of risk with increased duration of exposure. Exposure to the PI class showed a null effect that became slightly protective with the longest duration of exposure quartile across each lag period. No effect was noted for exposure to the FI in a small number of cases with fracture and there were no exposures to EIs among cases with fracture.

Discussion

The drug exposure summary methods in this report introduce an alternative approach for pharmacovigilance and drug safety studies when using pharmacy claims from an administrative database. Traditional analyses of pharmacoepidemiology studies typically do not use the complete, and often complex, drug histories found within administrative pharmacy claims

Table 5. Cumulative exposure-response findings of ritonavir, stavudine, and lamivudine for fracture in a nested case-control study of 11,621 persons with human immunodeficiency virus infection.

Antiretroviral drug	Case N=2,477	Unadjusted OR[a.] (95% CI)	Adjusted OR[a.,b.] (95% CI)
No Effect			
Ritonavir			
Cumulative exposure (mg-months)			
>0-<591.4	145	0.99 (0.82-1.20)	1.01 (0.83-1.22)
591.4-<1455.4	125	1.04 (0.85-1.28)	1.06 (0.86-1.31)
1455.4-<3206.6	136	0.95 (0.78-1.15)	0.95 (0.78-1.16)
≥3206.6	135	0.90 (0.74-1.10)	0.90 (0.73-1.09)
		$p^{g.}$=0.825 $p^{t.}$=0.356	$p^{g.}$=0.769 $p^{t.}$=0.389
Stavudine			
Cumulative exposure (mg-months)			
>0-<118.3	85	1.33 (1.03-1.72)	1.36 (1.05-1.76)
118.3-<301.6	71	1.10 (0.83-1.44)	1.13 (0.86-1.49)
301.6-<643.3	78	0.91 (0.70-1.17)	0.92 (0.71-1.19)
≥643.3	78	0.85 (0.66-1.09)	0.85 (0.66-1.10)
		$p^{g.}$=0.112 $p^{t.}$=0.369	$p^{g.}$=0.082 $p^{t.}$=0.450
Decreased Risk			
Lamivudine			
Cumulative exposure (mg-months)			
>0-<1064.5	223	0.95 (0.80-1.12)	0.98 (0.83-1.15)
1064.5-<2769.6	219	0.73 (0.62-0.86)	0.77 (0.65-0.90)
2469.6-<5854.6	223	0.70 (0.60-0.82)	0.71 (0.61-0.84)
≥5854.6	222	0.63 (0.54-0.74)	0.64 (0.55-0.76)
		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001	$p^{g.}$=<0.0001 $p^{t.}$=<0.0001

[a.]: Unexposed participants used as baseline in all models
[b.]: All models adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus, excess glucocorticoid use, treatment of osteoporosis with bisphosphonates, and advanced HIV infection
$p^{g.}$: Global p-value
$p^{t.}$: Trend p-value
mg-months: milligram months, which is cumulative exposure in milligrams using a monthly unit

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Table 6. Lagged antiretroviral (ARV) drug class duration of exposures (in months) and risk for fracture among 11,621 persons with HIV infection by different lag periods.

ARV drug class duration (months)	Case N=2,477	Odds ratio[a., b.] (95% CI) No lag	Case N=2,477	Odds ratio[a., b.] (95% CI) 3 month lag	Case N=2,477	Odds ratio[a., b.] (95% CI) 6 month lag	Case N=2,477	Odds ratio[a., b.] (95% CI) 12 month lag
Nucleoside reverse transcriptase inhibitors)								
>0-<4.5	319	0.83 (0.72-0.97)	311	0.71 (0.61-0.82)	286	0.69 (0.59-0.80)	261	0.80 (0.68-0.93)
4.5-<10.5	306	0.70 (0.61-0.82)	282	0.74 (0.63-0.86)	266	0.74 (0.64-0.87)	199	0.76 (0.64-0.90)
10.5-<20	304	0.64 (0.55-0.75)	291	0.71 (0.61-0.82)	248	0.69 (0.59-0.81)	190	0.68 (0.58-0.81)
20+	323	0.53 (0.46-0.61)	293	0.56 (0.48-0.65)	260	0.58 (0.50-0.67)	197	0.65 (0.55-0.77)
		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001
Non-nucleoside and non-nucleotide reverse transcriptase inhibitors								
>0-<3	157	0.89 (0.74-1.08)	146	0.79 (0.66-0.96)	152	0.88 (0.73-1.07)	141	0.97 (0.79-1.18)
3-<8	166	0.87 (0.72-1.05)	159	0.87 (0.73-1.05)	143	0.86 (0.70-1.04)	111	0.83 (0.67-1.03)
8-<18	166	0.63 (0.53-0.75)	158	0.68 (0.57-0.82)	140	0.69 (0.57-0.84)	104	0.64 (0.51-0.80)
18+	160	0.59 (0.49-0.70)	145	0.60 (0.50-0.73)	124	0.59 (0.48-0.72)	94	0.62 (0.49-0.78)
		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001		$p^{g.}$ =<0.0001 $p^{t.}$ =<0.0001		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001		$p^{g.}$=<0.0001 $p^{t.}$=<0.0001
Protease inhibitor								
>0-<4	211	0.99 (0.84-1.17)	205	0.92 (0.78-1.09)	178	0.79 (0.67-0.95)	147	0.87 (0.72-1.05)
4-<9	177	0.98 (0.82-1.17)	172	1.04 (0.87-1.25)	153	1.05 (0.87-1.27)	129	1.00 (0.82-1.23)
9-<18	195	0.97 (0.82-1.15)	181	0.97 (0.81-1.16)	158	0.91 (0.76-1.10)	113	0.85 (0.69-1.06)
18+	203	0.83 (0.70-0.99)	183	0.87 (0.73-1.04)	162	0.86 (0.71-1.04)	120	0.87 (0.70-1.08)
		$p^{g.}$=0.324 $p^{t.}$=0.070		$p^{g.}$=0.473 $p^{t.}$=0.221		$p^{g.}$=0.045 $p^{t.}$=0.096		$p^{g.}$=0.267 $p^{t.}$=0.074
Fusion inhibitor								
exposed[c]	29	0.97 (0.64-1.48) $p^{g.}$=0.883	27	0.98 (0.63-1.53) $p^{g.}$=0.943	26	1.04 (0.66-1.63) $p^{g.}$=0.857	18	1.08 (0.63-1.86) $p^{g.}$=0.779

No exposures to entry inhibitors; $p^{g.}$: global p-value; $p^{t.}$: trend p-value
[a.]Unexposed participants used as baseline in all models;
[b.]All models adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus, excess glucocorticoid use, treatment of osteoporosis with bisphosphonates, and advanced HIV infection
[c.]Drugs with 30 or less exposed cases were dichotomized as unexposed/exposed

data for patients. This may lead to incomplete descriptions of drug benefits and risks when studied using observational claims data. Historically, prescription claims in observational assessments of benefits and untoward events utilize either dichotomous or cumulative exposure to a single or few drugs, drug classes, or multidrug regimens. The restructure of the prescription claims into non-overlapping prescription histories in a defined study cohort permitted analysis of the data in ways that are not commonly executed in pharmacoepidemiology. The approaches we describe led to the quantifiable assessment of time-varying, ARV drug-specific exposure-response relationships. These exposure-response relationships employed duration of exposure, cumulative exposure, and average intensity of exposure, as is often done in occupational epidemiological research [**10**-**14**]. Additionally, pharmacoepidemiological studies can also readily incorporate exposure lags and latency into complex exposure-response assessments and well-designed comparative effectiveness research. These methods can be readily applied to time-varying drug exposures for chronic diseases where prescription histories are complex and evolve over time. The restructure of prescriptions into multidrug, daily-dose exposures allows capture of time-varying, multidrug prescription histories similar to occupational exposures that accumulate during an individuals' job history [**9**]. The restructure enabled the temporal re-alignment of same drug prescription overlaps and encompassments while giving proper attention to the gaps in the prescription history. Future investigative work can readily be expanded to include analysis of many concurrent exposures similar to analyses in occupational epidemiology [**10**]. Generalizing these methods for use with other pharmacy claims data-based studies of health outcomes and benefit-risk assessments is straightforward. The major objectives of the occupational studies that have employed such methods were to identify the health consequences of workplace exposure, provide data for setting standards for protection of

workers to potentially toxic substances, make projections of risk to less-exposed populations, and elucidate exposure-response relationships [11-14,20-23]. The exposures may be either continuous or intermittent and there may be several competing exposures and covariables that change over time. Phamacoepidemiology studies, particularly those involving chronic diseases that study aging, adverse drug events, cumulative comorbid conditions, and time-varying multidrug exposures have similar objectives for hypothesis generation and hypothesis testing of exposure-response relationships. To date, traditional analyses of pharmacoepidemiology studies often have not made complete use of drug exposure information contained within the complex drug histories found in pharmacy claims data. We have shown a method of restructuring the data that incorporates these complex drug histories more easily into exposure response analyses [10].

Models that include the accumulation of comorbid conditions and additional drug exposures over time will more reliably determine exposure-response estimates for untoward outcomes in chronic diseases such as HIV infection, heart disease, chronic obstructive pulmonary disease, and diabetes mellitus. We do, however, acknowledge limitations and biases associated with retrospective studies that use administrative pharmacy and medical claims to assess drug-exposure response relationships. These include information bias, measurement error, and misclassification of exposures and outcome. Known limitations of measuring drug exposure that may not be documented in claims data include imperfect medication adherence by patients, stretching of drug supply, pill splitting, free samples, and double supplies to cover absences. While the methods we propose do not eliminate these limitations and biases, our methods do allow a more complete summarization of complex drug exposures over time.

Conclusion

We report detailed methodology for the creation of non-overlapping, time-varying prescription histories from an administrative claims database. The adoption of occupational epidemiology methods to pharmacoepidemiology provided a quantified assessment of varied cumulative, combination ARV exposures for HIV treatment to the risk of fracture in a nested case-control study. These methods offer an alternative approach to the assessment of long-term untoward health outcomes among persons with complex drug exposures for chronic diseases.

Additional files

Appendix 1
Appendix 2

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	AOY	LMM	SSL	MFL	SJB
Research concept and design	✓	✓	--	--	✓
Collection and/or assembly of data	✓	--	✓	✓	--
Data analysis and interpretation	✓	--	--	✓	--
Writing the article	✓	✓	--	--	✓
Critical revision of the article	✓	✓	✓	--	✓
Final approval of article	✓	✓	✓	✓	✓
Statistical analysis	✓	--	--	--	--

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