Received: 14 June 2023 | Revised: 20 October 2023 | Accepted: 26 October 2023

https://doi.org/10.1016/j.rpth.2023.102251

ORIGINAL ARTICLE

Race, ethnicity, and immune tolerance induction in hemophilia A in the United States

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Handling Editor: Dr Bethany Samuelson Bannow

Abstract

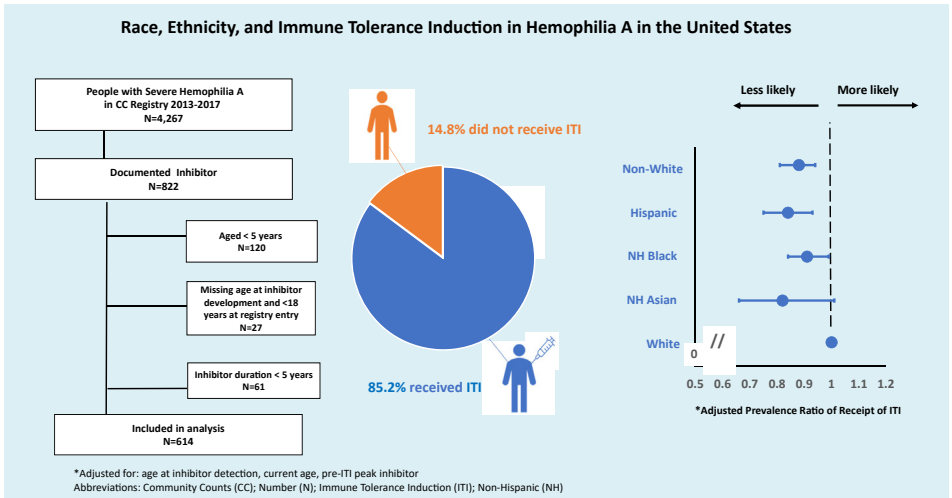
Background: In racially diverse communities, treatment of chronic diseases can vary across racial and ethnic groups.

Objectives: To examine healthcare disparities in hemophilia care in the United States by evaluating receipt of immune tolerance induction (ITI) among different racial and ethnic groups.

Methods: In this cross-sectional study, people with severe hemophilia A with an inhibitor who entered the Center for Disease Control and Prevention Community Counts registry between 2013 and 2017, were aged ≥5 years at study entry, and had a history of an inhibitor (n = 614) were included. The proportion of participants receiving ITI was examined according to race and ethnicity in bivariable analysis and multivariable analysis adjusting for demographic and clinical covariates. Unadjusted and adjusted prevalence ratios and corresponding 95% CIs were computed.

Results: Among 614 participants included in the study, 56.4% were non-Hispanic (NH) White, 19.7% were NH Black, 18.4% were Hispanic, and 4.9% were Asian. ITI was received by 85.2% of participants. On bivariable analysis, ITI treatment did not vary by race or ethnicity. On multivariable analysis, NH Black and Hispanic participants were significantly less likely to receive ITI compared to NH White participants (adjusted prevalence ratio, 0.91 [95% CI, 0.84-0.99] and 0.84 [95% CI, 0.75-0.93], respectively).

Conclusion: Although the role of ITI may evolve with growing use of emicizumab and the introduction of new hemophilia treatment products, understanding characteristics that influence care, particularly race and ethnicity, where physician bias and patient mistrust can occur, will remain relevant and applicable to other complex therapies, including gene therapy.



KEYWORDS
ethnicity, healthcare disparities, hemophilia A, racial groups

Essentials

- In racially diverse communities, treatment can vary across racial and ethnic groups.
- Receipt of immune tolerance induction (ITI), a treatment to treat inhibitors, was studied.
- Among 614 participants with severe hemophilia A with inhibitors, most (85.2%) received ITI.
- Non-Hispanic Black and Hispanic participants received ITI less often than non-Hispanic White participants.

1 | INTRODUCTION

A major complication of hemophilia A, an X-linked bleeding disorder that results from deficient factor VIII activity, is the development of an antibody (inhibitor) that neutralizes FVIII, rendering FVIII replacement therapy ineffective. Inhibitors develop in one-third of people with severe hemophilia A [1,2], and treatment for inhibitors includes the 2 broad goals of eradicating inhibitors and supporting hemostasis. Immune tolerance induction (ITI) is the only treatment available to eradicate the inhibitor and restore responsiveness to FVIII replacement therapy. ITI requires the frequent infusion of FVIII and can be difficult to administer. Fortunately, nonfactor products that mimic FVIII cofactor activity, such as emicizumab, effectively prevent bleeding in people with hemophilia A complicated by an inhibitor [3]. Prior to emicizumab approval in 2017, ITI was widely agreed to be the standard of care for treatment of people with severe hemophilia A complicated by an inhibitor [4,5]. Although emicizumab represents a major advance and can effectively suppress most bleeds in people with severe hemophilia A with inhibitors, leading some to question the importance of ITI, ITI is still believed to play a role given the need for additional hemostasis at the time of bleeding events and major surgery as well as the hemostatic superiority of FVIII replacement over bypassing agents [6].

Awareness of racial and ethnic healthcare disparities and their impact has been growing in recent years. Racial and ethnic differences in both access to healthcare as well as the quality of care that is delivered have been reported in several disease areas including but not limited to diabetes, obstetrics, and oncology [7]. Clinical situations that require significant clinical judgment or are complex to execute have a greater risk of being influenced by implicit bias and thus are at risk of healthcare disparities [8]. Given the complexity of ITI, which opens the opportunity for bias to influence decisions, we sought to explore healthcare disparities in hemophilia care by exploring how race and ethnicity may impact the likelihood of receiving ITI at federally funded hemophilia treatment centers (HTCs) in the United States prior to the availability of emicizumab. We chose to explore this in the pre-emicizumab era so that questions around the utility of ITI in the setting of emicizumab were not at play and the role of ITI was uniform across the study population.

2 | METHODS

This cross-sectional study used data from the Community Counts (CC) Registry for Bleeding Disorders Surveillance, which is a collaborative project of the US Hemophilia Treatment Center Network, the American Thrombosis & Hemostasis Network, and Centers for Disease Control and Prevention (CDC) [9]. The CC registry collects deidentified surveillance data from people with hemophilia who received care from one of 139 federally funded HTCs across the United States and authorize to have their information included in the registry. Approximately 80% of people with hemophilia in the United States, including

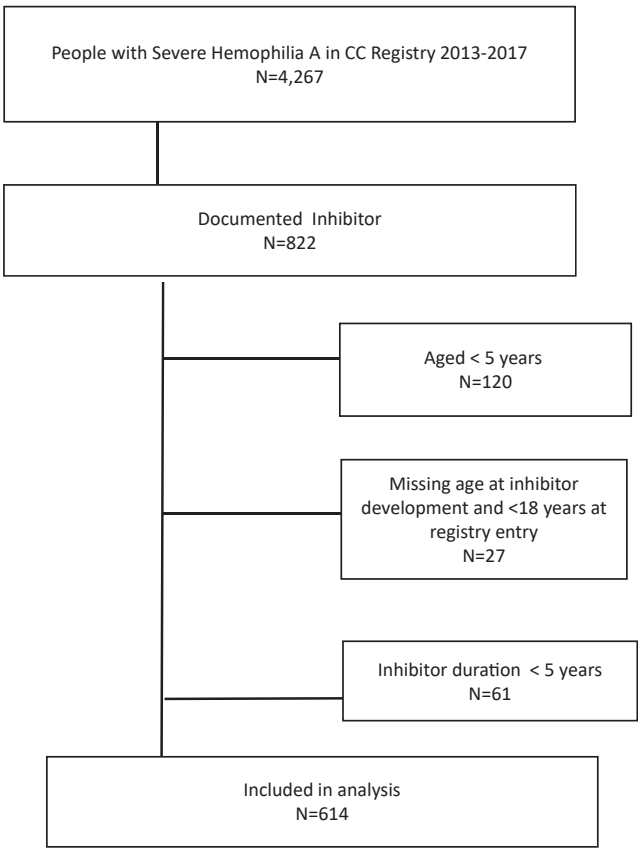


FIGURE Study population selection among people with severe hemophilia A in the Community Counts (CC) registry (2013-2017).

those with an inhibitor, receive care from an HTC [10,11]. This study was thus considered nonhuman subject research by the Emory University Institutional Review Board. The CC registry began in 2012 as an extension of the previous Universal Data Collection program, but data were not fully captured until 2013; thus, we did not begin our study until 2013 [9]. When people enter the registry, their clinical histories, including the age that an inhibitor developed, and contemporary sociodemographic, clinical, and laboratory data are collected with standardized initial visit forms [9]. Follow-up data are collected on an approximately annual basis with subsequent visit forms.

There were 822 people with severe hemophilia A with a documented history of an inhibitor who participated in the CC registry between 2013 and 2017 (Figure). People with severe hemophilia A who were aged <5 years (n = 147) or who had a history of an inhibitor for <5 years (n = 61) were excluded (Figure). There were 614 participants with a history of an inhibitor for at least 5 years and who participated in the CC registry between 2013 and 2017 who were included in the analyses. The 2013 to 2017 timeframe was chosen to eliminate emicizumab's potential influence on ITI treatment decisions; the Food and Drug Administration approved emicizumab in late 2017 [12]. The 5-year age and duration of inhibitor criteria were chosen to ensure that there was ample time to initiate ITI, thereby limiting the impact of practice variation between starting ITI immediately and delaying ITI initiation until the inhibitor titer has declined, as well as to have some time to evaluate ITI response. A history of an inhibitor was defined as having documentation of 2 or more positive inhibitor titers (>1 Nijmegen–Bethesda units or ≥0.5 chromogenic Bethesda units) or at least 1 positive inhibitor titer and inhibitor-related treatment (ITI, bypassing therapy use, or immune modulation therapy as defined by the HTC). The years since inhibitor onset was calculated as the time between the age that an inhibitor was first detected and the age at the initial CC visit form. There were 86 participants who were missing their age of inhibitor onset but were included because they were aged >18 years, thereby likely to have had their inhibitor for >5 years.

The primary outcome of the study was ITI treatment, which was ascertained on initial CC forms with the following question: "Does the patient have a history of immune tolerance induction (ITI)?" If ITI information was missing on the initial form, receipt of ITI was based on subsequent surveillance visit forms. Participants' self-reported race and ethnicity was our primary independent variable and was coded as Hispanic, non-Hispanic (NH) White, NH Black, Asian, and other. Race and ethnicity were considered as 1 variable because health inequities are likely a function of being in a minoritized group, whether it be a racial or ethnic group. Sociodemographic and clinical factors (the age at which an inhibitor was first detected, age when a person entered the registry, the year that an inhibitor was detected, and pre-ITI peak inhibitor value), measures of geographic access (driving distance and travel time), as well as HTC characteristics (volume and region) were also considered. A participant's peak inhibitor titer was based on the highest titer prior to ITI and grouped as ≤5, >5 to 200, and >200 Bethesda units/mL [13]. Driving distance and travel time were defined as the distance and miles between a participant's zip code and HTC zip code as determined by Google Maps application program interface, respectively [14]. HTC volume was defined as the number of people with severe hemophilia A seen at an HTC over the study period and was coded as low (<40 people) and high (≥40 people); these cutoff points were based on European principals of hemophilia care [15]. There are 10 HTC regions that were assigned a letter (A-J) with a random letter generator; HTC region was examined descriptively, and it was not considered in models due to small sample sizes across the 10 regions. History of infection with hepatitis C virus (HCV) or HIV was also examined in descriptive analyses but was not considered in models as they were highly dependent on the participant's age.

Sociodemographic, clinical, access, and HTC characteristics according to race and ethnicity and ITI treatment were compared with chi-squared, Fisher's exact, and Kruskal–Wallis tests. Logistic regression models with predicted marginals were used to estimate unadjusted and adjusted prevalence ratios of ITI treatment and corresponding 95% CIs. Adjusted models accounted for racial and ethnic group, sociodemographic characteristics, clinical characteristics, access, and HTC characteristics. We also conducted post hoc analyses in a subgroup of participants whose inhibitors were detected at ages ≤5 years to determine if there were potential racial and ethnic disparities among a group of participants where ITI treatment is anticipated to be especially common and to better control for age at inhibitor detection. All analyses were conducted with SAS version 9.4 (SAS Institute Inc) and SUDAAN software (RTI International). The data

TABLE 1 Characteristics according to immune tolerance induction treatment among people with severe hemophilia A with an inhibitor, Community Counts 2013 to 2017.

Characteristic	All people with severe hemophilia A with an inhibitor included in the study (*n* = 614)				People with severe hemophilia A with an inhibitor that was detected at ≤5 years of age (*n* = 422)			
	Total	No ITI	ITI	*P* value	Total	No ITI	ITI	*P* value
	N (%)	*N* (%)	*N* (%)		*N* (%)	*N* (%)	*N* (%)	
Total	614 (100)	91 (14.8)	523 (85.2)		422 (100)	30 (7.1)	392 (92.9)	
Race and ethnicity				.66				.007
White	343 (56.4)	46 (13.4)	297 (86.6)		226 (53.6)	7 (3.1)	219 (96.9)	
Black	120 (19.7)	20 (16.7)	100 (83.3)		79 (18.7)	8 (10.1)	71 (89.9)	
Hispanic	112 (18.4)	19 (17)	93 (83)		85 (20.1)	13 (15.3)	72 (84.7)	
Asian	30 (4.9)	6 (20)	24 (80)		24 (5.7)	-	-	
Other	-	-	-		-	-	-	
Missing	6 (1)	-	6 (100)		-	-	-	
Age at inhibitor detection				<.001				-
≤5 y	422 (68.7)	30 (7.1)	392 (92.9)		-	-	-	-
6-19 y	58 (9.4)	16 (27.6)	42 (72.4)		-	-	-	-
20-39 y	46 (7.5)	17 (37)	29 (63)		-	-	-	-
Missing	88 (14.3)	28 (31.8)	60 (68.2)		-	-	-	-
Age during the study				<.001				.002
5-19 y	320 (52.1)	23 (7.2)	297 (92.8)		301 (71.3)	20 (6.6)	281 (93.4)	
20-39 y	220 (35.8)	27 (12.3)	193 (87.7)		115 (27.3)	7 (6.1)	108 (93.9)	
40+ y	74 (12.1)	41 (55.4)	33 (44.6)		6 (1.4)	-	-	
Pre-ITI peak inhibitor (BU/mL)				.046				.13
≤5	94 (15.3)	6 (6.4)	88 (93.6)		77 (18.2)	-	73 (94.8)	
>5-200	289 (47.1)	50 (17.3)	239 (82.7)		208 (49.3)	16 (7.7)	192 (92.3)	
>200	112 (18.2)	20 (17.9)	92 (82.1)		77 (18.2)	9 (11.7)	68 (88.3)	
Missing	119 (19.4)	15 (12.6)	104 (87.4)		60 (14.2)	-	59 (98.3)	
Driving distance (miles)				.50				.60
≤15	186 (30.3)	25 (13.4)	161 (86.6)		127 (30.1)	7 (5.5)	120 (94.5)	
16-30	139 (22.6)	17 (12.2)	122 (87.8)		104 (24.6)	8 (7.7)	96 (92.3)	
31-90	175 (28.5)	28 (16)	147 (84)		113 (26.8)	7 (6.2)	106 (93.8)	
>90	114 (18.6)	21 (18.4)	93 (81.6)		78 (18.5)	8 (10.3)	70 (89.7)	
HTC size[a]				.015				<.001
<40	246 (40.1)	47 (19.1)	199 (80.9)		21 (13.4)	136 (86.6)	21 (13.4)	
≥40	368 (59.9)	44 (12)	324 (88)		9 (3.4)	256 (96.6)	9 (3.4)	
HIV				<.001				.002
No	565 (92)	70 (12.4)	495 (87.6)		403 (95.5)	27 (6.7)	376 (93.3)	
Yes	31 (5)	15 (48.4)	16 (51.6)		8 (1.9)	3 (37.5)	5 (62.5)	
Missing	18 (2.9)	6 (33.3)	12 (66.7)		11 (2.6)	0 (0)	11 (100)	
HCV				<.001				.017
No	462 (75.2)	33 (7.1)	429 (92.9)		373 (88.4)	23 (6.2)	350 (93.8)	
Yes	137 (22.3)	53 (38.7)	84 (61.3)		39 (9.2)	7 (17.9)	32 (82.1)	

(Continues)

TABLE 1 (Continued)

Characteristic	All people with severe hemophilia A with an inhibitor included in the study (*n* = 614)				People with severe hemophilia A with an inhibitor that was detected at ≤5 years of age (*n* = 422)			
	Total	No ITI	ITI	*P* value	Total	No ITI	ITI	*P* value
Missing	15 (2.4)	5 (33.3)	10 (66.7)		10 (2.4)	0 (0)	10 (100)	
HTC region				.62				
A	41 (6.7)	-	37 (90.2)		23 (5.5)	-	-	
B	60 (9.8)	10 (16.7)	50 (83.3)		38 (9)	-	-	
C	75 (12.2)	10 (13.3)	65 (86.7)		58 (13.7)	-	-	
D	77 (12.5)	13 (16.9)	64 (83.1)		60 (14.2)	-	-	
E	46 (7.5)	-	40 (87.0)		32 (7.6)	-	-	
F	24 (3.9)	-	22 (91.7)		20 (4.7)	-	-	
G	57 (9.3)	13 (22.8)	44 (77.2)		36 (8.5)	-	-	
H	101 (16.4)	11 (10.9)	90 (89.1)		61 (14.5)	-	-	
I	77 (12.5)	14 (18.2)	63 (81.8)		58 (13.7)	-	-	
J	56 (9.1)	8 (14.3)	48 (85.7)		36 (8.5)	-	-	
	Median (IQR)	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	Median (IQR)	
Age at inhibitor detection (y)	2 (1-4)	6 (2-22)	2 (1-4)	<.001	1 (1-2)	2 (1-3)	1 (1-2)	.002
Age during the study (y)	19 (12-38)	34 (19-52)	17 (11-25)	<.001	14 (10-20)	14 (12-24)	14 (10-20)	.143
Pre-ITI peak inhibitor (BU/mL)	40 (8-182.5)	65 (17-474)	35.2 (6.3-177.2)	.012	35 (6.3-177)	58.8 (19-485)	33 (6-160)	.095
Driving distance (miles)	27.1 (13-67.2)	34.4 (14.2-86.7)	26.6 (12.9-62.2)	.125	26.6 (12.6-60.7)	29.5 (16-100)	26 (12-60)	.548

Chi-squared tests were used to test differences in ITI treatment for categorical variables. Differences in continuous variables were tested with the Kruskal–Wallis test. Data not presented due to small sample size are noted as "-."

BU, Bethesda units; HCV, hepatitis C virus; HTC, hemophilia treatment center; ITI, immune tolerance induction.

[a]Computed as the number of people with severe hemophilia A in the Community Counts registry.

that support the findings of this study were used under a data use agreement with CDC, and there are restrictions to data access. However, data are available from the authors upon reasonable request and with permission of the CDC.

3 | RESULTS

3.1 | Participant characteristics

Among 614 participants included in the study, slightly over half (56.4%) were NH White, 19.7% were NH Black, 18.4% were Hispanic, and 4.9% were Asian. The average age at inhibitor detection was 5.6 years (SD, 9.9 years), and it was lower in NH Black, Hispanic, and Asian participants relative to NH White participants (Supplementary Table S1). The average age when entering the registry was 22.2 years (SD, 14.2 years; range, 5-79 years), and it was slightly higher among NH White participants relative to other racial and ethnic groups. Among those who had peak inhibitor values recorded, 82.0% had a high-titer inhibitor (>5 Bethesda units/mL); this proportion was lower among Hispanic (77.4%) and NH White (78.9%) participants compared to NH Black participants (91.8%) (Supplementary Table S1). Over half of participants were seen at higher-volume HTCs (≥40 people with severe hemophilia A) (59.9%); this proportion was higher among NH Black (64.2%) than Hispanic (52.7%) and NH White (58.6%) participants, but differences were not statistically significant (Supplementary Table S1). A history of HIV or HCV infection was seen in 5.0% and 22.3% of participants, respectively, and the majority of those with HCV or HIV infection were aged ≥30 years (HIV, 83.9%; HCV, 86.1%) when entering the registry.

3.2 | Race and ethnicity and receipt of ITI treatment

Most (85.2%) people with an inhibitor history received ITI. Participants who were Asian, NH Black, or Hispanic had slightly lower proportions of ITI treatment, relative to NH White participants, but these differences were not statistically significant in unadjusted analyses (Tables 1 and 2). In analyses accounting for clinical factors, driving distance, HTC size, and other factors, NH Black and Hispanic participants were statistically significantly less likely to have received ITI relative to NH White participants—9% and 12% respectively. Asian participants were nonsignificantly less likely to receive ITI in adjusted analyses. When all NH and non-White participants were grouped together, receipt of ITI was 12% lower when compared to that among NH White participants. In analyses restricted to participants whose

TABLE 2 Unadjusted and adjusted prevalence ratios of immune tolerance induction among people with severe hemophilia A with inhibitor, Community Counts registry 2013 to 2017.

	All people with severe hemophilia A with an inhibitor in the study (n = 614)[a]		People with severe hemophilia A with an inhibitor that was detected at ≤5 years of age (n = 422)[b]	
Race and ethnicity	Unadjusted PR (95% CI)	aPR (95% CI)	Unadjusted PR (95% CI)	aPR (95% CI)
White	1.00	1.00	1.00	1.00
Asian	0.92 (0.77-1.11)	0.82 (0.66-1.01)	0.95 (0.84-1.07)	0.89 (0.74-1.07)
Black	0.96 (0.88-1.05)	0.91 (0.84-0.99)	0.93 (0.86-1.00)	0.91 (0.84-0.99)
Hispanic	0.96 (0.87-1.05)	0.84 (0.75-0.93)	0.87 (0.80-0.96)	0.84 (0.77-0.92)
Non-White[c]	0.96 (0.90-1.03)	0.88 (0.81-0.94)	0.91 (0.86-0.96)	0.89 (0.83-0.95)

aPR, adjusted prevalence ratio; PR, prevalence ratio.
[a]Mainly included race and ethnicity, age at inhibitor detection, current age, pre–immune tolerance induction peak inhibitor, driving distance, and hemophilia treatment center volume. People with missing race and ethnicity (n = 6) were not included due to model instability.
[b]Models are restricted to people with severe hemophilia A with inhibitor whose inhibitors were detected when they were aged <5 years. Model included race and ethnicity, current age, pre–immune tolerance induction peak inhibitor, driving distance, and hemophilia treatment center volume.
[c]An additional model that was run to produce estimates grouping Asian, Black, Hispanic, and other races and ethnicities as non-White was included.

inhibitor was detected when they were aged ≤5 years, the proportion with ITI treatment was higher (92.9%), and racial and ethnic differences in ITI treatment remained (Table 1).

3.3 | Other characteristics associated with receipt of ITI

In unadjusted and adjusted analyses, those who were older during the study period (aged ≥40 vs 5-19 years) were less likely to have received ITI, relative to their younger counterparts (Table 1 and Supplementary Table S2). The time period in which an inhibitor was detected was considered in a separate model; in these analyses, history of ITI treatment was significantly lower among people whose inhibitor was detected in or before 1995 compared to those whose inhibitor was detected in 2006 or later. The age at inhibitor detection was significantly associated with a history of ITI treatment in unadjusted analyses, but not after accounting for current age (Supplementary Table S2).

In terms of HTC characteristics, a history of ITI treatment was consistently lower among HTCs with <40 vs ≥ 40 people with severe hemophilia A in unadjusted and adjusted models (Supplementary Table S2). The proportion receiving ITI ranged from 77.2% to 90% across the 10 HTC regions, but these differences were not statistically significant based on chi-squared statistics (Table 1). Driving distance and travel time were not significantly associated with ITI treatment.

4 | DISCUSSION

Given the growing awareness that race and ethnicity can impact access to care, and the importance of inhibitor eradication in long-term care of people with severe hemophilia A, we sought to understand the impact of race and ethnicity on receipt of ITI. In this study, most participants received ITI (>85%); however, receipt of ITI was slightly less common among NH Black (83.3%) and Hispanic participants (83%) and those seen at HTC with <40 people with severe hemophilia A (81%) in the CC registry.

The association with race and ethnicity and receipt of ITI appears to be robust and was also present on subgroup analysis for the subset of study participants whose inhibitor was detected at <5 years of age. Furthermore, when the analysis was limited to those with an inhibitor detected at <5 years of age at larger centers (2 characteristics strongly tied to receipt of ITI), 100% of NH White (n = 137/137) participants received ITI, whereas only 89.7% (n = 52/58) of NH Black participants received ITI (chi-square $P < .001$; data not shown). Lower rates of ITI receipt may be due to perceptions that Black or Hispanic families are not able to undertake the intensive and complex treatment required for successful ITI. This may be due to perceived barriers present because of a physician's implicit bias [16] or real barriers resulting from poverty and other socioeconomic stressors. It may also be that ITI is discussed by the healthcare team and offered to people with hemophilia and their family, but families may choose not to participate due to lack of trust in the healthcare system, which has been widely documented in Black communities [17], or due to structural barriers such as lack of paid sick leave, which is more common in Black and Hispanic persons in the general population [18]. Furthermore, minoritized racial and ethnic groups may also experience language and resulting healthcare literacy barriers that may impact the healthcare team's prescription of ITI or the willingness by the patient/patient's family to undertake ITI [19,20].

Other studies have noted racial and ethnic disparities in hemophilia treatment and outcomes. On bivariable analysis of the Hemostasis and Thrombosis Research Society database, similar racial and ethnic differences in receipt of ITI and success of ITI were also noted [21]. Another study of 80 young adults found that non-White persons were more likely to suffer from chronic pain and have lower quality of life scores than White persons; these differences persisted after adjustment for age, clinical characteristics, insurance status, and family educational level [22]. In other disease states, there are similar

disparities in receipt of therapies such as direct acting antivirals for the treatment of HCV [23], autologous transplantation for lymphoma [23], and treatment for breast cancer [24,25].

People with severe hemophilia with an inhibitor treated at smaller HTCs were found to be less likely to receive ITI. This may be an artifact of smaller centers being less likely to enroll subjects in the CC registry. It may also be due to seeing fewer people with hemophilia and, thus, having less experience and comfort in undertaking ITI. In other disease areas, such as diabetes, the size of the treating center has been shown to impact outcomes, with the smallest and largest centers having worse outcomes compared with medium sized centers [26]. HTC regions may benefit from more formalized channels of support between larger and smaller HTCs in a hub and spoke model [15]. Although not statistically significant in the current study, exploring regional variation is important as it provides an opportunity for discussion and dissemination of best practices. On analysis of data drawn for Center for Medicare and Medicaid Services, regional variation was identified as impacting outcomes of several chronic diseases [27]. Although it is not currently a standard practice among US HTCs to benchmark quality measures as in other chronic disease states, such as cystic fibrosis, analysis of regional variations provides an opportunity to identify mechanisms to improve care.

The strength of the study is that the CC registry includes a large number of people with hemophilia across the United States, allowing for evaluation of racial and ethnic disparities. A limitation of the data used in this study is that it only includes those who authorize participation in the registry; however, among people with severe hemophilia A, the racial and ethnic distribution in the registry is similar to those seen at HTCs [28]. Our study population included a slightly higher proportion of Black males (20%) compared to what is observed in the CC registry (15%), which is to be expected in a cohort of people with severe hemophilia A complicated by inhibitor given the higher risk of inhibitor among Black and Hispanic people with severe hemophilia A [29]. Thus, the specific results of this study are likely generalizable to the US HTC population. A limitation is that the data related to ITI were retrospectively reported to the registry, and thus, there may be recall bias. The findings were consistent on subgroup analyses that included only subjects with inhibitor onset prior to 5 years of age and were independent of the year of inhibitor detection; thus, we do not believe that a large degree of ITI misclassification is at play. About 19% of participants in our study were missing a peak inhibitor titer and those with a missing titer were older. However, the missing peak inhibitor titer values did not vary by racial and ethnic group. We did not have all characteristics related to prediction of ITI success, such as pre-ITI inhibitor titer, which may influence whether ITI is prescribed or not. This analysis is also unable to tease apart who was offered and declined ITI vs who was not offered ITI. Health insurance at the time of ITI was not collected; therefore, we were unable to measure the potential influence of access to care on ITI. Furthermore, HTC region was only examined descriptively due to a limited sample size; thus, we were unable to tease out potential regional differences in clinical practice and participants' experience of bias or explore societal barriers that may vary by region.

5 | CONCLUSION

In the modern era of hemophilia care, but prior to availability of emicizumab, the majority of people with severe hemophilia A with an inhibitor were receiving ITI, which is considered the standard of care. Despite this high level of ITI use, we identified small but statistically significant differences in care among racial and ethnic groups, with NH Black and Hispanic participants receiving ITI less often. The process of providing care to the people with hemophilia has many challenges that may lead people with hemophilia and providers away from best practices. These same challenges may exist in other complex chronic hematological conditions and in other parts of the world where systemic racial and ethnic disparities exist. The barriers to equitable care may persist even with gene therapy, where bias may occur when considering who can and cannot meet the demands of frequent monitoring in the early postinfusion period. Understanding that racial disparities occur is an important first step toward addressing them.

ACKNOWLEDGMENTS

The data from Community Counts used for this publication were supported by a cooperative agreement (cooperative agreement number DD001155), funded by the Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC, the Department of Health and Human Services, American Thrombosis and Hemostasis Network (ATHN), or the Hemophilia Treatment Center Network. Data reported in this publication (journal article, etc.) were collected through collaboration of ATHN, CDC, and the Hemophilia Treatment Center Network using ATHN Study Manager.

FUNDING

The Community Counts registry is funded by the Centers for Disease Control and Prevention. The writing of this manuscript had no direct funding.

ETHICS STATEMENT

This study was considered nonhuman subject research by the Emory University Institutional Review Board.

AUTHOR CONTRIBUTIONS

C.L.K. and A.B.P. conceived the project and created the analysis plan. S.A.F. and C.L.K. performed the analysis. S.A.F. and C.L.K. drafted the manuscript. A.B.P. reviewed the analysis and contributed to and finalized the manuscript.

RELATIONSHIP DISCLOSURE

C.L.K. has received honoraria for participation in advisory boards from Biomarin, Pfizer, Genentech, and Spark. S.A.F. and A.B.P. have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2023.102251