



Daily Antiretroviral Pill Burden Effects on Medication Adherence, Hospitalization Risk, and Health Care Utilization and Costs in a United States Medicaid Population With HIV

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4 1 **Daily Antiretroviral Pill Burden Effects on Medication Adherence,**
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6 2 **Hospitalization Risk, and Health Care Utilization and Costs in a United**
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15 5 **Short Title:** Antiretroviral Pill Burden in Medicaid Patients
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20 7 **Authors and Affiliations:** Calvin Cohen,¹ Juliana L. Meyers,² Keith L. Davis²
21

22 8 ¹ CRI New England, Harvard Medical School, Boston, MA, USA
23

24 9 ² RTI Health Solutions, Research Triangle Park, NC, USA
25
26
27 10

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39 15 **Corresponding Author**

40
41 16 Keith L. Davis, MA
42

43 17 RTI Health Solutions
44

45 18 200 Park Offices Drive
46

47
48 19 Research Triangle Park, NC 27709 USA
49

50 20 Telephone: 1.919.541.1273
51

52
53 21 Fax: +1.919.541.7222
54

55 22 E-mail: kldavis@rti.org
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3 **ABSTRACT**
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6 **Objectives:** Lower pill burden leads to improved adherence to antiretroviral therapy (ART)
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8 among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have not been
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10 widely explored in real-world populations. We retrospectively assessed health care utilization
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12 and costs in Medicaid enrollees with HIV treated with ART as a once-daily single-tablet regimen
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14 (STR) or two or more pills per day (2+PPD).
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18 **Design:** Patients with an HIV diagnosis from 2005- 2009 receiving complete ART (i.e., 2
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20 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for 60 days or more as
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22 STR or 2+PPD were selected and followed until the first of 1) discontinuation of the complete
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24 ART, 2) loss of continuous enrollment, or 3) end of the database. Adherence was measured using
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26 the medication possession ratio. Monthly utilization and costs were observed from regimen
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28 initiation until discontinuation and reported overall and by care setting (inpatient, emergency
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30 department, office, pharmacy, other). To assess predictors of hospitalization, Poisson models,
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32 counting the number of hospitalizations and covariates for demographics, comorbidities, and
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34 ART-naïve status, were estimated.
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38 **Results:** Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and
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40 5,584 with 2+PPD. STR patients were significantly more likely to reach a 95% adherence
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42 threshold and had fewer hospitalizations than 2+PPD patients (both: $P < 0.01$). STR patients had
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44 mean (SD) total monthly costs of \$2,959(\$4,962); 2+PPD patients had \$3,544(\$5,811)
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46 ($P < 0.001$). Hospital costs accounted for 53.8% and pharmacy costs accounted for 32.5% of this
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48 difference. Multivariate analyses found that STR treatment led to a 23% reduction in
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50 hospitalizations and a 17% reduction in health care costs.
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45 **Conclusions:** While it was expected that STR patients would have lower pharmacy costs, we
46 also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD
47 patients, resulting in significantly lower total health care costs for STR patients.

For peer review only

ARTICLE SUMMARY

Article Focus

- To assess the effect of a single-tablet-per-day ART regimen (STR) on adherence and hospitalization risk in a large population of Medicaid enrollees in the United States who received treatment for HIV infection

Key Messages

- Patients who received ART as a single pill per day were significantly more likely to be highly adherent to therapy than patients who received multiple-pill regimens.
- Improved adherence among patients treated with STR conferred a lower risk of hospitalization.
- The use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which were higher in patients with less-than-complete medication adherence.

Strengths and Limitations of This Study

- This retrospective analysis used pharmacy refill dates as the best available proxy for pill-taking behavior; one advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis the timing in between refills, which also notes the amount of medication dispensed each time.
- Rates of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should measures of overall monthly health care utilization and costs.

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3 70 ▪ While our prescription claims-based measure of adherence has been found to be a valid
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5 71 proxy for actual medication-taking behavior, we had no measure of actual patient
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8 72 adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
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10 73 ▪ Because we did not randomize patients to the two different treatment regimens, we
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12 74 cannot exclude unmeasured confounding factors that may have influenced our outcomes;
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14 75 although we attempted to control for some of these variables through the use of
15
16 76 multivariable models that included some of these factors (substance abuse and psychiatric
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18 77 diagnoses), residual confounding may remain.
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20 78 ▪ We had no laboratory results from patients and thus cannot confirm the degree of
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22 79 virologic suppression obtained across the regimens.
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80 **ADMINISTRATIVE STATEMENTS**

81 **Protection of Human Subjects**

82 The research organization that conducted this study, RTI Health Solutions, a business unit of
83 RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17,
84 2014) from the Department of Health and Human Services (DHHS) Office for Human Research
85 Protections (OHRP) that allows us to review and approve human subjects protocols through our
86 Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified
87 patient data were analyzed for this study, which involved no patient contact or medical
88 interventions and therefore no patient consent forms, the RTI IRB committee approved this study
89 as exempt.

90 **Author Contributions**

91 Calvin Cohen assisted in development of the study design, evaluated and interpreted the
92 study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith
93 Davis assisted in development of the study design, obtained study funding, conducted all analytic
94 programming and statistical analyses, assisted with evaluation and interpretation of the study

95 **Funding Statement**

96 This study was funded by Gilead Sciences, which is conducting clinical research in and
97 markets current treatments for HIV/AIDS.

98 **Data Sharing**

99 Raw data used for this study are unavailable for public sharing (per terms of the private data
100 use agreement governing original data acquisition).

101 **Acknowledgments**

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103 input on the study design and manuscript.

104 INTRODUCTION

105 The 2012 Department of Health and Human Services guidelines state that there are four
106 preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults.
107 Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating
108 physicians can choose from among these four preferred regimens, using the criteria of greatest
109 efficacy, safety, and simplicity. The latter category is important because regimen simplicity is
110 associated with greater long-term adherence. For example, all four preferred regimens are
111 constructed with a relatively low pill burden (i.e., between one and four tablets per day), and
112 three of the four regimens have once-daily dosing. While randomized trials have compared the
113 components of some of these four regimens with each other, to date no studies compared the four
114 regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study
115 trials have been blinded.[2,3]

116 Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical
117 outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased
118 risk for incomplete viral suppression; and unless a new suppressive regimen is quickly
119 constructed to reestablish virologic suppression, viremia is associated with an increased risk of
120 disease progression, and death.[4-8] In the past several years, the availability of fixed-dose
121 combinations and agents with prolonged half-lives have simplified pill burden and thus increased
122 regimen adherence.[1,9] Several clinical trials and cohort studies support the conclusion that
123 once-daily single tablet regimens (STR) can lead to significantly improved adherence, patient
124 satisfaction, and virological outcomes.[10-13] For example, among homeless or marginally
125 housed patients, those receiving an ART regimen composed of a single tablet per day had better
126 virologic outcomes and a 26% increase in adherence than patients receiving other multi-pill
127 regimens.[13] One recently published study analyzing a claims database noted that compared

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3 128 with various multi-pill regimens, a STR was associated with increased adherence (as determined
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6 129 by pharmacy refill data). Furthermore, the increased likelihood of complete adherence was
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8 130 associated with a 25% decrease in the rate of hospitalization.[14]
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11 131 In this study, we sought to assess how robust these findings were by analyzing similar
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13 132 metrics in a separate data set. The primary objective of this retrospective database analysis was
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15 133 to assess the effect of a single-tablet-per-day ART on adherence and hospitalization in a large
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17 134 population of Medicaid enrollees in the United States who received treatment for HIV infection.
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3 135 **METHODS**
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6 136 Data for this analysis were taken from the MarketScan Medicaid Multi-State Database,
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8 137 which contains health care claims from approximately 30 million Medicaid enrollees from
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10 138 11 geographically dispersed states. The database includes patient-level demographics; periods of
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12 139 Medicaid enrollment; primary and secondary diagnoses; and detailed information about
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14 140 hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and
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16 141 prescription drug use. In compliance with the Health Insurance and Portability and
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18 142 Accountability Act of 1996, all data were de-identified to protect the privacy of individual
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20 143 patients, physicians, and hospitals. Because the data were retrospective, pre-existing, and de-
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22 144 identified, RTI International's institutional review board determined that this study met all
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24 145 criteria for exemption.
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30 146 Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis
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32 147 (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code
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34 148 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have
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36 149 evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse
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38 150 transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse
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40 151 transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease
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42 152 inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of
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44 153 receipt of a complete regimen was termed the index date. ART agents were identified in the
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46 154 claims database by using National Drug Codes associated with relevant generic and brand
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48 155 names. Patients also were required to remain on the complete ART regimen for at least 60 days
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50 156 following their index dates and to have evidence of continuous enrollment in Medicaid during
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52 157 this period. To assess treatment-naïve versus experienced status and baseline comorbidities,
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54 158 patients were required to have at least 6 months of pre-index date Medicaid enrollment, with
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3 159 enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible
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5 160 index date).

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8 161 Patients were grouped into two mutually exclusive cohorts according to the daily pill count
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10 162 of their complete ART regimen. Patients were assigned to the STR cohort if they received an
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12 163 ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection
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14 164 window, regardless of prior or subsequent use of other regimens. At the time of this study, only
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16 165 coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned
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18 166 to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or
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20 167 more pills per day during the selection window and if they did not receive an STR at any point
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22 168 during that time.

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27 169 Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006,
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29 170 the study index date) until the earliest date of regimen discontinuation, disenrollment from the
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31 171 health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving
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33 172 2+PPD were allowed to change medications, providing the patients continued to receive a
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35 173 complete regimen. Patients receiving STR were followed for as long as they remained on the
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37 174 STR. Discontinuation was defined as 60 consecutive days in which no refills were observed for
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39 175 any component of the regimen. Females with an ICD-9-CM diagnosis code indicating a
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41 176 pregnancy during the follow-up period were excluded from the analysis because the one
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43 177 available STR is not recommended for pregnant women, and hospitalizations for labor and
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45 178 delivery may have biased results in favor of the STR.

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50 179 Patient characteristics measured at the index date included age, sex, and ART classes
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52 180 received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide
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54 181 reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence
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56 182 of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-
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3 183 index period, using an established algorithm, the Charlson Comorbidity Index (CCI) score.[15]
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5 184 This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and procedure
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8 185 codes), such as myocardial infarction and chronic pulmonary disease, which are weighted to
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10 186 correspond to the severity of the comorbid condition of interest. A higher comorbidity score
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12 187 represents a higher overall comorbidity burden during the pre-index period. Additionally, the
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14 188 incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx through 319.xx) and
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16 189 drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through 305.xx) during the 6-
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18 190 month pre-index period also was assessed.
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22 191 Medication adherence was assessed using the medication possession ratio (MPR), which has
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24 192 been shown to be the most widely adopted measure (57% of all studies) in published claims-
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26 193 based analyses of medication adherence [16] and has been used in studies of ART adherence
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28 194 among individuals with HIV.[17] The MPR, which is a proxy for refill compliance, generally
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30 195 measures the proportion of the ART exposure period in which supply was maintained for all
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32 196 ART components comprising the regimen. Specifically, MPR was calculated as the number of
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34 197 filled prescription days for all ART regimen components (using the days supplied in the
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36 198 pharmacy claims) divided by the number of days from the first observed prescription in the
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38 199 regimen through the earliest of either the exhaustion of the days supplied of the last observed
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40 200 prescription or the end of follow-up. For each patient in our study, the MPR was calculated over
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42 201 the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD
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44 202 cohort, late refills and resulting days of missing supply for one or more ART components were
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46 203 all factored against their adherence measurements. For example, patients in the 2+PPD cohort
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48 204 with a supply for only one of the ART components on a given day were considered to have zero
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50 205 adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR
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52 206 achieved, we also reported the numbers and percentages of patients achieving various adherence
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3 207 thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-
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5 208 95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).
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8 209 To further understand adherence to ART regimens, for each patient in the 2+PPD cohort,
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10 210 complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components
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12 211 of a complete regimen), and no medication days also were assessed. Specifically, we reported the
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14 212 percentage of days that each patient had complete, partial, and no medications available, along
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16 213 with the mean number of days that the patient had complete, partial and no medications.
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18 214 Additionally, we also reported the maximum number of consecutive days the patient had either
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20 215 an incomplete regimen or no medications available.
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24 216 Hospitalizations were identified from the claims database using relevant place of service
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26 217 codes. Hospitalizations were observed from the index date until the earliest date of regimen
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28 218 discontinuation, end of enrollment in the health plan, or end of the database. The number and
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30 219 percentage of patients with at least one hospitalization were reported, along with the mean (SD)
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32 220 number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we
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34 221 compared and reported the number of hospitalizations per 100 patient-years, along with the rate
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36 222 ratios and 95% confidence intervals, for both cohorts.
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41 223 For each patient, overall health care utilization and associated costs were aggregated across
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43 224 all encounters, regardless of reason, that were observed during the follow-up period; we reported
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45 225 these costs by average and per-month amounts. The following categories of overall health care
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47 226 utilization and costs were evaluated and reported: inpatient, emergency department, office visit,
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49 227 home health visit, laboratory service, pharmacy, other outpatient care, and total. For each
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51 228 category of overall health care, the number and percentage of patients, the mean (SD) number of
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53 229 visits per month, and monthly per-patient costs were reported. Additionally, for patients with an
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3 230 inpatient visit, the average number of inpatient days per month among patients with at least one
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6 231 stay during follow-up also was reported.

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8 232 All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical
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10 233 software. Descriptive analyses were conducted for all outcome measures and included means and
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12 234 SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical
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14 235 variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort.
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16 236 Health care costs were updated to 2010 US dollars using the medical care component of the
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18 237 consumer price index.

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22 238 A generalized linear model with a log link and a Poisson distribution was estimated to assess
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24 239 the relationship between the number of pills per day and the number of hospitalizations observed
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26 240 during follow-up. The dependent variable was a count of hospitalizations during exposure to the
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28 241 ART regimen. Additionally, a generalized linear model with a log link and a negative binomial
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30 242 distribution were estimated to assess monthly health care costs, adjusted for the patient and
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32 243 treatment characteristics. The dependent variables were monthly total costs and monthly total
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34 244 costs excluding costs pharmacy costs. For both models, independent variables included the
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36 245 following: treatment regimen received (i.e., STR vs. 2+PPD), age, sex, CCI score, treatment-
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38 246 naïve status, pre-index presence of mental health disorders, pre-index presence of alcohol or drug
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40 247 abuse disorders, length of follow-up (in days, hospital model only), and whether or not the
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42 248 patient met a 0.95 adherence threshold (cost model only). For the hospital model, incidence rate
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44 249 ratios (IRRs) were reported for all covariates, along with the mean predicted number of
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46 250 hospitalizations for patients receiving an STR versus patients receiving a 2+PPD. For the cost
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48 251 model, adjusted predicted mean costs were reported.

RESULTS

A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART regimen as a STR. On average, patients were approximately 42 years of age. Approximately 46% of patients were female (Table 1). Across both cohorts, the average CCI score was approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD. Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of patients receiving 2+PPD.

Table 1. Characteristics of the study sample, by cohort.

| Characteristic | STR | | 2+PPD | |
|---|-------|---------|-------|---------|
| All Patients (N, %) | 1,797 | 100.00% | 5,584 | 100.00% |
| Age, mean (SD) | 41.6 | (10.56) | 42.32 | (11.37) |
| Age category (N, %) | | | | |
| Aged less than 18 years | 40 | 2.23% | 271 | 4.85% |
| Aged 18 to 24 years | 95 | 5.29% | 139 | 2.49% |
| Aged 25 to 34 years | 269 | 14.97% | 661 | 11.84% |
| Aged 35 to 44 years | 622 | 34.61% | 1,975 | 35.37% |
| Aged 45 to 54 years | 591 | 32.89% | 1,875 | 33.58% |
| Aged 55 to 64 years | 176 | 9.79% | 638 | 11.43% |
| Aged 65+ years | 4 | 0.22% | 25 | 0.45% |
| Gender (N, %) | | | | |
| Male | 945 | 52.59% | 3,063 | 54.85% |
| Female | 852 | 47.41% | 2,521 | 45.15% |
| Charlson comorbidity index score, mean (SD) | 0.67 | (1.38) | 0.65 | (1.36) |
| Charlson comorbidities (N, %) | | | | |
| Myocardial infarction | 11 | 0.61% | 44 | 0.79% |
| Congestive heart failure | 39 | 2.17% | 141 | 2.53% |

| Characteristic | STR | | 2+PPD | |
|---|--------|----------|--------|----------|
| | N | % | N | % |
| Peripheral vascular disease | 14 | 0.78% | 58 | 1.04% |
| Cardiovascular disease | 52 | 2.89% | 148 | 2.65% |
| Dementia | 4 | 0.22% | 10 | 0.18% |
| Chronic pulmonary disease | 259 | 14.41% | 704 | 12.61% |
| Rheumatological disease | 11 | 0.61% | 23 | 0.41% |
| Peptic ulcer disease | 9 | 0.50% | 25 | 0.45% |
| Mild liver disease | 20 | 1.11% | 49 | 0.88% |
| Severe liver disease | 117 | 6.51% | 333 | 5.96% |
| Diabetes mellitus without chronic complications | 145 | 8.07% | 445 | 7.97% |
| Diabetes mellitus with chronic complications | 16 | 0.89% | 89 | 1.59% |
| Paraplegia | 6 | 0.33% | 34 | 0.61% |
| Renal disease | 11 | 0.61% | 80 | 1.43% |
| Cancer | 82 | 4.56% | 221 | 3.96% |
| Metastatic cancer | 11 | 0.61% | 26 | 0.47% |
| Concomitant comorbidities (N, %) | | | | |
| Mental disorders | 382 | 21.26% | 1,340 | 24.00% |
| Drug or alcohol abuse | 338 | 18.81% | 856 | 15.33% |
| Treatment naïve at index (N, %) | 853 | 47.47% | 1,366 | 24.46% |
| Mean (SD) regimen length | 348.17 | (259.32) | 433.46 | (351.50) |
| Index medications (N, %) | | | | |
| NRTI | 1,797 | 100.00% | 5,584 | 100.00% |
| NNRTI | 1,797 | 100.00% | 1,500 | 26.86% |
| PI | 0 | 0.00% | 4,064 | 72.78% |
| Kaletra at index | --- | --- | 1,633 | 40.18% |
| Boosted PI at index | --- | --- | 1,664 | 40.94% |
| Non-boosted PI at index | --- | --- | 767 | 18.87% |
| PE | 0 | 0.00% | 1,712 | 30.66% |
| Other | 0 | 0.00% | 87 | 1.56% |

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD

(Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either a partial regimen or no medications available); patients receiving 2+PPD had, on average, a maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

Table 2. Adherence to antiretroviral therapy, by cohort.

| Cohort | Number of Patients | Mean (SD) MPR | MPR/Persistence Ratio (N, %) | | | | | | | | | |
|-------------------|--------------------|---------------|------------------------------|--------|-------------|--------|-------------|--------|-------------|--------|----------|--------|
| | | | <0.8 | | 0.8 - <0.85 | | 0.85 - <0.9 | | 0.9 - <0.95 | | 0.95 - 1 | |
| STR | 1,797 | 0.84 (0.14) | 537 | 29.88% | 178 | 9.91% | 243 | 13.52% | 385 | 21.42% | 454 | 25.26% |
| 2+PPD | 5,584 | 0.80 (0.15) | 2,255 | 40.38% | 621 | 11.12% | 779 | 13.95% | 957 | 17.14% | 972 | 17.41% |
| Overall | 7,381 | 0.81 (0.15) | 2,792 | 37.83% | 799 | 10.83% | 1,022 | 13.85% | 1,342 | 18.18% | 1,426 | 19.32% |
| P-Value (1 vs. 2) | | <.0001 | <.0001 | | 0.1491 | | 0.6477 | | <.0001 | | <.0001 | |

NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation; STR = once-daily single-tablet regimen.

Table 3. Summary of incomplete adherence, by cohort.

| Adherence Characteristic | STR | 2+PPD |
|--|-----------------|-----------------|
| Percentage of days with complete adherence | 84.42% | 80.37% |
| Percentage of days with partial adherence | --- | 5.56% |
| Percentage of days with no ART medications | 15.58% | 14.07% |
| Complete adherence days, mean (SD) | 299.36 (234.56) | 361.87 (315.03) |
| Partial adherence days, mean (SD) | --- | 22.24 (45.58) |
| Days with no medication available, mean (SD) | 48.81 (54.24) | 49.35 (57.11) |
| Total follow-up duration, mean (SD) | 348.17 (259.31) | 433.46 (351.50) |
| Maximum consecutive gap in therapy, ^a mean (SD) | 19.48 (15.89) | 23.92 (16.67) |

NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR = once-daily single-tablet regimen.

^a Represents either days with a partial regimen or days with no medications.

Among patients receiving an STR, 21.0% had at least one hospitalization, compared with 24.4% of patients receiving 2+PPD ($P = 0.003$) (Table 4). Among patients with a hospitalization, patients receiving an STR had numerically similar, although significantly fewer, hospitalizations over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD; $P = 0.001$).

Table 4. All-cause average monthly per patient health care utilization and costs, by cohort.

| Resource Used | STR | | 2+PPD | | P-Value |
|---|-------|-----------|---------|-----------|---------|
| Hospitalizations | | | | | |
| Had ≥ 1 hospital admission (N, %) ^a | 378 | 21.04% | 1,365 | 24.44% | 0.0031 |
| Number of hospitalizations over all follow-up, ^b mean (SD) | 1.88 | (1.59) | 2.1 | (2.23) | 0.0012 |
| Inpatient days over all follow-up, ^b mean (SD) | 9.99 | (12.33) | 12.33 | (18.90) | 0.0228 |
| Number of admissions per month | | | | | |
| Mean (Std. Dev) | 0.05 | (0.00) | 0.05 | (0.15) | 0.1429 |
| Median | 0 | | 0 | | |
| Range (Min, Max) | 0 | 2 | 0 | 1.97 | |
| Days in hospital per month^c | | | | | |
| Mean (SD) | 1.32 | (2.21) | 1.45 | (2.71) | 0.3975 |
| Median | 0.58 | | 0.5 | | |
| Range (Min, Max) | 0.03 | 21.5 | 0.03 | 32.43 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$834 | (\$4,480) | \$1,152 | (\$5,212) | 0.0203 |
| Median | \$0 | | \$0 | | |
| Range (Min, Max) | \$0 | \$143,530 | \$0 | \$97,626 | |
| Emergency Room (ER) | | | | | |
| Had ≥ 1 ER visit (N, %) ^a | 903 | 50.25% | 2,749 | 49.23% | 0.4517 |
| Number of visits | | | | | |
| Mean (Std. Dev) | 0.97 | (3.00) | 1.01 | (2.99) | 0.6107 |
| Median | 0.03 | | 0 | | |
| Range (Min, Max) | 0 | 67 | 0 | 89.91 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$45 | (\$160) | \$46 | (\$135) | 0.873 |
| Median | \$0 | | \$0 | | |
| Range (Min, Max) | \$0 | \$3,063 | \$0 | \$4,161 | |
| Office Visits (Primary Care) (N, %) | | | | | |
| Had ≥ 1 office visit (N, %) ^a | 1,509 | 83.97% | 4,699 | 84.15% | 0.8576 |

| Resource Used | STR | | 2+PPD | | P-Value |
|--|---------|-----------|---------|-----------|---------|
| Number of visits | | | | | |
| Mean (Std. Dev) | 1.52 | (3.00) | 1.43 | (2.19) | 0.1669 |
| Median | 0.92 | | 0.86 | | |
| Range (Min, Max) | 0 | 61 | 0 | 40.30 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$75 | (\$229) | \$70 | (\$291) | 0.5087 |
| Median | \$30 | | \$26 | | |
| Range (Min, Max) | \$0 | \$5,012 | \$0 | \$15,499 | |
| Home Health (N, %) | | | | | |
| Had ≥ 1 home health visit (N, %) ^a | 504 | 28.05% | 1,861 | 33.33% | <.0001 |
| Number of visits | | | | | |
| Mean (Std. Dev) | 0.64 | (3.00) | 0.79 | (3.16) | 0.0625 |
| Median | 0 | | 0 | | |
| Range (Min, Max) | 0 | 45 | 0 | 43.06 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$47 | (\$198) | \$88 | (\$642) | 0.007 |
| Median | \$0 | | \$0 | | |
| Range (Min, Max) | \$0 | \$4,142 | \$0 | \$36,653 | |
| Laboratory (N, %) | | | | | |
| Had ≥ 1 lab order (N, %) ^a | 1,168 | 65.00% | 3,530 | 63.22% | 0.1722 |
| Number of claims | | | | | |
| Mean (Std. Dev) | 1.24 | (2.00) | 1.19 | (1.69) | 0.2962 |
| Median | 0.66 | | 0.57 | | |
| Range (Min, Max) | 0 | 16 | 0 | 19.96 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$52 | (\$94) | \$46 | (\$120) | 0.0401 |
| Median | \$20 | | \$17 | | |
| Range (Min, Max) | \$0 | \$1,689 | \$0 | \$7,246 | |
| Pharmacy (N, %) | | | | | |
| Had ≥ 1 pharmacy claim (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of claims | | | | | |
| Mean (Std. Dev) | 4.99 | (4.00) | 6.73 | (4.05) | <.0001 |
| Median | 3.96 | | 5.76 | | |
| Range (Min, Max) | 0.37 | 27 | 0.69 | 37.17 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$1,593 | (\$1,105) | \$1,779 | (\$1,307) | <.0001 |
| Median | \$1,494 | | \$1,617 | | |
| Range (Min, Max) | \$0 | \$27,034 | \$0 | \$54,232 | |
| OP/ancillary (N, %) | | | | | |
| Had ≥ 1 other OP/ancillary (N, %) ^a | 1,754 | 97.61% | 5,469 | 97.94% | 0.3957 |
| Number of visits | | | | | |
| Mean (Std. Dev) | 0.15 | (0.00) | 0.14 | (0.13) | 0.0078 |
| Median | 0.12 | | 0.11 | | |
| Range (Min, Max) | 0 | 1 | 0 | 0.52 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$313 | (\$607) | \$363 | (\$733) | 0.0087 |
| Median | \$139 | | \$159 | | |
| Range (Min, Max) | \$0 | \$8,946 | \$0 | \$15,936 | |

| Resource Used | STR | | 2+PPD | | P-Value |
|--|---------|-----------|---------|-----------|---------|
| Total Health Care Utilization & Costs | | | | | |
| Had ≥ 1 medical visit/encounter (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of total encounters | | | | | |
| Mean (Std. Dev) | 14.69 | (14.00) | 16.97 | (13.72) | <.0001 |
| Median | 11.34 | | 13.13 | | |
| Range (Min, Max) | 0.56 | 250 | 0.96 | 232.02 | |
| Costs | | | | | |
| Mean (Std. Dev) | \$2,959 | (\$4,962) | \$3,544 | (\$5,811) | 0.0001 |
| Median | \$1,916 | | \$2,182 | | |
| Range (Min, Max) | \$0 | \$146,367 | \$0 | \$103,103 | |

NOTE: SD = standard deviation.

^aEstimated over all available follow-up.

^bAmong hospitalized patients.

^cAmong patients with at least one admission over all follow-up.

The multivariate Poisson regression model showed that receiving an STR was associated with a significantly lower risk of hospitalization than receiving the 2+PPD regimen (IRR = 0.8457; $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients were significantly more likely to be hospitalized if they had the following characteristics: a concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis; IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male; IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization increased with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$).

Table 5. Predictors of hospitalization, using multivariate Poisson regression, and controlling for treatment cohort.

| Specification: Adherence Covariate Excluded | Poisson Count Model | | |
|---|---------------------|----------------------|---------|
| | Parameter Estimate | Incidence Rate Ratio | P-Value |
| Received a STR (vs. 2+PPD regimen) | -0.1654 | 0.8475 | 0.0001 |
| Female (vs. male) | 0.1003 | 1.1069 | 0.003 |
| Age (vs. less than 35) | | | |
| 35 to 44 years | 0.1016 | 1.2482 | 0.0669 |
| 45 to 54 years | 0.2217 | 1.555 | <.0001 |
| 55+ years | 0.4415 | 1.1056 | <.0001 |
| Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1) | | | |
| Between 1 and 2 | 0.8662 | 2.3779 | <.0001 |
| Greater than 2 | 0.972 | 2.6432 | <.0001 |
| Treatment naïve (vs. treatment experienced) | 0.1196 | 1.127 | 0.0033 |
| Had a mental disorder diagnosis (vs. no mental disorder diagnosis) | 0.256 | 1.2917 | <.0001 |
| Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis) | 0.7109 | 2.0357 | <.0001 |
| Length of follow-up (in days) | 0.0013 | 1.0013 | <.0001 |

NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

From the Poisson regression analysis described above, we found the adjusted rate of hospitalization to be significantly lower for patients receiving an STR than for patients receiving 2+PPD (i.e., 39.5 hospitalizations per 100 patients receiving STR vs. 51.2 hospitalizations per 100 patients receiving 2+PPD) (Figure 2). These adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients receiving an STR, compared with patients receiving 2+PPD.

The percentage of patients with at least one home health visit was significantly lower among patients receiving STR than for patients receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the percentage of patients with at least one emergency room, office visit, or laboratory claim. Similarly, no significant differences were found in the number of emergency room, office visits, home health visits, or laboratory claims per month. However, patients who received an STR had significantly lower costs per month associated with inpatient,

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3 334 home health, laboratory, pharmacy, other, and total health care than patients receiving 2+PPD.
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6 335 Mean (SD) total health care costs per month were \$2,959 (\$4,962) among patients receiving an
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8 336 STR and \$3,544 (\$5,811) among patients receiving 2+PPD; thus, patients receiving an STR
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10 337 accrued, on average per month, \$585 less than patients receiving 2+PPD ($P < 0.001$). The largest
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12 338 difference in costs between the two cohorts was observed for inpatient admissions (\$317 more
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14 339 for patients receiving 2+PPD), followed by pharmacy costs (\$187 more for patients receiving
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16 340 2+PPD).
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20 341 When monthly health care costs were adjusted for demographic, clinical, and treatment
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22 342 characteristics, patients receiving an STR had monthly total costs averaging \$2,947; patients
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24 343 receiving 2+PPD had monthly total costs averaging \$3,549 (Figure 3). Thus, patients receiving
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26 344 2+PPD had \$602 more in monthly health care costs, which corresponded to a 17% reduction in
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28 345 costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy
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30 346 costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving
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32 347 an STR had monthly total costs averaging \$1,370; patients receiving 2+PPD had monthly total
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34 348 costs averaging \$1,797. Thus, patients receiving 2+PPD had \$427 more in adjusted monthly
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36 349 health care costs, which corresponded to a 23.8% reduction in costs associated with STR.
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DISCUSSION

This retrospective database analysis examined adherence to ART regimens among patients with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking behavior. One advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis of the timing in between refills, which also notes the amount of medication dispensed each time. The rate of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should the overall monthly health care utilization and costs.

This analysis largely confirms the previous report from Sax et al.[14]: we found that patients receiving an STR had significantly better adherence rates than patients receiving multiple pills per day. Our other finding was that higher rates of adherence were associated with similar or lower rates of hospitalization, regardless of the regimen; less-than-complete adherence was associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens were associated both with lower rates of complete adherence and correspondingly higher overall health care costs. We observed a significantly higher rate of hospitalizations occurring in patients receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total health care costs were due to differences in both the pharmacy costs of the regimen components as well as the costs of hospitalizations and associated care. Therefore, one implication of our findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in little to no total health care cost-savings for a payer, given the potential risk of more frequent hospitalizations in patients receiving multiple-pill regimens.

Similar to previous studies [18,19], we found that patients who were adherent to therapy were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among patients with the highest levels of complete adherence—at least 95%. This was consistent across

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3 374 both treatment cohorts. This finding suggests that the differences observed in the rates of
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5 375 hospitalizations across regimens are primarily due to differences in adherence rates between the
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8 376 STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially
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10 377 address the potential contribution of channeling bias, a concern with any observational data set.
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12 378 We found that adherent patients on any regimen have similar rates of hospitalization, which
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14 379 suggests that there may not have been a consistent bias to prescribe to more clinically
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16 380 immunosuppressed patients or to patients who were at greater risk for hospitalization due to
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18 381 other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer
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20 382 hospitalizations for patients receiving an STR was consistent when we compared hospitalization
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22 383 risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In
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24 384 the latter group, the impact of stage of illness prior to treatment would be lessened, given the
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26 385 impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen.
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28 386 Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV
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30 387 have shown that patients receiving ART are completely non-adherent (i.e., days with no ART
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32 388 supply/coverage on hand) for approximately 14% of their regimen duration regardless of the
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34 389 number of pills in the regimen [20]. This finding suggests that clinicians are not channeling more
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36 390 adherent patients to STRs. Together, these data support the observation that facilitating greater
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38 391 adherence to ART at any stage of illness may result in reducing hospitalization risk.

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41 392 One follow-up question our study findings raises is whether the observed reduction in
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43 393 hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in
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45 394 patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on
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47 395 hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We
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49 396 found that the majority (~70%) of both STR and 2+PPD patients had no other CCI
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51 397 comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a
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3 398 hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further,
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5 399 among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization
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8 400 compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no
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10 401 comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-
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12 402 adherent patients. Results of this sensitivity analysis, combined with the observation that the vast
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14 403 majority of patients in our study had no major comorbidities (from the CCI) requiring other
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16 404 chronic treatment, suggest that the observed association between poorer adherence and higher
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18 405 hospitalization was likely due to reduced ART adherence and not due to reduced adherence with
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20 406 other medications patients were taking.
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24 407 There were several measurable differences present in the study population at baseline. Our
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26 408 study attempted to control for effects these differences may have had on rates of adherence and
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28 409 hospitalization. We used multivariate regressions to control for patient demographics, treatment
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30 410 characteristics (i.e., treatment naïve vs. experienced, type of ART received, year the ART was
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32 411 received), and clinical characteristics (i.e., CCI score, concomitant mental disorder, drug and
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34 412 alcohol abuse diagnoses). We found a number of factors were associated with an increased risk
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36 413 of poor adherence, including having a CCI score greater than 3; having a drug or alcohol abuse
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38 414 diagnosis; and being treatment experienced. Similarly, having a CCI score greater than 1, or
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40 415 having a concomitant mental disorder or drug or alcohol abuse diagnosis were associated with an
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42 416 increased risk of hospitalization. Nevertheless, after controlling for these factors, we still
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44 417 detected an independent effect of the regimen.
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50 418 One hypothesis for a plausible mechanism by which these outcomes could occur stems from
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52 419 observations in the SMART study.[21] That study, comparing continuous antiviral treatment
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54 420 versus periodic treatment interruptions, demonstrated that HIV treatment interruptions that were
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56 421 of sufficient length of time to lead to recurrent HIV viremia were associated with a significantly
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3 422 higher risk of all-cause morbidity and mortality. Our analysis was consistent with those findings:
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5 423 the mean maximum duration of nonadherence was about 3 weeks, which is a sufficient length of
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8 424 time to expect a return of HIV viremia. The SMART study noted that the higher risk of illness
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10 425 was not necessarily proximal to the time of the interruption but was observed for months
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12 426 afterwards. While there are differences between the SMART study design and population and
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14 427 our study population, our findings are consistent with SMART and with what might be expected
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16 428 in a population who periodically are without antivirals for an average time of more than 3 weeks.
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18 429 Of note, short cycle interruptions of 2 days were not associated with virologic rebound in
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20 430 patients receiving the STR that was used in the SMART study [22]. Therefore, our finding that
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22 431 the typical interruptions were much longer than this is supportive of a mechanism that could
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24 432 have resulted in increased patient morbidity.
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29 433 It is also important to note that patients in this study generally were reasonably adherent to
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31 434 ART, with a mean adherence of just over 80% regardless of the number of pills received per day.
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33 435 This rate of adherence is consistent with other published reports of adherence, although other
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35 436 reports found even higher adherence rates to an STR.[11,12] Furthermore, the difference
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37 437 observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent
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39 438 with what was observed by Sax et al. of 2.2%.[14] This difference is also consistent with the
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41 439 differences in adherence rates reported when comparing average improvement between once-
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43 440 daily and twice-daily regimens (2.9%).[23] It is important to note that there also were highly
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45 441 nonadherent patients to both the STR and the 2+PPD regimes in this study population,
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47 442 supporting the generalizability of this population.
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53 443 Of further note, the differences observed in our study were associated with factors that
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55 444 typically are not present during randomized clinical trials. Randomized trials typically actively
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57 445 work for patient adherence to study medications and use study coordinators to regularly monitor
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3 446 patients to minimize missed doses. In our observational study, these typical adherence supports
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5 447 are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling
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8 448 prescriptions, including partial regimen refills, which would not be observed in clinical trials.
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10 449 While there are concerns about the interpretation of observational data and the determination of
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12 450 causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill
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14 451 regimen would be able to detect the observed differences unless there was less patient support
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16 452 than is standard in clinical trials.
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20 453 Our data do not suggest that all patients should be on an STR. There are many factors that
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22 454 weigh in the decision of which regimen is best for any given patient, including pre-existing
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24 455 virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in
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26 456 association with a lower pill burden is relevant but should not be construed as a suggestion that
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28 457 an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data
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30 458 do support the continued development of additional STR options, to broaden the number of
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32 459 patients for whom this is an option and the number of subsequent beneficial outcomes.
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36 460 Our study has several limitations common to observational claims database analyses.
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38 461 Adherence was calculated by using pharmacy refill dates, and we have no measure of actual
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40 462 patient adherence to the prescriptions they filled. However, this measure has been found to be a
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42 463 useful proxy for actual medication adherence.[24] Because we did not randomize patients to the
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44 464 two different treatment regimens, we cannot exclude unmeasured confounding factors that may
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46 465 have influenced our outcomes. Among the most important of these factors in this study was that
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48 466 multiple trials have shown that medication resistance at the time of virologic failure is
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50 467 significantly less common in boosted PI treatments than on other regimens, including
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52 468 nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.[25,26] Clinicians
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54 469 could have chosen to prescribe a boosted-PI-containing regimen (all of which contain three or
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3 470 more pills per day) to their less-adherent patients. It cannot be determined from this data set that
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5 471 these patients would have been more adherent on an STR. Although we attempted to control for
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8 472 some of these variables through the use of multivariable models that included some of these
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10 473 factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In
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12 474 addition, we had no laboratory results from patients and thus cannot confirm the degree of
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14 475 virologic suppression obtained across the regimens.

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17 476 In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated
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19 477 population) were excluded from the analysis due to their having received incomplete ART
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21 478 regimens. We did not have sufficient data on these patients to explain why their regimens were
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23 479 incomplete. However, a previous study found that physician medication errors were somewhat
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25 480 common in individuals with HIV, with the most common error occurring with boosted PIs
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27 481 (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens
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29 482 observed in our analysis.[27] Increased adoption of fixed-dose combinations as part of HIV
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31 483 treatment may help to alleviate the issue of incomplete regimens.

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34 484 During our study period, the only available single-pill ART regimen was coformulated
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36 485 efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not
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38 486 be generalizable to other one- and multi-pill regimens if other treatments have different efficacy
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40 487 and toxicity profiles. With the recent approval by the Food and Drug Administration of two other
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42 488 STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and
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44 489 cobicistat), it may eventually be possible to explore the applicability of our observations to other
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46 490 STRs.

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49 491 In summary, this study supported the results as reported by Sax et al.[14] We found that
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51 492 patients who received ART as a single pill per day were significantly more likely to be highly
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53 493 adherent to therapy than patients who received multiple-pill regimens. This difference in
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3 494 adherence was associated with a lower risk of hospitalizations: patients with less-than-complete
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6 495 adherence were more likely to be hospitalized. While we acknowledge the limitations associated
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8 496 with any observational study, our data support our finding that the use of an STR may reduce
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10 497 health care costs as well as patient morbidity by decreasing hospitalization rates, which are
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12 498 higher in patients with less-than-complete medication adherence.
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585 **FIGURE LEGENDS**

586 **Figure 1. Sample Selection Flow Chart**

587 **Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort**

588 **Figure 3. Adjusted Monthly Health Care Costs, by Cohort**

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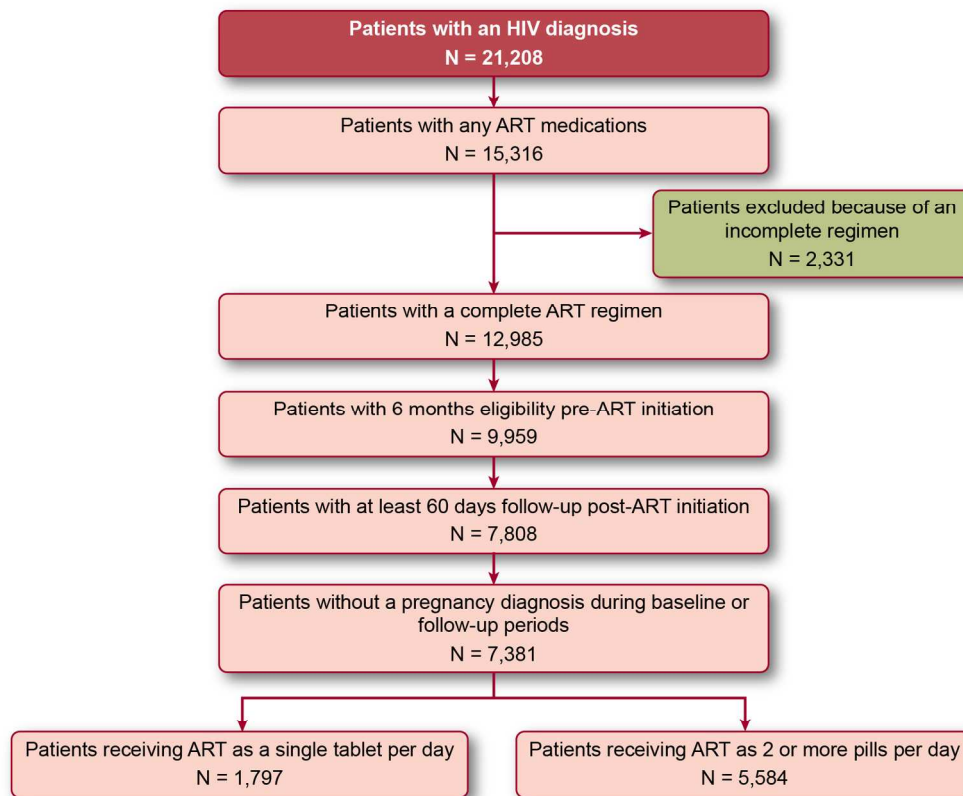


Figure 1. Sample Selection Flow Chart
159x131mm (300 x 300 DPI)

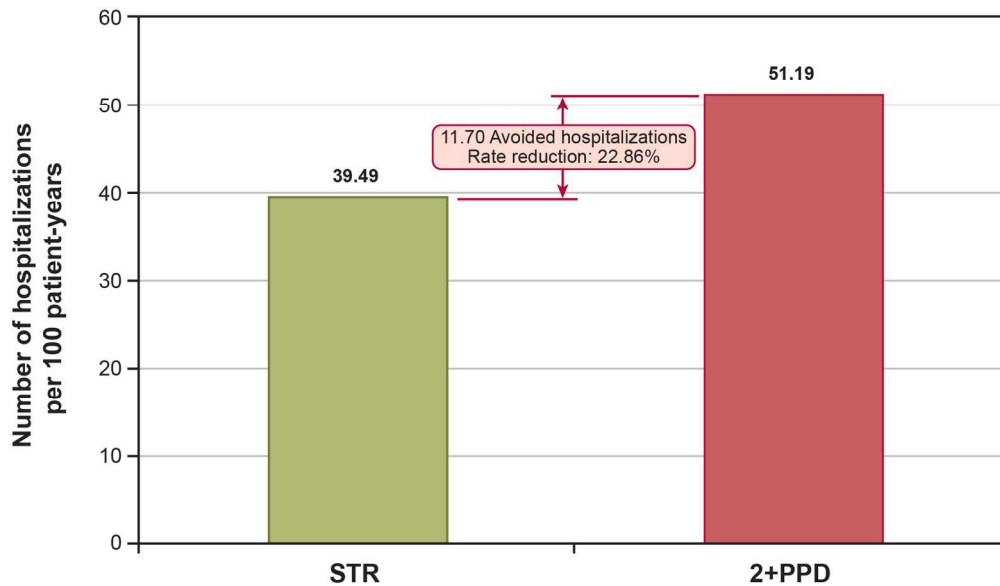


Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort
152x89mm (300 x 300 DPI)

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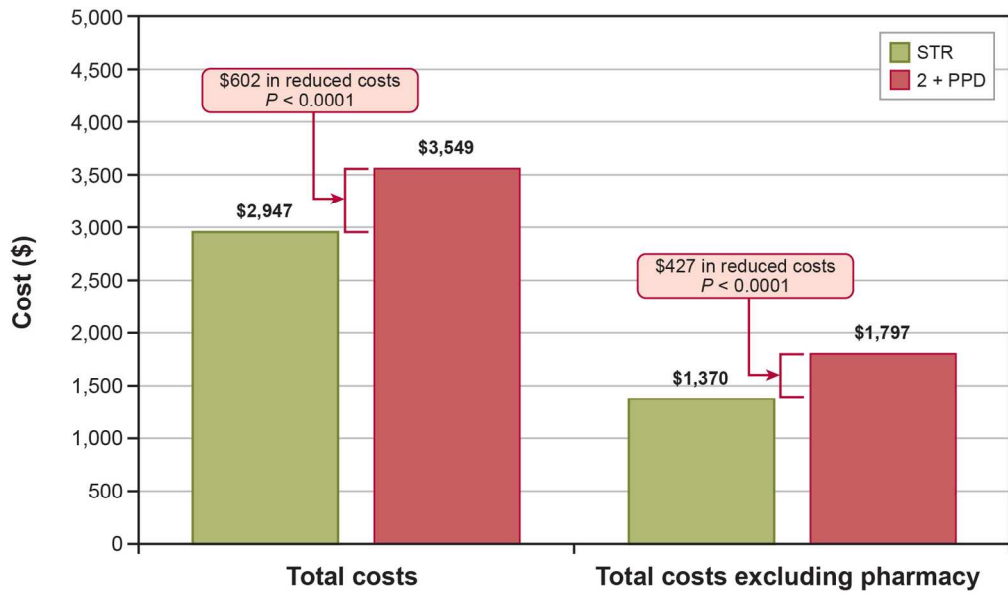


Figure 3. Adjusted Monthly Health Care Costs, by Cohort
152x89mm (300 x 300 DPI)

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Association between Daily Antiretroviral Pill Burden and Treatment Adherence, Hospitalization Risk, and Other Health Care Utilization and Costs in a United States Medicaid Population with HIV

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| Keywords: | HIV & AIDS < INFECTIOUS DISEASES, HEALTH ECONOMICS, THERAPEUTICS |
| | |

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4 1 **Association between Daily Antiretroviral Pill Burden and Treatment**
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6 2 **Adherence, Hospitalization Risk, and Other Health Care Utilization**
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9 3 **and Costs in a United States Medicaid Population with HIV**
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15 5 **Short Title:** Antiretroviral Pill Burden in Medicaid Patients
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20 7 **Authors and Affiliations:** Calvin Cohen,¹ Juliana L. Meyers,² Keith L. Davis²
21

22 8 ¹ CRI New England, Harvard Medical School, Boston, MA, USA
23

24 9 ² RTI Health Solutions, Research Triangle Park, NC, USA
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37
38 15 **Corresponding Author**
39

40 16 Keith L. Davis, MA
41
42

43 17 RTI Health Solutions
44

45 18 200 Park Offices Drive
46
47

48 19 Research Triangle Park, NC 27709 USA
49

50 20 Telephone: 1.919.541.1273
51

52 21 Fax: +1.919.541.7222
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55 22 E-mail: kldavis@rti.org
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3 **ABSTRACT**
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6 **Objectives:** Lower pill burden leads to improved antiretroviral therapy (ART) adherence
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8 among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have not been
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10 widely explored in real-world populations. We retrospectively assessed ART adherence, all-
11
12 cause hospitalization risk and costs, and other health care utilization and costs in Medicaid
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14 enrollees with HIV treated with ART as a once-daily single-tablet regimen (STR) or two or more
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16 pills per day (2+PPD).
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20 **Design:** Patients with an HIV diagnosis from 2005-2009 receiving complete ART (i.e., 2
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22 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for ≥ 60 days as STR or
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24 2+PPD were selected and followed until the first of (1) discontinuation of the complete ART, (2)
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26 loss of enrollment, or (3) end of database. Adherence was measured using the medication
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28 possession ratio. Monthly all-cause health care utilization and costs were observed from regimen
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30 initiation until follow-up end.
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34 **Results:** Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and
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36 5,584 with 2+PPD. STR patients were significantly more likely to reach 95% adherence and had
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38 fewer hospitalizations than 2+PPD patients (both $P < 0.01$). STR patients had mean (SD) total
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40 monthly costs of \$2,959 (\$4,962); 2+PPD patients had \$3,544 (\$5,811) ($P < 0.001$). Hospital costs
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42 accounted for 53.8% and pharmacy costs accounted for 32.5% of this difference. Multivariate
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44 analyses found that STR led to a 23% reduction in hospitalizations and a 17% reduction in
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46 overall health care costs. ART adherence appears to be a key mechanism mediating
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48 hospitalization risk, as patients with $\geq 95\%$ adherence (regardless of regimen type) had a lower
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50 hospitalization rate compared with $< 95\%$ adherence.
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3 45 **Conclusions:** While it was expected that STR patients would have lower pharmacy costs, we
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6 46 also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD
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8 47 patients, resulting in significantly lower total health care costs for STR patients.
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ARTICLE SUMMARY

Article Focus

- To assess the association between a single-tablet-per-day ART regimen (STR) and treatment adherence, all-cause hospitalization risk, and other all-cause health care utilization and costs in a large population of Medicaid enrollees in the United States who received treatment for HIV infection

Key Messages

- Patients who received ART as a single pill per day were significantly more likely to be highly adherent ($\geq 95\%$) to therapy than patients who received multiple-pill regimens.
- Improved adherence among patients treated with STR conferred a lower risk of hospitalization.
- The use of an STR may reduce health care costs as well as patient morbidity by decreasing hospitalization rates, which were higher in patients with less-than-complete medication adherence.

Strengths and Limitations of This Study

- This retrospective analysis used pharmacy refill dates as the best available proxy for pill-taking behavior; one advantage to this method is that we can identify those patients who may not have had all or some of their medications available on any given date based on an analysis the timing in between refills, which also notes the amount of medication dispensed each time.
- Rates of hospitalization and correlates of hospitalization also were assessed from these claims data and should be highly accurate, as should measures of overall monthly health care utilization and costs.

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3 71 ▪ While our prescription claims-based measure of adherence has been found to be a valid
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5 72 proxy for actual medication-taking behavior, we had no measure of actual patient
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7 73 adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
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10 74 ▪ Because we did not randomize patients to the two different treatment regimens, we
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12 75 cannot exclude unmeasured confounding factors that may have influenced our outcomes;
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14 76 although we attempted to control for some of these variables through the use of
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16 77 multivariable models that included some of these factors (substance abuse and psychiatric
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18 78 diagnoses), residual confounding may remain.
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22 79 ▪ We had no laboratory results from patients and thus cannot confirm the degree of
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24 80 virologic suppression obtained across the regimens.
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81 **ADMINISTRATIVE STATEMENTS**

82 **Protection of Human Subjects**

83 The research organization that conducted this study, RTI Health Solutions, a business unit of
84 RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17,
85 2014) from the Department of Health and Human Services (DHHS) Office for Human Research
86 Protections (OHRP) that allows us to review and approve human subjects protocols through our
87 Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified
88 patient data were analyzed for this study, which involved no patient contact or medical
89 interventions and therefore no patient consent forms, the RTI IRB committee approved this study
90 as exempt.

91 **Author Contributions**

92 Calvin Cohen assisted in development of the study design, evaluated and interpreted the
93 study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith
94 Davis assisted in development of the study design, obtained study funding, conducted all analytic
95 programming and statistical analyses, assisted with evaluation and interpretation of the study

96 **Funding Statement**

97 This study was funded by Gilead Sciences, which is conducting clinical research in and
98 markets current treatments for HIV/AIDS.

99 **Data Sharing**

100 Raw data used for this study are unavailable for public sharing (per terms of the private data
101 use agreement governing original data acquisition).

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104 input on the study design and manuscript.

105 INTRODUCTION

106 The 2012 Department of Health and Human Services guidelines state that there are four
107 preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults.
108 Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating
109 physicians can choose from among these four preferred regimens, using the criteria of greatest
110 efficacy, safety, and simplicity. The latter category is important because regimen simplicity is
111 associated with greater long-term adherence. For example, all four preferred regimens are
112 constructed with a relatively low pill burden (i.e., between one and four tablets per day), and
113 three of the four regimens have once-daily dosing. While randomized trials have compared the
114 components of some of these four regimens with each other, to date no studies compared the four
115 regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study
116 trials have been blinded.[2,3]

117 Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical
118 outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased
119 risk for incomplete viral suppression; and unless a new suppressive regimen is quickly
120 constructed to reestablish virologic suppression, viremia is associated with an increased risk of
121 disease progression and death.[4-8] It has been suggested that an ART adherence rate of at least
122 95% is required to achieve a lower risk of virologic failure, fewer hospital days, and reduced
123 morbidity and mortality in patients with HIV[8-9], although one previous study indicated that
124 viral suppression may be possible at less than 95% adherence.[10] In the past several years, the
125 availability of fixed-dose combinations and agents with prolonged half-lives have simplified pill
126 burden and thus increased regimen adherence.[1,11] Several clinical trials and cohort studies
127 support the conclusion that once-daily single tablet regimens (STR) can lead to significantly
128 improved adherence, patient satisfaction, and virological outcomes.[12-15] For example, among

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3 129 homeless or marginally housed patients, those receiving an ART regimen composed of a single
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6 130 tablet per day had better virologic outcomes and a 26% increase in adherence than patients
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8 131 receiving other multi-pill regimens.[15] One recently published study analyzing a claims
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10 132 database noted that compared with various multi-pill regimens, a STR was associated with
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12 133 increased adherence (as determined by pharmacy refill data). Furthermore, the increased
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14 134 likelihood of complete adherence was associated with a 25% decrease in the rate of
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16 135 hospitalization.[16]

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20 136 In this study, we sought to assess how robust these findings were by analyzing similar
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22 137 metrics in a separate data set. The primary objective of this retrospective database analysis was
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24 138 to assess the association between a single-tablet-per-day ART regimen and treatment adherence,
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26 139 all-cause hospitalization risk, and total all-cause health care costs in a large population of
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28 140 Medicaid enrollees in the United States (US) who received treatment for HIV infection. The
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30 141 secondary objective of this study was to examine the association between STR and other types of
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32 142 all-cause health care utilization (emergency department, pharmacy, outpatient, and other service
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34 143 types) and costs.
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3 144 **METHODS**
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6 145 Data for this analysis were taken from the MarketScan Medicaid Multi-State Database,
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8 146 which contains health care claims from approximately 30 million Medicaid enrollees from
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10 147 11 geographically dispersed states. The database includes patient-level demographics; periods of
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12 148 Medicaid enrollment; primary and secondary diagnoses; and detailed information about
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14 149 hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and
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16 150 prescription drug use. Each medical and pharmacy claim in the database also includes original
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18 151 cost information, which represents direct paid amounts (in US dollars) from Medicaid to
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20 152 providers for each service or prescription. In compliance with the Health Insurance and
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22 153 Portability and Accountability Act of 1996, all data were de-identified to protect the privacy of
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24 154 individual patients, physicians, and hospitals. Because the data were retrospective, pre-existing,
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26 155 and de-identified, RTI International's institutional review board determined that this study met
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28 156 all criteria for exemption from requirements of patient consent.
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34 157 Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis
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36 158 (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code
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38 159 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have
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40 160 evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse
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42 161 transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse
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44 162 transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease
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46 163 inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of
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48 164 receipt of a complete regimen was termed the index date. ART agents were identified in the
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50 165 claims database by using National Drug Codes associated with relevant generic and brand
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52 166 names. Patients also were required to remain on the complete ART regimen for at least 60 days
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54 167 following their index dates and to have evidence of continuous enrollment in Medicaid during
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3 168 this period. To assess treatment-naïve versus experienced status and baseline comorbidities,
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5 169 patients were required to have at least 6 months of pre-index date Medicaid enrollment, with
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8 170 enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible
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10 171 index date).

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13 172 Patients were grouped into two mutually exclusive cohorts according to the daily pill count
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15 173 of their complete ART regimen. Patients were assigned to the STR cohort if they received an
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17 174 ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection
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20 175 window, regardless of prior or subsequent use of other regimens. At the time of this study, only
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22 176 coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned
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24 177 to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or
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27 178 more pills per day during the selection window and if they did not receive an STR at any point
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29 179 during that time.

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32 180 Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006,
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34 181 the study index date) until the earliest date of regimen discontinuation, disenrollment from the
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36 182 health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving
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39 183 2+PPD were allowed to change medications comprising the regimen, provided that the patients
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41 184 continued to receive a combination of agents that could still be classified as a complete 2+PPD
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43 185 regimen. Patients receiving STR were followed for as long as they remained on the STR.
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46 186 Discontinuation was defined as 60 consecutive days in which no refills were observed for any
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48 187 component of the regimen. Females with an ICD-9-CM diagnosis code indicating a pregnancy
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50 188 during the follow-up period were excluded from the analysis because the one available STR is
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53 189 not recommended for pregnant women, and hospitalizations for labor and delivery may have
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55 190 biased results in favor of the STR.
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3 191 Patient characteristics measured at the index date included age, sex, and ART classes
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6 192 received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide
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8 193 reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence
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10 194 of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-
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12 195 index period, using an established algorithm, the Charlson Comorbidity Index (CCI) score.[17]
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15 196 This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and procedure
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17 197 codes), such as myocardial infarction and chronic pulmonary disease, which are weighted to
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19 198 correspond to the severity of the comorbid condition of interest. A higher comorbidity score
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21 199 represents a higher overall comorbidity burden during the pre-index period. Additionally, the
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23 200 incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx through 319.xx) and
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25 201 drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through 305.xx) during the 6-
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27 202 month pre-index period also was assessed.
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31 203 Medication adherence was assessed using the medication possession ratio (MPR), which has
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33 204 been shown to be the most widely adopted measure (57% of all studies) in published claims-
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35 205 based analyses of medication adherence [18] and has been used in studies of ART adherence
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37 206 among individuals with HIV.[19] The MPR, which is a proxy for refill compliance, generally
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39 207 measures the proportion of the ART exposure period in which supply was maintained for all
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41 208 ART components comprising the regimen. Specifically, MPR was calculated as the number of
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43 209 filled prescription days for all ART regimen components (using the days supplied in the
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45 210 pharmacy claims) divided by the number of days from the first observed prescription in the
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47 211 regimen through the earliest of either the exhaustion of the days supplied of the last observed
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49 212 prescription or the end of follow-up. For each patient in our study, the MPR was calculated over
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51 213 the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD
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53 214 cohort, late refills and resulting days of missing supply for one or more ART components were
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3 215 all factored against their adherence measurements. For example, patients in the 2+PPD cohort
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6 216 with a supply for only one of the ART components on a given day were considered to have zero
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8 217 adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR
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10 218 achieved, we also reported the numbers and percentages of patients achieving various adherence
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12 219 thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-
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14 220 95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).

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17 221 To further understand adherence to ART regimens, for each patient in the 2+PPD cohort,
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19 222 complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components
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21 223 of a complete regimen), and no medication days also were assessed. Specifically, we reported the
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23 224 percentage of days that each patient had complete, partial, and no medications available, along
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25 225 with the mean number of days that the patient had complete, partial and no medications.
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27 226 Additionally, we also reported the maximum number of consecutive days the patient had either
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29 227 an incomplete regimen or no medications available.

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32 228 Hospitalizations were identified from the claims database using relevant place of service
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34 229 codes. Hospitalizations were observed from the index date until the earliest date of regimen
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36 230 discontinuation, end of enrollment in the health plan, or end of the database. The number and
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38 231 percentage of patients with at least one hospitalization were reported, along with the mean (SD)
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40 232 number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we
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42 233 compared and reported the number of hospitalizations per 100 patient-years, along with the rate
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44 234 ratios and 95% confidence intervals, for both cohorts as well as by adherence status (at least 95%
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46 235 vs. less than 95%).

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49 236 For each patient, overall health care utilization and associated costs were aggregated across
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51 237 all encounters, regardless of reason, that were observed during the follow-up period; we reported
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53 238 these costs by average and per-month amounts. The following categories of overall health care
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3 239 utilization and costs were evaluated and reported: inpatient, emergency department, office visit,
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6 240 home health visit, laboratory service, pharmacy, other outpatient care, and total. For each
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8 241 category of overall health care, the number and percentage of patients, the mean (SD) number of
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10 242 visits per month, and monthly per-patient costs were reported. Additionally, for patients with an
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12 243 inpatient visit, the average number of inpatient days per month among patients with at least one
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15 244 stay during follow-up also was reported. All cost data, which represented payments incurred by
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17 245 the Medicaid system, were standardized at the claim level to 2010 US dollars using the medical
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20 246 care component of the US Consumer Price Index.

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22 247 All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical
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24 248 software. Descriptive analyses were conducted for all outcome measures and included means and
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27 249 SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical
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29 250 variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort.
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31 251 Health care costs were updated to 2010 US dollars using the medical care component of the
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34 252 consumer price index.

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36 253 A generalized linear model with a log link and a Poisson distribution was estimated to assess
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38 254 the relationship between the number of pills per day and the number of hospitalizations observed
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41 255 during follow-up. The dependent variable was a count of hospitalizations during exposure to the
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43 256 ART regimen. Additionally, a generalized linear model with a log link and a negative binomial
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46 257 distribution were estimated to assess monthly health care costs, adjusted for the patient and
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48 258 treatment characteristics. The dependent variables were monthly total costs and monthly total
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50 259 costs excluding costs pharmacy costs. For both models, based on previous work by Sax et al.
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53 260 [16], independent variables included the following: treatment regimen received (i.e., STR vs.
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55 261 2+PPD), age, sex, CCI score, treatment-naïve status, pre-index presence of mental health
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58 262 disorders, pre-index presence of alcohol or drug abuse disorders, length of follow-up (in days,
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3 263 hospital model only), and whether or not the patient met a 0.95 adherence threshold (cost model
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6 264 only). For the hospital model, incidence rate ratios (IRRs) were reported for all covariates, along
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8 265 with the mean predicted number of hospitalizations for patients receiving an STR versus patients
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10 266 receiving a 2+PPD. For the cost model, adjusted predicted mean costs were reported.
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267 RESULTS

268 A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients
 269 (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART
 270 regimen as a STR. On average, patients were approximately 42 years of age. Approximately
 271 46% of patients were female (Table 1). Across both cohorts, the average CCI score was
 272 approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65
 273 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental
 274 disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients
 275 receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months
 276 shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD.
 277 Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of
 278 patients receiving 2+PPD.

279 **Table 1. Characteristics of the study sample, by cohort.**

| Characteristic | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P Value |
|--------------------------------------|--------------------|---------|----------------------|---------|---------|
| Age , mean (SD) | 41.6 | (10.56) | 42.32 | (11.37) | 0.0137 |
| Gender (N, %) | | | | | |
| Male | 945 | 52.59% | 3,063 | 54.85% | 0.1123 |
| Female | 852 | 47.41% | 2,521 | 45.15% | 0.1439 |
| Race (N, %) | | | | | |
| White | 387 | 21.54% | 1,221 | 21.87% | 0.8893 |
| Black | 1,187 | 66.05% | 3,658 | 65.51% | 0.6877 |
| Hispanic | 18 | 1.00% | 82 | 1.47% | 0.7844 |
| Other | 204 | 11.35% | 621 | 11.12% | 0.7846 |
| Unknown | 1 | 0.06% | 2 | 0.04% | 0.8766 |
| Basis of Medicaid Eligibility (N, %) | | | | | |
| Aged | 1 | 0.06% | 8 | 0.14% | 0.5634 |
| Disabled | 1,089 | 60.60% | 4,071 | 72.90% | <.0001 |
| Income | 583 | 32.44% | 1,159 | 20.76% | <.0001 |
| Other | 58 | 3.23% | 202 | 3.61% | 0.8710 |
| Unknown | 65 | 3.62% | 141 | 2.53% | 0.0487 |
| Medicare Eligibility (N, %) | | | | | |

| Characteristic | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P Value |
|--|--------------------|----------|----------------------|----------|---------|
| | N | % | N | % | |
| Not dually eligible | 1,791 | 99.67% | 5,558 | 99.53% | 0.9987 |
| Dually eligible | 5 | 0.28% | 24 | 0.43% | 0.6523 |
| Unknown | 1 | 0.05% | 2 | 0.04% | 0.9014 |
| Charlson comorbidity index score, mean (SD) | 0.67 | (1.38) | 0.65 | (1.36) | 0.5919 |
| Concomitant mental health and substance abuse comorbidities (N, %) | | | | | |
| Mental disorders | 382 | 21.26% | 1,340 | 24.00% | 0.0456 |
| Drug or alcohol abuse | 338 | 18.81% | 856 | 15.33% | 0.0323 |
| Treatment naïve at index (N, %) | 853 | 47.47% | 1,366 | 24.46% | <.0001 |
| Regimen length, mean (SD) | 348.17 | (259.32) | 433.46 | (351.50) | <.0001 |
| Index medications (N, %) | | | | | |
| NRTI | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| NNRTI | 1,797 | 100.00% | 1,500 | 26.86% | <.0001 |
| PI | --- | --- | 4,064 | 72.78% | --- |
| Kaletra at index | --- | --- | 1,633 | 40.18% | --- |
| Boosted PI at index | --- | --- | 1,664 | 40.94% | --- |
| Non-boosted PI at index | --- | --- | 767 | 18.87% | --- |
| PE | --- | --- | 1,712 | 30.66% | --- |
| Other | --- | --- | 87 | 1.56% | --- |

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD (Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which

294 was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on
 295 average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either
 296 a partial regimen or no medications available); patients receiving 2+PPD had, on average, a
 297 maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

298 **Table 2. Adherence to antiretroviral therapy, by cohort.**

| Cohort | Number of Patients | Mean (SD) MPR | MPR/Persistence Ratio (N, %) | | | | |
|-------------------|--------------------|---------------|------------------------------|-------------|--------------|--------------|--------------|
| | | | <0.8 | 0.8 - <0.85 | 0.85 - <0.9 | 0.9 - <0.95 | 0.95 - 1 |
| STR | 1,797 | 0.84 (0.14) | 537 29.88% | 178 9.91% | 243 13.52% | 385 21.42% | 454 25.26% |
| 2+PPD | 5,584 | 0.80 (0.15) | 2,255 40.38% | 621 11.12% | 779 13.95% | 957 17.14% | 972 17.41% |
| Overall | 7,381 | 0.81 (0.15) | 2,792 37.83% | 799 10.83% | 1,022 13.85% | 1,342 18.18% | 1,426 19.32% |
| P-Value (1 vs. 2) | | <.0001 | <.0001 | 0.1491 | 0.6477 | <.0001 | <.0001 |

299 NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation;
 300 STR = once-daily single-tablet regimen.

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302 **Table 3. Summary of incomplete adherence, by cohort.**

| Adherence Characteristic | STR (n = 1,797) | 2+PPD (n = 5,584) | P Value |
|--|-----------------|-------------------|---------|
| Percentage of days with complete adherence | 84.42% | 80.37% | <.0001 |
| Percentage of days with partial adherence | --- | 5.56% | --- |
| Percentage of days with no ART medications | 15.58% | 14.07% | 0.0356 |
| Complete adherence days, mean (SD) | 299.36 (234.56) | 361.87 (315.03) | <.0001 |
| Partial adherence days, mean (SD) | --- | 22.24 (45.58) | --- |
| Days with no medication available, mean (SD) | 48.81 (54.24) | 49.35 (57.11) | 0.0356 |
| Total follow-up duration, mean (SD) | 348.17 (259.31) | 433.46 (351.50) | <.0001 |
| Maximum consecutive gap in therapy, ^a mean (SD) | 19.48 (15.89) | 23.92 (16.67) | <.0001 |

303 NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR =
 304 once-daily single-tablet regimen.

305 ^a Represents either days with a partial regimen or days with no medications.

306

307 Among patients receiving an STR, 21.0% had at least one hospitalization, compared with

308 24.4% of patients receiving 2+PPD ($P = 0.003$) (Table 4). Among patients with a hospitalization,

309 patients receiving an STR had numerically similar, although significantly fewer, hospitalizations

310 over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9

311 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD;
 312 $P = 0.001$).

313 **Table 4. All-cause average per patient health care utilization and costs, by cohort.**

| Resource Used | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P-Value |
|--|--------------------|-----------|----------------------|-----------|---------|
| Hospitalizations | | | | | |
| Had ≥ 1 hospital admission (N, %) ^a | 378 | 21.04% | 1,365 | 24.44% | 0.0031 |
| Number of hospitalizations (over all follow-up) ^b mean (SD) | 1.88 | (1.59) | 2.1 | (2.23) | 0.0012 |
| Inpatient days (over all follow-up) ^b mean (SD) | 9.99 | (12.33) | 12.33 | (18.90) | 0.0228 |
| Costs per month, mean (SD) | \$834 | (\$4,480) | \$1,152 | (\$5,212) | 0.0203 |
| Emergency Room (ER) | | | | | |
| Had ≥ 1 ER visit (N, %) ^a | 903 | 50.25% | 2,749 | 49.23% | 0.4517 |
| Number of visits per month, mean (SD) | 0.97 | (3.00) | 1.01 | (2.99) | 0.6107 |
| Costs per month, mean (SD) | \$45 | (\$160) | \$46 | (\$135) | 0.873 |
| Office Visits (Primary Care) (N, %) | | | | | |
| Had ≥ 1 office visit (N, %) ^a | 1,509 | 83.97% | 4,699 | 84.15% | 0.8576 |
| Number of visits per month, mean (SD) | 1.52 | (3.00) | 1.43 | (2.19) | 0.1669 |
| Costs per month, mean (SD) | \$75 | (\$229) | \$70 | (\$291) | 0.5087 |
| Home Health (N, %) | | | | | |
| Had ≥ 1 home health visit (N, %) ^a | 504 | 28.05% | 1,861 | 33.33% | <.0001 |
| Number of visits per month, mean (SD) | 0.64 | (3.00) | 0.79 | (3.16) | 0.0625 |
| Costs per month, mean (SD) | \$47 | (\$198) | \$88 | (\$642) | 0.007 |
| Laboratory (N, %) | | | | | |
| Had ≥ 1 lab order (N, %) ^a | 1,168 | 65.00% | 3,530 | 63.22% | 0.1722 |
| Number of lab tests per month, mean (SD) | 1.24 | (2.00) | 1.19 | (1.69) | 0.2962 |
| Costs per month, mean (SD) | \$52 | (\$94) | \$46 | (\$120) | 0.0401 |
| Pharmacy (N, %) | | | | | |
| Had ≥ 1 pharmacy claim (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of prescriptions per month, mean (SD) | 4.99 | (4.00) | 6.73 | (4.05) | <.0001 |
| Costs per month, mean (SD) | \$1,593 | (\$1,105) | \$1,779 | (\$1,307) | <.0001 |
| OP/ancillary (N, %) | | | | | |
| Had ≥ 1 other OP/ancillary (N, %) ^a | 1,754 | 97.61% | 5,469 | 97.94% | 0.3957 |
| Number of visits per month, mean (SD) | 0.15 | (0.00) | 0.14 | (0.13) | 0.0078 |
| Costs per month, mean (SD) | \$313 | (\$607) | \$363 | (\$733) | 0.0087 |
| Total Health Care Utilization and Costs | | | | | |
| Had ≥ 1 medical visit/encounter (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of total encounters per month, mean (SD) | 14.69 | (14.00) | 16.97 | (13.72) | <.0001 |
| Costs per month, mean (SD) | \$2,959 | (\$4,962) | \$3,544 | (\$5,811) | 0.0001 |

314 NOTE: SD = standard deviation.

315 ^aEstimated over all available follow-up.

316 ^bAmong hospitalized patients.

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319 The multivariate Poisson regression model showed that receiving an STR was associated
 320 with a significantly lower hospitalization rate than receiving the 2+PPD regimen (IRR = 0.8457;
 321 $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients
 322 were significantly more likely to be hospitalized if they had the following characteristics: a
 323 concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis;
 324 IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant
 325 drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR
 326 increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to
 327 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male;
 328 IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased
 329 with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555
 330 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization
 331 increased slightly with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$). Finally,
 332 being treatment naïve prior to index was predictive of an approximately 13% higher
 333 hospitalization rate as compared with being treatment experienced (IRR = 1.1270; $P = 0.0033$).

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335 **Table 5. Predictors of hospitalization, using multivariate Poisson regression, and**
 336 **controlling for treatment cohort.**

| Specification: Adherence Covariate Excluded | Poisson Count Model | | |
|---|---------------------|----------------------|---------|
| | Parameter Estimate | Incidence Rate Ratio | P-Value |
| Received a STR (vs. 2+PPD regimen) | -0.1654 | 0.8475 | 0.0001 |
| Female (vs. male) | 0.1003 | 1.1069 | 0.003 |
| Age (vs. less than 35) | | | |
| 35 to 44 years | 0.1016 | 1.2482 | 0.0669 |

| Specification: Adherence Covariate Excluded | Poisson Count Model | | |
|---|---------------------|----------------------|---------|
| | Parameter Estimate | Incidence Rate Ratio | P-Value |
| 45 to 54 years | 0.2217 | 1.5550 | <.0001 |
| 55+ years | 0.4415 | 1.1056 | <.0001 |
| Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1) | | | |
| Between 1 and 2 | 0.8662 | 2.3779 | <.0001 |
| Greater than 2 | 0.972 | 2.6432 | <.0001 |
| Treatment naïve (vs. treatment experienced) | 0.1196 | 1.1270 | 0.0033 |
| Had a mental disorder diagnosis (vs. no mental disorder diagnosis) | 0.256 | 1.2917 | <.0001 |
| Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis) | 0.7109 | 2.0357 | <.0001 |
| Length of follow-up (in days) | 0.0013 | 1.0013 | <.0001 |

NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

From the Poisson regression analysis described above, we found the adjusted rate of hospitalization to be significantly lower for patients receiving an STR than for patients receiving 2+PPD (i.e., 39.5 hospitalizations per 100 patient-years for patients receiving STR vs. 51.2 hospitalizations per 100 patient-years for those receiving 2+PPD) (Figure 2). These adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients receiving an STR, compared with patients receiving 2+PPD. As shown in Figure 3, adherence status seems to be a key mechanism mediating hospitalization risk as patients with at least 95% adherence (regardless of regimen type) had a statistically significant lower hospitalization rate compared to patients with less than 95% adherence. Improved adherence among patients treated with STR therefore appears to confer a lower risk of hospitalization and associated costs.

Examining other types of health care utilization, the percentage of patients with at least one home health visit was significantly lower among patients receiving STR than for patients receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the percentage of patients with at least one emergency room, office visit, or laboratory claim.

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3 353 Similarly, no significant differences were found in the number of emergency room, office visits,
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5 354 home health visits, or laboratory claims per month. However, patients who received an STR had
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8 355 significantly lower costs per month associated with inpatient, home health, laboratory, pharmacy,
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10 356 other, and total health care than patients receiving 2+PPD. Mean (SD) total health care costs per
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12 357 month were \$2,959 (\$4,962) among patients receiving an STR and \$3,544 (\$5,811) among
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14 358 patients receiving 2+PPD; thus, patients receiving an STR accrued, on average per month, \$585
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16 359 less than patients receiving 2+PPD ($P < 0.001$). The largest difference in costs between the two
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18 360 cohorts was observed for inpatient admissions (\$317 more for patients receiving 2+PPD),
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20 361 followed by pharmacy costs (\$187 more for patients receiving 2+PPD).

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22 362 When monthly health care costs were adjusted for demographic, clinical, and treatment
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24 363 characteristics, patients receiving an STR had monthly total costs averaging \$2,947; patients
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26 364 receiving 2+PPD had monthly total costs averaging \$3,549 (Figure 4). Thus, patients receiving
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28 365 2+PPD had \$602 more in monthly health care costs, which corresponded to a 17% reduction in
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30 366 costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy
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32 367 costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving
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34 368 an STR had monthly total costs averaging \$1,370; patients receiving 2+PPD had monthly total
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36 369 costs averaging \$1,797. Thus, patients receiving 2+PPD had \$427 more in adjusted monthly
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38 370 health care costs, which corresponded to a 23.8% reduction in costs associated with STR.
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3 371 **DISCUSSION**
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6 372 This retrospective database analysis examined adherence to ART regimens among patients
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8 373 with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking
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10 374 behavior. One advantage to this method is that we can identify those patients who may not have
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12 375 had all or some of their medications available on any given date based on an analysis of the
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14 376 timing in between refills, which also notes the amount of medication dispensed each time. The
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16 377 rate of hospitalization and correlates of hospitalization also were assessed from these claims data
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20 378 and should be highly accurate, as should the overall monthly health care utilization and costs.
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23 379 This analysis largely confirms the previous report from Sax et al.[16]: we found that patients
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25 380 receiving an STR had significantly better adherence rates than patients receiving multiple pills
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27 381 per day. Our other finding was that higher rates of adherence were associated with similar or
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29 382 lower rates of hospitalization, regardless of the regimen; less-than-complete adherence was
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31 383 associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens
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33 384 were associated both with lower rates of complete adherence and correspondingly higher overall
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35 385 health care costs. We observed a significantly higher rate of hospitalizations occurring in patients
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37 386 receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total
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39 387 health care costs were due to differences in both the pharmacy costs of the regimen components
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41 388 as well as the costs of hospitalizations and associated care. Therefore, one implication of our
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43 389 findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in
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45 390 little to no total health care cost-savings for a payer, given the potential risk of more frequent
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47 391 hospitalizations in patients receiving multiple-pill regimens.
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52 392 Similar to previous studies [20,21], we found that patients who were adherent to therapy
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54 393 were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among
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56 394 patients with the highest levels of complete adherence—at least 95%. This was consistent across
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3 395 both treatment cohorts. This finding suggests that the differences observed in the rates of
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5 396 hospitalizations across regimens are primarily due to differences in adherence rates between the
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8 397 STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially
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10 398 address the potential contribution of channeling bias, a concern with any observational data set.
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12 399 We found that adherent patients on any regimen have similar rates of hospitalization, which
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14 400 suggests that there may not have been a consistent bias to prescribe to more clinically
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16 401 immunosuppressed patients or to patients who were at greater risk for hospitalization due to
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18 402 other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer
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20 403 hospitalizations for patients receiving an STR was consistent when we compared hospitalization
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22 404 risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In
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24 405 the latter group, the impact of stage of illness prior to treatment would be lessened, given the
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26 406 impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen.
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28 407 Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV
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30 408 have shown that patients receiving ART are completely non-adherent (i.e., days with no ART
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32 409 supply/coverage on hand) for approximately 14% of their regimen duration regardless of the
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34 410 number of pills in the regimen [22]. This finding suggests that clinicians are not channeling more
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36 411 adherent patients to STRs. Together, these data support the observation that facilitating greater
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38 412 adherence to ART at any stage of illness may result in reducing hospitalization risk.
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46 413 One follow-up question our study findings raises is whether the observed reduction in
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48 414 hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in
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50 415 patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on
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52 416 hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We
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54 417 found that the majority (~70%) of both STR and 2+PPD patients had no other CCI
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56 418 comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a
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3 419 hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further,
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5 420 among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization
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7 421 compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no
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9 422 comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-
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11 423 adherent patients. Results of this sensitivity analysis, combined with the observation that the vast
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13 424 majority of patients in our study had no major comorbidities (from the CCI) requiring other
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15 425 chronic treatment, suggest that the observed association between poorer adherence and higher
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17 426 hospitalization was likely due to reduced ART adherence and not due to reduced adherence with
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19 427 other medications patients were taking.
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24 428 There were several measurable differences present in the study population at baseline. Our
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26 429 study attempted to control for effects these differences may have had on rates of hospitalization
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28 430 between STR and 2+PPD patients. We used multivariate regressions to control for patient
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30 431 demographics, treatment characteristics (i.e., treatment naïve vs. experienced, type of ART
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32 432 received), and clinical characteristics (i.e., CCI score, concomitant mental disorder, drug and
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34 433 alcohol abuse diagnoses). We found that a number of factors were associated with an increased
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36 434 risk of hospitalization independent of treatment regimen, including having a CCI score greater
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38 435 than 1; having a concomitant drug or alcohol abuse diagnosis; having a concomitant mental
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40 436 health disorder; being female and of older age; and being treatment naïve.
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45 437 Even after controlling for the factors noted above, we still detected an independent
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47 438 association of regimen type with hospitalization rates and, in fact, observed an increase in the
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49 439 apparent protective effect of STR based on the predicted, adjusted hospitalization rate derived
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51 440 from the Poisson model (39.5 per 100 patients in the STR group vs. 51.2 per 100 patients in the
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53 441 2+PPD group; see Figure 2). One possible explanation for this difference is that the Poisson
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55 442 model corrected a substantial imbalance in the proportion of patients who were treatment naïve
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3 443 at index (47.5% of STR patients vs. 24.5% of 2+PPD patients). Lack of or naivety to ART
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5 444 exposure has been shown in some studies to be a positive predictor of hospitalization in HIV
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7 445 patients [23], perhaps because approximately one-third of HIV patients wait to seek care until
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9 446 their disease has progressed to the point that they need acute treatment. [24, 25] As noted in a
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11 447 recent study by Metsch et al. [26], these patients often obtain initial care in emergency
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13 448 departments and hospital inpatient wards, and they tend not to be persistent with follow-up
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15 449 outpatient care. This pattern of treatment induction may further increase their risk of infection
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17 450 and re-hospitalization in the short-term. Because being treatment naïve was shown in our data to
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19 451 be predictive of hospitalization, the Poisson model's adjustment for the overrepresentation of
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21 452 treatment naivety in the STR group may therefore have resulted in the larger difference between
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23 453 STR and 2+PPD in hospitalizations than observed in the crude, unadjusted comparison.
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29 454 One hypothesis for a plausible mechanism by which the outcomes observed in our study
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31 455 could occur stems from observations in the SMART study.[27] That study, comparing
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33 456 continuous antiviral treatment versus periodic treatment interruptions, demonstrated that HIV
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35 457 treatment interruptions that were of sufficient length of time to lead to recurrent HIV viremia
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37 458 were associated with a significantly higher risk of all-cause morbidity and mortality. Our
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39 459 analysis was consistent with those findings: the mean maximum duration of nonadherence was
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41 460 about 3 weeks, which is a sufficient length of time to expect a return of HIV viremia. The
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43 461 SMART study noted that the higher risk of illness was not necessarily proximal to the time of the
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45 462 interruption but was observed for months afterwards. While there are differences between the
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47 463 SMART study design and population and our study population, our findings are consistent with
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49 464 SMART and with what might be expected in a population who periodically are without antivirals
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51 465 for an average time of more than 3 weeks. Of note, short cycle interruptions of 2 days were not
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53 466 associated with virologic rebound in patients receiving the STR that was used in the SMART
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3 467 study [28]. Therefore, our finding that the typical interruptions were much longer than this is
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6 468 supportive of a mechanism that could have resulted in increased patient morbidity.

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8 469 It is also important to note that patients in this study generally were reasonably adherent to
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10 470 ART, with a mean adherence of just over 80% regardless of the number of pills received per day.
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12 471 This rate of adherence is consistent with other published reports of adherence, although other
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14 472 reports found even higher adherence rates to an STR.[13,14] Furthermore, the difference
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16 473 observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent
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18 474 with what was observed by Sax et al. of 2.2%.[16] This difference is also consistent with the
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20 475 differences in adherence rates reported when comparing average improvement between once-
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22 476 daily and twice-daily regimens (2.9%).[29] It is important to note that there also were highly
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24 477 nonadherent patients to both the STR and the 2+PPD regimes in this study population,
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26 478 supporting the generalizability of this population.

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29 479 Of further note, the differences observed in our study were associated with factors that
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31 480 typically are not present during randomized clinical trials. Randomized trials typically actively
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33 481 work for patient adherence to study medications and use study coordinators to regularly monitor
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35 482 patients to minimize missed doses. In our observational study, these typical adherence supports
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37 483 are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling
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39 484 prescriptions, including partial regimen refills, which would not be observed in clinical trials.
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41 485 While there are concerns about the interpretation of observational data and the determination of
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43 486 causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill
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45 487 regimen would be able to detect the observed differences unless there was less patient support
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47 488 than is standard in clinical trials.

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49 489 Our data do not suggest that all patients should be on an STR. There are many factors that
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51 490 weigh in the decision of which regimen is best for any given patient, including pre-existing
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3 491 virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in
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5 492 association with a lower pill burden is relevant but should not be construed as a suggestion that
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8 493 an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data
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10 494 do support the continued development of additional STR options, to broaden the number of
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12 495 patients for whom this is an option and the number of subsequent beneficial outcomes.

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15 496 Our study has several limitations common to observational claims database analyses.

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17 497 Adherence was calculated by using pharmacy refill dates, and we have no measure of actual
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19 498 patient adherence to the prescriptions they filled. However, this measure has been found to be a
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21 499 useful proxy for actual medication adherence.[30] Because we did not randomize patients to the
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23 500 two different treatment regimens, we cannot exclude unmeasured confounding factors that may
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25 501 have influenced our outcomes. Among the most important of these factors in this study was that
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27 502 multiple trials have shown that medication resistance at the time of virologic failure is
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29 503 significantly less common in boosted PI treatments than on other regimens, including
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31 504 nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.[31,32] Clinicians
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33 505 could have chosen to prescribe a boosted-PI-containing regimen (all of which contain three or
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35 506 more pills per day) to their less-adherent patients. It cannot be determined from this data set that
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37 507 these patients would have been more adherent on an STR. Although we attempted to control for
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39 508 some of these variables through the use of multivariable models that included some of these
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41 509 factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In
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43 510 addition, we had no laboratory results from patients and thus cannot confirm the degree of
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45 511 virologic suppression obtained across the regimens. Finally, although our data include
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47 512 information from the Medicaid programs in 11 states, the authors were blinded (as per data
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49 513 privacy rules) as to which specific states are captured. Although the database's documentation
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3 514 suggests that the states are geographically dispersed, we cannot assert that our findings would be
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5 515 fully representative of the general Medicaid population in the US.
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8 516 In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated
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10 517 population) were excluded from the analysis due to their having received incomplete ART
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12 518 regimens. We did not have sufficient data on these patients to explain why their regimens were
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14 519 incomplete. However, a previous study found that physician medication errors were somewhat
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16 520 common in individuals with HIV, with the most common error occurring with boosted PIs
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18 521 (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens
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20 522 observed in our analysis.[33] Increased adoption of fixed-dose combinations as part of HIV
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22 523 treatment may help to alleviate the issue of incomplete regimens.
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27 524 During our study period, the only available single-pill ART regimen was coformulated
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29 525 efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not
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31 526 be generalizable to other one- and multi-pill regimens if other treatments have different efficacy
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33 527 and toxicity profiles. With the recent approval by the Food and Drug Administration of two other
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35 528 STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and
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37 529 cobicistat), it may eventually be possible to explore the applicability of our observations to other
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39 530 STRs.
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43 531 In summary, this study supported the results as reported by Sax et al.[16] We found that
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45 532 patients who received ART as a single pill per day were significantly more likely to be highly
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47 533 adherent to therapy than patients who received multiple-pill regimens. This difference in
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49 534 adherence was associated with a lower risk of hospitalizations: patients with less-than-complete
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51 535 adherence were more likely to be hospitalized. While we acknowledge the limitations associated
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54 536 with any observational study, our data support our finding that the use of an STR may reduce
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537 health care costs as well as patient morbidity by decreasing hospitalization rates, which are
538 higher in patients with less-than-complete medication adherence.

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641 **FIGURE LEGENDS**

642 **Figure 1. Sample Selection Flow Chart**

643 **Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort**

644 **Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence**

645 **Figure 4. Adjusted Monthly Health Care Costs, by Cohort**

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10 1 Association between Daily Antiretroviral Pill Burden Effects on and
11 2 Medication Treatment Adherence, Hospitalization Risk, and Other
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14 3 **Health Care Utilization and Costs in a United States Medicaid**
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16 4 **Population with HIV**
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20 6 **Short Title:** Antiretroviral Pill Burden in Medicaid Patients
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24 8 **Authors and Affiliations:** Calvin Cohen,¹ Juliana L. Meyers,² Keith L. Davis²
25

26 9 ¹ CRI New England, Harvard Medical School, Boston, MA, USA
27

28 10 ² RTI Health Solutions, Research Triangle Park, NC, USA
29
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31
32 12 **Key Words:** HIV, Medicaid, Adherence, Hospitalization, Health Care Utilization
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35 14 **Word Count:** 5,453
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39 16 **Corresponding Author**

40
41 17 Keith L. Davis, MA
42

43 18 RTI Health Solutions
44

45 19 200 Park Offices Drive
46

47 20 Research Triangle Park, NC 27709 USA
48

49 21 Telephone: 1.919.541.1273
50

51 22 Fax: +1.919.541.7222
52

53 23 E-mail: kldavis@rti.org
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24 **ABSTRACT**

25 **Objectives:** Lower pill burden leads to improved ~~adherence to~~ antiretroviral therapy (ART)
 26 ~~adherence~~ among human immunodeficiency virus (HIV) patients. Simpler dosing regimens have
 27 not been widely explored in real-world populations. We retrospectively assessed ~~ART~~
 28 ~~adherence, all-cause hospitalization risk and costs, and other~~ health care utilization and costs in
 29 Medicaid enrollees with HIV treated with ART as a once-daily single-tablet regimen (STR) or
 30 two or more pills per day (2+PPD).

31 **Design:** Patients with an HIV diagnosis from 2005-2009 receiving complete ART (i.e., 2
 32 nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent) for ≥ 60 days ~~or more~~ as
 33 STR or 2+PPD were selected and followed until the first of (1) discontinuation of the complete
 34 ART, (2) loss of ~~continuous~~ enrollment, or (3) end of ~~the~~ database. Adherence was measured
 35 using the medication possession ratio. Monthly ~~all-cause health care~~ utilization and costs were
 36 observed from regimen initiation until ~~discontinuation follow-up end, and reported overall and by~~
 37 ~~care setting (inpatient, emergency department, office, pharmacy, other). To assess predictors of~~
 38 ~~hospitalization, Poisson models, counting the number of hospitalizations and covariates for~~
 39 ~~demographics, comorbidities, and ART naïve status, were estimated.~~

40 **Results:** Of the 7,381 patients who met inclusion criteria, 1,797 were treated with STR and
 41 5,584 with 2+PPD. STR patients were significantly more likely to reach ~~a~~ 95% adherence
 42 ~~threshold~~ and had fewer hospitalizations than 2+PPD patients (both: $P < 0.01$). STR patients had
 43 mean (SD) total monthly costs of \$2,959 (\$4,962); 2+PPD patients had \$3,544 (\$5,811)
 44 ($P < 0.001$). Hospital costs accounted for 53.8% and pharmacy costs accounted for 32.5% of this
 45 difference. Multivariate analyses found that STR ~~treatment~~ led to a 23% reduction in
 46 hospitalizations and a 17% reduction in ~~overall~~ health care costs. ~~ART adherence appears to be a~~

Comment [k1]: Text eliminated to stay within 300 word limit of abstract after requested changes/additions by reviewer. Other minor edits made throughout abstract to comply with word count.

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9 47 | key mechanism mediating hospitalization risk, as patients with $\geq 95\%$ adherence (regardless of
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11 48 | regimen type) had a lower hospitalization rate compared with $< 95\%$ adherence.

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13 49 | **Conclusions:** While it was expected that STR patients would have lower pharmacy costs, we
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15 50 | also found that STR patients had fewer hospitalizations and lower hospital costs than 2+PPD
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17 51 | patients, resulting in significantly lower total health care costs for STR patients.
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9 52 **ARTICLE SUMMARY**

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11 53 **Article Focus**

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13 54 | ▪ To assess the effect of association between a single-tablet-per-day ART regimen (STR) ~~on~~
14 55 and treatment adherence ~~and~~, all-cause hospitalization risk, and other all-cause health
15 56 care utilization and costs in a large population of Medicaid enrollees in the United States
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17 57 who received treatment for HIV infection

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20 58 **Key Messages**

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22 59 | ▪ Patients who received ART as a single pill per day were significantly more likely to be
23 60 highly adherent (≥ 95%) to therapy than patients who received multiple-pill regimens.
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25 61 | ▪ Improved adherence among patients treated with STR conferred a lower risk of
26 62 hospitalization.
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28 63 | ▪ The use of an STR may reduce health care costs as well as patient morbidity by
29 64 decreasing hospitalization rates, which were higher in patients with less-than-complete
30 65 medication adherence.

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32 66 **Strengths and Limitations of This Study**

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36 67 | ▪ This retrospective analysis used pharmacy refill dates as the best available proxy for pill-
37 68 taking behavior; one advantage to this method is that we can identify those patients who
38 69 may not have had all or some of their medications available on any given date based on
39 70 an analysis the timing in between refills, which also notes the amount of medication
40 71 dispensed each time.
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42 72 | ▪ Rates of hospitalization and correlates of hospitalization also were assessed from these
43 73 claims data and should be highly accurate, as should measures of overall monthly health
44 74 care utilization and costs.

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9 75 ▪ While our prescription claims-based measure of adherence has been found to be a valid
10 76 proxy for actual medication-taking behavior, we had no measure of actual patient
11 77 adherence (i.e., daily ingestion/consumption) to the prescriptions they filled.
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14 78 ▪ Because we did not randomize patients to the two different treatment regimens, we
15 79 cannot exclude unmeasured confounding factors that may have influenced our outcomes;
16 80 although we attempted to control for some of these variables through the use of
17 81 multivariable models that included some of these factors (substance abuse and psychiatric
18 82 diagnoses), residual confounding may remain.
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24 83 ▪ We had no laboratory results from patients and thus cannot confirm the degree of
25 84 virologic suppression obtained across the regimens.
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9 85 **ADMINISTRATIVE STATEMENTS**

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11 86 **Protection of Human Subjects**

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13 87 The research organization that conducted this study, RTI Health Solutions, a business unit of
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15 88 RTI International (RTI), holds a Federal-Wide Assurance (FWA #3331 effective until June 17,
16
17 89 2014) from the Department of Health and Human Services (DHHS) Office for Human Research
18
19 90 Protections (OHRP) that allows us to review and approve human subjects protocols through our
20
21 91 Institutional Review Board (IRB) committees. Since pre-existing, retrospective, de-identified
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23 92 patient data were analyzed for this study, which involved no patient contact or medical
24
25 93 interventions and therefore no patient consent forms, the RTI IRB committee approved this study
26
27 94 as exempt.

28 95 **Author Contributions**

29
30 96 Calvin Cohen assisted in development of the study design, evaluated and interpreted the
31
32 97 study results, and drafted and critically revised the manuscript text. Juliana Meyers and Keith
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34 98 Davis assisted in development of the study design, obtained study funding, conducted all analytic
35
36 99 programming and statistical analyses, assisted with evaluation and interpretation of the study

37
38 100 **Funding Statement**

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40 101 This study was funded by Gilead Sciences, which is conducting clinical research in and
41
42 102 markets current treatments for HIV/AIDS.

43 103 **Data Sharing**

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45 104 Raw data used for this study are unavailable for public sharing (per terms of the private data
46
47 105 use agreement governing original data acquisition).

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49 106 **Acknowledgments**

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51 107 The Authors would like to thank Francois Everhard (Gilead Sciences) for his support and
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53 108 input on the study design and manuscript.

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109 INTRODUCTION

110 The 2012 Department of Health and Human Services guidelines state that there are four
111 preferred regimens for initiating human immunodeficiency virus (HIV) treatment in adults.
112 Furthermore, there are multiple alternatives to these four regimens.[1] Patients and their treating
113 physicians can choose from among these four preferred regimens, using the criteria of greatest
114 efficacy, safety, and simplicity. The latter category is important because regimen simplicity is
115 associated with greater long-term adherence. For example, all four preferred regimens are
116 constructed with a relatively low pill burden (i.e., between one and four tablets per day), and
117 three of the four regimens have once-daily dosing. While randomized trials have compared the
118 components of some of these four regimens with each other, to date no studies compared the four
119 regimens to each other as they are prescribed (i.e., in a real-world setting), given that these study
120 trials have been blinded.[2,3]

121 Adherence to antiretroviral therapy (ART) is essential for achieving durable clinical
122 outcomes in patients with HIV. Patients with inadequate adherence to ART are at an increased
123 risk for incomplete viral suppression; and unless a new suppressive regimen is quickly
124 constructed to reestablish virologic suppression, viremia is associated with an increased risk of
125 disease progression, and death.[4-8] It has been suggested that an ART adherence rate of at least
126 95% is required to achieve a lower risk of virologic failure, fewer hospital days, and reduced
127 morbidity and mortality in patients with HIV[8-9], although one previous study indicated that
128 viral suppression may be possible at less than 95% adherence.[10] In the past several years, the
129 availability of fixed-dose combinations and agents with prolonged half-lives have simplified pill
130 burden and thus increased regimen adherence.[1,9,11] Several clinical trials and cohort studies
131 support the conclusion that once-daily single tablet regimens (STR) can lead to significantly
132 improved adherence, patient satisfaction, and virological outcomes.[10-13,12-15] For example,

Comment [k2]: Added citation for balance

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9 133 among homeless or marginally housed patients, those receiving an ART regimen composed of a
10 134 single tablet per day had better virologic outcomes and a 26% increase in adherence than patients
11 135 receiving other multi-pill regimens.^[1315] One recently published study analyzing a claims
12 136 database noted that compared with various multi-pill regimens, a STR was associated with
13 137 increased adherence (as determined by pharmacy refill data). Furthermore, the increased
14 138 likelihood of complete adherence was associated with a 25% decrease in the rate of
15 139 hospitalization.^[1416]

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22 140 In this study, we sought to assess how robust these findings were by analyzing similar
23 141 metrics in a separate data set. The primary objective of this retrospective database analysis was
24 142 to assess the effect association between of a single-tablet-per-day ART regimen and on treatment
25 143 adherence, and all-cause hospitalization risk, and total all-cause health care costs -in a large
26 144 population of Medicaid enrollees in the United States (US) who received treatment for HIV
27 145 infection. The secondary objective of this study was to examine the association between STR
28 146 and other types of all-cause health care utilization (emergency department, pharmacy, outpatient,
29 147 and other service types) and costs.

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9 148 **METHODS**

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11 149 Data for this analysis were taken from the MarketScan Medicaid Multi-State Database,
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13 150 which contains health care claims from approximately 30 million Medicaid enrollees from
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15 151 11 geographically dispersed states. The database includes patient-level demographics; periods of
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17 152 Medicaid enrollment; primary and secondary diagnoses; and detailed information about
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19 153 hospitalizations and therapeutic procedures, inpatient and outpatient physician services, and
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21 154 prescription drug use. Each medical and pharmacy claim in the database also includes original
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23 155 cost information, which represents direct paid amounts (in US dollars) from Medicaid to
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25 156 providers for each service or prescription. In compliance with the Health Insurance and
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27 157 Portability and Accountability Act of 1996, all data were de-identified to protect the privacy of
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29 158 individual patients, physicians, and hospitals. Because the data were retrospective, pre-existing,
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31 159 and de-identified, RTI International's institutional review board determined that this study met
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33 160 all criteria for exemption from requirements of patient consent.

34 161 Patients were selected for inclusion if they received at least one HIV or AIDS diagnosis
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36 162 (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code
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38 163 042.xx) between June 1, 2006, and December 31, 2009. Patients also were required to have
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40 164 evidence of receipt of a complete ART regimen, defined as two nucleoside/nucleotide reverse
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42 165 transcriptase inhibitors plus a third agent (i.e., another nucleoside/nucleotide reverse
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44 166 transcriptase inhibitor, a nonnucleoside/nucleotide reverse transcriptase inhibitor, a protease
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46 167 inhibitor [PI], a chemokine receptor R5 antagonist, or an integrase inhibitor). The first date of
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48 168 receipt of a complete regimen was termed the index date. ART agents were identified in the
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50 169 claims database by using National Drug Codes associated with relevant generic and brand
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52 170 names. Patients also were required to remain on the complete ART regimen for at least 60 days
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54 171 following their index dates and to have evidence of continuous enrollment in Medicaid during

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9 172 this period. To assess treatment-naïve versus experienced status and baseline comorbidities,
10 173 patients were required to have at least 6 months of pre-index date Medicaid enrollment, with
11 174 enrollment information available from January 1, 2006 (i.e., 6 months before the earliest possible
12 175 index date).

16 176 Patients were grouped into two mutually exclusive cohorts according to the daily pill count
17 177 of their complete ART regimen. Patients were assigned to the STR cohort if they received an
18 178 ART regimen consisting of a single tablet (i.e., an STR) at any point during the selection
19 179 window, regardless of prior or subsequent use of other regimens. At the time of this study, only
20 180 coformulated tenofovir/emtricitabine/efavirenz was available as an STR. Patients were assigned
21 181 to the two-or-more-pills-per-day (2+PPD) cohort if they received a regimen consisting of two or
22 182 more pills per day during the selection window and if they did not receive an STR at any point
23 183 during that time.

31 184 Patients were followed from the start of their complete ART regimen (i.e., after June 1, 2006,
32 185 the study index date) until the earliest date of regimen discontinuation, disenrollment from the
33 186 health plan, or the end of the database (i.e., March 31, 2009). Furthermore, patients receiving
34 187 2+PPD were allowed to change medications comprising the regimen, providing-provided that the
35 188 patients continued to receive a combination of agents that could still be classified as a complete
36 189 2+PPD regimen. Patients receiving STR were followed for as long as they remained on the STR.
37 190 Discontinuation was defined as 60 consecutive days in which no refills were observed for any
38 191 component of the regimen. Females with an ICD-9-CM diagnosis code indicating a pregnancy
39 192 during the follow-up period were excluded from the analysis because the one available STR is
40 193 not recommended for pregnant women, and hospitalizations for labor and delivery may have
41 194 biased results in favor of the STR.

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9 195 Patient characteristics measured at the index date included age, sex, and ART classes
10 196 received (i.e., nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside/nucleotide
11 197 reverse transcriptase inhibitors, PIs, ritonavir boosting therapy, or other therapies). The presence
12 198 of comorbid medical conditions other than HIV or AIDS were assessed during the 6-month pre-
13 199 index period, using an established algorithm, the Charlson Comorbidity Index (CCI)
14 200 score.^[4517] This score is made up of 17 comorbidities (defined by ICD-9-CM diagnosis and
15 201 procedure codes), such as myocardial infarction and chronic pulmonary disease, which are
16 202 weighted to correspond to the severity of the comorbid condition of interest. A higher
17 203 comorbidity score represents a higher overall comorbidity burden during the pre-index period.
18 204 Additionally, the incidence of other concomitant mental disorders (ICD-9-CM codes 306.xx
19 205 through 319.xx) and drug and alcohol abuse (ICD-9-CM codes 292.xx and 303.xx through
20 206 305.xx) during the 6-month pre-index period also was assessed.

21 207 Medication adherence was assessed using the medication possession ratio (MPR), which has
22 208 been shown to be the most widely adopted measure (57% of all studies) in published claims-
23 209 based analyses of medication adherence ^[4618] and has been used in studies of ART adherence
24 210 among individuals with HIV. ^[4719] The MPR, which is a proxy for refill compliance, generally
25 211 measures the proportion of the ART exposure period in which supply was maintained for all
26 212 ART components comprising the regimen. Specifically, MPR was calculated as the number of
27 213 filled prescription days for all ART regimen components (using the days supplied in the
28 214 pharmacy claims) divided by the number of days from the first observed prescription in the
29 215 regimen through the earliest of either the exhaustion of the days supplied of the last observed
30 216 prescription or the end of follow-up. For each patient in our study, the MPR was calculated over
31 217 the period in which the patient remained on his or her ART regimen. For patients in the 2+PPD
32 218 cohort, late refills and resulting days of missing supply for one or more ART components were

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9 219 all factored against their adherence measurements. For example, patients in the 2+PPD cohort
10 220 with a supply for only one of the ART components on a given day were considered to have zero
11 221 adherence for that day. In addition to reporting the mean (standard deviation [SD]) MPR
12 222 achieved, we also reported the numbers and percentages of patients achieving various adherence
13 223 thresholds (i.e., MPRs of 1.0-0.95, 0.94-0.90, 0.89-0.85, and 0.84-0.80, corresponding to 100%-
14 224 95%, 94%-90%, 89%-85%, and 84%-80% adherence, respectively).

15 225 To further understand adherence to ART regimens, for each patient in the 2+PPD cohort,
16 226 complete (i.e., having a complete regimen), partial (i.e., receiving some but not all components
17 227 of a complete regimen), and no medication days also were assessed. Specifically, we reported the
18 228 percentage of days that each patient had complete, partial, and no medications available, along
19 229 with the mean number of days that the patient had complete, partial and no medications.
20 230 Additionally, we also reported the maximum number of consecutive days the patient had either
21 231 an incomplete regimen or no medications available.

22 232 Hospitalizations were identified from the claims database using relevant place of service
23 233 codes. Hospitalizations were observed from the index date until the earliest date of regimen
24 234 discontinuation, end of enrollment in the health plan, or end of the database. The number and
25 235 percentage of patients with at least one hospitalization were reported, along with the mean (SD)
26 236 number of hospitalizations, and the mean (SD) number of inpatient days. Furthermore, we
27 237 compared and reported the number of hospitalizations per 100 patient-years, along with the rate
28 238 ratios and 95% confidence intervals, for both cohorts as well as by adherence status (at least 95%
29 239 vs. less than 95%).

30 240 For each patient, overall health care utilization and associated costs were aggregated across
31 241 all encounters, regardless of reason, that were observed during the follow-up period; we reported
32 242 these costs by average and per-month amounts. The following categories of overall health care

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9 243 utilization and costs were evaluated and reported: inpatient, emergency department, office visit,
10 244 home health visit, laboratory service, pharmacy, other outpatient care, and total. For each
11 245 category of overall health care, the number and percentage of patients, the mean (SD) number of
12 246 visits per month, and monthly per-patient costs were reported. Additionally, for patients with an
13 247 inpatient visit, the average number of inpatient days per month among patients with at least one
14 248 stay during follow-up also was reported. All cost data, which represented payments incurred by
15 249 the Medicaid system, were standardized at the claim level to 2010 US dollars using the medical
16 250 care component of the US Consumer Price Index.

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22 251 All analyses were carried out using SAS (version 9; Cary, North Carolina) statistical
23 252 software. Descriptive analyses were conducted for all outcome measures and included means and
24 253 SDs for continuous variables of interest (e.g., MPR) and frequency distributions of categorical
25 254 variables of interest (e.g., geographic region). All descriptive analyses were stratified by cohort.
26 255 Health care costs were updated to 2010 US dollars using the medical care component of the
27 256 consumer price index.

28 257 A generalized linear model with a log link and a Poisson distribution was estimated to assess
29 258 the relationship between the number of pills per day and the number of hospitalizations observed
30 259 during follow-up. The dependent variable was a count of hospitalizations during exposure to the
31 260 ART regimen. Additionally, a generalized linear model with a log link and a negative binomial
32 261 distribution were estimated to assess monthly health care costs, adjusted for the patient and
33 262 treatment characteristics. The dependent variables were monthly total costs and monthly total
34 263 costs excluding costs pharmacy costs. For both models, based on previous work by Sax et al.
35 264 [16], independent variables included the following: treatment regimen received (i.e., STR vs.
36 265 2+PPD), age, sex, CCI score, treatment-naïve status, pre-index presence of mental health
37 266 disorders, pre-index presence of alcohol or drug abuse disorders, length of follow-up (in days,

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9 267 hospital model only), and whether or not the patient met a 0.95 adherence threshold (cost model
10 268 only). For the hospital model, incidence rate ratios (IRRs) were reported for all covariates, along
11 269 with the mean predicted number of hospitalizations for patients receiving an STR versus patients
12 270 receiving a 2+PPD. For the cost model, adjusted predicted mean costs were reported.
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9 271 **RESULTS**

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11 272 A total of 7,381 patients met the selection criteria (Figure 1). Of these, 5,584 patients
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13 273 (75.7%) received their ART regimen as 2+PPD; 1,797 patients (24.3%) received their ART
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15 274 regimen as a STR. On average, patients were approximately 42 years of age. Approximately
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17 275 46% of patients were female (Table 1). Across both cohorts, the average CCI score was
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19 276 approximately the same (mean [SD]: 0.67 [1.38] among patients receiving an STR and 0.65
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21 277 [1.36] among patients receiving 2+PPD). Furthermore, the incidence of concomitant mental
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23 278 disorders and drug and alcohol abuse diagnoses did not vary substantially by cohort. Patients
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25 279 receiving an STR had a mean regimen duration of 348 days; this was approximately 2.8 months
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27 280 shorter than the mean regimen duration of 433 days observed for patients receiving 2+PPD.
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281 Forty-seven percent of patients receiving an STR were treatment naïve, compared with 24.5% of
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30 282 patients receiving 2+PPD.

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32 283 **Table 1. Characteristics of the study sample, by cohort.**

| Characteristic | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P Value |
|--------------------------|--------------------|---------|----------------------|---------|---------|
| All Patients (N, %) | 1,797 | 100.00% | 5,584 | 100.00% | |
| Age, mean (SD) | 41.6 | (10.56) | 42.32 | (11.37) | 0.0137 |
| Age category (N, %) | - | - | - | - | |
| —Aged less than 18 years | 40 | 2.23% | 274 | 4.85% | |
| —Aged 18 to 24 years | 95 | 5.29% | 139 | 2.49% | |
| —Aged 25 to 34 years | 269 | 14.97% | 664 | 11.84% | |
| Aged 35 to 44 years | 622 | 34.61% | 1,975 | 35.37% | |
| Aged 45 to 54 years | 594 | 32.89% | 1,875 | 33.58% | |
| Aged 55 to 64 years | 176 | 9.79% | 638 | 11.43% | |
| Aged 65+ years | 4 | 0.22% | 25 | 0.45% | |
| Gender (N, %) | | | | | |
| Male | 945 | 52.59% | 3,063 | 54.85% | 0.1123 |
| Female | 852 | 47.41% | 2,521 | 45.15% | 0.1439 |
| Race (N, %) | | | | | |
| White | 387 | 21.54% | 1,221 | 21.87% | 0.8893 |
| Black | 1,187 | 66.05% | 3,658 | 65.51% | 0.6877 |
| Hispanic | 18 | 1.00% | 82 | 1.47% | 0.7844 |

| Characteristic | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P Value |
|---|--------------------|----------|----------------------|----------|---------|
| Other | 204 | 11.35% | 621 | 11.12% | 0.7846 |
| Unknown | 1 | 0.06% | 2 | 0.04% | 0.8766 |
| Basis of Medicaid Eligibility (N, %) | | | | | |
| Aged | 1 | 0.06% | 8 | 0.14% | 0.5634 |
| Disabled | 1,089 | 60.60% | 4,071 | 72.90% | <.0001 |
| Income | 583 | 32.44% | 1,159 | 20.76% | <.0001 |
| Other | 58 | 3.23% | 202 | 3.61% | 0.8710 |
| Unknown | 65 | 3.62% | 141 | 2.53% | 0.0487 |
| Medicare Eligibility (N, %) | | | | | |
| Not dually eligible | 1,791 | 99.67% | 5,558 | 99.53% | 0.9987 |
| Dually eligible | 5 | 0.28% | 24 | 0.43% | 0.6523 |
| Unknown | 1 | 0.05% | 2 | 0.04% | 0.9014 |
| Charlson comorbidity index score, mean (SD) | 0.67 | (1.38) | 0.65 | (1.36) | 0.5919 |
| Charlson comorbidities (N, %) | | | | | |
| – Myocardial infarction | 11 | 0.61% | 44 | 0.79% | |
| – Congestive heart failure | 39 | 2.17% | 141 | 2.53% | |
| – Peripheral vascular disease | 14 | 0.78% | 58 | 1.04% | |
| – Cardiovascular disease | 52 | 2.89% | 148 | 2.65% | |
| – Dementia | 4 | 0.22% | 10 | 0.18% | |
| – Chronic pulmonary disease | 259 | 14.41% | 704 | 12.61% | |
| – Rheumatological disease | 11 | 0.61% | 23 | 0.41% | |
| – Peptic ulcer disease | 9 | 0.50% | 25 | 0.45% | |
| – Mild liver disease | 20 | 1.11% | 49 | 0.88% | |
| – Severe liver disease | 117 | 6.51% | 333 | 5.96% | |
| – Diabetes mellitus without chronic complications | 145 | 8.07% | 445 | 7.97% | |
| – Diabetes mellitus with chronic complications | 16 | 0.89% | 89 | 1.59% | |
| – Paraplegia | 6 | 0.33% | 34 | 0.61% | |
| – Renal disease | 11 | 0.61% | 80 | 1.43% | |
| – Cancer | 82 | 4.56% | 221 | 3.96% | |
| – Metastatic cancer | 11 | 0.61% | 26 | 0.47% | |
| Concomitant mental health and substance abuse comorbidities (N, %) | | | | | |
| Mental disorders | 382 | 21.26% | 1,340 | 24.00% | 0.0456 |
| Drug or alcohol abuse | 338 | 18.81% | 856 | 15.33% | 0.0323 |
| Treatment naïve at index (N, %) | 853 | 47.47% | 1,366 | 24.46% | <.0001 |
| Mean (SD) rRegimen length, mean (SD) | 348.17 | (259.32) | 433.46 | (351.50) | <.0001 |
| Index medications (N, %) | | | | | |
| NRTI | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| NNRTI | 1,797 | 100.00% | 1,500 | 26.86% | <.0001 |
| PI | --- | --- | 4,064 | 72.78% | --- |

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| Characteristic | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P Value |
|-------------------------|--------------------|-----|----------------------|--------|---------|
| Kaletra at index | --- | --- | 1,633 | 40.18% | --- |
| Boosted PI at index | --- | --- | 1,664 | 40.94% | --- |
| Non-boosted PI at index | --- | --- | 767 | 18.87% | --- |
| PE | --- | --- | 1,712 | 30.66% | --- |
| Other | --- | --- | 87 | 1.56% | --- |

NOTE. 2+PPD = two or more pills per day; NNRTI = nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PE = pharmacokinetic enhancer; PI = protease inhibitor; SD = standard deviation; STR = once-daily single-tablet regimen.

Patients receiving an STR had significantly better adherence than patients receiving 2+PPD (Table 2). Approximately 25.3% of patients receiving an STR achieved 95% adherence or greater, compared with 17.4% of patients receiving 2+PPD ($P \leq 0.0001$). Mean (SD) MPR was 0.84 (0.14) among patients receiving an STR and 0.80 (0.15) among patients receiving 2+PPD (Table 2). Patients in the 2+PPD cohort received a complete regimen for 80.3% of the follow-up period (mean [SD]: 361.9 [315.0] days), a partial regimen for 5.6% of the follow-up period (mean [SD]: 22.2 [45.6] days), and no available medications for 14.1% of the follow-up period (mean [SD]: 49.4 [57.1] days) (Table 3). Alternatively, patients in the STR cohort received a complete regimen for 84.4% of the follow-up period (mean [SD]: 299.4 [234.6] days) and no available medications for 15.6% of the follow-up period (mean [SD]: 48.8 [54.2] days), which was a similar percentage of days as patients receiving 2+PPD. Patients receiving an STR had, on average, a maximum of 19.5 (SD: 15.9) consecutive days without a complete regimen (i.e., either a partial regimen or no medications available); patients receiving 2+PPD had, on average, a maximum of 23.9 (SD: 16.7) consecutive days without a complete regimen.

Table 2. Adherence to antiretroviral therapy, by cohort.

| Cohort | Number of Patients | Mean (SD) MPR | MPR/Persistence Ratio (N, %) | | | | |
|--------|--------------------|---------------|------------------------------|-------------|-------------|-------------|------------|
| | | | <0.8 | 0.8 - <0.85 | 0.85 - <0.9 | 0.9 - <0.95 | 0.95 - 1 |
| STR | 1,797 | 0.84 (0.14) | 537 29.88% | 178 9.91% | 243 13.52% | 385 21.42% | 454 25.26% |
| 2+PPD | 5,584 | 0.80 (0.15) | 2,255 40.38% | 621 11.12% | 779 13.95% | 957 17.14% | 972 17.41% |

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| Cohort | Number of Patients | Mean (SD) MPR | MPR/Persistence Ratio (N, %) | | | | |
|-------------------|--------------------|---------------|------------------------------|-------------|--------------|--------------|--------------|
| | | | <0.8 | 0.8 - <0.85 | 0.85 - <0.9 | 0.9 - <0.95 | 0.95 - 1 |
| Overall | 7,381 | 0.81 (0.15) | 2,792 37.83% | 799 10.83% | 1,022 13.85% | 1,342 18.18% | 1,426 19.32% |
| P-Value (1 vs. 2) | | <.0001 | <.0001 | 0.1491 | 0.6477 | <.0001 | <.0001 |

NOTE. 2+PPD = two or more pills per day; MPR = medication possession ratio; SD = standard deviation; STR = once-daily single-tablet regimen.

Table 3. Summary of incomplete adherence, by cohort.

| Adherence Characteristic | STR (n = 1,797) | 2+PPD (n = 5,584) | P Value |
|--|--------------------|----------------------|---------|
| Percentage of days with complete adherence | 84.42% | 80.37% | <.0001 |
| Percentage of days with partial adherence | --- | 5.56% | --- |
| Percentage of days with no ART medications | 15.58% | 14.07% | 0.0356 |
| Complete adherence days, mean (SD) | 299.36 (234.56) | 361.87 (315.03) | <.0001 |
| Partial adherence days, mean (SD) | --- | 22.24 (45.58) | --- |
| Days with no medication available, mean (SD) | 48.81 (54.24) | 49.35 (57.11) | 0.0356 |
| Total follow-up duration, mean (SD) | 348.17 (259.31) | 433.46 (351.50) | <.0001 |
| Maximum consecutive gap in therapy, ^a mean (SD) | 19.48 (15.89) | 23.92 (16.67) | <.0001 |

NOTE. 2+PPD = two or more pills per day; ART = antiretroviral therapy; SD = standard deviation; STR = once-daily single-tablet regimen.

^a Represents either days with a partial regimen or days with no medications.

Among patients receiving an STR, 21.0% had at least one hospitalization, compared with 24.4% of patients receiving 2+PPD ($P = 0.003$) (Table 4). Among patients with a hospitalization, patients receiving an STR had numerically similar, although significantly fewer, hospitalizations over all available follow-up, when compared with patients receiving 2+PPD (mean [SD]: 1.9 [1.6] among patients receiving an STR vs. 2.1 [2.2] among patients receiving 2+PPD; $P = 0.001$).

Table 4. All-cause average monthly per patient health care utilization and costs, by cohort.

Comment [k3]: Removed this because hospitalization use (not cost) data are shown for all available follow-up.

| Resource Used | STR (n = 1,797) | 2+PPD (n = 5,584) | P-Value |
|------------------|--------------------|----------------------|---------|
| Hospitalizations | | | |

| Resource Used | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P-Value |
|---|--------------------|------------|----------------------|------------|---------|
| Had ≥ 1 hospital admission (N, %) ^a | 378 | 21.04% | 1,365 | 24.44% | 0.0031 |
| Number of hospitalizations <u>(over all follow-up)</u> ^b mean (SD) | 1.88 | (1.59) | 2.1 | (2.23) | 0.0012 |
| Inpatient days <u>(over all follow-up)</u> ^b mean (SD) | 9.99 | (12.33) | 12.33 | (18.90) | 0.0228 |
| Number of admissions per month | - | - | - | - | - |
| Mean (Std. Dev) | 0.05 | (0.00) | 0.05 | (0.15) | 0.1429 |
| Median | 0 | - | 0 | - | - |
| Range (Min, Max) | 0 | 2 | 0 | 1.07 | - |
| Days in hospital per month ^c | - | - | - | - | - |
| Mean (SD) | 1.32 | (2.21) | 1.45 | (2.71) | 0.3975 |
| Median | 0.58 | - | 0.5 | - | - |
| Range (Min, Max) | 0.03 | 21.5 | 0.03 | 32.43 | - |
| Costs <u>per month, mean (SD)</u> | \$834- | (\$4,480)- | \$1,152- | (\$5,212)- | 0.0203- |
| Mean (Std. Dev) | \$834 | (\$4,480) | \$1,152 | (\$5,212) | 0.0203 |
| Median | \$0 | - | \$0 | - | - |
| Range (Min, Max) | \$0 | \$143,530 | \$0 | \$97,626 | - |
| Emergency Room (ER) | | | | | |
| Had ≥ 1 ER visit (N, %) ^a | 903 | 50.25% | 2,749 | 49.23% | 0.4517 |
| Number of visits <u>per month, mean (SD)</u> | 0.97- | (3.00)- | 1.01- | (2.99)- | 0.6107- |
| Mean (Std. Dev) | 0.97 | (3.00) | 1.01 | (2.99) | 0.6107 |
| Median | 0.03 | - | 0 | - | - |
| Range (Min, Max) | 0 | 67 | 0 | 89.94 | - |
| Costs <u>per month, mean (SD)</u> | \$45- | (\$160)- | \$46- | (\$135)- | 0.873- |
| Mean (Std. Dev) | \$45 | (\$160) | \$46 | (\$135) | 0.873 |
| Median | \$0 | - | \$0 | - | - |
| Range (Min, Max) | \$0 | \$3,063 | \$0 | \$4,161 | - |
| Office Visits (Primary Care) (N, %) | | | | | |
| Had ≥ 1 office visit (N, %) ^a | 1,509 | 83.97% | 4,699 | 84.15% | 0.8576 |
| Number of visits <u>per month, mean (SD)</u> | 1.52- | (3.00)- | 1.43- | (2.19)- | 0.1669- |
| Mean (Std. Dev) | 1.52 | (3.00) | 1.43 | (2.19) | 0.1669 |
| Median | 0.92 | - | 0.86 | - | - |
| Range (Min, Max) | 0 | 64 | 0 | 40.30 | - |
| Costs <u>per month, mean (SD)</u> | \$75- | (\$229)- | \$70- | (\$291)- | 0.5087- |
| Mean (Std. Dev) | \$75 | (\$229) | \$70 | (\$291) | 0.5087 |
| Median | \$30 | - | \$26 | - | - |
| Range (Min, Max) | \$0 | \$5,012 | \$0 | \$15,499 | - |
| Home Health (N, %) | | | | | |
| Had ≥ 1 home health visit (N, %) ^a | 504 | 28.05% | 1,861 | 33.33% | <.0001 |
| Number of visits <u>per month, mean (SD)</u> | 0.64- | (3.00)- | 0.79- | (3.16)- | 0.0625- |
| Mean (Std. Dev) | 0.64 | (3.00) | 0.79 | (3.16) | 0.0625 |
| Median | 0 | - | 0 | - | - |

| Resource Used | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P-Value |
|---|--------------------|------------|----------------------|------------|---------|
| Range (Min, Max) | 0 | 45 | 0 | 43.06 | - |
| Costs per month, mean (SD) | \$47- | (\$198)- | \$88- | (\$642)- | 0.007- |
| Mean (Std. Dev) | \$47 | (\$198) | \$88 | (\$642) | 0.007 |
| Median | \$0 | - | \$0 | - | - |
| Range (Min, Max) | \$0 | \$4,142 | \$0 | \$36,653 | - |
| Laboratory (N, %) | | | | | |
| Had ≥ 1 lab order (N, %) ^a | 1,168 | 65.00% | 3,530 | 63.22% | 0.1722 |
| Number of claimslab tests per month, mean (SD) | 1.24- | (2.00)- | 1.19- | (1.69)- | 0.2962- |
| Mean (Std. Dev) | 1.24 | (2.00) | 1.19 | (1.69) | 0.2962 |
| Median | 0.66 | - | 0.57 | - | - |
| Range (Min, Max) | 0 | 16 | 0 | 19.96 | - |
| Costs per month, mean (SD) | \$52- | (\$94)- | \$46- | (\$120)- | 0.0401- |
| Mean (Std. Dev) | \$52 | (\$94) | \$46 | (\$120) | 0.0401 |
| Median | \$20 | - | \$17 | - | - |
| Range (Min, Max) | \$0 | \$1,689 | \$0 | \$7,246 | - |
| Pharmacy (N, %) | | | | | |
| Had ≥ 1 pharmacy claim (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of claimsprescriptions per month, mean (SD) | 4.99- | (4.00)- | 6.73- | (4.05)- | <.0001- |
| Mean (Std. Dev) | 4.99 | (4.00) | 6.73 | (4.05) | <.0001 |
| Median | 3.96 | - | 5.76 | - | - |
| Range (Min, Max) | 0.37 | 27 | 0.69 | 37.17 | - |
| Costs per month, mean (SD) | \$1,593- | (\$1,105)- | \$1,779- | (\$1,307)- | <.0001- |
| Mean (Std. Dev) | \$1,593 | (\$1,105) | \$1,779 | (\$1,307) | <.0001 |
| Median | \$1,494 | - | \$1,617 | - | - |
| Range (Min, Max) | \$0 | \$27,034 | \$0 | \$54,232 | - |
| OP/ancillary (N, %) | | | | | |
| Had ≥ 1 other OP/ancillary (N, %) ^a | 1,754 | 97.61% | 5,469 | 97.94% | 0.3957 |
| Number of visits per month, mean (SD) | 0.15- | (0.00)- | 0.14- | (0.13)- | 0.0078- |
| Mean (Std. Dev) | 0.15 | (0.00) | 0.14 | (0.13) | 0.0078 |
| Median | 0.12 | - | 0.11 | - | - |
| Range (Min, Max) | 0 | 4 | 0 | 0.52 | - |
| Costs per month, mean (SD) | \$313- | (\$607)- | \$363- | (\$733)- | 0.0087- |
| Mean (Std. Dev) | \$313 | (\$607) | \$363 | (\$733) | 0.0087 |
| Median | \$139 | - | \$159 | - | - |
| Range (Min, Max) | \$0 | \$8,946 | \$0 | \$15,936 | - |
| Total Health Care Utilization & and Costs | | | | | |
| Had ≥ 1 medical visit/encounter (N, %) ^a | 1,797 | 100.00% | 5,584 | 100.00% | --- |
| Number of total encounters per month, mean (SD) | 14.69- | (14.00)- | 16.97- | (13.72)- | <.0001- |
| Mean (Std. Dev) | 14.69 | (14.00) | 16.97 | (13.72) | <.0001 |
| Median | 11.34 | - | 13.13 | - | - |

| Resource Used | STR (n = 1,797) | | 2+PPD (n = 5,584) | | P-Value |
|----------------------------|--------------------|------------|----------------------|------------|---------|
| Range (Min, Max) | 0.56 | 250 | 0.96 | 232.02 | - |
| Costs per month, mean (SD) | \$2,959- | (\$4,962)- | \$3,544- | (\$5,811)- | 0.0001- |
| Mean (Std. Dev) | \$2,959 | (\$4,962) | \$3,544 | (\$5,811) | 0.0001 |
| Median | \$1,916 | - | \$2,182 | - | - |
| Range (Min, Max) | \$0 | \$146,367 | \$0 | \$103,103 | - |

NOTE: SD = standard deviation.

^aEstimated over all available follow-up.

^bAmong hospitalized patients.

^cAmong patients with at least one admission over all follow-up.

The multivariate Poisson regression model showed that receiving an STR was associated with a significantly lower risk of hospitalization rate than receiving the 2+PPD regimen (IRR = 0.8457; $P < 0.001$) (Table 5). When the received regimen type was controlled for, we found that patients were significantly more likely to be hospitalized if they had the following characteristics: a concomitant mental disorder diagnosis (vs. no concomitant mental disorder diagnosis; IRR = 1.2917; $P < 0.001$), a concomitant drug or alcohol abuse diagnosis (vs. no concomitant drug or alcohol abuse diagnosis; IRR = 2.0357; $P < 0.001$), a CCI score greater than 1 (IRR increased with increasing CCI score, from 2.3779 among patients with a CCI between 1 and 2 to 2.6432 among patients with a CCI greater than 3; all $P < 0.001$), were female (vs. male; IRR = 1.1069; $P = 0.003$), or were older than 35 years (vs. younger than 35 years; IRR increased with increasing age, up to 54 years, from 1.2482 among patients aged 35-44 years to 1.555 among patients aged 45-54 years; both $P < 0.1$). Additionally, the likelihood of a hospitalization increased slightly with each additional day of follow-up (IRR = 1.0013; $P < 0.0001$). Finally, being treatment naïve prior to index was predictive of an approximately 13% higher hospitalization rate as compared with being treatment experienced (IRR = 1.1270; $P = 0.0033$).

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342 **Table 5. Predictors of hospitalization, using multivariate Poisson regression, and**
 343 **controlling for treatment cohort.**

| Specification: Adherence Covariate Excluded | Poisson Count Model | | |
|---|---------------------|----------------------|---------|
| | Parameter Estimate | Incidence Rate Ratio | P-Value |
| Received a STR (vs. 2+PPD regimen) | -0.1654 | 0.8475 | 0.0001 |
| Female (vs. male) | 0.1003 | 1.1069 | 0.003 |
| Age (vs. less than 35) | | | |
| 35 to 44 years | 0.1016 | 1.2482 | 0.0669 |
| 45 to 54 years | 0.2217 | 1.5550 | <.0001 |
| 55+ years | 0.4415 | 1.1056 | <.0001 |
| Charlson comorbidity index score (vs. Charlson comorbidity index score less than 1) | | | |
| Between 1 and 2 | 0.8662 | 2.3779 | <.0001 |
| Greater than 2 | 0.972 | 2.6432 | <.0001 |
| Treatment naïve (vs. treatment experienced) | 0.1196 | 1.1270 | 0.0033 |
| Had a mental disorder diagnosis (vs. no mental disorder diagnosis) | 0.256 | 1.2917 | <.0001 |
| Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis) | 0.7109 | 2.0357 | <.0001 |
| Length of follow-up (in days) | 0.0013 | 1.0013 | <.0001 |

344 NOTE. 2+PPD = two or more pills per day; STR = once-daily single-tablet regimen.

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346 From the Poisson regression analysis described above, we found the adjusted rate of
 347 hospitalization to be significantly lower for patients receiving an STR than for patients receiving
 348 2+PPD (i.e., 39.5 hospitalizations per 100 patient-years ~~receiving for patients receiving~~ STR vs.
 349 51.2 hospitalizations per 100 patient-years ~~for those~~ receiving 2+PPD) (Figure 2). These
 350 adjusted hospitalization rates translated to a 23% lower risk of hospitalization among patients
 351 receiving an STR, compared with patients receiving 2+PPD. As shown in Figure 3, adherence
 352 status seems to be a key mechanism mediating hospitalization risk as patients with at least 95%
 353 adherence (regardless of regimen type) had a statistically significant lower hospitalization rate

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354 compared to patients with less than 95% adherence. Improved adherence among patients treated
355 with STR therefore appears to confer a lower risk of hospitalization and associated costs.

356 Examining other types of health care utilization. The percentage of patients with at least one
357 home health visit was significantly lower among patients receiving STR than for patients
358 receiving 2+PPD (Table 4). Between the two cohorts, no differences were observed in the
359 percentage of patients with at least one emergency room, office visit, or laboratory claim.
360 Similarly, no significant differences were found in the number of emergency room, office visits,
361 home health visits, or laboratory claims per month. However, patients who received an STR had
362 significantly lower costs per month associated with inpatient, home health, laboratory, pharmacy,
363 other, and total health care than patients receiving 2+PPD. Mean (SD) total health care costs per
364 month were \$2,959 (\$4,962) among patients receiving an STR and \$3,544 (\$5,811) among
365 patients receiving 2+PPD; thus, patients receiving an STR accrued, on average per month, \$585
366 less than patients receiving 2+PPD ($P < 0.001$). The largest difference in costs between the two
367 cohorts was observed for inpatient admissions (\$317 more for patients receiving 2+PPD),
368 followed by pharmacy costs (\$187 more for patients receiving 2+PPD).

369 When monthly health care costs were adjusted for demographic, clinical, and treatment
370 characteristics, patients receiving an STR had monthly total costs averaging \$2,947; patients
371 receiving 2+PPD had monthly total costs averaging \$3,549 (Figure 34). Thus, patients receiving
372 2+PPD had \$602 more in monthly health care costs, which corresponded to a 17% reduction in
373 costs associated with STR. Additionally, when monthly health care costs, excluding pharmacy
374 costs, were adjusted for demographic, clinical, and treatment characteristics, patients receiving
375 an STR had monthly total costs averaging \$1,370; patients receiving 2+PPD had monthly total
376 costs averaging \$1,797. Thus, patients receiving 2+PPD had \$427 more in adjusted monthly
377 health care costs, which corresponded to a 23.8% reduction in costs associated with STR.

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9 378 **DISCUSSION**

10 379 This retrospective database analysis examined adherence to ART regimens among patients
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12 380 with HIV infection, using pharmacy refill dates as the best available proxy for pill-taking
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14 381 behavior. One advantage to this method is that we can identify those patients who may not have
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16 382 had all or some of their medications available on any given date based on an analysis of the
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18 383 timing in between refills, which also notes the amount of medication dispensed each time. The
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20 384 rate of hospitalization and correlates of hospitalization also were assessed from these claims data
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22 385 and should be highly accurate, as should the overall monthly health care utilization and costs.
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24 386 This analysis largely confirms the previous report from Sax et al.^[416]: we found that
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26 387 patients receiving an STR had significantly better adherence rates than patients receiving
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28 388 multiple pills per day. Our other finding was that higher rates of adherence were associated with
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30 389 similar or lower rates of hospitalization, regardless of the regimen; less-than-complete adherence
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32 390 was associated with higher rates of hospitalization and overall costs. Thus, multiple-pill regimens
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34 391 were associated both with lower rates of complete adherence and correspondingly higher overall
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36 392 health care costs. We observed a significantly higher rate of hospitalizations occurring in patients
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38 393 receiving multiple-pill regimens ($P < 0.001$) than in patients receiving an STR. The greater total
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40 394 health care costs were due to differences in both the pharmacy costs of the regimen components
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42 395 as well as the costs of hospitalizations and associated care. Therefore, one implication of our
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44 396 findings is that choosing a multiple-pill regimen for its cost alone might inadvertently result in
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46 397 little to no total health care cost-savings for a payer, given the potential risk of more frequent
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48 398 hospitalizations in patients receiving multiple-pill regimens.

49 399 Similar to previous studies ^[420,421], we found that patients who were adherent to therapy
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51 400 were less likely to be hospitalized. Our data demonstrated similar rates of hospitalizations among
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53 401 patients with the highest levels of complete adherence—at least 95%. This was consistent across
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9 402 both treatment cohorts. This finding suggests that the differences observed in the rates of
10 403 hospitalizations across regimens are primarily due to differences in adherence rates between the
11 404 STR and 2+PPD regimens rather than any concerns for toxicities. This finding also may partially
12 405 address the potential contribution of channeling bias, a concern with any observational data set.
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14 406 We found that adherent patients on any regimen have similar rates of hospitalization, which
15 407 suggests that there may not have been a consistent bias to prescribe to more clinically
16 408 immunosuppressed patients or to patients who were at greater risk for hospitalization due to
17 409 other factors than a multiple-pill regimen. Furthermore, we found that the outcome of fewer
18 410 hospitalizations for patients receiving an STR was consistent when we compared hospitalization
19 411 risks for treatment-naïve patients with hospitalization risks for treatment-experienced patients. In
20 412 the latter group, the impact of stage of illness prior to treatment would be lessened, given the
21 413 impact of prior treatment on improving pretreatment immunosuppression, with an STR regimen.
22 414 Of final note regarding channeling bias, previous analyses of Medicaid beneficiaries with HIV
23 415 have shown that patients receiving ART are completely non-adherent (i.e., days with no ART
24 416 supply/coverage on hand) for approximately 14% of their regimen duration regardless of the
25 417 number of pills in the regimen [2220]. This finding suggests that clinicians are not channeling
26 418 more adherent patients to STRs. Together, these data support the observation that facilitating
27 419 greater adherence to ART at any stage of illness may result in reducing hospitalization risk.
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43 420 One follow-up question our study findings raises is whether the observed reduction in
44 421 hospitalization risk and costs with STR was also due to less prevalent chronic comorbidities in
45 422 patients prescribed STR. To assess this possibility, we replicated key descriptive analyses on
46 423 hospitalization rates for patients with no baseline comorbidities as reported by the CCI. We
47 424 found that the majority (~70%) of both STR and 2+PPD patients had no other CCI
48 425 comorbidities. Among STR patients with no other comorbidities from the CCI, 13.9% had a
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9 426 hospitalization compared with 18.3% of 2+PPD patients with no other comorbidities. Further,
10 427 among STR patients with no comorbidities, 11.4% of adherent patients had a hospitalization
11 428 compared with 14.7% of non-adherent patients. Similarly, among 2+PPD patients with no
12 429 comorbidities, 12.4% of adherent patients had a hospitalization compared with 19.7% of non-
13 430 adherent patients. Results of this sensitivity analysis, combined with the observation that the vast
14 431 majority of patients in our study had no major comorbidities (from the CCI) requiring other
15 432 chronic treatment, suggest that the observed association between poorer adherence and higher
16 433 hospitalization was likely due to reduced ART adherence and not due to reduced adherence with
17 434 other medications patients were taking.

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26 435 There were several measurable differences present in the study population at baseline. Our
27 436 study attempted to control for effects these differences may have had on rates of ~~adherence and~~
28 437 hospitalization ~~between STR and 2+PPD patients~~. We used multivariate regressions to control
29 438 for patient demographics, treatment characteristics (i.e., treatment naïve vs. experienced, type of
30 439 ART received, ~~year the ART was received~~), and clinical characteristics (i.e., CCI score,
31 440 concomitant mental disorder, drug and alcohol abuse diagnoses). We found ~~that~~ a number of
32 441 factors were associated with an increased risk of ~~poor adherence hospitalization independent of~~
33 442 ~~treatment regimen~~, including having a CCI score greater than ~~3~~1; having a ~~concomitant~~ drug or
34 443 alcohol abuse diagnosis; ~~having a concomitant mental health disorder; being female and of older~~
35 444 ~~age~~; and being treatment ~~experienced~~naïve. ~~Similarly, having a CCI score greater than 1, or~~
36 445 ~~having a concomitant mental disorder or drug or alcohol abuse diagnosis were associated with an~~
37 446 ~~increased risk of hospitalization.~~

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39 447 ~~Nevertheless, Even~~ after controlling for these ~~se~~ factors ~~noted above~~, we still detected an
40 448 independent ~~effect association~~ of ~~the~~ regimen ~~type~~ with hospitalization rates and, in fact,
41 449 ~~observed an increase in the apparent protective effect of STR based on the predicted, adjusted~~

Comment [k4]: Did not notice this typo in earlier drafts. This should have said "hospitalization."

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9 450 hospitalization rate derived from the Poisson model (39.5 per 100 patients in the STR group vs.
10 451 51.2 per 100 patients in the 2+PPD group; see Figure 2). One possible explanation for this
11 452 difference is that the Poisson model corrected a substantial imbalance in the proportion of
12 453 patients who were treatment naïve at index (47.5% of STR patients vs. 24.5% of 2+PPD
13 454 patients). Lack of or naivety to ART exposure has been shown in some studies to be a positive
14 455 predictor of hospitalization in HIV patients [23], perhaps because approximately one-third of
15 456 HIV patients wait to seek care until their disease has progressed to the point that they need acute
16 457 treatment. [24, 25] As noted in a recent study by Metsch et al. [26], these patients often obtain
17 458 initial care in emergency departments and hospital inpatient wards, and they tend not to
18 459 persistent with follow-up outpatient care. This pattern of treatment induction may further
19 460 increase their risk of infection and re-hospitalization in the short-term. Because being treatment
20 461 naïve was shown in our data to be predictive of hospitalization, the Poisson model's adjustment
21 462 for the overrepresentation of treatment naivety in the STR group may therefore have resulted in
22 463 the larger difference between STR and 2+PPD in hospitalizations than observed in the crude,
23 464 unadjusted comparison.

24 465 One hypothesis for a plausible mechanism by which these outcomes observed in our study
25 466 could occur stems from observations in the SMART study.[24-27] That study, comparing
26 467 continuous antiviral treatment versus periodic treatment interruptions, demonstrated that HIV
27 468 treatment interruptions that were of sufficient length of time to lead to recurrent HIV viremia
28 469 were associated with a significantly higher risk of all-cause morbidity and mortality. Our
29 470 analysis was consistent with those findings: the mean maximum duration of nonadherence was
30 471 about 3 weeks, which is a sufficient length of time to expect a return of HIV viremia. The
31 472 SMART study noted that the higher risk of illness was not necessarily proximal to the time of the
32 473 interruption but was observed for months afterwards. While there are differences between the

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9 474 SMART study design and population and our study population, our findings are consistent with
10 475 SMART and with what might be expected in a population who periodically are without antivirals
11 476 for an average time of more than 3 weeks. Of note, short cycle interruptions of 2 days were not
12 477 associated with virologic rebound in patients receiving the STR that was used in the SMART
13 478 study [2228]. Therefore, our finding that the typical interruptions were much longer than this is
14 479 supportive of a mechanism that could have resulted in increased patient morbidity.

20 480 It is also important to note that patients in this study generally were reasonably adherent to
21 481 ART, with a mean adherence of just over 80% regardless of the number of pills received per day.
22 482 This rate of adherence is consistent with other published reports of adherence, although other
23 483 reports found even higher adherence rates to an STR.[413,4214] Furthermore, the difference
24 484 observed in our study between the STR and 2+PPD regimens (approximately 4%) is consistent
25 485 with what was observed by Sax et al. of 2.2%.[4416] This difference is also consistent with the
26 486 differences in adherence rates reported when comparing average improvement between once-
27 487 daily and twice-daily regimens (2.9%).[2329] It is important to note that there also were highly
28 488 nonadherent patients to both the STR and the 2+PPD regimes in this study population,
29 489 supporting the generalizability of this population.

39 490 Of further note, the differences observed in our study were associated with factors that
40 491 typically are not present during randomized clinical trials. Randomized trials typically actively
41 492 work for patient adherence to study medications and use study coordinators to regularly monitor
42 493 patients to minimize missed doses. In our observational study, these typical adherence supports
43 494 are not in place; thus, our data may reflect real-world lapses in patient behavior in refilling
44 495 prescriptions, including partial regimen refills, which would not be observed in clinical trials.
45 496 While there are concerns about the interpretation of observational data and the determination of
46 497 causal relationships, it is not clear if a randomized study comparing an STR with a multiple-pill

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9 498 regimen would be able to detect the observed differences unless there was less patient support
10 499 than is standard in clinical trials.

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12 500 Our data do not suggest that all patients should be on an STR. There are many factors that
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14 501 weigh in the decision of which regimen is best for any given patient, including pre-existing
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16 502 virologic resistance and tolerability. In our study, the anticipated adherence benefits observed in
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18 503 association with a lower pill burden is relevant but should not be construed as a suggestion that
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20 504 an STR is the ideal choice for the entire population of patients with HIV. Nevertheless, our data
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22 505 do support the continued development of additional STR options, to broaden the number of
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24 506 patients for whom this is an option and the number of subsequent beneficial outcomes.

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26 507 Our study has several limitations common to observational claims database analyses.
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28 508 Adherence was calculated by using pharmacy refill dates, and we have no measure of actual
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30 509 patient adherence to the prescriptions they filled. However, this measure has been found to be a
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32 510 useful proxy for actual medication adherence.^[2430] Because we did not randomize patients to
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34 511 the two different treatment regimens, we cannot exclude unmeasured confounding factors that
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36 512 may have influenced our outcomes. Among the most important of these factors in this study was
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38 513 that multiple trials have shown that medication resistance at the time of virologic failure is
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40 514 significantly less common in boosted PI treatments than on other regimens, including
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42 515 nonnucleoside/nucleotide reverse transcriptase inhibitor-based treatments.^[2531,2632] Clinicians
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44 516 could have chosen to prescribe a boosted-PI-containing regimen (all of which contain three or
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46 517 more pills per day) to their less-adherent patients. It cannot be determined from this data set that
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48 518 these patients would have been more adherent on an STR. Although we attempted to control for
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50 519 some of these variables through the use of multivariable models that included some of these
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52 520 factors (substance abuse and psychiatric diagnoses), residual confounding may remain. In
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54 521 addition, we had no laboratory results from patients and thus cannot confirm the degree of

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9 522 virologic suppression obtained across the regimens. Finally, although our data include
10 523 information from the Medicaid programs in 11 states, the authors were blinded (as per data
11 524 privacy rules) as to which specific states are captured. Although the database's documentation
12 525 suggests that the states are geographically dispersed, we cannot assert that our findings would be
13 526 fully representative of the general Medicaid population in the US.

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18 527 In our study, a large proportion of HIV-treated individuals (15% of the total HIV-treated
19 528 population) were excluded from the analysis due to their having received incomplete ART
20 529 regimens. We did not have sufficient data on these patients to explain why their regimens were
21 530 incomplete. However, a previous study found that physician medication errors were somewhat
22 531 common in individuals with HIV, with the most common error occurring with boosted PIs
23 532 (estimated at 5.3% of patients); such errors may explain some of the incomplete regimens
24 533 observed in our analysis.^[2733] Increased adoption of fixed-dose combinations as part of HIV
25 534 treatment may help to alleviate the issue of incomplete regimens.

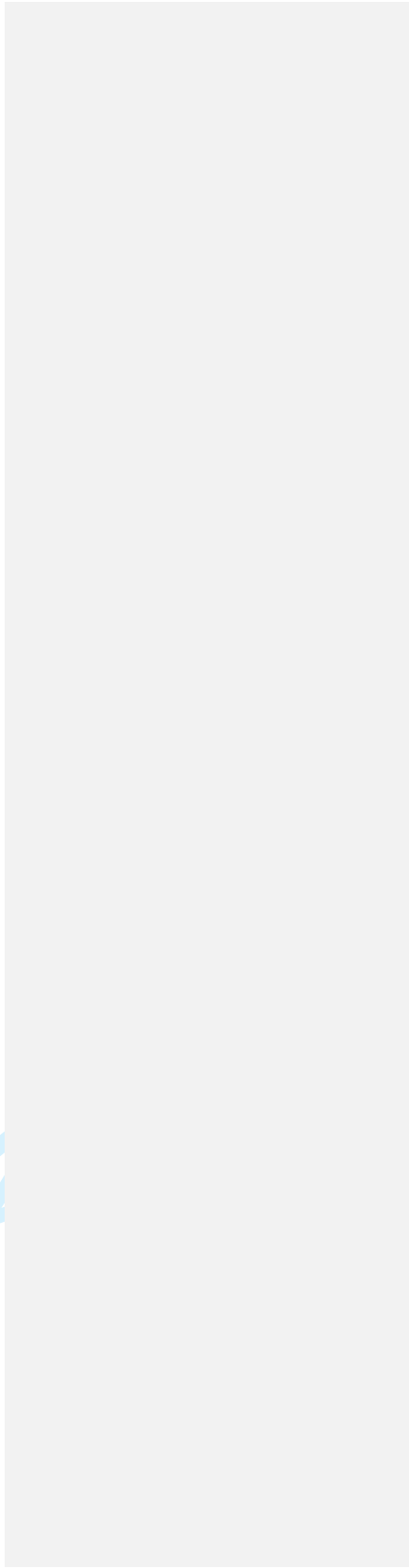
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33 535 During our study period, the only available single-pill ART regimen was coformulated
34 536 efavirenz/emtricitabine/tenofovir disoproxil fumarate. It is possible that these results would not
35 537 be generalizable to other one- and multi-pill regimens if other treatments have different efficacy
36 538 and toxicity profiles. With the recent approval by the Food and Drug Administration of two other
37 539 STRs (i.e., tenofovir, emtricitabine, and rilpivirine and tenofovir, emtricitabine, elvitegravir and
38 540 cobicistat), it may eventually be possible to explore the applicability of our observations to other
39 541 STRs.

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46 542 In summary, this study supported the results as reported by Sax et al.^[416] We found that
47 543 patients who received ART as a single pill per day were significantly more likely to be highly
48 544 adherent to therapy than patients who received multiple-pill regimens. This difference in
49 545 adherence was associated with a lower risk of hospitalizations: patients with less-than-complete

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546 adherence were more likely to be hospitalized. While we acknowledge the limitations associated
547 with any observational study, our data support our finding that the use of an STR may reduce
548 health care costs as well as patient morbidity by decreasing hospitalization rates, which are
549 higher in patients with less-than-complete medication adherence.

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654 **FIGURE LEGENDS**

655 **Figure 1. Sample Selection Flow Chart**

656 **Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort**

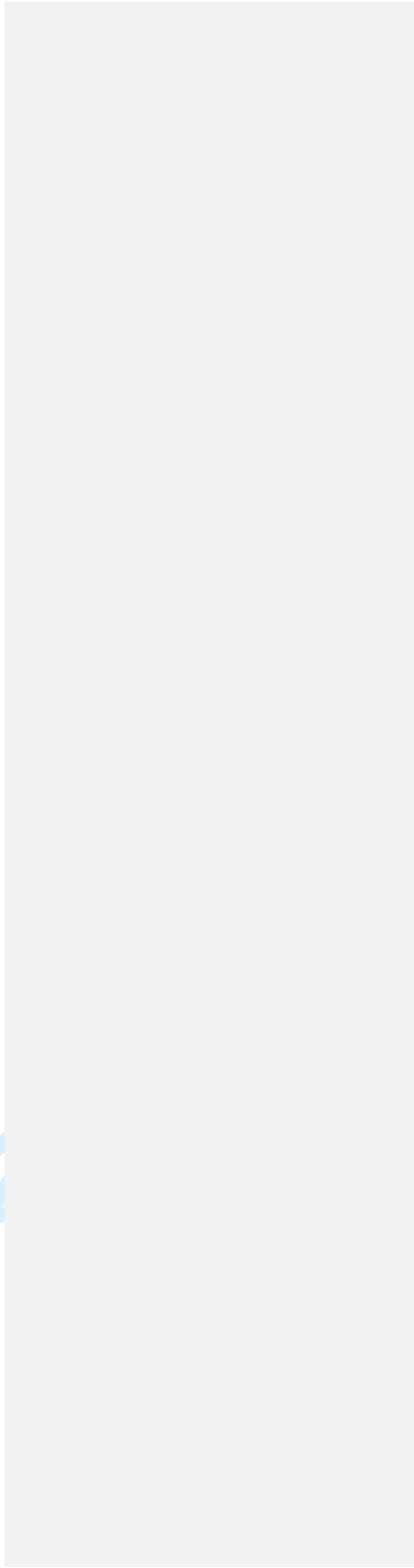
657 **Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence**

658 **Figure 43. Adjusted Monthly Health Care Costs, by Cohort**

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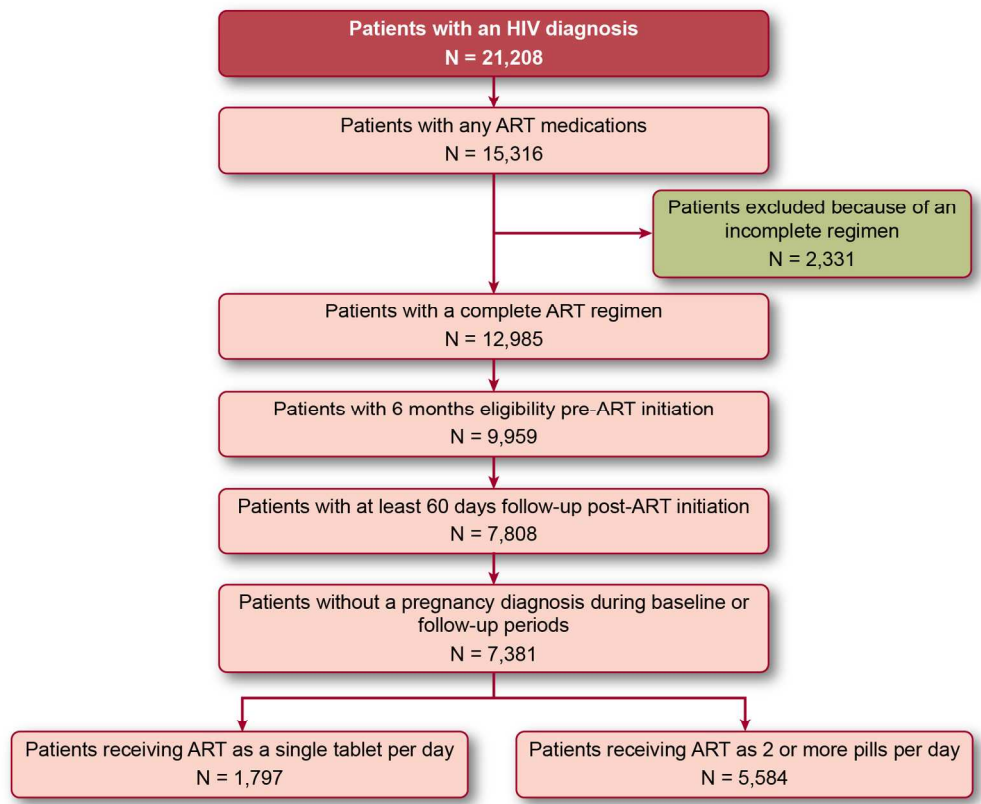


Figure 1. Sample Selection Flow Chart
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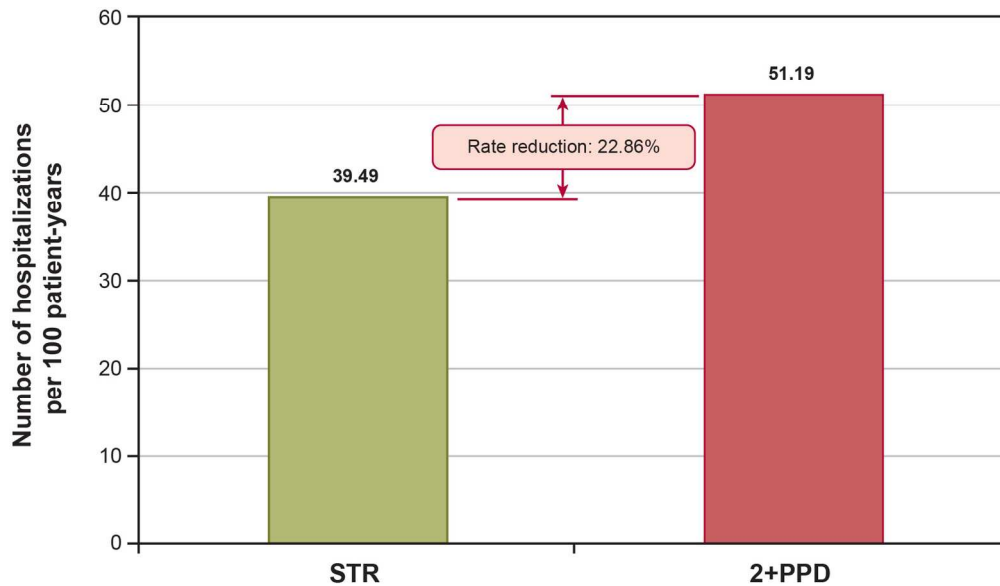


Figure 2. Adjusted Rate of Hospitalizations per 100 Patient-years, by Cohort
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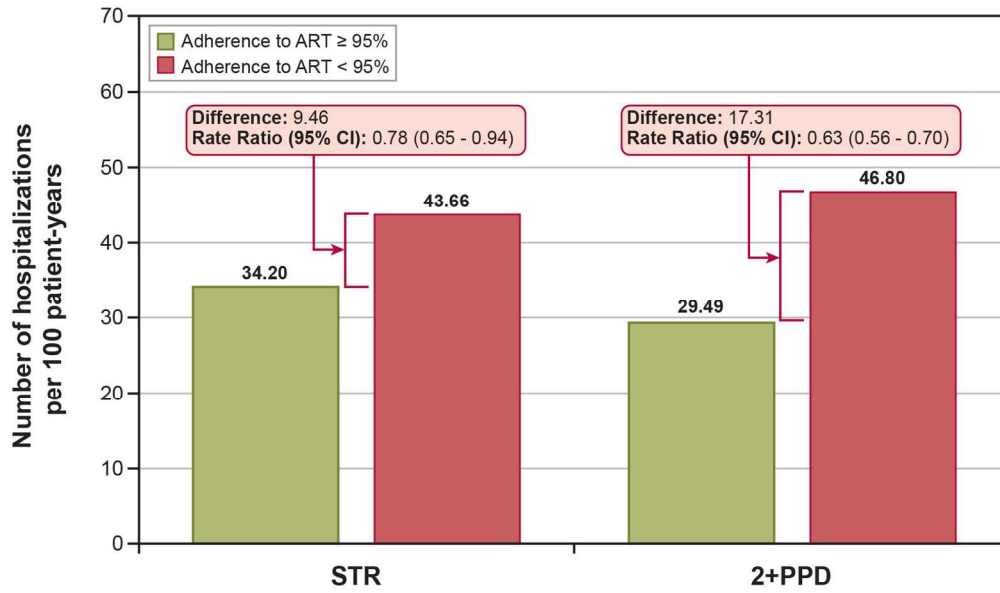


Figure 3. Hospitalizations per 100 Patient-Years, by Cohort and Adherence
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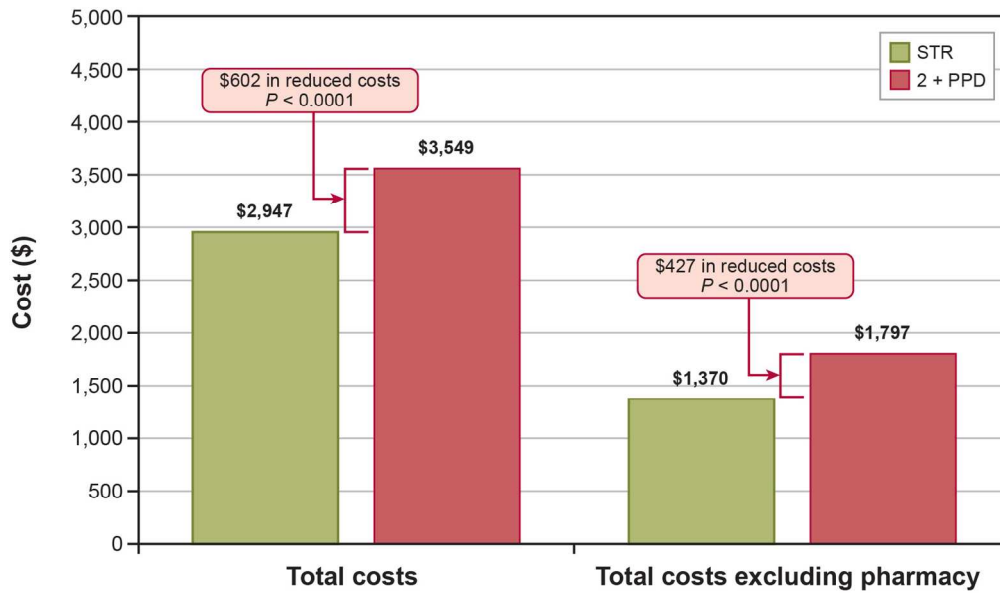


Figure 4. Adjusted Monthly Health Care Costs, by Cohort
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