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Preference for daily oral pills over long-acting antiretroviral therapy options among people with HIV

Douglas Barthold[a], Enrique M. Saldarriaga[a], Aaron T. Brah[b], Brett Hauber[a,c], Pallavi Banerjee[d], Shanil M. Fuller[e], Divine McCaslin[e], Ana Maria Moldoveanu[e], Vincent C. Marconi[f,g], Jane M. Simoni[h,i] and Susan M. Graham[i,j,k]

Objective: To examine the characteristics of people with HIV (PWH) who prefer remaining on daily oral antiretroviral therapy (ART), rather than switching to long-acting ART (LA-ART).

Design: Building upon a discrete choice experiment (DCE), we examined characteristics of individuals who always selected their current daily oral tablet regimen over either of two hypothetical LA-ART options presented in a series of 17 choice tasks.

Methods: We used LASSO to select sociodemographic, HIV-related, and other health-related predictors of preferring current therapy over LA-ART, and logistic regression to measure the associations with those characteristics.

Results: Among 700 PWH in Washington State and Atlanta, Georgia, 11% of participants ($n = 74$) chose their current daily treatment over LA-ART in all DCE choice tasks. We found that people with lower educational attainment, good adherence, more aversion to injections, and who participated from Atlanta to be more likely to prefer their current daily regimen over LA-ART.

Conclusions: Gaps in ART uptake and adherence remain, and emerging LA-ART treatments show promise to address these challenges and help a larger portion of PWH to achieve viral suppression, but preferences for these new treatments are understudied. Our results show that certain drawbacks of LA-ART may help to maintain demand for daily oral tablets, especially for PWH with certain characteristics. Some of these characteristics (lower educational attainment and Atlanta participation) were also associated with a lack of viral suppression. Future research should focus on overcoming barriers that impact preferences for LA-ART among those patients who could benefit most from this innovation.

AIDS 2023, **37**:1545–1553

Keywords: discrete choice experiment, long-acting antiretroviral therapy, patient preferences, people with HIV

[a]The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, University of Washington, Seattle, Washington, [b]School of Medicine, Oregon Health and Science University, Portland, Oregon, [c]Pfizer, Inc, New York, New York, [d]Information School, University of Washington, Seattle, Washington, [e]Division of Infectious Diseases, Emory School of Medicine, [f]Department of Medicine, Emory University School of Medicine, [g]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, [h]Department of Psychology, [i]Department of Global Health, [j]Division of Allergy & Infectious Diseases, Department of Medicine, and [k]Department of Epidemiology, University of Washington, Seattle, Washington, USA.

Correspondence to Douglas Barthold, 1959 Pacific St NE, Seattle, WA 98195, USA.

E-mail: barthold@uw.edu

Received: 5 March 2023; revised: 1 May 2023; accepted: 4 May 2023.

DOI:10.1097/QAD.0000000000003620

Introduction

To accelerate the end of the HIV epidemic, the United Nations AIDS Program (UNAIDS) declared their 95–95–95 goals: 95% of people with HIV (PWH) will know their status, 95% of diagnosed PWH will be receiving treatment, and 95% of treated PWH will achieve viral suppression [1]. In the United States, these goals remain distant, with the Centers for Disease Control and Prevention (CDC) estimating in 2020 that 74% of people diagnosed with HIV were receiving HIV care, and only 65% of those in care were virally suppressed [2]. Accordingly, HIV remains a major public health problem, with 18 489 deaths in the United States in 2020 [3].

The CDC has responded to the problem with the *Ending the HIV Epidemic in the US* initiative [4]. One of its pillars is a strategy to rapidly and effectively treat PWH to reach sustained viral suppression [5]. The standard treatment for HIV is antiretroviral therapy (ART) with an oral regimen consisting of one or more tablets, most often taken once daily. Encouragingly, viral suppression has been increasing among people receiving care as regimens have improved in potency and decreased in complexity [6]. However, despite these advances in ART regimens, many PWH in the United States still find it challenging to consistently take their oral regimen every day as prescribed, due to barriers such as HIV stigma, treatment fatigue, missed visits or refills, forgetfulness, and adverse effects [7–9].

Newly emerging long-acting therapies (LA-ART), including injections, implants, and long-acting oral pills, show promise in alleviating some of these challenges and could improve uptake and adherence as needed to increase viral suppression rates. In order for this improvement to occur, the new therapies need to be acceptable for patients, particularly those who have not achieved viral suppression on an oral regimen taken every day. To examine the preferences of PWH for different potential LA-ART regimens, we developed and conducted a discrete choice experiment (DCE), which is a method of preference elicitation in which respondents make a series of choices between treatment options with different characteristics. The results allow us to measure how patients make trade-offs across the key attributes of these new therapies and evaluate how these preferences relate to the acceptability of their current ART [10,11].

Qualitative research, as well as the initial piloting of this DCE, have shown that some PWH are not interested in switching from their current therapies to LA-ART [11]. For those patients who have not attained viral suppression or struggle to remain suppressed on their current ART, preferences related to LA-ART are of critical importance. In addition, while there is no clinical reason for a patient with viral suppression on their current regimen to switch to LA-ART, issues related to convenience, stigma, swallowing challenges, and side effects could lead them to prefer LA-ART. To better understand patient preferences for emerging LA-ART regimens that are on the market currently or in the development pipeline, we analyzed individual characteristics that are associated with PWH preferring to remain on current oral ART taken every day rather than either of two hypothetical LA-ART options with substantially lower dosing frequency and how these characteristics relate to viral suppression.

Methods

Study setting and population

Participants were recruited from University of Washington (UW) HIV clinics in western Washington State and from the Grady Health System Ponce de Leon Center affiliated with Emory University in Atlanta, Georgia. Recruitment occurred between March 2021 and June 2022 via e-mail and telephone using patient registries at each site or in-person outreach at regular clinic appointments. All participants were at least 18 years of age, had established care at an affiliated clinic, were fluent in English, and provided informed consent. We excluded individuals who were currently taking LA-ART, those who were 'elite controllers' (undetectable viral load without taking ART [12]), and those who were perceived by research staff to be cognitively impaired or under the influence of drugs or alcohol during screening. The final sample included 700 participants – 350 in Washington State and 350 in Atlanta. We chose the sample size in accordance with recommendations from published guidelines [13], and our desire to obtain precise estimates of preferences across patient subgroups. Participants accessed the survey at home, via an emailed invitation link or in a private area within their clinic. Eligibility was assessed with a screening survey in REDCap, after which electronic consent was obtained before survey administration [14]. The UW and Emory University both approved the informed consent documents and study protocols, and the UW served as institutional review board (IRB) of record (STUDY00007390).

The discrete choice experiment (DCE)

We developed a DCE that examined patient preferences across four treatment types: long-acting oral pills, injections under the skin, injections into the muscle, and implants. Every choice task offered three options: two hypothetical long-acting treatments and the participant's current therapy (Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/C905). In addition to treatment type, six other attributes were used to define each of the hypothetical treatment profiles: location for receiving treatment, frequency, pain associated with taking treatment, pretreatment viral suppression, pretreatment negative reaction testing, and late dose leeway (i.e. flexibility in dosing timing before breakthrough viremia). All attributes, and the possible levels for each, are shown

Table 1. Attributes and levels of a discrete choice experiment examining patient preferences for long-acting antiretroviral therapies.

Attribute	Levels
Treatment type	Long-acting oral pills, injections under the skin, injections into the muscle, implants
Location	Home, pharmacy, clinic
Frequency	Once every: week, month, 2 months, 3 months, 6 months, year
Pain	None, mild, moderate
Pretreatment viral suppression	Not at all, 3 months, 6 months
Pretreatment negative reaction testing	Not needed, needed
Late dose leeway	Short period, long period

in Table 1. A literature review and 12 key informant interviews identified attributes and levels that would be plausible for LA-ART, including restrictions on combinations of levels (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C905) [10]. We developed an unlabeled experimental design comprising 64 choice tasks using Ngene software (ChoiceMetrics, Sydney, NSW, Australia). For all choice tasks presented, the participant's current ART regimen, which could be any number of oral pills taken at least once daily, was presented as an 'opt-out' alternative.

Survey components

The DCE, along with the rest of the survey, was pilot tested with 50 participants over a series of 10 waves with iterative improvement, described in detail in our prior work [11]. The full survey began with a description of the purpose of the study and provided details of the hypothetical modalities of LA-ART products and the relevant levels for each treatment's attributes. Five questions were used to ensure content comprehension. Prior to the DCE choice tasks, participants were shown instructional videos that explained the components of an example choice task in the exact format of the actual DCE. The participants were then shown 17 DCE choice tasks, each of which featured a constant opt-out option of current therapy.

After completion of the DCE, participants were asked about personal characteristics hypothesized to affect LA-ART preferences. These included sociodemographic characteristics, sexual orientation, labor force participation, internalized HIV stigma, and access to healthcare. In every question in the survey, participants could choose 'Prefer not to say,' rather than answer the question. The survey was administered using SurveyEngine (SurveyEngine GmbH [15], Berlin, Germany) and can be found in the electronic supplementary material.

Measures

In this analysis, the outcome of interest was a binary variable equal to 'one' if the participant chose their current therapy in all 17 choice tasks that they answered, and zero otherwise. Individuals with a 'one' for this variable indicated no interest in switching to a hypothetical long-acting treatment option. Our independent variables were characteristics that might be related to treatment preferences (Table 2), categorized as sociodemographic, HIV-related, and other-health related characteristics. Most were measured using the questions in the survey, but clinical measures of past diagnoses, lab results, and healthcare utilization were also obtained for individuals who consented to link their medical chart data. Some participants ($n = 30$) declined to link their chart data, and others preferred not to disclose some of their personal characteristics. We defined separate variables flagging participants who chose not to disclose different types of information; these are listed at the bottom of Table 2.

Statistical analysis

We calculated unadjusted frequencies and percentages for each personal characteristic, stratified by whether or not participants ever chose an LA-ART option in the DCE. Since the clinical benefit of LA-ART may be greater for those without viral suppression, we also examined personal characteristics stratified by whether the participant was currently virally suppressed (viral load $\leq$40 copies/ml) or not.

In three separate multivariable logistic regressions, we measured the association between preferring current therapy (binary dependent variable) and the three categories of participant characteristics: sociodemographics, HIV-related, and other-health related. To adjust for nondisclosure of certain characteristics by some participants, these regressions also included the Table 2 variables capturing whether or not the participant disclosed the relevant information, allowing for a sample size of 700 in all regressions.

Our primary analysis featured two steps. First, we used a penalized regression for irrelevant variables (LASSO) to select variables in each of the three covariate categories that predicted preferring current therapy over LA-ART. LASSO is a regression analysis that performs variable selection and regularization by choosing the set of covariates that minimize the residual sum of squares, subject to a constraint on the sum of the absolute values of the coefficient estimates [16]. In each of the three regressions, we used a leave-one-out cross-validation to find the regularization parameter (lambda) that minimized the extended Bayesian information criterion (EBIC) and identified the most influential predictors of preference for current therapy over LA-ART [17]. In the

Table 2. Characteristics of participants.

	All participants	Chose LA-ART at least once	Never chose LA-ART	*P*-value[a]
N	700 (100%)	626 (89%)	74 (11%)	
Scenarios chose current therapy (mean, SD)	5.4 (6.4)	4.0 (5.3)	17.0 (0)	<0.01
Survey duration in minutes (mean, SD)	30.5 (11.3)	30.6 (11.3)	29.4 (11.3)	0.37
Comprehension questions correct on first try, out of five questions (mean, SD)	4.5 (0.8)	4.5 (0.8)	4.2 (0.9)	<0.01
Sociodemographic characteristics				
Washington State participant	350 (50%)	333 (53%)	17 (23%)	<0.01
Atlanta participant	350 (50%)	293 (47%)	57 (77%)	<0.01
Age in years (mean, SD)	48.6 (12.1)	48.1 (12.3)	53.4 (9.7)	<0.01
Black race[b]	347 (50%)	297 (47%)	50 (68%)	<0.01
White race[b]	279 (40%)	262 (42%)	17 (23%)	<0.01
Other race[b]	90 (13%)	83 (13%)	7 (9%)	0.36
Hispanic ethnicity	61 (9%)	57 (9%)	4 (5%)	0.29
Female gender	168 (24%)	139 (22%)	29 (39%)	<0.01
Transgender[c]	21 (3%)	19 (3%)	2 (3%)	0.87
Heterosexual	227 (32%)	191 (31%)	36 (49%)	<0.01
Works full time	192 (27%)	182 (29%)	10 (14%)	<0.01
Education – high school or less	243 (35%)	196 (31%)	47 (64%)	<0.01
Income – less than $2000/month	438 (63%)	385 (62%)	53 (72%)	0.09
HIV-related characteristics				
Year since HIV diagnosis (mean, SD)	17.9 (9.8)	17.5 (9.8)	20.9 (9.2)	<0.01
Years on ART (mean, SD)	15.6 (8.7)	15.2 (8.6)	19.4 (8.5)	<0.01
ART for <5 years	63 (9%)	58 (9%)	5 (7%)	0.48
Viral load ≤40 copies/mL	586 (84%)	525 (84%)	61 (82%)	0.75
CD4 count <200 cells/μl	51 (7%)	47 (8%)	4 (5%)	0.51
CD4 count 200–349 cells/μl	92 (13%)	82 (13%)	10 (14%)	0.92
Past HIV regimens: 0 or 1	184 (26%)	160 (26%)	24 (32%)	0.20
AIDS ever diagnosed	292 (42%)	262 (42%)	30 (41%)	0.83
Good adherence[d]	370 (53%)	318 (51%)	52 (70%)	<0.01
Can get to HIV clinic easily	539 (77%)	478 (76%)	61 (82%)	0.24
Other health-related characteristics				
Injection drug use	18 (3%)	16 (3%)	2 (3%)	0.94
Pills for non-HIV per day: 0 or 1	254 (36%)	229 (37%)	25 (34%)	0.64
Aversion to injections[e]	267 (38%)	222 (35%)	45 (61%)	<0.01
Substance use[f]				
Tobacco	117 (17%)	94 (15%)	23 (31%)	<0.01
Alcohol	61 (9%)	46 (7%)	15 (20%)	<0.01
Marijuana	21 (3%)	19 (3%)	2 (3%)	0.87
Other[g]	626 (89%)	558 (89%)	68 (92%)	0.47
Mental health disorders[f]				
Depressive[h]	297 (42%)	261 (42%)	36 (49%)	0.25
Anxiety	136 (19%)	128 (20%)	8 (11%)	0.05
PTSD	31 (4%)	28 (4%)	3 (4%)	0.87
Psychosis	32 (5%)	30 (5%)	3 (4%)	0.42
Characteristics that participant preferred not to disclose				
Identity-related[i]	47 (7%)	42 (7%)	5 (7%)	0.99
Income and work	79 (11%)	64 (10%)	15 (20%)	0.01
Education	25 (4%)	19 (3%)	3 (4%)	0.03
HIV-related[j]	14 (2%)	11 (2%)	3 (4%)	0.18
AIDS – ever diagnosed	14 (2%)	13 (2%)	1 (1%)	0.67
Other health-related[k]	14 (2%)	9 (1%)	5 (7%)	<0.01
No consent to link chart data	30 (4%)	25 (4%)	5 (7%)	0.27

Characteristics of 700 participants in a discrete choice experiment examining patient preferences for long-acting antiretroviral therapies. All participants were age 18+ and living with HIV. SD, standard deviation; LA-ART, long-acting antiretroviral therapy; PTSD, posttraumatic stress disorder.

[a]*P*-values are from two-sided *t*-test for equality between Ever LA-ART and Never LA-ART.

[b]Race categories were not mutually exclusive.

[c]Transgender were individuals who self-reported as a transman or transwoman.

[d]Good adherence was defined as reporting to always or almost always take ART as instructed.

[e]Aversion to injections was defined as reporting strongly agree or somewhat agree with the statement 'I HATE getting injections and try to avoid getting them whenever possible.'

[f]Substance use and mental health disorders were extracted from medical chart review.

[g]Other substances consist of benzodiazepines, cocaine, heroin, methamphetamines, opioids, or 'other.'

[h]Depressive mental health disorders included bipolar, dysthymia, depression, mood, and suicidality.

[i]Identity-related characteristics included gender, sexual orientation, and race.

[j]HIV-related characteristics (preferred not to disclose) included ART initiation year, HIV diagnosis year, number of past regimens, ART adherence, and getting to clinic easily.

[k]Other health-related characteristics (preferred not to disclose) included number of non-HIV pills, and aversion to injections.

second step, the chosen covariates from each of the three categories were included together in a single multivariable logistic regression, which also featured the Table 2 variables indicating whether the participant chose not to link chart data or not to disclose other information. To test the sensitivity of the findings of our primary analyses, a single logistic regression was performed on all measured covariates together without selection by category.

Results

Sample characteristics

Table 2 presents the full list of participant characteristics, with frequencies and percentages stratified by preferring current therapy over LA-ART. Among all 700 participants, the mean number of tasks in which current therapy was selected was 5.4 [standard deviation (SD) = 6.4]. Seventy-four participants (11%) chose their current therapy in all 17 choice tasks. Those who never chose LA-ART had a similar survey duration and number of comprehension questions answered correctly on the first try as those who ever chose LA-ART (details in Table 2). Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C905 presents participant characteristics stratified by viral suppression and shows that good adherence (reporting always or almost always taking HIV-medications as they 'are supposed to') was more common for people who were virally suppressed (56%) than for those who were not virally suppressed (31%).

Regressions with categories of covariates

Table 3 shows results of the multivariable logistic regressions for three separate categories of covariates. Among the sociodemographic characteristics, the following variables exhibited statistically significant associations with preferring current therapy over LA-ART: age <30 years [adjusted odds ratio (aOR) = 0.20, 95% confidence interval (CI) = 0.04–0.95], age 30–49 years (aOR = 0.42, CI = 0.23–0.76), high school education or less (aOR = 3.40, CI = 1.91–6.05), and preferring not to disclose education (aOR = 3.65, CI = 1.11–12.03). With respect to the HIV-related characteristics, good adherence had a significant association with the outcome (aOR = 2.38, CI = 1.34–4.23). Among the other health-related characteristics, the following variables showed significant associations: self-reported aversion to injections (aOR = 3.03, CI = 1.75–5.23), use of tobacco (aOR = 2.20, CI = 1.23–3.95), use of alcohol (aOR = 2.81, CI = 1.43–5.50), anxiety disorder (aOR = 0.44, CI = 0.19–0.99), and preferring not to disclose other health-related characteristics (aOR = 5.31, CI = 1.55–18.22).

LASSO regressions using the same three categories of covariates were used for variable selection, which resulted in a subset of variables that largely coincided with the statistically significant variables in the three characteristic-type logistic regressions (Table 3). For the sociodemographic characteristics, the selected variables were binary variables for Washington State study location, age of 50 and higher, and education of high school or less (lambda = 61.71, EBIC = −1680.71). For the HIV-related characteristics, the only selected variable was a binary indicator for good adherence (lambda = 47.04, EBIC = −1648.16). For the other health-related characteristics, the selected variables were binary variables for use of tobacco, use of alcohol, and aversion to injections (lambda = 47.61, EBIC = −1668.94).

Primary results

The results of the combined multivariable logistic regression of the most important predictors of preferring current therapy over to LA-ART are reported in Table 4. Having a high school education or less was associated with a higher odds of having preference for current therapy over LA-ART (aOR = 2.73, CI = 1.41–5.27), and preferring not to disclose education was associated with a higher odds of preferring current therapy over LA-ART (aOR = 4.37, CI = 1.29–14.78). Washington State participants were less likely to prefer their current therapy than Atlanta participants (aOR = 0.43, CI = 0.22–0.83). Those who reported good adherence to their HIV medications were more likely to prefer their current therapy (aOR = 2.51, CI = 1.42–4.46), as were those with self-reported aversion to injections (aOR = 2.63, CI = 1.50–4.59). The magnitudes of association for the age variables suggest that younger people are less likely to prefer their current therapy, but these associations were not statistically significant. Results of a sensitivity analysis with all covariates in a single logistic regression are in Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C905 and show no meaningful differences from the main results.

Viral suppression was not a significant predictor of preferring current therapy in the main analyses, but participants who were virally suppressed chose current therapy in more scenarios on average than participants who were not virally suppressed (Table 2, Supplemental Digital Content http://links.lww.com/QAD/C905). Additionally, several significant predictors in our primary analyses (lower education, Atlanta, lower adherence) were also associated with lack of viral suppression (Table 2, Supplemental Digital Content http://links.lww.com/QAD/C905).

Discussion

In a DCE designed to elicit preferences for hypothetical LA-ART options compared to current daily oral ART among 700 PWH in Washington State and Atlanta, we found that 11% of participants stated in every choice task

Table 3. Multivariable associations between participant characteristics and preferring to remain on current regimen rather than long-acting antiretroviral therapy, measured in three separate logistic regressions.

	Adjusted odds ratio	95% CI	*P*-value
Sociodemographic characteristics regression			
Washington State	0.40	(0.15–1.02)	0.05
Atlanta	Reference		
Age <30	0.20	(0.04–0.95)	0.04
Age 30-49	0.42	(0.23–0.76)	<0.01
Age 50+	Reference		
Black race[a]	0.77	(0.33–1.78)	0.54
Other race[a]	1.01	(0.37–2.75)	0.98
Hispanic ethnicity	0.97	(0.31–2.98)	0.95
Female gender	1.18	(0.63–2.23)	0.60
Transgender[b]	1.09	(0.21–5.79)	0.92
Heterosexual	0.89	(0.46–1.71)	0.72
Education – high school or less	3.40	(1.91–6.05)	<0.01
Work full time	0.79	(0.33–1.88)	0.60
Income <$2000/month	1.13	(0.47–2.74)	0.78
PNTS – income or work	1.51	(0.59–3.86)	0.39
PNTS – education	3.65	(1.11–12.03)	0.03
PNTS – identity-related[c]	0.64	(0.22–1.86)	0.41
HIV-related characteristics regression			
ART for <5 years	0.56	(0.21–1.51)	0.25
Viral load ≤40 copies/ml	0.88	(0.36–2.17)	0.79
$CD4^+$ count <200 cells/μl	0.75	(0.24–2.29)	0.61
$CD4^+$ count 200–349 cells/μl	1.15	(0.54–2.42)	0.72
Past HIV regimens: 0 or 1	1.44	(0.85–2.44)	0.18
AIDS ever diagnosed	0.88	(0.53–1.47)	0.63
Good adherence[d]	2.38	(1.34–4.23)	<0.01
Get to clinic easily	1.45	(0.78–2.70)	0.24
No consent to link chart data	1.78	(0.48–6.54)	0.39
PNTS – HIV-related[e]	3.33	(0.84–13.10)	0.09
PNTS – AIDS ever diagnosed	0.50	(0.06–4.28)	0.52
Other health-related characteristics regression			
Injection drug use	0.90	(0.29–2.75)	0.85
Pills for non-HIV per day: 0 or 1	0.95	(0.54–1.65)	0.84
Aversion to injections[f]	3.03	(1.75–5.23)	<0.01
Substance use[g]			
Tobacco	2.20	(1.23–3.95)	0.01
Alcohol	2.81	(1.43–5.50)	<0.01
Marijuana	1.28	(0.25–6.67)	0.77
Other[h]	1.24	(0.44–3.50)	0.68
Mental health disorders[g]			
Depressive[i]	1.40	(0.79–2.50)	0.25
Anxiety	0.44	(0.19–0.99)	0.05
PTSD	0.86	(0.22–3.39)	0.83
Psychosis	0.46	(0.10–2.16)	0.33
No consent to link chart data	2.26	(0.77–6.68)	0.14
PNTS – other health-related[j]	5.31	(1.55–18.22)	0.01

Results of three separate multivariable logistic regressions (i.e., one for each category presented above), with a binary dependent variable equal to 1 if the participant chose to remain on their current therapy in 100% of choice scenarios in a discrete choice experiment examining preferences for long-acting antiretroviral therapies among 700 people living with HIV age 18+ in Washington State and Atlanta, Georgia. All three regressions used robust standard errors. ART, antiretroviral therapy; PNTS, prefer not to say; PTSD, posttraumatic stress disorder.
[a]Race categories were not mutually exclusive.
[b]Transgender were individuals who self-reported as a trans man or trans woman.
[c]Identity-related characteristics included gender, sexual orientation, and race.
[d]Good adherence was defined as reporting to always or almost always take ART as instructed.
[e]HIV-related characteristics (preferred not to disclose) included ART initiation year, HIV diagnosis year, number of past regimens, ART adherence, and getting to clinic easily.
[f]Aversion to injections was defined as reporting to strongly agree or somewhat agree with the statement 'I HATE getting injections and try to avoid getting them whenever possible.'
[g]Substance use and mental health disorders were extracted from medical chart review.
[h]Other substances consist of benzodiazepines, cocaine, heroin, methamphetamines, opioids, or ''other.''
[i]Depressive mental health disorders included bipolar, dysthymia, depression, mood, and suicidality.
[j]Other health-related characteristics (preferred not to disclose) included number of non-HIV pills, and aversion to injections.

that they prefer their current therapy (oral tablets taken every day) to all hypothetical long-acting treatment options with less frequent dosing. We examined the characteristics of the individuals who exhibited this reluctance to switch treatment modalities and found that low educational attainment (or being unwilling to disclose education), participation in Atlanta, self-reported good adherence, and aversion to injections were highly

Table 4. Multivariable associations between preference for current ART over long-acting antiretroviral therapy and selected participant characteristics.

	Adjusted odds ratio	95% CI	*P*-value
Washington State	0.43	(0.22–0.83)	0.01
Age <30	0.27	(0.06–1.27)	0.10
Age 30–49	0.56	(0.30–1.06)	0.07
Education – high school or less	2.73	(1.41–5.27)	<0.01
Good adherence[a]	2.51	(1.42–4.46)	<0.01
Substance use[b]			
Tobacco	1.92	(0.99–3.71)	0.05
Alcohol	2.03	(0.96–4.27)	0.06
Aversion to injections[c]	2.63	(1.50–4.59)	<0.01
No consent to link chart data	1.93	(0.71–5.22)	0.20
PNTS – education	4.37	(1.29–14.78)	0.02
PNTS – HIV-related[d]	0.76	(0.12–4.88)	0.77
PNTS – other health-related[e]	2.83	(0.71–11.30)	0.14

Results of a multivariable logistic regression with robust standard errors, and a binary dependent variable equal to 1 if the participant chose to remain on their current daily oral therapy in 100% of choice scenarios in a discrete choice experiment examining preferences for long-acting antiretroviral therapies among 700 people living with HIV aged 18+ in Washington State and Atlanta, Georgia. ART, antiretroviral therapy; PNTS prefer not to say.
[a]Good adherence was defined as reporting to always or almost always take ART as instructed.
[b]Substance use was extracted from medical chart review.
[c]Aversion to injections was defined as reporting to strongly agree or somewhat agree with the statement 'I HATE getting injections and try to avoid getting them whenever possible.'
[d]HIV-related characteristics (preferred not to disclose) included ART initiation year, HIV diagnosis year, number of past regimens, ART adherence, and getting to clinic easily.
[e]Other health-related characteristics (preferred not to disclose) included number of non-HIV pills, and aversion to injections.

predictive of preference for current therapy over LA-ART. Results were robust across analytic methods.

LA-ART has the potential to improve adherence and viral suppression for PWH, but some individuals prefer to remain on their current daily therapies. This suggests that for PWH who prefer to stay on their current therapy, the perceived potential benefits related to LA-ART are insufficient to outweigh the downsides of injections, implants, or even weekly or monthly oral tablets. It is also possible that some participants perceived a cost of switching, or felt uncertainty around outcomes and experiences with a new medication or formulation, despite assurances that the new treatments would be equally effective. Among those who consistently preferred their current therapy over LA-ART, 70% reported that they have good adherence (always or almost always taking their HIV medications as they "are supposed to"), compared to 51% of individuals who were willing to consider LA-ART (Table 2). Importantly, this self-reported measure of adherence aligns with viral suppression (Table 2, Supplemental Digital Content http://links.lww.com/QAD/C905), and there is no proven clinical benefit of LA-ART for individuals who are virally suppressed. Additionally, it is logical that those with good adherence would be less interested in LA-ART, as they are likely to have an existing regimen that they like and is effective and routine for them.

Other strong predictors of preference for current therapy over LA-ART were low educational attainment, aversion to injections, and location in Atlanta. The tendency of participants with aversion to injections to prefer their current therapy is logical, as two of the hypothetical modalities were injections, and another was implants that are more invasive than injections. Viral suppression was not significantly predictive of preference for current therapy, but suppression was less common for Atlanta participants and for those with lower educational attainment (Table 2, Supplemental Digital Content http://links.lww.com/QAD/C905). Both groups for whom rates of viral suppression were lower showed a strong preference for current therapy, despite the potential of LA-ART to improve adherence and, thereby, viral suppression. This raises the possibility that patients who could benefit most from LA-ART are among the least willing to take it. If this is the case, increased education and outreach focused on the benefits of LA-ART may be needed. Similarly, it is possible that physician recommendations, peer influences, and the removal of access barriers may change attitudes and ultimately the acceptability of LA-ART for this population.

The association between low educational attainment and preference for current therapy over LA-ART could potentially be related to several aspects of survey design and comprehension. First, education may relate to comprehension of the survey content, including the details of the hypothetical LA-ART options, affecting respondents' willingness to consider the LA-ART options in the DCE. Performance on the five comprehension questions, which was slightly worse in the group that chose current daily oral treatment in all choice tasks, supports this explanation (Table 2). Second, there is evidence that medical mistrust is higher and health literacy is lower among people with lower educational

attainment [18,19], both of which may contribute to unwillingness to try new treatments. Health literacy and medical mistrust, which are consequences of historic and ongoing systemic racism, may be more prevalent in the predominantly Black Atlanta patient population than in the predominantly white patient population in western Washington state (see Table 4, Supplemental Digital Content http://links.lww.com/QAD/C905 for characteristics of the respondents at the two sites). If so, this could explain why being part of the Atlanta sample may be associated with higher rates of always choosing current treatment. However, this is only speculation as neither medical mistrust nor health literacy were assessed in the survey. Third, the preference for current therapy by those with lower educational attainment could be influenced by current therapy being the opt-out alternative in this DCE; indeed, past evidence on DCE design has shown that choosing to opt-out is associated with lower educational attainment [20]. Finally, decisional conflict, defined as uncertainty experienced when making treatment-related medical decisions, is more common for those with lower educational attainment, and this conflict is also associated with greater likelihood of choosing the opt-out option in DCEs [21].

Notably, many of the LA-ART options that were proposed in the choice tasks were long-acting oral tablets. Despite being presented with these options, participants who never selected LA-ART maintained their preference for their current daily oral tablets. This suggests a degree of inertia in treatment preferences, wherein the attributes of the hypothetical long-acting treatments were not relevant to their decision. Under this scenario, these individuals may have been simply unwilling to consider LA-ART, regardless of the attributes and levels. This type of choice selection behavior undermines the measurement of attribute preferences in a DCE, and thus has important implications for analysis of DCE results. Another possibility is that, even though we asked participants to assume no differences in price, effectiveness, or safety across the treatment options, concerns related to those assumptions drove their stated preferences.

The strengths of our study include the large sample of participants from two different sites in the United States, a carefully designed and piloted survey and DCE [10,11], and rigorous statistical analysis. Limitations include the possibility that stated responses may deviate from real-world behavior. Also, the self-reported adherence measure used in our analyses is subject to social desirability and recall bias; however, this measure correlates well with viral suppression (89% of people with good self-reported adherence were virally suppressed, compared to 77% of those without good self-reported adherence), suggesting that the self-reported measure is an appropriate proxy. Another possible limitation is that our survey may not have given sufficient information about the treatment options for effective responses by participants with less formal education or low health literacy. It is also possible that some participants may have given insufficient attention to their responses – this would bias our results if those giving less attention were more likely to always choose their current therapy. However, the mean survey duration was similar between those who never chose LA-ART and those who ever chose LA-ART (29.4 and 30.6 min, respectively), suggesting that there were not substantial attention differences. Other limitations are that our results may not generalize to settings outside the United States, and that our sample included relatively few participants of Hispanic ethnicity (only 9%). Finally, it is important to acknowledge that most of the LA-ART regimens we investigated are hypothetical and only one (cabotegravir/rilpivirine) has become widely available to patients, albeit with substantial insurance and logistical hurdles [22,23]. Since we designed the study, an additional new agent, lenacapavir, became available as a subcutaneous injection every 6 months, and in combinations with other regimens; we did not assess these options in our DCE [24].

Conclusion

LA-ART is an important improvement in HIV treatment, with potential to overcome adherence and initiation problems that exist with current ART options. The results of this study can help inform the role that LA-ART will have in the future of HIV treatment, especially for drug manufacturers and policy makers evaluating the limits and attractiveness of LA-ART. Although these treatments will be one possible tool for increasing viral suppression and treatment satisfaction for some patients [22,23], oral tablets taken every day will likely remain the standard of care indefinitely. Certain drawbacks of LA-ART (costs, injections, need for refrigeration), will likely help to maintain demand for daily oral tablets, especially for PWH with certain characteristics, including less education, good adherence, and aversion to injections. In order to improve treatment outcomes, including viral suppression, more research is needed on overcoming barriers that impact preferences for LA-ART among patients who could benefit most from this innovation.

Acknowledgements

We are grateful for the contributions of study participants and key informants.

Funding: This work was supported by NIH grant R01 MH121424, and by the University of Washington/Fred Hutch Center for AIDS Research, an NIH-funded program under award number AI027757 which is supported by the following NIH Institutes and Centers: NIAID, NCI, NIMH, NIDA, NICHD, NHLBI, NIA, NIGMS, NIDDK. D.B. is supported by NIA K01AG071843. J.M.S. and S.M.G. were supported by the University of Washington Behavioral Research

Center for HIV (BIRCH), a NIMH-funded program (P30 MH123248). V.C.M. has received support from the Emory CFAR (P30 AI050409).

Ethics approval: Granted by the University of Washington Institutional Review Board (STUDY00007390).

Consent to participate: All participants provided electronic informed consent.

Consent for publication: All participants provided electronic consent.

Availability of data: Deidentified data will be made available upon publication.

Code availability: The code is available upon request.

Authors' contributions: S.M.G., J.M.S., B.H., E.S., V.C.M., and D.B. designed the study; S.M.G. and J.M.S. acquired funding; A.T.B., S.M.F., D.M., and A.M.M. collected data; D.B., P.B., and E.S. analyzed the data; D.B., A.T.B., B.H., and E.D. wrote the initial manuscript. All authors contributed to and approved of the final manuscript.

Conflicts of interest

B.H. is an employee of Pfizer. S.M.G. has received support from Gilead and Cepheid for her research. V.C.M. has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences, and ViiV. The other authors declare that they have no conflicts of interest directly relevant to the content of this article.

References

1. UNAIDS. *Understanding fast-track: accelerating action to end the AIDS epidemic by 2030.* Geneva: UNAIDS; 2015.
2. Centers for Disease Control and Prevention. *Monitoring selected national HIV prevention and care objectives by using HIV surveillance data United States and 6 dependent areas, 2020.* Atlanta, GA: CDC; 2020.
3. Centers for Disease Control and Prevention. *HIV basic statistics.* Atlanta, GA: CDC; 2022.
4. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. **Ending the HIV epidemic: a plan for the United States.** *JAMA* 2019; **321**:844–845.
5. Centers for Disease Control and Prevention. *Ending the HIV epidemic in the U.S.* Atlanta, GA: CDC; 2022.
6. Nance RM, Delaney JC, Simoni JM, Wilson IB, Mayer KH, Whitney BM, *et al*. **HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study.** *Ann Intern Med* 2018; **169**:376–384.
7. Katz IT, Ryu AE, Onuegbu AG, Psaros C, Weiser SD, Bangsberg DR, *et al*. **Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis.** *J Int AIDS Soc* 2013; **16**:18640.
8. Claborn KR, Meier E, Miller MB, Leffingwell TR. **A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy.** *Psychol Health Med* 2015; **20**:255–265.
9. Simoni JM, Amico KR, Pearson CR, Malow R. **Strategies for promoting adherence to antiretroviral therapy: a review of the literature.** *Curr Infect Dis Rep* 2008; **10**:515–521.
10. Brah AT, Barthold D, Hauber B, Collier AC, Ho RJ, Marconi VC, *et al*. The systematic development of attributes and levels for a discrete choice experiment of HIV patient preferences for long-acting antiretroviral therapies. Unpublished Research Square preprint. 2021. Available at: https://doi.org/10.21203/rs.3.rs-719332/v1.
11. Barthold D, Brah AT, Graham SM, Simoni JM, Hauber B. **Improvements to survey design from pilot testing a discrete-choice experiment of the preferences of persons living with HIV for long-acting antiretroviral therapies.** *Patient* 2022; **15**:511–520.
12. Olson AD, Meyer L, Prins M, Thiebaut R, Gurdasani D, Guiguet M, *et al*. **An evaluation of HIV elite controller definitions within a large seroconverter cohort collaboration.** *PLoS One* 2014; **9**: e86719.
13. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, *et al*. **Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force.** *Value Health* 2011; **14**:403–413.
14. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, *et al*. **The REDCap consortium: building an international community of software platform partners.** *J Biomed Inform* 2019; **95**:103208.
15. SurveyEngine GmbH. SurveyEngine. Berlin, Germany; 2021. Available at: www.surveyengine.com.
16. Tibshirani R. **Regression shrinkage and selection via the LASSO.** *J Roy Stat Soc B (Methodol)* 1996; **58**:267–288.
17. Chen J, Chen Z. **Extended Bayesian information criteria for model selection with large model spaces.** *Biometrika* 2008; **95**:759–771.
18. Bazargan M, Cobb S, Assari S. **Discrimination and medical mistrust in a racially and ethnically diverse sample of California adults.** *Ann Fam Med* 2021; **19**:4–15.
19. Martin LT, Ruder T, Escarce JJ, Ghosh-Dastidar B, Sherman D, Elliott M, *et al*. **Developing predictive models of health literacy.** *J Gen Intern Med* 2009; **24**:1211–1216.
20. Veldwijk J, Lambooij MS, de Bekker-Grob EW, Smit HA, de Wit GA. **The effect of including an opt-out option in discrete choice experiments.** *PLoS One* 2014; **9**:e111805.
21. Sutphin J, DiSantostefano RL, Leach C, Hauber B, Mansfield C. **Exploring decisional conflict with measures of numeracy and optimism in a stated preference survey.** *MDM Policy Pract* 2021; **6**:23814683211058663.
22. Scarsi KK, Swindells S. **The promise of improved adherence with long-acting antiretroviral therapy: what are the data?** *J Int Assoc Provid AIDS Care* 2021; **20**:23259582211009011.
23. Qazzaz H, Parganas C, Cory TJ. **An evaluation of long-acting cabotegravir+ rilpivirine for the treatment of virologically suppressed adults living with HIV.** *Expert Opin Pharmacother* 2022; **23**:1485–1495.
24. Gupta SK, Berhe M, Crofoot G, Benson P, Ramgopal M, Sims J, *et al*. **Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial.** *Lancet HIV* 2023; **10**:e15–e23.