European
AIDS Treatment
Group

PROMs in HIV Research and Development:
Analysis of Community Needs and Engagement

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EATG European AIDS Treatment Group

CONTENTS

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Purpose

The purpose of this document is to describe the current use of patient-reported outcome measures (PROMs) in HIV research and development and to inform an advocacy agenda to guide the use and development of PROMs, highlighting the role of communities living with or affected by HIV in this agenda.

Introduction

HIV disease has become a chronic condition, with much progress in reaching the 2020 UNAIDS 95-95-95 targets[1]. Viral suppression is not sufficient. People need to be able to lead healthy, productive lives and this should not just be about the absence of disease but also about health and wellness.[2,3] In order to facilitate this, health services must become person-centred and integrated.[4] Silos that exist between HIV and non-HIV services must be eliminated because people living with HIV experience more multiple morbidities than the general population and need seamless access to services to support their health and wellbeing.[5]

PROMs

Patient-reported outcomes provide data that only patients can deliver. They represent the patient's perception of a state, feeling or experience. Patient-Reported Outcome Measures – or PROMs – are tools that help elicit patient perceptions in a standardised way. Patient-reported experience measures (PREMs) are instruments that capture patients' experience with service provision. For the sake of simplicity, this document will refer to PROMs generically unless otherwise indicated. PROMs can be used in clinical trials, clinical practice, health care management and product regulatory and reimbursement assessments.[6,7] PROMs can be generic or disease-specific, and sometimes both can be used in a particular setting to capture different types of patient-reported data.[8] The use of PROMs in clinical practice for individual patients have been shown to positively influence the patient-physician interaction and increase patient engagement.[9]

PROMs in HIV

PROMs for HIV can be used in many ways[10]. The use of PROMs at the individual level can inform clinical decisions that facilitate individualised care for people living with HIV. They provide the basis for individual case management, allowing the people living with HIV and their physicians to prioritise their discussions on current needs, discuss preventative strategies and develop a follow-up plan. At the *institutional* level, patient-reported outcomes in the form of PREMs elicit a person's experience with health services, for quality assurance purposes. Some jurisdictions use PREMs to compare the quality of services among institutions, which can be part of a value-based health care approach[11] . Additionally, aggregated PROMs data can be used to evaluate clinical effectiveness of services provided. Stigma and discrimination in health care settings that lead to negative impacts on access to care can be identified through the use of PROMs.[12] At the *population* level, PROMs provide insight into the effectiveness of the health system in addressing the diverse needs of people

living with HIV. Finally, at the *country* level, the PLHIV Stigma Index is an example of a PROM that provides an overview of systemic problems faced by people living with HIV in different sectors, including health care.[13]

PROMs are becoming increasingly popular in clinical practice. PROMs are useful in assisting with shared decision making by improving patient engagement and the interaction between clinicians and patients. More training for physicians is needed for PROMs to be used optimally in shared decision making in order for physicians to understand the benefit of introducing them into their practice. An approach tailored to service users and providers that addresses the needs of both patients and physicians is required to support the use of PROMs.[14,15,16] The PROgress Project describes strategies for implementing PROMs in clinical practices and provides evidence and a toolkit, primarily from the provider's perspective.[17]

PROMs can be designed to measure a variety of patient perceptions and experiences, including health-related quality of life (HRQoL), adherence-related experiences, health care service experience (PREMs), mental health challenges, physical symptoms, coping strategies, HIV self-management and self-care capability, body image, social support, issues related to sexual and reproductive health and disability.[18] In other words, PROMs can be developed to address almost all of the needs and challenges that people living with HIV might face, which are well documented in the Positive Health Dignity and Prevention Framework.[19,20]

Many PROMs are used in HIV but there is no consensus on which to use or when. Some are generic and others are specific to HIV. PROMs are complex and dependent on the setting where they are used and the population using them, including the language they speak and their culture. PROMs are like any type of measurement tool in that they must be valid (able to measure what they intend to measure) and reliable (the results can be reproduced over repeated measurements). This is referred to as psychometric integrity, which in order to be preserved, requires that they be used intact and unaltered. For instance, if a PROM was validated with a population from Europe, that PROM might not be valid for another setting. Similarly, if a PROM is developed in English, it cannot be simply translated into Russian. In both cases, the PROM would need to be tested once again to ensure its validity. Another example is that a PROM must be used in its entirety. If questions are taken out or added, then the PROM must once again be validated. This points to the need for bespoke PROMs for specific uses.[21] However, this can be costly, time consuming and prevent the possibility of comparing across different groups, which is one of the reasons why generic PROMs are often used.

PROMs and EATG

The EATG has been involved in investigating how PROMs affect research and development for several years. In 2018, PROMs were the theme of one of the European Community Advisory Board (ECAB) meetings where members and pharmaceutical companies discussed the use of PROMs in clinical studies, the development and use of HIV-specific PROMs and the involvement of the community in the development of PROMs. Separately that year, EATG held a webinar led by Diana Barger of the University of Bordeaux to look at the use of PROMs in research and development.[22] EATG has also been part of a consensus-building consortium addressing health outcomes, with patient reported outcomes being one aspect thereof.[23] The EmERGE consortium, of which EATG was a member, used PROMs to measure patient outcomes in the 5-year EmERGE project.[24]

PROMS in other diseases

PROMs are commonly used in clinical practice for other disease areas. In Wales, a national system for collecting PROMs in both English and Welsh has been established.[25] A national system has been implemented in England, reporting on hip and knee surgeries.[26] PROM data provide insight into improvements in quality of life while PREM data provide insight into the quality of services provided as part of value-based health care. The Canadian Institute for Health Information collects data from all of Canada's provinces and territories to drive improvements in health care. They started to collect PROM data at the national level since 2015, with hip and knee replacement surgeries as the initial focus.[27] A systematic literature review showed that the use of PROMs in clinical paediatric practice has shown to improve health-related quality of life (HRQoL).[28]

PROMs are commonly used in cancer research and care and have shown to increase patient engagement and improve HRQoL. Barriers to implementing PROMs into clinical practice include technical barriers, such as connection with existing technology, digital literacy and divide; behavioural issues, such as patients or clinicians not understanding the benefit of PROMs; and service-level issues, such as the lack of clear protocols and lack of integration into the clinical workflow.[29,30]

PROMs in HIV Research and Development

Characteristics of HIV R&D trials

In a clinical trial for medicine research and development, manufacturers and researchers compare a new product with either a standard product or a placebo in a randomised controlled trial (RCT), which is the gold standard for showing differences between the two products. Various types of endpoints can be used, such as a biological marker (blood pressure), a clinical endpoint (survival) or a surrogate measure (liver enzymes to alert for liver failure).[31] It is important that these endpoints have the following characteristics[32] :

- Closely related to the disease (proximal)
- Measurable
- Sensitive to the treatment intervention
- Valid and reliable
- Commonly used by clinicians

The endpoint chosen will be determined by the goal of therapy, including, for example, cure of disease, preventing death and symptom alleviation. Intermediate endpoints can be chosen where final endpoint measurement is not possible; however, there must be a demonstrable link between the intermediate and final endpoint. An ideal endpoint should also add no extra risk or inconvenience to the patient and be part of testing and data capture during routine clinical care.[33]

PROMs as Endpoints

PROMs can be effective endpoints in clinical trials if they embody, as closely as possible, the characteristics of other endpoints.[34] Although PROMs have been implemented in clinical research, there are issues with their use and the impact they have. The use of PROMs for the sake of using them is not in the patient's best interest. It is important that PROMs are well designed to have a beneficial impact on society. A multi-stakeholder approach and adhering to PROMs guidance will optimise PROMs data, minimise research waste and ultimately benefit patients in the future.[35]

Given that HIV treatment is effective and safe, PROMs provide an opportunity as a differentiating endpoint for new product research and development by adding the element of patient erceptions.[36] The types of PROMs used in HIV clinical trials include HRQoL (general or HIV-specific), HIV symptoms, sleep disturbances, psychological symptoms (anxiety, depression, stress and medication beliefs), among

others. Disease-specific PROMs can be useful for Health Technology Assessment agencies (HTAs) when they show an overwhelming advantage of one treatment intervention for that disease compared to another. A good example is the new treatment standard for Hepatitis C treatment. Not only was that intervention found to be clinically superior to the old treatment, the HRQoL of people taking the new treatment was far greater than those who took the old treatment.

However, disease-specific PROMs in HIV trials do not provide the opportunity for comparisons through the calculation of utility, often expressed in quality-adjusted life years (QALYs).[37] This type of health economic analysis provides for a means to compare different treatment interventions among various health conditions by showing the effect of interventions on HRQoL. A perfect score for a QALY is 1, representing one year of perfect health. That might be compared to another intervention with a QUALY of 0.5, representing one year at half the quality of life. These QALY comparisons help to provide information in a non-clinical way to support investment decisions. HTAs, which are responsible for determining if a medicine is reimbursed or not, rely on generic PROMs and health economic analyses to facilitate these comparisons. With limited health-related funds available in a society, health economics helps policy makers and HTAs to compare among competing disease states for scarce funding.

HIV Clinical Study Examples using PROMs

An Italian study showed improvement of patient satisfaction with the switch from a two-pill regimen to a single pill darunavir/cobicistat, based on the use of PROMs. The result supported the goal for the "Fourth 90", with 90% of people who switched and reached viral suppression, achieving a good quality of life, according to the PROMs used.[38] There are many other examples of PROM use in switch trials.[39,40,41] A 48-week trial studying switching HIV regimens showed that it is possible over longer periods to detect and attribute changes in patient-reported outcomes[42]; however, new products must be evaluated with endpoints that are sensitive within the time constraints of clinical trials.

In the assessment of long-acting cabotegravir and rilpivirine versus oral ART, patient-reported outcomes were used and showed improvements from baseline in the patients taking injectable ART.[43] Two main registers of clinical studies are "clinicaltrials.gov" from the National Institutes of Health in the USA and "clinicaltrialsregister.eu" from European Medicines Agency. Several studies from these registers show the use of PROMs in phase II and III studies, mostly as secondary endpoints and related to acceptability, injection site pain or tolerability, treatment satisfaction, medication worry and disclosure worry, as well as generic

HRQoL instruments.[44,45,46,47,48,49,50] A study of leronlimab (PRO 140) subcutaneous injection for HIV treatment looked at the effect of monotherapy on adherence as a primary endpoint and tolerance to subcutaneous injection as a secondary endpoint.[51]

Regulatory authorities and Payers and HTA perspectives

The United States Food and Drug Administration (FDA) published guidance for PROMs in 2009 that addresses the way in which PROMs should be used to substantiate label claims of products submitted for approval.[52] The European Medicines Agency (EMA) published a reflection document in 2005 on the use of health-related quality of life measures in market authorisation applications.[53] In addition, the EMA published guidance on Integrating patients' views in clinical studies of anticancer medicines to inform clinical studies developed for cancer studies.[54]

A review of new FDA product authorisations between 2011 and 2015 showed that only 24.1% of new medicines received labelling corresponding to patient-reported outcomes. The authors suggest that the FDA guidance in 2009 does not adequately incentivise the use of patient-reported outcomes for labelling purposes. There is an opportunity for manufacturers to work closely with patient groups and other stakeholders to identify PROMs as secondary endpoints.[55] In a review comparing EMA and FDA approvals based on PROMs for orphan drugs, the authors found less use of PROMs for this category of medicines than for other categories. They also found that EMA was more likely to approve a product based on PROMs than the FDA[56], which reflects earlier findings on this point.[57]

In general, for the FDA and EMA, PROM endpoints must be contextualised and connected to the various other study endpoints. Both agencies require randomised blind clinical studies; and both require that the instruments be psychometrically sound. Differences include that the EMA's guidance is focussed on HRQoL, whereas the FDA includes all types of PROMs; the FDA prefers short recall methodologies, such as a daily diary, as opposed to instruments where patients must recall their perceptions for longer intervals; and the FDA prefers placebo-controlled trials whereas the EMA includes comparator trials as well as placebo-controlled trials that last for at least 3 months.[58]

Some of the reasons that PROMS-based labelling claims by manufacturers are rejected include lack of PROM validity, poor study design, poor statistical analysis, inadequate documentation and inability to show the benefits of treatment.[59] This infers that more attention must be paid to the quality of PROMs-based clinical trial research, and not limited just to the quality of the PROM itself.

Goals for people living with and affected by HIV

The need for better antiretrovirals: Patient satisfaction

ViiV's Positive Perspectives study showed a range of patient satisfaction with their treatment in Europe: Spain (45%), Austria (47%), UK (58%), Germany (61%). Sixty-five percent of all respondents reported concerns about the long-term effects of their treatment.[60] ViiV's HOPE survey[61] in the USA found that almost one-third of patients were sub-optimally treated. Their definition described people who were unsatisfied with their treatment, even though they had achieved viral suppression. Some of the issues that led to dissatisfaction included issues related to lifestyle, scheduling, skipping doses to avoid side effects, changing diet or missing social or work-related events due to the side effects they experienced. Similar results were seen in another study conducted by ViiV Healthcare in Portugal which revealed that, although most respondents had achieved viral suppression, many experienced challenges with taking their medications, including difficulty swallowing, being stressed by taking doses on a daily basis, and feeling reminded of their HIV status when taking their medications.[62]

A French study found that women living with HIV reported a median of 12 symptoms in the previous 12 months with only half of the women being able to implement self-care strategies to help them cope. Seventeen percent of the women reported making changes to their HIV regimen and, of those, one-third did not inform their clinicians of the changes. Women with financial problems coped less well with side effects. Those who had good relationships with their physicians or had connections with HIV organisations fared better.[63]

Some people living with HIV can benefit from medication reviews with the goal of optimising their ART regimens. Deprescribing can contribute to better patient experiences and it is suggested that patients who had achieved viral suppression, especially those over 50 years old with comorbidities, be evaluated for "pruning back" their ART regimens through reduction of pill burden, switching to a two-drug regimen or switching to long-acting therapy. These strategies will reduce the patient's medicine-related burden, which comprises by pill burden, toxicity and drug-drug interactions.[64]

Survey Results

EATG conducted a survey between 10 November and 1 December 2020 in two languages: English (Annex 1) and Russian (Annex 2). The surveys were distributed via social media (Facebook and LinkedIn) to a broad audience. Only people living with HIV taking treatment were invited to complete the survey.

Demographics

For a full reporting of the demographics of both the English and the Russian version of the survey, refer to the annexes. A total of 96 people responded to the survey: 41 people from 16 countries for the English version and 55 people from 10 countries for the Russian version. The demographics demonstrate the differences in the HIV epidemic in the West and in the East. In both cases, the respondents were mostly male, but with more females reported in the Russian version. The age distribution was similar, except for the inclusion of more young people in the English version. Time of diagnosis and time of starting treatment showed much more variance in the English version, which could be attributable to the delay in the AIDS response in some countries in Eastern Europe. Many more respondents in the English version identified with the MSM and LGBT communities, whereas the majority of Russian-language respondents identified as people who inject drugs, with more than half indicating that the question asking for how they identify was not applicable to them. However, both surveys resulted in a diverse range of identities including migrants, non-injecting drug users, sex workers, prisoners and young people. The total of people with work in both versions was about the same; however, a quarter of those responding in Russian indicated that they had difficulties paying their bills on a monthly basis, while for the English version, this was only 12%. Education level was higher in respondents in the English version.

Analysis

Only 63% of respondents to the Russian version were satisfied with their treatment regimen, compared to over 80% for the English version. This survey shows that people living with HIV have diverse experiences with their treatment. For disturbances (severity and coping), none of the symptoms stood out above the other, except for perhaps sleeping disturbances. The distribution of responses was fairly even in both the English and Russian versions. The ranking in both versions showed similar results, with fatigue, weight gain/loss and sleeping disturbances being the most frequently identified as most important for elimination. In the Russian version, seven people identified gastrointestinal problems while in the English version, none reported, which could be due to the use different ART regimens in the two regions. The question is whether or not PROMs would be useful endpoints to address these side effects in R&D trials, given that many of the disturbances listed are affected by other factors, such as stigma, ageing and being part of marginalised communities. These effects are interrelated and there is a need to ensure that PROMs are attributable to the interventions used in R&D trials. It will be important to find ways to reduce the confounding factors affecting psychosocial and emotional-related PROMs.

In both survey versions, respondents indicated a high level of satisfaction with how their treatment regimen fit with their lifestyle. There were only small differences in the preferences for future treatment options within the English and Russian-speaking groups, with only a variance of approximately one full ranking point among preference items. This was similar for both groups, which can be shown in the following tables.

Table 1: Preference for improving treatment, English-speaking respondents

Improvement preference	**Rank**	**Average**
Fewer pills per dose / day	1	2.29
Hide taking treatment (e.g., through injections instead of pills)	2	2.69
Fewer medications (e.g., dual or mono therapy)	3	3.05
Fewer side effects	4	3.22
Long-acting medication (not having to take medication every day)	4	3.22

Table 2: Preference for improving treatment, Russian-speaking respondents

Improvement preference	**Rank**	**Average**
Fewer pills per dose / day	1	1.71
Hide taking treatment (e.g., through injections instead of pills)	2	2.24
Fewer medications (e.g., dual or mono therapy)	3	2.75
Fewer side effects	4	2.87
Long-acting medication (not having to take medication every day)	5	2.89

It is difficult to draw conclusions from these data; however, while the majority of people are satisfied with their treatment and feel that it fits well within their lifestyle, they would like to see improvements in their treatment. From the survey, there is no trend in terms of what types of disturbances should be prioritised for elimination, but the responses were extremely diverse, including most of the items presented in the survey prompts. Most of those identified are psychosocial, emotional and non-specific and can also be linked with factors unrelated to HIV treatment, making the use of PROMs in trials difficult for this purpose.

Similarly, there is no consensus on what types of innovations people would like to see in their future treatment, making it difficult to prioritise. This heterogeneity could be due to the survey design, with many priority options and a limited number of respondents. Another reason for the lack of convergence in the ranking of options

is due to the fact that the options presented are not mutually exclusive from one another. HIV treatment is currently highly effective with minimal toxicities. This survey shows that, while people are generally happy with their treatment regimens, there are many diverse opinions of how treatment could be improved in the future.

This survey has several limitations. The population was self-selected after the survey was distributed widely on social media. The limited response could have been caused by survey fatigue that evolved in 2020 due to the numerous surveys conducted during the COVID-19 pandemic. The title of the survey, "EATG PROMs in HIV R&D", was not properly understood by many potential participants and did not address why it would be important or interesting for them to take part.

How the use of PROMs in R&D add value for PLHIV (stakeholder interviews)

Stakeholder interviews and focus groups were undertaken to complement the survey of people living with and affected by HIV and the limited amount of research available on PROMs use specifically in HIV research and development. The input from stakeholders does not represent consensus from each sector but rather provides an indication of the perspectives from individuals who are currently using and/or interested in PROMs use in HIV.

Academics

This project's Academic Advisors pointed out that the therapeutic and toxicity profiles of HIV medicines are becoming increasingly similar, making it difficult for companies to demonstrate their products' superiority. As such, companies are turning to PROMs as a way to demonstrate the added value of new products, thus distinguishing them from existing highly effective options. However, the advisors cautioned that PROMs might not always be ideal endpoints because it might be difficult to attribute any changes in these to the product itself, especially when comparing highly effective and generally well-tolerated products.

The FDA has developed guidelines but these address trials mostly in the context of diseases like cancer where historically, patients were exposed to toxic drugs and experienced serious side effects. Many PROMs for HIV look at psychosocial and emotional problems, which can be affected by other factors, such as ageing and comorbidities. The ability for a new product to have an impact on these problems, therefore, may be limited. Most current trials in HIV are non-blinded. The interpretation of PROMS in such trials is unclear due to the strong influence of knowledge of treatment allocation on subjective trial outcomes. It is important to distinguish between PROMs being developed for clinical settings, as opposed to trial settings because they are not necessarily interchangeable. The former requires PROMs to be designed to be responsive to the intervention under study; in other words, a PROM that is totally affected by age-related comorbidities is unlikely to change during a trial if the intervention does not do anything to modify these comorbidities. As with PROMs used for clinical care, PROMS used in clinical trials must be valid and reliable. However, they should also be responsive to change over the period generally covered by the trial (e.g., 12-48 months), as well at specific timepoints during the trial.

In order to determine whether or not a patient-reported outcome is affected by the treatment or another confounding issue, like ageing, one could suggest a longitudinal observational study that would track people's perceptions over time. The challenge with such a study is that it would require timelines beyond normal medicine trial length, and it introduces bias because such studies are not blinded. A trial stratified by age might show confounding effects of ageing versus treatment; however, this might be difficult to implement in R&D trials. PROMs might be useful in short medicine trials and there might be ways in which to reduce confounding for some treatments, in some populations and for some outcomes. However, using PROMs as endpoints in medicine trials is challenging due to the short timelines and generally homogeneous nature of trial participants.

The use of PROMs in any setting are useful when they reflect what is important to people. Therefore, it is important to engage people from the beginning in PROMs development.

Clinicians

Three clinicians were interviewed, one from the Netherlands and two from Italy. All of the clinicians agreed that PROMs have become increasingly important for clinical practice. Treatment is effective and generally tolerable, and clinicians have turned to PROMs to measure HRQoL, which address many factors, including patients' experiences with their treatment. Many PROM instruments are old and include side effects that are no longer relevant. Some of the instruments available are more useful than others. For instance, it is possible to identify psychological issues using PROM tools in clinical practice. However, instruments that measure stigma, for instance, rely on older tools that are based on outdated clinical presentation of HIV disease. Instruments that address sexuality, sleeping difficulties and social support are useful for improving communications between clinician and patient but they are not yet as helpful in problem resolution in the clinic setting. As with clinical trials, attribution of PROMs to treatment is challenging in clinical practice because outcomes can be confounded by age or comorbidities. For example, patients who complain of sleeping disturbances can be switched to another treatment combination with a different side-effect profile. Even when treatment is switched several times, patients' complaints of especially psychosocial and emotional outcomes, including sleeping problems, often remain, making it difficult to rely on these instruments to drive clinical care, underscoring that treatment and care for people living with HIV comprise more than just the antiretroviral medicines they take.

Originally administered in the form of long checklist-type questionnaires, advances in technology and the onset of the COVID-19 crisis have enabled advances in PROM collection. Technology allows for continuous monitoring of patient reported outcomes over time instead of relying on clinic visits. Developments using mobile phone apps, such as the Happi app[65] in the Netherlands, not only collect patient-reported outcome data but do so through prompts over time that encourage responses. The introduction of gamification functionalities addresses patient concerns about filling in multiple questionnaires at a single sitting and its pharmacy function provides automated home delivery of medicines. Similarly, the use of in-home smart speakers, such as Amazon's Alexa in Italy, provides people with in-home prompts over time to check in with how there are feeling, what they have eaten that day and other lifestyle-related questions. Both approaches allow for data collection which then can be stored and analysed to generate algorithms that can inform practice perhaps even better than validated PROM instruments.

Clinicians in both countries agreed that there is no one solution for improving treatment of HIV or comorbidities for people living with HIV. Even the most perfect drug will be faced by diverse patient population living in diverse environmental situations. Therefore, it is important that PROMs evolve to inform the development of products that address a diverse set of patient needs. This is essential to ensure a good quality of life for people living with HIV so that they can enter and remain in the continuum of care not only to benefit their own health but also to remain non-infectious, which is a clear differentiating factor for HIV disease. Therefore, it is important for future research to quantify and qualify the impact of psychosocial and emotional factors, such as mental health and stigma, on adherence and the wellbeing of people living with HIV in order to convince stakeholders to invest in, approve and reimburse innovative new treatments for HIV. To support this, clinical trial design, which currently looks at short timelines with homogeneous patients, must focus in the future on patient stratification, clustering and the potential for PROMs to become primary clinical endpoints.

Pharmaceutical Companies

PROMs are important to pharmaceutical companies in order to differentiate new products and drive product development. While it is generally accepted that current HIV treatment is effective with limited toxicity, patient-reported outcomes can address important needs of people taking treatment. For instance, it was thought that in some cases side effects disappear after several weeks of initiating treatment. However, it has been found that, rather than the side effects disappearing, people have simply become used to them. Switching treatment regimens for some people becomes a relief as these symptoms finally disappear. PROMs can be

useful in tracking these issues and identifying potential opportunities for product improvement.

The industry uses different sorts of PROMs, including generic, HIV-specific and bespoke PROMs. They place an emphasis on making sure the instruments are psychometrically sound: valid, specific and reliable. The role of the industry is complex. Aside from bringing novel products to market, the industry is jointly responsible for the appropriate use of their products and, as such, use PROMs for reimbursement decisions and to inform policy guidelines and clinical practice. Presently, PROMs are mostly used as secondary or even exploratory endpoints, not primary endpoints. In order for PROMs to gain traction as primary endpoints, many things would need to happen, including identifying important concepts to measure, and developing and validating new PROMs with greater sensitivity to differentiate between treatment arms. Regulatory authorities need to provide better guidance around the implementation of PROMs for labelling purposes in assessing HIV treatment.

The future goal of inclusion of PROMs in HIV drug development is to establish PROMs as a key endpoint to differentiate on important concepts and to be added to product labels. PROMs have been used to incorporate patients' voices in drug development, an example of which is cabotegravir/rilpivirine injectable. At first, stakeholders including health care professionals speculated that people living with HIV would reject injections due to pain and the need to go to facilities. PROMs included in clinical trials were able to assess patient preferences between intra-muscular injections and daily therapy. The group pointed to the development of other long-acting forms of treatment as areas where PROMs might be useful.

Patient diversity is an issue that is difficult to address in R&D trials. Given the homogeneity of the population and the short duration of the trials, it is difficult to develop PROMs that will be predictive of perceptions of diverse groups of people living with HIV. That said, there is an important after-market role for pharmaceutical companies to play in supporting clinical trials in diverse populations to inform clinical practice. There is also the possibility for PROMs to inform adjustments to labelling as a result of longer-term observational studies; however, this is less likely to drive product development and will be more useful in defining good clinical practice.

Pharmaceutical companies look forward to collaborations with patient groups, physicians and regulators to discuss the further development and implementation of PROMs.

Regulators / HTA

Regulatory bodies did not agree to participate in a focus group for this project. We did get input from an expert who participates as a member of the HTA Patient and Citizen Involvement in HTA Interest Group. He indicated that PROMs are generally only one of many elements of evidence that are submitted for HTA appraisal. HTA agencies can be very different in their approaches, but there are two main categories of assessment methods used: relative clinical effectiveness (does a product deliver clinical benefits beyond what we have with current treatments) and cost effectiveness analysis (does the value of benefits provided to patients and the healthcare system reflect its cost). The latter applies the same cost threshold across all disease areas and generally looks to recommend reimbursing medicines that fall under these cost thresholds. Importantly, cost effectiveness analysis often use a general measure of benefit that applies across disease areas, called a Quality Adjusted Life Year (QALY).

The problem with PROMs in cost-effectiveness analyses is that they favour the use of generic PROMs that can be compared across disease areas. Disease-specific PROMs cannot be compared across diseases in the same way. An additional challenge is that, although there is a proliferation of disease-specific PROMs that could be useful for regulatory approval, many are not necessarily familiar to the HTA bodies. The development of new PROMs in a disease area also means it is hard for decision makers to compare the results with those of earlier treatments that used different PROM tools.

People may want to take one pill per day instead of two for convenience but, unless there is a demonstrable outcome benefit to the decreased pill burden, like, for instance a marked improvement in adherence and subsequent decrease in viral resistance, HTAs are not likely to recognise the value in their assessments. Therefore, while PROMs may provide evidence of an incremental improvement in quality of life, the assessors will be looking for additional evidence that shows how this translate to meaningful outcomes that have not been possible with previous therapies.

There is also a growing divergence between the approach of regulators and HTA bodies regarding the evidence they need for their respective assessments. Regulators are looking at innovative trial designs and looking for ways to shorten the time to the regulatory approval of a medicine, which can lead to clinical studies of a shorter duration, or without an active comparator. HTA bodies find it very hard to assess a medicine in comparison to available therapies when this kind of abbreviated evidence is presented to them.

Pharmaceutical companies should take advantage of the opportunity for early dialogues with regulators and HTAs in which patients often also participate. They can present evidence-generation plans, including PROMs. This way, they can identify the benefits of PROMs for patients, the industry, regulators and HTAs.

Role of People Living with HIV

People living with HIV should be involved in every stage of the development or adaptation of PROMs and this is also true for other disease areas.[66] PROMs development without patient engagement leads to the design of instruments that do not address what is important to patients. Patient groups can be useful in several ways, according the European Patients' Academy on Therapeutic Innovation (EUPATI).[67] The most obvious role lies in the necessity for patients to be involved in the validation of PROMs to ensure that they measure what they are supposed to measure. However, before this stage, patients should be involved in the creation of conceptual frameworks that link different aspects of disease and wellness to the treatment intervention. This informs drug development from the start and demonstrates to regulatory bodies and HTA agencies that the manufacturer is addressing the expressed needs of patients in their research and development. Patient groups can be helpful in endorsing PROMs and disseminating information about them.

An HIV-specific PROM that was developed with the involvement of people living with HIV is the Positive Outcomes HIV PROM, which is designed to be used in the clinical setting. People living with HIV were involved as part of the steering group and were consulted at all stages in the research.[68]

Patient groups can work together to provide testimony in favour (or not) of a particular new medicine that is in the approval process. A good example of this is the submission of a patient input report by a coalition of HIV and LGBTQ organisations to the Canadian Agency for Drugs and Technologies in Health that provided important person-centred information about the need for long-acting injectable ARTs that supported ViiV's application for cabotegravir-rilpivirine injections.[69]

Guidance from the FDA and EMA call for patient involvement and Wiering suggests that patients need to be consulted to establish face and content validity of PROMs.[70] While in agreement, Blackburn argues that patients should be integrated into the PROM research team and be engaged to fully participate in the entire spectrum of activities from developing the PROM to research to interpretation of results.[71] This will sound familiar to people living with HIV in that the fullest implementation of GIPA requires integrated involvement at all levels.

In fact, although the FDA advises that patients should be involved in PROM validation, patients should be involved in all aspects of PROM development,

including citing the need for a new PROM, developing a conceptual model, developing the instrument, being involved in the survey design and analysis and, as mentioned previously promoting and disseminating information about the PROM. Some of the challenges of including patients in all aspects of PROM development include time and cost, building relationships, planning for patient engagement, finding ways to support people with limited capacity to participate (children, people with disabilities and people with mental health issues), and dealing with variances in culture and language. However, the benefit of patient involvement is that it will improve the quality of the end product.[72]

Patients are not always involved in the development of PROMs and, when they are, there is no consistency to their level of involvement. This occurs in spite of the availability of published guidance and the need for patients to validate PROM instruments. There is a need for better guidance and consensus building to promote more and better patient involvement.[73]

The following figure is taken from Addario et al. and clearly outlines the depth and breadth of patient involvement in the PRO lifecycle. The goal of patient involvement is to improve design, reduce missing data and positively impact regulatory processes, policy decisions, shared decision making, and ultimately patient outcomes.[74,75]

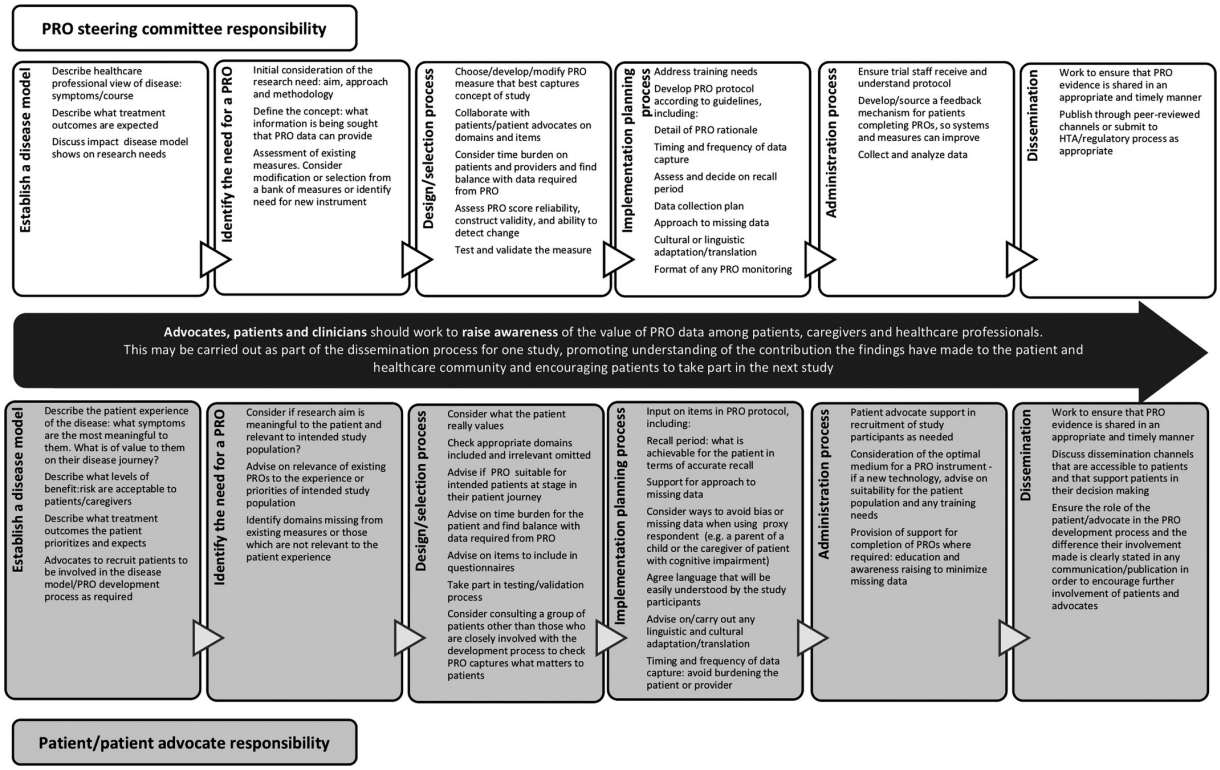

FIGURE 1 Including the patient voice in the development and implementation of patient-reported outcomes in cancer clinical trials from Addario et al.[76]

The similarities are apparent between patient engagement in PROMs and the greater involvement of people living with HIV. The following figure compares levels of patient involvement in PROM development with an early simplistic representation of GIPA, the greater involvement of people living with HIV showing the parallels between the two.

Figure 1. A pyramid of involvement by PWHAS
This pyramid models the increasing levels of involvement advocated by GIPA, with the highest level representing complete application of the GIPA principle. Ideally, GIPA is applied at all levels of organization.

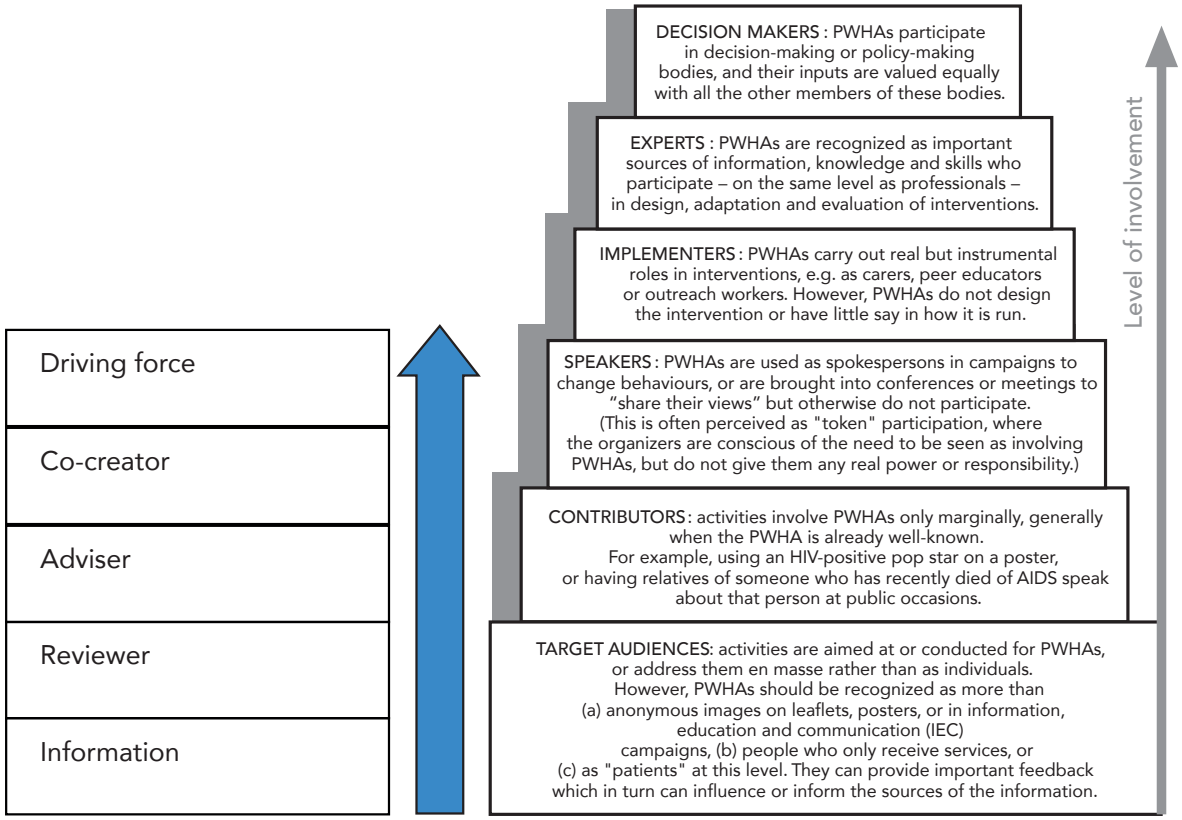

FIGURE 2 LEFT: Levels of patient and patient advocate engagement (adapted from Wilson et al, cited in Addario et al.[77])

RIGHT: Pyramid of involvement of PWHAS (UNAIDS, 1999[78])

Recommendations

Organisations working on behalf of people living with and affected by HIV

Role of People Living with HIV

Similar to the GIPA principle, the practice of engagement of people living with HIV should be integrated at all levels of PROMs development and execution as engaged stakeholders at all times.

Needs of People Living with HIV

The needs of people living with HIV are diverse. People living with HIV reported in the EATG survey and other sources that they experience disturbances (side effects) and have preferences for changes in their treatment. In both cases, the needs are variable, with no clear trend on priorities. Many of the experiences are related to psychosocial and emotional factors associated with HIV and/or treatment. More work needs to be carried out to further qualify and quantify the diverse needs of people living with HIV and translate these into opportunities for new product development. To facilitate this, PROMs can be used in clinical trials; however, more emphasis on finding PROMs that are suitable for R&D timelines is required. PROMs need to be linked to clinical outcomes in order for regulatory bodies and HTAs to find product superiority, not just in comparison to current HIV treatment but also compared to funds available to support other healthcare interventions.

PROM Literacy

Organisations working on behalf of people living with and affected by HIV should provide capacity building for people to understand the role and importance of PROMs in their health and wellbeing, including in their clinical care and participation in research and development trials. They should be able to take decisions on engaging with PROMs that optimise health outcomes while minimising extra reporting burden and research waste.

Pharmaceutical Companies

Pharmaceutical companies should include PROMs in HIV R&D only when it makes sense to do so based on consultation with people living with HIV. Given the short timelines of R&D clinical trials, it is unlikely that PROMs will become the main primary endpoints. However, when PROMs are used, they should be developed and implemented in a meaningful and efficient way, in collaboration with people living with HIV, in order to minimise research waste and optimise results. Observational trials, which tend to be longer in duration, should be investigated for their ability to inform product development with PROMs as endpoints. Companies working to

design pre-market clinical trials should investigate the development of more sensitive PROMs for issues that are important to people living with HIV. Pharmaceutical companies should continue to work with people living with HIV and researchers to identify ways that PROMs can influence practice guidance after market authorisation in phase IV trials and beyond.

Researchers and Clinicians

Researchers and clinicians should be encouraged to continue research into new PROMs instruments that are useful in clinical practice, as well as clinical research. The development of new PROMs tools that are sensitive to shorter timeframes and allow for better attribution to treatment arms would improve the possibility for PROMs to be used in HIV R&D. Connecting these enhanced PROMs related to psychosocial and emotional issues, such as mental health, to clinical outcomes in the continuum of care will help to build the investment, regulatory and reimbursement case for new and improved treatments for HIV. Investigations into better and more meaningful ways to collect patient data will improve response rates and provide pools of data that can be mined to develop algorithms to inform clinical care and the development of new products.

Regulatory Bodies and HTAs

Regulatory bodies should develop better guidance that addresses labelling as a result of the use of PROMs in HIV research and development. Dialogue among regulatory bodies, HTAs, the pharmaceutical industry and groups of people living with HIV will lead to the development of products that will better address the challenges that people living with HIV face and ultimately improve their clinical results and save money. Given that HIV is a chronic disease with lifetime intake of medicines, it will be important for pharmaceutical companies and regulators to continually monitor the effects of long-term side effects and, because of this, adjust product labelling to reflect new information obtained from clinicians and people living with HIV, through pharmacovigilance and after-market reporting of PROMs.

HIV is an infectious disease and addressing the disturbances that people living with HIV face can reduce the number of people who become resistant to treatment or lost to care, thereby reducing the risk of onward transmission. While a reduction of pill burden for someone living with hypertension might be seen as a luxury, for a person living with HIV, it might be the difference between whether or not their viral load becomes undetectable and therefore untransmissible. Therefore, regulatory agencies and HTAs should implement stronger guidance for the development and use of PROMs in HIV, ensuring the involvement of people living with HIV at every stage of development.

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Annex 1: PROMise Survey Results – English

Part 1 - Demographics[1]

1. Country	% Each	N Each	% Total	N Total
CZ	29	12	29	12
D	10	4	10	4
I, NL, R, UK	7	3	28	12
F, GR, E	4,8	2	14	6
B, HR, IS, IE, RF, TR, VA	2,4	1	17	7

2. Age	%	N
21-29	22%	10
30-50	32%	13
>50	10%	4

4. Year of diagnosis	%	N
Pre-1996	22	9
1996 and after	37	15
Those who responded "other"	40	17

6. Year starting treatment	%	N
Pre-1996	12	5
Post-1996	47	19
Those who responded "other"	40	17

7. Undetectable	%
Yes	85
No	2
Don't know	12

8. Gender Identity	%
Man	85
Woman	7
Non-binary	2
No answer	2

[1] Total number of respondents = 43. Note that variances in totals and percentages are due to missing responses.

9. Gender assigned at birth	%
Cis	90
Trans	5
No answer	5

10. Identity with key population groups	%
MSM	33
LGBT	28
Migrant	10
Non-injecting drug user	9
Sex worker	4
Young people	4
Injecting drug user	3
People with disabilities	3
Prisoners	1

11. Education	%
University	71
Post-secondary	22
Up to secondary	7

12. Employment	%
Employed	46
Self-employed	29
Retired	15
Student	2
Unemployed	7

13. Ability to cover monthly costs	1 (not difficult)	2 (somewhat difficult)	3 (neutral)	4 (very difficult)	5 (extremely difficult)
%	46	12	29	7	5
	58% not at all to so-mewhat			12% v difficult to extremely diff	

14. Satisfied with treatment	1 (not at all satisfied)	2 (somewhat satisfied)	3 (neutral)	4 (very satisfied)	5 (extremely satisfied)
%	0	7	10	27	56
				83% v satisfied to extremely satisfied	

15. Experience Disturbances	Number	%
Yes	16	39
No	25	61

Part 2 - Current Treatment[2]

1. Symptom 1	Number of responses	Severity	Ability to manage
Sleeping problems	3,2	2,2	5
Stomach / intestinal problems	4	2	1
Lipodystrophy	3	2	1
Neurological problems	3	3	1
Weight disturbances	3,5	2,8	4
Fatigue	3	3	1

2. Symptom 2	Number of responses	Severity	Ability to manage
Sleeping problems	3	2	2
Neurological problems	3.5	2.5	2
Weight disturbances	1	0	1
Fatigue	3	2,7	3
Neuropathy	5	1	1
Psychological problems	2	3	1

3. Symptom 3	Number of responses	Severity	Ability to manage
Sleep problems	4	3	1
Fatigue	2,5	3	2
Neuropathy	4	3	1
Other	2	2	3

[2] Respondents were asked in questions 1, 2 and 3 to identify the top 3 disturbances (side effects) they experience, along with the severity (1 low to 5 high) and ability to manage (1 not well at all to 5 very well).

4. Treatment fits with lifestyle	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very well)
%	5	10	15	20	50
				70% Fits well or very well	

5. Does anything else make it difficult to take medicines regularly?	
No	80%
Yes	8%

Part 3 – Future Treatment

1. Importance of decreasing disturbances	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very important)
%	2	0	15	2	80

2. Is reducing disturbances more or less important than dealing with other difficult aspects of your life	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very important)
%	5	5	27	37	27

3. Ranking of preferences for measures to improve future treatment.	Average	Rank	Missing data
Fewer pills	2.29	1	2
Hide medication (eg. injections)	2.69	2	1
Fewer medications	3.05	3	3
Fewer side effects	3.22	4	4
Long acting medications	3.22	4	4

4. Priority of which side effect to eliminate (based on selecting top three)	**%**
Weight gain	18
Fatigue	16
Sleeping problems	12
Stomach / intestinal problems	10
Lipodystrophy	9
Neuropathy	8
Sexual problems	8
Psychological problems	7
Neurological problems	5
Musculoskeletal problems	3
Weight loss	2
Skin problems	1

Annex 2: PROMise Survey Results – Russian

Part 1 - Demographics[1]

1. Country	% Each	N Each	% Total	N Total
RU	40	22	40	22
UA	40	22	40	22
EE	5	3	5	3
KZ	4	2	4	2
BY, KG, LV, CZ, MD, CH	2	1	14	6

2. Age	%	N
21-29	2	1
30-50	80	44
>50	18	10

4. Year of diagnosis	%	N
Pre-1996	2	1
1996 and after	98	54

6. Year starting treatment	%	N
Pre-1996	0	0
Post-1996	100	55

7. Undetectable	%
Yes	93
No	2
Don't know	2

8. Gender Identity	%
Man	69
Woman	17
Non-binary	0
No answer	0

[1] Total number of respondents = 55. Note that variances in totals and percentages are due to missing responses.

9. Gender assigned at birth	%
Cis	98
Trans	0
No answer	2

10. Identity with key population groups	%
MSM	11
LGBT	2
Migrant	2
Non-injecting drug user	8
Sex worker	3
Young people	0
Injecting drug user	15
People with disabilities	8
Prisoners	2
Not applicable	52

11. Education	%
University	45
Post-secondary	51
Up to secondary	4

12. Employment	%
Employed	65
Self-employed	18
Retired	2
Student	0
Unemployed	4
Other	11

13. Ability to cover monthly costs	1 (not difficult)	2 (somewhat difficult)	3 (neutral)	4 (very difficult)	5 (extremely difficult)
%	13	11	49	18	9
	24% not at all to so-mewhat		Neutral	27% v difficult to extremely diff	

14. Satisfied with treatment	**1** (not at all satisfied)	**2** (somewhat satisfied)	**3** (neutral)	**4** (very satisfied)	**5** (extremely satisfied)
%	2	9	25	25	38
				63% v satisfied to extremely satisfied	

Part 2 - Current Treatment[2]

1. Symptom 1	**Number of responses**	**Severity**	**Ability to manage**
Sleeping problems	3	3	3
Stomach / intestinal problems	3	3	1
Lipodystrophy	4	2	1
Neurological problems	0	0	0
Weight disturbances	4	2,3	4
Fatigue	3.3	2.7	3
Neuropathy	5	1	1
Musculoskeletal problems	4	3,5	2
Psychological problems	1	3	1

2. Symptom 2	**Number of responses**	**Severity**	**Ability to manage**
Sleeping problems	3	3	3
Neurological problems	0	0	0
Weight	3.5	2	2
Fatigue	4	2,5	5
Neuropathy	2	1	1
Psychological problems	3	2	2
Musculoskeletal problems	4	1	2
Stomach / intestinal problems	3	3	2

[2] Respondents were asked in questions 1, 2 and 3 to identify the top 3 disturbances (side effects) they experience, along with the severity (1 low to 5 high) and ability to manage (1 not well at all to 5 very well).

3. Symptom 3	Number of responses	Severity	Ability to manage
Sleeping problems	0	0	0
Fatigue	3	3	1
Neuropathy	0	0	0
Musculoskeletal problems	5	1	1
Stomach / intestinal problems	3,6	1,8	5
Weight disturbances	4	3	1
Psychological problems	4	3	1
Other	0	0	0

4. Treatment fits with lifestyle	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very well)
%	4	5	2	4	85
				89% Fits well or very well	

5. Does anything else make it difficult to take medicines regularly?	
No	78%
Yes	22%

Part 3 – Future Treatment

1. Importance of decreasing disturbances	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very important)
%	4	5	2	4	85
				89% say it's very important	

2. Is reducing disturbances more or less important than dealing with other difficult aspects of your life	1 (not at all)	2 (somewhat)	3 (neutral)	4 (well)	5 (very important)
%	9	22	25	18	25
				43% say it's more important	

3. Ranking of preferences for measures to improve future treatment.	Average	Rank	Missing data
Fewer pills	1.71	1	several
Hide medication (eg. injections)	2.24	2	several
Fewer medications	2.75	3	several
Fewer side effects	2.87	4	several
Long acting medications	2.89	5	several

4. Priority of which side effect to eliminate (based on selecting top three)	%
Fatigue	16
Weight gain	15
Sleeping problems	11
Stomach / intestinal problems	10
Lipodystrophy	10
Psychological problems	9
Sexual problems	7
Neurological problems	7
Neuropathy	6
Musculoskeletal problems	5
Weight loss	2
Skin problems	1

European
AIDS Treatment
Group

About the European AIDS Treatment Group:

The European AIDS Treatment Group (EATG) is a patient-led NGO that advocates for the rights and interests of people living with or affected by HIV/ AIDS and related co-infections within the WHO Europe region. Founded in 1992, the EATG is a network of more than 180 nationally-based members from 47 countries in Europe. Our members are PLHIV and representatives of different communities affected by HIV/AIDS and co-infections. EATG represents the diversity of more than 2.3 million people living with HIV (PLHIV) in Europe as well as those affected by HIV/AIDS and co-infections. For more information, please visit www.eatg.org