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Major Article

HIV-associated comorbidities as mediators of the association between people living with HIV and hospital-acquired infections

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Background: Hospital-acquired infections (HAIs) lead to poor health outcomes in hospitalized patients and may be disproportionately affecting the aging population of people living with HIV (PLWH). This study determined the association between HIV and HAIs, and analyzed the potential mediating effects of comorbidities.
Methods: The Louisiana Hospital Inpatient Discharge Database for the years 2011-2015 was used. All patients with at least 1 HAI diagnosis within this source population were included as cases in the case-control study, and a 1:1 ratio of controls was randomly selected from the same hospitals.
Results: Of the 1,852,769 eligible hospital discharges that occurred from 2011 through 2015, there were 7,422 patients with at least 1 HAI. Marginal logistic regressions of the case-control sample showed a strong association between HIV and central line–associated bloodstream infections (CLABSIs), but an inverse association between HIV and any HAI. However, the mediation analyses revealed that having at least 1 comorbidity mediates the association between HIV and CLABSIs.
Discussion: The unexpected inverse association between HIV and HAI could be attributed to the sample size of the exposed group of patients, or it could be explained by the mechanisms of treatment for HIV patients.
Conclusions: This study found that people living with HIV are at an increased risk of developing a CLABSI, which is consistent with the published literature. The mediation analyses indicated that having at least 1 comorbidity mediated the association between HIV and CLABSI diagnosis.

In 2011, the Centers for Disease Control and Prevention (CDC) estimated 648,000 hospitalized patients in the United States experienced at least 1 hospital-acquired infection (HAI), which is the equivalent to approximately 1 in every 25 hospitalized persons. Of these HAIs, pneumonias and surgical site infections (SSIs) were the 2 most common manifestations.[1] HAIs especially affect vulnerable and immunocompromised populations who are at an increased risk for infections, such as people living with HIV (PLWH). This can lead to poor health outcomes, including increased lengths of stay in the hospital. There is an estimated 6% mortality rate owing to complications associated with HAIs among the general population.[1-5] The CDC recognizes the most common types of site-specific HAIs as catheter-associated urinary tract infections (CAUTIs), ventilator-associated pneumonias (VAPs), SSIs, and central line–associated bloodstream infections (CLABSIs).[6,7] These HAIs stem from devices that are generally used in people with more severe conditions and/or people who require more lengthy hospitalizations, such as aging PLWH.

Previous studies have estimated that 8% of hospitalized HIV patients contract a HAI, with an incidence rate of 6.1 per 1,000 patient days, which is twice as high as the overall hospital HAI incidence rate.[5] A 1998 study[11] conducted in Italian infectious disease units observed that nosocomial bloodstream infections were the most common type of HAI among PLWH. A more recent study conducted in 2014 involving 4 hospitals in New York City reported that 8.6% of discharged PLWH had at least 1 HAI diagnosis.[12] Although it has been documented that hospitalizations for PLWH have decreased over

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time owing to the effectiveness of antiretroviral therapy (ART), these PLWH are now being admitted to hospitals for chronic diseases and older age- related health events.[13-15] The published literature on HIV infection shows that an older HIV population experiences a higher rate of non-HIV/AIDS-related comorbidities in the post-ART era compared with the pre-ART era.[13-15] Higher rates of these comorbidities have been significantly associated with HIV infection compared with the general population[15,19,20]; the presence of these comorbidities results in greater morbidity and mortality rates compared with PLWH without these comorbidities.[16-18]

The burden and impact of HAIs in Louisiana is currently unknown. However, according to the CDC's National and State Healthcare-Associated Infections Progress Report from 2016, Louisiana had a significantly higher standardized infection ratio in 2014 when compared with the national standardized infection ratio for CLABSIs.[8,9] This increased rate of HAIs in Louisiana may negatively influence the health of the growing population of PLWH in the state. According to the CDC's HIV Surveillance Report, New Orleans and Baton Rouge are consistently ranked among the top 5 cities for HIV case rates, and Louisiana is ranked second among U.S. states. Based on the 2015 Louisiana State STD/HIV Surveillance Report, Louisiana had 20,398 PLWH.[10]

The immunosuppression experienced by PLWH may be exacerbating the rate at which this population is diagnosed with a HAI. The aims of this study were to determine the association between HIV and HAIs in Louisiana and to examine older age-related comorbidities for any potential mediating effects within the HIV to HAI pathway.

METHODS

Data sources

The source population was obtained from discharge records for the years 2011-2015, from acute care hospitals throughout the state of Louisiana, from the Louisiana Hospital Inpatient Discharge Database (LAHIDD), which is maintained by the Louisiana Office of Public Health's Bureau of Health Informatics. The data contained ICD-9 codes for all diagnoses during the hospital stay, length of stay, and demographic variables. Patients included in the study were 18 years and older and had a hospital stay of at least 2 days to fulfill the definition of a HAI. Discharges with no listed diagnostic codes and records with an erroneous principal diagnosis or an admission diagnosis of a HAI were excluded from the analysis to control for misclassification of the outcome (n = 592). All discharges were linked to the Louisiana HIV surveillance system (eHARS) within the Louisiana Office of Public Health's STD/HIV Program to assign and confirm HIV status. The final source population contained 1,852,769 hospital discharges.

Study design and variables of interest

The exposure of interest was the presence or absence of an HIV diagnosis, as determined by an individual's presence within the eHARS dataset, and the mediators of interest are the comorbidity variables, which are binary and indicate the presence or absence of any comorbidity of interest and of each specific comorbidity type. Based on the previous literature, we chose to use cardiovascular disease (CVD), liver disease, diabetes mellitus, kidney disease, and all non-AIDS-defining cancers as the comorbidities of interest in this present study. Appendix A shows a list of the HIV/AIDS-defining cancers that were excluded. The confounders were age, gender, race, length of hospital stay, and number of hospitalizations during the study period. These confounders were chosen on the basis that, generally, patients with a HAI are older and more likely to be female than patients without a HAI, whereas race was used as a confounder to account for the health disparities experienced by different races in Louisiana. Because of the rarity of the outcome of interest, HAIs (~0.41%) within the source population, a case-control study was conducted using all discharges for the 7,422 individual cases diagnosed, with at least 1 HAI identified from the 1,852,769 discharge records. A total of 7,418 controls were randomly selected from the same hospitals that gave rise to the cases for a total study population of 14,840 individual patients, with a cumulative total of 45,920 discharge records. The outcome was measured as a binary variable assessing the presence or absence of any HAI and 4 individual binary variables for each HAI type (CAUTI, SSI, VAP, and CLABSI), which were identified using the HAI-specific ICD-9 codes. Appendix B shows a list of the codes.

Statistical analysis

Data analyses were performed using all discharges of the individual patients in the case-control study throughout the study period to account for both between subject and within subject variability. Univariate and bivariate analyses were performed on each variable to assess potential associations. Marginal logistic regressions were run using generalized estimating equations to account for the repeated observations contributed by each patient. Each of these models were adjusted for age, gender, race, length of hospital stay, and number of hospitalizations as potential confounders of the association. Additionally, mediation analyses were performed using the specified comorbidities as the mediators. The Valeri and VanderWeele SAS macro for the counterfactual approach to mediation analysis was modified to perform the necessary functions for this specific study design.[21] The macro was deconstructed so that it would run the outcome regression on the case-control study using the repeated measures approach and then run the mediator regression only on the control population.[22,23] Using the parameter estimates from the marginal logistic regression, the direct (Eq. [C.1]) and indirect effects (Eq. [C.2]) and the 95% confidence intervals were calculated (Appendix C).[21] All analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

The overall incidence rate in the LAHIDD population was 1.5 HAI cases per 1,000 person-years, whereas the incidence rate in the LAHIDD HIV population was 1.3 HAI cases per 1,000 person-years. The study population consisted of 7,422 case patients who had at least 1 HAI diagnosis and 7,418 controls (Table 1). Compared with controls, cases were more likely to be older, HIV negative, white, female, and have at least 1 of the comorbidities of interest. Comorbidities such as cardiovascular disease (CVD), kidney disease, diabetes, non-AIDS-defining cancers, and liver disease were more prevalent among cases than controls ($P < .0001$). Cases also had a significantly longer average length of stay in the hospital and significantly more hospitalizations than controls.

There were 8,038 HAI diagnoses among the 7,422 case patients (Table 2). From 2011-2015, in Louisiana the majority of the HAIs that occurred were SSIs. The total prevalence of HAIs was higher among HIV-negative patients than PLWH ($P = .003$), specifically, HIV-negative patients had a higher proportion of SSIs (12%) than PLWH (6%; $P < .0001$). However, PLWH had a statistically significantly higher percentage of CLABSIs than HIV-negative patients (2.4% and 0.9%, respectively; $P = .004$). There were no statistically significant differences in CAUTIs and VAPs between PLWH and HIV-negative patients.

After adjusting for age, race, gender, length of stay, and number of hospitalizations, HIV was inversely associated with the risk of any HAI diagnosis (Table 3). PLWH were 38% less likely to have a HAI diagnosis during their hospital stay, from 2011-2015 (odds ratio [OR]) = 0.62; confidence limits [CL], 0.49-0.78). Females were less likely to have been diagnosed with a HAI compared with males (OR = 0.89; 95%

Table 1
Characteristics of hospital-acquired infection (HAI) cases and controls in the Louisiana Hospital Inpatient Discharge Database (LAHIDD), from 2011-2015

Patient characteristic	Case patients (N = 7,422)	Control patients (N = 7,418)	*P* value
	Mean (SD)	Mean (SD)	
Age (y)	59.8 (16.8)	53.7 (20.8)	<.0001
Length of stay (d)	9.6 (11.2)	5.6 (6.6)	<.0001
No. of hospitalizations	4.6 (4.3)	1.6 (1.9)	<.0001
	% (N)	% (N)	
HIV status			
Positive	0.7 (48)	1.1 (82)	.003
Negative	99.3 (7,374)	98.9 (7,336)	—
Race			
White	62.5 (4,640)	59.4 (4,404)	.0002
Black	28.0 (2,077)	29.6 (2,199)	—
Other	9.5 (705)	11.0 (815)	—
Gender			
Male	48.8 (3,624)	39.3 (2,913)	<.0001
Female	51.2 (3,798)	60.7 (4,505)	—
Comorbidity			
Present	90.1 (6,685)	68.4 (5,071)	<.0001
Absent	9.9 (737)	31.6 (2,347)	—
Comorbidity type			
CVD	84.9 (6,304)	63.7 (4,722)	<.0001
Kidney disease	38.7 (2,873)	19.4 (1,441)	<.0001
Diabetes	29.9 (2,220)	17.2 (1,278)	<.0001
Non-AIDS-defining cancer	17.5 (1,299)	8.6 (639)	<.0001
Liver disease	7.4 (546)	4.2 (310)	<.0001

CVD, cardiovascular disease.

CL, 0.85-0.92). Blacks and 'other race' were also less likely to have been diagnosed with a HAI compared with whites (OR = 0.87; 95% CL, 0.83-0.92 and OR = 0.84; 95% CL, 0.78-0.92, respectively). For every 1-day increase in length of hospital stay, the odds of a HAI diagnosis increased by 5%; whereas a 1 unit increase in the number of hospitalizations decreased the odds of a HAI by 9%.

When evaluating the HAI subgroup analyses, HIV was inversely associated with the risk of a CAUTI, a VAP, and a SSI, however, positively associated with a CLABSI after covariate adjustment (OR = 2.32; 95% CL, 1.35-3.97) (Table 4). A 1-year increase in age was associated with a 3% increase in the odds for a CAUTI, whereas being female was associated with a 31% decrease in the odds for a CAUTI and a 35% decrease in the odds of a VAP. When comparing blacks with whites, the OR of a SSI was protective (OR = 0.72; 95% CL, 0.67-0.76), the odds of a CAUTI were 1.43 (1.28, 1.60), and the odds of a VAP were 1.36 (1.08, 1.71). When comparing other races with whites, patients of other races had a decreased odds of SSIs (OR = 0.83; 95% CL, 0.75-0.92) and an increased odds of VAPs (OR = 1.41; 95% CL, 1.01-1.97). Length of hospital stay was positively associated with an increased OR of each specific HAI. The number of hospitalizations during the study period was associated with an increased odds of a CLABSI, but decreased the odds of SSIs and VAPs.

Table 2
Distribution of hospital-acquired infection (HAI) diagnoses by HIV status in the Louisiana Hospital Inpatient Discharge Database (LAHIDD), from 2011-2015

HAIs	Total (N = 8,038) % (N)	HIV positive (N = 47) % (N)	HIV negative (N = 7,991) % (N)	*P* value (.003)
SSI	68.3 (5,488)	6.0 (25)	12.0 (5,463)	<.0001
CAUTI	21.6 (1,739)	2.1 (9)	3.8 (1,730)	.09
VAP	5.4 (436)	0.7 (3)	1.0 (433)	.80
CLABSI	4.9 (395)	2.4 (10)	0.9 (385)	.004

CAUTI, catheter-associated urinary tract infection; *CLABSI*, central line—associated bloodstream infection; *SSI*, surgical site infection; *VAP*, ventilator-associated pneumonias.

Table 3
Odds ratios (OR) of the association between HIV and any hospital-acquired infection (HAI) diagnosis in the Louisiana Hospital Inpatient Discharge Database (LAHIDD), from 2011-2015

Parameters	Crude OR	95% CL	Adjusted OR*	95% CL
HIV	**0.59**	(0.46, 0.76)	**0.62**	(0.49, 0.78)
Age (y)	**1.00**	(1.00, 1.01)	**1.00**	(1.00, 1.002)
Female gender	**0.84**	(0.80, 0.88)	**0.89**	(0.85, 0.92)
Race				
Black vs white	**0.88**	(0.83, 0.92)	**0.87**	(0.83, 0.92)
Other vs white	**0.88**	(0.81, 0.96)	**0.84**	(0.78, 0.92)
Length of stay (d)	**1.05**	(1.04, 1.05)	**1.05**	(1.04, 1.05)
No. of hospitalizations	**0.92**	(0.91, 0.92)	**0.91**	(0.91, 0.92)

NOTE. Bold type represents statistically significant odds ratios with a *P* value <.05.
CL, confidence limit.
*Adjusted odds ratios were adjusted for all variables shown in the table.

CLABSI was the only HAI with a positive association with HIV, and, therefore, the only association tested for mediation. The mediation analyses showed that the ORs were stronger for direct effects than for indirect effects (Table 5) for the increased odds of a CLABSI in PLWH. The indirect effects through any comorbidity were statistically significant in the association between HIV and CLABSI; however, the proportion mediated was almost negligible (0.34%). There were no significant indirect effects when examining mediation through the individual comorbidities (CVD, liver disease, kidney disease, non-HIV/AIDS-defining cancers, and diabetes) in the association between HIV and CLABSI.

DISCUSSION

To our knowledge, this study is the first to determine the association between HIV and HAIs in Louisiana, and to examine whether chronic comorbidities mediate the association of HAIs among PLWH. We have estimated the prevalence of the top HAIs in Louisiana among PLWH using the LAHIDD. In Louisiana, the 5-year incidence for HAIs, in both PLWH and HIV-negative patients, is less than 1%, which is lower than other states. However, PLWH were significantly more likely to acquire a CLABSI than HIV-negative patients, which is consistent with published literature. However, HIV-negative patients were more likely to have been diagnosed with SSIs, CAUTIs, and VAPs than PLWH. Our data show that PLWH in Louisiana were 38% less likely to have a HAI compared with HIV-negative patients when adjusting for age, gender, race, length of stay, and number of hospitalizations.

The unexpected inverse association between HIV and HAI in this study could have been owing to the small number of patients with HIV infection in the case-control study (~1%), which may have skewed the results. Although the percentage of HIV patients was low, the proportion of PLWH in the study was representative of both the total LAHIDD population and the population of Louisiana. Another potential explanation for this inverse association is the improved health and life expectancy of the HIV population owing to advances in HIV treatment methods. Several studies have found that the life expectancy of a PLWH at age 20 has increased between 10 and 20 years, making their average lifespan about 70 years, which approaches that of the average healthy person.[24-26] Although PLWH are suffering more chronic diseases owing to the premature aging effect, this increased lifespan could also be making this population more comparable to the general population in terms of health status. If the hospitalized HIV population in Louisiana is actually mirroring the general hospitalized population, it is likely that having the disease may actually not affect the chance of getting a HAI. When evaluating specific HAIs, PLWH were the most protected against SSIs, which may reflect a lower rate of surgeries among PLWH in Louisiana. Last, there is also a possibility that HIV patients are being

Table 4
Odds Ratios (OR) of the association between HIV and the odds of specific hospital-acquired infections (HAIs) in the Louisiana Hospital Inpatient Discharge Database (LAHIDD), from 2011-2015

Parameters	SSI OR*	95% CI	CAUTI OR*	95% CI	VAP OR*	95% CI	CLABSI OR*	95% CI
HIV	**0.50**	(0.34, 0.74)	0.77	(0.42, 1.40)	0.68	(0.21, 2.15)	**2.32**	(1.35, 3.97)
Age (y)	**0.99**	(0.99, 1.00)	**1.03**	(1.03, 1.04)	1.00	(0.99, 1.01)	**0.98**	(0.98, 0.99)
Female gender	0.99	(0.94, 1.05)	**0.69**	(0.62, 0.76)	**0.65**	(0.53, 0.80)	0.98	(0.79, 1.20)
Race								
Black vs white	**0.72**	(0.67, 0.76)	**1.43**	(1.28, 1.60)	**1.36**	(1.08, 1.71)	1.12	(0.89, 1.40)
Other vs white	**0.83**	(0.75, 0.92)	0.83	(0.68, 1.01)	**1.41**	(1.01, 1.97)	0.80	(0.53, 1.20)
Length of stay (d)	**1.04**	(1.03, 1.04)	**1.01**	(1.00, 1.01)	**1.05**	(1.04, 1.05)	**1.04**	(1.03, 1.04)
No. of hospitalizations	**0.86**	(0.85, 0.87)	1.00	(0.99, 1.01)	**0.88**	(0.84, 0.92)	**1.05**	(1.03, 1.06)

NOTE. Bold type represents statistically significant odds ratios with a *P* value <.05.
CI, confidence interval; *CAUTI*, catheter-associated urinary tract infection; *CLABSI*, central line–associated bloodstream infection; *SSI*, surgical site infection; *VAP*, ventilator-associated pneumonias.
*Odds ratios were adjusted for all variables shown in the table.

treated with more precautions, owing to their greater susceptibility to infection during their stay in the hospital than their uninfected hospital counterparts.

This study used the unique, modified Valeri and VanderWeele macro in a repeated measures case-control analysis to determine the effect of potential mediators on the association between HIV and CLABSIs. Although the macro was modified to fit the matched case-control design, the Valeri and VanderWeele method of calculation was still used and any potential bias from exposure-mediator interaction was controlled. The mediation analyses indicated that the presence of at least 1 comorbidity mediated the association between HIV and CLABSI diagnosis, albeit a small proportion. However, there were no significant indirect effects by the specific types of comorbidities, which indicates that there was no mediation in the association between HIV and CLABSI through the specific comorbidities analyzed. As an additional sensitivity analysis, the comorbidities were tested for moderation effects. Only the association between HIV and CAUTIs produced a significant result; non-HIV/AIDS-defining cancers increased the odds of a CAUTI among PLWH (data not shown).

Limitations

Although 1 of the distinctive aspects of this study was that it used hospital discharges from all regions of Louisiana within a single database, it is also one of its limitations. LAHIDD was created in 1998 as the designated registry containing inpatient discharge data submitted by licensed hospitals in the state. However, according to the Louisiana Office of Public Health's Bureau of Health Informatics, prior to 2015 only 50% of the hospitals in Louisiana were reporting to LAHIDD. This limited reporting likely resulted in an underestimation of the prevalence of HAIs in Louisiana and in the low exposure count observed. It is also likely that it limited the generalizability of the results, as there may be significant differences among the patient populations of those hospitals that did report and those that did not report. However, the hospitals in the regions that have the highest prevalence of PLWH were reporting hospitals, and therefore, the majority of the exposed population was captured. There are also limitations stemming from the use of specific ICD-9 codes for the HAIs, as HAIs may not always be coded as such, potentially owing to penalties from the Centers for Medicare and Medicaid Services, coding errors, or misclassification owing to another pre-existing condition. Additionally, studies have shown that although ICD-9 codes can be used to compare rates of infections, they are not 100% reliable in outcomes research owing to the variability of HAI definitions, particularly when identifying SSIs from medical records and patient encounters.

Additional limitations arise from the lack of information on potential confounders specifically associated with HIV disease and each HAI, such as viral suppression status, device-days, wound class, and severity of illness. Information on these elements of disease would be helpful in explaining the results from this study, mainly the inverse association between HIV and HAIs. These factors were not included in the analysis because LAHIDD did not contain detailed medical information that would be found in medical records, and the Office of Public Health did not approve the use of this protected health information for outside research. In spite of these limitations, this study contributed new knowledge in the field of hospital infection in Louisiana and examined the unknown effects of HIV status and comorbidities on risk of HAIs using a novel design approach.

Conclusions

This study provided preliminary insight into the association between HIV and HAIs. Future studies that can account for level of immune suppression, use of ART, and duration of HIV infection would

Table 5
Estimates of the direct and indirect effects of the association between HIV and the odds of a central line-associated bloodstream infection (CLABSI) mediated through comorbidities in the Louisiana Hospital Inpatient Discharge Database (LAHIDD), from 2011-2015

Comorbidity type	Direct effect OR* (95% CI)	Indirect effect OR*(95% CI)	Total effect OR* (95% CI)	Proportion mediated through comorbidity, %
CLABSI and any comorbidity*	**2.10** (1.22, 3.60)	**1.00** (1.00, 1.00)	**2.11** (1.23, 3.61)	0.34%
CLABSI and CVD	**2.20** (1.28, 3.78)	1.01 (0.99, 1.02)	**2.22** (1.29, 3.82)	1.66%
CLABSI and liver disease	**2.19** (1.28, 3.75)	1.04 (0.93, 1.16)	**2.29** (1.32, 3.94)	7.26%
CLABSI and kidney disease	**2.10** (1.25, 3.54)	1.09 (0.98, 1.21)	**2.29** (1.35, 3.89)	14.73%
CLABSI and non-AIDS-defining cancer	**2.29** (1.29, 4.08)	1.03 (0.85, 1.24)	**2.37** (1.29, 4.34)	5.39%
CLABSI and diabetes	**2.33** (1.36, 3.99)	0.99 (0.96, 1.02)	**2.31** (1.35, 3.95)	—

NOTE. Bold type represents statistically significant odds ratios with a *P* value <.05.
OR, odds ratio; *CVD*, cardiovascular disease.
*Odds ratios were adjusted for age, race, gender, length of stay, and number of hospitalizations.

be useful in further elucidating the role of HIV in HAIs. Additionally, it would be important to examine the HIV and HAI relationship in additional geographic areas to attain more generalizable results.

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APPENDIX A

HIV/AIDS-defining cancers excluded:

Cervical cancer, Kaposi sarcoma, Burkitt lymphoma, immunoblastic lymphoma, primary CNS lymphoma

APPENDIX B

ICD-9 Codes: Hospital-Acquired Infections

Catheter-Associated Urinary Tract Infection = 996.64
Ventilator-Associated Pneumonia = 997.31
Surgical Site Infection = 998.59
Central Line-Associated Bloodstream Infection = 999.32

ICD-9 Codes: Comorbidities

Cardiovascular Disease = 391-459.81
Liver Disease = 456.0-456.2, 570-573.9
Diabetes = 249-250.93
Kidney Disease = 583-586
Non-HIV/AIDS-Defining Cancers = 140-175.9, 179-202.8, 202.9-209.3

APPENDIX C

Regression Equations:

$$NDE^{OR} \cong \frac{e^{\gamma_1 a}\left(1 + e^{\gamma_2+\gamma_3 a+\beta_0+\beta_1 a^*+\beta'_2 c}\right)}{e^{\gamma_1 a^*}\left(1 + e^{\gamma_2+\gamma_3 a^*+\beta_0+\beta_1 a^*+\beta'_2 c}\right)} \quad (C.1)$$

$$NIE^{OR} \cong \frac{\left(1 + e^{\beta_0+\beta_1 a^*+\beta'_2 c}\right) * \left(1 + e^{\gamma_2+\gamma_3 a+\beta_0+\beta_1 a+\beta'_2 c}\right)}{\left(1 + e^{\beta_0+\beta_1 a+\beta'_2 c}\right) * \left(1 + e^{\gamma_2+\gamma_3 a+\beta_0+\beta_1 a^*+\beta'_2 c}\right)} \quad (C.2)$$

Special characters in mathematical equations:

All lowercase— gamma, beta

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