Curriculum Vitae

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- Conducted advanced statistical analyses, including time-to-event, interrupted time series, generalized linear and mixed models, and generalized estimating equations, to demonstrate the health and economic value of therapies for HIV/AIDS, COVID-19, and psychiatric conditions.
- Co-authored publications and presentations to communicate research findings to funding agencies, academic and industry researchers, and the general public.
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CCW and IQVIA datasets in accordance with subject area specific protocol guidelines (e.g., STROBE and CHEERS).
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- Evaluated internal databases appropriate for studies including CMS Chronic Conditions Data Warehouse, IQVIA-Pharmetrics, and Healthcare Utilization Project.
- Created procedures for study analytics of descriptive and inferential statistics.
- Organized statewide workgroups of state and local public health officials from 24 jurisdictions and several government and non-profit agencies.
- Led identification of relevant funding announcements and evaluated areas of unmet need based on previously funded grants on NIH Reporter.
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December 2015 – July 2016 Johns Hopkins University
Senior Research Program Coordinator

- Developed and implemented changes to research protocols and program operations on large HIV Prevention Network studies.
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Facility-level Factors Associated with Penetration and Spread of SARS-COV-19 in Nursing Homes in the US.
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Oncology and Psychopharmacologics
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Retrospective cohort study using IQVIA Pharmetrics data and employing propensity score matching to investigate pharmacologic treatment of pain, including opioids, sedatives, and gabapentin and among patients with cancer. All cancer type subgroups (e.g., bone, pancreatic, lung, head and neck) were found to be undertreated for pain when compared to the prevalence of pain in these groups in clinical trials.

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1. Le, T., **Fleming, S.,** Kuzucan, A., Dizik, A., Simoni-Wastila, L. "Query Mandates in Prescription Drug Monitoring Programs Reduce Opioid Use among Commercially Insured Patients with Cancer." *Journal of the American Pharmacists Association, Online June 2021, 1-7. (co-designed and determined analytic method, provided statistical interpretation, and co-wrote manuscript).*
2. Le, T., **Fleming, S.,** Simoni-Wastila, L. "Patterns of Opioid Use among Commercially Insured Patients with Cancer." *Am J Manag Care.* (In Press). *(co-designed and determined analytic method, provided statistical interpretation, and co-wrote manuscript).*
3. Qato, D., **Fleming, S.**, Wallem, A., Simoni-Wastila, L. "Racial Disparities in Nursing Home Resident and Staff COVID-19 Vaccination Rates." *Journal of Health Care for the Poor and Underserved.* (In Press). *(Designed and determined analytic method, conducted all analyses, provided statistical interpretation, and co-wrote manuscript).*
4. Simoni-Wastila, L., Wallem, A., **Fleming, S.**, Le, T., Kepczynska, P., Yang, J., Qato, D. "Staffing and Protective Equipment Access Mitigated COVID-19 Penetration and Spread in US Nursing Homes During the Third Surge." *Journal of American Medical Directors Association.* Volume 22, Issue 12, 2021, Pages 2504-2510, ISSN 1525-

8610, https://doi.org/10.1016/j.jamda.2021.09.030. *(co-designed and determined analytic method, conducted analyses, provided statistical interpretation, and co-wrote manuscript).*
5. **Fleming, S**. (2011). "Parental Cultural Capital and Adolescent Educational Pathways during an Economic Depression." *Silicon Valley Notebook, 9,* 53-61.

Submitted or In-Revision Peer-reviewed journal articles

1. Olopoenia, A., Qato, D., **Fleming, S.,** Simoni-Wastila, L. "Trends in Gabapentin Utilization among Medicare Beneficiaries, 2006-2015." (Submitted).
2. Holmes, S., Kuzucan, A., Brandt, N., Briesacher, B., Desai, A., Feng, Z., **Fleming, S.**, Johnson, A., Olopoenia, A., Qato, D., Wallem, A., Zarowitz, B., Wastila, L. "Care Transitions among Medicare Nursing Home Residents by Use of Antipsychotic Medications." (Submitted).
3. Lee, M., Zarowitz, B., Pellegrin, K., Cooke, C., **Fleming, S.**, and Brandt, N. "Social Determinants Predict Whether Medicare Beneficiaries are Offered a Comprehensive Medication Review." (Submitted).

Non-Peer Reviewed Reports

1. Simoni-Wastila, L., **Fleming, S.**, et al. "Substance Use and Mental Health among High School Cannabis Users." Maryland SEOW, 2020.
2. Simoni-Wastila, L., **Fleming, S.**, et al. "Pharmacy Drug User Health Project Evaluation." Maryland SEOW, 2019.
3. Simoni-Wastila, L., **Fleming, S.**, et al. "Cannabis Policy and Outcomes: A Review." Maryland SEOW, 2019.
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2. **Fleming, S.,** Simoni-Wastila, L., Wallem, A., Le, T., Kepczynska, P., Yang, J., Qato, D. Gerontological Society of America, November 2021, Virtual, Paper Presentation "COVID-19 Cases, Hospitalizations, and Deaths in Nursing Homes: Factors Impacting the Third Surge."

3. **Fleming, S.,** Stafford, K., Greene, M. Onukwugha, E., Slejko, J., Simoni-Wastila, L. Department of Pharmaceutical Health Services Research Seminar, November 2021, Baltimore, MD, Oral Presentation "Trends in Health Care Resource Utilization and Related Costs among Medicare Beneficiaries Living with HIV, 2014-2019."
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14. **Fleming, S**. "Ambitions, Advising, and the Economic Crisis." From Data to Delivery: Using Data for Research Enrichment Symposium in Santa Clara, CA 2011.

Abstract

Background: Single tablet antiretroviral regimens (STR) are associated with better adherence and lower healthcare resource utilization (HcRU) and costs compared to multi-tablet regimens (MTR) among commercially insured people living with HIV under 50 years of age. This dissertation aimed to detail patterns of STR and MTR use and the associated HcRU and costs among Medicare beneficiaries living with HIV.

Methods: Using a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) we identified beneficiaries living with HIV from January 1, 2014 through December 31, 2019. We used generalized estimating equations to estimate trends in antiretroviral and other HcRU. We estimated 1-year incremental total direct medical costs with an instrumental variable approach via two-stage least squares. HcRU and cost estimates were used to build a five-year budget impact model.

Results: The probability of STR receipt was 0.24 (99% Confidence Interval (CI): 0.23-0.26) higher in 2019 (56.92%) than 2014 (26.99%), and integrase-based regimens were predominant among both STR (79.75%) and MTR (74.18%) by 2019. Among 7,044 beneficiaries who initiated a new ART regimen, the instrumented STR variable was associated with statistically significant lower 1-year incremental total direct medical costs compared to MTR (-$13,487.70, (95% CI: -$16,750.77 to -$10,224.63)). Our budget impact model predicted $1.8 billion in additional costs in year 5 under a scenario where current trends in ART utilization and list prices continue compared to 2019 levels. The excess costs were driven by $2.3 billion in greater ART spending despite reductions in all other HcRU and related costs.

Conclusion: These findings demonstrate the predominance of STR and integrase-based regimens among Medicare beneficiaries living with HIV. STRs were associated with significantly lower 1-year total direct medical costs compared to MTR among this understudied population. However, future increases in ART costs at the rates observed during the study period may not be affordable despite savings associated with reductions in HcRU. The costs of caring for people living with HIV in Medicare will likely continue to grow as a proportion of total spending and may be markedly impacted by policies aimed at controlling prescription drug expenditures.

Healthcare Resource Utilization and Costs Associated with Antiretroviral Regimen Complexity

by
Sean P. Fleming

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List of Abbreviations

ABM	Andersen's Behavioral Model
AIDS	Acquired Immune Deficiency Syndrome
AME	Average Marginal Effect
ART	Antiretroviral Therapy
BIA	Budget Impact Analysis
BIM	Budget Impact Model
cART	Combination Antiretroviral Therapy
CCI	Charlson Comorbidity Index
CCW	Chronic Conditions Data Warehouse
CDC	Centers for Disease Control
ED	Emergency Department
FDA	Food and Drug Administration
FY	Fiscal Year
GEE	Generalized Estimating Equations
GLM	Generalized Linear Model
HAART	Highly Affective Antiretroviral Therapy
HHS	Department of Health and Human Services
HcRU	Healthcare Resource Utilization

HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IP	Inpatient
IV	Instrumental Variable
LATE	Local Average Treatment Effect
MTR	Multi-Tablet Regimen
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NRTTI	Nucleoside Reverse Transcriptase Transfer Inhibitor
OLS	Ordinary Least Squares
OP	Outpatient
PE	Pharmacokinetic Enhancer
PI	Protease Inhibitor
PLHIV	People Living with Human Immunodeficiency Virus
QMB	Qualified Medicare Beneficiary
2SLS	Two-Stage Least Squares
STR	Single Tablet Regimen
US	United States

1 Overview

1.1 Statement of the Problem

Over the past three decades the effectiveness of antiretroviral therapy (ART) has significantly reduced Acquired Immune Deficiency Syndrome (AIDS)-related mortality.[1] The development of numerous antiretroviral agents and novel regimens have helped usher in an era of chronic disease management for people living with HIV (PLHIV) that has replaced the palliative approach previously utilized for a condition once considered fatal. Indeed, half of all PLHIV in the United States (US) are now 50 years of age or older;[2] however, with increased age and as a consequence of HIV infection and its treatments, older PLHIV face increased non-AIDS-related morbidity and consequent treatments, both of which can complicate care.[1,3,4] This aging PLHIV population accounts for increased healthcare costs, with fifty percent of federal HIV/AIDS funding appropriated through Medicare,[5] the public insurance program for adults aged 65 and older and those who qualify on the basis of disability. Medicare's Part D program also reimburses all ART medications as a protected class.[6]

ART is now recommended for all people regardless of their disease stage.[7] While lifesaving, ART can pose problems for users, such as decreases in bone mineral density associated with tenofovir disoproxil fumarate (TDF).[8] There is also the potential for drug-drug interactions, including commonly prescribed calcium channel blockers and statins among others.[9] As well, resistance to individual ART medications can reduce the number of regimens available to the patient, which may further increase regimen complexity.[10] Regimens which include multiple ART medications in combination as single tablet regimens (STR) have been shown to improve adherence and effectiveness.[11–14] Since

2015, the Food and Drug Administration (FDA) has approved 17 HIV-related drugs, 10 of which are STR products.[15] STRs are now first-line therapy in managing HIV, but their dosing convenience comes at an expense—STRs cost approximately 1.5 times more than the combined cost of the individual medications among both public and private payers.[16] Although significant cost-savings are possible due to present—and future— generic availability of components of STRs, the difficulty in producing generic STRs stems from new and existing drug patents and marketing exclusivities. Lower-cost brand ART, coined quasi-generics, further add to the complexity of the ART pricing landscape; currently, only two quasi-generic STRs are commercially available (Symfi® and Symfi Lo®).[15] Many STRs are slated to lose patent protection in the latter half of this decade, yet half retain patent protection beyond 2030. It remains unclear if the clinical and quality of life benefits of STRs outweigh these additional financial costs.

Although advancements in ART have developed rapidly, more information is needed to understand treatment and outcomes in the population of PLHIV in Medicare. As well, although increased attention is paid to HIV care management as a chronic condition, little research has delineated patterns of ART regimens and their impacts on healthcare resource utilization and expenditures in Medicare beneficiaries with HIV. Further, penetration of STR use among this population is unknown. These findings have significant implications for the potential cost savings generic substitution may hold for Medicare as the single largest payor of HIV-related care. The consequences of these knowledge gaps remaining unfilled include potential budgetary waste for STRs that may not provide significant improvements in healthcare utilization and costs over MTRs, which combined may also erode patient preference for STRs.

The focus on Medicare beneficiaries, who are medically complex and resource intensive, is timely as the PLHIV population is aging and a larger proportion will be covered by Medicare in the future. The use of a nationally representative claims database provides a large sample from which we can assess utilization and expenditure patterns among this cohort of PLHIV. In turn, findings from claims data will support simulation analyses that provide customizable quantitative evidence for policy makers regarding the effects of potential policies and resource allocation strategies.

1.2 Specific Aims and Hypotheses

The primary goals of this dissertation are to: 1) detail patterns of ART use, healthcare resource utilization, and expenditures; 2) identify incremental costs associated with ART regimen complexity; and 3) assess the impact of ART regimen prescribing on Medicare spending among PLHIV. The proposed specific aims include both claims- and simulation- based methods to contribute to the body of knowledge regarding regimen complexity and related costs among PLHIV in Medicare.

Aim 1) Describe patterns of ART regimens and inpatient, emergency department, outpatient, and prescription drug utilization and costs among PLHIV in Medicare (2014-2019) by STR and MTR receipt.

Hypothesis 1) STR utilization and associated costs will increase, while MTR related costs will also increase despite decreases in utilization.

Aim 2) Estimate 1-year total incremental direct medical costs associated with STR compared to MTR among PLHIV in Medicare (2014-2019).

Hypothesis 2) STRs will be associated with lower total direct medical costs compared to MTRs.

Aim 3) Estimate the budget impact of STR and overall antiretroviral utilization trends on inpatient, emergency department, outpatient, prescription drug, and total direct medical costs among PLHIV in Medicare.

Hypothesis 3) Increasing STR use will be associated with decreases in all non-ART utilization and related costs but increases in ART and total direct medical costs.

1.3 Significance

The combination of claims- and simulation- based analyses allows us to harness available data on prescribing practices and healthcare utilization and expenditures while efficiently quantifying the cost impact of current and future market and treatment trends. While older PLHIV are a small fraction of Medicare beneficiaries they represent a significant and growing proportion of Federal spending on HIV.[5] As the primary payer for antiretroviral (ART) medications, a market characterized by low generic competition and perennial price increases exceeding inflation,[17] Medicare has a prime opportunity to control costs in an era of significant healthcare expenditures. This dissertation is not only important from a budgetary standpoint, but also from a patient-centered perspective, as it will provide estimates of regimen complexity and related costs. Patients stand to gain from research that informs providers and policy makers of the current clinical and economic landscape among understudied Medicare beneficiaries with HIV.

This study addresses gaps in current knowledge about the impact of ART regimen complexity on healthcare utilization and costs among Medicare beneficiaries with HIV. Due to the significant burden of multimorbidity and polypharmacy on these beneficiaries, the minimization of such outcomes are critical goals for this population. Cost and utilization studies are important in ensuring patients are receiving optimal care and calibrating reimbursement accordingly. Research on PLHIV is widespread, yet there are gaps in populations that are older and burdened by increased multimorbidity and polypharmacy. This study not only examines these populations, but improves upon prior study designs, limitations, and capacity for causal inference. Our study employed a new-user design and an instrumental variable analysis to account for non-random treatment assignment, while examining a more contemporary study period allowing the capture of new therapies. These improvements are essential as little evidence is available on regimen choice in medically complex older adults with HIV due to their frequent exclusion from randomized control trials (RCT) historically.[18]

The use of the Chronic Conditions Data Warehouse offers an opportunity to examine a growing population in Medicare. Medical care for older PLHIV is challenging due to the potential for drug-drug and drug-disease interactions due to the high prevalence of comorbidities and concomitant medications.[1,3,4,19–21] ART prescribing has been greatly simplified and more HIV-related care is being shifted to primary care physicians and away from infectious disease specialists,[22] but prescribing errors are still observed in practice. The complexity of such care may lead to sub-optimal outcomes. While research on HIV is challenging in claims data due to missing clinical measurements, sophisticated study design and analytic methods, as implemented in this study, can provide evidence to Medicare utilizing the payer's own data. Results from this study can be used to support regimen choice for older Medicare beneficiaries with HIV, and to better understand the implications of policies impacting ARTs and related spending. The long-term impact of this research is to improve care by maximizing patient quality of life and minimizing healthcare utilization and costs for Medicare beneficiaries with HIV.

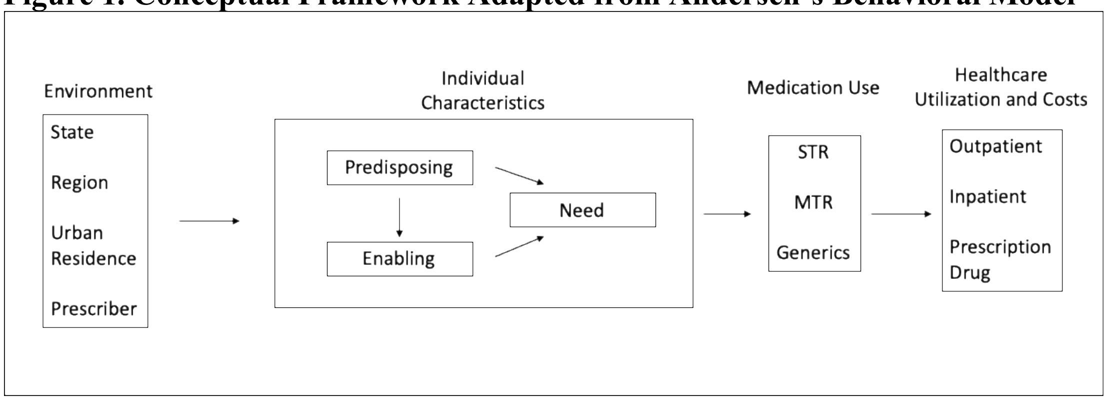
1.4 Conceptual Framework

Andersen's Behavioral Model (ABM)[23] has been adapted to serve as the theoretical framework for this study (**Figure 1**). The framework illustrates a modified ABM hypothesizing how ART regimen complexity impacts healthcare resource utilization and costs. ABM has been used extensively in the health economics literature and among vulnerable groups to conceptualize factors leading to the utilization of health services and related outcomes.

Initially developed in the mid-twentieth century to frame components that may impact access to and use of healthcare the ABM has been iteratively revised as the knowledge base has grown. The version used in this proposal categorizes factors and characteristics into different levels (i.e., environment, population, individual) and provides further labeling as predisposing, enabling, and need features that impact access to health services. Predisposing features include sociodemographics (e.g., age, sex, race/ethnicity). Features indicating need include both prior healthcare utilization (e.g., hospitalizations, physician visits) and utilization understood to indicate health beliefs and behaviors (e.g., immunizations, preventative screenings). Enabling features include the availability of health services (e.g., insurance coverage, distance to health services).

Figure 1 adapts the ABM to show the hypothesized relationship between environmental factors (e.g., geographical location, prescriber specialty), individual-level predisposing, need, and enabling factors, their impact on ART regimen complexity (i.e., single versus multiple tablet), and subsequent outcomes (i.e., inpatient, outpatient, and prescription drug utilization and costs). The original ABM frames outcomes in terms of "satisfaction" with health services.[23] In **Figure 1**, "satisfaction" is defined as individuals being less likely to use health services. Individuals who are "dissatisfied" with the effectiveness of their ART regimen will be more likely to use inpatient, outpatient, and prescription drug services to address manifestations of HIV disease, and therefore accruing excess costs. Determinants of ART regimen complexity, based on prior literature and expert opinion, were categorized into the predisposing, enabling, and need factors. This conceptual framework was used to inform selection of covariates across the three proposed aims. Inherent to claims-based analyses is the limitation that select features at each level are unmeasurable (e.g., social supports, complete disease and utilization history). Specific variables can be found in **Appendix Table 1**.

Figure 1. Conceptual Framework Adapted from Andersen's Behavioral Model



*Examples: Predisposing- race, sex, age; Need- Opportunistic Infections; Enabling- Dual eligibility

2 Background

2.1 Overview of the Human Immunodeficiency Virus

The Human Immunodeficiency Virus (HIV) is a retrovirus that infects and eliminates T cells (specifically $CD4^+$), thus progressively weakening the immune system.[7] Acquired Immune Deficiency Syndrome (AIDS) is the late stage of HIV infection, clinically defined as $CD4^+$ count fewer than 200 cells per cubic millimeter of blood (<200 cells/mm^3) and/or the development of specific opportunistic infections at any $CD4^+$ count level.[7] HIV is a lifelong infection transmitted through bodily fluids (e.g., blood, semen, vaginal fluids, breast milk) with no known cure. Left untreated HIV progresses at various rates with the gradual impairment of immune function manifesting in symptoms including fatigue, weight loss, opportunistic infections, some cancers, and neurological deficits.[24]

The advent of highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART) in the mid-1990's substantially reduced the prevalence of HIV-related complications and mortality.[24] ART reduces HIV viral load by inhibiting its ability to replicate, thus protecting and supporting the proliferation of $CD4^+$ cells and immune function.[7,24] Achieving an undetectable viral load or viral suppression (plasma HIV RNA <50 or <20 copies/mL) is a marker of both individual and community treatment success as it protects an individual's health and prevents further transmission.[7] Complete ART regimens typically include three or more medications from at least two of the seven drug classes.[7] Since 2012, the Department of Health and Human Services has recommended universal ART for all individuals at diagnosis, whereas prior guidelines had relied on $CD4^+$ count thresholds.[7]

ART has improved the health of PLHIV substantially, but it cannot fully combat the deleterious effects of the disease and higher prevalence of comorbidities due to immune activation and resulting inflammatory response.[1,24,25] PLHIV are at higher risk for conditions associated with normal aging, despite their adherence to ART.[1,24,25] This risk is observed earlier and continues to progress as individuals age.[24] Pharmaceutical treatments for these comorbidities lead to increased medication burden in PLHIV with the most common classes including antihypertensives, statins, antidepressants, and anticholinergics.[1,24,25] The complexity and burden of multimorbidity and polypharmacy, both of which are more prevalent in PLHIV than the general population, is substantial and will grow to predominate care as the population ages and near normal lifespans are more commonly observed.[26]

2.2 Epidemiology of HIV

HIV affects nearly 1.2 million adults in the US with an estimated 268,338 (25.78%) aged 50-59 years, 112,247 (10.74%) 60-64 years, and 115,803 (11.08%) ≥65 years as of 2019.[2] The Centers for Disease Control (CDC) estimates there were 15,465 deaths among people with HIV in 2019, of which 11,281 (72.95%) were 50 years of age and older.[27] Of the 36,398 new diagnoses in 2019, 6,102 (16.76%) were among those over 50.[27] Prevalent and incident cases likely differ most significantly in length of infection, immune function, and treatment experience. However, these factors are complicated by disease stage at diagnosis, treatment adherence and effectiveness, and transmitted and acquired viral resistance.[7] Individuals initiating new regimens will undergo resistance testing regardless of this distinction as it does not disqualify one from inherited viral resistance requiring specific and often more complex ART regimens though this is less common in the integrase strand transfer inhibitor (INSTI) era.[7]

Trends by age and calendar year show an increasing prevalence of HIV among adults over 50, which is projected to continue to grow over the coming decade.[27] Overall, new diagnoses remain fairly stable with the growth of this cohort being driven by individuals aging with HIV.[27] Older adults are at higher risk for diagnosis at later disease stages as perceived risk of infection is low among individuals and healthcare providers and routine screening is less common.[1,25] Late diagnosis leads to treatment initiation delays, further immune function damage, and development of additional comorbidities.[1] This results in premature aging, over and above the cellular aging seen during all seroconversions, characterized by increasing degenerative comorbidity burden, polypharmacy, and their additive impact on chronic inflammation.[24] Therefore, the growth of the aging HIV population, the complexity of the clinical profiles, and the cumulative effects on functional status can be expected to become even more prevalent in the future.

2.3 Economic burden associated with HIV

There are an estimated 150,000 Medicare Fee-For-Service (FFS) beneficiaries living with HIV, of which the majority (79%) are under 65 years old (2014).[28] Domestic HIV funding by the federal government exceeded $28 billion in Fiscal Year (FY) 2019, of which nearly three-quarters is mandatory funding primarily for Medicare, Medicaid, and Social Security Disability Insurance.[5] Over fifty-four percent ($11 billion) of mandatory federal HIV spending is administered through Medicare (FY 2019);[5] this will only grow over time as the number of beneficiaries with HIV balloons to over half a million in the coming decades.[27] The largest sources of discretionary spending include the Ryan White HIV/AIDS program ($2.3 billion) and component AIDS Drug Assistance Program (ADAP) ($900.3 million), Department of Veterans Affairs ($1.2 billion), and research funded through the National Institutes of Health (NIH) ($2.5 billion).[5]

Initially, spending gradually increased as the number of Medicare beneficiaries with HIV increased. Significant HIV spending shifted to Medicare in 2006, when Federal Medicaid spending for prescription drugs for dually eligible beneficiaries with HIV became covered under the Medicare Part D drug benefits program.[28] In 2014, average per capita Medicare spending on PLHIV was approximately $45,489; 59% ($26,761) going towards prescription drugs.[28] Total Medicare expenditures on ART exceeded $5.5 billion in FY 2017.[17] Additionally, ART list prices far exceeded inflation in recent years with 73% of all price increases exceeding inflation by at least 5% between 2016-2017.[17]

The estimated discounted mean lifetime total medical cost of a person infected with HIV is $326,500 (2012 USD).[29] Seventy-five percent of this total is attributed to medication costs: 60% for ART and 15% for the treatment of other chronic conditions.[29] The same study estimated individuals receiving optimal care to be $435,200 with ART costs 47% higher than the base case.[29] Optimal care was defined as all individuals initiating care at $CD4^+$ counts >500 cells/mm^3;[29] taken in the context of universal treatment recommendations the true lifetime medical costs may be closer to this optimal case. Other sensitivity analyses demonstrate the impact of later age at diagnosis and increasing generic medication use on lower lifetime costs.[29]

It is evident that the economic burden is substantial when considering Medicare beneficiaries with HIV make up about 10% of the HIV population, but account for 50%

of domestic Federal spending on HIV.[5,28] Achieving viral suppression is essential to maximizing individuals' health, controlling viral spread, and minimizing related utilization and costs. Viral suppression is achieved through adherence to ART, which inhibits the virus' ability to replicate and damage the immune system.[7] We are unaware of estimates of the number of Medicare beneficiaries receiving complete ART regimens and achieving durable virologic suppression. In 2016, only 53% of HIV infected individuals in the US were virally suppressed, slightly less than the 59% over 45 years old.[30] These are well below the U.S. National HIV/AIDS Strategy goal of 80% viral suppression among those diagnosed with HIV (72% of all PLHIV).[31] Older PLHIV have been shown to be more adherent to ART than younger PLHIV and also demonstrate higher rates of known diagnoses, engagement in care, and viral suppression.[30,32–35] If national surveillance estimates are observed or even exceeded among Medicare beneficiaries significant opportunity to improve care and outcomes exist in this population. Consequently, if national goals for ending the epidemic are achieved, then the total budget impact for Medicare will be significant.

Proposals to address the price of prescription drugs overall would have implications for ART and HIV care. Antiretrovirals are the only medication class, of six protected classes, with exemptions for prior authorization and step-therapy requirements from Part D sponsors.[36,37] Both of these utilization management strategies are decried by infectious disease experts as wholly inappropriate for PLHIV.[37] The risk of virologic failure and resistance from even minor treatment delays is too great in the setting of limited treatment options.[37] However, other cost-saving proposals may serve to lower costs without compromising care quality, including allowing Part D coverage exclusions for new formulations of old drugs that do not offer new routes of administration or improved safety, effectiveness, or adherence.[36] The aim of these policies is to encourage the development of better drugs, while discouraging various patent-extending practices. This clearly has relevance to ART, as generic availability remains low and only one novel route of administration (i.e., Cabenuva®—long acting injectable) has been brought to market in the US.[38] Novel mechanisms of action have been limited, though within-class improvements in efficacy and toxicity profiles have been realized and new antiretroviral classes are in late stage clinical trials.[39]

Greater competition is expected over the coming decade as generic components of first-line regimens become available. Few generic and quasi-generic regimens are available as STRs, and first-line regimens would require deconstruction to an MTR, though some are not possible as MTRs at all. Most notably is the recent generic availability of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in September 2020 as a fixed dose combination (FDC) and an STR component.[40] TDF/FTC is a component of two out of the top five ARTs by total Part D spending in 2017; totaling over $832 million USD for those two formulations alone.[28] TAF is a prodrug of TDF and is a component of the regimen with the highest total Part D spending in 2017 totaling nearly $690 million USD.[28] TAF is marketed for its improvements in bone mineral density and kidney function though these are accompanied by troublesome effects on lipids and possibly weight gain.[41–45] These tradeoffs may preserve utilization of both despite large differences in price as generic TDF becomes more widely available. Barring any transformative developments in treatment, this scenario will repeat itself among other highly utilized HIV medications. Hesitancy to increase pill-burden in this way is borne from concern over increased risk of non-adherence and resistance without significant incentives for providers and patients.[16] Uncertainty about higher out-of-pocket costs are often cited as MTRs may require multiple copayments compared to STRs.[16]

2.4 Antiretroviral Treatment

Treatment guidelines have evolved substantially over the four decades since the discovery of HIV. The advent of HAART in 1995, a combination of three or more medications one of which was a boosted protease inhibitor (PI), was a drastic turning point in mortality and morbidity.[7] Guidelines continued to rapidly integrate advancing scientific knowledge over time, but generally recommended ART initiation based on a person's $CD4^+$ count falling below a specific threshold (e.g., <350 cells/mm^3). The US Department of Health and Human Services (HHS) guidelines published in 2012, marked the beginning of universal treatment; this recommends all people diagnosed with HIV to initiate ART regardless of their $CD4^+$ count barring any other severe contraindication.[7] The majority of regimens currently recommended as first-line therapy for treatment-naïve adults consist of two NRTIs plus an INSTI.[7] The one exception being the only FDA approved initial two-drug therapy consisting of only one NRTI (Lamivudine (3TC)) and one INSTI (Dolutegravir (DTG)).[7] Other acceptable regimens that are most common include two NRTIs plus at least one active ARV from another class (i) an INSTI, (ii) NNRTI, or (iii) boosted PI.[7]

Recommended regimens in the treatment-experienced patient can be more complex, but is broadly delineated by whether the regimen choice is driven by virologic failure or by regimen optimization.[7] Virologic failure can be due to persistent viral resistance or acquired resistance, typically developed through poor ART adherence.[7] Regimen optimization may be undertaken to maintain viral suppression while preventing the development of viral resistance, minimizing toxicities, and preserving future treatment options.[7] Adverse events, drug-drug or drug-disease interactions, and other factors may precipitate such regimen switches.[7] Regardless of the motivation for switching regimens in the treatment experienced, as with the treatment naïve, it is imperative to account for the full ART history including cumulative resistance testing, patient preferences, and prior treatment response.[7]

Advancements in ART include the discovery of novel classes/mechanisms of action, reduced toxicity and side effect profiles, fixed dose combination products, and the first STR (2006).[1] The robust scientific knowledge base is built on randomized controlled trials (RCT) primarily regarding a medications efficacy in viral suppression among other secondary outcomes. A significant proportion of these have been designed, analyzed, or interpreted as non-inferiority trials.[46] While invaluable in regulatory decision making these RCT endpoints may not prove to be as useful to patients, providers, or policy makers. Further, these studies are most often conducted in younger patients with fewer comorbidities.[18] Observational studies provide the opportunity to examine regimen effectiveness in less supportive, real world settings in the context of multimorbidity and polypharmacy. Death, AIDS defining illnesses, and overall utilization and costs might be of more interest to patients, providers, and payers, which observational studies may better address.

Despite three cases of HIV being effectively cured in patients who underwent stem cell transplants,[47] there is no cure for HIV; the goal of treatment is to achieve durable viral suppression (plasma HIV RNA <50 or <20 copies/mL), slow $CD4^+$ deterioration and support $CD4^+$ rebound, and prevent further transmission.[7] The choice of ART regimen depends on several factors, including resistance profiles and patient preference (e.g., dosing frequency, side-effects, out-of-pocket cost).[7] Additionally, the severity of disease activity when therapy is initiated and the patient's response to prior treatments, if known, impact regimen selection.[7] The presence of comorbid conditions (e.g., hepatitis B or C, or tuberculosis) factor into a clinician's prescribing practice.[7]

Currently, there are eight classes of ART: 1) Nucleoside Reverse Transcriptase Inhibitors (NRTI); 2) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI); 3) Protease Inhibitors (PI); 4) Fusion Inhibitors (FI); 5) CCR5 Antagonists (CCR5-A); 6) Integrase Strand Transfer Inhibitors (INSTI); 7) Post-Attachment Inhibitors (PAI), and 8) Attachment Inhibitors (AI).[7,15] Additionally, there are two pharmacokinetic enhancers (PE) approved for the treatment of HIV in combination with other ARTs: i) Cobicistat (COBI) and ii) Ritonavir (RTV) which is primarily used as a PE despite being a PI.[7,15] The most common classes used in the US are NRTI, INSTI, NNRTI, and boosted PI (i.e., PI plus PE).[7] CCR5-A, FI, PAI, and AI all belong to a broader class of entry inhibitors, which are less commonly prescribed in the US as other classes show greater efficacy, effectiveness, tolerability, simplicity, and lower cost.[7]

Robust RCT investment has generated evidence that guides regimen choice. While essential, these designs may not capture rare adverse events or those that develop beyond typical trial follow-up times. For example, INSTIs and PIs have been found to be associated with increased prevalence of metabolic comorbidities (e.g., weight gain, elevated lipids) exceeding the elevated risk already observed across ART classes.[7,42–45] Efavirenz (EFV) has been scrutinized for its association with depression, suicidal ideation, and other psychiatric conditions (e.g., cognitive decline).[7,48,49] Both of these are concerning as PLHIV are known to be at higher risk for these conditions independently of regimen choice. Although these regimens were found to be non-inferior for viral suppression and other surrogate endpoints (e.g., bone mineral density, kidney function) it is unclear if "non-inferiority" is realized in real-world settings with clinical endpoints (e.g., fractures, heart disease) and other unmeasured endpoints. RCTs are generally not designed to provide evidence in more complex clinical populations or for the totality of their comorbidity profiles. Further examination of the consequences of guidelines and real-world prescribing practices based on RCTs (e.g., predominance of INSTIs as third agents in all first-line regimens due to highly favorable resistance profiles despite observed metabolic disturbances) are essential as they may prove to be increasingly problematic in an aging population of PLHIV.

RCT populations are known to be more adherent to prescribed medications due to characteristics of participants and provided support, both of which are not representative of the general population and the care they receive. Real-world adherence is an issue with most drugs but is especially important in infectious disease and HIV due to the potential for irreversible consequences at multiple levels of infection control. For this reason, significant attention has been paid to regimen simplification, side effect reduction, and other behavioral interventions aimed at supporting a patient's quality-of-life while maximizing the probability of treatment success.

Adherence to ART is paramount in order to attain viral suppression and prevent drug resistance.[24] Early ART regimens were notorious for their complexity and problematic adherence due to high pill burdens, demanding dosing schedules, side effect severity, and unfavorable risk and resistance profiles.[24] While improvements in efficacy and safety can still be achieved, simplicity may be seen as the component of regimen choice with the most potential to improve adherence and durable viral suppression. Simplicity is conceptualized as reduced pill burden and dosing frequency. Regimen simplification is offered by STR while maintaining non-inferiority in viral suppression. STRs are defined as a complete ART regimen requiring one pill once a day. STRs contain medications in fixed doses appropriate for most adults with HIV. Most STR regimens can be constructed as multi-tablet regimens (MTR), though not all components are available individually or as part of other fixed dose combination (FDC) products (e.g., INSTIs elvitegravir and bictegravir are only available in STRs). STRs are preferred for their simplicity, patient preference, and observed improvements in adherence.[50]

Nearly all medications approved since 2015 have been either STRs (i.e., a complete regimen in one pill) or FDCs (i.e., more than one drug in combination but insufficient for complete regimen alone), indicating overwhelming demand for these formulations.[15] The appeal of STRs is clear and supported by both clinical and patient preference, evidence of non-inferiority in select populations (e.g., younger, healthier, commercially insured).[11,50,51] Most RCTs are not designed to determine whether an STR is superior to an MTR either due to double blinding or choice of comparator. Network meta-analyses could provide some evidence regarding formulations that were not compared head-to-head though this approach would not generate evidence for use in more complex populations.

STRs have been found to be associated with lower healthcare costs and utilization in observational studies among commercially insured individuals.[12,14,52] Findings indicate these decreases are due to better adherence to STRs.[12–14,52] However, over 70% of individuals under study had no comorbidities as defined by the Charlson Comorbidity Index (CCI).[14,53] We are aware of only one study examining STRs in complex populations with perceived barriers to adherence such as comorbidities (e.g., psychiatric, substance abuse), disability, and homelessness; STRs were again associated with improved adherence and viral suppression.[13] However, this study along with others have several limitations including prevalent user designs, probable exposure misclassification, and the availability of only a single STR.[12–14,52] We are unaware of any studies in a population with higher prevalence of multi-morbidity and polypharmacy.

3 Aim 1 Manuscript

Aim 1) Describe patterns of ART regimens and inpatient, emergency department, outpatient, and prescription drug utilization and costs among PLHIV in Medicare (2014-2019).

Abstract

Background Single tablet antiretroviral regimens (STR) offer one-pill, once-a-day dosing for people living with HIV. In commercially insured populations under 50 years of age, these formulations have been associated with better adherence and lower healthcare resource utilization and costs compared to multi-tablet regimens (MTR). The primary objective of this study was to estimate trends in STR and MTR receipt among Medicare beneficiaries living with HIV. Secondary objectives were to assess trends in inpatient (IP), emergency department (ED), outpatient (OP), and prescription drug (ART and non-ART) utilization and related costs by STR and MTR receipt.

Methods This is a repeat cross-sectional study using a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) to describe trends in STR receipt among beneficiaries living with HIV from January 1, 2014 through December 31, 2019. We also compared annual trends in monthly IP, ED, OP, non-ART, and ART utilization and associated costs by STR and MTR receipt. We reported the average marginal effect (AME) of the year of observation on the probability of STR receipt and 99% confidence intervals (99% CI) estimated from generalized estimating equations. In stratified analyses we report the AME (99% CI) of year on the probability of any utilization in each respective utilization category among the full sample and on incremental costs among those with any utilization in a month.

Results A total of 8,316 unique Medicare beneficiaries contributed 282,258 person-months of observation that met inclusion and exclusion criteria. Overall, STR receipt was 24% more likely in 2019 (57%) than it was in 2014 (27%), and integrase-based regimens were predominant among both STR (80%) and MTR (74%) by 2019. The probability (99% CI) of inpatient (IP) (3% (3%-4%)), emergency department (ED) (6% (6%-7%)), and outpatient (OP) (35% (34-37)) utilization in a month were largely unchanged among STR recipients (all p>.01). MTR recipients experienced increases in IP (3% (3%-4%) to 4% (4%-4%)) and OP (40% (38%-41%) to 44% (43%-46%)) (p<.01), but no change in the probability of ED utilization (6% (6%-8%)) (p>.01). Monthly incremental costs rose for STR: IP (AME (99% CI): $2,191.97 ($266.11-$4,117.83)), OP (AME: $100.94 ($31.94-$169.94), and ART (AME: $751.55 ($712.33-$790.78) and MTR: IP (AME: $2,100.42 ($51.37-$4,252.20), OP (AME: $133.19 ($42.52-$223.87), and ART (AME: $840.07 ($769.83-$910.31) utilization from 2014 to 2019. Both groups experienced reductions in monthly non-ART incremental costs: STR (AME: -$3,357.46 (-$3,558.27 to -$3,156.65)) and MTR (AME: -$2,138.48 (-$2,278.53 to -$1,998.43)).

Conclusion These findings demonstrate the adoption and predominance of STR and integrase-based regimens among Medicare beneficiaries living with HIV. Further, the results reflect no significant changes in utilization patterns in inpatient, emergency department, outpatient, and prescription drug healthcare resource utilization among STR recipients, but increases in IP and OP utilization among MTR. HcRU-related incremental costs increased among both groups except for significant decreases observed in non-ART-related costs.

Introduction

Three out of four first-line antiretroviral (ART) regimens recommended in the 2021 Department of Health and Human Services (HHS) guidelines for treating adults living with Human Immunodeficiency Virus (HIV) are available as single tablet regimens (STR).[7] These formulations offer one-pill, once-a-day dosing and preference for them has grown consistently since the first product approval in 2006.[1] Today, thirteen unique STR products, including all four of the major antiretroviral (ART) classes, are available in the United States (US),[7] yet only one is available as a generic (Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF)).[40] The majority of first-line and alternative regimens can be constructed as MTR requiring an increased pill burden (i.e., >1) while offering generic substitutions and cost savings for several component drugs.[16]

Adherence to ART is paramount in order to achieve durable viral suppression (plasma HIV RNA <20 copies/mL), reduce $CD4^+$ deterioration and support $CD4^+$ rebound, and prevent further transmission, which all help preserve health and prevent excess health services utilization.[7,24] STRs have been found to be associated with better adherence and lower health care costs and utilization in observational studies among commercially insured individuals under 50 years of age.[12–14,52,54,55] However, about sixty percent of all PLHIV in the US are now older than 50 years of age,[2] and over half of all federal HIV/AIDS funding is appropriated through Medicare,[28] the federal health insurance program for adults with disabilities and adults aged 65 years and older. Despite these demographic shifts, little research has delineated patterns of ART prescriptions, penetration of STR use, and the associated impacts on healthcare resource utilization and expenditures among Medicare beneficiaries living with HIV.[52]

Older PLHIV (age ≥50) have been shown to have higher rates of ART adherence than their younger counterparts (age <50) and in general compared to younger counterparts have better metrics along the care continuum with higher rates of known HIV diagnoses, receipt and retention in care, and viral suppression as proxy for better adherence.[30] Thus, it is unclear if STR offer comparable improvements in adherence and reductions in utilization and costs compared to MTR among Medicare beneficiaries. Hesitancy to increase pill-burden by switching to MTR is borne from concern over increased risk of non-adherence and resistance, as well as patient preference for simpler regimens.[11,16,50,51,56] These concerns are substantiated by studies showing higher rates of discontinuation[12,13,55] and lower adherence[11,13,14,52,54] among individuals receiving MTR though, again, findings among older adults and Medicare beneficiaries are lacking.

In 2014, average per capita Medicare spending on PLHIV was approximately $45,489, of which 59% ($26,761) was attributable to prescription drugs.[28] The generic availability of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in September 2020 holds potentially significant cost savings for Medicare.[40] TDF/FTC is a component of two out of the top five ART drugs by total Part D spending in 2017, totaling over $832 million USD for those two formulations alone.[28] A prodrug (i.e., a drug the body converts into the pharmacologically active drug after administration)[57] of TDF, tenofovir alafenamide fumarate (TAF), is a component of the drug with the highest total Part D spending in 2017 totaling nearly $690 million USD (Genvoya®).[28] Regimen deconstruction and use of TDF in place of TAF will not be appropriate for all beneficiaries, but this is illustrative of the significant cost savings that are possible today and in the future with MTRs.

In this study we aimed to address a gap in the literature by examining STR use in an understudied and growing population.[27] The primary objective of this study was to estimate trends in STR use among Medicare beneficiaries living with HIV from 2014 through 2019. The secondary objectives were to estimate trends in inpatient, emergency department, outpatient, and prescription drug healthcare resource utilization and related costs among STR and MTR recipients, respectively.

Methods

Study Design and Data Source

This is a repeat cross-sectional study using a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) to describe trends in STR use among beneficiaries living with HIV/AIDS from January 1, 2014 through December 31, 2019. We also compared annual trends in monthly inpatient (IP), emergency department (ED), outpatient (OP), and non-antiretroviral (non-ART) and antiretroviral (ART) prescription drug utilization and associated costs by STR and MTR receipt. The CCW data files used in this study include the Master Beneficiary Summary Files (MBSF), which contain beneficiary sociodemographics, such as age, race/ethnicity, sex, reason for eligibility, and date of death. The IP file includes Part A claims for hospitalizations for each calendar year, including dates of service, diagnoses and procedure codes. The OP file contains all claims from institutional outpatient providers and the carrier file contains claims for non-institutional providers for Part B health services. The Part D file includes claims for prescription drugs covered by Medicare.

Study Cohort

The unit of analysis of this study is the person-month. Fee-for-service beneficiaries contributed person-months for inclusion following evidence of an HIV diagnosis defined using a validated algorithm requiring: (1) at least one inpatient claim or (2) at least two outpatient claims on different dates with ICD9/10 codes for HIV (**Appendix Table 2**).[58] Concurrent enrollment in Parts A, B, and D per month was required for inclusion. ART on-hand for at least 80% of days in a month was also required for inclusion. Exclusion criteria were any evidence of Part C coverage, long-term care residence, hospice claims, or death in a month. Beneficiaries could contribute non-consecutive months to the analysis following evidence of certain non-terminal states (e.g., leaving Part C for fee-for-service coverage during open enrollment).

Measures

The primary independent measures of interest are indicators for calendar year (2014-2019). The dependent measures of interest are STR and MTR receipt, healthcare resource utilization, and related costs.

Healthcare Resource Utilization

IP utilization was defined as any unique inpatient hospital stay during a month. ED utilization was defined using the Yale method,[59] a validated algorithm utilizing revenue center codes to identify ED visits. Any ED stay that occurred within the from- and thru- dates of an IP stay was only counted as an IP admission. OP visits were defined as those outpatient claims without a revenue center code indicating ED and without overlap with an IP stay. Prescription drug utilization was delineated as antiretroviral and non-antiretroviral utilization. Non-antiretroviral utilization was summarized as the number of unique products per month by generic name.

Antiretroviral Regimens

Antiretroviral utilization was defined based on criteria for a complete regimen.[7] Beneficiaries were deemed to be covered by a complete regimen if they received at least three antiretrovirals from at least two different classes concurrently for at least 80% of the days of the respective month (i.e., <7 day gap between component medication fills).[12,14,58,60] Beneficiaries receiving Food and Drug Administration (FDA) approved two-drug regimens and the equivalent multi-tablet regimens were also included as complete regimens.[7] Early fills were pushed forward to the end of the prior prescription. Early fills were censored at the end of the month if eligibility criteria were not met in the subsequent month.

Costs

This study was conducted from the Medicare perspective; thus, only costs paid by Medicare were analyzed (i.e., patient out-of-pocket costs were not included). We reported mean monthly costs by STR and MTR receipt and year. All costs were adjusted for inflation to 2019 US dollars using the health care component of the Personal Consumption Expenditures Index.[61]

Statistical Analyses

Descriptive statistics were used to compare demographic characteristics by calendar year and STR/MTR receipt. Drug class is reported as the number of complete antiretroviral regimens containing at least one drug from that respective class. Healthcare resource utilization was described as the proportion of person-months with any utilization from each of the respective utilization categories. Frequency distributions of utilization were assessed among the full sample (i.e., both beneficiaries with and without utilization) and among those person-months with any utilization in each category (i.e., only beneficiaries with utilization), respectively. Measures of central tendency for utilization-related costs were estimated among the full sample and among those person-months with any utilization in each category, respectively.

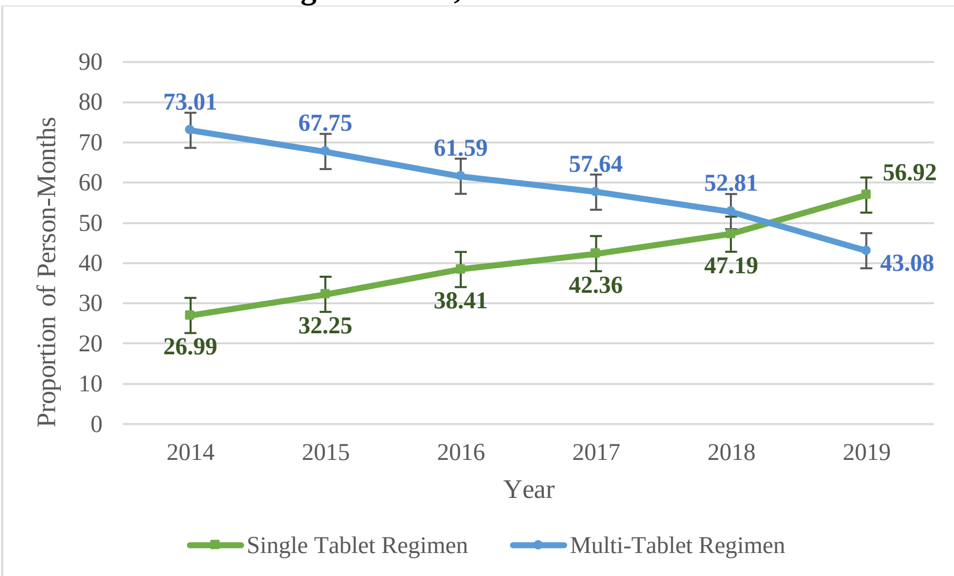
Trends in STR and MTR receipt were estimated in a single model. Stratified analyses, by STR and MTR, were used when estimating healthcare resource utilization and associated costs. Regression equations can be found in the **Appendix Table 3**. Primary analyses were adjusted for age group quartiles, sex, race, and original reason for entitlement (e.g., age, disability, or end stage renal disease (ESRD)) based on prior literature and ability to measure on a monthly basis. Two-part models were fit for the IP, ED, and OP utilization outcomes due to the high number of person-months without utilization. The high number of person-months without utilization was expected due to the nature of the outcomes and short time period of measurement. The first stage models were not conducted for non-ART and ART utilization because less than two percent of person-months did not include any utilization.

To account for clustering at the beneficiary-level we employed generalized estimating equations (GEE) for both the binary and continuous outcome models. The first step logistic models were fit with an exchangeable correlation structure. The second step models with costs as the dependent variables were fit with a gamma distribution, log link, and exchangeable correlation structure. Graphic and statistical representation of all cost distributions can be found in **Appendix Figures 1-5**. Correlation structure was chosen based on visual and descriptive analysis of the data and minimization of Akaike's Information Criterion (AIC).[62] The modified Park test was used to assess the family of the distribution[63] and the Pregibon link test was used to assess the link selection.[64] Model diagnostics can be found in **Appendix Tables 4-13.** The average marginal effect (AME) is reported for all results and 99% confidence intervals were calculated using the delta method.[65] The AME is an absolute measure that is interpretable in the outcome's original unit of measurement (e.g., dollars) thereby facilitating use in policy arenas.[66] The threshold for statistical significance was set at alpha .01 in all analyses.

Results

We identified 8,316 unique Medicare beneficiaries contributing 282,258 person-months of observation. STR receipt was observed among 114,989 (40.74%) person-months over the entire study period. This proportion grew from 26.99% (n=12,271) in 2014 to 56.92% (n=26,458) in 2019 (**Figure 2**). The demographic characteristics of the sample by STR and MTR receipt can be found in **Table 1** and **Table 2.** Statistically significant increasing trends among age groups 57-64 years (2014: 18.73%, 2019: 25.31%) and ≥65 years (2014: 16.78%, 2019: 31.51%) were observed among STR and MTR: 57-64 years (2014: 21.74%, 2019: 25.60%) and ≥65 years (2014: 18.12%, 2019: 31.74%) (all p<.001). Both groups were predominantly male (2014- STR: 71.91%; MTR: 73.88%), and either white or black race (2014- STR: 45.51%, 44.02%; MTR: 45.45%, 44.71%) with no statistically significant trends throughout the study period (all p>.01). An increasing trend in the proportion of beneficiaries whose original reason for eligibility was older age was observed among both STR (2014: 12.03%, 2019: 19.45%) and MTR (2014: 9.86%, 2019: 15.97%) (all p<.001). A decreasing trend of beneficiaries dually eligible for Medicare-Medicaid (2014: 70.68%, 2019: 63.75%) and full or partial Low-Income Subsidies (2014: 82.51%, 2019: 76.33%), assistance for prescription drug costs for low-income beneficiaries, was observed among STR (all p<.001). Similar trends were also observed among MTR: dually eligible (2014: 82.78%, 2019: 77.61%) (all p<.001).

Figure 2. Trends in Single and Multi- Tablet Antiretroviral Regimens among Medicare Beneficiaries Living with HIV, 2014-2019



Trends in class components of STR and MTR are listed in **Table 3 and Table 4.** Statistically significant decreasing trends in person-months including at least 1 nucleoside reverse transcriptase inhibitor (NRTI) were observed among STR (2014: 100%, 2019: 95.42%) and MTR (2014: 91.15%, 2019: 84.00%) (all p<.001). Non-nucleoside reverse transcriptase inhibitor (NNRTI) decreased among STR (2014: 81.78%, 2019: 21.60%) and MTR (2014: 25.75%, 2019: 23.75%) (all p<.001). Integrase strand transfer inhibitors (INSTI) increased among STR (2014: 18.31%, 2019: 79.75%) and MTR (2014: 39.44%,

Table 1. Beneficiary Characteristics of Single Tablet Regimen Recipients, 2014-2019

	2014	2015	2016	2017	2018	2019	*p*
Age Groups							
<50 years	552 (35.89%)	620 (32.17%)	679 (29.42%)	655 (27.41%)	672 (24.16%)	710 (22.00%)	<.001
50-56 years	440 (28.61%)	524 (27.19%)	584 (25.30%)	566 (23.68%)	619 (22.25%)	684 (21.19%)	<.001
57-64 years	288 (18.73%)	397 (20.60%)	512 (22.18%)	539 (22.55%)	675 (24.26%)	817 (25.31%)	<.001
≧65 years	258 (16.78%)	386 (20.03%)	533 (23.09%)	630 (26.36%)	816 (29.33%)	1,017 (31.51%)	<.001
Sex							
Female	432 (28.09%)	536 (27.82%)	621 (26.91%)	639 (26.74%)	732 (26.31%)	871 (26.98%)	0.26
Male	1,106 (71.91%)	1,391 (72.18%)	1,687 (73.09%)	1,751 (73.26%)	2,050 (73.69%)	2,357 (73.02%)	0.26
Race and Ethnicity							
Black	677 (44.02%)	844 (43.80%)	977 (42.33%)	1,046 (43.77%)	1,204 (43.28%)	1,379 (42.72%)	0.48
Hispanic	108 (7.02%)	136 (7.06%)	163 (7.06%)	174 (7.28%)	210 (7.55%)	245 (7.59%)	0.30
Other/Unknown	53 (3.45%)	68 (3.53%)	90 (3.90%)	90 (3.77%)	110 (3.95%)	134 (4.15%)	0.17
White	700 (45.51%)	879 (45.61%)	1,078 (46.71%)	1,080 (45.19%)	1,258 (45.22%)	1,470 (45.54%)	0.72
Original Reason for Eligibility							
Aged	185 (12.03%)	258 (13.39%)	347 (15.03%)	401 (16.78%)	514 (18.48%)	628 (19.45%)	<.001
Disabled/ESRD	1,353 (87.97%)	1,669 (86.61%)	1,961 (84.97%)	1,989 (83.22%)	2,268 (81.52%)	2,600 (80.55%)	<.001
Dual Eligibility Medicare-Medicaid							
No	451 (29.32%)	611 (31.71%)	777 (33.67%)	823 (34.44%)	966 (34.72%)	1,170 (36.25%)	<.001
Yes	1,087 (70.68%)	1,316 (68.29%)	1,531 (66.33%)	1,567 (65.56%)	1,816 (65.28%)	2,058 (63.75%)	<.001
Low-Income Subsidy							
No	269 (17.49%)	347 (18.01%)	469 (20.32%)	518 (21.67%)	628 (22.57%)	764 (23.67%)	<.001
Yes	1,269 (82.51%)	1,580 (81.99%)	1,839 (79.68%)	1,872 (78.33%)	2,154 (77.43%)	2,464 (76.33%)	<.001

*Unique beneficiaries each year measured at the first month of enrollment
#Cochrane-Armitage Test for Trend used for all p values; significance set at α .01

Table 2. Beneficiary Characteristics of Multi-Tablet Regimen Recipients, 2014-2019

	2014	**2015**	**2016**	**2017**	**2018**	**2019**	***p***
Age Groups							
<50 years	1,400 (31.91%)	1,194 (28.05%)	1,017 925.12%)	845 (23.18%)	731 (21.07%)	559 (19.26%)	<.001
50-56 years	1,239 (28.24%)	1,190 (27.96%)	1,124 (27.77%)	988 (27.11%)	871 (25.10%)	679 (23.40%)	<.001
57-64 years	954 (21.74%)	983 (23.10%)	971 (23.99%)	907 (24.88%)	900 (25.94%)	743 (25.60%)	<.001
≧65 years	795 (18.12%)	889 (20.89%)	936 (23.12%)	905 (24.83%)	968 (27.90%)	921 (31.74%)	<.001
Sex							
Female	1,086 (26.12%)	1,026 (25.42%)	1,007 (26.09%)	929 (26.88%)	832 (25.29%)	688 (25.26%)	0.60
Male	3,072 (73.88%)	3,010 (74.58%)	2,853 (73.91%)	2,527 (73.12%)	2,458 (74.71%)	2,036 (74.74%)	0.60
Race and Ethnicity							
Black	1,859 (44.71%)	1,805 (44.72%)	1,713 (44.38%)	1,541 (44.59%)	1,435 (43.62%)	1,184 (43.47%)	0.20
Hispanic	283 (6.81%)	260 (6.44%)	251 (6.5%)	218 (6.31%)	237 (7.2%)	181 (6.64%)	0.74
Other/Unknown	126 (3.03%)	123 (3.05%)	111 (2.88%)	106 (3.07%)	102 (3.1%)	77 (2.83%)	0.82
White	1,890 (45.45%)	1,848 (45.79%)	1,785 (46.24%)	1,591 (46.04%)	1,516 (46.08%)	1,282 (47.06%)	0.06
Original Reason for Eligibility							
Aged	414 (9.96%)	460 (11.40%)	485 (12.56%)	460 (13.31%)	477 (14.50%)	435 (15.97%)	<.001
Disabled/ESRD	3,771 (90.69%)	3,566 (88.35%)	3,375 (87.44%)	2,996 (86.69%)	2,813 (85.50%)	2,289 (84.03%)	<.001
Dual Eligibility Medicare-Medicaid							
No	1,198 (28.81%)	1,221 (30.25%)	1,205 (31.22%)	1,057 (30.58%)	1,064 (32.34%)	911 (33.44%)	<.001
Yes	2,960 (71.19%)	2,815 (69.75%)	2,655 (68.78%)	2,399 (69.42%)	2,226 (67.66%)	1,813 (66.56%)	<.001
Low-Income Subsidy							
No	716 (17.22%)	721 (17.86%)	751 (19.46%)	673 (19.47%)	675 (20.52%)	610 (22.39%)	<.001
Yes	3,442 (82.78%)	3,315 (82.14%)	3,109 (80.54%)	2,783 (80.53%)	2,615 (79.48%)	2,114 (77.61%)	<.001

*Unique beneficiaries each year measured at the first month of enrollment

#Cochrane-Armitage Test for Trend used for all p values; significance set at α .01

Table 3. Antiretroviral Regimen Class Components - Single Tablet Regimens, 2014-2019

	2014	2015	2016	2017	2018	2019	*p*
Total Person-Months, N (row%)	12,271 (10.67%)	15,138 (13.16%)	18,487 (16.08%)	20,257 (17.62%)	22,378 (17.62%)	26,458 (23.01%)	
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	12,271 (100%)	15,138 (100%)	18,487 (100%)	20,257 (100%)	22,024 (98.42%)	25,247 (95.42%)	<.001
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	10,035 (81.78%)	9,782 (64.62%)	8,924 (48.27%)	7,346 (36.26%)	6,476 (28.94%)	5,714 (21.60%)	<.001
Protease Inhibitor (PI)	0	0	0	0	0	847 (3.20%)	<.001
Pharmacokinetic Enhancer (PE)	2,247 (18.31%)	2,992 (19.76%)	4,930 (26.67%)	6,962 (34.37%)	7,298 (32.61%)	6,708 (25.35%)	<.001
Integrase Strand Transfer Inhibitor (INSTI)	2,247 (18.31%)	5,381 (35.55%)	9,630 (52.09%)	12,961 (63.98%)	16,330 (72.97%)	21,100 (79.75%)	<.001

Table 4. Antiretroviral Regimen Class Components - Multi-Tablet Regimens, 2014-2019

	2014	2015	2016	2017	2018	2019	*p*
Total Person-Months, N (row%)	33,188 (19.84%)	31,807 (19.02%)	29,641 (17.72%)	27,567 (16.48%)	25,042 (14.97%	20,024 (11.97%)	
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	30,251 (91.15%)	28,606 (89.94%)	26,081 (87.99%)	23,898 (86.69%)	21,499 (85.85%)	16,820 (84.00%)	<.001
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	8,546 (25.75%)	8,255 (25.95%)	7,521 (25.37%)	6,540 (23.72%)	5,662 (22.61%)	4,755 (23.75%)	<.001
Protease Inhibitor (PI)	22,779 (68.64%)	20,627 (64.85%)	18,234 (61.52%)	15,681 (56.88%)	13,328 (53.22%)	10,118 (50.53%)	<.001
Pharmacokinetic Enhancer (PE)	247 (0.01%)	1,450 (4.56%)	3,927 (13.25%)	5,212 (18.91%)	5,602 (22.37%)	5,046 (25.20%)	<.001
Integrase Strand Transfer Inhibitor (INSTI)	13,090 (39.44%)	14,519 (45.65%)	15,976 (53.90%)	17,022 (61.75%)	17,064 (68.14%)	14,853 (74.18%)	<.001

Note: Cells indicate the Number (Percent) of person-month regimens containing at least one drug from the respective class.

#Cochrane-Armitage Test for Trend used for all p values; significance set at α .01

*Cell suppressed per data use agreement

2019: 74.18%) (all p<.001). Increasing use of pharmacokinetic enhancers (PE) were observed among STR (2014: 18.31%, 2019: 25.35%) and MTR (2014: 0.01%, 2019: 25.20%)(all p<.001). Protease inhibitors (PI) increased among STR from 0.00% in 2014 to 3.20% in 2019 and decreased among MTR from 68.64% in 2014 to 50.53% in 2019 (all p<.001). No CCR5, attachment, or post-attachment inhibitors were observed during the study in either group. Only 250 person-months (0.08%) included fusion inhibitor use, all observed among MTR, though no person-months of this class were observed in the final year of the study period (data not shown).

Descriptive trends in healthcare resource utilization (**Table 5** and **Table 6)** and related costs (**Table 7** and **Table 8)** among STR and MTR are reported below. About 2.56% of STR person-months included any inpatient (IP) and 5.96% any emergency department (ED) utilization in 2014 with no significant trend observed over the study period (2019: 2.86%, 6.43%) (all p>.01). The proportion of MTR person-months including any IP utilization significantly increased (2014: 3.43%, 2019: 3.87%, p<.01), but no significant trend was observed in any ED utilization (2014: 6.75%, 2019: 6.82%, p>.01). The mean (standard deviation (SD)) IP or ED visits among the full and conditional STR and MTR samples did not significantly change over the study period. Among STR person-months with any IP utilization the mean (SD) IP visits was 1.21 (0.61) in 2014 and 1.14 (0.43) in 2019 (p>.01). Among STR person-months with any ED utilization the mean (SD) ED visits was 2.18 (2.48) in 2014 and 1.90 (1.74) in 2019 (p>.01). Among MTR person-months with any IP utilization the mean (SD) IP visits was 1.15 (0.42) in 2014 and 1.18 (0.47), p>.01; and among MTR person-months with any ED utilization the mean (SD) ED visits was 1.94 (1.51) in 2014 and 1.86 (1.57) in 2019, p>.01).The proportion of person-months with any Outpatient (OP) utilization increased among both STR (2014: 34.99%, 2019: 37.08%) and MTR (2014:40.12%, 2019: 44.12%) (all p<.01). The mean (SD) OP visits in the full STR sample increased from 0.58 (1.05) to 0.62 (1.09), and the full MTR sample mean (SD) OP visits increased from 0.70 (1.18) to 0.80 (1.31) over the study period (all p<.01). Among STR person-months with any OP utilization the mean (SD) OP visits increased from 1.66 (1.15) in 2014 to 1.68 (1.20) in 2019, p<.01. Among MTR person-months with any OP utilization the mean (SD) OP visits increased from 1.74 (1.28) in 2014 to 1.81 (1.42) in 2019, p<.01.

A statistically significant decreasing trend in the proportion of person-months involving any non-antiretroviral (non-ART) prescription drug utilization was observed among both STR (2014: 98.33%, 2019: 97.76%) and MTR (2014: 99.04%, 2019: 98.64%) (all p<.01). Mean (SD) non-ART prescriptions per month decreased among the full STR sample (2014: 4.86 (3.65), 2019: 3.78 (3.49)) and the full MTR sample (2014: 7.61 (4.16), 2019: 4.65 (3.82)) (all p<.01). Among STR person-months with any non-ART utilization the mean (SD) non-ART prescriptions decreased from 4.94 (3.63) in 2014 to 4.51 (3.36) in 2019, p<.01. Among MTR person-months with any non-ART utilization the mean (SD) non-ART prescriptions decreased from 7.68 (4.11) in 2014 to 5.19 (3.68) in 2019, p<.01. The mean (SD) number of antiretrovirals (ART) per STR person-month increased from 3.18 (0.39) in 2014 to 3.21 (0.51) in 2019, p<.01. The mean (SD) number of ART per MTR person-month increased from 3.66 (0.88) in 2014 to 3.68 (1.15) in 2019, p<.01.

Among person-months involving any IP utilization mean (SD) IP-related costs increased among STR (2014: $13,120.98 ($12,739.40), 2019: $15,186.17 ($16,120.29)) and MTR (2014: $18,055.79 ($24,643.35), 2019: $18,499.26 ($22,405.64)) (all p<.01). No significant trend was observed in conditional ED-related mean (SD) costs among STR (2014: $1,275.60 ($2,653.26), 2019: $1,210.59 ($2,284.23)) or MTR (2014: $1,144.72 ($2,001.89), 2019: $1,237.22 ($2,197.04)) (all p>.01). Among person-months involving any non-ART utilization mean (SD) costs decreased among STR (2014: $2,766.02 ($3,202.72), 2019: ($574.86 ($2,243.94) and MTR (2014: $3,511.96 ($3,336.46), 2019: $849.96 ($2,885.41)) (all p<.01). ART-related costs significantly increased among STR (2014: $2,268.77 ($766.15), 2019: $3,019.62 ($928.18)) and MTR (2014: $2,813.32 ($1,135.13), 2019: $3,617.25 ($1,549.14)) (all p<.01).

Table 5. Healthcare Resource Utilization per Person-Month among Single Tablet Regimen Recipients, 2014-2019

	2014		2015		2016		2017		2018		2019		*p*
Proportion of Person-Months with Any Healthcare Resource Utilization													
Summary Statistics	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Inpatient Hospitalization	314	2.56%	398	2.63%	485	2.62%	519	2.56%	601	2.69%	756	2.86%	0.07*
Emergency Department	731	5.96%	914	6.04%	1,169	6.32%	1,262	6.23%	1,378	6.16%	1,701	6.43%	0.09*
Outpatient Hospital	4,294	34.99%	5,223	34.50%	6,642	35.93%	7,039	34.75%	7,907	35.33%	9,810	37.08%	<.01*
Non-ART Prescriptions	12,066	98.33%	14,847	98.08%	18,186	98.37%	19,848	97.98%	21,893	97.83%	25,865	97.76%	<.01*
Healthcare Resource Utilization (Full Sample)													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	0.03 (0.21)	0.00	0.03 (0.22)	0.00	0.03 (0.19)	0.00	0.03 (0.20)	0.00	0.03 (0.21)	0.00	0.03 (0.20)	0.00	0.06#
Emergency Department	0.13 (0.79)	0.00	0.12 (0.67)	0.00	0.12 (0.59)	0.00	0.13 (0.76)	0.00	0.12 (0.63)	0.00	0.12 (0.64)	0.00	0.09#
Outpatient Hospital	0.58 (1.05)	0.00	0.57 (1.06)	0.00	0.58 (1.01)	0.00	0.55 (0.97)	0.00	0.59 (1.06)	0.00	0.62 (1.09)	0.00	<.01#
Non-ART Prescriptions	4.86 (3.65)	4.00	4.89 (3.71)	4.00	4.92 (3.65)	4.00	4.78 (3.53)	4.00	4.75 (3.55)	4.00	3.78 (3.49)	3.00	<.01*
ART Prescriptions	3.18 (0.39)	3.00	3.20 (0.40)	3.00	3.27 (0.45)	3.00	3.35 (0.48)	3.00	3.31 (0.50)	3.00	3.21 (0.51)	3.00	<.01#
Healthcare Resource Utilization among those with Any Utilization													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	1.21 (0.61)	1.00	1.21 (0.62)	1.00	1.15 (0.38)	1.00	1.15 (0.51)	1.00	1.18 (0.50)	1.00	1.14 (0.43)	1.00	0.11#
Emergency Department	2.18 (2.48)	1.00	2.00 (1.90)	1.00	1.86 (1.53)	1.00	2.03 (2.31)	1.00	1.97 (1.70)	1.00	1.90 (1.74)	1.00	0.35#
Outpatient Hospital	1.66 (1.15)	1.00	1.66 (1.20)	1.00	1.62 (1.08)	1.00	1.58 (1.04)	1.00	1.67 (1.18)	1.00	1.68 (1.20)	1.00	<.01#
Non-ART Prescriptions	4.94 (3.63)	4.00	4.99 (3.69)	4.00	5.00 (3.63)	4.00	4.87 (3.50)	4.00	4.86 (3.52)	4.00	4.51 (3.36)	4.00	<.01#

*Cochrane-Armitage Test for Trend
#Jonkheere Terpstra Test for Trend

Table 6. Healthcare Resource Utilization and Costs per Person-Month among Multi-Tablet Regimen Recipients, 2014-2019

	2014		2015		2016		2017		2018		2019		*p*
Proportion of Person-Months with Any Healthcare Resource Utilization													
Summary Statistics	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Inpatient Hospitalization	1,138	3.43%	1,326	3.61%	1,347	3.93%	1,279	4.02%	1,240	4.29%	774	3.87%	<.01*
Emergency Department	2,239	6.75%	2,410	6.56%	2,453	7.16%	2,297	7.22%	2,030	7.02%	1,365	6.82%	0.16*
Outpatient Hospital	13,316	40.12%	14,925	40.60%	14,284	41.67%	13,561	42.62%	12,545	43.37%	8,834	44.12%	<.01*
Non-ART Prescriptions	32,868	99.04%	36,204	98.49%	33,738	98.42%	31,290	98.34%	28,345	98.00%	19,751	98.64%	<.01*
Healthcare Resource Utilization (Full Sample)													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	0.04 (0.22)	0.00	0.04 (0.23)	0.00	0.04 (0.24)	0.00	0.04 (0.25)	0.00	0.05 (0.25)	0.00	0.05 (0.24)	0.00	0.06[#]
Emergency Department	0.13 (0.63)	0.00	0.12 (0.60)	0.00	0.14 (0.64)	0.00	0.14 (0.66)	0.00	0.13 (0.71)	0.00	0.13 (0.62)	0.00	0.11[#]
Outpatient Hospital	0.70 (1.18)	0.00	0.69 (1.19)	0.00	0.71 (1.18)	0.00	0.75 (1.23)	0.00	0.77 (1.25)	0.00	0.80 (1.31)	0.00	<.01[#]
Non-ART Prescriptions	7.61 (4.16)	7.00	7.45 (4.16)	7.00	7.31 (4.11)	7.00	7.22 (4.11)	7.00	7.02 (4.09)	6.00	4.65 (3.82)	4.00	<.01[#]
ART Prescriptions	3.66 (0.88)	4.00	3.66 (0.94)	4.00	3.71 (1.03)	4.00	3.68 (1.02)	3.00	3.67 (1.04)	3.00	3.68 (1.15)	3.00	<.01[#]
Healthcare Resource Utilization among those with Any Utilization													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	1.15 (0.42)	1.00	1.17 (0.47)	1.00	1.19 (0.50)	1.00	1.19 (0.52)	1.00	1.18 (0.47)	1.00	1.18 (0.47)	1.00	0.11[#]
Emergency Department	1.94 (1.51)	1.00	1.89 (1.48)	1.00	1.91 (1.56)	1.00	1.90 (1.68)	1.00	1.90 (2.00)	1.00	1.86 (1.57)	1.00	0.35[#]
Outpatient Hospital	1.74 (1.28)	1.00	1.71 (1.32)	1.00	1.73 (1.28)	1.00	1.77 (1.34)	1.00	1.79 (1.33)	1.00	1.81 (1.42)	1.00	<.01[#]
Non-ART Prescriptions	7.68 (4.11)	7.00	7.56 (4.10)	7.00	7.41 (4.04)	7.00	7.32 (4.05)	7.00	7.15 (4.01)	6.00	5.19 (3.68)	4.00	<.01[#]

*Cochrane-Armitage Test
[#]Jonkheere Terpstra Test

Table 7. Healthcare Resource Utilization-related Costs per Person-Month among Single Tablet Regimen Recipients, 2014-2019

	2014		2015		2016		2017		2018		2019		*p*
Healthcare Resource Utilization-related Costs (Full Sample)													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	\$336 (\$2,904)	\$0	\$373 (\$3,280)	\$0	\$395 (\$3,455)	\$0	\$438 (\$7,760)	\$0	\$416 (\$4,447)	\$0	\$434 (\$3,717)	\$0.00	<.01[#]
Emergency Department	\$76 (\$714)	\$0	\$57 (\$408)	\$0	\$66.74 (\$523)	\$0	\$74 (\$688)	\$0	\$79 (\$668)	\$0	\$78 (\$651)	\$0.00	0.85[#]
Outpatient Hospital	\$141 (\$570)	\$0	\$172 (\$913)	\$0	\$176 (\$1,205)	\$0	\$167 (\$1,053)	\$0	\$204 (\$1,333)	\$0	\$221 (\$972)	\$0.00	<.01[#]
Non-ART Prescriptions	\$2,719 (\$3,196)	\$2,332	\$3,054 (\$4,084)	\$2,498	\$3,002 (\$2,985)	\$2,962	\$3,022 (\$2,241)	\$2,867	\$3,135 (\$2,184)	\$3,026	\$482 (\$2,066)	\$59	<.01[#]
ART Prescriptions	\$2,269 (\$766)	\$2,229	\$2,405 (\$757)	\$2,374	\$2,564 (\$764)	\$2,568	\$2,702 (\$767)	\$2,727	\$2,869 (\$847)	\$2,885	\$3,020 (\$928)	\$3,019	<.01[#]
Healthcare Resource Utilization-related Costs among those with Any Utilization													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	\$13,121 (12,739)	\$10,123	\$14,171 (14,638)	\$10,130	\$15,043 (15,336)	\$10,565	\$17,076 (45,500)	\$10,272	\$15,474 (22,456)	\$10,517	\$15,186 (16,120)	\$11,075	<.01[#]
Emergency Department	\$1,276 (\$2,653)	\$501	\$947 (\$1,383)	\$469	\$1,055 (\$1,814)	\$442	\$1,183 (\$2,509)	\$500	\$1,289 (\$2,386)	\$533	\$1,211 (\$2,284)	\$508	0.60[#]
Outpatient Hospital	\$403 (\$908)	\$166	\$499 (\$1,502)	\$170	\$489 (\$1,972)	\$173	\$480 (\$1,744)	\$162	\$576 (\$2,194)	\$183	\$596 (\$1,525)	\$179	<.01[#]
Non-ART Prescriptions	\$2,766 (\$3,203)	\$2,341	\$3,113 (\$4,101)	\$2,507	\$3,052 (\$2,984)	\$2,700	\$3,085 (\$2,221)	\$2,878	\$3,204 (\$2,157)	\$3,030	\$575 (\$2,244)	\$94	<.01[#]
ART Prescriptions	\$2,269 (\$766)	\$2,229	\$2,405 (\$757)	\$2,374	\$2,564 (\$764)	\$2,567	\$2,702 (\$767)	\$2,727	\$2,869 (\$847)	\$2,885	\$3,020 (\$928)	\$3,019	<.01[#]

[#]Jonkheere Terpstra Test

Table 8. Healthcare Resource Utilization-related Costs per Person-Month among Multi-Tablet Regimen Recipients, 2014-2019

	2014		2015		2016		2017		2018		2019		*p*
Healthcare Resource Utilization-related Costs (Full Sample)													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	$673 ($5,835)	$0	$563 ($4,210)	$0	$613.82 ($4,552)	$0	$636 ($4,696)	$0	$742 ($5,443)	$0	$760 ($5,840)	$0	<.01#
Emergency Department	$79 ($599)	$0	$70 ($521)	$0	$79 ($589)	$0	$86 ($658)	$0	$84 ($645)	$0	$85 ($656)	$0	0.85#
Outpatient Hospital	$317 ($1,335)	$0	$308 ($1,470)	$0	$331 ($1,336)	$0	$374 ($1,696)	$0	$389.75 ($1,472)	$0	$460 ($1400)	$0	<.01#
Non-ART Prescriptions	$3,478 ($3,338)	$3,012	$3,783 ($4,244)	$3,130	$3,820 ($3,686)	$3,317	$3,874 ($3,090)	$3,492	$3,914 ($2,948)	$3,605	$761 ($2,743)	$111	<.01#
ART Prescriptions	$2,813 ($1,135)	$2,759	$2,969 ($1,192)	$2,896	$3,197 ($1,246)	$3,107	$3,343 ($1,320)	$3,278	$3,489 ($1,443)	$3,421	$3,617 ($1,549)	$3,536	<.01#
Healthcare Resource Utilization-related Costs among those with Any Utilization													
Summary Statistics	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	*Mean (SD)*	*Median*	
Inpatient Hospitalization	$18,056 (24,643)	$12,620	$16,378 (16,014)	$12,111	$16,738 (17,185)	$11,567	$17,128 (17,647)	$12,641	$18,467 (20,260)	$12,498	$18,500 (22,406)	$12,815	<.01#
Emergency Department	$1,145 ($2,002)	$499	$1,073 ($1749)	$484	$1,123 ($1,933)	$475	$1,213 ($2,170)	$520	$1,220 ($2,152)	$530	$1,237 ($2,197)	$559	0.60#
Outpatient Hospital	$781 ($2,008)	$206	$769 ($2,243)	$204	$807 ($1,992)	$224	$888 ($2,524)	$227	$903 ($2,134)	$243	$1,032 ($1,951)	$256	<.01#
Non-ART Prescriptions	$3,512 ($3,336)	$3,018	$3,835 ($4,249)	$3,140	$3,873 ($3,684)	$3,324	$3,931 ($3,077)	$3,503	$3,984 ($2,926)	$3,623	$850 ($2,885)	$159	<.01#
ART Prescriptions	$2,813 ($1,135)	$2,759	$2,969 ($1,192)	$2,896	$3,197 ($1,246)	$3,107	$3,343 ($1,320)	$3,278	$3,489 ($1,444)	$3,421	$3,617 ($1,549)	$3,536	<.01#

#Jonkheere Terpstra Test

All years (i.e., 2015 to 2019) were associated with a statistically significant increased probability of STR receipt compared to 2014. The probability was smallest in 2015 (AME: 0.04 (0.04-0.05)) and largest in 2019 (AME: 0.24 (0.23-0.26)) (all *p*<.01) (**Table 9**).

Table 9. Average Marginal Effect of Year on the Probability of Single Tablet Regimen Receipt			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.04+	0.04	0.05
2016	0.09+	0.08	0.09
2017	0.14+	0.13	0.15
2018	0.19+	0.18	0.20
2019	0.24+	0.23	0.26

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

The probability (99% Confidence Limits) of any IP utilization in a month was approximately 0.03 among STR over the study period (2014: 0.03 (0.02-0.03), 2019: 0.03 (0.02-0.03)) (*p*<.01) (**Table 10a**). No statistically significant differences were observed between 2014 and 2019 (AME: 0.003 (-0.001–0.002) (p>.01) (**Table 10b**) Among any STR person-month with an IP visit the overall incremental IP-related costs in 2014 were $14,873.23 ($13,525.14-$16,221.32) and $16,982.54 ($15,467.04-$18,498.04) in 2019 (all p<.01) (**Table 11a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: $2,191.97 ($266.11-$4,117.83)) (all p<.01) (**Table 11b**).

The probability (99% Confidence Limits) of any IP utilization in a month increased from approximately 0.03 (0.03-0.04) in 2014 to 0.04 (0.04-0.04) in 2019 among MTR (*p*<.01) (**Table 12a**). Statistically significant differences were observed in all years (AME: 2015 ((0.001 (0.0001-0.0021), 2019 ((0.006 (0.0004-0.0112)) (p<.01) (**Table 12b**). Among any MTR person-month with an IP visit the overall incremental IP-related costs in 2014 were $17,226.32 ($16,047.77-$18,404.88) and $19,326.74 ($18,027.35-$20,626.12) in 2019 (all p<.01) (**Table 13a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: $2,100.42 ($51.37-$4,252.20)) (all p<.01) (**Table 13b**).

Table 10. Overall Effect of Year on the Probability of Any Inpatient Hospitalization among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	0.03+	0.02	0.03
2015	0.03+	0.02	0.03
2016	0.03+	0.02	0.03
2017	0.03+	0.02	0.03
2018	0.03+	0.02	0.03
2019	0.03+	0.02	0.03
Table 10. Average Marginal Effect of Year on the Probability of Any Inpatient Hospitalization among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.0005	-0.001	0.002
2016	0.001	-0.001	0.003
2017	0.002	-0.002	0.005
2018	0.002	-0.002	0.007
2019	0.003	-0.001	0.002

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 11. Overall Effect of Year on Inpatient Hospitalization Costs among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$14,873.23+	$13,525.14	$16,221.32
2015	$15,273.02+	$14,104.30	$16,441.73
2016	$15,683.55+	$14,614.02	$16,753.07
2017	$16,105.11+	$15,012.80	$17,197.42
2018	$16,538.01+	$15,288.93	$17,787.09
2019	$16,982.54+	$15,467.04	$18,498.04
Table 11. Average Marginal Effect of Year on Inpatient Hospitalization Costs among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	$414.31+	$71.01	$757.60
2016	$840.32+	$133.67	$1,546.98
2017	$1,278.38+	$187.45	$2,369.31
2018	$1,728.81+	$231.79	$3,225.83
2019	$2,191.97+	$266.11	$4,117.83

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 12. Overall Effect of Year on the Probability of Any Inpatient Hospitalization among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	0.03+	0.03	0.04
2015	0.04+	0.03	0.04
2016	0.04+	0.03	0.04
2017	0.04+	0.04	0.04
2018	0.04+	0.04	0.04
2019	0.04+	0.04	0.04
Table 12. Average Marginal Effect of Year on the Probability of Any Inpatient Hospitalization among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.001+	0.0001	0.0021
2016	0.002+	0.0003	0.0042
2017	0.003+	0.0004	0.0065
2018	0.005+	0.0004	0.0088
2019	0.006+	0.0004	0.0112

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 13. Overall Effect of Year on Inpatient Hospitalization Costs among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$17,226.32+	$16,047.77	$18,404.88
2015	$17,627.30+	$16,758.32	$18,496.28
2016	$18,037.61+	$17,390.03	$18,685.19
2017	$18,457.47+	$17,803.12	$19,111.81
2018	$18,887.10+	$17,974.66	$19,799.55
2019	$19,326.74+	$18,027.35	$20,626.12
Table 13. Average Marginal Effect of Year on Inpatient Hospitalization Costs among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	$400.98+	$9.50	$792.45
2016	$811.29+	$9.57	$1,613.00
2017	$1,231.15+	$0.25	$2,462.54
2018	$1,660.78+	$20.40	$3,341.96
2019	$2,100.42+	$51.37	$4,252.20

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

The probability (99% Confidence Limits) of any ED utilization in a month was approximately 0.06 among STR over the study period (2014: 0.06 (0.05-0.07), 2019: 0.06 (0.06-0.06)) (*p*<.01) (**Table 14a**). No statistically significant differences were observed between 2014 and 2019 (AME: 0.004 (-0.005–0.012) (p>.01) (**Table 14b**) Among any STR person-month with an ED visit the overall incremental ED-related costs in 2014 were $969.59 ($830.05 -$1,109.13) and $1,097.62 ($981.63-$1,213.61) in 2019 (all p<.01) (**Table 15a**). No statistically significant differences were observed in any year (all p>.01) (**Table 15b**).

The probability (99% Confidence Limits) of any ED utilization in a month was approximately 0.07 among MTR over the study period (2014: 0.07 (0.06-0.07), 2019: 0.07 (0.07-0.08) (all *p*<.01) (**Table 16a**). No statistically significant differences were observed in any year (2019 AME: 0.003 (-0.0045-0.0099)) (all p>.01) (**Table 16b**).

Among any MTR person-month with an ED visit the overall incremental ED-related costs in 2014 were $1,044.71 ($982.17-$1,107.24) and $1,203.98 ($1,118.22-$1,289.73) in 2019 (all p<.01) (**Table 17a**). All years were associated with statistically significant increased costs per month with the greatest effect size in 2019 (AME: $159.27 ($4.87-$313.67)) (all p<.01) (**Table 17b**).

Table 14. Overall Effect of Year on the probability of Any Emergency Department Utilization among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	0.06^{+}	0.05	0.07
2015	0.06^{+}	0.06	0.07
2016	0.06^{+}	0.06	0.07
2017	0.06^{+}	0.06	0.07
2018	0.06^{+}	0.06	0.07
2019	0.06^{+}	0.06	0.07
Table 14. Average Marginal Effect of Year on the probability of Any Emergency Department Utilization among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.001	-0.001	0.002
2016	0.001	-0.002	0.004
2017	0.002	-0.003	0.007
2018	0.003	-0.004	0.009
2019	0.004	-0.005	0.012

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 15. Overall Effect of Year on Emergency Department Costs among Single Tablet Regimen Exposed

	Overall Effect	99% Confidence Limits	
2014	$969.59[+]	$830.05	$1,109.13
2015	$993.94[+]	$890.41	$1,097.48
2016	$1,018.91[+]	$947.10	$1,090.71
2017	$1,044.50[+]	$986.74	$1,102.25
2018	$1,070.73[+]	$994.08	$1,147.38
2019	$1,097.62[+]	$981.63	$1,213.61

Table 15b. Average Marginal Effect of Year on Emergency Department Costs among Single Tablet Regimen Exposed

	AME	99% Confidence Limits	
2014	*Reference*		
2015	$24.35	-$29.67	$78.37
2016	$49.31	-$61.54	$160.17
2017	$74.90	-$95.72	$245.52
2018	$101.13	-$132.28	$334.55
2019	$128.03	-$171.35	$427.40

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 16. Overall Effect of Year on the Probability of Any Emergency Department Utilization among Multi-Tablet Regimen Exposed

	Overall Effect	99% Confidence Limits	
2014	0.07[+]	0.06	0.07
2015	0.07[+]	0.06	0.07
2016	0.07[+]	0.07	0.07
2017	0.07[+]	0.07	0.07
2018	0.07[+]	0.07	0.07
2019	0.07[+]	0.07	0.08

Table 16. Average Marginal Effect of Year on the Probability of Any Emergency Department Utilization among Multi-Tablet Regimen Exposed

	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.001	-0.0009	0.0019
2016	0.001	-0.0018	0.0039
2017	0.002	-0.0027	0.0059
2018	0.002	-0.0036	0.0079
2019	0.003	-0.0045	0.0099

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 17. Overall Effect of Year on Emergency Department Costs among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$1,044.71+	$982.17	$1,107.24
2015	$1,074.78+	$1,024.67	$1,124.89
2016	$1,105.72+	$1,061.25	$1,150.19
2017	$1,137.55+	$1,087.76	$1,187.33
2018	$1,170.29+	$1,105.47	$1,235.11
2019	$1,203.98+	$1,118.22	$1,289.73
Table 17. Average Marginal Effect of Year on Emergency Department Costs among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	$30.07+	$2.60	$57.55
2016	$61.01+	$4.42	$117.59
2017	$92.84+	$5.45	$180.22
2018	$125.58+	$5.62	$245.55
2019	$159.27+	$4.87	$313.67

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

The probability (99% Confidence Limits) of any OP utilization in a month was approximately 0.35 (0.33-0.36) in 2014 and 0.37 (0.35-0.38) in 2019 among STR (p<.01) (**Table 18a**). No statistically significant differences were observed between 2014 and 2019 (all p>.01) (**Table 18b**) Among any STR person-month with an OP visit the overall incremental OP-related costs in 2014 were $446.04 ($396.10-$495.98) and $546.98 ($494.74-$599.22) in 2019 (all p<.01) (**Table 19a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: $100.94 ($31.94-$169.94)) (all p<.01) (**Table 19b**).

The probability (99% Confidence Limits) of any OP utilization in a month increased from approximately 0.40 (0.38-0.41) in 2014 to 0.44 (0.43-0.46) in 2019 among MTR (p<.01) (**Table 20a**). Statistically significant differences were observed in all years over the study period (AME: 2015 ((0.009 (0.005-0.012), 2019 ((0.043 (0.025-0.061)) (p<.01) (**Table 20b**). Among any MTR person-month with an OP visit the overall incremental OP-related costs in 2014 were $626.13 ($569.68-$682.59) and $759.33 ($691.39-$827.27) in 2019 (all p<.01) (**Table 21a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: $133.19 ($42.52-$223.87)) (all p<.01) (**Table 21b**).

Table 18. Overall Effect of Year on the Probability of Any Outpatient Hospital Utilization among Single Tablet Regimen Exposed

	Overall Effect	99% Confidence Limits	
2014	0.35+	0.33	0.36
2015	0.35+	0.33	0.36
2016	0.35+	0.34	0.37
2017	0.36+	0.35	0.37
2018	0.36+	0.35	0.37
2019	0.37+	0.35	0.38

Table 18. Average Marginal Effect of Year on the Probability of Any Outpatient Hospital Utilization among Single Tablet Regimen Exposed

	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.004	-0.0004	0.0080
2016	0.008	-0.0009	0.0161
2017	0.011	-0.0013	0.0242
2018	0.015	-0.0019	0.0325
2019	0.019	-0.0024	0.0408

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 19. Overall Effect of Year on Outpatient Hospital Costs among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	446.04^+$	$396.10	$495.98
2015	464.61^+$	$421.30	$507.93
2016	483.96^+$	$445.16	$522.76
2017	504.11^+$	$465.91	$542.32
2018	525.11^+$	$482.31	$567.90
2019	546.98^+$	$494.74	$599.22
Table 19. Average Marginal Effect of Year on Outpatient Hospital Costs among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	18.58^+$	$6.96	$30.19
2016	37.92^+$	$13.66	$62.18
2017	58.08^+$	$20.09	$96.07
2018	79.07^+$	$26.19	$131.95
2019	100.94^+$	$31.94	$169.94

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 20. Overall Effect of Year on the Probability of Any Outpatient Hospital Utilization among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	0.40$^+$	0.38	0.41
2015	0.41$^+$	0.39	0.42
2016	0.41$^+$	0.40	0.43
2017	0.42$^+$	0.41	0.44
2018	0.43$^+$	0.42	0.45
2019	0.44$^+$	0.43	0.46
Table 20. Average Marginal Effect of Year on the Probability of Any Outpatient Hospital Utilization among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	0.009$^+$	0.005	0.012
2016	0.017$^+$	0.010	0.024
2017	0.026$^+$	0.015	0.037
2018	0.035$^+$	0.020	0.049
2019	0.043$^+$	0.025	0.061

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 21. Overall Effect of Year on Outpatient Hospital Costs among Multi-Tablet Regimen Exposed

	Overall Effect	99% Confidence Limits	
2014	$626.13+	$569.68	$682.59
2015	$650.76+	$603.01	$698.50
2016	$676.35+	$633.59	$719.11
2017	$702.95+	$658.65	$747.25
2018	$730.60+	$677.37	$783.82
2019	$759.33+	$691.39	$827.27

Table 21. Average Marginal Effect of Year on Outpatient Hospital Costs among Multi-Tablet Regimen Exposed

	AME	99% Confidence Limits	
2014	*Reference*		
2015	$24.62+	$9.19	$40.06
2016	$50.22+	$18.08	$82.36
2017	$76.82+	$26.62	$127.01
2018	$104.46+	$34.78	$174.14
2019	$133.19+	$42.52	$223.87

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

The overall incremental non-ART-related costs among STR in 2014 were $4,794.80 ($4,624.83-$4,964.76) and $1,437.33 ($1,370.68-$1,503.99) in 2019 (all p<.01) (**Table 22a**). All years were associated with statistically significant decreased costs per month with the greatest difference in 2019 (AME: -$3,357.46 (-$3,558.27 to -$3,156.65)) (all p<.01) (**Table 22b**). The overall incremental non-ART-related costs among MTR in 2014 were $4,483.07 ($4,377.62-$4,588.51) and $2,344.58 ($2,250.62-$2,438.55) in 2019 (all p<.01) (**Table 23a**). All years were associated with statistically significant decreased costs per month with the greatest difference in 2019 (AME: -$2,138.48 (-$2,278.53- -$1,998.43)) (all p<.01) (**Table 23b**).

Table 22. Overall Effect of Year on Non-Antiretroviral Costs among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$4,794.80+	$4,624.83	$4,964.76
2015	$3,768.15+	$3,666.49	$3,869.80
2016	$2,961.32+	$2,891.69	$3,030.95
2017	$2,327.25+	$2,264.30	$2,390.20
2018	$1,828.94 +	$1,763.92	$1,893.97
2019	$1,437.33+	$1,370.68	$1,503.99
Table 22. Average Marginal Effect of Year on Non-Antiretroviral Costs among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	-$1,026.65+	-$1,107.68	-$945.62
2016	-$1,833.48+	-$1,967.98	-$1,698.98
2017	-$2,468.55+	-$2,636.15	-$2,298.94
2018	-$2,965.85+	-$3,155.14	-$2,776.57
2019	-$3,357.46+	-$3,558.27	-$3,156.65

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 23. Overall Effect of Year on Non-Antiretroviral Costs among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$4,483.07+	$4,377.62	$4,588.51
2015	$3,937.98+	$3,856.95	$4,019.01
2016	$3,459.17+	$3,384.67	$3,533.66
2017	$3,038.57+	$2,959.66	$3,117.48
2018	$2,669.12+	$2,582.41	$2,755.82
2019	$2,344.58+	$2,250.62	$2,438.55
Table 23. Average Marginal Effect of Year on Non-Antiretroviral Costs among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	-$545.09+	-$589.20	-$500.98
2016	-$1,023.90+	-$1,102.49	-$945.31
2017	-$1,444.49+	-$1,549.64	-$1,339.35
2018	-$1,813.95+	-$1,939.18	-$1,688.72
2019	-$2,138.48+	-$2,278.53	-$1,998.43

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

The overall monthly incremental ART-related costs among STR in 2014 were \$2,277.18 (\$2,249.04-\$2,305.33) and \$3,028.74 (\$3,001.93-\$3,055.54) in 2019 (all p<.01) (**Table 24a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: \$751.55 (\$712.33-\$790.78)) (all p<.01) (**Table 24b**). The overall incremental ART-related costs among MTR in 2014 were \$2,834.93 (\$2,793.73-\$2,376.12) and \$3,674.99 (\$3,608.12-\$3,741.87) in 2019 (all p<.01) (**Table 25a**). All years were associated with statistically significant increased costs per month with the greatest difference in 2019 (AME: \$840.07 (\$769.83-\$910.31)) (all p<.01) (**Table 25b**).

Table 24. Overall Effect of Year on Antiretroviral Costs among Single Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	\$2,277.18+	\$2,249.04	\$2,305.33
2015	\$2,410.85+	\$2,386.72	\$2,434.99
2016	\$2,552.37+	\$2,531.55	\$2,573.19
2017	\$2,702.19+	\$2,682.77	\$2,721.61
2018	\$2,860.81+	\$2,839.48	\$2,882.14
2019	\$3,028.74+	\$3,001.93	\$3,055.54
Table 24. Average Marginal Effect of Year on Antiretroviral Costs among Single Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	\$133.67+	\$127.55	\$139.79
2016	\$275.19+	\$262.16	\$288.21
2017	\$425.01+	\$404.22	\$445.80
2018	\$583.63+	\$554.13	\$613.12
2019	\$751.55+	\$712.33	\$790.78

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Table 25. Overall Effect of Year on Antiretroviral Costs among Multi-Tablet Regimen Exposed			
	Overall Effect	99% Confidence Limits	
2014	$2,834.93+	$2,793.73	$2,376.12
2015	$2,985.96+	$2,947.34	$3,024.59
2016	$3,145.05+	$3,105.59	$3,184.52
2017	$3,312.61+	$3,267.99	$3,357.24
2018	$3,489.10+	$3,435.12	$3,543.08
2019	$3,674.99+	$3,608.12	$3,741.87
Table 25. Average Marginal Effect of Year on Antiretroviral Costs among Multi-Tablet Regimen Exposed			
	AME	99% Confidence Limits	
2014	*Reference*		
2015	$151.04+	$139.70	$162.38
2016	$310.12+	$286.20	$334.05
2017	$477.69+	$439.82	$515.55
2018	$654.17+	$600.91	$707.44
2019	$840.07+	$769.83	$910.31

*Adjusted for age, sex, race, and original reason for entitlement
+Significant at p<.01

Discussion

This repeat cross-sectional study used Medicare claims to estimate STR and MTR use and related healthcare resource utilization (HcRU) and costs from 2014 through 2019. We provided both descriptive statistics and AME to better characterize changes in utilization and costs over the study period. Overall, STR receipt was 24% more likely in 2019 than it was in 2014 (**Table 4**), reflecting the shift in ART regimen prescription as more variation in STR class components were brought to market. Also, the greater availability of INSTIs and the class' inclusion in all HHS first-line regimens since 2017[7] is evident in the class' prevalence in nearly 80% of STR and 74% of MTR in 2019. While not all regimens can be constructed as both STR and MTR, approximately 90% of regimens observed in this study could be constructed with exact product equivalents as either (data not shown). However, an STR may not be feasible for beneficiaries requiring a PI-inclusive regimen due to the single formulation (i.e., darunavir, cobicistat, emtricitabine, TAF (Symtuza®)) available,[7] which likely explains the stark differences in PI utilization we observed between STR and MTR.

We did not directly compare STR and MTR due to our inability to accurately measure confounders, such as comorbidities, on a monthly basis in alignment with our continuous enrollment and ART criteria. Our findings descriptively illustrate STR are associated with lower HcRU and related costs among Medicare beneficiaries as observed in other populations.[11–14,52,54] These results indicate MTR recipients may be older and burdened with more significant comorbidity and polypharmacy. The probability of any IP utilization in a month was about 3% among STR, while among MTR the probability ranged from 3-4% over the study period though within-group differences were not significant in either group. However, both groups saw significant increases of over $2,000 in conditional IP-related costs from 2014 to 2019. These increases over and above inflation suggest Medicare beneficiaries may be presenting with more complex and costly issues as the cohort ages. The probability of ED utilization in a month was largely unchanged among both STR (6%) and MTR (7%) over the study period as well. Though ED-related costs tended to rise by similar amounts among both groups, the difference was only statistically significant among MTR. Much of these ED-related costs of approximately $1-$1.2 thousand are likely avoidable as these visits did not result in hospitalization and many may have been handled at less expensive settings, such as urgent care, although our study was unable to assess this explicitly. About one-third (35-37%) of STR recipients utilized OP services in a month with costs rising to nearly $550 per month in 2019, an increase of about $100 over the study period. MTR saw a statistically significant rise in OP utilization from 40% to 44% over the study period, while costs increased to about $760 per month – an increase of $130. Again, increases exceeding inflation suggest beneficiaries needing more costly treatments, and MTR recipients demonstrating greater need for services.

Nearly all beneficiaries utilized at least one non-ART prescription per month throughout the study, but non-ART-related costs dropped substantially over this time: over $3,300 among STR and more than $2,100 per month among MTR. The primary driver was significant utilization of curative Hepatitis C treatments following their approval at the beginning of the study and the rapid reduction in utilization at the end of our study period.[67] Higher costs and more modest decreases among MTR are in-part explained by the greater non-ART utilization in this group, but may also point to the group experiencing more compromised health status. However, MTR recipients experienced significant reductions in the number of non-ART prescriptions from a median of 7 in 2014 to 4 in 2019 suggesting increased attention to polypharmacy and deprescribing might be employed more widely in this group.[1,19–21] This reduction among MTR recipients may also partially be the result of a larger proportion of beneficiaries aging into Medicare eligibility (10% in 2014 to 16% in 2019 in our sample) who may be healthier than those who qualify by disability.

ART costs per month for STR were about $3,000 in 2019- a $750 increase above inflation since 2014. MTR saw an even larger increase of $850 per month leading to ART costs of nearly $3,700 in 2019. Higher ART costs among MTR are likely explained by the greater number of ART prescriptions per month compared to STR (3.68 vs. 3.21 in

2019). Also, our inclusion of salvage regimens (i.e., 5 or more medications), which are not available as STR likely contributed to this phenomenon. Salvage regimens accounted for less than 5% of regimens observed and are subject to over counting due to the way we handled potential regimen switches by accounting for all prescription fills through their entire days' supply (data not shown). Excluding salvage regimens would likely lower the estimated incremental costs among MTR, but we chose to include these beneficiaries to obtain the most complete picture of those in treatment in Medicare. Further, about 90% of ART prescriptions in Medicare are for branded products even when generic equivalents are available. As this is the primary cost containment option in prescription drug spending it is unsurprising that costs are not reduced when a larger number of branded therapies are used each month.[5]

Our study demonstrates the rapid adoption of INSTIs among both STR (18% in 2014 to 80% in 2019) and MTR (39% to 74%) recipients, which is consistent with the class' inclusion in all four HHS first-line regimens[7] and mirrors utilization trends in other populations.[68] INSTI-based STRs including elvitegravir (Stribild® and Genvoya®) and bictegravir (Biktarvy®) comprise the population unable to deconstruct their regimen to an MTR due to these two INSTIs being unavailable as single drug or fixed dose combination products.[7] This limits the regimen choices for both INSTI-based STRs and MTRs as raltegravir and dolutegravir are the only INSTIs available for MTR.[7] INSTIs are preferred for their higher barriers to resistance and tolerability, which has led to the approval of two-drug INSTI-based regimens.[68] These approvals sparked ongoing debates regarding the wisdom of two-drug regimens after over two decades of triple therapy being stressed.[69,70] The inferiority of two-drug regimens is well established,[70,71] but the advent of INSTIs and their approval as part of two-drug regimens for both initial and maintenance therapy should be monitored closely in real world studies as they may prove to be attractive options among providers for older Medicare beneficiaries with mounting polypharmacy burdens.[3,4] Currently, only dolutegravir (Juluca® and Dovato®) is approved as part of a two drug regimen in the United States,[7] but if other INSTIs prove to be viable alternatives and manufacturers choose to bring them to market then more diverse formulations and potential for additional INSTI-based STR and MTR may come to fruition.

Strengths

The strengths of this study include the use of claims data to explore previously unexamined HcRU and costs in Medicare beneficiaries living with HIV by type of regimen formulation received. This allows for the investigation of a population that is understudied and largely excluded from RCTs due to their clinical complexity, but increasingly represent the realities of long-term HIV infection. We utilized advanced statistical methods to account for correlation between measures contributed from the same beneficiary allowing us to utilize the greatest amount of data possible. Additionally, our enrollment criteria (e.g., concurrent Parts A, B, and D coverage) helped minimize missing utilization and costs due to changes in insurance coverage.

Limitations

This study has several important limitations inherent to observational claims-based analyses and cross-sectional designs. We did not control for HIV disease severity as $CD4^+$ counts and viral load are not available in claims. Additional unmeasured variables including comorbidities may bias study findings, but the inclusion of a comorbidity index measure on a monthly unit of analysis is not valid. Measures of medication use reflect dispensed medications and not consumed medications. Our measures likely overestimate medication use if patients did not take them as prescribed. The outcome measures (costs) are known to contain errors due to the complexity of reimbursement in the US. Specifically, our measure of prescription drug costs reflects the amount Medicare is "willing" to pay for that prescription but does not necessarily reflect the exact amount paid by Medicare. Also, it does not take into account any manufacturer rebates for prescription drugs as these are proprietary in nature yet prevent the ascertainment of a "true-cost" to Medicare. Similarly, hospital reimbursements may be altered due to regulations and incentives related to readmissions and other measures of care quality.

Conclusion

Our findings demonstrate the predominance of STR and INSTIs among Medicare beneficiaries living with HIV/AIDS. Further, the results reflect patterns in inpatient, emergency department, outpatient, and prescription drug healthcare resource utilization and related costs by STR receipt in this understudied population. Lower utilization and costs observed among person-months exposed to STR are consistent with findings in other populations. However, future studies are needed to directly compare healthcare resource utilization and related costs associated with STR versus MTR. These designs should aim to account for significant sources of potential bias including non-random treatment assignment and other unmeasured confounding.

4 Aim 2 Manuscript

Aim 2) Estimate 1-year total incremental direct medical costs associated with single tablet regimens (STR) compared to multi-tablet regimens (MTR) among PLHIV in Medicare (2014-2019).

Abstract

Background The validity of findings from observational studies can be threatened by several sources of bias, including non-random treatment assignment. Several studies of people living with HIV (PLHIV) have concluded single tablet ART regimens (STR) improve adherence and reduce healthcare costs compared to multi-tablet regimens (MTR). These studies, however, fail to account for endogeneity in treatment assignment and other sources of unmeasured confounding. Regression modeling with instrumental variables, a method with a foundation in econometrics, offers the potential to control for confounding due to non-random treatment assignment and may lead to more accurate conclusions of the costs associated with regimen complexity. In addition to improving upon prior study designs we conducted our study using an understudied and growing population of Medicare beneficiaries living with HIV. The primary objective of this study was to estimate the one-year total incremental direct medical costs associated with STR compared to MTR among PLHIV enrolled in Medicare.

Methods This is a retrospective cohort study using a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) to estimate 1-year total incremental direct medical costs associated with STR compared to MTR among beneficiaries living with HIV from January 1, 2015 through December 31, 2018. Beneficiaries with evidence of an incident ART regimen and 12 months continuous pre- and post- index Parts A, B, and D coverage were included in the study. We employed two-stage least squares regression with a prescriber preference instrumental variable defined as the proportion (≥/< 50%) of ART regimens prescribed as STR in the 6 months preceding the incident regimen. We report the incremental total direct medical costs associated with the instrumented treatment variable after controlling for clinical and sociodemographic covariates.

Results We identified 7,044 people who newly started ART of either a STR (n=3,348, 47.53%) or MTR (n=3,696, 52.47%) between January 1, 2015, and December 31, 2018. The predicted STR instrument level included 1,270 beneficiaries and the predicted MTR group included 5,774. The instrumented STR variable was associated with statistically significant lower 1-year incremental total direct medical costs compared to MTR (-$13,487.70, (95% Confidence Interval: -$16,750.77 to -$10.224.63), p<.001). The 1-year total incremental costs associated with the instrumented STR treatment variable among the ≥95% adherence strata were -$10,922.57 (-$14,069.75 to -$7,875.40) (p<.001), which included 81.33% (n=5,729) of the sample. The incremental cost associated with the instrumented STR treatment variable among specific ART regimens was ≥1 NRTI (-$13,002.15 (-$16,880.13 to -$9,124.18)), 1 INSTI (-$21,614.51 (-$27,677.91 to -$15,551.10)), and no PIs (-$13,238.85 (-$20,093.66 to -$6,384.04)), respectively (all p<.001).

Conclusion Our findings demonstrate STRs are associated with significantly lower 1-year total direct medical costs compared to MTR. This study addresses a gap in the literature by demonstrating total direct medical costs associated with different ART formulations among an understudied population—Medicare beneficiaries living with

HIV. This study improves upon prior study designs and demonstrates the usefulness of prescriber preference IVs. Further, it demonstrates the potential future cost-savings for Medicare if STR utilization continues to increase and possibly as greater diversity in STR class composition proliferates. Future research employing larger sample sizes and clinical measures of key indicators of HIV disease severity (i.e., CD4 count, opportunistic infections) and other treatment complexities (e.g., resistance profiles) would further confirm confidence in these findings and conclusions.

Introduction

Administrative claims are rich sources of healthcare utilization data among the insured, which can be harnessed to characterize epidemiologic and economic outcomes of interest in this population. These data offer large sample sizes and significantly lower costs as compared to primary data collection methods. Studies conducted with these data, however, are susceptible to several sources of bias, including non-random treatment assignment and selection bias.[72,73] The absence of random allocation to treatment as implemented in randomized control trials (RCT) may lead to imbalances in measured and unmeasured risk-factors between comparator treatment groups, potentially limiting capacity for causal inference of treatment effects.[73] Several quasi-experimental approaches are available to address this source of confounding when conducting observational studies, including instrumental variables (IV) via two-stage least squares (2SLS).[73] While propensity scores and other methods can account for measured confounders, IVs were developed to control for unmeasured confounders. IVs achieve this by uncovering a natural experiment in the observed data and exploiting the IV's inducement of variation in the exposure to estimate the causal treatment effect.[73,74]

Antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) is a setting where IVs offer the opportunity to estimate causal treatment effects that would likely not be estimated (or available) from RCTs. Though costs and adherence can be measured in RCTs, observational data provide real world estimates among more representative and less selected populations. ART formulations, which include multiple ART medications in combination as single tablet regimens (STR), have been found to be associated with better adherence and lower health care costs and utilization in observational studies among commercially-insured individuals under 50 years of age compared to multi-tablet regimens (MTR).[12–14,52,54,55] These studies, however, were susceptible to several sources of bias arising from prevalent user designs, the availability of only a single STR, and failure to account for non-random treatment assignment.[12–14,52] Reproducing these findings under more stringent design criteria would increase confidence in the conclusions, inform treatment decisions, and motivate future drug development.

Improvements in adherence associated with STR, and subsequent reductions in costs and utilization, have been attributed to the simplified dosing frequency and reduced pill burden, as adherence to ART is essential in order to suppress viral replication and improve or preserve immune function.[7,24] However, STR drugs cost approximately 1.5 times more than the combined cost of the individual medications of multi-tablet regimens (MTR) among both public and private payers.[16] To the best of our knowledge, no studies have examined this relationship among Medicare beneficiaries living with HIV. Furthermore, it remains unclear if the cost savings associated with STR will be observed among Medicare beneficiaries who differ from prior cohorts in several ways.[3,60] Higher ART treatment adherence observed in other cohorts of adults aging with HIV[75,76] may limit the cost differences between STR and MTR if similar rates of adherence are observed among Medicare beneficiaries.

Beneficiaries qualify for Medicare on the basis of age (≥65 years old) or disability, with nearly 80% of people living with HIV (PLHIV) in Medicare gaining eligibility through the latter.[28] Older age and disability are associated with greater healthcare costs,[77] which are only amplified and accelerated for PLHIV due to the deleterious effects of viral replication and inflammation.[58,76,78] Coupled with the marked improvements in survival as HIV has become a manageable chronic infection, lifetime medical costs for PLHIV continue to grow and represent a significant expenditure for Medicare as the largest primary payer for ART medications.[5,28,29] PLHIV in Medicare have a higher comorbidity burden[3] compared to commercially-insured PLHIV, but prior studies demonstrating cost-savings associated with STR were conducted among cohorts of which over 70% of individuals had no comorbidities (as defined by the Charlson Comorbidity Index (CCI)), adding further uncertainty as to whether cost savings associated with STR will be observed among a more adherent but sicker population.[14,53] Assessing incremental total direct medical costs among Medicare beneficiaries while improving upon prior study designs and capacity for causal inference would help demonstrate the cost impact of STR compared to MTR in an understudied population.

In this study we aimed to address a gap in the literature by assessing whether cost savings associated with STR compared to MTR would be observed among Medicare beneficiaries. In addition to estimating this relationship in an understudied population, we will employ more rigorous observational research methods to account for non-random treatment assignment than prior studies. The primary objective was to estimate the total incremental direct medical costs associated with STR compared to MTR among Medicare beneficiaries living with HIV.[27] As findings in prior studies were sensitive to post-index adherence, we also estimated the total incremental direct medical costs associated with STR compared to MTR among strata based on post-index adherence. We also conducted sensitivity analyses by specific regimen class composition to assess how robust our findings were to class inclusions and exclusions due to the potential for unmeasured confounders, such as resistance.

Methods

Study Design and Data Source

This retrospective cohort study used a 5% (2014-2019) random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) to compare 1-year total incremental direct medical costs among Medicare beneficiaries living with HIV by single- and multi- tablet antiretroviral regimen receipt. The CCW data files used in this study are listed in **Appendix Table 14** and include the Master Beneficiary Summary Files (MBSF), the inpatient (IP) claims file, the outpatient claims (OP) file, and the Part D event file, all of which have been described previously in the methods section of Aim 1. In addition we used the following claims files: carrier (e.g., non-institutional claims, such as physician office visits), durable medical equipment (e.g., wheelchairs, home oxygen equipment), home health agency (e.g., in-home wound care, injections), skilled nursing facility (e.g., <100 days non-custodial care, physical or occupational therapy), hospice (e.g., all care related to a terminal illness), and the outpatient revenue center file (i.e., CD4 count and HIV RNA genotyping).

Study Cohort

The study included Fee-for-Service beneficiaries with evidence of an HIV diagnosis defined using a validated algorithm requiring: (1) at least one inpatient claim or (2) at least two outpatient claims on different dates with ICD9/10 codes for HIV (**Appendix Table 2)**.[58] The index date was the date of a new, complete antiretroviral regimen prescription defined as no use of the exact regimen in the preceding 12 months in any formulation (e.g., a beneficiary switching from an STR to an identical MTR did not qualify). Components of MTRs were required to be filled within 7 days of each other and the last prescription's fill date was used as the index date. Evidence of at least 60 days of exposure following the index was required to ensure the identified prescriptions were an intended regimen and wash out any pre-index fills where the days' supply carried over into the post-index period.[12,14]

A complete regimen was defined as at least three ART medications from at least two classes or Juluca®, a two drug regimen, recommended in the 2021 Department of Health and Human Services (HHS) guidelines for treating adults living with Human Immunodeficiency Virus (HIV).[7] Beneficiaries initiating a "salvage regimen" defined as five or more ART were excluded as they would all be assigned to the MTR group and their response to treatment is known to be suboptimal due to virologic resistance to more than one antiretroviral class.[7] Continuous enrollment in Parts A, B, and D and no Part C 12 months pre- and post- index was required.

Measures

The primary independent variable of interest is regimen complexity (STR vs. MTR) (**Appendix Table 15**). The primary outcome measure was one-year total incremental direct medical costs defined as the sum of all inpatient, outpatient, Part D prescription drugs, non-institutional carrier, skilled nursing facility, durable medical equipment, home health, and hospice costs. A third-party payer perspective was used, and only costs paid by Medicare were included. We reported total costs by STR and MTR receipt and instrument level, which is described below in the Instrumental Variable section. All costs were adjusted for inflation to 2019 US dollars using the health care component of the Personal Consumption Expenditures Index.[61]

Covariates were chosen based on our theoretical framework in **Appendix Table 1** and included age, sex, race, original reason for entitlement, dual eligibility for Medicare and Medicaid, and region of residence. Additionally, we constructed a binary measure of the presence of any opportunistic infection (OI) included in the Centers for Disease Control (CDC) definition of Stage 3 HIV infection indicating a $CD4^+$ count approximately below <200 cells/mm^3.[79] Presence of OIs assessed in the 12 months pre-index are listed in **Appendix Table 16**.[80] HIV genotyping can only be conducted in the presence of a detectable viral load, thus we used this as a crude binary indicator of viremia (**Appendix Table 17**).[7] $CD4^+$ count testing is recommended every 3-6 months during the first two-years of ART or CD4 counts <300 cells/mm^3 and every 12 months beyond these minimums.[7] We constructed a binary flag indicating whether or not the beneficiary underwent CD4 testing in the 12 months pre-index as a proxy for engagement in care. Pre-index adherence was calculated as the proportion of days covered by any complete ART regimen in the 12 months preceding the index date without any requirement for length of each regimen. Year fixed effects were also included to control for factors changing each year common to both treatment groups.

Statistical Analyses

Descriptive statistics were used to compare clinical, demographic, and cost characteristics by STR and MTR receipt. Continuous variables were summarized using mean (standard deviation) and median (interquartile range (IQR)). Categorical measures were summarized using frequency (percentage). Standardized differences were used to compare covariate balance between STR and MTR receipt and instrument level as it is a measure independent of sample size and considered more appropriate in a quasi-experimental design setting than traditional significance testing.[81,82] Graphic and statistical representation of total cost distributions can be found in **Appendix Figure 11**. The effect of STR receipt was estimated using two-stage least squares (2SLS) regression models. The first stage of 2SLS treats STR receipt as the dependent variable with the instrumental variable (IV) and covariates as independent variables providing the predicted probability of exposure conditional on the IV and covariates. In the second stage the cost outcome is the dependent variable with the fitted values from stage 1 and measured covariates as independents. The coefficient on the predicted value of treatment in stage 2 is the estimated causal effect of STR. Cluster robust standard errors were obtained using STATA's "ivreg" command with prescriber as the clustering unit. Significance was pre-specified at alpha .05. All statistical analyses were performed using SAS version 9.4. (data manipulation) and STATA/MP version 16.0.097 (2SLS modeling).

Instrumental Variables

The instrumental variable (IV) approach was used to minimize bias due to unmeasured confounding as a strong IV enables a causal interpretation of the treatment effect relative to the IV (i.e., Local Average Treatment Effect (LATE)) in this context. We suspect our exposure of interest, STR and MTR receipt, may be vulnerable to endogeneity; i.e., its value is influenced by one or more variables in the system.[83] The threat of non-random treatment assignment in this case requires a quasi-experimental approach to enable valid inference.[83] The absence or insufficient measurement of key indicators of HIV disease severity that may be associated with both the exposure and the outcome make other methods, such as propensity scores, insufficient due to their reliance on assumptions of no unmeasured confounding.[73]

HIV RNA viral load (VL) is the primary outcome in the majority of ART clinical trials due to its indication of the efficacy of an ART regimen controlling viral replication and the established improvements in and maintenance of health status that accompany viral suppression.[84] The HHS HIV treatment guidelines also specify VL thresholds at which initiation with different ART regimens is indicated or not.[7] Further, we are unable to definitively measure beneficiaries' $CD4^+$ counts, a measure of immune function, that may also be associated with both the exposure and the outcome. Our inability to precisely measure VL and $CD4^+$ counts may result in unobserved and uncontrolled imbalance in disease severity between treatment groups as both are taken into account by providers when selecting a treatment and are known to be associated with total healthcare costs.[29,76,78]

Preference-based IVs attempt to exploit natural variation in treatment patterns among individual providers, hospitals, or regions. This assumes that these units have preferences for different treatments, which can be approximated through examination of past prescribing behavior. In this paper we utilized physician prescribing preference as the instrument. Due to the availability of first-line ART regimens that can be constructed as either STR or MTR we reason that the observed prescription is influenced by the physician's prescribing preference (i.e., certain physicians will prescribe an STR more often while others will prescribe an MTR more often). Prior studies have demonstrated the use of observed prescriptions as proxy for physician prescribing preference.[85–87] We defined a binary, provider-level preference IV defined as the proportion of ART prescriptions written in the previous 6 months for STR that was greater than or equal to or less than 50%.[85,87]

Total direct medical costs were modeled using 2SLS regression and were specified in the following forms:

First stage:

$$STR = b_0 + b_1 IV + b_{i \ldots n}(Covariates)$$

Second Stage:

$$Costs_{\ (Total\ Healthcare\ Costs)} = b_0 + b_1(IV\_STR) + b_{i \ldots n}(Covariates)$$

The second stage model includes the predicted value of exposure, fitted values from the first stage, and measured covariates.

Key assumptions underlying the validity of instruments include: 1) the IV is strongly associated with the treatment; 2) the IV is not associated with unmeasured confounders after conditioning on measured covariates; and 3) the IV is only associated with the outcome through the treatment.[83,88] Due to the importance of these assumptions to the validity of the IV and the precision of results (i.e., standard error) we tested them in multiple ways.

Assumption #1 was tested by calculating the difference of the treatment assignment rate and calculating the F-statistic with 1 degree of freedom in a regression of the form specified above as the first stage.[89] An F-statistic above 10 is a well-cited threshold of instrument strength in the econometrics literature.[90] However, F-statistics can increase as sample size increases even with weak IVs, thus due to our expected large sample size we pre-specified a minimum F-statistic of 50.[89] The partial r^2 from this regression can be interpreted as the percentage of unexplained variance that can be explained by the IV.[89] A partial r^2 above 0.1 was pre-specified as a baseline threshold of strength to be considered in concert with the proportion of compliers (i.e., patients who would always be prescribed a respective provider's preferred treatment). A larger proportion of compliers (e.g., >25% or >50%) accompanied with larger proportions of subjects assigned IV=1 (i.e., provider preference for STR >15% or >40%) would lead to consideration of lower partial r^2 (e.g., below 0.1 and 0.25), while the inverse will lead to requiring higher partial r^2.[89] **Appendix Table 18** details the framework, formula, and calculations of the complier subgroup.

Assumption #2 cannot be definitively confirmed with observed data, but balance of measured confounders between IV levels may help test this assumption.[89] We calculated the standardized difference of all covariates between STR and MTR exposed and levels of the instrument.[89] A standardized difference >0.2 between treatment groups and >(0.2*proportion compliers) between instrument levels were used as indicators of significant imbalance between groups.[82,89] We will control for these variables in the regression models, but imbalance on multiple covariates was used as an indicator of a potentially weak instrument. Improvement in covariate balance (i.e., smaller standardized difference), specifically on measures of comorbidity and disease severity, was used as an indication of the IV not being associated with unmeasured covariates.[83]

Assumption #3 again relies heavily on theoretical justification and conceptual argument, but may be partially tested by regressing a potential confounder on the IV and measured covariates.[89] A significant p-value of the IV coefficient alone is not indicative of a violation, but may indicate one when coupled with theoretical suspicion of the IV being associated with other covariates (e.g., other treatments) that may also be associated with the outcome.[89] We regressed all covariates on the instrument in crude and fully adjusted (i.e., instrument and all other covariates) analyses and report the p value for the instrument coefficient for every model.

The Durbin Score statistic[91] and Wu-Hausman statistic[92] were used as tests for endogeneity under which the null hypotheses are that the variable suspected of being endogenous is in fact exogenous. A significant p value (i.e., <0.05) would indicate that the Ordinary Least Squares Estimator (OLS) is more consistent than the 2SLS estimator.[91,92] However, a failure to reject the null hypothesis may also occur under the scenario of a weak instrument, thus is insufficient evidence alone to indicate that endogeneity is not a concern in the regression.[91,92]

Preference-based IVs may be invalid if patient mix differs significantly between providers that prefer different treatments, the providers treat patients differently, or if the skill of these providers differ between preference groups. We assessed patient mix as the prevalence of the top five conditions in the prescriber's practice 6 months preceding the index prescription among patients with HIV and all patients, respectively. Also, we assessed the prevalence of the five most common prescriptions providers wrote for their patient population with HIV and overall. We assessed the volume of ART prescribing in the 6 months pre-index as a proxy for provider skill as the proportion of total prescriptions. We report the p value from chi^2 tests for all measures.

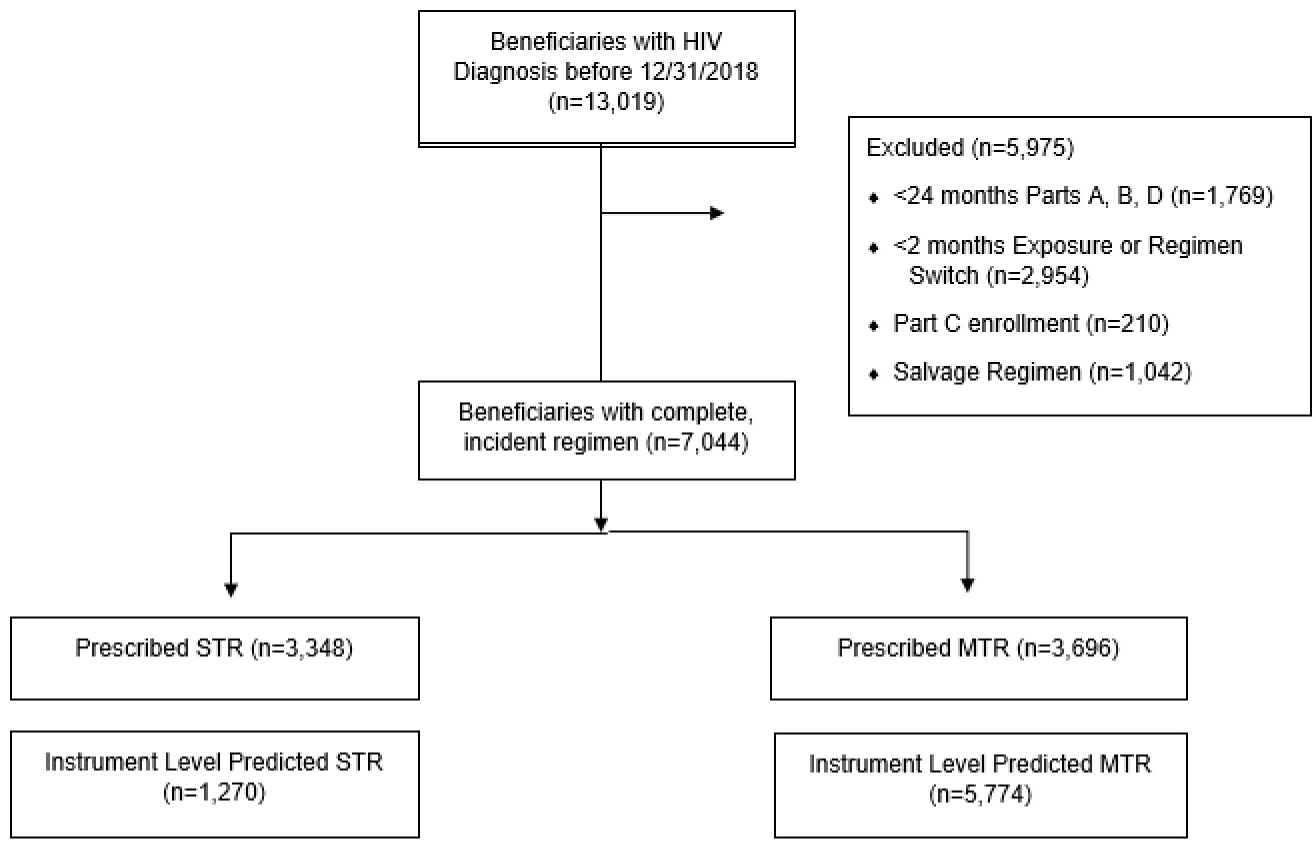
Sensitivity Analyses

We attempted to minimize structural uncertainty through the specification testing detailed above and through stratified analyses of those with post-index adherence >95%, 85-94%, and <85% defined by proportion of days covered (PDC). We also ran stratified models of those with at least one NRTI, one INSTI, and no PIs, respectively, to assess how robust our results were to regimen class composition.

Results

We identified 7,044 new starters of either an STR (n=3,348, 47.53%) or MTR (n=3,696, 52.47%) between January 1, 2015, and December 31, 2018. The predicted STR instrument level included 1,270 beneficiaries and the predicted MTR group included 5,774. The cohort selection flow chart is displayed in **Figure 3.**

Figure 3. Sample Selection Flow Chart



The results of the proposed tests for endogeneity and instrument strength indicate our instrument was not weak; results are listed in **Appendix Tables 19-22**. The baseline characteristics of the observed and predicted treatment groups are listed in **Table 26.** Those exposed to STR were more likely to be under 50 years of age (27.21% vs. 24.23%), female (28.07% vs. 25.24%), to have aged into Medicare eligibility (18.02% vs. 16.05%), not dually eligible for Medicare and Medicaid (29.53% vs. 25.70%), and residing in the Midwest (15.04% vs. 13.12%) compared to MTR exposed. Clinically, those exposed to STR were less likely to meet criteria for CDC Stage 3 HIV/AIDS (8.03% vs. 9.05%), have hepatitis C (10.55% vs. 12.99%), have evidence of HIV RNA genotyping (16.36% vs. 17.79%), and have CD4 count testing (14.74% vs. 16.32%). STR exposed were also more likely to have a CCI score of 0 (65.27% vs. 57.57%) or 1 (16.91% vs. 14.81%) and less likely to have scores of 2 (9.19% vs. 10.88%) or ≥3 (8.63% vs. 16.74%). However, STR exposed had a lower pre-index adherence compared to MTR (0.86 vs 0.89).

Overall covariate balance between the predicted STR and predicted MTR groups did not exceed the specified threshold of 0.11 (0.2*53% (proportion compliers)). However, balance decreased compared to the observed treatment groups across some demographic characteristics, including age 57-64 years (SDiff=-0.04) and ≥65 years (SDiff=0.05). Clinically the covariate balance improved between the predicted treatment groups, including CCI of 0 (SDiff=0.08) or ≥3 (SDiff=-0.1), HIV RNA genotyping (SDiff=-0.02), Hepatitis C (SDiff=-0.02), and pre-index adherence (SDiff=-0.09).

The antiretroviral regimen class compositions by treatment observed and instrument level are listed in **Table 27**. STR more often included at least one nucleoside reverse transcriptase inhibitor (NRTI) (98.32%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (31.28%), a pharmacokinetic enhancer (PE) (37.77%), or an integrase strand transfer inhibitor (INSTI) (79.76%). A smaller majority of MTR included an NRTI (74.71%) or an INSTI (54.37%), while 21.94% included an NNRTI and 16.20% a PE. Protease inhibitors (PI) were observed more frequently among MTR (52.56%) compared to STR (12.62%). The predicted STR group more often included at least one NRTI (95.33% vs. 82.81%), NNRTI (33.59% vs. 24.49%), PE (36.36% vs. 23.35%), or INSTI (72.85% vs. 63.77%) compared to the predicted MTR group. PIs were observed more frequently among MTR (39.97% vs. 11.74%) compared to STR. All of the standardized differences shrunk between the treatment observed and instrument level comparisons: NRTI (0.74 to 0.41), NNRTI (0.21 to 0.20), PI (-0.94 to -0.68), PE (0.50 to 0.29), and INSTI (0.56 to 0.20).

The mean (standard deviation (SD)) and median (interquartile range (IQR)) one-year total direct medical costs for the full sample, observed treatment groups, and instrument levels are listed in **Table 28**. Overall, the full-sample mean (SD) total costs were \$55,450.18 (\$32,068.67), with median costs (IQR) of \$45,432.45 (\$25,135.16). The observed STR group had mean (SD) \$50,031.56 (\$28,834.35) and median (IQR) \$41,529.25 (\$17,546.89), while the MTR group had mean (SD) \$60,420.82 (\$34,027.92) and median (IQR) \$51,381.12 (\$29,390.83) total costs (all $p<0.001$). The predicted STR group had mean (SD) \$50,088.15 (\$29,535.14) and median (IQR) \$41,768.39 (\$16,684.09), while the MTR group had mean (SD) \$56,636.81 (\$32,487.45) and median (IQR) \$46,615.37 (\$26,503.69) total costs (all $p<0.001$).

Table 26. Covariate Balance by Treatment Received and Instrument Level						
Covariates N(col%)	**Treatment Received**		**SDiff**	**Instrument Level**		**SDiff**
	STR	**MTR**		**Predicted STR**	**Predicted MTR**	
Age Group	n=3348	n=3696		n=1270	n=5774	
<50 years	911 (27.21)	896 (24.23)	0.07	336 (26.43)	1459 (25.26)	0.05
50-56 years	850 (25.39)	1048 (28.35)	-0.07	337 (26.50)	1587 (27.48)	-0.07
57-64 years	742 (22.16)	828 (22.41)	-0.01	267 (21.04)	1303 (22.56)	-0.04
≧65 years	845 (25.24)	924 (25.01)	0.01	331 (26.03)	1426 (24.70)	0.05
Sex						
Female	940 (28.07)	933 (25.24)	0.06	334 (26.29)	1501 (25.99)	0.07
Male	2408 (71.93)	2762 (74.76)	-0.06	936 (73.71)	4273 (74.01)	-0.07
Race/Ethnicity						
Black	1371 (40.94)	1531 (41.43)	-0.01	528 (41.54)	2374 (41.12)	0.01
Hispanic	272 (8.13)	277 (7.50)	0.02	98 (7.72)	451 (7.81)	0
Other/Unknown	149 (4.44)	101 (2.74)	0.09	47 (3.73)	203 (3.51)	0.01
White	1556 (46.48)	1786 (48.32)	-0.04	597 (47.01)	2746 (47.56)	-0.01
Original Reason for Eligibility						
Aged	603 (18.02)	593 (16.05)	0.05	218 (17.17)	953 (16.51)	0.07
Disabled/ESRD	2745 (81.98)	3103 (83.95)	-0.05	1052 (82.83)	4821 (83.49)	-0.07
Dual Eligibility Medicare-Medicaid						
No	989 (29.53)	950 (25.70)	0.09	372 (29.29)	1567 (27.13)	0.05
Yes	2359 (70.47)	2746 (74.30)	-0.09	897 (70.71)	4208 (72.87)	-0.05
CDC Stage 3 (CD4<200)						
Yes	269 (8.03)	334 (9.05)	-0.04	103 (8.12)	500 (8.66)	-0.02
No	3079 (91.97)	3362 (90.95)	0.04	1167 (91.88)	5274 (91.34)	0.02
Charlson Comorbidity Score						
0	2185 (65.27)	2128 (57.57)	0.16	779 (61.31)	3496 (60.55)	0.08
1	566 (16.91)	547 (14.81)	0.06	208 (16.38)	906 (15.69)	0.02
2	308 (9.19)	402 (10.88)	-0.06	131 (10.32)	591 (10.24)	-0.03
≧3	289 (8.63)	619 (16.74)	-0.25	152 (11.99)	781 (13.52)	-0.1
Hepatitis C						
Yes	353 (10.55)	480 (12.99)	-0.08	144 (11.32)	689 (11.94)	-0.02
No	2995 (89.45)	3216 (87.01)	0.08	1126 (88.68)	5085 (88.06)	0.02
Region						
Midwest	504 (15.04)	485 (13.12)	0.06	193 (15.17)	745 (12.91)	0.17
Northeast	826 (24.68)	923 (24.97)	-0.01	323 (25.43)	1426 (24.70)	0.02
South	1416 (42.30)	1587 (42.94)	-0.01	529 (41.62)	2513 (43.52)	-0.1
West	602 (17.97)	700 (18.93)	-0.02	226 (17.78)	1088 (18.85)	-0.05

Table 26. Continued

Pre-Index Adherence						
Mean (SD)	0.86 (0.29)	0.89 (0.26)	-0.12	0.86 (0.29)	0.88 (0.27)	-0.09
HIV RNA Genotyping						
Yes	548 (16.36)	657 (17.79)	-0.04	210 (16.51)	995 (17.24)	-0.02
No	2800 (83.64)	3039 (82.21)	0.04	1060 (83.49)	4779 (82.76)	0.02
CD4 Count						
Yes	493 (14.74)	603 (16.32)	-0.04	183 (14.38)	914 (15.83)	-0.04
No	2854 (85.26)	3093 (83.68)	0.04	106 (85.62)	4860 (84.17)	0.04

*SDiff=Standardized Difference; SD=Standard Deviation

Table 27. Antiretroviral Class Components by Treatment Received and Instrument Level

	Treatment Received			Instrument Level		
Antiretroviral Class N(col%)	**STR**	**MTR**	**SDiff**	**Predicted STR**	**Predicted MTR**	**SDiff**
NRTI	3292 (98.32)	2761 (74.71)	0.74	1211 (95.33)	4781 (82.81)	0.41
NNRTI	1047 (31.28)	811 (21.94)	0.21	427 (33.59)	1414 (24.49)	0.2
PI	423 (12.62)	1943 (52.56)	-0.94	149 (11.74)	2308 (39.97)	-0.68
PE	1265 (37.77)	599 (16.20)	0.5	462 (36.36)	1348 (23.35)	0.29
INSTI	2670 (79.76)	2010 (54.37)	0.56	925 (72.85)	3682 (63.77)	0.2

*SDiff=Standardized Difference

Table 28. 1-year costs by Single- and Multi- Tablet Regimen Exposure and Instrument Level

	Full Sample		***p***
Mean (Standard Deviation)	$55,450.18 ($32,068.67)		
Median (Interquartile Range)	$45,432.45 ($25,135.16)		
	Treatment Received - STR	**Treatment Received - MTR**	
Mean (Standard Deviation)	$50,031.56 ($28,834.35)	$60,420.82 ($34,027.92)	<.001
Median (Interquartile Range)	$41,529.25 ($17,546.89)	$51,381.12 ($29,390.83)	
	Instrument Level - STR	**Instrument Level - MTR**	
Mean (Standard Deviation)	$50,088.15 ($29,535.14)	$56,636.81 ($32,487.45)	<.001
Median (Interquartile Range)	$41,768.39 ($16,684.09)	$46,615.37 ($26,503.69)	

Table 29 lists the 1-year total incremental direct medical costs estimated from the second stage of the 2SLS model. The instrumented STR variable was associated with statistically significant lower 1-year incremental total direct medical costs compared to MTR (-\$13,487.70 (95% Confidence Interval: -\$16,750.77 to -\$10.224.63), $p<0.001$). Covariates associated with lower total costs were female sex (-\$3,895.93 (-\$5,829.10 to -1,962.76)) compared to male sex and residence in the South (-\$5,119.86 (-\$7,368.74 to -\$2,870.98)) compared to the Midwest (all $p<0.05$). Covariates associated with higher 1-year total incremental costs included: CDC Stage 3 HIV/AIDS (\$15,097.94 (\$12,141.90 - \$18,053.98)), Hepatitis C (\$27,003.19 (\$24,581.81 - \$29,424.57)), dual eligibility for Medicare and Medicaid (\$10,762.22 (\$9,490.36 - \$12,034.08)), and disability as the original reason for Medicare entitlement (\$5,457.17 (\$1,571.44 - \$9,342.90)) (all $p<0.05$). CCI scores of 1 (\$5,655.66 (\$3,677.98 - \$7,633.34)), 2 (\$9,384.02 (\$6,664.60 - \$12,103.44)), or ≥3 (\$28,249.96 (\$25,379.68 – \$31,120.24)) were also associated with higher 1-year total incremental direct medical costs compared to those with CCI scores of 0 (all $p<0.001$). However, no association was observed between those with and without HIV RNA genotyping, with and without CD4 counts, or pre-index adherence. No association was observed between most demographic groups, including Black, Hispanic, or Other race compared to White race, age 50 to 56 years, 57 to 64 years, or ≥65 years compared to those <50 years of age, or residence in the Northeast or West compared to the Midwest.

Table 30 lists the results of the sensitivity analyses from the 2SLS models by post-index adherence strata. The 1-year total incremental costs associated with the instrumented STR treatment variable among the ≥95% adherence strata were

Table 29. Two Stage Least Squares Model of the 1-Year Incremental Costs Associated with Single versus Multi- Tablet Regimen Use among Medicare Beneficiaries Living with HIV				
Covariates	Coefficient	Lower 95% Confidence Interval	Upper 95% Confidence Interval	*p*
Instrument Level				
MTR		*reference*		
STR	-$13,487.70	-$16,750.77	-$10,224.63	<.01
Age Groups				
<50 years		*reference*		
50-56 years	-$2,949.45	-$6,147.34	$248.38	0.13
57-64 years	-$2,448.43	-$4,969.94	$72.92	0.23
≧65 years	-$4,307.46	-$8,915.21	$299.71	0.13
Sex				
Female	-$3,895.93	-$5,829.10	-$1,962.76	0.02
Male		*reference*		
Race/Ethnicity				
Black	$189.01	-$947.54	$1,325.56	0.91
Hispanic	$2,310.34	-$1,056.44	$5,677.12	0.40
Other/Unknown	$1.40	-$5,557.59	$5,560.39	1.00
White		*reference*		
Original Reason for Eligibility				
Aged		*reference*		
Disabled/ESRD	$5,457.17	$1,571.44	$9,342.90	0.04
Dual Eligibility Medicare-Medicaid				
No		*reference*		
Yes	$10,762.22	$9,490.36	$12,034.08	<.01
CDC Stage 3 (CD4<200)				
No		*reference*		
Yes	$15,097.94	$12,141.90	$18,053.98	<.01
Charlson Comorbidity Index Score				
0		*reference*		
1	$5,655.66	$3,677.98	$7,633.34	<.01
2	$9,384.02	$6,664.60	$12,103.44	<.01
≧3	$28,249.96	$25,379.68	$31,120.24	<.01
Hepatitis C				
No		*reference*		
Yes	$27,003.19	$24,581.81	$29,424.57	<.01
Region				
Midwest		*reference*		
Northeast	-$2,757.87	-$5,635.77	$120.97	0.24
South	-$5,119.86	-$7,368.74	-$2,870.98	0.02
West	-$2,167.84	-$5,066.37	$730.69	0.39
HIV RNA Genotyping				
No		*reference*		
Yes	-$460.79	-$6,383.39	$5,471.82	0.91
CD4 Count				
No		*reference*		
Yes	$2,653.10	-$2,534.09	$7,840.29	0.53
Pre-Index Adherence	-$1,960.31	-$5,148.25	$1,227.63	0.46

*Controlling for Year Fixed Effects

-$10,922.57 (-$14,069.75 to -$7,875.40) (p<.001), which included 81.33% (n=5,729) of the sample. The coefficient on the instrumented treatment variable was not significant in both the 85-94% and <85% post-index adherence groups (all p>0.05). All sensitivity analyses by ART class inclusion showed lower 1-year total incremental healthcare costs associated with STR: ≥1 NRTI (-$13,002.15 (-$16,880.13 to -$9,124.18)), 1 INSTI (-$21,614.51 (-$27,677.91 to -$15,551.10)), and no PIs (-$13,238.85 (-$20,093.66 to -$6,384.04)) (all p<0.001).

Table 30. One-Year Incremental Costs Associated with Single versus Multi- Tablet Regimen Use among Medicare Beneficiaries Living with HIV by Post-index Adherence Strata

Strata	**Coefficient**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**	***p***
≧95% Adherence (n=5729)				
IV MTR (n=4690)	*reference*			
IV STR (n=1039)	-$10,922.57	-$14,069.75	-$7,875.40	<.01
85-94% Adherence (n=539)				
IV MTR (n=461)	*reference*			
IV STR (n=78)	-$41,864.84	-$84,802.86	$1,073.17	0.07
<85% Adherence (n=776)				
IV MTR (n=624)	*reference*			
IV STR (n=152)	-$14,613.56	-$29,882.36	$655.07	0.06

*All models fully adjusted for age, sex, race, dual eligibility, original reason for entitlement, region, CDC Stage 3 HIV/AIDS, Hepatitis C, CCI Score, HIV RNA Genotyping, CD4 Count, Pre-Index Adherence, and Year Fixed Effects.

Table 31. One-Year Incremental Costs Associated with Single versus Multi- Tablet Regimen Use among Medicare Beneficiaries Living with HIV by ART Class Components

Strata	**Coefficient**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**	***p***
≧1 Nucleoside Reverse Transcriptase Inhibitor (NRTI) (n=5,992)				
IV MTR (n=4,781)	*reference*			
IV STR (n=1,211)	-$13,002.15	-$16,880.13	-$9,124.18	<.01
1 Integrase Strand Transfer Inhibitor (INSTI) (n=4,607)				
IV MTR (n=3,682)	*reference*			
IV STR (n=925)	-$21,614.51	-$27,677.91	-$15,551.10	<.01
No Protease Inhibitor (PI) (n=4,587)				
IV MTR (n=3,466)	*reference*			
IV STR (n=1,121)	-$13,238.85	-$20,093.66	-$6,384.04	<.01

*All models fully adjusted for age, sex, race, dual eligibility, original reason for entitlement, region, CDC Stage 3 HIV/AIDS, Hepatitis C, CCI Score, HIV RNA Genotyping, CD4 Count, Pre-Index Adherence, and Year Fixed Effects.

Discussion

Our 2SLS model results indicate STR are associated with significant annual cost savings ($13,487 USD) among Medicare beneficiaries living with HIV. This is substantial as average per capita Medicare spending on PLHIV was approximately $45,489, with 59% ($26,761) going towards prescription drugs at the beginning of our study (2014).[28] While growth in healthcare costs exceeded inflation during our study period (2014-2019),[17] this is a non-trivial amount with potential to be more widely realized with the expansion of STR use. Contrary to findings in prior studies,[12,14,52] STR was found to be cost-saving among strata of beneficiaries with greater than 95% post-index adherence. Over 80% of our sample was in this stratum demonstrating the high levels of adherence characteristic of adults aging with HIV. This relationship may differ among Medicare beneficiaries due to greater comorbidity and polypharmacy burden, which have the potential to reduce adherence despite observed drug-on-hand or reduce the ART to subtherapeutic levels. The treatment coefficients among those with adherence 85-94% and <85% were non-significant, and the wide confidence intervals and small sample sizes in these strata make us more cautious in our interpretation.

In sensitivity analyses of regimens containing at least one NRTI we assessed the impact of excluding patients who may have resistance to NRTIs or other unobserved factors that would lead a provider to select a nuc-sparing regimen (i.e., a regimen that does not include an NRTI) (**Table 31**).[93] We found the point estimate and confidence intervals overlapping our main model estimate indicating this is unlikely to be a significant source of bias in our study. We found similar findings when excluding beneficiaries on PI-based regimens due to the lack of multiple PI-inclusive STR options[94] though the confidence intervals were much wider. Among regimens including an INSTI, STR were associated with greater cost-savings ($21,614.51) compared to MTR though again the confidence intervals were much wider and overlapping those of our primary estimate. This subgroup is of particular interest as the prevalence of INSTI-based regimens continues to increase.[94] Choice of INSTIs is limited by the fact that Dolutegravir is the only INSTI available as both STR and MTR, while Raltegravir is only available as MTR and Elvitegravir and Bictegravir are only available as STR (**Appendix Table 15**). This lack of parity and Raltegravir's availability as only twice-daily dosing for a majority of the study period[95] adds further uncertainty to the analysis that we would be unable to assess except in comparing those on Dolutegravir-based regimens, which would limit our sample considerably.

The large residual imbalances in ART regimen components (**Table 27**) is multifactorial and expected as we designed our study to compare all HHS-sanctioned regimens without respect to class. The inclusion of at least one NRTI in nearly all STRs (**Table 27**) is a function of both the strength of evidence behind NRTI regimens and the availability of only a single nuc-sparing (i.e., no NRTI component) STR (Juluca®), which is a two-drug regimen indicated for patients who have been virally suppressed for at least 6 months.[96] As almost two-thirds of MTR included an NRTI it appears that choice of a nuc-sparing regimen is not a significant driver for prescribing MTR over STR in this sample (**Table 27**). We are unable to assess why a nuc-sparing MTR regimen was prescribed in our sample, but it is likely due to NRTI drug resistance, past patient adherence difficulty leading a provider to select a nuc-sparing regimen, or patient preference.

The large differences in PI use between groups is driven by the availability of only one PI-inclusive STR (Symtuza®) and the drug's approval late in our study period (**Table 27**). In post-hoc analyses of 2019 data, we found greater prescribing of PI-inclusive STR though it still remained far below the incidence of PI-inclusive MTR (17.63% vs. 49.89%) (data not shown). Although the instrument improved the balance of ART classes, large standardized differences persisted as expected. This imbalance does not appear to significantly impact results due to the requirement of an HHS approved regimen in both groups and their respective high levels of effectiveness when taken as prescribed. However, future research with larger sample sizes and potentially greater parity in regimen availability would help further understanding of the real-world effectiveness of regimen choice among this vulnerable population of Medicare beneficiaries.

We are confident in the strength and validity of our instrument due to the significant Durbin Score and Wu-Hausman statistics (**Appendix Table 19)**, the large and statistically significant F statistic (1,525.47, $p<0.001$) and large partial r^2 (0.32) (**Appendix Table 20),** coupled with the substantial proportion of compliers in our study (53%) (**Appendix Table 18**). Demographically, our sample was well-balanced with residence in the Midwest (SDiff=0.17), the only variable with a standardized difference >0.11 (0.2*0.53 proportion compliers) **(Table 26**). More importantly the improvement in balance of clinical covariates between the predicted treatment groups, including CCI scores, HIV RNA genotyping, Hepatitis C, and pre-index adherence all support the strength and validity of our prescriber preference IV (**Table 26**).

All IV coefficients were non-significant in the fully adjusted models when regressing the covariates on the IV (all $p>0.05$) supporting the conclusion that there is no violation of the exclusion restriction (**Appendix Table 21**). The association between the IV and a confounder can indicate a violation as it is seen as a sign that the IV may also be associated with unmeasured confounders.[97] The relationships that may be indications of differences in prescribing behavior due to greater health deficits, include CCI scores ≥3 and residence in the South where the prevalence of chronic disease, poverty, other barriers to healthcare exceed national estimates.[98] The improvement in balance of beneficiaries with CCI scores ≥3 and other measures of disease severity in our models indicate that our IV is likely strong enough to balance unmeasured health deficits as well (**Table 26**). Further, we demonstrated that our IV is not associated with the most common comorbid conditions in the providers' patient populations (**Appendix Table 22**). We did find statistically significant differences in the prevalence of non-ART prescriptions and ART prescribing volume, but we would argue this is likely attributable to the large number of prescriptions assessed rather than clinically significant differences due to the relatively small difference in proportions (**Appendix Table 22**). Also, the assessment of single drugs by generic name instead of classes (e.g., prevalence of any statin) likely also explains some of the observed variation. The non-significant associations, improvement in balance between instrument levels, lack of association of the instrument with other treatments, and inclusion of these covariates in all models led us to conclude that the likelihood of violation of the exclusion restriction in our study was low.

The strengths of the study include the use of claims data to explore previously unexamined total healthcare costs in adults living with HIV in Medicare. This allows for the investigation of a unique population that is understudied and largely excluded from RCTs due to their clinical complexity, but increasingly represent the realities of long-term HIV infection. The use of an instrumental variable approach and a new user design supports inference based on our findings by accounting for the most common sources of bias in observational studies. However, our study is not without limitations with the most pressing being the reliance on theoretical and conceptual justification of the strength of our instrument to address nonrandom treatment assignment. Failing to satisfy the assumptions required would lead to bias in our estimates and potentially incorrect conclusion of the cost-savings of STR due to the accompanying large standard errors. We have attempted to theoretically and conceptually justify our instrument and provided quantitative evidence in support of our conclusions where possible. Although, we are unable to definitively measure beneficiaries' $CD4^{+}$ counts that may be associated with both the exposure and the outcome,[29,76,78] our instrument did improve balance between treatment groups based on our measure of CDC Stage 3 HIV disease. In addition, our study is subject to the limitations of claims data to measure diseases and their severity though we have attempted to account for the most likely sources of confounding. Our measures of medication use reflect dispensed medications and not consumed medications, which is of particular importance in HIV if patients are filling, but not taking, their regimens as prescribed. As an outcome measure, total direct medical costs are known to contain errors due to the complexity of reimbursement in the US and nature of administrative data.

Conclusion

Our findings demonstrate that STR are associated with significantly lower 1-year total incremental direct medical costs compared to MTR. This study addresses a gap in the literature by demonstrating the total costs associated with different ART formulations among a novel and growing population—Medicare beneficiaries living with HIV. Further, it demonstrates the potential future cost-savings for Medicare if STR utilization continues to increase and greater diversity in STR class composition continues to grow. Future research employing larger sample sizes and precise clinical measures of key indicators of HIV disease severity (i.e., viral load, CD4 count, and resistance profiles) would build further confidence in these findings and conclusions.

5 Aim 3 Manuscript

Aim 3) Estimate the budget impact of single tablet regimen (STR) and overall antiretroviral utilization trends on inpatient, emergency department, outpatient, prescription drug, and total direct medical costs among people living with HIV in Medicare.

Abstract

Background Increasing utilization of single tablet antiretroviral (ART) regimens (STR) is associated with reductions in healthcare resource utilization (HcRU) and costs among people living with HIV, but concurrent growth in ART prices poses significant budget implications for Medicare. Limited generic competition is likely to be further depressed by the advent of novel, patentable dosing methods, such as the first long-acting injectable, Cabenuva®. The objective of this budget impact model is to estimate the annual budget impact among beneficiaries living with HIV of expanding use of STR and other novel ART therapies from the Medicare payer perspective using Chronic Conditions Data Warehouse (CCW) claims data over a 5-year time horizon.

Methods We built a budget impact model in Microsoft Excel using cost and utilization estimates among beneficiaries living with HIV from the CCW (2014-2019). Model inputs included the annual cost and utilization of ART products and average annual inpatient (IP), emergency department (ED), outpatient (OP), ART, and non-ART prescription drug utilization. HcRU and related costs were estimated among four subgroups: recipients of STR, multi-tablet regimens, salvage regimens, and untreated beneficiaries to better characterize heterogeneity while preserving a simple cost calculator approach. Model outputs included the total annual budget impacts over the five-year time horizon, overall

and among each HcRU category. Sensitivity analyses were used to characterize potential variation in utilization and cost trends.

Results Our model predicted $1.8 billion in additional costs in year 5 under a scenario where current trends in ART utilization and list prices continue compared to a scenario where they remain at 2019 levels. The excess costs were driven by $2.3 billion in greater ART spending among the 147,953 beneficiaries living with HIV despite savings of $199 million in IP, $5.7 million in ED, $111 million in OP, $166 million in non-ART prescription drug costs. These savings were accompanied by 10,601 fewer IP, 7,635 fewer ED, 75,588 fewer OP, and 432,894 fewer non-ART prescription drug events. The base case scenario was most sensitive to inclusion of a linear trend in ART utilization and the cost of ART. In linear trend comparisons, uptake of the first long-acting injectable, Cabenuva®, showed small cost savings in nearly all scenarios ($19-203 million) except when ART price increases exceeded those predicted in the base case.

Conclusion Our model predicted $1.8 billion in additional costs to Medicare in year 5 if current trends in ART utilization and list prices continue. Despite lower spending in all other HcRU categories, $2.3 billion in additional ART costs drove this budget impact. The corresponding reduction in HcRU under this scenario is highly valuable but demonstrates the fiscal impact of current trends in ART costs. The next decade is likely to see significant changes in the number of Medicare beneficiaries living with HIV and the availability of novel and likely more expensive therapies. Though still small in number, the costs of caring for people living with HIV in Medicare will continue to grow as a proportion of total spending and will be markedly impacted by any policies aimed at controlling expenditures on prescription drugs.

Introduction

The demonstrated uptake of newer, branded antiretroviral therapies (ART) among Medicare beneficiaries living with HIV will have significant budget implications if current trends continue. Increasing utilization of single tablet regimens (STR) is associated with reductions in healthcare resource utilization (HcRU) and costs, but these savings are offset by higher ART spending overall and as a proportion of total direct healthcare costs. This is due to ART list prices exceeding inflation—73% of all ART price increases exceeded inflation by at least 5% between 2016-2017.[17] As a protected class under Medicare's Part D program,[99] plan sponsors are required to cover all ART creating little incentive for manufacturers to contain prices.[16] There is currently very little generic competition within ART and this is expected to remain the case throughout this decade as newer formulations have replaced those with the most potential to entice significant generic utilization (e.g., tenofovir alafenamide in place of tenofovir disoproxil fumarate).[16,100,101]

Novel routes of administration are likely to further discourage generic use and competition, such as the first long-acting injectable, Cabenuva® (cabotegravir/rilpivirine), which was approved by the Food and Drug Administration (FDA) in January 2021 and reimbursed under Medicare Part B as a provider administered drug.[38] Other novel methods, such as injectables dosed less often (e.g., every 6 months), implantables, and less frequent oral dosing (e.g., once-per-week) are also being studied in clinical trials.[39] These novel therapies have the potential to garner significant market share if they demonstrate the expected improvements in adherence and thus viral suppression. Even if real world effectiveness is comparable to existing oral therapy, especially among older Medicare beneficiaries who are likely already highly adherent, initial patient preference information indicates significant demand due to quality-of-life improvements.[102] Utilization and pricing of such therapies are challenging to predict, especially due to the need for provider administered injections in the case of Cabenuva®. However, provider incentives to prescribe such therapies due to current reimbursement under Part B (i.e., 'buy and bill'),[103] which includes a percentage of the drug price and an administration fee, suggests utilization and spending for these therapies will comprise a significant proportion of market share.

Total Medicare expenditures on ART exceeded $5.5 billion in Fiscal Year (FY) 2017,[17] while the estimated number of Medicare Fee-For-Service (FFS) beneficiaries living with HIV has hovered around 150,000 since 2010.[104] Based on the age distribution of people living with HIV in the US,[27] this number is unlikely to change significantly until the latter half of this decade as a greater number of individuals age into Medicare eligibility. Although Medicare beneficiaries living with HIV represent a minor proportion of total Medicare enrollment (i.e., 0.4% of 37,745,095 total Fee-for-Service beneficiaries in 2019),[104] they account for a sizable proportion of total Part D expenditures (e.g., >5% of $102 billion total in 2019).[105] The objective of this budget impact analysis (BIA) is to estimate the annual budget impact among beneficiaries living with HIV of expanding use of STR and other novel therapies from the Medicare payer perspective using Chronic Conditions Data Warehouse claims data over a 5-year time horizon.

Methods

This budget impact model (BIM) was built in Microsoft Excel (Microsoft Corp., Redmond, WA) following The Professional Society for Health Economics and Outcomes Research (ISPOR) Principles of Good Practice for Budget Impact Analysis.[106,107] Model inputs were drawn from a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) (2014-2019) where available. When we were unable to estimate input parameters from claims we relied on prior academic, governmental, industry, and payer publications, CMS enrollment reports, and the Medicare Part B and D Drug Spending dashboards.[108,109]

A simple cost-calculator approach was selected as the ISPOR guidelines recommend using the least complex analytic approach capable of answering the budget impact question at hand as these models are intended for an end-user without significant modeling training or expertise.[106,107] The cost calculator approach provides estimates with and without the change in the treatment mix.[110] This approach relies on simple formulas and is appropriate when changes in treatment sequences are not expected, and treatment- and disease- related outcomes do not differ significantly between the treatment mix scenarios.[110] A static model was selected as the size and disease severity mix of the population is unlikely to change significantly in the next 3 to 5 years. however, the model was built to enable future users to vary these parameters if needed. Although the population of people over age 65 living with HIV is growing, there has been no growth in the Medicare FFS population with HIV over the last twelve years. We are unaware of any publications documenting this phenomenon, but we suspect that a significant proportion of these beneficiaries are enrolling, or being automatically enrolled, in Medicare Advantage and its Special Needs Plans for HIV disease and dual eligibles.

Perspective, Population, and Setting

We assumed a Medicare payer perspective. The study population included all Fee-for-Service Medicare beneficiaries living with HIV as estimated by the Centers for Medicare and Medicaid Services (CMS) as of 2019.[104] We used the CMS estimate as opposed to extrapolating from the 5% sample of CCW data as it would have resulted in an overestimate. As Medicare spending is mandatory and thus less susceptible to consequences of appropriations processes, we assumed features of the healthcare system would remain unchanged throughout the time horizon. Further, we assumed ART would remain a protected class throughout the respective time horizon, thus administrative hurdles (e.g., utilization management strategies) are minimal and constant.[99] We assumed a five-year time horizon with annual estimates based on ISPOR guideline recommendations.[106,107]

Treatment Mix

The current treatment mix scenario included all ART with at least one drug claim in 2019. We fit a linear trend to predict changes in ART utilization over the five-year study horizon using data from 2014 to 2019. The market share of each antiretroviral drug, by generic name, was estimated from claims as the proportion of total days covered annually. We then estimated the total proportion of STR formulations used in combination with other products in order to attribute this use to the MTR subgroup; similar estimates were calculated among both STR and MTR products used by beneficiaries on salvage regimens (i.e., 5 or more medications).[7] These three ART utilization estimates and the estimated proportion of untreated beneficiaries allowed us to account for the assumed differences in healthcare resource utilization (HcRU) and related costs among these subpopulations. A floor of zero percent utilization was set to prevent negative utilization. All assumptions are listed in **Appendix Table 23**.

We assumed all changes in utilization in the current treatment mix resulted in substitution of one product or regimen for another. Expansion of the treated population due to uptake of newer therapies is unlikely as nearly 99% of Medicare beneficiaries living with HIV are diagnosed and in treatment.[3,28,60] Novel combinations of newer therapies may be more likely than expansion, but this phenomenon was deemed unlikely as three or four drug regimens will suffice for the vast majority of patients,[111] thus requiring substitution rather than addition. The model does not account for off-label use among beneficiaries without HIV.

The new treatment mix scenario in the base case included all drugs in the current treatment mix without a linear trend predicting future ART utilization; three additional therapies approved in 2020 (i.e., Rukobia®) and 2021 (i.e., Cabenuva® and Vocabria®) were also included in the new treatment mix. No trend was selected for the base case comparison to capture the scenario where all beneficiaries eligible for STR had already switched (i.e., MTR is the optimal regimen). Changes in ART utilization under this scenario were only allowed within the respective utilization groups. For example, Biktarvy® utilization was allowed to increase as a proportion of total STR or MTR utilization, but overall STR and MTR utilization were not allowed to exceed the level observed in 2019 claims. As no claims data and limited external data were available for the three new therapies, we estimated the approximate market share for these products based on preliminary data from the Medicare Part D Drug Spending Dashboard[109] (Rukobia® only) and uptake of ART medications with similar indications or class composition. We used Trogarzo®, a provider-administered infusion primarily indicated for highly treatment experienced patients who fail to achieve viral suppression on other regimens,[112] to estimate Rukobia's® utilization uptake. Although Rukobia® is an oral medication it shares a similar indication for patients with multi-drug resistant HIV and both are prescribed in combination with other ART,[112,113] thus we assumed its adoption would be similar and in competition with Trogarzo®. As Cabenuva® is the first long-acting injectable approved, we used Juluca®—the first two-drug regimen approved—to approximate market share and uptake due to both being first to market in their respective kind, both being two drug regimens, and the similarity in drug components: Juluca® contains rilpivirine and dolutegravir, and Cabenuva® contains rilpivirine and cabotegravir—a structural analogue of dolutegravir.[114] We assumed Vocabria®, the oral tablet of cabotegravir, would only be used for the indicated one-month lead-in prior to initiation of Cabenuva® injections and Cabenuva® would not be used in conjunction with other ARTs.

These comparators were also the primary target for substitution effects of these novel medications. In the new treatment mix, 50% of Rukobia®'s total market share was subtracted from Trogarzo®'s and 25% was added on to salvage regimens in the current treatment mix- the only instance where we did not model substitution due to the drugs explicit indication and clinical trial design.[111] The final 25% was subtracted from the market share of salvage regimen components proportional to the respective component's utilization in salvage regimens in the current treatment mix. We assumed 33% of

Cabenuva®'s market share would come from Juluca® and 33% would come other INSTI-based STRs—Triumeq®, Stribild®, Genvoya®, Biktarvy®, and Dovato®—proportional to the respective component's overall utilization as these have the same class compositions as the comparator treatments in the FLAIR and ATLAS trials demonstrating Cabenuva®'s non-inferiority.[102] The last 34% was subtracted from the market share of all other MTR components proportional to the respective component's utilization in the current treatment mix.

Antiretroviral Costs

The average annual costs for ART in the current treatment mix were estimated using the covered Part D payment amount and the low-income subsidy from Part D claims (2014-2019). This method allows us to calculate the average cost to the payer without burdening the model with the complexities of Part D benefit phases and differences in reimbursement.[99] Of note, approximately 92% of beneficiaries reached catastrophic coverage (i.e., Medicare covers 80% of drug costs)[99] by the end of February in each year analyzed (data not shown). We then fit a linear trend to predict the ART cost increases over the five-year time horizon.

As a provider administered drug covered under Medicare Part B, the cost of Cabenuva® was estimated as the cost of the drug plus a percentage and an administration fee under the physician fee schedule.[103] The price of Cabenuva® in the first year was the Wholesale Acquisition Cost[115,116] plus 3% to reflect CMS' approach to reimbursement prior to the availability of the Average Sales Price (ASP).[117] We used the ASP plus 6% for years 2 through 5 from the January 2022 ASP Drug Pricing File reflecting 2021 third quarter sales data.[118] We then estimated the proportion of beneficiaries who are Qualified

Medicare Beneficiaries (QMBs) as Medicare covers the 20% coinsurance on Part B drugs for these beneficiaries in addition to the 80% coverage for all FFS beneficiaries.[119] We assumed the proportion of QMBs receiving Cabenuva® and Trogarzo® would be identical to the proportion of QMBs in the full population. The total cost of these therapies was multiplied by the proportion paid by Medicare (i.e., 80% or 100%) then by the proportion of QMBs and summed. Predicted price increases over the time horizon were estimated from their respective comparator. Drug rebates were not included in the model as they are delivered to the Part D sponsor. Discounting was not applied per the ISPOR BIA guidelines[106] as the budget holder's interest lies in the impact in each budget year as opposed to the net present value.

Healthcare Resource Utilization and Costs

We estimated the average annual number of inpatient (IP) visits, emergency department (ED) visits, outpatient (OP) visits, and non-antiretroviral (non-ART) prescriptions among STR, MTR, salvage regimen recipients, and untreated beneficiaries from claims data. Annual HcRU among these subgroups was held constant throughout the time horizon. Average HcRU-related costs per event were also estimated from claims data, but only held constant throughout the time horizon in the no linear trend scenarios; we fit a linear trend to predict changes in HcRU-related costs in the linear trend scenarios based on 2014-2019 CCW data. We assumed Cabenuva® recipients would have identical HcRU and related costs per event as STR recipients; however, the additional OP utilization costs required for in-office injections were captured under ART costs. Definitions of HcRU categories in CCW claims can be found in Aims 1 and 2. Indirect costs, such as productivity losses, were not included per ISPOR recommendations[106] as they are not attributable to Medicare's budget.

Model Outputs

The primary model outputs are the total annual budget impacts—the difference between the current treatment mix with linear trend and the new treatment mix with no trend in the base case. All sensitivity analyses utilize this base case current treatment mix with linear trend and vary parameters under the new treatment mix scenario. Additional model outputs include total annual IP, ED, OP, ART, and non-ART prescription drug utilization and related costs.

Analyses

The total annual budgets were calculated by summing the respective HcRU category costs across all subgroups—STR, MTR, salvage, and untreated. ART costs were calculated by multiplying the treated population by ART utilization per drug and the average annual drug cost as seen in Equation 1 where 'n' indexes each unique generic drug name.

Equation 1

$$\Sigma_{\text{Drug 1-n}} [(\text{Population}*\text{Proportion Treated})*\text{ART utilization}_{\text{Drug 1-n}})*\text{ART cost}_{\text{Drug 1-n}})]$$

HcRU-related costs were calculated by multiplying the treated population by the subgroup proportions - STR, MTR, salvage regimen, and untreated. Each subgroup population was then multiplied by their respective annual HcRU estimate and average HcRU cost per event. All subgroup estimates were then summed to calculate each respective HcRU category budget shown in Equation 2.

Equation 2

$$\Sigma_{STR/MTR/Salvage/Untreated}\ [((\text{Treated Population})*\text{HcRU}_{STR/MTR/Salvage})*\text{HcRU costs}_{STR/MTR/Salvage}))+((\text{Untreated}*\text{HcRU}_{Untreated})*\ \text{HcRU costs}_{Untreated})]$$

The total annual budget was calculated as the sum of equations 1 and 2 for each treatment mix scenario. The difference between the current and new treatment mix budgets is the annual budget impact.

Sensitivity Analyses

Uncertainty is important to represent in a BIA, thus one-way sensitivity and scenario analyses were used to characterize a range of plausible alternatives per ISPOR guideline recommendations.[106] We attempted to address several types of uncertainty, including parameter uncertainty, which concerns the values chosen as inputs for the model and the extent to which they represent the *true* value of those parameters.[120] We addressed parameter uncertainty by varying the cost and utilization inputs in the sensitivity analyses (SA) described below. Structural uncertainty concerns the correct functional form for combining model inputs.[120] We addressed structural uncertainty by varying the cost and utilization among STR and MTR subgroups and by including a no trend and a linear trend scenario in each SA described below. We attempted to balance the reality of differential disease severity, utilization, and costs by building in these broad subgroups while maintaining a simple cost calculator approach. Methodological uncertainty concerns lack of clarity about the most appropriate analytic approach.[120] We addressed methodological uncertainty by choosing a five year time horizon with annual budget impact estimates as it includes a three year estimate and these are the two horizons recommended by ISPOR.[106,107] The reporting of annual budgets for each HcRU category in addition to the total budget could also be seen as an approach to account for methodological uncertainty.

Details of all sensitivity analysis scenarios of interest are listed in **Appendix Table 24**. These can be grouped into two broad categories where the new treatment mix is based on the assumption of no linear trend in total STR and overall ART utilization as seen in the base case and new treatment mix scenarios involving a linear trend in STR and ART utilization in concert and competition with novel therapies. Other scenarios explore the impact of various differences in utilization and costs. The magnitude of changes in the SAs was selected based on a best case, worst case scenario as recommended by the ISPOR guidelines.[106,107] All inputs apart from those specified in **Appendix Table 24** were identical to the respective base case or adjusted using identical criteria applied in the base case. Costs and utilization among the salvage regimen subgroup, including Rukobia® utilization, were not varied in any scenario as the population is small and even large variation in utilization is unlikely to significantly impact annual budgets. However, the model is built so a user could implement such sensitivity analyses if required.

We originally proposed a sensitivity analysis scenario to demonstrate the potential impact of the Most Favored Nation Model, an interim final rule published on November 27, 2020,[121] which would have changed reimbursement for Medicare Part B physician administered drugs through use of international reference pricing. We did not proceed with this scenario as the rule was met with immediate legal challenges leading to an injunction[122] halting its implementation and the eventual withdrawal of the proposal altogether.[123] We also chose not to include scenarios where novel, first-in-class therapies and dosing methods entered the market at the end of the time horizon due to the relevant trials being placed on full or partial clinical holds in December 2021[124,125] making market entrance unlikely within the study horizon.

Results

Base Case

In the base case, the total predicted budget impact in year 5 was over $1.8 billion in additional costs under the current treatment mix among 147,953 Medicare beneficiaries living with HIV (**Figure 4**). Exact budget estimates overall and among each HcRU category by treatment mix scenario can be found in **Table 32**. The model predicted $13.1 billion in spending under the linear ART trend scenario compared to $11.3 billion under the no ART trend scenario. STR utilization grew to 82.31% by year 5 in the linear trend scenario compared to a small decrease to 53.75% under no trend due to shifts in market share to Cabenuva®. This growth in utilization occurred primarily among INSTI-based products: Biktarvy® (36.75%), Genvoya® (11.97%), and Triumeq® (11.62%). Utilization of Cabenuva® in the new treatment mix scenario was predicted to account for 3.04% of total market share in year 1 and 6.02% in year 5. The total annual cost of Cabenuva® ranged from $51,914 in year 1 to $60,160 in year 5.

The excess costs were driven by higher ART spending despite lower HcRU and related costs in the current treatment mix. The budget impact was largely accounted for

Table 32. Total Annual Budgets and Component Healthcare Resource Utilization Budgets by Treatment Mix Scenario, Base Case

	Year 1	Year 2	Year 3	Year 4	Year 5
Current Treatment Mix					
Antiretroviral	$6,768,705,832	$8,121,088,144	$9,270,915,444	$9,955,196,069	$10,491,626,980
Inpatient	$1,197,980,696	$1,104,890,919	$1,034,928,007	$1,007,033,593	$991,380,634
Emergency Department	$171,121,556	$169,089,324	$167,552,247	$166,950,441	$166,610,324
Outpatient	$593,136,038	$540,841,458	$501,544,098	$485,870,052	$477,075,885
Non-Antiretroviral	$1,156,264,089	$1,079,594,489	$1,021,961,012	$998,995,284	$986,105,236
Total Annual Budget	$9,887,208,211	$11,015,504,333	$11,996,900,808	$12,614,045,440	$13,112,799,060
New Treatment Mix					
Antiretroviral	$6,837,581,223	$7,147,645,718	$7,511,673,215	$7,871,990,197	$8,222,522,692
Inpatient	$1,192,890,290	$1,190,141,356	$1,187,172,565	$1,187,885,692	$1,190,844,460
Emergency Department	$171,510,421	$171,712,790	$171,838,929	$172,080,062	$172,374,487
Outpatient	$590,001,033	$588,312,261	$586,539,324	$586,815,695	$588,351,237
Non-Antiretroviral	$1,152,656,516	$1,150,699,423	$1,148,477,689	$1,149,328,912	$1,152,034,656
Total Annual Budget	$9,944,639,483	$10,248,511,548	$10,605,701,723	$10,968,100,559	$11,326,127,532
Total Budget Impact	-$57,431,272	$766,992,785	$1,391,199,085	$1,645,944,882	$1,786,671,528

Figure 4. Total Annual Budgets

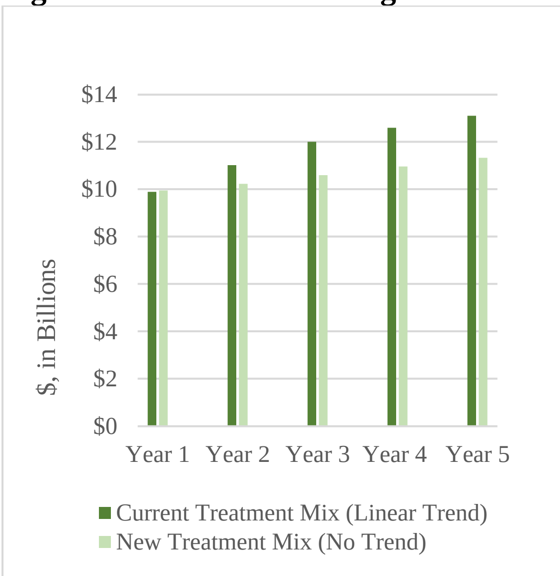


Figure 5. Total Annual Antiretroviral Prescription Budgets

Figure 6. Total Annual Non-Antiretroviral Prescription Budgets

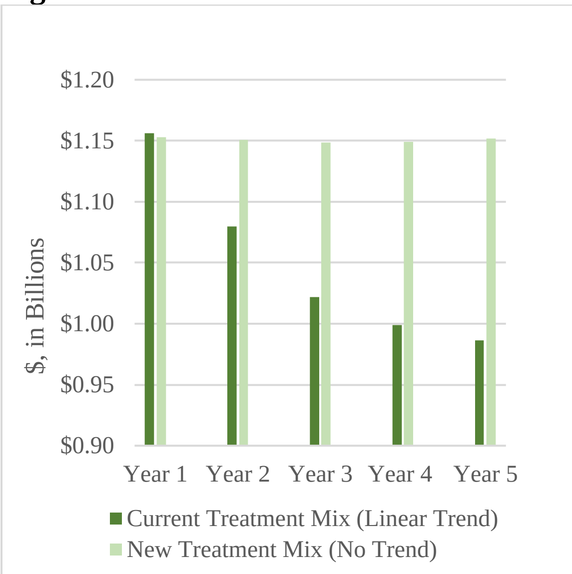


Figure 7. Total Annual Inpatient Budgets

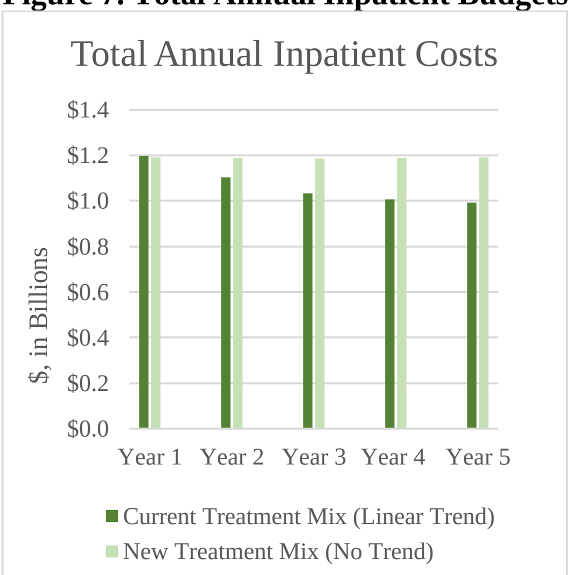


Figure 8. Total Annual Outpatient Budgets

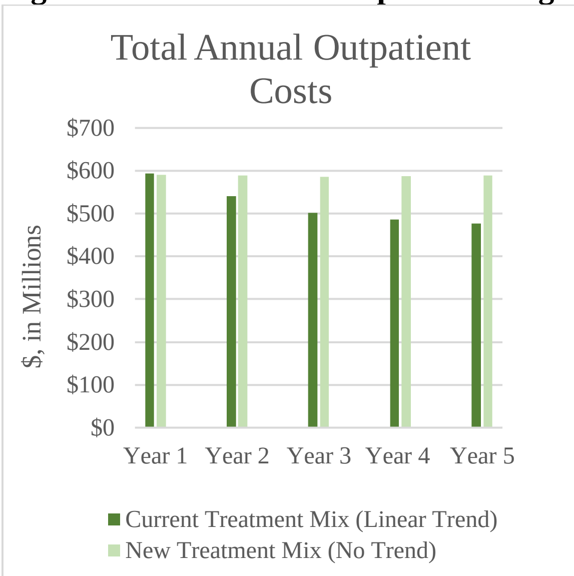
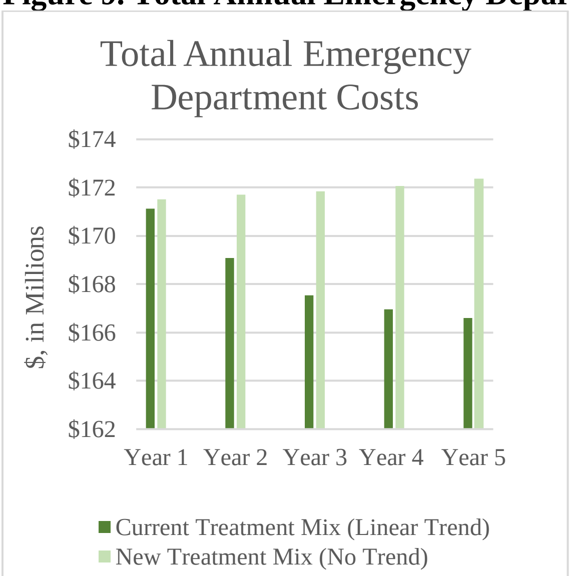


Figure 9. Total Annual Emergency Department Budget



by the $2.3 billion in additional ART expenditures under the current treatment mix compared to the new mix in year 5 ($10.5 vs. $8.2 billion) (**Figure 5**). The current treatment mix saw cost savings in all HcRU categories every year except year 1, which was also the only year the current mix was cost saving ($57 million). The annual HcRU-related savings in year 5 were predicted to be $199 million in IP costs, $5.7 million in ED costs, $111 million in OP costs, $166 million in non-ART prescription drug costs (**Figures 6-9**) under the current treatment mix. Total annual utilization was predicted to be lower among the current treatment mix in all HcRU categories every year except for IP utilization in year 1. By year 5 the increase in STR utilization was predicted to be associated with 10,601 fewer IP, 7,635 fewer ED, 75,588 fewer OP, and 432,894 fewer non-ART prescription drug events annually (**Figures 10-13**).

Figure 10. Total Annual Non-Antiretroviral Utilization

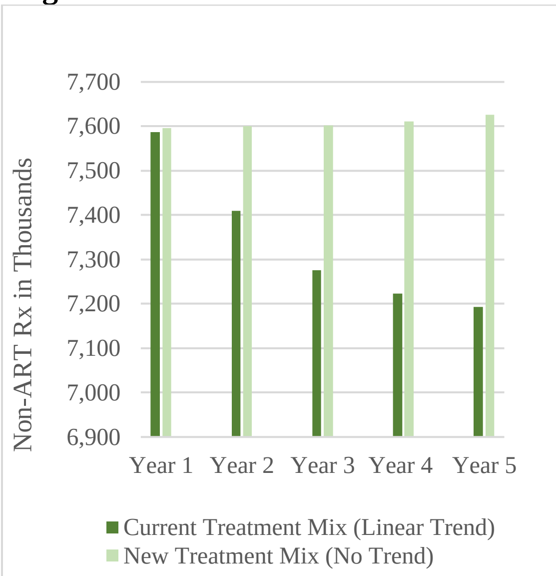


Figure 11. Total Annual Inpatient Utilization

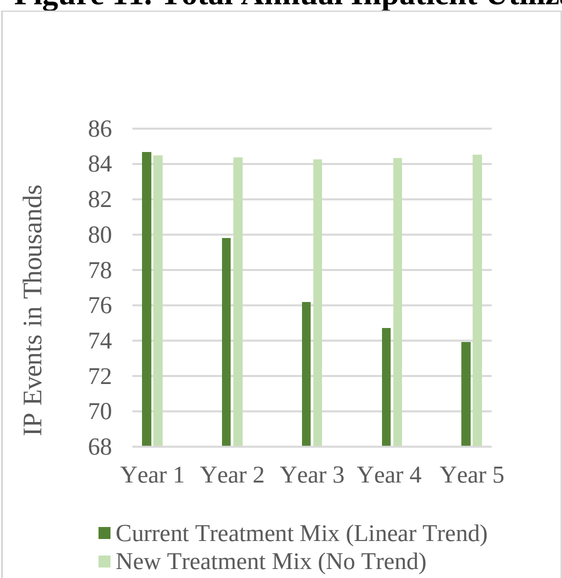


Figure 12. Total Annual Outpatient Utilization

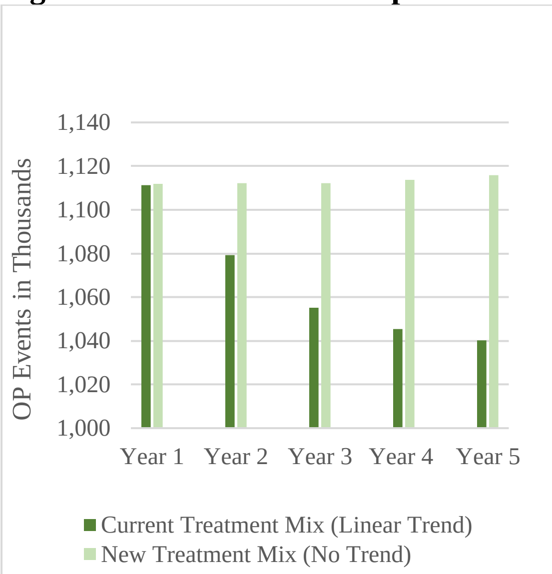
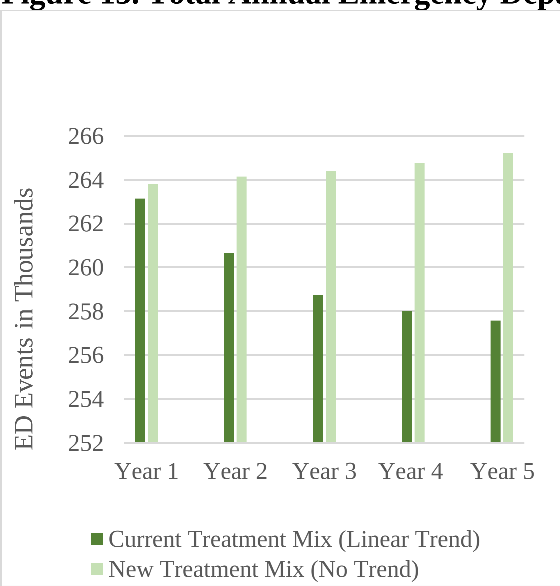


Figure 13. Total Annual Emergency Department Utilization

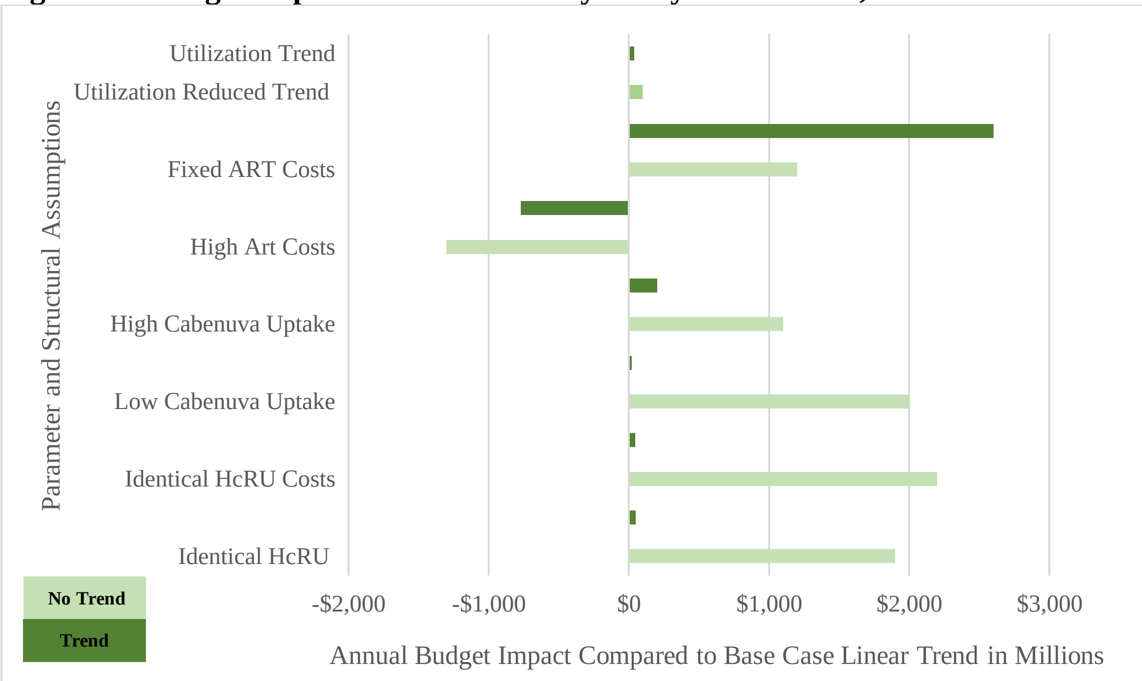


Sensitivity Analyses

The predicted budget impact in the base case scenario was most sensitive to the inclusion of a linear trend of ART utilization and the cost of ART (**Figure 11**). In year 5, SA #1 predicted $39 million in savings when Cabenuva® and Rukobia® were modeled as part of the new linear trend scenario. When the slope of the linear trend was reduced in the new treatment mix the base case linear trend scenario was associated with $98 million in additional costs in year 5. In the scenarios where the new treatment mix involved fixed ART treatment costs, the no trend scenario (SA #3) was associated with nearly $1.2 billion in savings and over $2.6 billion in savings in the linear trend scenario (SA #4) compared to the base linear trend in year 5. Under scenarios with ART cost increases 50% higher than the base case trend, the model predicted $1.3 billion in additional costs with no trend (SA #5) and $769 million in additional costs with a linear trend (SA #6) in year 5.

When high uptake of Cabenuva® was modeled, the scenario of no trend had a predicted $1.1 billion in cost savings (SA #7), while the linear trend had a predicted cost savings of over $203 million (SA #8) by year 5. Low Cabenuva® uptake was associated with approximately $2 billion in savings under the no trend scenario, but only $19 million in savings under a linear trend scenario in year 5. When HcRU costs per event were assumed to be identical between STR and MTR users, the model predicted $2.2 billion in cost savings under no trend and $45 million in savings under the new linear trend in year 5. Identical annual average HcRU between STR and MTR recipients resulted in a prediction of $1.9 billion in cost savings under the no trend scenario and $49 million in savings under the linear trend scenario in year 5.

Figure 14. Budget Impact Under Sensitivity Analysis Scenarios, Year 5



Discussion

Our budget impact model indicates that the price of antiretroviral therapy (ART) is the primary driver of overall budget growth compared to alternative scenarios among Medicare beneficiaries living with HIV. Our model predicted $1.8 billion in additional costs when ART utilization and related costs continue to increase as they did from 2014-2019 compared to remaining largely fixed at current levels of utilization and cost. This amount grew to as large as $2.6 billion when ART were fixed at 2019 estimates, but utilization changes continued. The only scenarios where the current treatment mix was cost saving was under scenarios where prices for ART grew to even higher levels over the time horizon- both when utilization remain unchanged or changed in similar ways to the base case. Despite these additional costs the changes in utilization under the linear trend in the base case and new mix scenarios represent significant improvements in other

HcRU. Though the reduction in costs compared to ART spending may be modest, the avoidance of nearly 11,000 hospitalizations, 8,000 emergency department visits, 76,000 outpatient visits, and 433,000 non-ART prescriptions likely represent significant improvements in beneficiary quality-of-life and health compared to the rates observed today.

The impact of utilization of the first long-acting injectable brought to market, Cabenuva®, can be most easily seen in the linear trend scenarios where all but one of these new treatment mixes was associated with cost savings compared to the base case- the greatest being the high Cabenuva® uptake scenario with $203 million in savings. While the uptake of Cabenuva® in Medicare is uncertain, the effect it may have on adherence and other HcRU in this population of Medicare beneficiaries is also unclear as they appear to demonstrate high levels of adherence to oral therapy based on findings in Aims 1 and 2. However, if uptake is high and the price of the injectable continues to rise it could have a significant impact on Medicare Part B spending- our model predicted year 5 spending on Cabenuva® ranging from $528 million to $1.1 billion. Cabenuva® was not yet approved and thus did not appear on CMS' initial lists of top 50 drugs targeted by the MFN Part B spending reforms,[103] but it has the potential to reach this threshold based on our projections. Future efforts to lower Part B drug spending would likely impact the therapy's pricing and potentially its availability though the magnitude will depend on the policies adopted.

We did not include two first-in-class ART therapies widely held as the most promising candidates to enter and garner significant market share[39] due to clinical trial pauses.[124,125] Islatravir, a nucleoside reverse transcriptase transfer inhibitor (NRTTI), had the highest probability of entering the market within the five-year time horizon, but 13 studies in various phases were placed on full or partial or clinical holds in December 2021,[124] making market entrance within the study horizon unlikely. Lenacapavir, a capsid inhibitor, was only beginning phase 3 trials in 2021, which made approval and marketing unlikely in the time horizon and even more so as the leading trial was voluntarily halted in December 2021[125] as the product was being studied in combination with Islatravir. These products and others are being tested as novel dosing schedules including other long-acting injectables with dosing up to 6 months apart, implantable products, and once-a-week oral dosing[39]. Though none of these are likely to enter the market during the study horizon they are indicative of transformative advances in HIV treatment and prevention synonymous with triple combination ART in 1995,[126] STR in 2006,[11] and pre-exposure prophylaxis in 2011.[127] Barring curative HIV therapy these novel treatments will undoubtedly have an impact on Medicare spending for beneficiaries living with HIV.

This study has several limitations including the lack of exact cost information due to the complexity of health care spending in the US. The method we used to predict future utilization is likely overly simplistic compared to market realities. We attempted to characterize plausible scenarios in our sensitivity analyses in order to assess the impact of such variation. Further, the crude subpopulations fail to capture the complexities of the disease state in addition to other chronic conditions. However, our study has several strengths including the use of the payer’s own claims data to estimate HcRU and related costs and use these as model inputs to predict the budget impact of future utilization and spending trends. We also built the model to allow for the end user to be able to easily change inputs (e.g., population size, disease severity mix, utilization trends) to incorporate more precise knowledge regarding costs and uptake.

Conclusion

Our model predicted additional costs to Medicare if current trends in ART utilization and list prices continue. In year 5, the current treatment mix was predicted to have $1.8 billion in additional spending compared to a scenario where ART utilization remained fixed at 2019 levels. These additional costs were driven by $2.3 billion in additional ART spending despite lower spending in all other HcRU categories. The corresponding reduction in HcRU under this scenario is highly valuable but demonstrates the fiscal impact of current trends in ART costs. The next decade is likely to see significant changes in the number of Medicare beneficiaries living with HIV and the availability of novel and likely more expensive therapies. Though still small in number, the costs of caring for people living with HIV in Medicare will likely continue to grow as a proportion of total spending and will be markedly impacted by any policies aimed at controlling expenditures on prescription drugs.

6 Overall Conclusions, Implications, and Future Research

The overall objective of this dissertation was to detail patterns of STR and MTR use and the associated healthcare utilization, incremental costs, and overall budget impact among Medicare beneficiaries living with HIV. We relied on Andersen's Behavioral Model, Generalized Estimating Equations (GEE), instrumental variable regression, and budget impact modeling to answer these questions.

In aim 1, we conducted a repeat cross-sectional study using a 5% random sample of Medicare Fee-for-Service beneficiaries from the Chronic Conditions Data Warehouse (CCW) to describe trends in STR and MTR use from 2014 through 2019. We also compared annual trends in monthly inpatient (IP), emergency department (ED), outpatient (OP), and non-antiretroviral (non-ART) and antiretroviral (ART) prescription drug utilization and associated costs stratified by STR and MTR receipt. We hypothesized STR utilization and costs would increase, while MTR costs would also increase despite decreases in utilization. Further, we hypothesized that STR use would be associated with lower healthcare resource utilization and costs overall.

To contribute a respective month to the analysis, we required Medicare enrollment in Parts A, B, and D and 80% of days covered by a complete ART regimen. Healthcare resource utilization was described as the proportion of person-months with any utilization in each category. As the study was conducted from the Medicare payer perspective, only costs paid by Medicare were analyzed and were adjusted for inflation to 2019 US dollars. To account for clustering at the beneficiary-level we employed GEE for both the binary (HcRU) and continuous (costs) outcome models and reported the average marginal effect (AME) and 99% confidence intervals.

Overall, STR receipt was 24% more likely in 2019 than it was in 2014 and nearly 80% of STR and 74% of MTR included an INSTI component in 2019. Both STR- and MTR- related cost increases exceeded inflation over the study period with average monthly STR costs of about $3,000 and nearly $3,700 in MTR costs in 2019. Nearly all beneficiaries utilized at least one non-ART prescription per month throughout the study, but average monthly non-ART-related costs dropped substantially among STR (over $3,300) and MTR (over $2,100) over the study period. No statistically significant differences in the probability of any IP utilization in a month was observed among STR (3%) or MTR (3-4%), but both saw increases of over $2,000 in conditional IP-related costs from 2014 to 2019. Over one-third (35-37%) of STR recipients utilized OP services in a month, while OP utilization among MTR increased from 40% to 44% over the study period. Both groups saw only modest increases in OP-related costs.

Our findings from this aim add to the limited literature estimating ART use and related healthcare resource utilization and costs among an understudied population of Medicare beneficiaries living with HIV. They also reflect the shift in ART regimen prescriptions as more variation in STR class components were brought to market over the study period. Specifically, the greater availability of INSTIs and the class' inclusion in all HHS first-line regimens since 2017[7] is driving the class' predominance among Medicare beneficiaries as seen in other populations.[68] We did not directly compare STR and MTR, but our findings descriptively illustrate lower HcRU and related costs among Medicare beneficiaries using STR as observed in other populations.[11–14,52,54] These results indicate MTR recipients may be older and burdened with more significant comorbidity or HIV-related disease severity or treatment complexity requiring greater need for services. These factors have the potential to limit or inform ART treatment choices, thus were explored explicitly in aim 2 analyses. Cost increases exceeding inflation are illustrative

In aim 2, we conducted a retrospective cohort study using a 5% (2014-2019) sample of CCW data to estimate 1-year total incremental direct medical costs among Medicare beneficiaries living with HIV by STR and MTR receipt. We hypothesized that STR would be associated with lower total direct medical costs compared to MTR. We employed an instrumental variable approach via two-stage least squares (2SLS) regression with a prescriber preference instrument to control for confounding due to non-random treatment assignment. Beneficiaries with an incident ART regimen between January 1, 2015 through December 31, 2018 and 12 months continuous pre- and post-index Parts A, B, and D were included in the analysis.

Predicted STR receipt was associated with nearly $13,500 less in 1-year total direct medical costs compared to MTR after controlling for sociodemographic and clinical characteristics. The covariates associated with the largest incremental costs included CDC Stage 3 HIV/AIDS (>$15,000), Hepatitis C (>$27,000), and Charlson Comorbidity Index Score ≥3 (>$28,000). In sensitivity analyses, STR was associated with nearly $11,000 in cost-savings among strata of beneficiaries with greater than 95% post-index adherence, while no difference was observed among less adherent strata. Even greater STR cost-savings were observed among strata of regimens containing an INSTI component (>$21,000), while NRTI inclusive regimens and those without PIs saw similar STR savings as the full sample.

These cost-savings are substantial, especially when viewed in context of the average per capita Medicare spending on PLHIV ($45,489) estimated in another study in

2014.[28] This is evidence of the potential savings that may accompany further STR penetration, and could be viewed as caution to payers considering incentivizing or mandating MTR use as a means of increasing generic ART utilization. Our finding of cost-savings associated with STR among >95% adherence strata is contrary to findings in prior studies[12,14,52] that found no difference in HcRU and costs when both groups are highly adherent. Potential explanations for this include fewer interactions and treatment complexities arising with STR compared to MTR with other non-ART medications. One pill once a day is both simpler to adhere to and accommodate in a daily medication schedule, which may lead to fewer side effects and greater adherence. However, it is possible that residual unmeasured differences informing treatment assignment are at play as well. The fact that over 80% of our sample was in this >95% post-index adherence stratum is consistent with the high levels of adherence characteristic of adults aging with HIV in other studies.[33–35]

Our findings from aim 2 demonstrate STRs are associated with significantly lower 1-year total direct medical costs compared to MTR when controlling for significant sources of bias not addressed in prior studies. Also, this aim fills a gap in the literature by estimating total direct medical costs associated with STR and MTR among an understudied population—Medicare beneficiaries living with HIV. This study also provides support for the usefulness of prescriber preference IVs in claims-based analyses of patients with HIV. Future research employing larger sample sizes and clinical measures of key indicators of HIV disease severity (i.e., CD4 count, opportunistic infections) and other treatment complexities (e.g., resistance profiles) would further confirm confidence in these findings and conclusions.

In aim 3, we estimated the annual budget impact of expanding use of STR and other novel ART therapies among beneficiaries living with HIV from the Medicare payer perspective over a 5-year time horizon. We used utilization and cost estimates drawn from CCW claims data in addition to estimates from prior academic and governmental publications and enrollment reports, and the Medicare Part B and D Drug Spending dashboards.[108,109] We hypothesized that increasing STR use would be associated with decreased non-antiretroviral utilization and related costs but increased total direct medical costs. We built a model in Microsoft Excel with the following inputs: average annual cost and utilization of ART, inpatient (IP), emergency department (ED), outpatient (OP), ART, and non-ART prescription drugs. HcRU and related costs were estimated among four subgroups: recipients of STR, MTR, salvage regimens, and untreated beneficiaries to better characterize heterogeneity while preserving a simple cost calculator approach.

Our model predicted $1.8 billion in additional costs in year 5 under a scenario where current trends in ART utilization and costs continue compared to a scenario where they remain at 2019 levels. The excess costs were driven by $2.3 billion in greater ART spending among the 147,953 beneficiaries living with HIV despite savings of $199 million in IP, $5.7 million in ED, $111 million in OP, $166 million in non-ART prescription drug costs. These savings were accompanied by 10,601 fewer IP, 7,635 fewer ED, 75,588 fewer OP, and 432,894 fewer non-ART prescription drug events. The base case scenario was most sensitive to inclusion of a linear trend in ART utilization and the cost of ART. In linear trend comparisons, uptake of the first long-acting injectable, Cabenuva®, showed small cost savings in nearly all scenarios ($19-203 million) except when ART price increases exceeded those predicted in the base case.

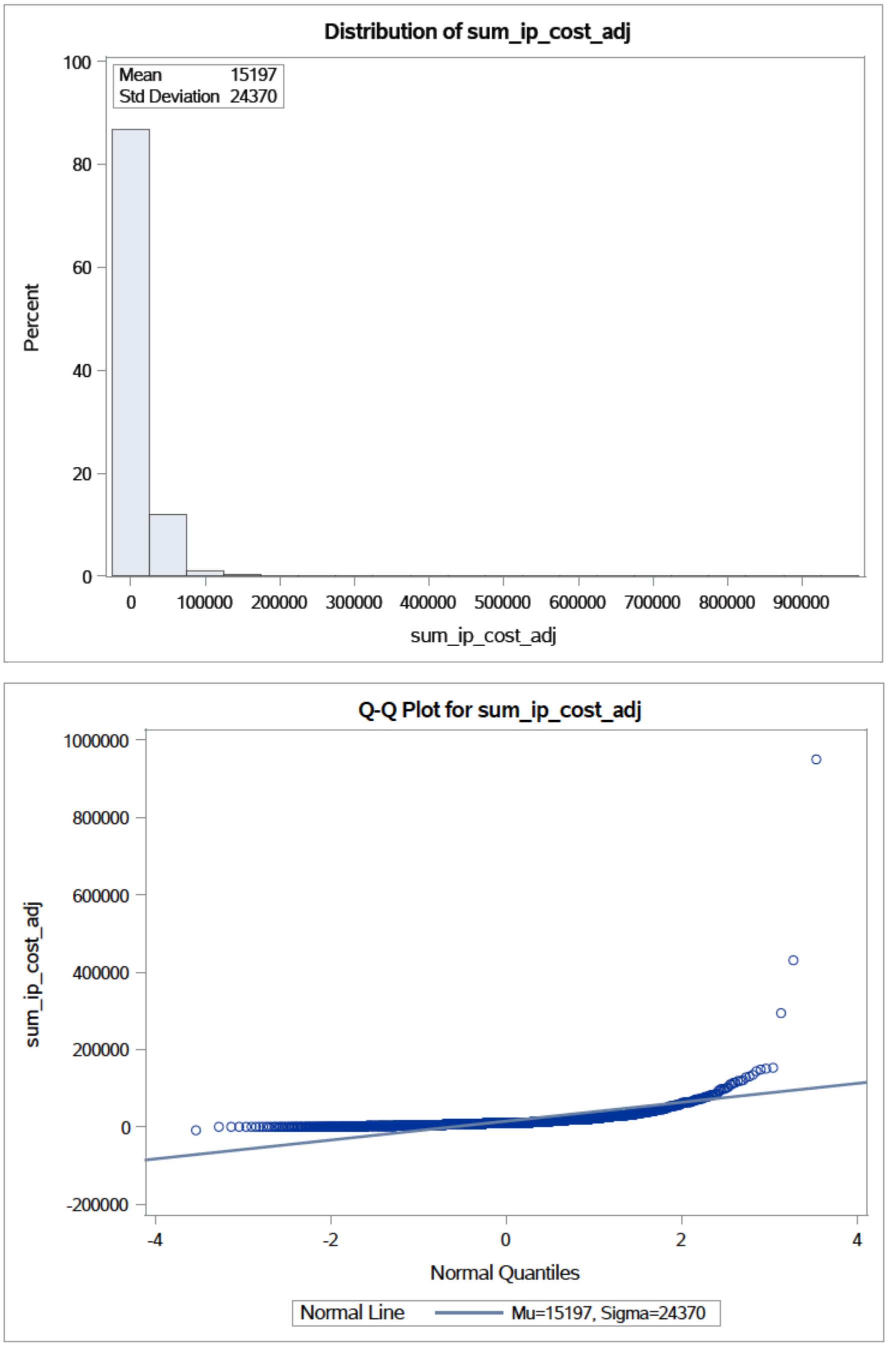
7 Appendix

Appendix Table 1. Framework for Covariate Selection and Model Specification	
Predisposing	**Race/Ethnicity** (White/Black/Hispanic/Other) **Age**, years (quartiles based on bivariate analysis) **Sex** (male/female)
Enabling	**Original Reason for Medicare Eligibility** (Disability/ESRD or Age) **Dual eligibility** (MBSF)
Need	(HIV/AIDS severity) Opportunistic Infections, Detectable Viral Load Comorbidity burden (Charlson Comorbidity Index)
Medication Use	HIV medications (classes, regimen complexity); non-antiretrovirals
Environment	**Geographic region** (Midwest, Northeast, South, West)

Appendix Table 2. ICD-9 and ICD-10 Codes for HIV	
ICD-9 Code	**Description**
042	Human Immunodeficiency Virus Disease
V08	Asymptomatic Human Immunodeficiency Virus Infection
ICD-10 Code	
B20	Human Immunodeficiency Virus Disease
Z21	Asymptomatic Human Immunodeficiency Virus Infection

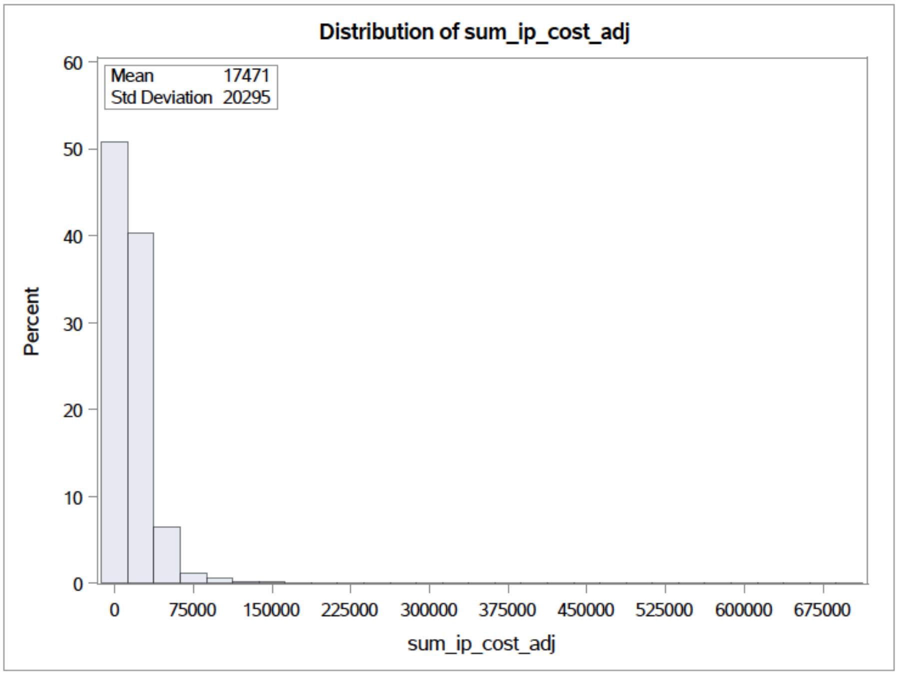
Appendix Table 3. Regression Equations for Aim 1
STR/MTR = $b_0 + b_1 YEAR + b_{i \dots n}(Covariates)$
IP/ED/OP$_{(0/1)}$ = $b_0 + b_1 YEAR + b_{i \dots n}(Covariates)$
IP/ED/OP/Non-ART Costs$_{(STR/MTR)}$ = $b_0 + b_1 YEAR + b_{i \dots n}(Covariates)$

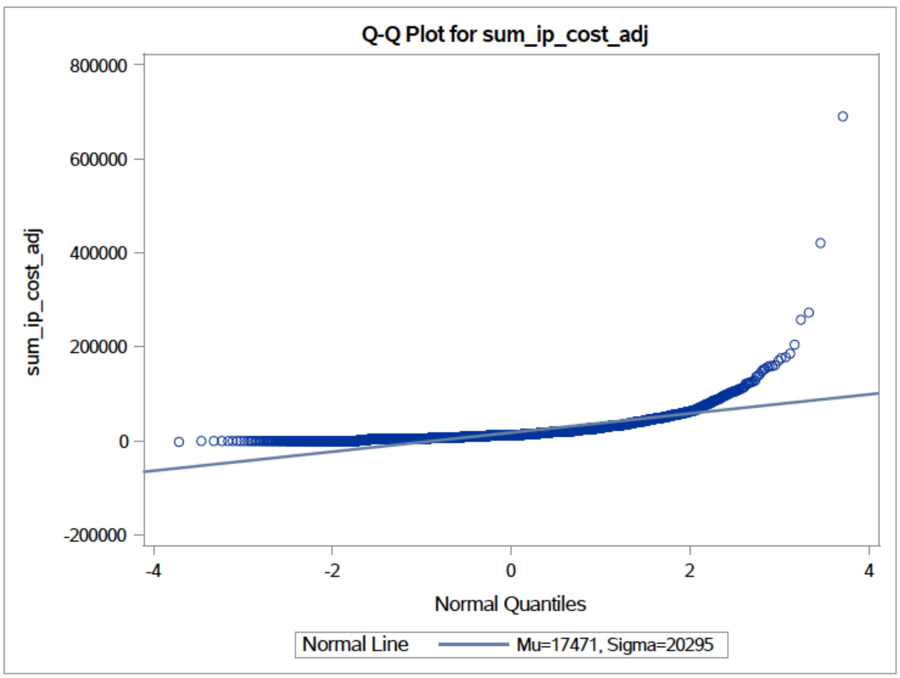
Appendix Figure 1. Inpatient Cost Histogram and Q-Q Plot – Single Tablet



Skewness: 21.334225
Kurtosis: 740.156962

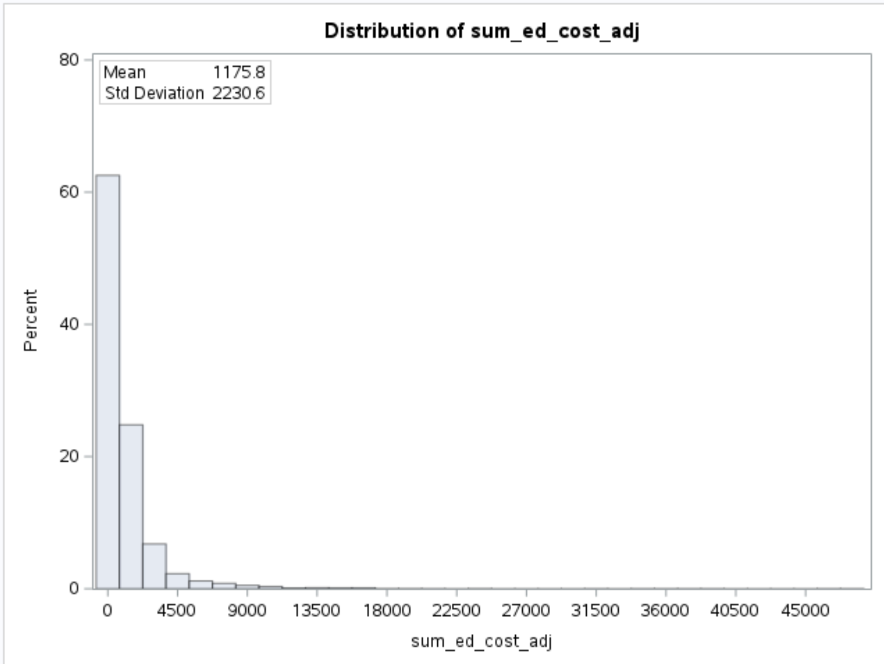
Appendix Figure 2. Inpatient Cost Histogram and Q-Q Plot – Multi-Tablet

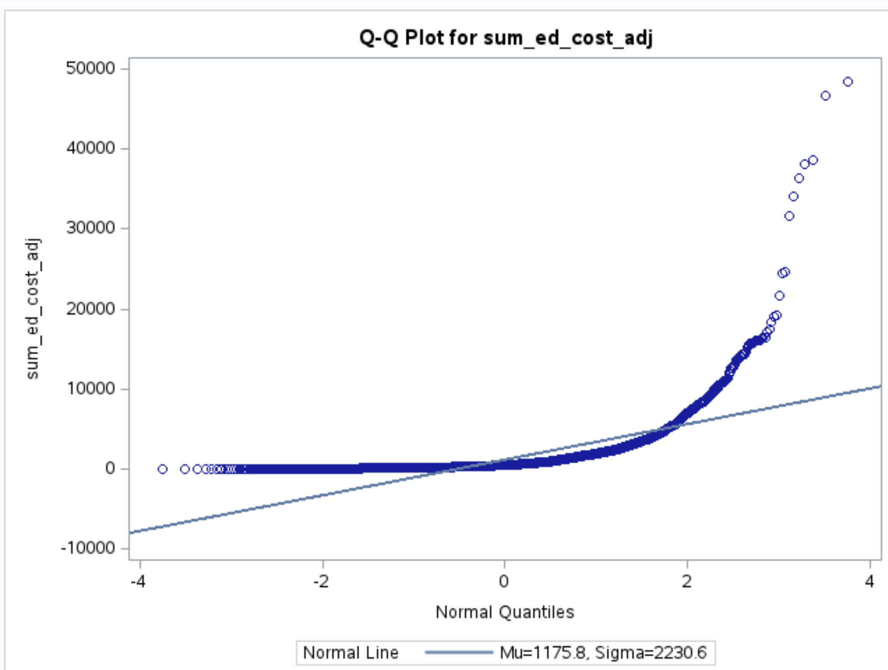




Skewness: 9.78433668
Kurtosis: 237.191536

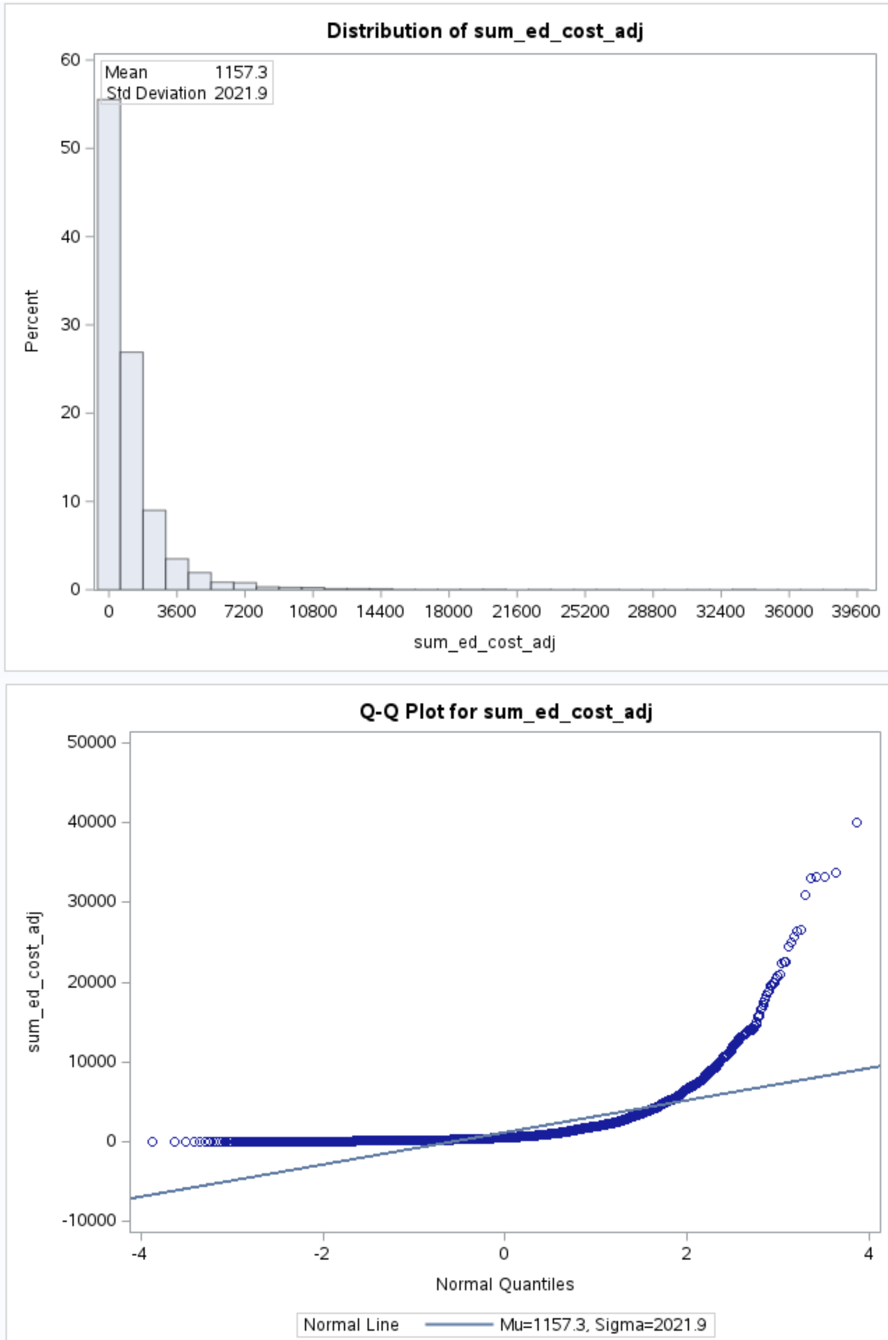
Appendix Figure 3. Emergency Department Cost Histogram and Q-Q Plot – Single Tablet





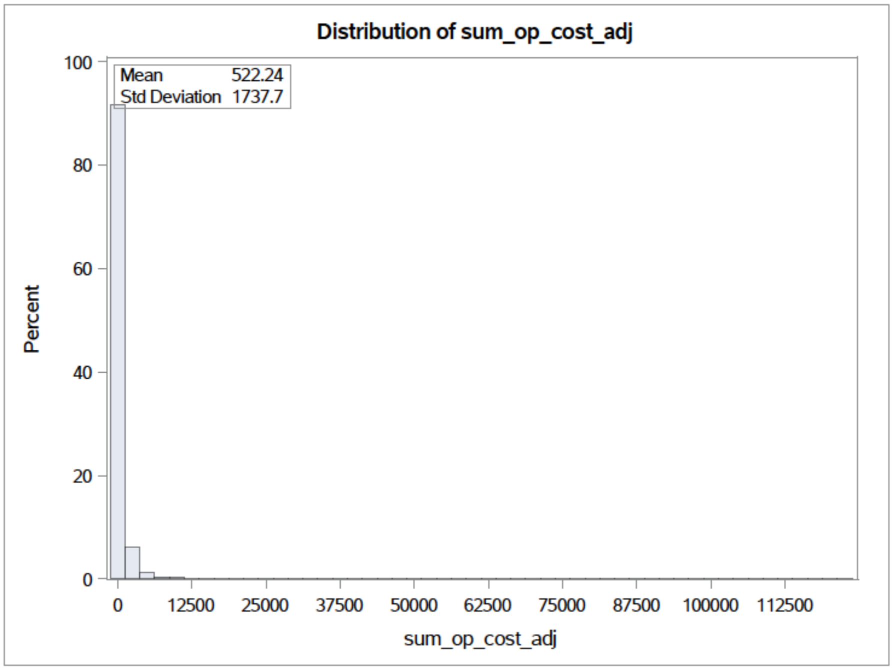
Skewness: 7.90451425
Kurtosis: 108.323084

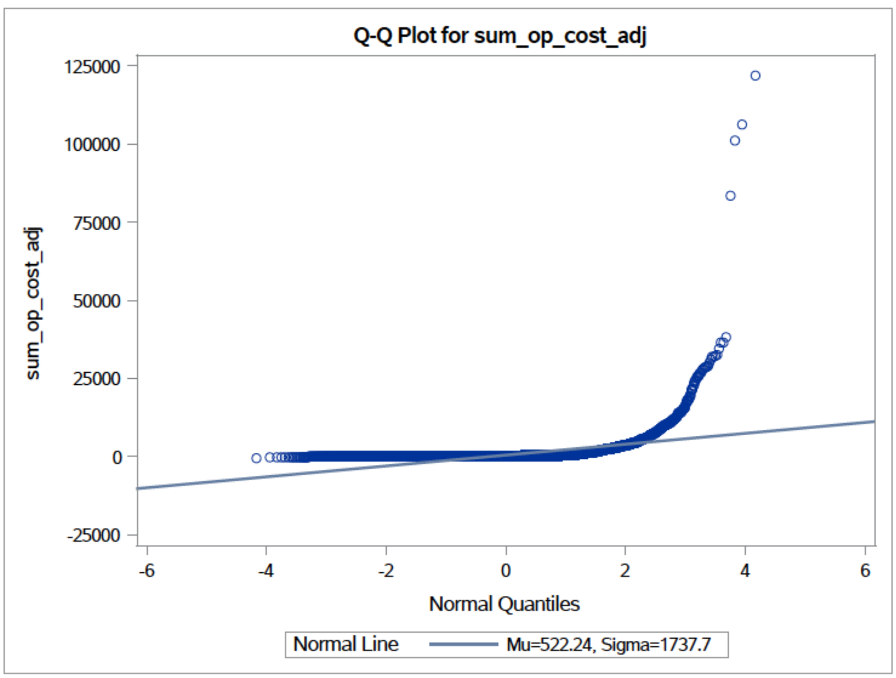
Appendix Figure 4. Emergency Department Cost Histogram and Q-Q Plot – Multi-Tablet



Skewness: 6.24437439
Kurtosis: 65.220402

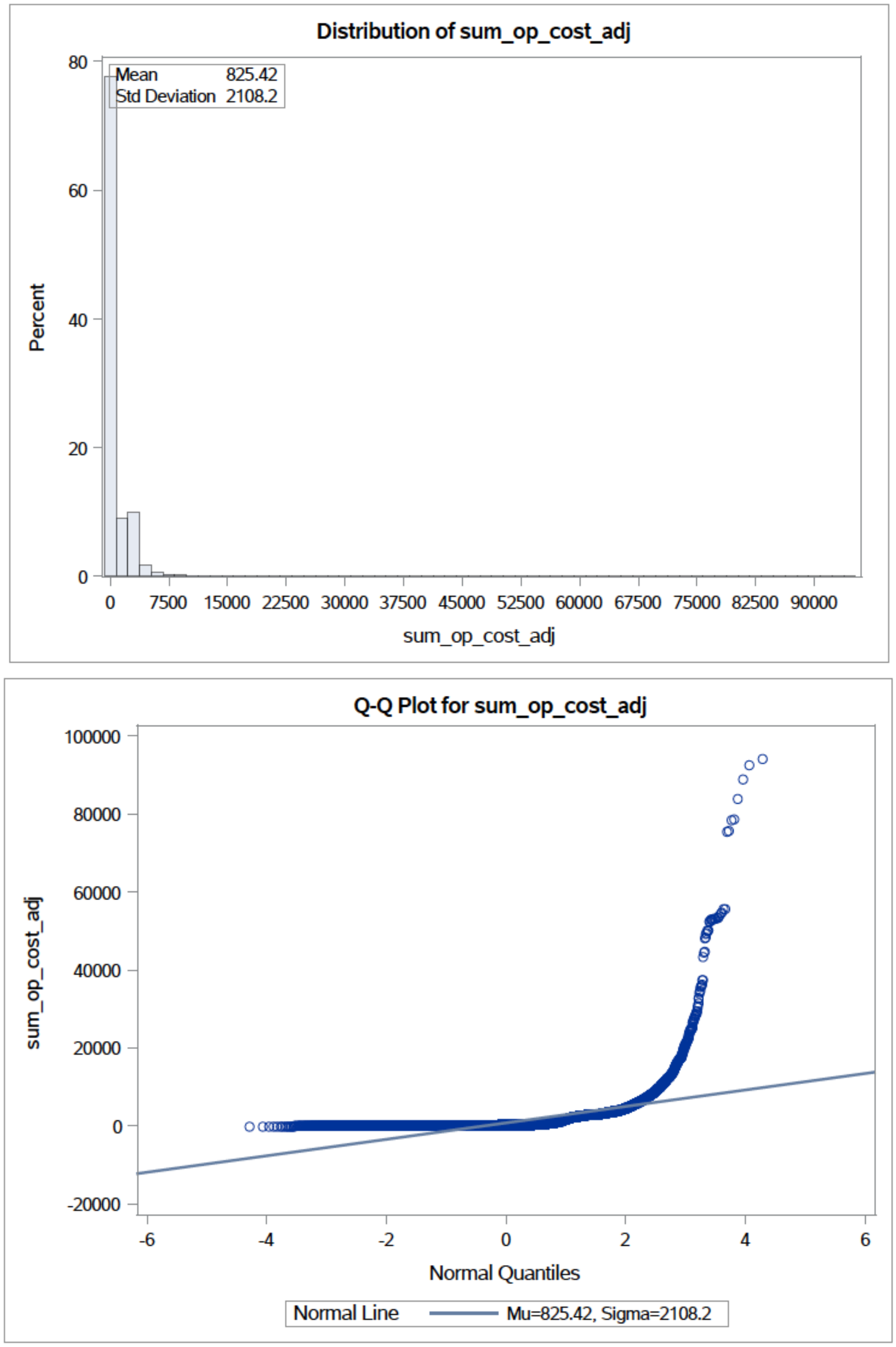
Appendix Figure 5. Outpatient Cost Histogram and Q-Q Plot – Single Tablet





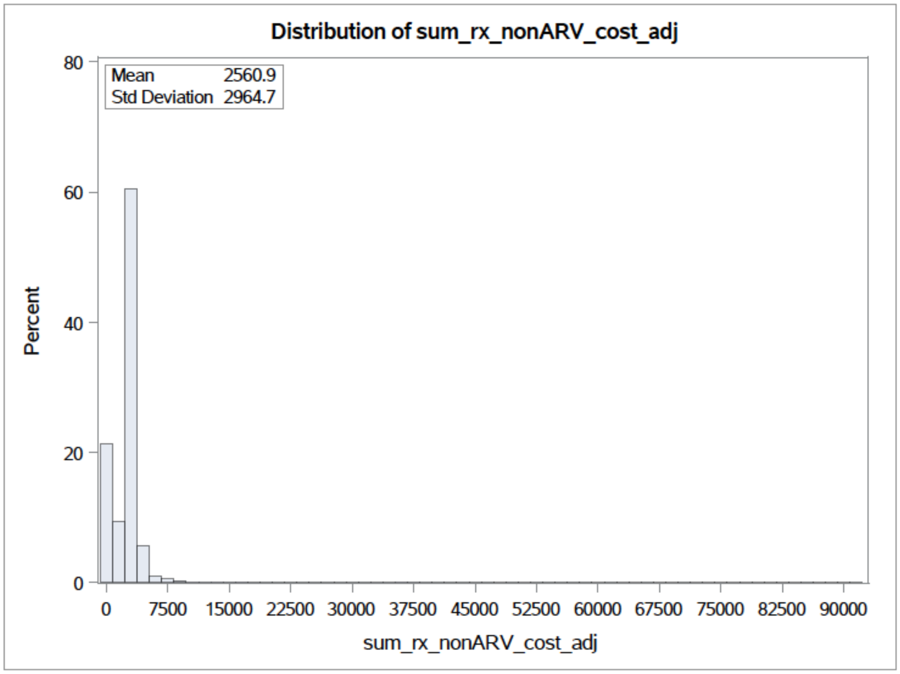
Skewness: 26.7437277
Kurtosis: 1387.4667

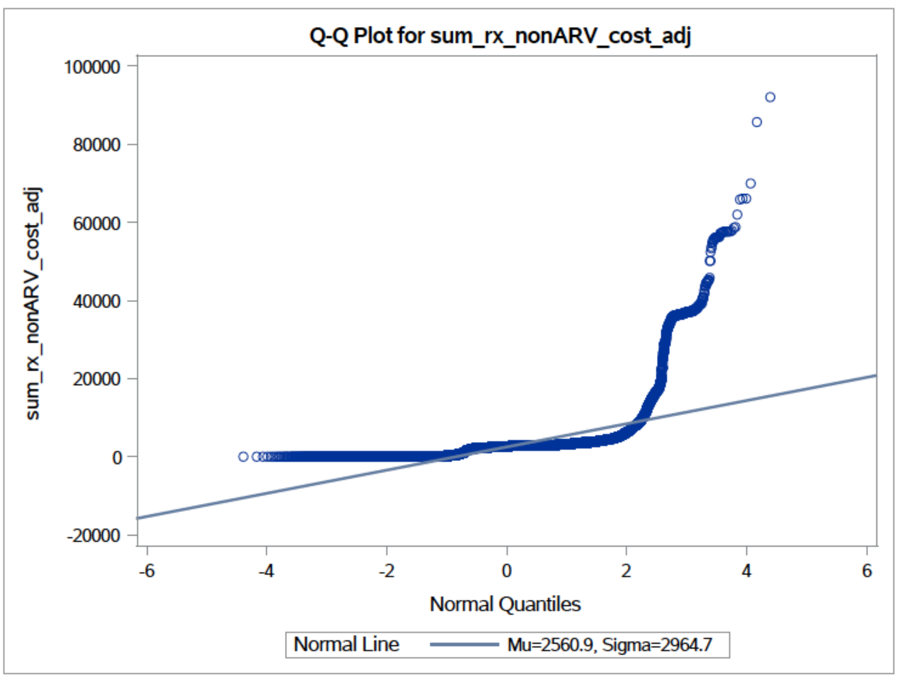
Appendix Figure 6. Outpatient Cost Histogram and Q-Q Plot – Multi-Tablet



Skewness: 15.5093879
Kurtosis: 439.191691

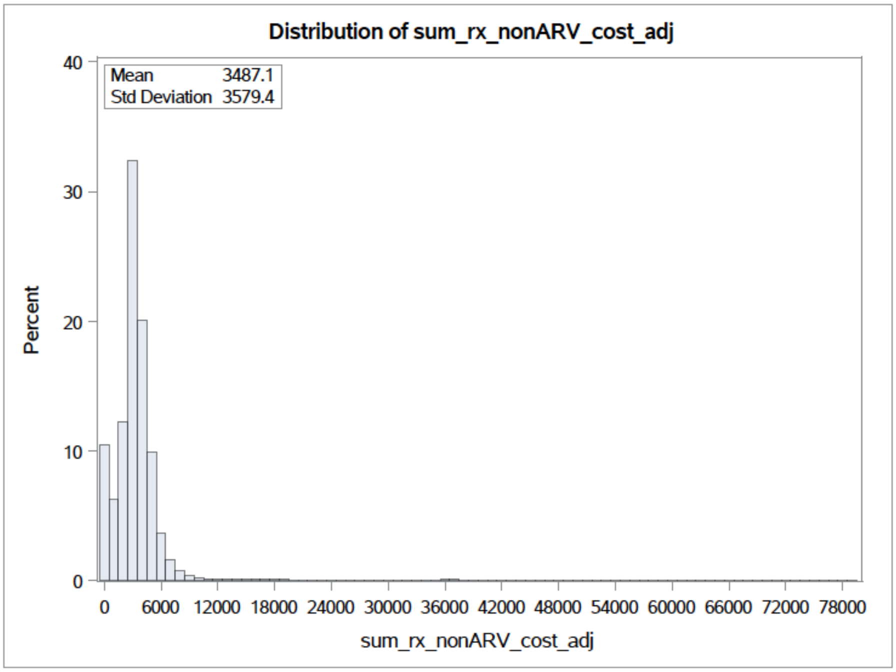
Appendix Figure 7. Non-Antiretroviral Cost Histogram and Q-Q Plot – Single Tablet

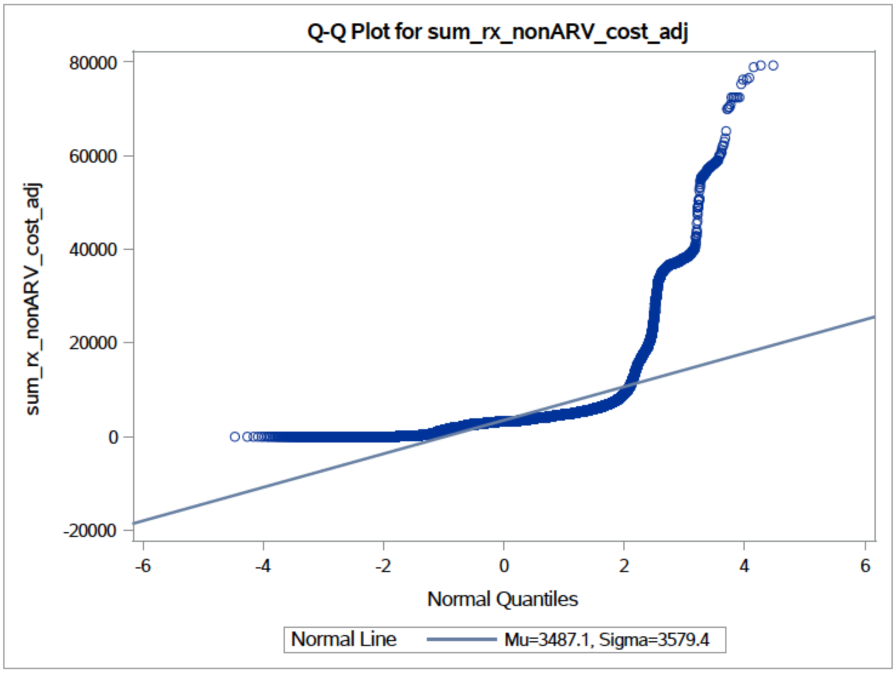




Skewness: 8.96835341
Kurtosis: 120.027626

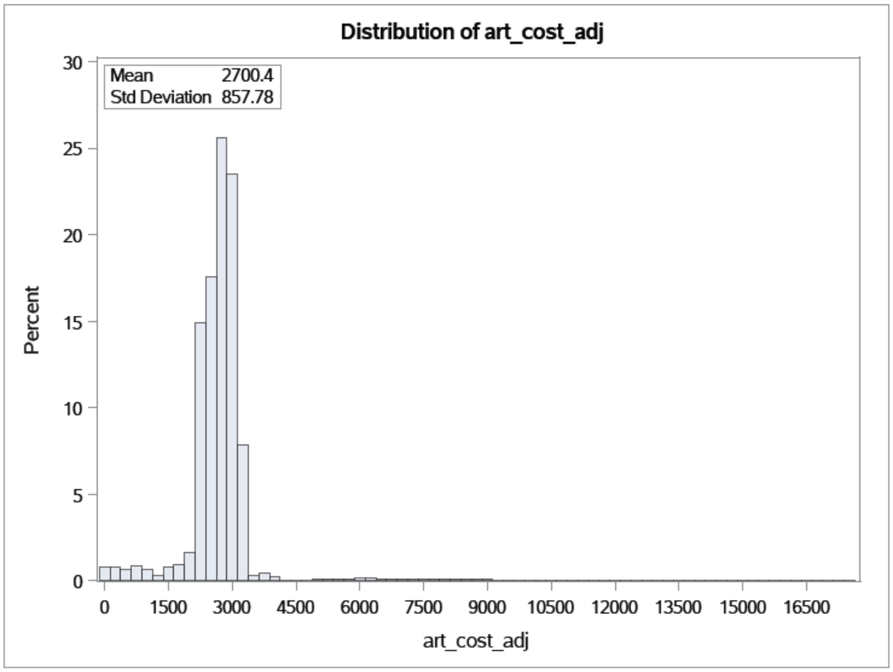
Appendix Figure 8. Non-Antiretroviral Cost Histogram and Q-Q Plot – Multi-Tablet

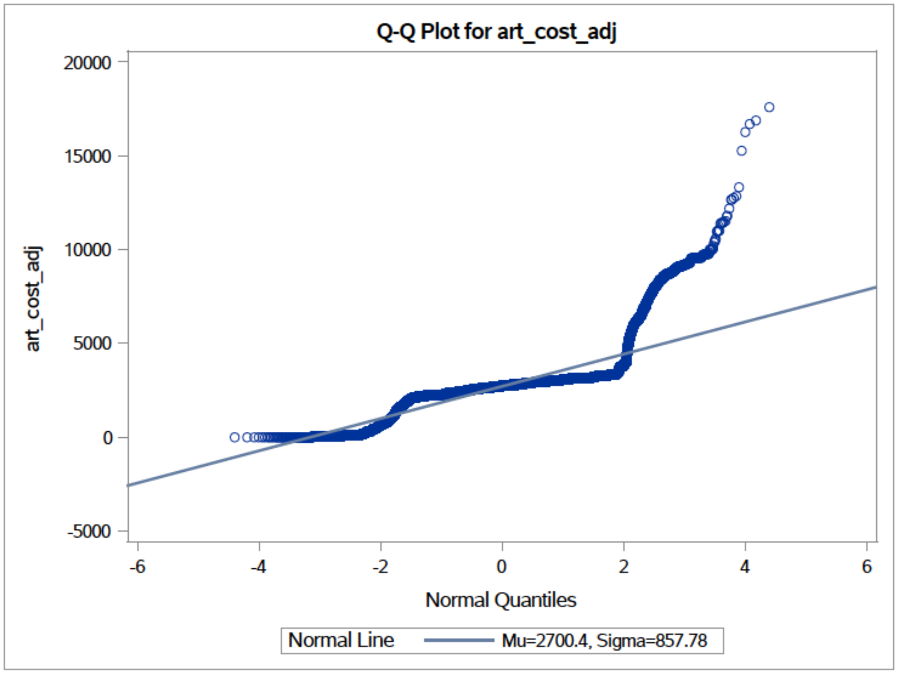




Skewness: 7.528042
Kurtosis: 79.4492012

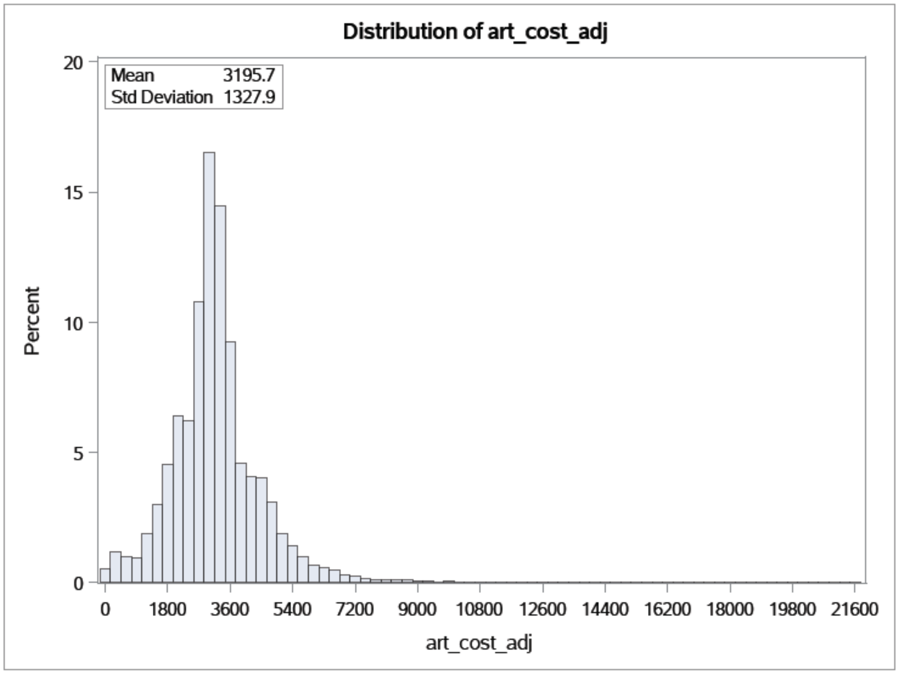
Appendix Figure 9. Antiretroviral Cost Histogram and Q-Q Plot – Single Tablet

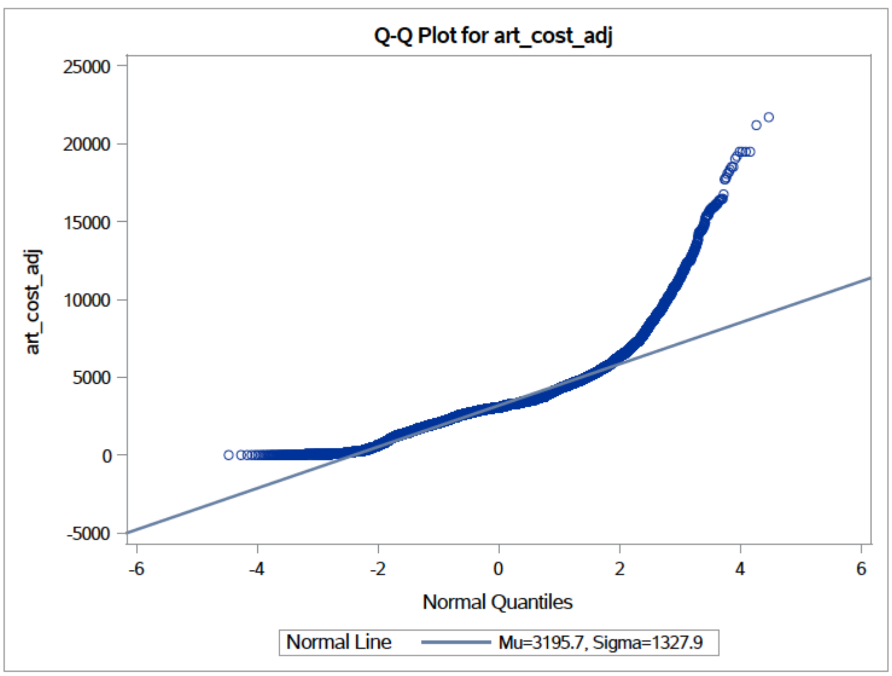




Skewness: 2.90741324
Kurtosis: 24.8398539

Appendix Figure 10. Antiretroviral Cost Histogram and Q-Q Plot – Multi-Tablet





Skewness: 1.5474804
Kurtosis: 9.13562089

Appendix Table 4. Inpatient Cost Model Misspecification Testing – Single Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.06	Pass
Pregibon Link Test: Log	0.93	Pass
Specification: Inverse Gaussian Distribution with Log link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	0.03	Fail

Appendix Table 5. Inpatient Cost Model Misspecification Testing – Multi-Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.07	Pass
Pregibon Link Test: Log	0.76	Pass
Specification: Inverse Gaussian Distribution with Log link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

Appendix Table 6. Emergency Department Cost Model Misspecification Testing – Single Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	<.01	Fail*
Pregibon Link Test: Log	<.01	Fail
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

*Gamma distribution was selected despite failing the Modified Park Test as it offered the best fit over Normal and Poisson distributions.

Appendix Table 7. Emergency Department Cost Model Misspecification Testing – Multi-Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	<.01	Fail*
Pregibon Link Test: Log	<.01	Fail
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

*Gamma distribution was selected despite failing the Modified Park Test as it offered the best fit over Normal and Poisson distributions.

Appendix Table 8. Outpatient Cost Model Misspecification Testing – Single Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.05	Pass
Pregibon Link Test: Log	0.56	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	0.01	Fail

Appendix Table 9. Outpatient Cost Model Misspecification Testing – Multi-Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.08	Pass
Pregibon Link Test: Log	0.68	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

Appendix Table 10. Non-Antiretroviral Cost Model Misspecification Testing – Single Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.07	Pass
Pregibon Link Test: Log	0.32	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

Appendix Table 11. Non-Antiretroviral Cost Model Misspecification Testing – Multi-Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.10	Pass
Pregibon Link Test: Log	0.59	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	<.01	Fail

Appendix Table 12. Antiretroviral Cost Model Misspecification Testing – Single Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.045	Fail*
Pregibon Link Test: Log	0.82	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	<.01	Fail
Pregibon Link Test: Identity	0.03	Fail

*Gamma distribution was selected despite failing the Modified Park Test as it offered the best fit over Normal and Poisson distributions.

Appendix Table 13. Antiretroviral Cost Model Misspecification Testing – Multi-Tablet		
	p-value	Interpretation
Specification: Gamma Distribution with Log link		
Modified Park Test: Gamma	0.03	Fail*
Pregibon Link Test: Log	0.89	Pass
Specification: Normal Distribution with Identity link		
Modified Park Test: Normal	0.05	Fail
Pregibon Link Test: Identity	0.02	Fail

*Gamma distribution was selected despite failing the Modified Park Test as it offered the best fit over Normal and Poisson distributions.

Appendix Table 14. Chronic Condition Data Warehouse Files	
File name	**Description**
Master Beneficiary Summary File (MBSF)	Chronic condition diagnoses Demographic variables Enrollment
Inpatient (Part A)	Hospitalizations
Outpatient (Part B)	Outpatient and Emergency visits
Carrier	Physician and Non-Institutional visits
Part D Event (PDE)	Prescription Drugs
Home Health Agencies (HHA)	Home health services
Hospice & Long-Term Care (LTC)	Hospice and long-term care
Skilled Nursing Facility File (SNF)	Nursing home

Appendix Table 15. Antiretroviral Medications, Approvals, and Class(es)			
Generic Components	**Brand**	**FDA Approval**	**Class(es)**
Single Tablet Regimens			
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF)	Atripla	12-Jul-06	NNRTI/NRTI/NRTI
Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF)	Complera	10-Aug-11	NRTI/NNRTI/NRTI
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF)	Stribild	27-Aug-12	INSTI/PE/NRTI/ NRTI
Abacavir/Lamivudine/Dolutegravir (ABC/3TC/DTG)	Triumeq	22-Aug-14	NRTI/NRTI/INSTI
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF)	Genvoya	05-Nov-15	INSTI/PE/NRTI/ NRTI
Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF)	Odefsey	01-Mar-16	NRTI/NNRTI/NRTI
Dolutegravir/Rilpivirine (DTG/RPV)	Juluca	21-Nov-17	INSTI/NNRTI
Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)	Biktarvy	07-Feb-18	INSTI/NRTI/NRTI
Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate (EFV/3TC/TDF)	Symfi Lo	05-Feb-18	NNRTI/NRTI/NRTI
Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate (EFV/3TC/TDF)	Symfi	23-Mar-18	NNRTI/NRTI/NRTI

Appendix Table 15. Continued

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (DRV/COBI/FTC/TAF)	Symtuza	17-Jul-18	PI/PE/NRTI/NRTI
Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF)	Delstrigo	30-Aug-18	NNRTI/NRTI/NRTI
Dolutegravir/Lamivudine (DTG/3TC)	Dovato	08-Apr-19	INSTI/NRTI
Multi-Tablet Regimen Components			
Zidovudine (ZDV)	Retrovir	19-Mar-87	NRTI
Stavudine (D4T)	Zerit	27-Jun-94	NRTI
Lamivudine (3TC)	Epivir	17-Nov-95	NRTI
Abacavir (ABC)	Ziagen	17-Dec-98	NRTI
Didanosine (DDL)	Videx ec	31-Oct-00	NRTI
Tenofovir Disoproxil Fumarate (TDF)	Viread	26-Oct-01	NRTI
Emtricitabine (FTC)	Emtriva	02-Jul-03	NRTI
Nevirapine (NVP)	Viramune	21-Jun-96	NNRTI
Nevirapine ER	Viramune XR	25-Mar-11	NNRTI
Efavirenz (EFV)	Sustiva	17-Sep-98	NNRTI
Delavirdine Mesylate (DLV)	Rescriptor	16-May-01	NNRTI
Etravirine (ETR)	Intelence	18-Jan-08	NNRTI
Rilpivirine (RPV)	Edurant	20-May-11	NNRTI
Doravirine (DOR)	Pifeltro	30-Aug-18	NNRTI
Saquinavir (SQV)	Invirase	06-Dec-95	PI
Ritonavir (RTV)	Norvir	1-Mar-96	PI
Indinavir (IDV)	Crixivan	13-Mar-96	PI
Nelfinavir (NFV)	Viracept	14-Mar-97	PI
Atazanavir (ATV)	Reyataz	20-Jun-03	PI
Fosamprenavir (FPV)	Lexiva	20-Oct-03	PI
Tipranavir (TPV)	Aptivus	22-Jun-05	PI
Darunavir (DRV)	Prezista	23-Jun-06	PI
Enfuvirtide (T-20)	Fuzeon	13-Mar-03	FI
Maraviroc (MVC)	Selzentry	06-Aug-07	CCR5-A
Raltegravir (RAL)	Isentress	12-Oct-07	INSTI
Raltegravir (RAL)	Isentress HD	26-May-17	INSTI
Dolutegravir (DTG)	Tivicay	13-Aug-13	INSTI
Ibalizumab-uiyk	Trogarzo	06-Mar-18	PAI
Cobicistat (COBI)	Tybost	24-Sep-14	PE
Lamivudine/Zidovudine (3TC/ZDV)	Combivir	27-Sep-97	NRTI/NRTI
Lopinavir/Ritonavir (LPV/RTV)	Kaletra	15-Sep-00	PI/PI
Abacavir/Lamivudine/Zidovudine (ABC/3TC/ZDV)	Trizivir	14-Nov-00	NRTI/NRTI/NRTI
Abacavir/Lamivudine (ABC/3TC)	Epzicom	02-Aug-04	NRTI/NRTI
Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)	Truvada	02-Aug-04	NRTI/NRTI
Atazanavir/Cobicistat (ATV/COBI)	Evotaz	29-Jan-15	PI/PKE
Darunavir/Cobicistat (DRV/COBI)	Prezcobix	29-Jan-15	PI/PKE
Emtricitabine/Tenofovir Alafenamide (FTC/TAF)	Descovy	04-Apr-16	NRTI/NRTI
Lamivudine/Tenofovir Disoproxil Fumarate (3TC/TDF)	Cimduo	28-Feb-18	NRTI/NRTI
Fostemsavir Tromethamine (FTR)	Rukobia	02-Jul-20	AI
Cabotegravir/Rilpivirine (CAB/RPV)*	Cabenuva	21-Jan-21	INSTI/NNRTI
Cabotegravir (CAB)	Vocabria	21-Jan-21	INSTI

Appendix Table 16. Opportunistic Infections and Malignancies		
Opportunistic Infection	**ICD9**	**ICD10**
Toxoplasmosis	130.x	B58.x
Pneumocystis jivorecci (carinii) Pneumonia	136.3	B59
Mycobacterium Avium Complex (MAC)	031.x	A31.2
Cryptococcosis, extrapulmonary	117.5	B45.1, 321.0
Cytomegalovirus	78.5	B25.x
Candidiasis (Thrush)	112.x	B37.x
Herpes Simplex	054.x	B00.x
Pulmonary Tuberculosis (TB)	011.x	A15.x
Coccidioidomycosis	114	B38.9
Salmonellosis	3.9	A02.x
Histoplasmosis	115.x	B39.x
Cryptosporidiosis	7.4	A07.2
Cystoisosporiasis	7.2	A07.3
Microsporidiosis	136.8	B60.8, B99.8
Weight loss/wasting	783.21-22	R63.4, R63.6
Bacterial pneumonia	482.9	J15.x
History of Recurrent Pneumonia	V12.61	Z87.01
AIDS-defining malignancies		
Kaposi sarcoma	176.x	C46
Non-Hodgkin's lymphoma	202.8	C85.80
Primary CNS lymphoma	200.5	C83.80
Burkitt's lymphoma	200.2x	C83.7x
Cervical, invasive	180.x	C53.x

Appendix Table 17. Laboratory Tests		
Test	**HCPCS**	**CPT**
CD4:CD8		86360
CD4 Total		86361
CD4 count documented	G9214 (Since 2015)	
HIV-1-RNA (Viral Load)		87536
Genotype and Coreceptor Tropism		87900, 87901, 87906

Appendix Table 18. Compliers Framework and Calculation			
Composition	**Instrument Level**		**Treatment**
Compliers + Never Takers	Control (Z=0)		W=0
Always Takers	Control (Z=0)		W=1
Never Takers	Treatment (Z=1)		W=0
Compliers + Always Takers	Treatment (Z=1)		W=1
Number of Compliers Calculation			
Group	**Formula**		**Calculation**
Always Takers	P(W=1|Z=0) = Always Takers / (Compliers + Never Takers)		2200 / 5774 = 0.38
Never Takers	P(W=0|Z=1) = Never Takers / (Compliers + Always Takers)		122 / 1270 = 0.09
Compliers	1 - (Proportion Never Takers) - (Proportion Always Takers)		1 - 0.38 - 0.09 = 0.53
Instrument Level by Treatment Observed			
Instrument Level N(row%)	**Treatment Observed**		
	MTR (W=0)	STR (W=1)	Total
MTR (Z=0)	3574 (61.90)	2200 (38.10)	5774
STR (Z=1)	122 (9.61)	1148 (90.40)	1270
Total	3696	3348	7044

*53% of our cohort were compliers

Appendix Table 19. Tests for Endogeneity		
Test	**P value**	**Interpretation**
Durbin Score chi^2 Statistic	0.044	Pass
Wu-Hausman Statistic	0.044	Pass

H_0: Variable is Exogenous; Both the Durbin Score statistic and Wu-Hausman statistic had significant p values (<.05) in the tests for endogeneity (**Table vii**).

Appendix Table 20. First Stage Regression Statistics				
Variable	**Partial r^2**	**F statistic**	**P value**	**Interpretation**
Treatment (STR/MTR)	0.32	1,525.47	<.0001	Pass

F-test H_0: Instrument is weak; The F statistic in the first stage regression was 1,525.47 (p<0.001). The partial r^2 (0.32) indicates the instrument explains approximately 32% of the variation in the treatment exposure after controlling for other covariates.

Appendix Table 21. Regressing Potential Confounders on the Instrument		
Outcome	**Crude IV p value**	**Adjusted IV p value**
Age Groups		
50-56 years	0.10	0.14
57-64 years	0.36	0.30
≧65 years	0.18	0.58
Sex (Female)	0.06	0.06
Race and Ethnicity		
Black	0.83	0.66
Hispanic	0.93	0.63
Other/Unknown	0.77	0.88
Disability	0.08	0.37
Dual Eligibility	0.30	0.26
CDC Stage 3 (CD4<200)	0.63	0.97
Charlson Comorbidity Index Score		
1	0.64	0.85
2	0.45	0.38
≧3	0.03	0.08
Hepatitis C	0.63	0.74
Region		
Northeast	0.67	0.05
South	0.01	0.05
West	0.19	0.11
Pre-Index Adherence	0.34	0.11
HIV RNA Genotyping	0.63	0.34
CD4 Count	0.32	0.16

When we regressed all covariates on the instrument most of the IV coefficients were non-significant ($p>0.05$) except for CCI score ≥3 ($p=0.03$) and residence in the South ($p=0.01$) in the crude analyses. All IV coefficients were non-significant in the fully adjusted models (all $p>0.05$).

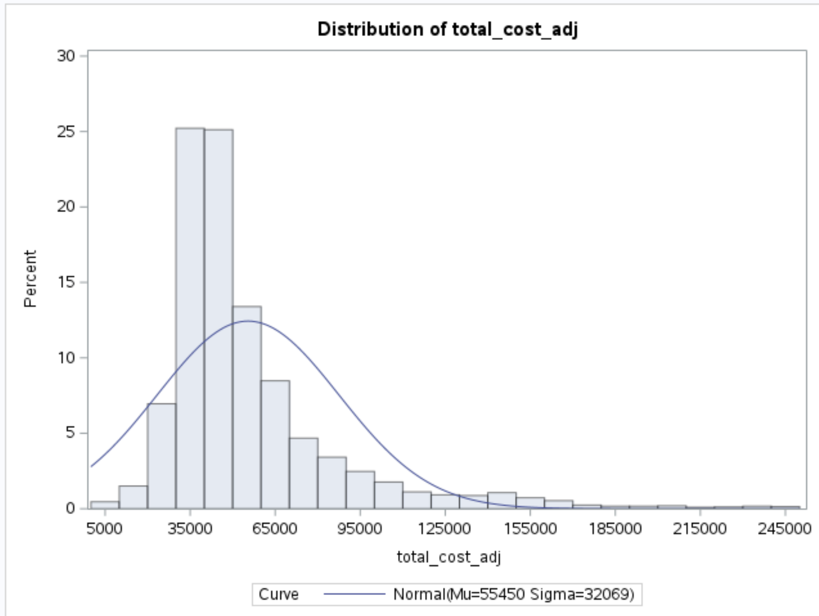
Appendix Table 22. Assessing for Differences in Patient Mix and Provider Skill			
	Instrument Level		
	Predicted STR	**Predicted MTR**	***p***
Prevalence of 5 Most Common Diagnoses - HIV Population*			
Hypertension	55.34%	56.74%	>.05
Hyperlipidemia	51.89%	50.13%	>.05
Diabetes	31.31%	28.79%	>.05
COPD	30.90%	31.87%	>.05
Depression	24.94%	23.97%	>.05
Prevalence of 5 Most Common Diagnoses - Total Population*			
Hypertension	32.90%	33.12%	>.05
Hyperlipidemia	28.74%	29.67%	>.05
Ischemic Heart Disease	16.45%	16.02%	>.05
Rheumatoid Arthritis	15.96%	14.43%	>.05

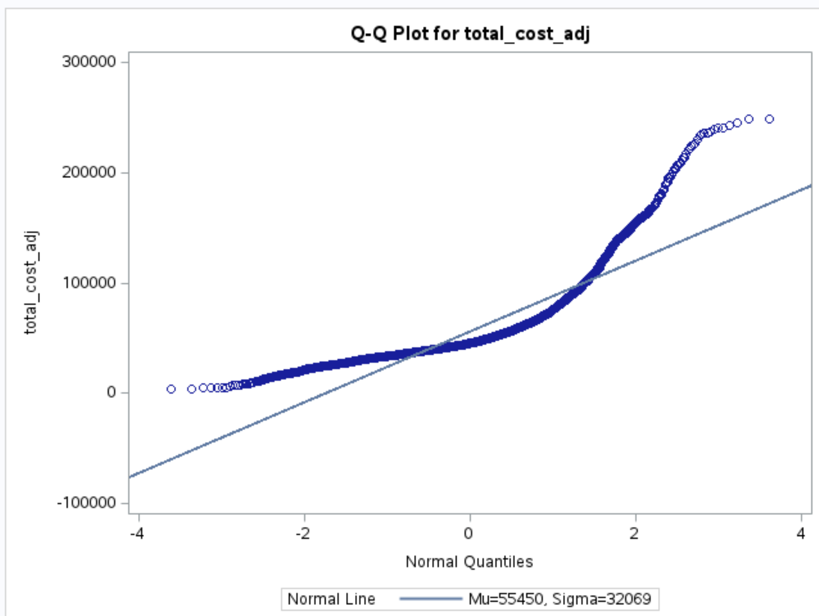
Appendix Table 22. Continued

Diabetes	14.39%	13.68%	>.05
Prevalence of 5 Most Common Prescriptions - HIV Population[#]			
Atorvastatin	3.55%	3.96%	<.05
Omeprazole	2.92%	3.04%	<.05
Amlodipine	2.61%	2.31%	<.05
Albuterol	2.34%	1.94%	<.05
Gabapentin	2.12%	2.42%	<.05
Prevalence of 5 Most Common Prescriptions - Total Population[#]			
Lisinopril	1.62%	1.75%	<.05
Amlodipine	1.48%	1.42%	<.05
Simvastatin	1.29%	1.97%	<.05
Omeprazole	1.24%	2.23%	<.05
Hydrocodone-Acetaminophen	1.18%	1.45%	<.05
Volume of ART Prescribing[&]	21.03%	21.64%	<.05

*Proportion of patients with condition / total patients
[#]Proportion of prescriptions by generic name / total prescriptions
[&]Proportion of ART regimen prescriptions / total prescriptions

Appendix Figure 11. 1-year Total Cost Histogram and Q-Q Plot





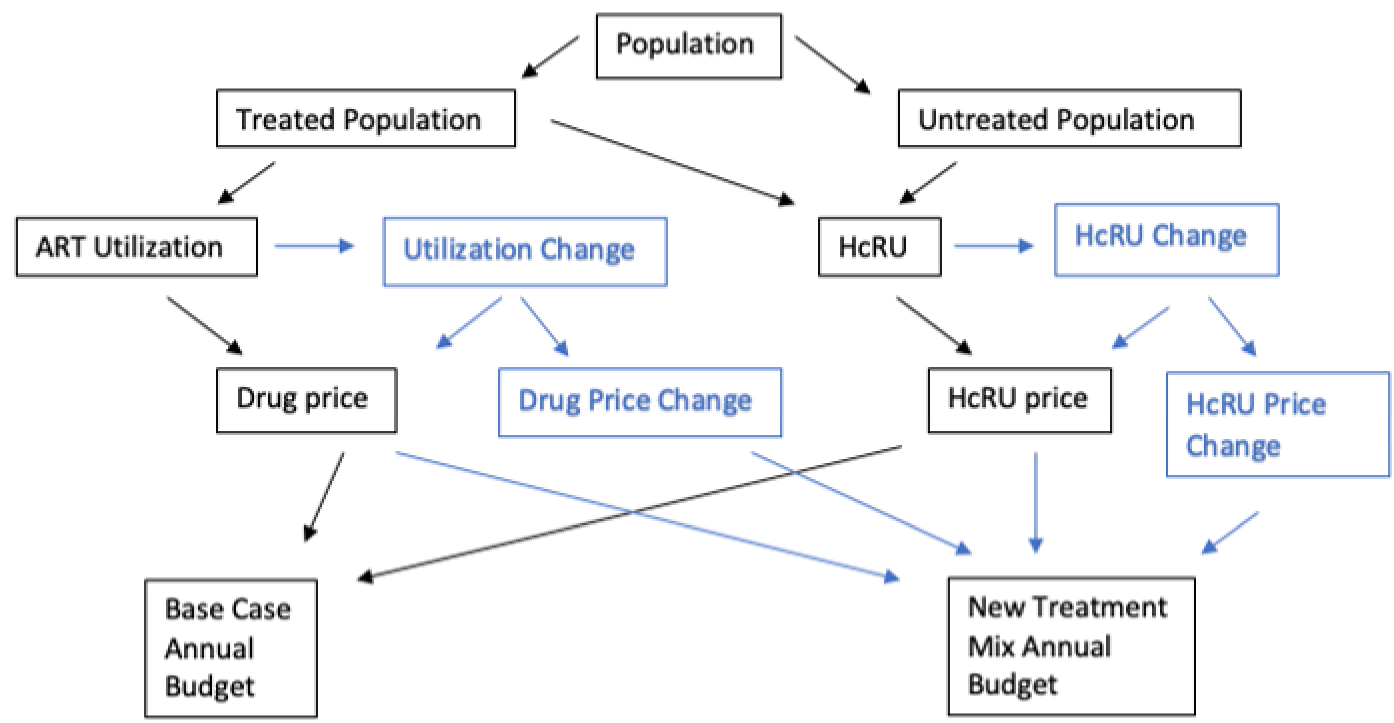
Skewness: 2.40
Kurtosis: 7.4567

Appendix Table 23. Budget Impact Model Assumptions
1. Static model - assumes no changes in population size or disease severity mix over the time horizon.
2. Change in ART Utilization - modeled by fitting a linear trend using CCW data 2014-2019. Negative utilization not allowed (floor of 0%); No trend scenario was modeled using 2019 market share of STR vs MTR, but within each group market share of newer therapies were modeled based on historical trends.
3. Healthcare Resource Utilization - average annual utilization for each subgroup (STR, MTR, Salvage, Untreated) held constant throughout time horizon.
4. ART costs - modeled by fitting a linear trend using CCW data 2014-2019 as sum of covered Part D payment and low-income subsidy per drug.
5. HcRU Costs - modeled by fitting a linear trend using CCW data 2014-2019 by STR, MTR, salvage, untreated subgroup, respectively.

Appendix Table 24. Budget Impact Model Sensitivity Analyses

Scenario	No Trend – STR Utilization	Trend – STR Utilization
Linear Trend in ART utilization plus novel therapies	-	SA#1
Lower STR increases (50% lower than base case)	-	SA#2
Fixed ART Costs (2019)	SA #3	SA #4
High ART Costs (50% higher than base case)	SA #5	SA #6
High Cabenuva® uptake (50% higher than base case)	SA #7	SA #8
Low Cabenuva® uptake (50% lower than base case)	SA #9	SA #10
Identical HcRU-related costs (using STR costs)	SA #11	SA #12
Identical HcRU (using STR utilization)	SA #13	SA #14

Appendix Figure 12. Budget Impact Model Analytic Framework



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