Resistance in Enterobacterales Is Higher Among People Living With Human Immunodeficiency Virus

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Background. Multidrug-resistant Enterobacterales (MDR-E) are important pathogens. People living with human immunodeficiency virus (HIV; PLWH) may be at greater risk for MDR-E infection given relatively high antibiotic exposure and burden of comorbidities.

Methods. We analyzed data from 36 521 patients in a healthcare system in North Carolina who had a clinical culture with growth of an Enterobacterales species from 2000 to 2018; 440 were PLWH. We used generalized linear models to estimate prevalence ratios and differences, contrasting PLWH and people not living with HIV (PNLWH) for resistance to individual antibiotic classes, as well as MDR-E. We assessed trends in prevalence over time by calculating the 5-year moving average and fitting restricted cubic spline models.

Results. The overall prevalence of MDR-E was higher among PLWH (21.5%; 95% confidence interval [CI], 18.2%–25.1%) vs PNLWH (16.5%; 95% CI, 16.2%–16.9%), with an adjusted prevalence ratio of 1.38 (95% CI, 1.14–1.65). PLWH had higher rates of antimicrobial resistance than PNLWH for all antibiotic classes analyzed, including penicillins, penicillin/beta lactamase inhibitor combinations, and sulfonamides. MDR-E prevalence was 3 to 10 percentage points higher among PLWH than PNLWH throughout the study period based on the 5-year moving average.

Conclusions. In a large clinical study population in the southeastern United States from 2000 to 2018, the prevalence of antibacterial resistance among Enterobacterales was consistently higher among PLWH than PNLWH. These data highlight the importance of identifying and mitigating the factors that contribute to antimicrobial resistance in PLWH, given the potential clinical consequences of these resistant pathogens.

Keywords. antimicrobial-resistant Enterobacterales; HIV; epidemiology.

Antimicrobial resistance (AMR) is a global public health challenge that disproportionately affects medically vulnerable patients and impacts all aspects of medicine, leading to longer duration of illness, greater mortality, and increased costs of treatment [1–4]. Enterobacterales are a large order of gram-negative bacteria, including some of the most important healthcare-associated pathogens, that cause severe invasive infections with high mortality [5–7]. Clinically important multidrug-resistant Enterobacterales (MDR-E) include carbapenem-resistant Enterobacterales (CRE) and extended-spectrum beta-lactamase–producing Enterobacterales (ESBL-E), which have been classified by the US Centers for Disease Control and Prevention as urgent and serious threats, respectively [2]. MDR-E infections in the United States are usually healthcare-associated, although community-associated infections are increasingly prevalent [8, 9]. Risk factors include healthcare exposures (particularly extended hospital stays and use of invasive medical devices), residence in long-term care facilities, antibiotic exposure, and immunosuppression [10–18]. As MDR-E infection is not a nationally notifiable condition in the United States, no nationwide surveillance system monitors its incidence; however, an estimated 13 000 CRE and 197 400 ESBL-E infections occurred in 2017 in the United States [2].

People living with human immunodeficiency virus (HIV; PLWH) may be at greater risk for MDR-E infection as a consequence of immunosuppression and higher incidence of many clinical comorbidities [19–21]. Compared with the general population, PLWH are at increased risk for cancer, metabolic disorders, chronic kidney disease, cardiovascular disease, liver disease, lung disease, and multimorbidity [21–24]. Due to this burden of clinical conditions, PLWH may be more likely to have contact with healthcare facilities and exposure to invasive medical procedures relative to people not living with HIV (PNLWH), which may increase their risk of MDR-E infection. In addition to a higher prevalence of general MDR-E risk factors among PLWH than the general population, PLWH may also be

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more susceptible to MDR-E acquisition due to HIV-specific factors. For example, antibiotic prophylaxis for prevention of opportunistic infections may contribute to multidrug resistance of pathogens, and HIV-associated gut microbiome changes and intestinal inflammation may lower the barrier to colonization with MDR-E [25–30].

More data are needed on the burden of MDR-E infections to better inform prevention measures, including data on populations that may be at increased risk. In this study, we compared the prevalence of AMR in Enterobacterales isolates in PLWH to that in PNLWH over a 19-year period in all hospitals and clinics within a large healthcare system in North Carolina.

METHODS

Patients

We compared the prevalence of AMR in Enterobacterales isolates from PLWH to that in isolates from PNLWH who were patients in the UNC Health system in North Carolina from 2000 to 2018 using data from the UNC Health institutional electronic health records (EHR) system. The EHR includes patients seen at the UNC Medical Center in Chapel Hill, 11 affiliate hospitals, and more than 100 community-based practices located across the state. We also included data from participants in the UNC Center for AIDS Research HIV Clinical Cohort (UCHCC), which contains data on more than 7000 PLWH who have received care in the Chapel Hill–based UNC Infectious Diseases Clinic since 1996 [31]. The UNC Office of Human Research Ethics/Institutional Review Board approved the study protocol, with UCHCC participants providing informed consent and a waiver of consent granted for other participants.

Our study included patients in the UNC Health system who had at least 1 clinical culture with growth of an Enterobacterales species and who were aged ≥18 years on the date the culture was obtained. We included patients only from UNC Health system locations that treated PLWH during the study period (Supplementary Figure 1). Information collected for each isolate included the date the culture was obtained, patient date of birth, location of culture collection (ie, outpatient clinic name or hospital department), and specimen source (eg, blood, sputum, wound). We selected the first isolate of a given Enterobacterales species per patient, thereby excluding repeat cultures of a species, and grouped all specimen sources as "blood," "respiratory," "urine," or "other."

To establish HIV status for each patient with a positive culture, we first matched the medical record numbers of the patients to those of UCHCC participants. We then obtained all laboratory results with "HIV" in the test name or description, along with any HIV-related *International Classification of Diseases* (ICD)-9 or ICD-10 diagnosis codes from the EHR. We identified additional patients who had positive HIV diagnostic test results or HIV-related diagnosis codes and verified their HIV status by reviewing the EHR (H. I. H.). We classified participants as PLWH if they had documentation of HIV infection before the Enterobacterales-positive culture result.

Microbiology

Microbiological data were obtained from the UNC Hospitals Clinical Laboratory, including species and antibiotic susceptibility data on bacterial cultures obtained during all hospitalizations, clinic visits, and emergency department (ED) visits. Susceptibility breakpoints for some antibiotics changed during the study period; therefore, we used numeric zone of inhibition measurements or minimum inhibitory concentrations (MICs) to standardize susceptibility interpretations to the current breakpoints published by the Clinical and Laboratory Standards Institute [32]. Approximately 20% of results from susceptibility testing were MICs reported as less than or greater than a certain dilution (rather than an exact dilution) and, therefore, could not be reclassified; for these, the original susceptibility interpretation was retained. These MIC results are summarized in Supplementary Table 1.

Species–antibiotic combinations were classified as nonsusceptible to an antibiotic if the zone of inhibition or MIC interpretation was "intermediate" or "resistant" using current breakpoints. An isolate was classified as nonsusceptible to an antibiotic class if it was nonsusceptible to at least 1 member of that class, after removing results that corresponded to intrinsically resistant species–antibiotic combinations. MDR isolates were classified as those that were nonsusceptible to at least 1 antibiotic from at least 3 separate antibiotic classes [33]. We removed susceptibility results for carbapenems due to few results prior to 2009 and low levels of nonsusceptibility throughout the study period, and we removed susceptibility results for first-generation cephalosporins due to separate breakpoints for cefazolin depending on the type of isolate (eg, complicated vs uncomplicated urinary tract infections).

Statistical Analyses

Our primary outcome of interest was an MDR-E isolate, with secondary analyses including isolates with nonsusceptibility to a clinically relevant antibiotic class. The exposure of interest was HIV infection. Covariates extracted from the EHR were patient age, sex, race, specimen source, year of specimen collection, and location of specimen collection. First, we analyzed the crude association between each covariate and prevalence of MDR-E. To assess the association of age with MDR-E prevalence, we used restricted cubic splines; based on the functional form of age and MDR-E prevalence, we dichotomized age as ≤50 and >50 years for the crude association analysis.

To explore trends over the study period, we calculated the 5-year moving average using the crude proportions of isolates that were nonsusceptible to each antibiotic class, as well as those that were MDR, for each year of the study period. To

assess differences in prevalence of MDR-E between PLWH and PNLWH over calendar time, we fit restricted cubic spline models for the time trend. Using generalized linear models, we estimated prevalence ratios and differences as measures of association, with 95% confidence intervals.

In multivariable models to assess the association between HIV infection and MDR-E, we modeled age and year as continuous variables using quadratic terms; categorical variables were sex, race (White, Black, other), specimen source (blood, respiratory, urine, other), and location of specimen collection (ED, inpatient, intensive care unit, outpatient). We used a Poisson distribution with a robust variance estimator to estimate prevalence ratios and a Gaussian distribution with a robust variance estimator to estimate prevalence differences [34, 35]. A 2-sided *P* value of <.05 was considered statistically significant. All analyses were performed using R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria) [36].

RESULTS

Study Participants and Enterobacterales Isolates

From March 2000 to December 2018, 1 450 091 Enterobacterales species–antibiotic susceptibility results were obtained, corresponding to 119 104 isolates and 72 147 unique patients. Among these, 421 607 susceptibility results, corresponding to 42 386 isolates and 36 521 patients, met the inclusion criteria. In this study population, there were 440 PLWH with 536 isolates (Supplementary Figure 1).

PLWH (n = 440) were younger than PNLWH (n = 36 081), with median ages of 46 and 59 years, respectively (Table 1). The most common location of specimen collection differed between groups, with the ED most common among PNLWH (41.6%) and outpatient clinics most common among PLWH (45.7%). In both groups, the majority of isolates were from urine. The most common species isolated were *Escherichia coli* (58.5% of all isolates), *Klebsiella pneumoniae* (15.7%), and *Proteus mirabilis* (7.5%). Most patients had only 1 species isolated during the study period (87.4% in PNLWH and 82.5% in PLWH), and few had more than 2 species isolated (2.5% in PNLWH and 3.6% in PLWH).

Among 324 PLWH with CD4 counts available prior to the culture date, the median most recent result was 393 cells/mm^3 (interquartile range [IQR], 190–616); the median nadir CD4 cell count was 70 cells/mm^3 (IQR, 9–217). For the 315 PLWH with HIV viral load results available prior to the culture date, 190 had a most recent viral load <400 copies/mL (ie, undetectable in assays available at the start of the study period).

Multidrug Resistance Among Enterobacterales Isolates

The overall prevalence of MDR-E was 16.6% (95% confidence interval [CI], 16.2%–16.9%) and was higher among PLWH (21.5%; 95% CI, 18.2%–25.1%) compared with PNLWH

Table 1. Characteristics of the Study Population

Characteristic		People Not Living With HIV, N = 36 081	People Living With HIV, N = 440
		N (%) or Median (IQR)	N (%) or Median (IQR)
Patient sex	Male	9217 (25.6)	199 (45.2)
Age, years		59 (40–73)	46 (38–53)
Patient race	White	23 216 (64.6)	106 (24.1)
	Black	9052 (25.2)	295 (67.2)
	Other	3163 (8.8)	34 (7.7)
	Unknown	517 (1.4)	4 (0.9)
Specimen source	Blood	2918 (8.1)	58 (13.2)
	Respiratory	1077 (3.0)	12 (2.7)
	Urine	29 967 (83.1)	328 (74.5)
	Other	2119 (5.9)	42 (9.5)
Location of specimen collection	Emergency department	15 006 (41.6)	129 (29.3)
	Inpatient	5126 (14.2)	71 (16.1)
	Intensive care unit	2416 (6.7)	23 (5.2)
	Outpatient clinic	11 938 (33.1)	201 (45.7)
	Unknown	1595 (4.4)	16 (3.6)
Unique isolates per patient	1	31 530 (87.4)	363 (82.5)
	2	3659 (10.1)	61 (13.9)
	3+	892 (2.5)	16 (3.6)
Species isolated [a]	*Escherichia coli*	24 502 (58.5)	280 (52.2)
	Klebsiella pneumoniae	6568 (15.7)	96 (17.9)
	Proteus mirabilis	3130 (7.5)	38 (7.1)
	Other	7650 (18.3)	122 (22.8)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Denominator is the total number of isolates: people not living with HIV (41 850), people living with HIV (536).

(16.5%; 95% CI, 16.2%–16.9%; Figure 1). The higher prevalence among PLWH was sustained across all study years, with overall MDR-E positivity more than doubling from 2002 to 2010 and then declining slightly after 2012 (Figure 2, bottom right). The increased MDR-E prevalence among PLWH was also observed across calendar time in restricted cubic spline analyses, with relatively greater prevalence in years 2004–2008 and 2012–2015 (Supplementary Figure 2). The overall unadjusted prevalence ratio for MDR-E comparing PLWH with PNLWH was 1.3 (95% CI, 1.1–1.6). After adjustment for covariates, the association was similar (adjusted prevalence ratio, 1.4; 95% CI, 1.1–1.7).

Being aged >50 years was associated with increased prevalence of MDR-E among both PLWH and PNLWH, with relative increases of 21% and 24%, respectively (Table 2). Among PNLWH, MDR-E positivity increased with age up to approximately 60 years and stabilized thereafter, whereas among PLWH, MDR-E positivity was stable until approximately 50 years and increased thereafter, although estimates among younger and older PLWH were less precise (Supplementary Figure 3).

Antibiotic Class Nonsusceptibility Among Enterobacterales Isolates

Among antibiotic classes, nonsusceptibility was significantly higher in PLWH compared with PNLWH for penicillins, penicillin/beta-lactamase inhibitor combinations, and sulfonamides (Figure 1). Overall, compared with PNLWH, adjusted prevalence ratios for PLWH ranged from 1.2 to 1.4 for nonsusceptibility across antibiotic classes; for sulfonamides, however, the adjusted prevalence ratio for PLWH was more pronounced, at 1.6 (Table 3). The largest adjusted absolute difference in nonsusceptibility was observed for penicillins (prevalence difference, 14%; 95% CI, 8%–19%) and sulfonamides (prevalence difference, 12%; 95% CI, 8%–15%).

In general, these observed differences were consistent across calendar time. Five-year moving averages for prevalence of nonsusceptibility by antibiotic class showed marked increases in PNLWH for penicillins, penicillin/beta-lactamase inhibitor combinations, and quinolones (Figure 2, Supplementary Figure 4). In PLWH, there was a marked increase in prevalence of nonsusceptibility to penicillins, an increase followed by a decline in nonsusceptibility to penicillin/beta-lactamase inhibitor combinations, and no increase in quinolone nonsusceptibility. There was relatively little overall change during the study period in either group for nonsusceptibility to aminoglycosides, third-generation cephalosporins, or sulfonamides. Small numbers of susceptibility test results in PLWH prevented assessment of aminoglycosides, penicillin/beta-lactamase inhibitor combinations, and quinolones during the first years of the study period.

DISCUSSION

In this large patient population with Enterobacterales isolates from 2000 to 2018, PLWH had a 38% higher relative prevalence of MDR-E compared with that in PNLWH, as well as higher prevalence of nonsusceptibility to every antibiotic class evaluated. The greater relative MDR-E prevalence among PLWH was observed across calendar years 2000 through 2018, with overall MDR-E prevalence increasing from 2000 to 2010 followed by a slight decline. Among PNLWH, this increase reflected rising nonsusceptibility to penicillins, penicillin/beta-lactamase inhibitor combinations, and quinolones. In PLWH, the observed pattern appeared to be the result of nonsusceptibility to penicillins and penicillin/beta-lactamase inhibitor combinations.

The largest relative increase in prevalence of nonsusceptibility among PLWH was observed in sulfonamides, whereas

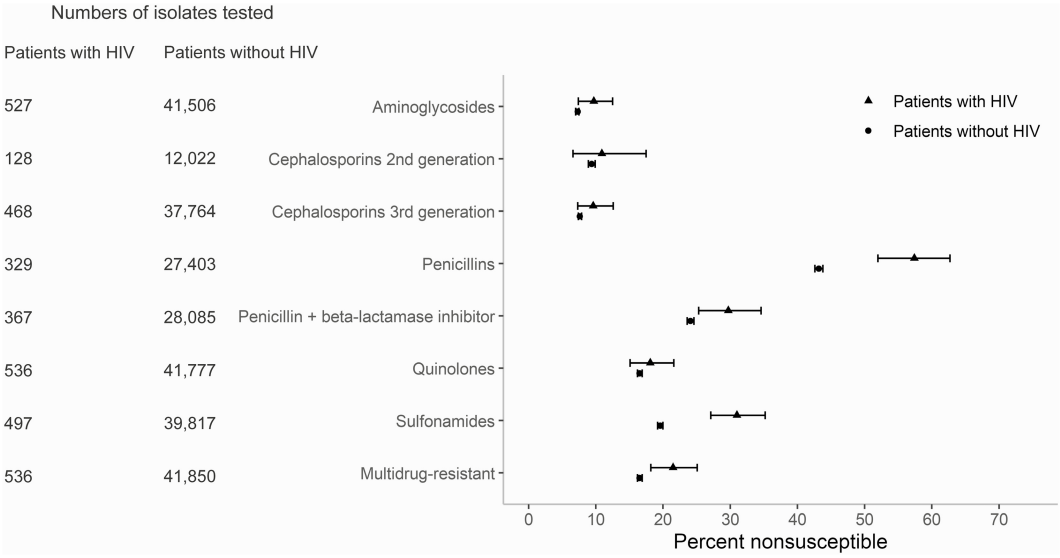

Figure 1. Percentages, with 95% confidence intervals, of isolates that were nonsusceptible to selected antibiotic classes or were multidrug resistant by HIV status. Abbreviation: HIV, human immunodeficiency virus.

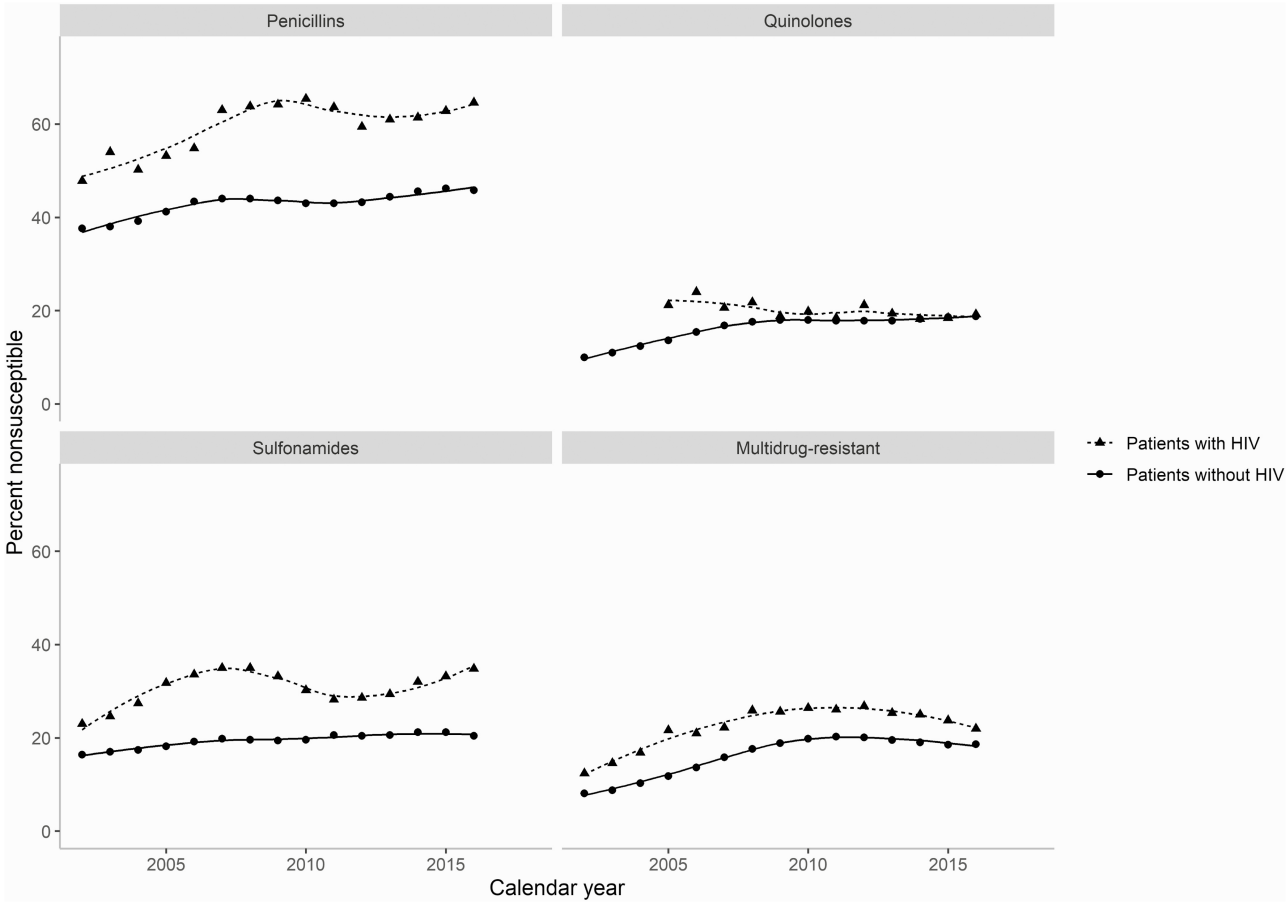

Figure 2. Five-year moving average percentage of isolates that were nonsusceptible to selected antibiotic classes or were multidrug resistant by calendar time and HIV status. Abbreviation: HIV, human immunodeficiency virus.

the largest absolute increase was in penicillins. Given that trimethoprim-sulfamethoxazole has long been used prophylactically against *Pneumocystis* infection in PLWH with low CD4 counts, it is not surprising that PLWH had a higher overall prevalence of sulfonamide-nonsusceptible Enterobacterales. We observed consistently higher rates of sulfonamide nonsusceptibility in PLWH compared with PNLWH over the study period. However, while trimethoprim-sulfamethoxazole prophylaxis has decreased over time, reflecting advances in antiretroviral therapy effectiveness, we did not observe an overall decrease in the prevalence of sulfonamide nonsusceptibility in PLWH in our cohort. This may reflect either additional drivers

Table 2. Unadjusted Associations of Covariates With Multidrug-Resistant Isolates by Human Immunodeficiency Virus Status

		People Not Living With HIV	People Living With HIV
Risk Factor		Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)
Patient sex	Male	1.21 (1.15 to 1.28)	1.32 (.91 to 1.90)
Age, years	>50	1.24 (1.18 to 1.30)	1.21 (.83 to 1.75)
Patient race			
(Referent: White)	Black	1.01 (.95 to 1.07)	1.17 (.76 to 1.89)
	Other	1.27 (1.17 to 1.37)	0.99 (.42 to 2.12)
Location of specimen collection			
(Referent: Outpatient clinic)	Emergency department	1.35 (1.27 to 1.43)	1.88 (1.19 to 2.99)
	Inpatient	1.40 (1.30 to 1.50)	2.19 (1.29 to 3.65)
	Intensive care unit	1.76 (1.61 to 1.93)	2.76 (1.33 to 5.26)
Specimen source			
(Referent: Urine)	Blood	0.99 (.90 to 1.08)	0.90 (.48 to 1.55)
	Respiratory	1.30 (1.14 to 1.46)	2.19 (.92 to 4.40)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

Table 3. Adjusted Associations Between Human Immunodeficiency Virus Infection and an Isolate With Nonsusceptibility to Selected Antibiotic Classes

Antibiotic Class	Referent Prevalence (in People Not Living With Human Immunodeficiency Virus) [a]	Prevalence Ratio (95% CI) [a]	Prevalence Difference (95% CI) [a]
Aminoglycosides	7.3	1.39 (1.03–1.82)	2.7 (.4–4.9)
Cephalosporins, second generation	9.3	1.28 (.72 to 2.11)	2.3 (–2.8 to 7.4)
Cephalosporins, third generation	7.6	1.21 (.88 to 1.61)	1.7 (–.7 to 4.1)
Penicillins	43.2	1.31 (1.13 to 1.51)	13.7 (8.3 to 19.1)
Penicillin + beta-lactamase inhibitor	24.1	1.26 (1.03 to 1.52)	6.1 (1.7 to 10.6)
Quinolones	16.5	1.17 (.95 to 1.43)	2.6 (–.6 to 5.7)
Sulfonamides	19.6	1.62 (1.37 to 1.89)	11.8 (8.2 to 15.3)
Multidrug resistance	16.5	1.38 (1.14 to 1.65)	6.0 (2.8 to 9.1)

Abbreviation: CI, confidence interval.

[a]Estimates are people living with human immunodeficiency virus (HIV) compared with people not living with HIV, with separate models fit for each antibiotic class and for multidrug resistance, adjusting for age, sex, race, specimen source, year, and location of specimen collection. Prevalence and prevalence difference estimates are per 100 isolates.

of resistance that are more common in PLWH or persistent carriage of antimicrobial-resistant bacteria after removal of antibiotic pressure.

Some studies outside the United States have suggested that PLWH may be at increased risk for MDR-E infection or colonization. Researchers in Brazil reported that among patients in an intensive care unit, AIDS was an independent risk factor for nosocomial infection with MDR bacteria, including *Klebsiella*, *Enterobacter*, and *E. coli* [10]. In a study of South African children with bacteremic, community-acquired lower respiratory tract infections, it was found that those living with HIV had a higher estimated incidence of infection with *E. coli* (risk ratio, 97.9; 95% CI, 11.4–838.2) than those not living with HIV. Among *E. coli* isolates cultured from children living with HIV, 86% were resistant to both trimethoprim-sulfamethoxazole and ampicillin [37]. Researchers in Cameroon reported that antibiotic resistance was significantly greater in PLWH vs PNLWH for enteric *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, and *Serratia* isolates [38]. Last, Reinheimer et al reported significantly higher prevalence of MDR gram-negative organisms isolated from rectal swabs in 109 hospitalized German males living with HIV (23.9%) compared with 109 age-matched controls (8.3%) [39].

Our results are consistent with results from these previous studies, with the prevalence of MDR-E found to be greater in PLWH compared with PNLWH throughout the study period. Our study is the first to longitudinally compare MDR-E prevalence between PLWH and PNLWH, as well as the first to comprehensively analyze a large patient population. These data highlight the importance of identifying and mitigating the factors that contribute to AMR in PLWH, given the potential clinical consequences of these resistant pathogens.

Strengths of this study include the identification of a large comprehensive cohort of patients with Enterobacterales from clinical cultures over a 19-year period, thereby minimizing selection bias. We were also able to verify susceptibility results of isolates to all antibiotic classes that were tested. However, the study is subject to several limitations. Although we adjusted for a number of likely confounders, there may be unmeasured confounding. Laboratory and EHR data are collected for clinical and billing purposes, rather than research, and are subject to inconsistencies over time. For instance, laboratory practices and data collection conventions changed over the analysis period. The antibiotics used in susceptibility testing changed over the study period and differed depending on the isolate; therefore, the numbers of results available for analysis varied between antibiotic classes. The definitions of susceptibility of some species–antibiotic combinations have changed over the study period. We corrected for these changes by updating all interpretations, where possible, to align with current susceptibility breakpoints. Although we reviewed medical records to identify individuals with HIV infection, it is likely we did not capture all patients infected with HIV. However, given the low prevalence of HIV in the study population, misclassification of PLWH as PNLWH would be expected only to reduce the power of the study, rather than to bias the results. The risk of MDR-E among PLWH likely varies according to certain HIV-specific factors, such as CD4 cell count and viral suppression, which were not available for this analysis. In future work, we will assess HIV-specific factors as predictors of MDR-E. Last, our study evaluated patients in a single health system in North Carolina, and these results do not necessarily generalize to other populations.

In conclusion, this study provides evidence that the prevalence of MDR-E, as well as Enterobacterales infections that were nonsusceptible to a number of clinically important antibiotic classes, was higher among PLWH compared with PNLWH. Research to evaluate risk factors for MDR-E infections in PLWH can inform approaches to prevention of MDR-E in order to better protect at-risk populations from these difficult-to-treat infections. Assessment of clinical management and outcomes of MDR-E among PLWH is also needed to guide approaches to improving outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. D. v. D. has received personal fees for serving on the advisory boards of Allergan, Achaogen, Qpex, Shionogi (received consulting fees), Karius, Sanofi-Pasteur, T2 Biosystems, NeuMedicine, Entasis, Utility, Roche (received consulting fees), MedImmune, Astellas, and Merck; received honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer; received research support from Shionogi, Merck, and NIH; and received editor stipend from BSAC. D. A. W. has served on the advisory boards of Gilead, Merck, ViiV, and Janssen and has received grants from Gilead, ViiV, and Merck. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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