Establishing content validity of three new patient-reported outcome (PRO) measures for use in HIV long-acting oral antiretroviral therapy (LA-OART) clinical trials

Bailey JR[1]; Javidnia P[1]; Fonseca E[2]; Borsa A[1]; Hawryluk E[1]; Gubernick SI[1]; de la Motte A[1]; Karantzoulis S[1]; Reaney M[3]; Saretsky TL[2]

[1]IQVIA, New York, NY, USA; [2]Merck & Co., Inc., Rahway, NJ, USA; [3]IQVIA, Reading, UK

Background

- Daily oral antiretroviral therapy (OART) has revolutionized outcomes in patients living with HIV (PLWH), leading to viral suppression and significantly improved survival
- However, in the real world, poor adherence can reduce the efficacy of daily OART
- Long-acting oral antiretroviral therapy (LA-OART) agents are currently being investigated to facilitate adherence and enhance the lives of millions of people worldwide
- Patient-reported outcome (PRO) measures can provide unique insights on the impacts of HIV disease and treatment and provide patient perspectives on adherence

- Described previously, a targeted literature review (TLR) and concept elicitation (CE) interviews with clinicians and PLWH were conducted to develop conceptual models capturing PLWH experiences of OART, adherence facilitators and barriers, and perspectives on a hypothetical switch to LA-OART, and an item generation meeting was convened with PRO and internal clinical experts[1]
  - **This work informed development of three new draft PRO measures, in paper and electronic formats, following FDA patient-focused drug development (PFDD) draft guidance[2] for use in LA-OART clinical trials to evaluate adherence attributes of and considerations in switching to LA-OART among PLWH**

FDA, U.S. Food and Drug Administration.

Objectives

This study describes cognitive debriefing (CD) interviews to demonstrate content validity of these new PRO measures (**Table 1**)

The primary objectives of the CD interviews were to:

- Determine the relevance of the draft PRO measures to PLWH and confirm the comprehensibility and comprehensiveness of the instructions, recall period, format and response scale, and appropriateness of the items to their treatment experience
- Finalize the drafted measures by incorporating insights generated from the interviews

Table 1. Draft PRO measures to evaluate perspectives of OART, OART change, and attributes of adherence[a]

PRO measure	Description	# of items	Sample item	Response options
HIV Patient Perspective of Regimen (HIV-PP-R)	Intended to explore patient perceptions (positive, negative, overall) of current HIV regimen	10	In the past 4 weeks… has your HIV regimen fit conveniently into your lifestyle?	Not at all; A little bit; Somewhat; Quite a bit; Very much
HIV Patient Perspective of Regimen Change (HIV-PP-RC)	Intended to explore patient perceptions (positive, negative, overall) of the current (trial) HIV regimen compared to the pre-trial HIV regimen	10 (same concepts as the HIV-PP-R)	Which HIV regimen serves as more of a reminder of your HIV status?	Current regimen more of a reminder; Current and prior regimen similar reminders; Prior regimen more of a reminder
Drivers of HIV Adherence Questionnaire (HIV-DAQ)	Intended to explore regimen taking behavior during the course of the trial	22	In the past 4 weeks… have you forgotten to take your HIV pills at the day(s) and time(s) that were advised by your health care provider?	Not at all; Some of the time; Most of the time; All of the time

[a]Informed by a TLR and CE interviews with clinicians and PLWH and developed following an item-generation meeting.

Methods

Study Design and Population

- The study was a non-interventional, cross-sectional qualitative interview study in the U.S.
- Eligible participants met the following eligibility inclusion criteria:
  - Adult aged 18-70 years old; Willing/able to provide informed consent to research; Resides within any state in the U.S. and can complete the interview in English; Has a confirmed diagnosis of HIV; Currently taking daily oral antiretroviral therapy; Willing/able to speak to the depth and breadth of their experience of treatment
- The target population was up to 30 adult PLWH. This sample was expected to be sufficient to achieve conceptual saturation[3]
- A specialist recruitment vendor applied an inclusive sampling strategy based on FDA guidance on representativeness and generalizability[3]
  - Several "aspirational" targets of greatest importance for recruitment were established for four subgroups of PLWH: men who have sex with men, heterosexual men or women, people who inject drugs, and transgender patients[4,5]
  - Targets by subgroup, age group, and race/ethnicity were broadly selected based on epidemiological data of HIV incidence and prevalence in the U.S.[6]
  - An aspirational target for "new to therapy" patients, defined for this study as patients who have six months or less on their first HIV regimen of daily OART, was created to represent subpopulations with less OART treatment experience
  - To ensure adequate representation of areas in the U.S. where the HIV infection rate is the highest, best efforts were made to recruit patients from CDC-prioritized areas for HIV[7]

CDC, Centers for Disease Control and Prevention.

Procedures

- A standardized patient CD interview discussion guide was developed to include open-ended questions to avoid bias and allow for a free-flowing discussion. It included sample probing questions to guide more in-depth discussion on topics
- Telephone interviews lasting 60-120 minutes were conducted via audio conference by trained qualitative researchers
  - Patients were asked to complete the three measures. Aligned with ISPOR good practices,[8] this process required patients to follow the "think aloud" technique, which asked them to verbalize the thought process involved in providing a response to each question
  - Patients also verbalized the meaning and relevance of the individual items, the fit and adequacy of the response scales to reflect their experience, and the clarity of the items, instructions and sentence structures
- Patients were provided an opportunity to suggest changes to the draft questionnaires during the interview
- Interviews were conducted across three waves to allow for updates to the measures and/or discussion guide between waves
  - Half of the patients tested the paper format; the other half tested the electronic format in each wave
- Both 2- and 4-week recall periods were tested for the HIV-PP-R and HIV-DAQ

Analyses

- Audio files from completed interviews were transcribed verbatim and de-identified
- All quantitative (categorical and continuous variables) data were analyzed to generate tables of descriptive statistics (count)
- Responses to each PRO item were reviewed. Patient feedback on comprehensiveness of PRO measure and relevance and comprehension of each item were analyzed
- Patient verbatims for items and the overall PRO measures were assembled to provide additional details on the language patients used to describe their experiences and to inform updates to the measures
- Where updates were deemed relevant, items were updated at the conclusion of each wave, and the updated measures were tested in the next wave of patients
- An item-tracking matrix was developed to track changes to the measures as the waves progressed

Results

Participant characteristics (Table 2)

- Thirty adult PLWH participated in the CD interviews – 10 in each of the three waves
- The mean age was approximately 47.2 (SD=11.7) years (range, 22-64 years)
  - 50% of participants were between the ages of 50 and 70 years old
- Subgroups (% of participants)
  - Men who have sex with men (MSM): (63%)
  - Transgender women: (7%)
  - People who inject drugs (PWIG): (7%)
  - Heterosexual men or women (33%)
- Nearly half of participants (47%) were African American
- A majority (77%) of participants were treatment experienced greater than 10 years
- A majority (60%) of participants resided in CDC-prioritized areas for HIV

Table 2. Patient characteristics

		Wave 1 (n = 10)	Wave 2 (n = 10)	Wave 3 (n = 10)	Total (n = 30)
Aspirational target groups	**Age groups**				
	18-29 years old	2	1	1	**4**
	30-49 years old	2	4	5	**11**
	50-70 years old	6	5	4	**15**
	Subgroups[a]				
	MSM	7	4	8	**19**
	Heterosexual men or women	3	5	2	**10**
	PWID	0	2	0	**2**
	Transgender	0	2	0	**2**
	Race/ethnicity				
	Caucasian or White	3	3	0	**6**
	African American, African or Black	5	4	5	**14**
	Hispanic/Latin/Central or Spanish origin	0	1	5	**6**
	Asian	2	0	0	**2**
	Other (mixed racial background, prefer not to say)	0	2	0	**2**
	Treatment experience (years) on daily OART				
	Less than 1 year	1	0	0	**1**
	1 year to less than 5 years	1	1	0	**2**
	5 years to less than 10 years	2	0	2	**4**
	Greater than 10 years	6	9	8	**23**
	Geography				
	CDC-prioritized area for HIV[7]	8	6	4	**18**
	Non-prioritized area	2	4	6	**12**
Other demographics	**Gender**				
	Man	8	5	8	**21**
	Woman	2	3	2	**7**
	Transgender woman	0	2	0	**2**
	Highest level of education completed				
	High school graduate, diploma or the equivalent	1	2	1	**4**
	Some college credit, no degree	3	3	5	**11**
	Trade/technical/vocational training	2	0	0	**2**
	Associate degree	1	2	0	**3**
	Bachelor's degree	2	1	3	**6**
	Some post-graduate work	0	1	0	**1**
	Post-graduate degree	1	1	1	**3**
	Employment status				
	Employed on a full-time basis	6	2	4	**12**
	Employed on a part-time basis	1	3	1	**5**
	Out of work and looking for work	0	1	1	**2**
	Out of work but not currently looking for work	1	2	0	**3**
	Retired	2	1	0	**3**
	Other (unable to work)	0	1	4	**5**
	Current living situation				
	Lives alone	6	3	5	**14**
	Lives with someone	4	7	5	**16**
	Treatment history with daily OART				
	Patient is on first daily OART regimen	3	1	0	**4**
	Patient is on second daily OART regimen	0	0	2	**2**
	Patient is on third or higher daily OART regimen	7	9	8	**24**
	Co-morbidities and/or health conditions in addition to living with HIV[b]	8	8	8	**24**
	Yes, patient has co-morbidities and/or health conditions in addition to living with HIV	2	1	2	**5**
	No, patient has no other co-morbidities and/or health conditions in addition to living with HIV				
	Other medications/vitamins/supplements[b]	7	8	7	**22**
	Yes, patient takes other medications, vitamins and/or supplements in addition to daily OART	3	1	3	**7**
	No, patient takes no other medications, vitamins and/or supplements in addition to daily OART				

MSM, men who have sex with men; PWID, people who inject drugs; OART, oral antiretroviral therapy; CDC, Centers for Disease Control and Prevention.
[a]A single patient may identify as one or more subgroups.
[b]Co-morbidities and/or health conditions in addition to living with HIV and other medications, vitamins and/or supplements taken in addition to daily OART not captured during the interview with PLWH-CD-11.

Patient CD Feedback

HIV-PP-R

Instructions/items

- One or more patients in each wave reported a reliance on lab results to inform their response to three medical items (e.g., "belief in treatment efficacy"). As a result, refinements were made to the instructions (**Table 3**)
- Following wave 2, the "willingness to continue trial regimen" item was removed per patient feedback and study team discussion (**Table 3**)
- Following wave 2 feedback, to improve overall questionnaire flow, the "fear of resistance from poor adherence," "reduced preoccupation with regimen-taking" and "fear of disclosure of HIV status" items were grouped together since they all included the same "have you been worried…" construction
- Following wave 2 feedback, minor refinements to three items ("reduced preoccupation with regimen taking," "medication side effects" and "overall burden") were made to improve clarity

Recall period

- Across all waves, patients reported the ability to recall the past 2 and 4 weeks but tended to prefer the 4-week recall period for certain medical items (e.g., "belief in treatment efficacy," and "use of medication to reduce risk of transmission") (**Table 3**)

Response options

- Following wave 2 feedback, minor refinements to the response options of two items ("medication side effects" and "overall satisfaction") were made to improve clarity
- Following wave 2 feedback, the "medication side effects" item was ungrouped from the five-point scale items to highlight the presence of the sixth response option for patients who had not experienced any side effects

Summary

Final HIV-PP-R was 10 items after one item was removed. Instructional text, wording of three items, and response options of two items were edited between waves. After the above refinements, the HIV-PP-R version in wave 3 was considered relevant, comprehensive and clear and easy to complete in paper and electronic formats. No further changes were made after wave 3 testing.

HIV-PP-RC

Instructions/items

- Minor refinements following waves 1 and 2 were made to the instructions for clarity and to emphasize the patient perspective was being sought to inform their response to three medical items rather than their understanding of lab results
- No items were removed
- Following wave 1, as a result of patients finding the language to be verbose and difficult to understand, the language of all items was simplified (**Table 3**)

Response options

- Following waves 1 and 2, the language of all response options was refined to improve clarity
- To improve ease of response selection per wave 1 feedback, the number of response options was reduced for specific items from five to three (**Table 3**)

Summary

The final HIV-PP-RC contains 10 items, and no items were removed. Minor refinements were made to the HIV-PP-RC instructions, the language and response options were simplified, and the number of response options for all items except the "overall satisfaction" item was reduced. Understandability and relevance of the final HIV-PP-RC, in paper and electronic format, was confirmed with the final wave of patients.

HIV-DAQ

Instructions/items

- No items were removed
- Following waves 1 and 2, the language of multiple items was refined (**Table 3**), and instructions were slightly modified to improve clarity
- Following wave 2, four items in the section testing facilitators to and barriers of adherence (e.g., "belief in treatment efficacy," "fear of disclosure of HIV status") were separated and grouped into a new section with a unique set of instructions to reaffirm that patient opinions on these items were being sought

Recall period

- Across waves, patients tended to prefer 4 weeks (vs 2 weeks), particularly for certain medical items (e.g., "belief in treatment efficacy," "use of medication to reduce risk of transmission") (**Table 3**)

Response options

- Following wave 2, the response scale of four items ("overall adherence," "ease of adherence," "accidental nonadherence," and "use of a regimen-taking reminder system") was decreased from a five-point scale to a four-point scale to improve distinguishability between options (**Table 3**)

Summary

The final HIV-DAQ contained 22 items, and no items were removed. The HIV-DAQ language of all items was refined, instructions were slightly modified, and the response options of four items were reduced to a four-point scale. Further, four items in the facilitators to and barriers of adherence section were grouped into a new section with clarifying instructions. Understandability and relevance of the final HIV-DAQ, in paper and electronic formats, were confirmed with the final wave of patients.

Table 3. Example revisions to PRO measures based on patient interviews

PRO	Measure attribute	Rationale	Selected patient quote	Revision
HIV-PP-R	Instructions: "We would like to know about your experience of the regimen you have been taking for your HIV. We would like to know about your experiences in the past 2 weeks. Please select one response for each question. There are no right answers – each person's experience will be different. We are interested in understanding your experience."	As patients in each wave reported a reliance on lab results to inform their response to certain medical items, instructions were refined to emphasize the patient perspective was being sought, rather than their understanding of their lab results.	*"How would I know that?...My response would be that I'm long-term undetectable and, in my situation, I just got my lab work yesterday, the results from my most recent lab work yesterday. So in my… If I'm answering this today, I know that my medication is effective because I just saw my lab work."* – PLWH-CD-11 ["belief in treatment efficacy" item, wave 2]	"We would like to know about your experiences **and opinions** of the regimen you have been taking for your HIV. We would like to know about your experiences and opinions in the past 4 weeks. Please select one response for each question below. There are no right **or wrong answers** – each person's experiences **and opinions** will be different. We are interested in understanding your experiences **and opinions**." ***Bold** indicates changes made.
	Item: Willingness to continue trial regimen	Five patients in wave 1 found the item to be misleading, less relevant and/or difficult to answer as phrased. Due to similar feedback from wave 2 patients and study team discussion, item was removed.	*"So, in the past, would I choose to continue my current regimen after the study was complete if given the option? See, that's not really clear. Is it the option of starting a different medication, or is it like you're going to give me permission after I complete this questionnaire to continue what I've been taking anyway? Do you follow me?"* – PLWH-CD-15 [wave 2]	Item **removed.**
	Recall period: 2 vs 4 weeks	Although patients were able to recall the past 2 and 4 weeks, they preferred the 4-week recall period for certain medical items (e.g., "belief in treatment efficacy").	*"No, [a 2-week recall period] actually doesn't really feel like a reasonable period. I would say probably maybe a month to 2 months would be more of an appropriate question. I don't know how much effectiveness you can really kind of measure in 2 weeks…But 2 weeks just seems a little premature to kind of focus on."* – PLWH-CD-04	Final measure included a **4-week recall period**.
PRO	**Measure attribute**	**Rationale**	**Selected patient quote**	**Revision**
HIV-PP-RC	Item: Overall burden "Is your current HIV regimen more or less burdensome than…"	For the "overall burden" item, six out of 10 patients in wave 2 were less familiar with the term "burdensome" and/or recommended an alternative term to improve clarity. Patients recommended using the term "a burden" in place of "burdensome."	*"You could put 'burden' or 'bother.' Don't even have the '-some.'"* – PLWH-CD-16 *"It's okay, but you may want to use a word saying it's 'more of a burden' to you."* – PLWH-CD-18	**"Which HIV regimen do you think is more of a burden?"** ***Bold** indicates changes made.
	Items overall: Example: "Does your current HIV regimen make you feel more or less worried about people seeing your HIV medication compared to your previous HIV regimen (from before the trial)?"	Five patients in wave 1 recommended removing the repeated language at the end of each item (e.g., "… [from before the trial]" or "… compared to your previous HIV regimen [from before the trial]").	*"You don't need, again, the comparison because we're on the study, and we know we're on something else."* – PLWH-CD-02 *"I feel like [the "from before the trial" language] makes the question a little more confusing, actually."* – PLWH-CD-08	**"Which HIV regimen makes you less worried** about people seeing your HIV medication?" ***Bold** indicates changes made.
	Response options from an example item: • Current regimen much better • Current regimen better • Current and prior regimen similar • Prior regimen more effective • Prior regimen much more effective	Seven patients in wave 1 found the language of the response options lengthy and/or difficult to understand. Five patients recommended reducing the number of response options to three (i.e., the second, third and fourth response options), or, in the case of "medication side effects," four options.	*"It's a lot to read, I will say that. It's a lot to read. Honestly, I… Okay, so see there's so much writing and so much wording that I just realized how you had it. That it goes 'current regimen is more effective' and then 'prior regimen is more effective.' That's just a lot."* – PLWH-CD-06 ["belief in treatment efficacy" item] *"It's not hard to understand, but if you want to answer it correctly, you probably have to pause a little bit and read it, and it's not intuitive."* – PLWH-CD-05 ["use of medication to reduce risk of transmission" item]	• **Current regimen better than prior regimen** • **Current and prior regimen similarly effective** • **Prior regimen better than current regimen** ***Bold** indicates changes made.
HIV-DAQ	Example item (from wave 2): "The risk of other people seeing my HIV medication (as I see it) …"	Seven patients from the first nine interviews of wave 2 had difficulty understanding the intention of the "(as I see it)" language and/or recommended its removal in the four items with this language.	*"I would eliminate the 'as I see it' at the end of the question. I'm not exactly sure what that's trying to say or imply."* – PLWH-CD-11 ["fear of disclosure of HIV status" item]	"The extent to which I believe my current HIV medication is good at controlling the risk of other people seeing my HIV medication…"
	Recall period: 2 vs 4 weeks "Please select from the below to indicate the reason(s) you did not take your medication on the day(s) and times that you were meant to in the past 2 weeks (past 4 weeks)…"	Patients reported the ability to recall the past 2 and 4 weeks but tended to prefer the 4-week recall period for certain medical items.	*"I just started a regimen. It takes at least 30 days really for you to even know…if it's going to disrupt your viral load. I don't think somebody really could answer that fully. I can answer it just because I know that I'm… You know what I mean? I've been taking it, and I know, but 2 weeks may not be a good way to ask for…I think [a 4-week recall period] would be more realistic…Normally, when you start on a new medication, you have to go back after 30 days to get blood work done, so you would know if it's working or if it's disrupted your viral load numbers."* –PLWH-CD-02 ["belief in treatment efficacy" item]	Please select from the below to indicate the reason(s) you did not take your medication on the day(s) and times that you were meant to in the **past 4 weeks…**
	Response options • Not at all • A little bit of the time • Somewhat of the time • Most of the time • All of the time	Based on input from four patients (2 in each of waves 1 and 2), the five-point scale of four items was reduced to a four-point scale to improve response option distinguishability.	*"'A little bit of the time,' the wording might be a little… You almost could get away, in my opinion, get away with four and leave out that 'A little bit of the time.' Just have it 'Not at all,' 'Somewhat of the time,' 'Most of the time,' 'All of the time.'"* – PLWH-CD-06 [wave 1] *"I feel it's too many answers…'A little bit' and 'somewhat,' isn't it almost the same? Maybe just four: 'not at all,' 'somewhat' or 'a little bit,' and 'most of the time,' and 'all of the time'…I feel five complicates things"* – PLWH-CD-17 [wave 2]	• Not at all • **Some of the time** • Most of the time • All of the time ***Bold** indicates changes made.

Limitations

- May include insufficient representation of the diverse HIV patient subgroups due in part to challenges with recruitment as not all "aspirational" targets were satisfied
- Conducting interviews over the telephone may be considered a limitation and/or create certain biases when compared to face-to-face interviewing[9,10]
  - To address these issues, interview moderators trained in the conduct of qualitative telephone interviews were used

Conclusions

- To our knowledge, this study is the first to develop PRO measures for use in clinical trials for PLWH to understand the treatment experience of taking daily OART and how the treatment experience may be altered upon the switch to weekly OART
- Patients who participated in CD interviews largely corroborated the relevancy of the items in the three measures
  - Measures were refined with patient feedback to improve clarity of instructions, items, and response options
  - The overall findings suggest the three new PRO measures are content valid
- Data from future weekly OART clinical trials will allow for the measurement properties and structure of the PROs to be determined
  - A formal scoring guide and definitions of meaningful change in scores can also be established

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