Sociodemographic, ecological, and spatiotemporal factors associated with HIV drug resistance in Florida: a retrospective analysis.

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Summary: In this study of 34,447 HIV-1 sequences collected in Florida, we observed high prevalence of drug resistance with significant sociodemographic and geospatial heterogeneity. Resistance was linked to counties with lower socioeconomic status, higher unemployment, and poor mental health.

Abstract

Background: Persons living with HIV (PWH) with resistance to antiretroviral therapy (ART) are vulnerable to adverse HIV-related health outcomes and can contribute to transmission of HIV drug resistance (HIVDR) when non-virally suppressed. The degree to which HIVDR contributes to disease burden in Florida –the US state with the highest HIV incidence– is unknown.

Methods: We explored sociodemographic, ecological, and spatial-temporal associations of HIVDR. HIV-1 sequences (n=34,447) collected during 2012-2017 were obtained from the Florida Department of Health. HIVDR was categorized by ART class: nucleoside reverse transcriptase inhibitors (NRTI), non-NRTI (NNRTI), protease inhibitors (PI), and integrase inhibitors (INSTI). Multi-drug resistance (MDR) and transmitted-drug resistance (TDR) were also evaluated. Multivariable fixed-effects logistic regression models were fitted to associate individual and county-level sociodemographic and ecological health indicators with HIVDR.

Results: HIVDR prevalence was 19.2% (NRTI), 29.7% (NNRTI), 6.6% (PI), 23.5% (TDR), 13.2% (MDR), and 8.2% (INSTI) with significant variation by Florida county. Individuals who were older, Black, or acquired HIV through mother-to-child transmission had significantly higher odds of HIVDR. HIVDR was linked to counties with lower socioeconomic status, higher unemployment, and poor mental health.

Conclusions: Our findings indicate HIVDR prevalence is higher in Florida than aggregate North American estimates with significant geographic and socioecological heterogeneity.

Keywords: HIV drug resistance; Antiretroviral therapy; HIV in the South

Background

Despite the success of combined antiretroviral therapy (ART) in reducing both morbidity and mortality attributed to HIV infection, prevalence of HIV drug resistance (HIVDR) remains a global concern (1). HIVDR can be transmitted or acquired and is characterized by mutations in the virus' genetic structure allowing it to escape the antiviral activity of ART (2). Likelihood of HIVDR transmission relies on the prevalence of resistance mutations among persons living with HIV (PWH) engaged in high risk behaviors in the population (3). This population is vulnerable to adverse health outcomes, since persons who harbor drug resistant infections are more likely to experience suboptimal viral suppression (2,4,5), accumulate additional resistance mutations (2,6), discontinue ART (2), and suffer premature mortality (2,7). Moreover, from a public health perspective, HIVDR presents substantial programmatic burden, contributing to roughly 9% of new infections by 2030 if current trends persist (7). HIVDR surveillance, prevention and response are therefore critical for achieving elimination of HIV as a public health threat by 2030 (2,8).

In the United States, aggregate estimates of HIVDR prevalence appear stable over time when compared to other regions (3,9); however, HIV epidemic dynamics differ dramatically across regions within the US (10). Overall estimates for North America (NA) suggest prevalence of HIVDR among PWH with molecular sequences is 7·2% for protease inhibitors (PI), 15·7% for nucleoside reverse transcriptase inhibitors (NRTI), 23·4% for non-nucleoside reverse transcriptase inhibitors (NNRTI), 11·5% for two-class (or "multi-drug") resistance (MDR), and 13·0% for transmitted drug resistance (TDR) for the period 2007-2016 (9). HIVDR prevalence at the regional-level is not well understood, however. The US epidemic epicenter is concentrated in the south, which contributed over half of all new HIV diagnoses in 2017 (11). That same year, the southern state Florida had the most new HIV diagnoses in the country (12) and the proportion of PWH virally suppressed (<200 copies/mL) was only 62% (13). The extent to which HIVDR contributes to the burden of HIV in Florida, a contributor to poor treatment outcomes, is not understood.

In 2019, seven largely urban Florida counties (Broward, Duval, Hillsborough, Miami-Dade, Orange, Palm Beach, and Pinellas), which include the major cities Jacksonville, Orlando, Tampa, and Miami, were identified as target regions for *Ending the HIV Epidemic: A Plan for America* (EHE) (14). One of the key strategies of EHE is to rapidly respond to potential outbreaks using cluster detection techniques (e.g. molecular surveillance), made possible through drug resistance testing (15). Over the past decade the Florida Department of Health (FDOH) has been collecting viral isolate sequences on individuals with a recent HIV diagnosis. Collection of these sequences started as part of the CDC funded: Variant, Atypical and Resistant HIV Surveillance (VARHS) program designed to monitor HIVDR starting in 2007 in Florida. Around 60,000 HIV sequences have been collected by FDOH since 2007.

To examine the burden of HIVDR among PWH in Florida, this study aimed to estimate the prevalence, investigate the sociodemographic and socioecological determinants, and describe the spatial-temporal characteristics of HIVDR in Florida during 2012-2017. This study capitalizes on the extensive HIV molecular sequence database maintained by FDOH and involves analysis of the largest collection of sequence data in Florida to date.

Methods

Ethics approval

This analysis and a waiver of informed consent were approved as exempt by the Institutional Review Boards (IRB) at the University of Florida (IRB201703199) and the FDOH.

Sequences

HIV nucleotide sequences were obtained from FDOH's enhanced HIV/AIDs reporting system (eHARs) collected as part of routine HIV Surveillance in Florida per Rule 64D-3·029. We selected HIV sequences of any subtype with a known sample year (2007 to 2017), encompassing the whole protease region (1-99 amino acids), at least the first 250 amino acids of the reverse transcriptase,

and/or at least 288 of the integrase region, using recommended consensus B and HXB2 nucleotide numbering as references (16). Analyses were restricted to sequences collected during 2012-2017, since sequences received by eHARs increased dramatically during this period when VARHS expanded reporting to all laboratories in the state. Only one sequence per person per year was retained, with no restriction on time from diagnosis, choosing the earliest sequence in cases of multiple entries per year.

Drug resistance

Drug resistance mutations were categorized according to their effect on ART drug classes: NNRTIs, NRTIs, PIs, and integrase strand transfer inhibitors (INSTIs). All eligible sequences were aligned to consensus B and HXB2 reference sequences, checking similarity and alignment quality, and then mutations were extracted from the reference in the protease, reverse transcriptase, and integrase regions through a local in-house program which uses a Smith-Waterman aligner (with modifications to the indel coding per Stanford University's HIVdb v.8.6.1 convention (17)). Mutation figures were passed on to another in-house program that calculated resistance to NRTIs, NNRTIs, PIs and INSTIs using Stanford's HIVdb mutation scoring algorithm. We had previously verified the consistency between our in-house program and the Stanford's HIVdb web-service. Resistance to a drug class (NRTI/NNRTI/PI/INSTI) was defined as standardized intermediate/resistant scoring for at least one drug belonging to that class. MDR was calculated as the presence of intermediate/resistant scoring for two or more drug classes (NRTI, NNRTI, or PI). We did not include integrase in the calculation of MDR since most of the population lacked sequencing coverage of this region. TDR was estimated separately using the WHO 2009 list of surveillance drug resistance mutations (18). Subtyping was performed with the Context-based Modeling for Expeditious Typing alignment-free subtyping tool which has comparable performance to phylogeny-based methods (19). Unassigned sequences were resolved with BLAST using the recombinant form reference set available from Los

Alamos we described previously (9). The reference set for subtyping was redundant with about three different representatives per subtype/circulating recombinant form (CRF) to increase robustness.

Covariates

Demographic information was accessed via eHARS and included age category (≤25, 26-33, 34-45, and ≥46 years), sex at birth (male or female), race/ethnicity (White, Black, Hispanic/Latino, or Other [American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, or Multi-race]), transmission category (heterosexual contact, injection drug use [IDU], male-to-male sexual contact [MTM], mother-to-child transmission [MCT], or unknown), country of birth (categorized as world region of birth: NA, Africa, Asia Pacific, Caribbean, Europe, or Latin America), test year, treatment status (i.e. prior exposure to NRTIs, NNRTIs, PIs, entry/fusion inhibitors, and INSTIs) and any evidence of viral suppression. County-level socioecological indicators were retrieved via the publicly accessible datasets available on the County Health Rankings (CHR) website (http://www.countyhealthrankings.org) (20). CHR reports rankings and statistics for >50 health indicators calculated for every county (21). Higher CHR (e.g. social economic factors rank) correspond to worse health. In this analysis, we considered indicators reported without interruption in all 67 Florida counties from 2012-2017. The complete list of indicators considered in this analysis can be found in the supplementary materials.

Statistical analysis

Prevalence was calculated for resistance to NNRTI, NRTI, PI, and INSTI as well as MDR for the ART-experienced population. TDR prevalence was calculated for presumed ART-naïve individuals who lacked an ART initiation date at the time of sample collection. Overall prevalence was calculated for each resistance outcome as the proportion of resistant sequences of all sequences genotyped over the study period. Annual prevalence was calculated as the proportion of sequences containing drug resistance mutations of all sequences tested per year, with only one sequence/person

permitted. Lowess interpolation and data bootstrapping were performed to account for uncertainty in prevalence estimates. For simplicity of data presentation, demographic and clinical characteristics of the study population were compared across two periods of genotype testing: 2012-2014,2015-2017. Prevalence quintiles were mapped for each county reporting ≥10 sequences over the study period. Counties with prevalence estimates above/below two standard deviations of the state prevalence were considered to have "significantly high/low" prevalence of HIVDR, respectively.

Socioecological variables were evaluated for associations with HIVDR in univariable and multivariable models. Relative risks for the univariable associations between HIVDR prevalence and county-level socioecological health indicators were estimated using a Bayesian conditional autoregressive model. Generalized linear mixed effects models were fitted to account for both individual- and county-level variations simultaneously in the estimation of county-level coefficients. Univariable and multivariable (bidirectional stepwise-selected) fixed-effects logistic regression models were fitted to associate individual (sociodemographic and clinical) characteristics and county-level socioecological health indicators with HIVDR.

Correlations between socioecological variables were computed and assessed prior to multivariable model fitting. Highly correlated variables (Pearson's correlation-coefficient ≥|0.5|) were identified and only the variables with the strongest association to MDR in the univariable mixed-effects regression models were retained. Bonferroni's correction to control the false-discovery rate was applied to p-values obtained by univariate analysis. All analyses were performed using R, version 3.5.1 (22). Packages: 'ggplot2' and 'maptools' were used to generate geographic maps by county and a relative risk heatmap of socioecological associations (23,24).

Results

HIVDR prevalence

There were 34,447 sequences (N=28,923 unique PWH with an average of 1.2 sequences per person) that met criteria for analysis of resistance to NRTI, NNRTI, and PI drug classes, in addition to MDR and TDR outcomes. Additionally, 11,107 sequences (n= 10,290 unique PWH with an average of 1.1 sequences per person) were available to evaluate resistance to INSTIs. HIVDR prevalence over the study period was 29·7% (95% confidence interval [CI]=29·2%-30·2%) for NNRTI, 19·2% (CI=18·8%-19·6%) for NRTI, 23·5% (CI=22·1%-24·9%) for TDR, 13·2% (CI=12·8%-13·6 for MDR, and 8·2% (CI=7·7%-8·7%) for INSTI, and 6·6% (CI=6·3%-6·9%) for PI (Figure 1).

Characteristics of study population

Overall, the population was majority male, aged ≥34 years, and born in NA (Table 1). The proportion of males increased from 68·4% (CI=67·5-69·2%) in 2012-2014 to 70.8% (CI=70·3-71·4%) in 2015-2017. The most frequent race/ethnicity was Black for both periods, however, the proportion of Hispanic/Latino individuals increased from 19·0% (CI=18·3-19·7%) in earlier years to 21·4% (CI=20·8-21·9%) in later years. Likewise, the proportion of Latin American-born individuals increased from 3·9% (CI=3·5-4·3%) in earlier years to 5·4% (CI=5·1-5·7%) in later years. MTM was the most frequent transmission category, increasing from 43·0% (CI=42·0%-43·9%) in earlier years to 47·4% (CI=46·7-48·0%) in more recently. B was the predominant subtype in this population; however, we observed a modest increase in the proportion of other recombinant subtypes [0·8% (CI=0·6-0·9%) in 2012-2014 vs 1·2% (CI=1·0-1·3%) in 2015-2017]. Subtype classification with the Rega tool yielded over 96% concordance overall, and 99% with the subtype B set.

Geographic associations

Spatial distributions of HIVDR prevalence are mapped by county in Figure 2. Counties with fewer than 10 sequences were excluded from the analysis. Prevalence of HIVDR varied significantly by county, with few discernable geographic trends. Counties with high HIVDR prevalence were often rural, including Glades, Washington, and Hardee counties. Interestingly, prevalence of HIVDR was not significantly higher/lower in any of the seven Florida counties included in EHE, where the major cities Miami, Orlando, Jacksonville, and Tampa are located.

Associations between HIVDR and county-level socioecological health indicators

A relative risk heatmap demonstrating univariate associations between HIVDR prevalence and county-level socioecological health indicators is presented in Figure 3. Notably, higher rates of resistance were consistently associated with higher percent unemployed. We also noted associations between NNRTI resistance and county-level rankings. County rankings for health factors, health outcomes, life quality, and social economic factors, as well as percent poor or fair health, percent limited access to healthy foods, percent unemployed, percent diabetic, and physically or mentally unhealthy days were all associated with higher NNRTI resistance. Further, median household income was inversely associated with MDR and NNRTI resistance.

Multivariable associations of individual characteristics and socioecological factors with HIVDR

Multivariable analyses revealed associations between individual sociodemographic characteristics including age, sex, race/ethnicity, and region of birth, and HIVDR. Older individuals (≥46 years), had significantly higher resistance compared to individuals ≤25 years in all models except for TDR (Table 2). In ART-naïve individuals, we observed decreased odds of TDR for those aged 26-33 years (versus ≤25 years) (odds ratio [OR]=0·73; CI=0·55-0·97). Modest sex differences were also observed in this population in relation to MDR and NRTI resistance, with males experiencing slightly higher odds. Compared to Black individuals, White individuals tended to have

lower odds of HIVDR – particularly for NRTI, NNRTI, INSTI, and MDR – but higher odds of PI resistance (OR=1·31; CI=1·16-1·48). Hispanic and Latino individuals had higher odds of PI resistance (vs. Black individuals) (OR=1·20; CI=1·06-1·37). Associations between region of birth and HIVDR were only significant for NNRTIs among those born in the Caribbean (vs. NA), in whom we observed decreased odds (OR=0·86; CI=0·79-0·93).

Differences in the odds of HIVDR by HIV transmission category were also observed. Persons with IDU had lower odds of HIVDR – particularly for NRTI, INSTI, and MDR compared to heterosexual transmission risk. Individuals with MCT had significantly increased odds for several resistance outcomes, including resistance to NRTIs (OR=4·87; CI=4·03-5·90), NNRTIs (OR=1·78; CI=1·50-2·11), PIs (OR=5·79; CI=4·46-7·51), MDR (OR=5·47; CI=4·40-6·80), and TDR (OR=3·09; CI=1·66-5·83). Individuals with MTM had higher odds of PI resistance (OR=1·24; CI=1·10-1·39).

HIV-1 subtype, genotype test year, and timing between diagnosis and genotype test were also associated with HIVDR. Compared to B subtypes, non-B subtypes were associated with lower odds of PI resistance (OR=0·32; CI=0·10-0·76) and B-recombinant and other-recombinant subtypes were associated with lower odds of NNRTI resistance (OR=0·70; CI=0·53-0·91 for B-recombinants and OR=0·57; CI=0·40-0·79 for other recombinants). We observed decreasing odds of TDR and NNRTI resistance and increasing odds of PIs and INSTI resistance with each incremental year increase (OR=1·15; CI=1·07-1·24 for PIs) and (OR=1·18; CI=1·01-1·39 for INSTIs) over the study period (2012-2017). Individuals who received genotype tests more than 12 months after diagnosis had significantly greater odds of all HIVDR outcomes compared to individuals who received the test within a year of diagnosis.

There were several associations between HIVDR and county-level socioecological factors (Table 2). Higher HIVDR rates were associated with higher socioeconomic factors rank (i.e. lower socioeconomic status), higher percent unemployed, more mentally unhealthy days, and higher percent elderly population (Table 2). Alternatively, lower rates of HIVDR were associated with higher

crime rates and lower percent rural population. Univariate model associations of sociodemographic, clinical, and socioecological factors with resistance outcomes are presented in Supplementary Tables 1-3.

Discussion

This study analyzed the prevalence, sociodemographic, ecological, and spatial-temporal determinants of HIVDR among PWH in Florida during 2012-2017. The results indicate HIVDR prevalence is higher in Florida compared to current NA estimates (9) and may be increasing for PI and INSTI. Compared to previously published estimates for NA from 2007-2016, HIVDR prevalence was higher in Florida for NRTI (15·7% vs 19·2%), NNRTI (23·4% vs. 29·7%), and MDR (11·5% vs. 13·2%) (9). Estimates were comparable for PI (7·2% vs 6·6%); however, we observed a positive association between increasing genotype year and prevalence of PI resistance. We likewise observed a positive association between increasing genotype year and prevalence of resistance to newer INSTI therapies over the study period, though this result may be linked to the increased frequency of integrase testing in more recent years.

Multivariable analyses revealed HIVDR was higher among PWH aged ≥46 years (vs. ≤25 years), individuals who acquired HIV through MCT (vs. heterosexual contact), Black (vs. White) individuals, and males (vs. females). These findings are similar to those from a previous study reporting comparable racial and sex differences with the odds non-viral suppression in Florida (25). Due to exposure to ART in utero or through breast milk after birth, individuals who acquire HIV through MCT often have high rates of pretreatment drug resistance (26), which may explain why this transmission group had the highest odds of all HIVDR outcomes studied. In contrast, individuals who acquired HIV through IDU had lower odds of HIVDR in the current study. This funding was initially puzzling since rates of homelessness and unemployment (linked to decreased care linkage/retention), are high among people who inject drugs (PWID) (27); yet, another study reported

lower incidence of drug resistance mutations among PWID as a result of the test-and-treat initiative (28). Further analysis of this finding is warranted.

Geographic analyses revealed considerable heterogeneity in HIVDR prevalence by Florida county. Interestingly, high prevalence of resistance was not detected in counties with the highest proportion of PWH or resistance testing. The seven Florida counties listed in the EHE, which together represent 73% of total PWH in the state, did not have significantly higher rates of HIVDR in the current study. The EHE targets largely urban Florida counties in which fewer barriers to care, such as lack of specialty health care providers, exist (29). Given that HIVDR contributes to poorer overall treatment outcomes, continued monitoring of HIVDR in rural regions is needed. Analysis of HIV-1 subtypes in Florida revealed most sequences were covered by the B subtype, which is typical in the US, but the increasing presence of recombinants warrants further investigation of the contribution of imported HIV transmissions in Florida.

The increased burden of HIVDR in Florida observed in this study may reflect the overall US HIV epidemic. Florida, like other southern states, has a disproportionately high burden of HIV infection compared to other regions. Nearly half of all HIV diagnoses in the US occur in the south, despite accounting for only one-third of the US population (30). Factors thought to be driving the HIV epidemic in the south include poverty, income inequality, cultural issues (e.g. homophobia, transphobia, and racism), and higher rates of comorbidities (e.g. obesity, diabetes, and cancer) (30). While this analysis could not account for factors such as socio-economic status or comorbiditiesat the individual-level, we did assess some of these factors at the county-level and found HIVDR was significantly associated with socioeconomic status, income level, unemployment, and mental health. This suggests there are socioeconomic and mental health factors contributing to acquired HIVDR, and future studies should investigate this relationship further at the individual-level.

This analysis had many strengths. To our knowledge, it was the largest and most comprehensive study of transmitted and acquired HIVDR in a state to date. Previous smaller-scale

studies have reported the prevalence and correlates of TDR in other US regions (31–33); however, fewer studies exist to describe trends in acquired HIVDR at the state-level, and no studies have assessed associations with spatial-temporal or socioecological factors. Our multivariable models combined individual-level sociodemographic and clinical factors with county-level health indicators to account for socioecological factors contributing to HIVDR patterns. The study provides important epidemiological information on the geographic regions and subpopulations with the greatest burden of HIVDR in a region with disproportionately high incidence of HIV. Moreover, these results justify the need for clinicians to order genotype tests to ensure ART regimen compatibility and for continued molecular surveillance for public health Florida.

This analysis also had limitations. Importantly, we lacked data on prescription ART information which prevented the ability to consider the impact of prescribing practices on HIVDR patterns. This may explain the significant annual increase in resistance to the newest group of therapies (INSTI) observed in this study, since we were unable to account for expected increased rates of INSTI prescriptions in more recent years. Another limitation of our analysis was the method of MDR determination. Although we did not assess specific mutations, presumably, the majority of NRTI resistance was M184V, and the majority of NNRTI resistance was K103N and related efavirenz (EFV) resistance mutations. Since many people with resistance to EFV also have resistance to M184V (due to the use of combination drugs like Truvada), this explains the similarly high prevalence of resistance to these two classes, and the apparent high prevalence of MDR. Thus, MDR estimates may be artificially inflated due to resistance to EFV+3TC/FTC. Because cross-resistance to specific drugs within ART classes can be common and pooled estimates contain less measurement error than resistance to single drugs, we preferred to run the analysis by ART class. Future studies should examine single drugs as well as commonly prescribed combination drugs in drug resistance analyses. Additionally, although coverage of genotype testing was near or above 50% throughout the study period according to the FDOH, selection bias likely occurred since our study population only included diagnosed PWH who received a genotype test, representing less than half of PWH in the state. These

findings do not necessarily represent the burden of resistance among non-virally suppressed PWH in Florida. Another potential limitation is that our modeling approach did not account for individuals contributing more than one sequence; however, the impact was likely inconsequential given the mean number of sequences available per person was 1.2. Further, results of the socioecological analysis of health indices at the county-level should not be interpreted at the individual-level. This approach was selected to improve model fitness and provide a source of socioeconomic data that would have otherwise been omitted. Deeper analysis of the individual-level sociodemographic/behavioral factors contributing to HIVDR patterns in the community (e.g. medication adherence) is needed. \

Conclusion

This was the most comprehensive analysis of HIVDR in Florida to date. It covered all 67 Florida counties, encompassed several consecutive years of genotype sampling, and analyzed associations with numerous epidemiological, spatial-temporal and socioecological factors to provide a complete depiction of HIVDR in a region with a disproportionately high burden of HIV. Our findings indicate prevalence of HIVDR in Florida is higher than published North American estimates, with considerable heterogeneity by geographic region. These results warrant further surveillance of HIV molecular epidemiology in Florida in support of EHE.

Conflict of interest

We declare no competing interests.

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Authors' contributions

MP and MS conceived of the idea, with input from SR, KP, and ES. KP and ES were responsible for data procurement. SR completed the data analysis with assistance from HH, RC, and MP. ES, KP, MP, RC, and CM assisted SR with data interpretation. All authors contributed to writing.

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Table 1. Sociodemographic and clinical characteristics of study population in Florida, 2012-2017.

	Genotype Test Year			
	2012-2014		2015-2017	
Age (years)	*Frequency*	*% (95% CI)*	*Frequency*	*% (95% CI)*
0-25	1207	10·9 (10·3-11·4)	2506	10·7 (10·3-11·1)
26-33	1970	17·7 (17·0-18·4)	4373	18·7 (18·2-19·2)
34-45	3209	28·9 (28·0-29·7)	6099	26·1 (25·6-26·7)
46+	4729	42·5 (41·6-43·5)	10354	44·4 (43·7-45·0)
Sex at birth				
Male	7599	68·4 (67·5-69·2)	16530	70·8 (70·3-71·4)
Female	3516	31·6 (30·8-32·5)	6802	29·2 (28·6-29·7)
Region of birth				
Africa	33	0·3 (0·2-0·4)	97	0·4 (0·3-0·5)
Asia Pacific	55	0·5 (0·4-0·6)	117	0·5 (0·4-0·6)
Caribbean	1589	14·3 (13·6-14·9)	3509	15·0 (14·6-15·5)
Europe	40	0·4 (0·2-0·5)	159	0·7 (0·6-0·8)
Latin America	433	3·9 (3·5-4·3)	1261	5·4 (5·1-5·7)
North America	8516	76·6 (75·8-77·4)	17131	73·4 (72·9-74·0)
Race/ethnicity				
Black	6264	56·4 (55·4-57·3)	12638	54·2 (53·5-54·8)
Hispanic/Latino	2111	19·0 (18·3-19·7)	4982	21·4 (20·8-21·9)
Other[#]	266	2·4 (2·1-2·7)	507	2·2 (2·0-2·4)
White	2474	22·3 (21·5-23·0)	5205	22·3 (21·8-22·8)
Transmission category				
Heterosexual contact	4147	37·3 (36·4-38·2)	8333	35·7 (35·1-36·3)
IDU	1527	13·7 (13·1-14·4)	2577	11·0 (10·6-11·4)
MTM	4776	43·0 (42·0-43·9)	11050	47·4 (46·7-48·0)
MCT	244	2·2 (1·9-2·5)	550	2·4 (2·2-2·6)
Unknown	421	3·8 (3·4-4·1)	822	3·5 (3·3-3·8)
HIV-1 subtype				

B	10822	97·4 (97·1-97·7)	22542	96·6 (96·4-96·8)
B recombinant	130	1·2 (1·0-1·4)	368	1·6 (1·4-1·7)
Non-B	79	0·7 (0·6-0·9)	148	0·6 (0·5-0·7)
Other recombinant	84	0·8 (0·6-0·9)	274	1·2 (1·0-1·3)

Results are presented as frequencies and percentages with corresponding 95% confidence intervals).

Abbreviations: IDU, injection drug use; MTM, male-to-male sexual contact; MCT, mother-to-child transmission.

[#]Other race/ethnicities included: 'American Indian/Alaska Native,' 'Asian,' 'Native Hawaiian/Pacific Islander,' and 'Multi-race.'

Table 2. Fixed effects multivariable model associations of individual (sociodemographic and clinical) characteristics and socioecological factors with resistance outcomes in Florida, 2012-2017.

			Ever on ART			ART naïve
	NRTI resistance	NNRTI resistance	PI resistance	INSTI resistance	MDR	TDR
	(n=6,204/30,788)	(n=9,333/30,788)	(n=2,110/30,788)	(n=954/11,107)	(n=4,265/30,788)	(n=859/3,659)
Age (years)						
26-33 *vs. 0-25*	1·02 (0·87-1·19)	1·02 (0·91-1·14)	0·87 (0·70-1·10)	1·43 (0·95-2·19)	1·04 (0·85-1·26)	0·73 (0·55-0·97)
34-45 *vs. 0-25*	1·62 (1·39-1·89)	1·21 (1·08-1·36)	1·15 (0·91-1·44)	1·97 (1·32-3·04)	1·86 (1·54-2·27)	0·96 (0·72-1·27)
46+ *vs. 0-25*	2·27 (1·96-2·63)	1·37 (1·23-1·52)	2·10 (1·70-2·62)	2·44 (1·65-3·72)	2·82 (2·35-3·41)	1·18 (0·90-1·55)
Sex at birth						
Male *vs. female*	1·22 (1·12-1·32)	…	…	…	1·19 (1·08-1·30)	…
Region of birth						
Africa *vs. NA*	…	0·90 (0·54-1·45)	…	…	…	…
Asia Pacific *vs. NA*	…	1·20 (0·79-1·81)	…	…	…	…
Caribbean *vs. NA*	…	0·86 (0·79-0·93)	…	…	…	…
Europe *vs. NA*	…	1·02 (0·70-1·46)	…	…	…	…
Latin America *vs. NA*	…	0·90 (0·78-1·04)	…	…	…	…
Race/ethnicity						
Hispanic/Latino *vs. Black*	0·98 (0·90-1·07)	0·99 (0·91-1·07)	1·20 (1·06-1·37)	1·10 (0·92-1·32)	1·03 (0·93-1·13)	…
Other *vs. Black*	0·79 (0·64-0·98)	0·81 (0·67-0·97)	1·03 (0·73-1·41)	0·92 (0·55-1·46)	0·84 (0·66-1·07)	…
White *vs. Black*	0·89 (0·82-0·96)	0·87 (0·82-0·94)	1·31 (1·16-1·48)	0·78 (0·64-0·95)	0·91 (0·82-1·00)	…
Transmission category						
IDU *vs. Hetero*	0·81 (0·74-0·90)	0·97 (0·89-1·05)	0·97 (0·83-1·14)	0·72 (0·56-0·92)	0·78 (0·70-0·88)	1·08 (0·82-1·41)
MTM *vs. Hetero*	1·01 (0·92-1·10)	0·96 (0·90-1·02)	1·24 (1·10-1·39)	1·12 (0·95-1·32)	1·01 (0·91-1·12)	1·11 (0·93-1·34)
MCT *vs. Hetero*	4·87 (4·03-5·90)	1·78 (1·50-2·11)	5·79 (4·46-7·51)	1·58 (0·95-2·55)	5·47 (4·40-6·80)	3·09 (1·66-5·83)
Unknown *vs. Hetero*	1·15 (0·97-1·35)	1·01 (0·88-1·16)	1·71 (1·36-2·14)	0·85 (0·55-1·27)	1·32 (1·10-1·58)	0·50 (0·24-0·92)
Subtype						
B recombinant *vs. B*	…	0·70 (0·53-0·91)	1·43 (0·92-2·13)	1·14 (0·95-1·37)	…	0·60 (0·30-1·07)
Non-B *vs. B*	…	0·79 (0·54-1·14)	0·32 (0·10-0·76)	2·56 (0·94-5·93)	…	0·16 (0·01-0·78)
Other *vs. B*	…	0·57 (0·40-0·79)	0·59 (0·27-1·13)	0·49 (0·12-1·33)	…	0·48 (0·18-1·05)

Ever suppressed						
No *vs. Yes*	0·65 (0·61-0·70)	0·67 (0·63-0·71)	0·81 (0·73-0·91)	…	0·63 (0·58-0·69)	…
Test Year	1·02 (1·00-1·05)	0·95 (0·93-0·98)	1·15 (1·07-1·24)	1·18 (1·01-1·39)	…	0·77 (0·61-0·97)
Time from Dx						
12+ *vs. ≤12 months*	3·56 (3·17-4·01)	1·67 (1·54-1·81)	1·92 (1·63-2·26)	4·25 (3·18-5·79)	4·31 (3·70-5·05)	2·26 (1·91-2·69)
Social economic factors rank	1·08 (1·03-1·14)	1·07 (1·03-1·12)	…	…	…	1·33 (1·04-1·69)
Physical environment rank	…	1·03 (1·00-1·07)	…	1·12 (1·02-1·24)	…	…
Mentally unhealthy days	1·10 (1·05-1·16)	1·08 (1·03-1·13)	…	0·83 (0·70-0·98)	1·11 (1·05-1·18)	…
Percent low birth weight	…	…	1·11 (1·01-1·22)	0·88 (0·74-1·04)	1·07 (0·99-1·15)	…
Percent diabetic screening	…	…	…	…	…	1·18 (0·96-1·46)
Percent unemployed	…	…	1·22 (1·07-1·40)	1·63 (1·25-2·12)	1·05 (1·00-1·10)	0·69 (0·45-1·07)
Violent crime rate	…	…	…	0·80 (0·70-0·92)	…	…
Percent > 65 years	…	1·06 (1·02-1·10)	1·07 (1·00-1·15)	…	1·07 (1·02-1·12)	…
Percent American Indian/ Alaskan Native	…	…	…	…	…	1·25 (0·94-1·64)
Percent rural	0·83 (0·77-0·91)	…	…	0·71 (0·51-0·94)	0·88 (0·80-0·96)	0·73 (0·55-0·98)
Percent diabetic	…	0·96 (0·93-0·99)	0·93 (0·88-0·98)	…	…	…
Percent uninsured adult	…	…	…	…	…	0·89 (0·80-1·00)
Murder rate	0·96 (0·92-1·00)	…	…	…	0·90 (0·86-0·94)	…
Rape rate	0·97 (0·92-1·01)	0·95 (0·92-0·99)	…	…	…	…
Robbery rate	1·04 (0·99-1·09)	1·05 (1·01-1·10)	…	…	1·05 (1·00-1·11)	…

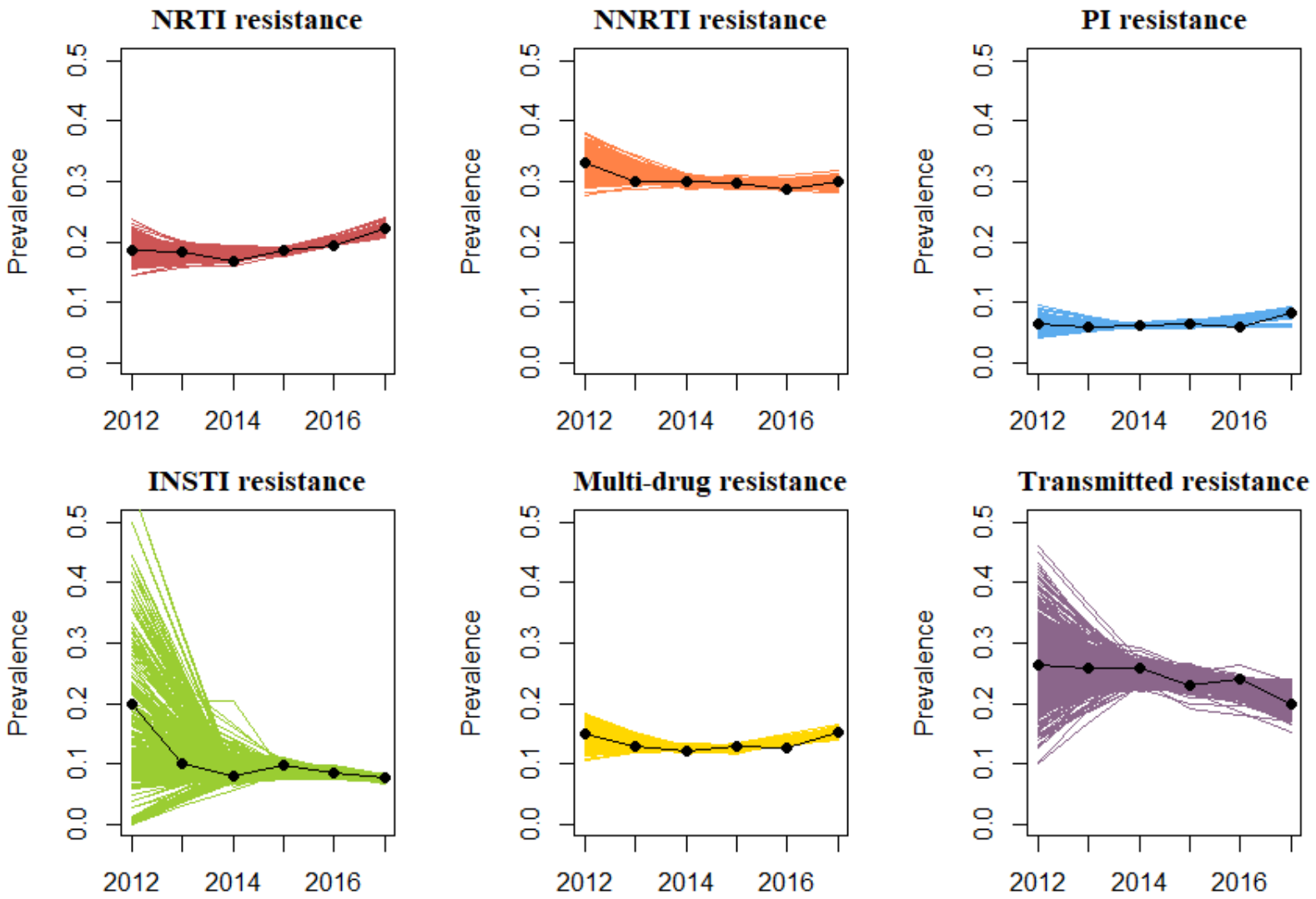
Results are presented as adjusted odds ratios and 95% confidence intervals.

Note. All associations are adjusted for individual demographic and clinical characteristics and county-level sociodemographic factors.

Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitors; MDR, multi-drug resistance, TDR, transmitted drug resistance, NA, North America; IDU, injection drug use; Hetero, heterosexual contact; MTM, male-to-male sexual contact; MCT, mother-to-child transmission.

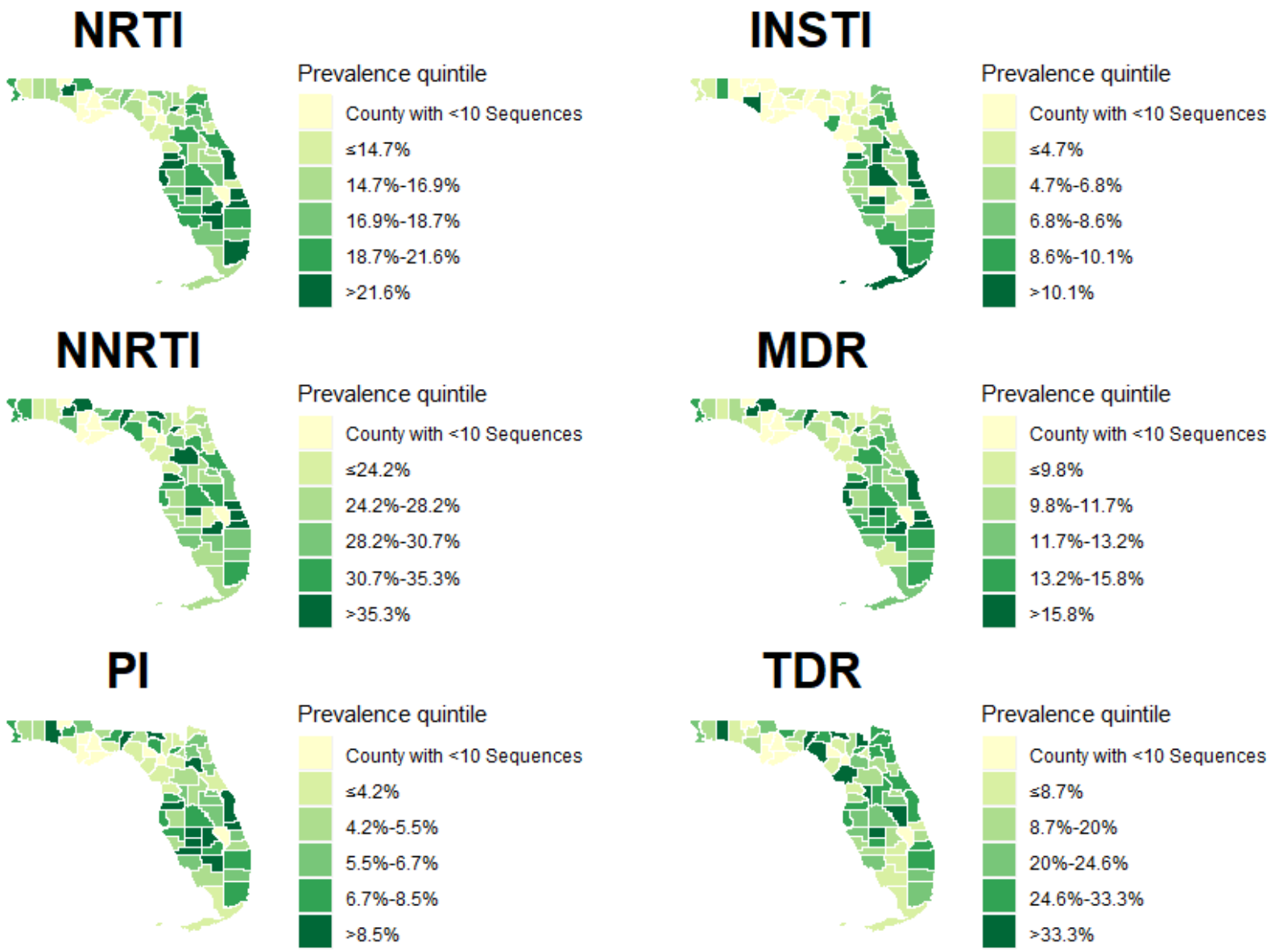
[#] Other race/ethnicities: 'American Indian/Alaska Native,' 'Asian,' 'Native Hawaiian/Pacific Islander,' and 'Multi-race.'

Figure 1. Annual prevalence of HIV drug resistance outcomes in Florida by test year.



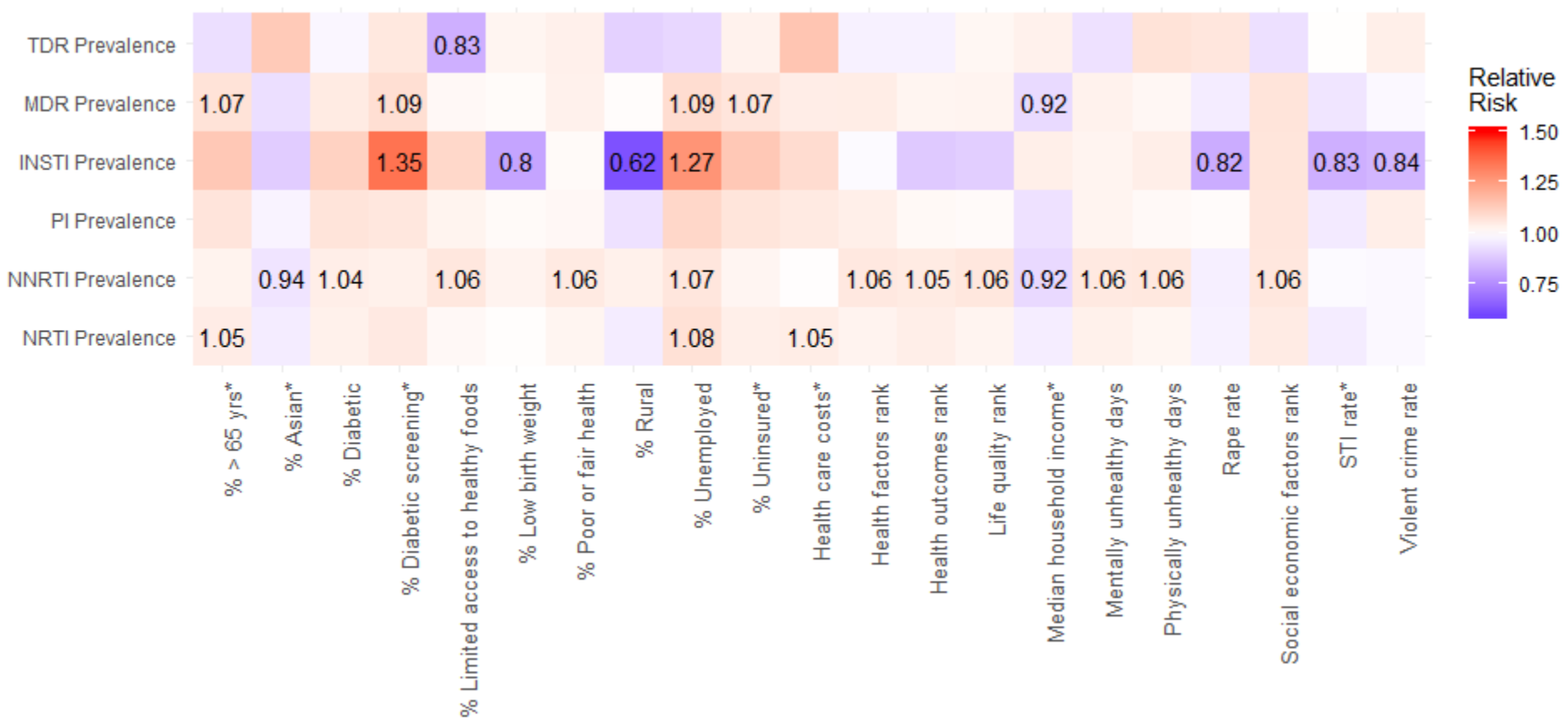
Prevalence of HIV drug resistance outcomes in Florida between 2012 and 2017. Estimates indicate annual prevalence per-year. Line estimates are drawn via lowess interpolation and data bootstrapping (500 times). **Abbreviations**: NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitors.

Figure 2. Maps of HIV drug resistance prevalence by county, 2012-2017.



Geographic distribution of the prevalence of drug resistance by Florida county between 2012 and 2017. Darker regions correspond to higher prevalence of drug resistance. Colored lines indicate counties with significantly high (red) or low (blue) prevalence of drug resistance compared to state averages. Counties with fewer than 10 sequences were excluded from the analysis (depicted in light yellow). Drug resistance outcomes included: nucleoside reverse transcriptase inhibitors (**NRTI**), non-nucleoside reverse transcriptase inhibitors (**NNRTI**), protease inhibitors (**PI**), integrase strand transfer inhibitors (**INSTI**), multi-drug resistance (**MDR**), and transmitted drug resistance (**TDR**).

Figure 3. Relative risk heatmap showing univariable associations between drug resistance prevalence and county-level socioecological health indicators.



Heat map of relative risk estimates for each drug resistance outcome according to county-level socioecological health indicators from County Health Rankings. Relative risk estimates significant at the 5% level are shown. *Indicates log-transformed variables. **Abbreviations**: TDR**,** transmitted drug resistance; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; MDR, multi-drug resistance; INSTI, integrase strand transfer inhibitors; PI, protease inhibitors; STI, sexually transmitted infection. **Note**: none of the factors were significantly associated with PI resistance.