

## Background

- Severe Haemophilia A (HA) is a congenital bleeding disorder characterised by the absence of Factor VIII (FVIII; <1 IU/dL), causing prolonged and repeated trauma-related and/or spontaneous intra-articular bleeding events. Repeated occurrence of intra-articular bleeding often results in haemophilia arthropathy, characterized by chronic inflammation, progressive joint deformity, chronic joint pain and varying levels of disability<sup>1</sup>
- To avoid the recurrence of bleeding episodes and prevent joint health deterioration, haemophilia A is currently managed with prophylactic FVIII infusions (2–3 times a week) or subcutaneous administration of NFT (1–4 times a month)
- Novel HA treatment approach, such as gene therapy or non-factor subcutaneous therapies offer possible reduction in clinical and treatment burden of HA, however, evidence on supplemental use of FVIII use in people treated with non-factor therapies (NFT) or gene therapy is scarce and warrants exploration
- To that effect, the aim of this study was to conduct an expert knowledge elicitation using the Sheffield Elicitation Framework (SHELF) with clinical experts from the UK to elicit the potential proportion of non-inhibitor severe HA patients requiring additional FVIII infusions while receiving NFT prophylaxis or after having received gene therapy, across differing levels of physical activity and joint health

## Methods

- A group of UK haemophilia and haematology clinical experts participated in a group meeting with the aim of estimating, through quantitative elicitation, any requirement for FVIII infusions in relation to breakthrough bleeding or as a preventative measure
- The cohort of interest was non-inhibitor severe HA patients participating in ‘low to moderate’ or ‘moderate to high’ physical activity
- The estimates and the uncertainty around the estimates was quantified using the SHELF methodology, which constructs a probability distribution representing expert input with a transparent and rigorous approach
- The quartile method was employed to ascertain variability and uncertainty on the parameters of interest<sup>3,4</sup>
- Expert opinion was quantified via a combined group workshop held in December 2022
- The exercise comprised two core-outcome questions:
  - The proportion of patients needing on-demand (OD) FVIII infusions** for any reason; and
  - In those requiring OD FVIII, **the number of FVIII infusions required** for any reason in a six month period
- The experts were asked to respond to these two questions accounting for two modifier parameters, chronic joint damage and physical activity:
  - Two-level chronic joint damage modifier** – via the problem joint metric which is defined as “a joint affected by chronic pain and/or limited range of motion due to compromised joint integrity (i.e., suffering from chronic synovitis, and/or haemophilic arthropathy), with or without recurrent bleeding”<sup>2</sup>
  - Two-level physical activity modifier** – ‘low to moderate’ (activities seldom performed that cause small increases in breathing and heart rate, with most of time spent sitting) and ‘moderate to high’ (activities or sports performed on a regular basis that may cause moderate or high increases in breathing and heart rate)

## Results

- The estimated proportion of patients requiring supplemental factor infusions ranged from 12.2% (average elicited mean) for GTx patients with no PJs and low/moderate activity to 27.2% for patients receiving NFT with 1+ PJs and moderate/high activity (Table 1)

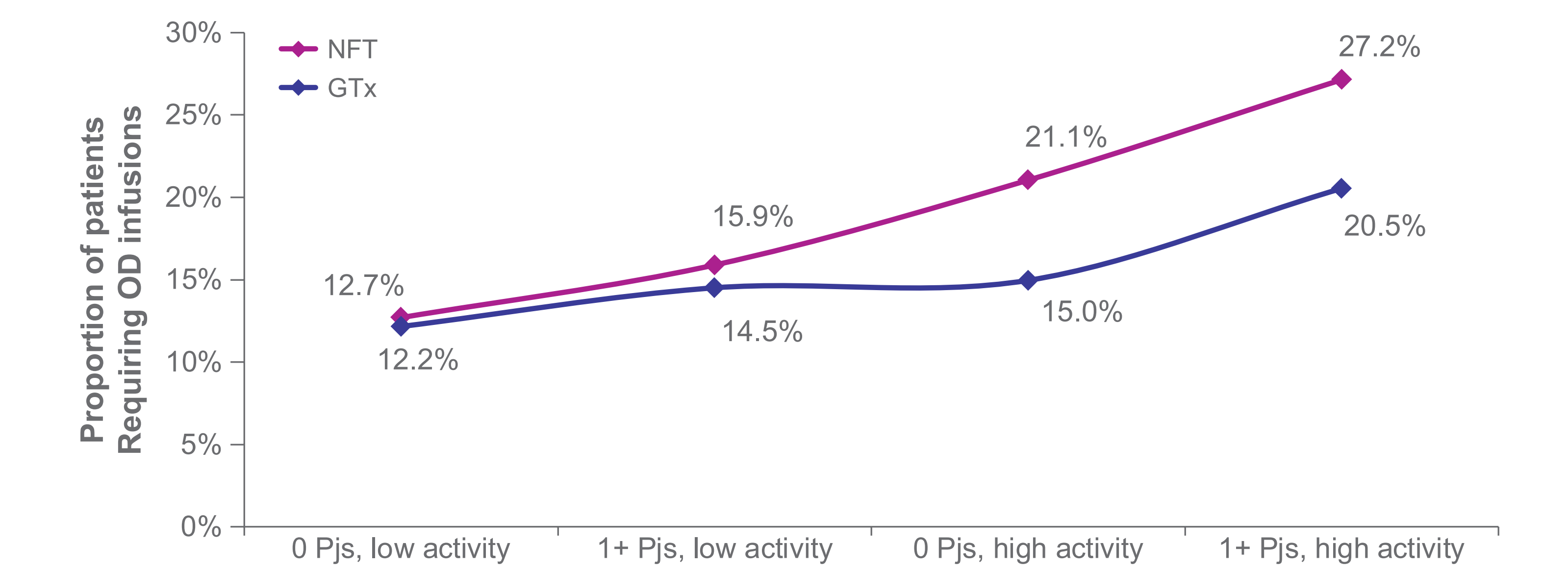
Table 1. Proportion of patients requiring OD infusions, elicited individual and pooled means

Treatment	Modifiers	Individual elicited mean (SD)				Pooled mean
		A	B	C	D	
NFT	0 PJs, LPA	17.9 (16.1)	10.0 (7.4)	8.5 (7.4)	14.4 (6.0)	12.7
GTx	0 PJs, LPA	14.2 (9.8)	10.0 (7.4)	4.4 (3.2)	20.0 (7.4)	12.2
NFT	1+ PJs, LPA	14.2 (9.8)	18.6 (11.5)	10.8 (7.8)	20.0 (7.4)	15.9
GTx	1+ PJs, LPA	15.0 (7.4)	10.0 (7.4)	4.4 (3.2)	28.6 (11.5)	14.5
NFT	0 PJs, HPA	22.9 (16.1)	15.0 (7.4)	10.8 (7.8)	35.5 (20.8)	21.1
GTx	0 PJs, HPA	16.9 (9.2)	11.4 (11.5)	4.4 (3.2)	27.1 (16.1)	15.0
NFT	1+ PJs, HPA	27.9 (16.1)	21.4 (11.5)	13.8 (7.8)	45.5 (20.8)	27.2
GTx	1+ PJs, HPA	20.0 (7.4)	16.4 (11.5)	7.1 (5.5)	38.6 (11.5)	20.5

NFT, Non-factor therapy; GTx, Gene therapy; PJ, problem joint; LPA, Low/moderate physical activity; HPA,moderate/high physical activity

- Individual estimates were consistent for NFT at low physical activity levels, with more variability amongst GTx
- At high activity levels, increased variability was observed in general, particularly in the NFT group, which also showed higher proportions, compared to the GTx group (Figure 1)

Figure 1. Proportion of patients requiring OD infusions, across joint damage and activity levels



- Among those requiring additional FVIII infusions, the number of infusion ranged from 4.5 for GTx patients with no PJs and low/moderate activity to 17.5 for patients receiving NFT and moderate/high activity (Table 2)

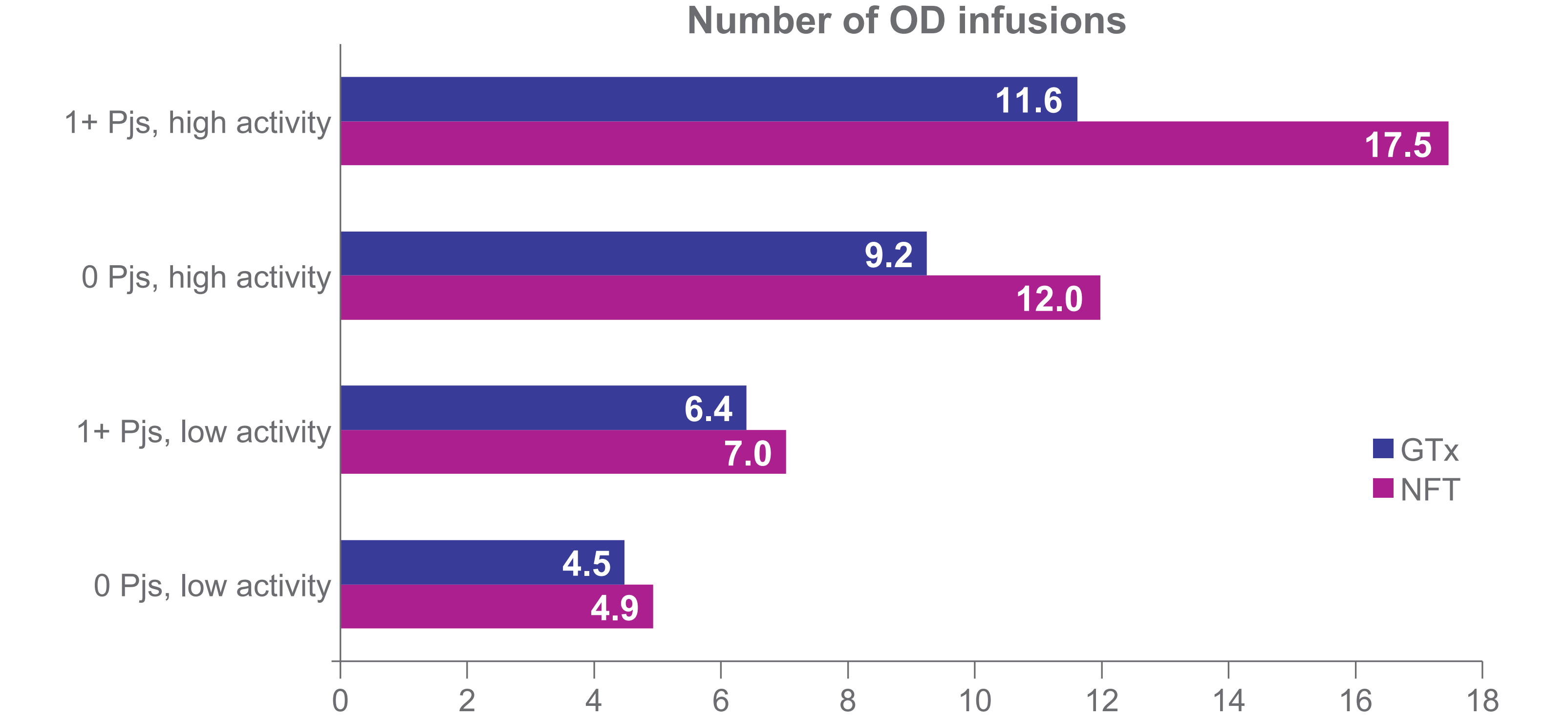
Table 2. Number of OD infusion needed (6-month period, any reason), elicited individual and pooled means

Treatment	Modifiers	Individual elicited mean (SD)				Pooled mean
		A	B	C	D	
NFT	0 PJs, LPA	10.0 (23.1)	2.1 (1.2)	1.0 (1.4)	6.6 (4.6)	4.9
GTx	0 PJs, LPA	5.9 (5.5)	1.5 (0.7)	1.0 (1.4)	9.5 (6.1)	4.5
NFT	1+ PJs, LPA	12.5 (24.3)	3.0 (1.5)	2.0 (1.5)	10.6 (4.6)	7.0
GTx	1+ PJs, LPA	9.5 (7.4)	1.9 (1.2)	1.1 (1.3)	13.2 (6.4)	6.4
NFT	0 PJs, HPA	22.9 (23.0)	3.0 (1.5)	2.0 (1.5)	20.0 (5.9)	12.0
GTx	0 PJs, HPA	17.9 (16.1)	2.5 (2.1)	1.0 (1.4)	15.6 (6)	9.2
NFT	1+ PJs, HPA	32.9 (23)	3.9 (1.9)	2.0 (1.5)	31.1 (12.1)	17.5
GTx	1+ PJs, HPA	21.4 (18.8)	3.1 (2.6)	1.1 (1.3)	20.9 (5.5)	11.6

NFT, Non-factor therapy; GTx, Gene therapy; PJ, problem joint; LPA, Low/moderate physical activity; HPA, Moderate/high physical activity

- The data showed some variation across experts and, similarly to the proportion estimations, in particular in the high physical activity cohort (Figure 2)

Figure 2. Number of OD infusions (6-month period, any reason), across joint damage and activity levels



- Increased requirement for infusion was observed in the NFT cohort with high physical activity, when compared to GTx. The groups were comparable at low physical activity levels

## Conclusions

- The expert elicitation indicated the potential extent to which factor infusions may be required for the UK severe non-inhibitor HA population treated with NFTs or GTx
- The NFT group had, according to the experts, a larger proportion of patients requiring OD FVIII infusions across all scenarios
  - A larger difference was noted between NFT and GTx in high physical activity scenarios
  - In the NFT cohort, the proportion seemed to be more affected by the presence of joint damage than the GTx cohort
- When evaluating the number of infusions, albeit with small differences at low physical activity levels, infusion requirement was estimated to be higher across all scenarios for NFTs
- A wider gap was observed at higher physical activity levels, with the NFT cohort requiring almost 30% more infusions than GTx in high physical activity scenarios
  - The presence of joint damage affected both treatment groups, with NFT seeing more marked increase in the requirement of OD infusions, when compared to GTx
  - The results indicated that a proportion of patients in both treatment groups are expected to require additional OD FVIII infusions, also suggesting that novel treatments may reduce some of the remaining unmet need in the non-inhibitor SHA population

### References

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