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MAJOR ARTICLE

# Antibiotic Prescribing for Acute Respiratory Illnesses in Persons With HIV Compared With Persons Without HIV

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***Background.*** Antibiotic overuse increases health care cost and promotes antimicrobial resistance. People with HIV (PWH) who develop acute respiratory infections (ARIs) may be assumed to be "higher risk," compared with non-PWH, but comparative antibiotic use evaluations have not been performed.

***Methods.*** This observational, single-center study compared antibiotic prescribing in independent clinical encounters for PWH and non-PWH diagnosed with ARI in outpatient clinical practices using International Classification of Diseases, 10th Revision, codes between January 1, 2014, and April 30, 2018. The Fisher exact test compared categorical variables with antibiotic prescribing patterns.

***Results.*** There were 209 patients in the PWH cohort vs 398 patients in the non-PWH cohort. PWH had a median CD4+ count of 610 cells/mm$^3$, with 91% on antiretroviral therapy and 78% virally suppressed. Thirty-seven percent of all visits resulted in an antibiotic prescription, and 89% were inappropriate. Antibiotics were prescribed more frequently in non-PWH (35% PWH vs 40% non-PWH; $P = .172$) and managed according to guidelines more often in PWH (37% PWH vs 30% non-PWH; $P = .039$). Antibiotics were prescribed appropriately most frequently in PWH managed by HIV clinicians (29% PWH managed by HIV clinician vs 12% PWH managed by non-HIV clinician vs 8% non-PWH; $P = .010$). HIV clinicians prescribed antibiotics for a mean duration of 5.9 days vs PWH managed by a non-HIV clinician for 9.1 days vs non-PWH for 7.6 days ($P < .0001$).

***Conclusions.*** Outpatient antibiotic overuse remains prevalent among patients evaluated for ARI. We found less frequent inappropriate antibiotic use in PWH. Prescriber specialty, rather than HIV diagnosis, was related to appropriateness of antimicrobial prescribing.

**Keywords.** antimicrobial stewardship; HIV medicine.

Antimicrobial resistance is a problem created and exacerbated by inappropriate prescribing and overuse of antibiotics. The 2019 Centers for Disease Control and Prevention Antibiotic Resistance Threat Report estimated that nearly 3 million people per year develop illnesses and ~35 000 people die annually from infections due to antibiotic-resistant organisms [1]. Much of the antibiotic overuse occurs in the ambulatory setting. A large Veterans Affairs health care system study found that up to two-thirds of ambulatory antibiotic prescriptions are inappropriate [2]. In another study, almost 50% of all ambulatory visits designated for acute respiratory infections (ARIs) resulted in an antibiotic prescription, and up to 30% of prescriptions were unnecessary [3]. Data from our own institution showed that outpatient prescribing for acute bronchitis (a diagnosis that almost never requires an antibiotic) varied considerably between clinics, from 40.8% to 74.5%, with a mean of 53.7% [4].

There is a paucity of data regarding outpatient antibiotic prescribing in high-risk or immunosuppressed populations, like people with HIV (PWH), who were excluded from evaluation in the previously cited studies. Furthermore, it is unknown how ambulatory antibiotic use differs between PWH and those without HIV (non-PWH). Previous studies of antibiotic prescribing in ARI demonstrated high rates of antibiotic prescribing in viral infections in PWH, but use was not compared with the general population [5, 6]. Furthermore, patients with immunosuppression are not addressed in guideline recommendations and are more likely to suffer consequences from antibiotic overuse such as *C. difficile* infection [7].

Antibiotic decision-making biases may be present when prescribing for PWH [8]. Clinician over- or underestimation of the degree of immunosuppression or the likelihood and consequences of bacterial infection may influence antimicrobial prescribing. Individual risk assessment in this population depends on CD4 status, antiretroviral therapy (ART) status, viral load, and current vaccination status. Contemporary data evaluating the management of ARI in PWH as compared with the general

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population have not been previously described. We evaluated the use of antibiotics for ambulatory ARI in PWH and compared this with use in non-PWH.

## METHODS

### Study Design

We conducted an observational, single-center, retrospective study comparing antibiotic prescribing practices for PWH and non-PWH diagnosed with ARI between January 1, 2014, and April 30, 2018. ARI visits were obtained by International Classification of Diseases, 10th Revision (ICD-10), codes for sinusitis (J01, J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9), bronchitis (J20.9), and common cold/viral upper respiratory infection (URI) (J06.9). Visits at 19 outpatient primary and urgent care clinics and 1 specialty care clinic in a single Midwest health care system were evaluated. PWH receive their HIV care at the specialty care clinic (SCC) and have the option to receive primary care at the SCC or at a primary care clinic of their choice.

Two independent reviewers (M.K. and A.A.) conducted the chart reviews after initial training. Variables extracted included antibiotic prescription (yes/no), agent prescribed, duration, appropriateness of prescription, and concordance with the guidelines. Exclusion criteria included patients diagnosed with chronic obstructive pulmonary disease (COPD), COPD exacerbations, bacterial pneumonia, and other concurrent conditions requiring antibiotics. Concurrent antibiotic use was determined based on chart review.

### Cohort Definitions

The PWH cohort was established by including the ICD-10 code for HIV (B20). The non-PWH cohort was obtained using the above ARI codes and frequency matching for gender and race. A subanalysis was performed that divided the PWH cohort further by the specialty of prescriber, HIV clinician vs non-HIV clinician. HIV clinician was defined as an infectious disease physician, fellow, or advanced practice provider (APP) who routinely provides care for PWH in the specialty care clinic.

### Guideline Definitions

Concordance with guidelines was defined based on if management was in alignment with published Infectious Diseases Society of America (IDSA) guidelines, regardless of whether an antibiotic was prescribed [9–11]. Appropriateness of prescribing was defined based on published IDSA guidelines and included evaluation of antibiotic choice and duration if an antibiotic was prescribed [9]. Bacterial infection was assumed based on severity of symptoms, duration of symptoms, or presence of double sickening. For example, if no bacterial infection was present and no antibiotic was prescribed, this was concordant with guidelines, but appropriateness of prescription was not evaluated as no prescription was provided. Similarly, if a bacterial infection was present and no antimicrobial was prescribed, this was discordant with the guidelines but not evaluated for appropriateness. If an antibiotic was prescribed and considered inappropriate for any reason (wrong drug, wrong duration, or no antibiotic required), this was considered discordant with guidelines and an inappropriate prescription. Only antibiotic prescriptions that were concordant with guidelines and appropriate dose and duration were considered concordant and appropriate (Figure 1).

### Statistical Analysis

The Fisher exact test compared categorical variables with antibiotic prescribing patterns. *P* values for pairwise comparisons

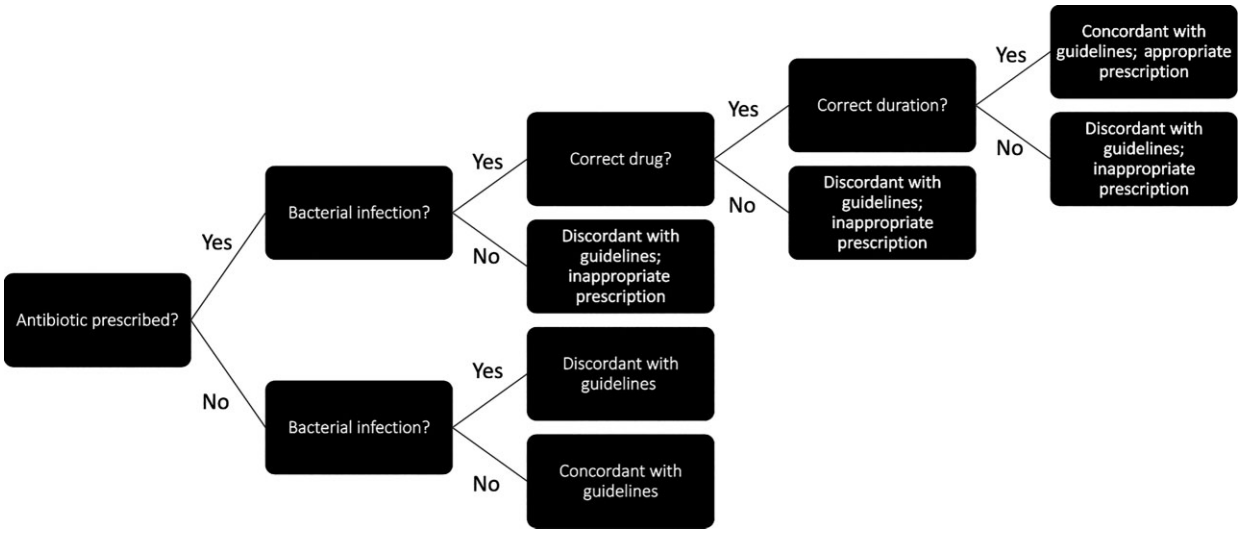


**Figure 1.** Decision tree for determining if management was according to guidelines and, if an antibiotic was prescribed, determining if that prescription was appropriate.

between prescribing patterns were adjusted using the Bonferroni method. Mean antibiotic duration was compared between clinician groups using analysis of variance, and pairwise comparisons were adjusted using Tukey's method. All visits from patients were included. A sensitivity analysis was done (data not shown) where the earliest clinic visit per patient was analyzed, and results resembled those obtained when including all visits and treating the visits as independent events. Multivariable logistic regression was used to determine if type of clinician was associated with appropriate prescribing after adjusting for age. Analysis of covariance (ANCOVA) was used to determine if duration of antibiotics prescribed differed by type of clinician adjusting for age. Pairwise comparisons between clinician groups were adjusted using Tukey's method. All analyses were done using SAS, version 9.4. $P < .05$ was considered statistically significant.

## RESULTS

### Cohort Description

In the PWH cohort, 209 patients accounted for 350 visits for acute respiratory infection within our time frame, and in the non-PWH cohort, 398 patients accounted for 492 visits. Demographics were similar between cohorts. Most PWH were immunologically preserved and virologically suppressed (Table 1). Ninety-one percent of PWH in the cohort were currently prescribed ART. Seventy-four percent of PWH in the cohort were treated by non-HIV clinicians for ARI encounters at primary care or at an immediate care center.

**Table 1. Patient Demographics and Characteristics**

| | PWH (n = 202) | Non-PWH (n = 391) | *P* Value |
|---|---|---|---|
| Self-reported gender in EMR,[a] No. (%) | | | |
| Male | 132 (65.4) | 258 (66.0) | |
| Female | 70 (34.7) | 133 (33.0) | |
| | | | .93 |
| Self-reported race,[b] No. (%) | | | |
| American Indian or Alaska Native | 2 (1.0) | 0 | |
| Asian | 2 (1.0) | 7 (1.8) | |
| Black or African American | 53 (27.2) | 90 (23.0) | |
| Native Hawaiian or other Pacific Islander | 1 (0.5) | 0 | |
| White | 135 (69.2) | 288 (73.7) | |
| Other | 2 (1.0) | 6 (1.5) | |
| Not reported | 7 (3.5) | … | |
| | | | .17 |
| Age | | | |
| Range, y | 20–72 | 20–76 | |
| Mean, y | 46.2 | 49.9 | |
| | | | .0003 |
| CD4 T-cell count | | | |
| Median, cells/mcL | 610 | … | |
| <200 cells/mcL, % | 10.3 | … | |
| >500 cells/mcL, % | 60.7 | … | |
| Viral load | | | |
| HIV viral load suppressed, % | 78 | … | |

Abbreviations: EMR, electronic medical record; PWH, people with HIV.

[a]During the time frame evaluated, only binary gender options were reported in the EMR.

[b]Information about ethnicity was not consistently available.

### Antibiotic Prescribing Patterns

Overall, 38% of visits for ARI resulted in an antibiotic prescription. Sixty-six percent of patients were managed according to guideline recommendations. There was no statistically significant difference between cohorts in frequency of antibiotic prescribing (35% PWH vs 40% non-PWH; $P = .172$). Overall, antibiotics, when prescribed, were considered appropriate 11% of the time, with 65.9% classified as inappropriate because an antibiotic was not indicated, 17.9% due to inappropriate drug choice, 15.8% were for too long of a duration, and 0.36% too short a duration. Appropriate prescribing was slightly more frequent in the PWH cohort, although this was not statistically significant (15% PWH vs 8% non-PWH; $P = .064$). Guideline-concordant management (irrespective of antibiotic prescription) was more frequent in PWH (70% PWH vs 63% non-PWH; $P = .039$) (Figure 2A). The most common reason antibiotics were considered inappropriate was due to no indication for an antibiotic (PWH 68% vs 64.8%). Non-PWH were more likely to receive the wrong drug (22.4% vs 10% in PWH; $P < .05$). PWH were more likely to be treated for too long a duration (22% vs 12.3% of non-PWH; $P < .05$).

HIV clinicians only cared for PWH, and management in this group was more frequently concordant with guidelines (82%) vs PWH managed by non-HIV clinicians (66%) vs non-PWH (also cared for by non-HIV clinicians; 63%; $P$ .0015) (Figure 2A). HIV clinicians were more likely to prescribe appropriately (29%) as well. Non-HIV clinicians prescribed appropriately 12% of the time for PWH and 8% of the time for non-PWH ($P$ .010). This difference was preserved when adjusted for age ($P < .05$). Comparing the management of PWH with non-PWH cared for by non-HIV clinicians, there was no difference in frequency of prescribing antibiotics ($P = .057$), appropriateness of antibiotics ($P = .87$), or guideline concordance ($P = 1.00$) (Table 2).

### Antibiotic Duration

HIV clinicians prescribed antibiotics for a mean of 5.9 days vs PWH managed by a non-HIV clinician, who received of 9.1 days of treatment. Non-PWH were treated with a mean of 7.6 days of antibiotics ($P < .0001$). When a pairwise comparison was performed, each pair was statistically different ($P < .05$) (Table 2). This difference persisted when multivariate regression analysis was performed adjusting for age.

### Prescriber Training Level

For the entire cohort, antibiotics were prescribed at a visit by an attending physician 38% of the time, a trainee (resident or

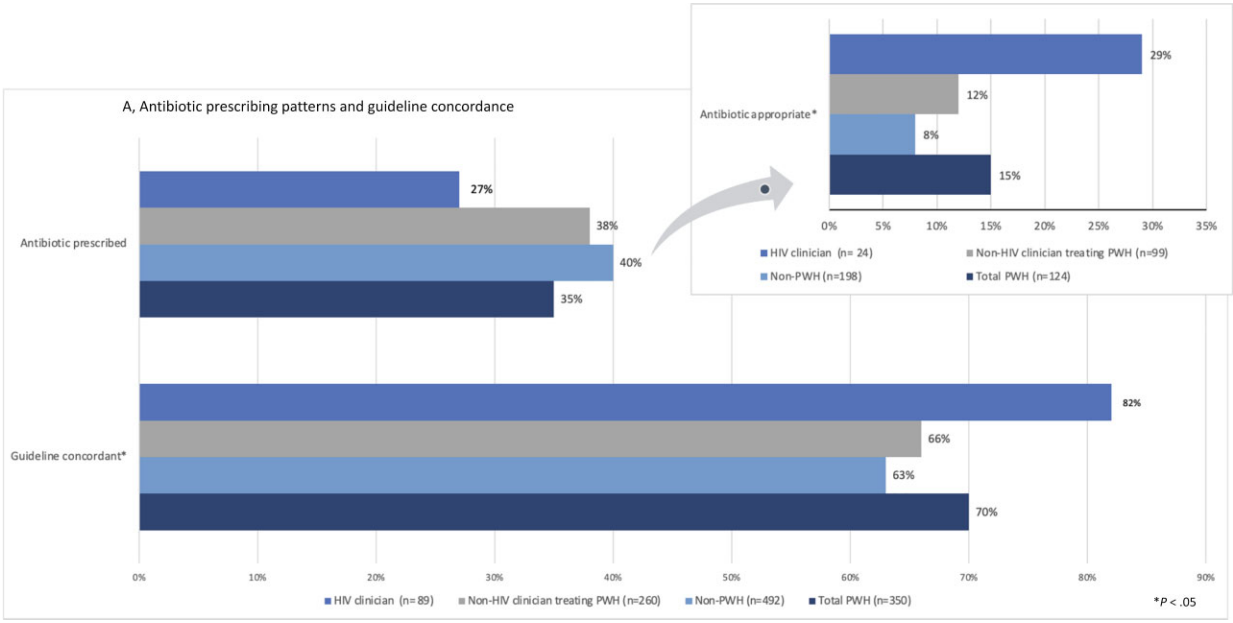


**Figure 2.** Antibiotic prescribing practices among cohorts. A, Antibiotic prescribing patterns comparing total PWH cohort, non-PWH cohort, HIV clinician subgroup, and non-HIV clinician treating PWH subgroup. HIV clinicians only prescribed to PWH. Inset evaluated the subset of patients prescribed an antibiotic. *$P < .05$. Abbreviation: PWH, persons with HIV.

**Table 2. Antibiotic Prescribing Patterns and Mean Duration of Antibiotic Use in Days Compared Between Cohorts**

| | Antibiotic Prescribed | Appropriate Prescription | Concordant With Guidelines | Mean Duration, d |
|---|---|---|---|---|
| Primary cohorts, No. (%) | | | | |
| PWH | 124/350 (35) | 19/124 (15) | 245/350 (70) | 8.5 |
| Non-PWH | 198/492 (40) | 16/198 (8) | 309/491 (63) | 7.6 |
| Overall | 322/842 (38) | 35/322 (11) | 554/842 (66) | 7.9 |
| | $P = .17$ | $P = .06$ | $P = .04$ | $P = .02$ |
| Subgroup cohorts, No. (%) | | | | |
| PWH: HIV clinician | 24/89 (27) | 7/24 (29) | 73/89 (82) | 5.9 |
| PWH: non-HIV clinician | 99/260 (38) | 12/99 (12) | 172/260 (66) | 9.1 |
| Non-PWH | 198/492 (40) | 16/198 (8) | 309/491 (63) | 7.6 |
| | $P = .06$ | $P = .01$ | $P = .002$ | $P < .0001$ |
| Clinician training level, No. (%) | | | | |
| Attending | 131/349 (38) | 14/131 (11) | 230/348 (66) | 7.8 |
| Trainee | 47/207 (23) | 12/47 (25) | 132/207 (83) | 8.7 |
| APP | 141/282 (50) | 9/141 (6) | 151/282 (54) | 7.8 |
| | $P < .0001$ | $P = .003$ | $P < .0001$ | $P = .17$ |

Abbreviations: APP, advanced practice provider; PWH, people with HIV.

fellow) 23% of the time, and an APP 50% of the time ($P < .001$). Management of ARI was concordant with guidelines in 66% of attending visits, 83% of trainee visits, and 56% of APP visits ($P < .0001$). Prescribed antibiotics were appropriate in 11% of attending physician prescriptions, 26% of trainee prescriptions, and 6% of APP prescriptions ($P = .0026$) (Table 2).

## DISCUSSION

Outpatient antibiotic overuse remains prevalent among patients evaluated for ARI. This study is unique in that it directly compares antibiotic use for ARI in PWH with antibiotic use in non-PWH. We initially hypothesized that PWH would be more likely to experience excessive antibiotic use and non-guideline-concordant management of ARI due to possible perception of increased risk for bacterial infection. The results did not entirely support this initial hypothesis.

Counterintuitively, we found that management of ARI in PWH was more likely to be appropriate and guideline-concordant than management of ARI in non-PWH. Further, the specialty of the prescribing clinician played a larger role in the appropriateness of antibiotic prescription and whether a patient was managed according to guidelines than HIV status in our study. Additional analysis of prescriber specialty demonstrated that antibiotics prescribed to PWH were more likely to be appropriate when prescribed by HIV clinicians. This was an expected finding given the expertise of our clinicians in the specialty care center and their knowledge of infection risk among PWH. PWH in our cohort were mostly immunologically controlled and virologically suppressed on ART; however, despite data suggesting that PWH on ART remain at higher risk for bacterial respiratory infections, particularly bacterial

pneumonia, than non-PWH [12], there are no data to support antibiotic treatment for ARI in this patient population.

We found a statistically significantly shorter mean duration of antibiotic use in the non-PWH cohort vs PWH managed by non-HIV clinicians. It is possible that even though these clinicians may not have considered HIV status in the decision to treat, they may have extended antibiotic duration in this population due to perceived risk for bacterial infection. HIV clinicians compared with non-HIV clinicians managing PWH also had statistically significantly shorter durations of therapy. This result may be skewed as HIV clinicians are better versed with antimicrobial usage and may have picked a shorter duration regardless of HIV status. Our data also support the findings of Schmidt et al., in which training level influenced the appropriateness of antibiotic usage [13]. Like Schmidt et al., we found that trainees were more likely to prescribe appropriately than APPs and attendings. Possible reasons include inclusion of antimicrobial stewardship training in residency and fellowship. This finding highlights the importance of continued antimicrobial stewardship training in practice, particularly in the primary care setting.

The findings from our study are limited by the retrospective design. We relied on ICD-10 coding for diagnosis ascertainment and study eligibility, so diagnoses that were not coded were not captured in our database. Further, although our cohorts were extracted from multiple clinics, this was a single institution, so our findings may not be generalizable to other populations or locations. The HIV cohort was mostly adherent on ART with immunologic and virologic control and thus may not be representative of other HIV cohorts. We did not evaluate other comorbid conditions beyond COPD or conditions that require antibiotics that may influence a clinician's decision to prescribe antibiotics. We also did not evaluate for antibiotic dosage or adverse reaction. Finally, our secondary analysis of clinician specialty decreased our cohort sizes and thus decreased the power of our study for that analysis.

In conclusion, our study results highlight the need for improved outpatient stewardship, especially for diagnoses that should rarely or never result in an antibiotic prescription such as ARI, and this is certainly not limited to the HIV community. A majority of PWH in our study were evaluated for ARI by non-HIV clinicians, and the discrepancy between the duration of antibiotics prescribed by HIV clinicians compared with the duration of antibiotics prescribed by non-HIV clinicians to PWH was significant. In an era in which more HIV care is conducted in a primary care setting, these findings emphasize the value of HIV specialty care consultation and education of non-HIV clinicians for appropriate antimicrobial stewardship within the HIV community.

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***Patient consent.*** The design of the work and waiver of patient consent have been approved by the University of Nebraska Medical Center Institutional Review Board.

***Prior presentation.*** Portions of these data were presented as an oral abstract at IDWEEK2019, October 3, 2019.

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