

## ORIGINAL ARTICLE

# ‘We want it all’: ART preferences assessed by Desirability of Outcome Ranking

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**Abstract**

**Objectives:** Understanding how people living with HIV (PLWH) view antiretroviral therapy (ART) prescribing choices is fundamental to patient-centred care. We used the Desirability of Outcome Ranking (DOOR) approach to explore patient ART preferences.

**Methods:** Seventy-four PLWH entered the study, 20 into the ‘pilot study’, and 54 in the ‘comparative study’. Participants ranked five different hypothetical patient stories by desirability. Each story comprised five narrative lines, each line addressing one treatment characteristic drawn from one of five pre-selected domains (treatment failure, treatment difficulty, adverse effects, long-term complications, life events). Narrative lines could be favourable or adverse. In the pilot study the number of adverse domains varied from one to five. Comparative study stories were fixed at two adverse versus three favourable domains, to test the relative ranking of different domains.

**Results:** The pilot study identified a relationship between the number of adverse domains and rank ( $R^2 = 0.54$ ;  $p < 0.0001$ , Friedman test), however pairwise differences in ranking were not significant beyond three adverse domains. In the comparative study, all domains were ranked equally across the cohort ( $p = 0.88$ ; Friedman test). In pre-defined demographic subgroup analyses, women ranked the ‘treatment failure’ domain significantly less desirable than men ( $p = 0.0014$ , Mann–Whitney test).

**Conclusions:** People living with HIV appear to care equally about all aspects of ART. The observation that male and female PLWH have different treatment priorities merits further investigation in larger studies. Interindividual differences highlight the importance of individualized shared decision-making and treatment personalization. DOOR may have a role as a pre-treatment assessment tool as well as a research technique.

**KEYWORDS**

antiretroviral therapy, HIV, patient choice, shared decision-making

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## INTRODUCTION

The development of effective antiretroviral therapy (ART) has transformed HIV infection from a fatal disease into a manageable chronic condition [1–4]. Over the last three decades, improvements in ART efficacy and wider treatment availability have led to a steady increase in the life expectancy of people living with HIV (PLWH) [3, 5, 6]. Ease of administration and greater adherence may also have contributed. Early ART regimens were harder to take and had a significant adverse effect burden [5], and hence patients would often tolerate certain adverse treatment characteristics if it allowed them to take a treatment with a preferred attribute; for example, being able to take a single-tablet regime might have meant accepting certain side-effects. The development of novel ART has overcome some of these problems and patients can now benefit from drugs with better side-effect profiles, simpler dosing and a reduced risk of virological failure [2, 7–9]. This continual development has provided PLWH with over 30 different ART drugs to choose from, available in a variety of combinations [10].

The availability of so many different types of antiretrovirals poses the question of how the optimal regimen for a particular patient should be chosen. It is evident that patient involvement in treatment decision-making is both implicitly appropriate – ‘No decision about me, without me’ [11] – and leads to increased satisfaction and better outcomes [12–16]. Although modern HIV guidelines acknowledge the importance of establishing patient preferences [17], evidence shows that, in practice, shared decision-making (SDM) is often limited. One study found that only 10% of discussions between PLWH and their doctors fulfilled all predetermined SDM criteria [18]. In a study from Austria, only 44% patients said they felt ‘totally involved’ in treatment decisions [19]. Some PLWH interviewed in a primary care setting felt they had little autonomy [20]. The complexity of ART combinations, limitations on availability driven by costs or purchasing agreements, and local treatment algorithms may limit the extent to which patients can be prescribed the drug they desire the most. Furthermore, the rightly endorsed use of multidisciplinary team meetings (MDTs) for ART decision-making means that clinical staff must convey to the meeting the wishes of the patient second-hand if they are to be heard at all.

One way to make the patient's voice heard more in HIV management decisions is by increasing understanding of patient preferences for specific treatment characteristics. This has been the objective of several investigations. Gazzard et al. looked at the ART preferences of a large cohort of European PLWH using a discrete choice experiment (DCE) [21]. They found that

adverse effects had the biggest impact on patients' treatment choice. Similarly, ranking exercises carried out by Ostermann et al. showed that the lowest ranked hypothetical ART regimens were those characterized by short- and long-term adverse effects [22]. Sijstermans et al., also using DCE methodology, demonstrated that PLWH want treatments that do not prevent them from partaking in physical activity [23]. Trade-off exercises carried out by Yelverton et al. demonstrated that PLWH accepted higher pill burdens in exchange for fewer adverse effects [24]. By contrast, Eaton et al. [25] and Hendriks et al. [26] found patients were most concerned about outcomes, life expectancy and treatment accessibility and costs. Although these studies have provided us with an invaluable insight into what PLWH want from their treatment, there are limitations. For example, direct questioning may bias towards one attribute of treatment over others whilst previous ranking exercises have involved only a single or a limited number of ART attributes.

One recently developed tool to capture generic preferences for alternative treatment options is the Desirability of Outcome Ranking (DOOR) approach. This conflates treatment attributes into domains and uses ranking of narratives to indirectly capture the desirability of different treatment characteristics. To date, DOOR has only been used to investigate alternative antibiotic regimens [27, 28], but as it is a generic tool, it can be tailored to many different settings. In this study we applied the DOOR methodology to investigate which ART attributes matter most to PLWH. We constructed narratives with favourable and adverse elements corresponding to different domains of treatment characteristic, then asked participants to rank them in order of desirability. We initially performed a ‘pilot’ study to test the feasibility of the DOOR approach in this setting and to determine whether participants would rank narratives in order of the number of adverse domains. Subsequently, we completed a larger ‘comparative’ study to test the hypothesis that ‘some treatment attributes are more desirable to PLWH than others’. Finally, we compared responses by demographic subgroups.

## METHODS

### Participants, setting and ethics

During recruitment periods, consecutive attendees at a London HIV clinic were invited to participate. Inclusion criteria were: age  $\geq 18$  years old; currently on ART, or considering ART (although none were in the latter category); and able to understand questionnaires in English. At first, 20 participants were recruited into the pilot

<p>Deep (fictional patient name)</p> <ul style="list-style-type: none"> <li>• Treatment difficulty (favourable option)</li> <li>• Long-term complications (favourable option)</li> <li>• Adverse effects (favourable option)</li> <li>• Treatment failure (adverse option)</li> <li>• Life events (adverse option)</li> </ul>
<p>Adam (fictional patient name)</p> <ul style="list-style-type: none"> <li>• Life events (favourable option)</li> <li>• Adverse effects (favourable option)</li> <li>• Long-term complications (adverse option)</li> <li>• Treatment difficulty (favourable option)</li> <li>• Treatment failure (adverse option)</li> </ul>
<p>Bernard (fictional patient name)</p> <ul style="list-style-type: none"> <li>• Treatment difficulty (favourable option)</li> <li>• Adverse effects (adverse option)</li> <li>• Treatment failure (favourable option)</li> <li>• Life events (favourable option)</li> <li>• Long-term complications (adverse option)</li> </ul>
<p>Edward (fictional patient name)</p> <ul style="list-style-type: none"> <li>• Long-term complications (favourable option)</li> <li>• Adverse effects (favourable option)</li> <li>• Life events (adverse option)</li> <li>• Treatment failure (favourable option)</li> <li>• Treatment difficulty (adverse option)</li> </ul>
<p>Charles (fictional patient name)</p> <ul style="list-style-type: none"> <li>• Treatment difficulty (adverse option)</li> <li>• Adverse effects (adverse option)</li> <li>• Long-term complications (favourable option)</li> <li>• Life events (favourable option)</li> <li>• Treatment failure (favourable option)</li> </ul>

**FIGURE 1** Example of comparative study storyboard layout. Each storyboard included five fictional stories of HIV patients describing their treatments, in random order. Each story consisted of five narrative lines, written in the third person, relating to the following treatment domains: treatment difficulty, treatment failure, long-term complication, adverse effect, life events. Each narrative line could be either adverse (shown in red) or favourable (shown in blue). Narrative lines were randomly ordered, as were the fictional patient names. Participants ranked stories by patient name from best (1) to worst (5). A worked example and the narrative line options are shown in the Supporting Information (Figures S2 and S3 respectively)

study. Pilot data and participant feedback were reviewed prior to proceeding with the design of and recruitment to the comparative study. Due to the lack of variance data, we were not able to perform an *a priori* power calculation to determine the optimal sample size for the study. For balanced narrative domain combinations, the sample size had to be divisible by 18; pragmatically, a sample size of 54 was chosen for this exploratory study.

The study was approved by the London-Brent Research Ethics Committee (ref. 20/PR/024). All participants gave written informed consent. The study period was between October 2020 and January 2022, with a pause for review of pilot study results before commencing the comparative study and interruptions to recruitment due to COVID-19 restrictions.

## Questionnaire

Based on previous studies using the DOOR methodology [27], we pre-defined five treatment domains: treatment difficulty, treatment failure, adverse effects, long-term complications and life events (impact of treatment on daily activities). Three alternative adverse options and one favourable option were drafted by the researchers for each domain (see Figures S2 and S3). Stories describing hypothetical ART regimens were constructed using random combinations of favourable or adverse options for each domain; these narrative lines were randomly ordered in each story. In the pilot study, each story had a different number of adverse domains (from one to five), whereas in the comparative study, stories each contained a fixed ratio of three favourable to two adverse domains. Five stories were included in a single ‘storyboard’ for both the pilot and comparative study, and each story was assigned a fictional patient name (see storyboard layout in Figure 1). Named stories were ordered non-alphabetically within storyboards.

Participants ranked stories from best (1) to worst (5) by writing down the fictional patient’s name assigned to each story in a response box. They were also asked to answer the open question ‘What would matter most to you?’ and to give study feedback in free text form. Demographic data were collected with a view to performing three pre-defined subgroup comparisons based on gender (male vs. female), age (above and below the median age) and self-declared ethnicity.

## Data analysis

Descriptive statistical analyses were carried out on demographic data and participant feedback. For the pilot study, the mean participant rank (MPR) was calculated for each domain. These were analysed by a Friedman test with multiple comparisons for significant differences in story ranking, and by linear regression analysis to identify the relationship between adverse domain number and story rank.

For the comparative study, weighted domain scores were calculated by multiplying the participant rank (1–5) by either a 1 (if the domain was adverse) or 0 (if the domain was favourable), and then summing these scores for each of the five domains. As each domain would occur in its ‘adverse’ option twice in each storyboard, the minimum weighted domain score (two best rankings) was 3 ( $1 \times 1 + 1 \times 2$ ) and the maximum (most adverse) was 9 ( $1 \times 4 + 1 \times 5$ ). Weighted domain scores were analysed by a Friedman test with multiple comparisons

TABLE 1 Pilot, comparative study and subgroup analysis results

Pilot	N	No. adverse domains	1	2	3	4	5	p-value (Q)
	20	MPR (SD)	1.55 (0.83)	1.80 (0.70)	3.65 (0.93)	3.75 (1.16)	4.25 (0.85)	< 0.0001 (49)
Comparative (all)	N	Domain	TD	TF	LTC	AE	LE	p-value (Q)
	54	MWDS (SD)	5.93 (1.88)	6.07 (1.95)	6.13 (1.95)	5.80 (1.85)	6.07 (1.65)	0.88 (1.2)
Comparative (subgroups)	N	Domain	TD	TF	LTC	AE	LE	p-value (Q)
Male	37	MWDS (SD)	6.38 (1.72)	5.54 (1.86)	6.22 (1.89)	5.89 (1.74)	5.97 (1.76)	0.61 (2.7)
Female	14	MWDS (SD)	5.14 (1.99)	7.50 (1.65)	5.57 (2.10)	5.64 (2.17)	6.14 (1.51)	0.10 (7.8)
Younger <sup>a</sup>	25	MWDS (SD)	5.60 (1.71)	6.32 (2.21)	6.52 (2.04)	5.08 (1.66)	6.48 (1.39)	0.09 (8.1)
Older <sup>a</sup>	27	MWDS (SD)	6.37 (1.96)	5.78 (1.65)	5.74 (1.77)	6.30 (1.82)	5.82 (1.78)	0.72 (2.1)
White	17	MWDS (SD)	6.29 (1.69)	5.35 (1.69)	6.12 (1.96)	5.76 (1.71)	6.47 (1.74)	0.43 (3.8)
Non-white	33	MWDS (SD)	5.76 (2.05)	6.30 (2.08)	6.24 (1.90)	5.85 (1.79)	5.85 (1.70)	0.76 (1.9)

Note: For the pilot study, data represent the mean participant rank (MPR) and standard deviation (SD) according to the number of adverse domains (1–5) within a story. In the comparative study, data represent the mean weighted domain score (MWDS) and SD for each domain, for all participants (middle frame) and for subgroups (lower frame). *p*-values and Friedman statistics (*Q*) from Friedman tests are shown on the right.

Abbreviations: AE, adverse effects; LE, life events; LTC, long-term complications; TD, treatment difficulty; TF, treatment failure.

<sup>a</sup>Younger/older were defined as below/above the median age (53 years).

for significant differences in domain ranking. Mean weighted domain scores (MWDS) were calculated as the average for each domain.

In subgroup analyses (gender, age, ethnicity), we used (i) Friedman test on weighted domain scores for each subgroup, to determine differences in domain ranking; and (ii) Mann–Whitney test to determine whether a particular domain was ranked higher or lower between subgroups. A Bonferroni correction and an odds ratio (OR), comparing the likelihood of giving a high ( $\geq 7$ ) versus a low ( $< 7$ ) weighted domain score according to the subgroup, was conducted where Mann–Whitney results were significant ( $p < 0.05$ ).

## RESULTS

### Demographics

Seventy-four clinic attendees participated, 20 in the pilot and 54 in the comparative study. Pilot study demographics are summarized in Table S1; comparative study demographics are included in Table 1. The study population was generally representative of the clinic population with a similar age (median 53 vs. 50 years, respectively) and ethnic mix (38% self-identifying as ‘white’ vs. 33%), although males were slightly over-represented in the comparative study cohort (70% vs. 58%). Most participants were heavily

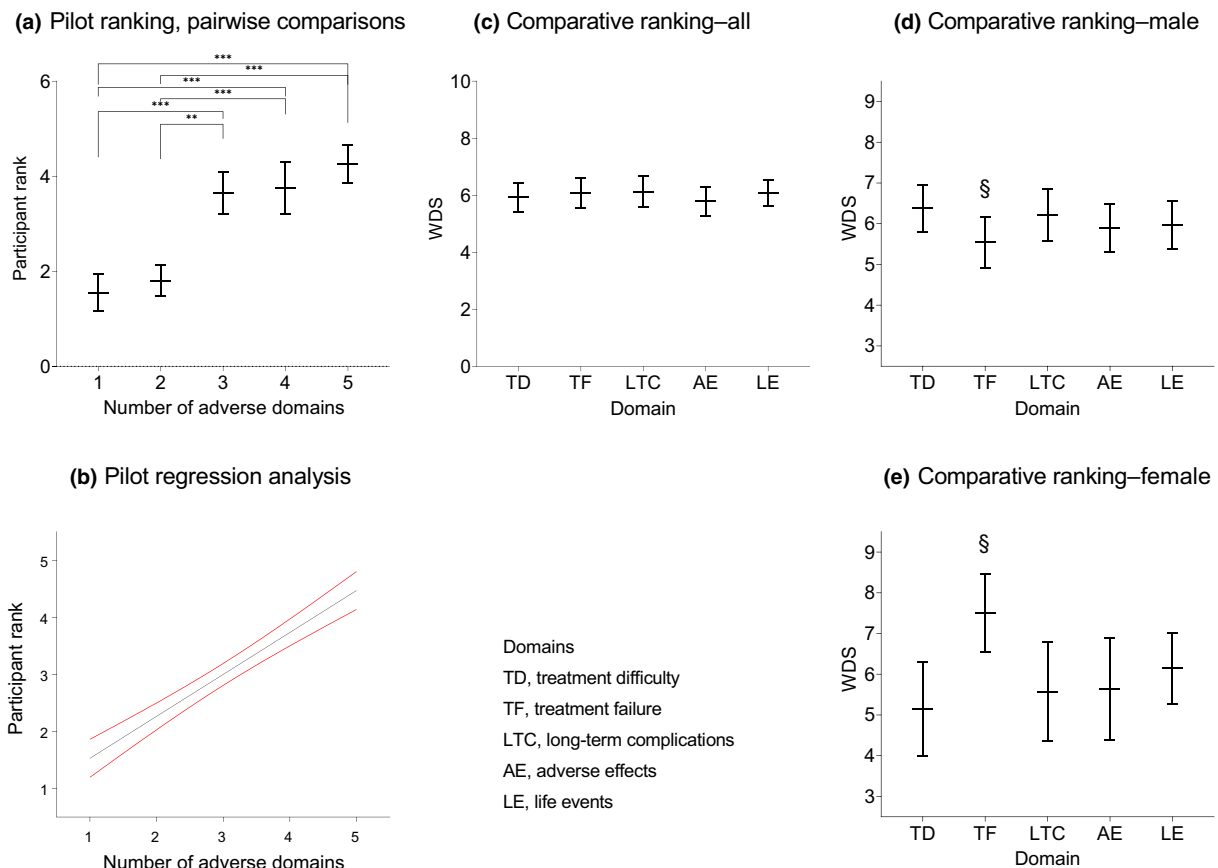
treatment-experienced; median time since start of first ART was 10 years (quartiles 6 and 18 years).

### Pilot study

The participant ranking (MPR) increased with each increase in the number of adverse domains per story (Table 1), a higher score indicating greater undesirability ( $p < 0.0001$ ,  $Q = 49$ ; Friedman’s test). Significant differences by pairwise comparison persisted up to three adverse domains per story, but not thereafter (Figure 2a). A simple linear regression model identified a positive association between the number of adverse domains and ranking (MPR, Figure 2b;  $R^2 = 0.54$ ,  $p < 0.0001$ ).

### Comparative study

In the comparative study, the MWDS were almost identical for all five domains (Table 1; Figure 2c;  $p = 0.88$ ,  $Q = 1.2$ ; Friedman test). Similarly, when we analysed results by subgroup, MWDS were similar across all domains for each subgroup and Friedman test gave no significant differences in domain ranking (Table 1; Figure 2d,e;  $p > 0.05$ ). However, comparisons of domain ranking between subgroups by Mann–Whitney test revealed that women ranked the ‘treatment failure’ domain significantly higher than men (Figure 2d,e;



**FIGURE 2** Ranking of narrative scores by number and nature of adverse domains. Horizontal bars show mean participant rank (with 95% confidence intervals) attributed to stories according to the number of adverse domains in the story in the pilot study (a) or the domain category in the comparative study (c–e). Panel (b) shows the linear regression model for participant rank in the pilot study; 95% confidence intervals in red. For (a),  $p < 0.001$  by Friedman test; pairwise comparisons by Dunn's multiple comparisons test: \*\* $p = 0.002$ , \*\*\* $p < 0.001$ . For (c–e), Friedman test was not significant so pairwise comparisons were not performed. Rankings for 'treatment failure' were significantly different between male and female subjects, § $p = 0.0014$  by Mann–Whitney test; other comparisons were not significant ( $p > 0.05$ ). WDS, weighted domain score. Domains as shown on figure: AE, adverse effects; LE, life events; LTC, long-term complications; TD, treatment difficulty; TF, treatment failure

$p = 0.0014$  with Bonferroni correction). Women were 53% more likely to give a high score ( $\geq 7$ ) for the treatment failure domain than men (OR = 1.53). There was also a trend towards higher ranking of the 'treatment difficulty' domain among older versus younger participants (above and below the median age of 53 years; Figure S1), which was significant by Mann–Whitney test ( $p = 0.031$ ), but not after Bonferroni correction.

## DISCUSSION

First, our study has demonstrated that the DOOR approach is a feasible and easily administered tool for assessing patient ART preferences. This was confirmed by the strong positive association between ranking (MPR) and the number of adverse domains. Second, we found in the comparative study that all domains

generated very similar, almost identical mean rank scores. Our conclusion from this observation is that, when taken as a whole, PLWH regard all treatment attributes to be equally important – to paraphrase the Queen song, 'We want it all'. There was no evidence that PLWH desired to 'trade off' one attribute against another, although this may have been a common paradigm in the past [24], and one prevalent when many in our cohort commenced ART (median start date 2011). Modern ART combinations often allow optimized tolerability without compromised efficacy, and hence there is rarely any need for a trade-off between attributes.

Although one interpretation of our results is that all treatment characteristics matter to PLWH, it is possible that the DOOR methodology had failed to identify true patient preferences (a type 2 error). This study may have been underpowered as it was intended to be exploratory; we did not have *a priori* variance data on which to base a

power calculation. However, a *post hoc* power calculation using the average standard deviation gathered from our study (1.8) showed that we had a 90% chance of detecting a 1.1-point difference between any two given domains in the comparative study with this sample size ( $n = 54$ ). Clearly, a larger study would have greater discriminatory power but graphical data visualizations (Figure 2c–e) did not identify any non-significant trends, intimating that a larger study may not identify major systematic differences in domain ranking.

Direct comparisons of our results with those from previous studies on patient ART preferences are difficult due to methodological and contextual differences. ART attitudes have changed with the development of novel therapies. Whereas some previous studies did find preferences, as discussed in the Introduction, the findings have been variable; some highlighting adverse effects [21, 22, 24] and others emphasizing efficacy, outcomes, treatment access [25, 26] or the importance of physical activity [23], a characteristic we endeavoured to capture in our ‘life events’ (LE) domain. Interestingly, although domain ranking was similar when the DOOR methodology was employed, most respondents (37%) in our study stated in free-text that adverse effects of ART was the most important treatment attribute to them, reflecting previous research.

Narrative lines in different domains were drafted aiming to reflect genuine clinical experience but also aiming to present options that were roughly equivalent in ‘adversity’ across domains. Hence the study could be viewed as demonstrating that participants evaluated adverse domains in the same way as the authors. The originators of DOOR claim that ‘Good studies evaluate the disease while great studies evaluate the patient’ [27]. It should be recognized, however, that DOOR, at least in this guise, only ‘evaluates the patient’ by comparison with the authors of the narrative lines. Involving patients in narrative writing and storyboard generation may have been desirable but would have become self-fulfilling as they would then have been asked to select treatment aspects they considered equally important. Domain ranking is fundamentally dependent on the choice of options presented to participants. We may have missed a true difference because of our choice of adverse domain categories and/or narrative content. For example, although administration by injection was included as an ‘adverse’ option, some PLWH view this favourably [25, 29]. To test whether inclusion of injection treatment as an adverse option affected ranking of the ‘treatment difficulty’ domain, we carried out a sensitivity analysis, excluding scores from storyboards with this option. We found that this did not affect domain ranking scores.

In subgroup analysis, an apparent difference – that female PLWH appear more concerned about ART failure than male PLWH – did emerge, as did a trend towards older people being more concerned about treatment difficulty. This, in our opinion, is the real power of the DOOR approach, to compare between patient subgroups presented with the same hypothetical treatment options. Subgroup preferences have been identified previously, women being more concerned about drug interactions than men [25] and older/younger people preferring different ART characteristics [26]. Ethnicity is also important; Hispanics in the USA showed most concern about treatment accessibility [25], an issue that was not directly addressed in our domains. We did not identify ranking differences between white and non-white participants. Our study was not powered for multiple subgroup analyses, however, and hence our subgroup observations should be considered hypothesis-generating. However, the fact that significant differences did emerge suggests that this area merits further investigation.

In terms of other study limitations, restricting ourselves to an English language questionnaire may have excluded a small number of clinic attendees; future studies could offer translations. Most participants reported no difficulties completing the questionnaire, but 12% said they did not fully understand some of the stories, and 10% said there were too many stories within the single storyboard. These factors may have made ranking more difficult. Finally, we failed to explore patient views on some pertinent treatment attributes; for example, several participants commented that we should have included sleep disturbance as an adverse attribute in some of the stories, and we did not explore treatment accessibility as we considered that beyond the remit of this study.

In conclusion, our findings suggest that the era of ‘trade-offs’ in ART is over – patients want combinations that are safe, tolerable, effective and do not interfere with their lives. Within that overall conclusion, however, our subgroup analyses suggest that some treatment attributes matter more to specific demographics; specifically, women may worry more about treatment failure. Reproducing and extending these observations in larger cohorts to reduce type 2 error would appear justified from these initial findings. Such generic observations can guide pre-treatment discussions and ART MDT decision-making. However, the variance in MWDS (Table 1; Figure 2c) probably includes differences in individual preferences. There is a tension here – analysis requires data to be grouped (or subgrouped) in order to make generalizable conclusions, agnostic of individual variation. However, if variance is significant and reflects real differences between individuals, this highlights the need for

treatment personalization. Capturing both in the pre-treatment or switch discussion is vital for optimal treatment. One potential development of the DOOR approach might therefore be as a pre-treatment clinical assessment tool (as opposed to a research technique) to explore individual patient preferences, generating a person-specific domain score prior to ART prescribing. Both generic (group-based) insight and individual input are required to ensure that the patient voice is heard during the ART decision-making process.

### AUTHOR CONTRIBUTIONS

IH and AP carried out the data collection. IH and DCM performed analyses and authored the manuscript. AP proofread the manuscript and suggested edits.

### ACKNOWLEDGEMENTS

We acknowledge the willing participation of clinic attendees at the Courtyard Clinic, St George's Hospital, London, the help of reception and nursing staff in recruiting to the study and clinical colleagues at St George's Hospital for useful feedback on the study design and manuscript preparation.

### CONFLICT OF INTEREST


The authors declare that they have no competing interests.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Homerova I, Patel A, Macallan DC. 'We want it all': ART preferences assessed by Desirability of Outcome Ranking. *HIV Med*. 2022;1-8. doi:[10.1111/hiv.13447](https://doi.org/10.1111/hiv.13447)