Characterizing Patterns in Antiretroviral Therapy for Individuals with Human Immunodeficiency Virus (HIV)

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# Background

Globally, approximately 38.4 million individuals were living with Human Immunodeficiency Virus (HIV) and an estimated 28.7 million people were accessing antiretroviral therapy (ART) for the treatment of HIV in 2021 [2]. ART has been extremely important for the achievement of viral suppression to both improve HIV-related morbidity and mortality and to prevent transmission [3]. Recent treatment guidelines in the United States involve initiating ART as soon as one has been diagnosed and received conclusive testing [4]. Antiretroviral therapy involves taking a combination of medications daily, where a typical regimen includes three medications from a minimum of two different drug classes [5]. The Food and Drug Administration (FDA) has approved more than 30 medications to treat HIV [6]. Single-tablet regimens have improved medication adherence and quality of life for people living with HIV [7]. However, treatment for HIV remains complex and often depends on a variety of clinical and personal factors [6]. Observational research provides a unique opportunity to evaluate heterogeneity in treatment for HIV in the real-world. It is important to establish real-world evidence for ART and further our understanding of the characteristics surrounding treatment for HIV. There are limited network studies within OHDSI that assess complexities related to care for microbial diseases and to the best of our knowledge, real-world evaluation of HIV antiretroviral therapy across a data network has not yet been conducted. Here we seek to evaluate pathways in HIV treatment within the OHDSI data network through identifying commonly used first-line antiretrovirals, characterizing cohort-level factors associated with treatment, evaluating temporal trends in treatment, and comparing antiretroviral treatment in the real-world to the often-complex clinical recommendations.

# Objectives

This is a retrospective, observational study with the purpose of characterizing and evaluating trends in pathways for antiretroviral therapy over time for individuals who have been diagnosed with Human Immunodeficiency Virus and have at least 12 months of continuous observation. Observed treatment patterns will be identified, evaluated over time, and compared to official clinical guidelines for HIV treatment in respective geographic regions. The primary goal to is to determine the prevalence of treatments prescribed and dispensed to reveal variation in treatment regimens with respect to each individual data source. The secondary goal is to determine the degree of guideline compliant therapy by comparing the treatment patterns observed to official clinical guidelines in retrospective geographic regions, and to further evaluate cohort-level factors associated with concordance. We hypothesize that this real-world evaluation of HIV antiretroviral therapy will reveal characteristics and patterns that differ with respect to prevalence of identified combinations and degree of clinical guideline concordance.

# Data sources

The analyses will be performed across a network of observational healthcare databases. Data partners will run the analysis package on their own data and return the extracted results. All databases have been transformed into the OMOP Common Data Model Version 5. The complete specification for OMOP Common Data Model Version 5.3 is available at: <https://github.com/OHDSI/CommonDataModel>. The following data sources will be included in this analysis:

* *Add list of data sources from data partners that agree to participate*
  + *Note:* *Some data sources may not be eligible if too few individuals within the HIV target cohort are identified*

*Describe Data Sources Above: Format*

*(Database Name*

*Database description: type of data, medication information available, demographic information available, geographic representation*

*The ETL specification for transforming said data into the OMOP CDM is available at: link*

*Data quality report if available via ACHILLES or DQD (ex: ACHILLES has been used to characterize the database and provide a Data quality assessment. The summary is available at: URL.)*

# Methods

### Study Population

The general approach to defining the population of interest consisting of individuals with HIV involves evaluating a variety of factors as discussed here (<https://forums.ohdsi.org/t/phenotype-phebruary-day-22-human-immunodeficiency-virus/16007>), as previous work from the OHDSI Phenotype Workgroup provided valuable insight into the develop of phenotype algorithms to identify people with HIV. Individuals with HIV are identified across the data network through diagnosis codes, laboratory tests, and exposures to antiretroviral medications. The HIV cohort ([*1781540*](https://atlas-demo.ohdsi.org/#/cohortdefinition/1781540)) was created using ATLAS and will be the target cohort included within the treatment pathway analysis [1].

The phenotype definition below outlines requirements that an individual must meet to be included within the HIV target cohort:

A diagnosis of HIV *(concept set* [*1872277*](https://atlas-demo.ohdsi.org/#/conceptset/1872277/included)*)* followed by at least one of the following events:

* HIV specific laboratory test: Antibody, Detection by Nucleic Acid Quantification or Assay *(concept set* [*1872364*](https://atlas-demo.ohdsi.org/#/conceptset/1872364/expression)*)*
* Second diagnosis of HIV or related condition (*see concept 1872277 for included concepts*)
* Exposure to an antiretroviral medication on the ingredient-level *(concept set* [*1872365*](https://atlas-demo.ohdsi.org/#/conceptset/1872365/expression)*)* with a diagnosis of HIV

The index date is considered to be the moment of time at which the individual enters the cohort when the qualifications as designated above are met. An observation period of 365 days will be required to evaluate treatments over time.

### Treatments of Interest

Treatments of Interest are antiretroviral therapies that can be prescribed or dispensed for the treatment of HIV [4, 6, 8]. Treatment consists of a regimen consisting of multiple antiretrovirals with differing mechanistic classes. The following eight mechanistic drug classes are approved for the treatment of HIV in the United States: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, a gp120 attachment inhibitor, a CD4 T lymphocyte post-attachment inhibitor, and pharmacokinetic enhancers (PK) [4]. The United States Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends an initial regimen of an INSTI with two NRTIs, but acknowledges that different combinations of NRTIs and drugs of other mechanistic classes are often used [4]. 23 different clinical scenarios are specifically mentioned by the DHHS Panel that are important for determining what ART regimen is the most appropriate for a given person [4]. We seek to evaluate treatment pathways defined by Hripcsak et al. as the ordered sequence of medications that an individual is prescribed [9]. Treatments of interest including single-ingredient antiretrovirals and co-formulated combination medications were identified (Table 1). Event cohorts for the treatment pathway analysis consist of the treatments of interest will be created using ATLAS [1]. The single ingredient antiretrovirals will be summarized using the RxNorm standard ingredient level. Combination medications will be summarized using the RxNorm and RxNorm Extension standard branded, clinical, marketed product levels.

Table 1. Treatments of Interest

|  |  |  |
| --- | --- | --- |
| **Single Ingredient Antiretrovirals** | | |
| **Name** | **Concept Set** | **DRC** |
| abacavir | [1871755](https://atlas-demo.ohdsi.org/#/conceptset/1871755/expression) | 9,432,765 |
| didanosine | [1871756](https://atlas-demo.ohdsi.org/#/conceptset/1871756/expression) | 647,609 |
| emtricitabine | [1871757](https://atlas-demo.ohdsi.org/#/conceptset/1871757/expression) | 41,509,474 |
| lamivudine | [1871758](https://atlas-demo.ohdsi.org/#/conceptset/1871758/expression) | 13,100,843 |
| stavudine | [1871759](https://atlas-demo.ohdsi.org/#/conceptset/1871759/expression) | 523,630 |
| tenofovir alafenamide | [1871760](https://atlas-demo.ohdsi.org/#/conceptset/1871760/expression) | 7,139,548 |
| tenofovir disoproxil | [1871761](https://atlas-demo.ohdsi.org/#/conceptset/1871761/expression) | 39,808,122 |
| zidovudine | [1871763](https://atlas-demo.ohdsi.org/#/conceptset/1871763/expression) | 4,090,164 |
| delavirdine | [1871763](https://atlas-demo.ohdsi.org/#/conceptset/1871763/expression) | 24,745 |
| doravirine | [1871764](https://atlas-demo.ohdsi.org/#/conceptset/1871764/expression) | 1,742 |
| efavirenz | [1871766](https://atlas-demo.ohdsi.org/#/conceptset/1871766/expression) | 13,551,718 |
| etravirine | [1871767](https://atlas-demo.ohdsi.org/#/conceptset/1871767/expression) | 1,806,916 |
| nevirapine | [1871768](https://atlas-demo.ohdsi.org/#/conceptset/1871768/expression) | 2,060,894 |
| rilpivirine | [1871769](https://atlas-demo.ohdsi.org/#/conceptset/1871769/expression) | 3,786,042 |
| atazanavir | [1871770](https://atlas-demo.ohdsi.org/#/conceptset/1871770/expression) | 5,950,948 |
| darunavir | [1871771](https://atlas-demo.ohdsi.org/#/conceptset/1871771/expression) | 7,220,033 |
| fosamprenavir | [1871772](https://atlas-demo.ohdsi.org/#/conceptset/1871772/expression) | 919,544 |
| indinavir | [1871773](https://atlas-demo.ohdsi.org/#/conceptset/1871773/expression) | 163,974 |
| lopinavir | [1871774](https://atlas-demo.ohdsi.org/#/conceptset/1871774/expression) | 2,967,888 |
| nelfinavir | [1871775](https://atlas-demo.ohdsi.org/#/conceptset/1871775/expression) | 577,507 |
| saquinavir | [1871776](https://atlas-demo.ohdsi.org/#/conceptset/1871776/expression) | 217,293 |
| tipranavir | [1871777](https://atlas-demo.ohdsi.org/#/conceptset/1871777/expression) | 70,644 |
| bictegravir | [1871778](https://atlas-demo.ohdsi.org/#/conceptset/1871778/expression) | 434,835 |
| dolutegravir | [1871779](https://atlas-demo.ohdsi.org/#/conceptset/1871779/expression) | 6,545,746 |
| elvitegravir | [1871780](https://atlas-demo.ohdsi.org/#/conceptset/1871780/expression) | 6,164,560 |
| raltegravir | [1871781](https://atlas-demo.ohdsi.org/#/conceptset/1871781/expression) | 6,732,319 |
| enfuvirtide | [1871782](https://atlas-demo.ohdsi.org/#/conceptset/1871782/expression) | 81,760 |
| maraviroc | [1871783](https://atlas-demo.ohdsi.org/#/conceptset/1871783/expression) | 622,807 |
| cobicistat | [1871786](https://atlas-demo.ohdsi.org/#/conceptset/1871786/expression) | 7,515,167 |
| ritonavir | [1871787](https://atlas-demo.ohdsi.org/#/conceptset/1871787/expression) | 14,865,589 |
| **Combination Antiretrovirals** | | |
| **Ingredients** | **Concept Set** | **\*Brand Name®** |
| bictegravir + tenofovir alafenamide + emtricitabine | [1871788](https://atlas-demo.ohdsi.org/#/conceptset/1871788/expression) | Biktarvy |
| dolutegravir + abacavir + lamivudine | [1871789](https://atlas-demo.ohdsi.org/#/conceptset/1871789/expression) | Triumeq |
| dolutegravir + rilpivirine | [1871790](https://atlas-demo.ohdsi.org/#/conceptset/1871790/expression) | Juluca |
| dolutegravir + lamivudine | [1871791](https://atlas-demo.ohdsi.org/#/conceptset/1871791/expression) | Dovato |
| elvitegravir + cobicistat + tenofovir alafendamide + emtricitabine | [1871792](https://atlas-demo.ohdsi.org/#/conceptset/1871792/expression) | Genvoya |
| elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine | [1871793](https://atlas-demo.ohdsi.org/#/conceptset/1871793/expression) | Stribild |
| atazanavir + cobicistat | [1871794](https://atlas-demo.ohdsi.org/#/conceptset/1871794/expression) | Evotaz |
| darunavir + cobicistat | [1871795](https://atlas-demo.ohdsi.org/#/conceptset/1871795/expression) | Prezcobix |
| darunavir + cobicistat + tenofovir alafenamide + emtricitabine | [1871796](https://atlas-demo.ohdsi.org/#/conceptset/1871796/expression) | Symtuza |
| lopinavir + ritonavir | [1871797](https://atlas-demo.ohdsi.org/#/conceptset/1871797/expression) | Kaletra |
| doravirine + tenofovir disoproxil fumarate + lamivudine | [1871798](https://atlas-demo.ohdsi.org/#/conceptset/1871798/expression) | Delstrigo |
| efavirenz + tenofovir disoproxil fumarate + emtricitabine | [1871799](https://atlas-demo.ohdsi.org/#/conceptset/1871799/expression) | Atripla |
| efavirenz + lamivudine + tenofovir disoproxil fumarate | [1871800](https://atlas-demo.ohdsi.org/#/conceptset/1871800/expression) | Symfi |
| rilpivirine + tenofovir alafenamide + emtricitabine | [1871801](https://atlas-demo.ohdsi.org/#/conceptset/1871801/expression) | Odefsey |
| rilpivirine + tenofovir disoproxil fumarate + emtricitabine | [1871802](https://atlas-demo.ohdsi.org/#/conceptset/1871802/expression) | Complera |
| abacavir + lamivudine | [1871803](https://atlas-demo.ohdsi.org/#/conceptset/1871803/expression) | Epzicom |
| abacavir + lamivudine + zidovudine | [1871804](https://atlas-demo.ohdsi.org/#/conceptset/1871804/expression) | Trizivir |
| tenofovir alafenamide + emtricitabine | [1871805](https://atlas-demo.ohdsi.org/#/conceptset/1871805/expression) | Descovy |
| tenofovir disoproxil fumarate + emtricitabine | [1871811](https://atlas-demo.ohdsi.org/#/conceptset/1871811/expression) | Truvada |
| tenofovir disoproxil fumarate + lamivudine | [1871812](https://atlas-demo.ohdsi.org/#/conceptset/1871812/expression) | Cimduo |
| zidovudine + lamivudine | [1871813](https://atlas-demo.ohdsi.org/#/conceptset/1871813/expression) | Combivir |

\*Brand names may be different depending on product and geographic region; however, the same formulations are included within the concept set

### Treatment Pathway Analysis

Treatment pattern analyses will be performed using the Cohort Pathways tool in ATLAS [1]. Cohort pathways is an analytic tool that allows one to look at the sequence of clinical events that occur within a population [9]. This treatment pathway analysis will describe the ordered sequence of antiretroviral medications that are prescribed or dispensed for an individual identified within the target cohort. The pathway analysis aims to summarize treatments received by individuals within the cohort from first exposure to antiretrovirals. The analysis will produce the proportion of persons receiving a specific treatment of interest based on their first-therapy initiated. Second-line, third-line, and fourth-line therapies will be evaluated when present and are helpful in determining the proportion of individuals that switch treatments over time. The treatment sequences during the post-index time window for individuals included within the target HIV cohort that initiate ART will be evaluated as both single ingredients and combination drugs. The use of both structures of event cohorts allows the heterogeneity in treatment utilization to be represented and assessed. For example, if an individual was exposed to a combination of bictegravir, tenofovir alafenamide, and emtricitabine and was not observed to take any other antiretroviral medications over time, then this combination would be considered the first-line treatment as well as the only identified ART regimen observed for this individual. The treatment pathway will reveal the proportion of individuals within the HIV target cohort receiving a specific combination of single ingredient antiretrovirals. Furthermore, if individuals are exposed to that specific single ingredient combination in the form of the coformulated drug, then the proportion for treatment with Biktarvy® would also overlap similarly with the proportion receiving the combination of the single ingredients bictegravir, tenofovir alafenamide, and emtricitabine.

Each data partner has the option to suppress any summary statistics below a minimum cell count number, the default will be *1*.

Single Ingredient Proposed Pathway Analysis: <https://atlas-demo.ohdsi.org/#/pathways/256>

Combination Proposed Pathway Analysis: <https://atlas-demo.ohdsi.org/#/pathways/257>

### Characterization

Due to the fact that treatment for HIV is dependent upon many clinical and demographic factors, a characterization analysis of the target cohort can provide insight into covariates that have the possibility to impact treatment [4,9]. For example, the presence of comorbidities such as hyperlipidemia, or coinfections with Hepatitis B or C can impact which ART regimen is most appropriate. Characterization analyses can be constructed using the Characterizations tool in ATLAS [1]. A cohort characterization will be conducted to describe the baseline and post-index characteristics of individuals included within the HIV target cohort. Descriptive statistics for comorbidities using condition group eras and socio-demographics will be characterized.

Characterization Proposed Analysis: <https://atlas-demo.ohdsi.org/#/cc/characterizations/815>

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