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Health-related Quality of Life Assessment after Antiretroviral Therapy: A Review of the Literature

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Abstract

Antiretroviral (ARV) treatment for HIV infection has resulted in significant improvement in immunologic and virologic parameters, as well as a reduction in AIDS-defining illnesses and death. Over 25 medications are approved for use, usually in combination regimens of three or four ARVs. Several ARVs are now available as combinatorial products, which have been associated with better adherence. However, while ARV therapy has prolonged life, ARVs also pose a challenge for quality of life as they can cause significant side effects in addition to the potential for drug toxicity and interaction. Given the many complications, side effects and symptoms of HIV/AIDS in addition to associated medical and psychiatric co-morbidities, the need to understand and assess how these interactions may affect health-related quality of life (HRQOL) has grown. Numerous instruments (some validated, others not) are available and have been applied to understanding how ARV treatment affects HRQOL in those with HIV infection, both in clinical trials and clinical practice. In general, ARV treatment improves HRQOL, but this is dependent on the population being studied, the HRQOL instrument being used and the timeframe during which HRQOL has been studied. This article provides a review of the literature on quality of-life assessment as it relates to ARV treatment in developed countries and briefly reviews the HRQOL instruments used, how they have been applied to ARV utilization, and where future research should be applied in HRQOL assessment and HIV infection.

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1 Introduction

The World Health Organization (WHO) estimates that there are over 34 million people infected with the human immunodeficiency virus (HIV)-1 globally, with the majority of those infected living in the developing world and 2.9 million new infections in 2010 [1]. The development and dissemination of antiretroviral (ARV) therapy (ART) has resulted in significant reductions in mortality associated with HIV infection and its complications worldwide. Despite international programs to produce and distribute low-cost ARVs among developing nations, only 8 million HIV-infected people have access to ART in these countries as of 2011, with the goal to start another 7 million on therapy by 2015 [1]. While utilization of ARVs in developed countries is more widespread and has led to significant improvement in outcomes, the incidence of new HIV infections remains stable in the US at approximately 50,000 new cases annually [2]. Multiple factors are likely contributory and include continued high-risk behavior among high-risk groups [i.e., injection drug users (IDU), men who have sex with men (MSM), and sex workers], lack of awareness of infection status, access to or retention in HIV care and ARV adherence issues leading to ARV-resistant virus transmission, among other factors.

For individuals infected with HIV, its effects are broad: day-to-day activities, relationships and health status are profoundly changed. In resource-rich settings what was once a death sentence is now a chronic illness, and this in turn has created new challenges for health care providers and the health care industry. As a result of these changes, HRQOL is becoming increasingly important as an outcome of therapy. Herein, we define HRQOL as per the Centers for Disease Control and Prevention (CDC)'s definition as those components that contribute to quality of life that can affect both physical and mental health [3].

Within the HRQOL field, there have been many tools developed specifically for HIV as well as general health questionnaires adapted for use in this population. This article provides an overview of the tools available, the methods used for validation, the impact that ART has had on the HRQOL of HIV-infected people, as well as looking at some of the most important adverse effects of ARVs and co-morbidities.

2 Discussion of Literature Search

For the review of HRQOL tools and measures, we did a literature search using PubMed, Web of Science, Cochrane, MEDLINE and Scopus. Specific search terms and their combinations included "HIV," "HRQOL Measures," "quality of life" and "health status." We additionally looked at the reference lists of other HIV HRQOL papers. Finally, to ensure that all tools were accounted for to the best of our knowledge, we utilized Internet databases to look for other HRQOL tools (http://www.proqolid.org). We found a total of 18 HIV-specific measures and 44 generic HRQOL measures. We excluded tools for further discussion if they were not represented within the HIV HRQOL literature, and therefore Table 1, which lists HRQOL tools, includes 24 generic measures.

The tools discussed in the review section include both generic and HIV-specific tools, which have a sufficient number of studies to comprehensively assess HRQOL. In addition, we also

briefly describe some tools that have been used in studies to assess HRQOL in patients receiving ARVs in the second part of the paper.

We excluded articles not in English, if they pertained more to adolescent and pediatric populations, if they primarily looked at populations in the developing world or if they were predominantly focused on socioeconomic, psychologic and/or cultural impacts of HIV on HRQOL.

In order to review HRQOL in HIV patients on ART, a literature search was done using broad search terms such as “HIV,” “health-related quality of life,” “antiretrovirals” and individual antiretroviral drug names. We excluded articles pertaining to cost effectiveness rather than quality of life of various regimens. The journal articles we discuss in detail in our review include ARVs currently in use.

3 Instruments

A good tool for HRQOL measurement must be both valid and reliable [4–6]. In addition, given the spectrum of disease, HRQOL tools must be able to discriminate across a spectrum of patients from the asymptomatic to patients at the end of life and ideally be applicable across a range of patient populations (i.e., women, different countries, languages) [4–6]. Given that HRQOL measures a patient’s perspective on their own health, ideal HRQOL tools should take into account patient preferences and instruments should be developed that utilize input from patient groups. Additionally, tools should be easy to administer and appropriate to the setting, i.e., in a clinical trial or during the clinic visit. Some tools may only take 5–10 min to complete and can be self-administered, while others are more time consuming and are administered by an interviewer.

Within the HRQOL field, certain measurements are utilized to determine the validity and reliability of the tools in question. The measurements must demonstrate construct validity as well as maintain reliability when patients are retested [4–7]. In addition, given the dynamic nature of patient’s attitudes toward their health at different disease stages, in response to adverse events, symptoms or ARV regimen changes, the HRQOL tools must be responsive to these changes [4, 5, 7]. Lin et al. [5] offer an excellent discussion of both how to select HRQOL tools for use in clinical trials as well as an explanation of validity and reliability as they apply in psychometric research.

The methods used to measure validity and reliability within the HRQOL research include the use of Cronbach’s alpha co-efficient [5, 7–9]. The Cronbach’s co-efficient is a measure that is used to calculate the internal consistency of a tool [5, 7–9]. The goal of HRQOL tools is to demonstrate high internal consistency with higher consistency having a Cronbach’s coefficient closer to 1 [8]. It is generally accepted that values greater than 0.7 indicate good reliability and thus validity [5, 7, 8]. Each time the test is administered, alpha coefficients should be measured, as they are only truly reliable if calculated during each administration [5, 8]. Additionally, tools must be developed that minimize the floor and ceiling effects that can occur when many of the subjects score either maximum or minimum scores; when this occurs it is difficult to detect changes that occur above or below the floor or ceiling [10]. Other important psychometric properties include reliability such that the answers remain

similar between repeated testing [9]. Additionally, construct and content validity must also be established. Content validity ensures that the tools measure all aspects of a given question, while construct validity ensures that the tool measures what it purports to measure [9]. Responsiveness assesses the tools' ability to detect changes within patients or populations over time [4, 9]. Finally, the Cohen's *d* test is a statistical measure that looks at the effect size that is standardized between two means [11].

Many HIV studies have utilized generic scales such as the Quality of Well-Being (QWB) scale, short form 36 (SF-36) and Euroqol-5D (EQ-5D), and these tools do have their place in the field. However, given the nature of HIV infection, specific HIV scales have been designed. With regard to specific HIV scales, the Medical Outcome Study-HIV (MOS-HIV) health survey and WHO quality of life-HIV (WHOQOL-HIV) scale are among the most commonly used. A number of review articles have assessed the HRQOL tools in use and have gone into more detail regarding which tools are most useful in particular situations, have better reliability and give greater detail about what is measured within each tool [4, 5, 9, 12, 13]. Some of the review articles were published early on [9, 14, 15] and others later in the HIV epidemic [4, 7, 12, 16]. We briefly discuss some of the tools used for HRQOL research.

Table 1 (Tools for Measuring HRQOL) lists the HRQOL instruments used in the articles reviewed in this paper including the tools that are discussed in more detail in Sect. 4. In addition, the table identifies other instruments that have been utilized in the HRQOL field. What follows is a brief discussion of these instruments that is not meant to be exhaustive. The tools discussed here were selected given their prevalence in the HIV HRQOL literature.

4 Brief Review of Selected HRQOL Tools

The Medical Outcomes Study-Based Quality of Life Measures (MOS) [17] are generic scales that have also been adapted into an HIV-specific scale (MOS-HIV). It is also known as the short form, and there are a number of short forms (SF) available [9, 15]. The tool has two summary scores—the physical health score and mental health score—and has up to nine domains: physical functioning, mental functioning, social functioning, clinical status, vitality, pain, health transition, role limitations and life satisfaction. Given that there are a number of scales, some scales have as few as 8 items and others as many as 149 items [4, 9, 12, 15]. The scales are self-administered and take anywhere from 5–40 min to complete. Within the short form 36 (SF-36), the scales are combined into the physical component summary (PCS) and the mental component summary (MCS) and range from 0 to 100, with higher scores associated with better quality of life [4, 9, 12]. The short form 8 (SF-8), on the other hand, has only eight questions, with each representing one domain, and is empirically based on the SF-36 but also draws from other questionnaires [18]. Given the variety of MOS instruments available, it is relatively easy to find one for use in specific scenarios or for time constraints [15].

The Quality of Well-Being (QWB) scale [19] was developed in the 1970s, is administered by an interviewer and takes approximately 20 min to complete [4, 13]. It looks at five domains: physical functioning, emotional functioning, mobility, self-care and social

functioning. It has been validated extensively and appears to correlate well with CDC stage of HIV disease [13]. It assigns a single numerical score that ranges from 0 to 1 (death to optimal well-being) [9, 13, 15]. The QWB is better able to assess physical impairments than mental/cognitive and therefore may miss some of the emotional challenges associated with HIV infection [15]. It can be used to look at data for groups of patients in addition to the individual patient [4].

The Nottingham Health Profile (NHP) [20] is a generic HRQOL measure that is self administered. It asks the patients for immediate recall information. The areas it is interested in include: pain, sleep, physical mobility, energy, social isolation and emotional reactions. The patient answers yes/no to a number of statements, and each section is scored from 0 to 100, with 0 corresponding to no problems/concerns within that area. It is relatively brief and has been in use for many years, and it therefore may be more easily interpretable.

The Quality-adjusted Time Without Toxicity (QTwist) is a generic measure that looks at both quality of life and quantity of life after adjustment for quality of life years [21]. It is used to look for patient survival related to complications or toxicities of the disease/therapy used. It may be used in population studies and is good for use in modeling studies.

The Sickness Impact Profile (SIP) [22] is a measure that has a total of 136 questions grouped into 12 domains: alertness, social interaction, communication, mobility, home management, ambulation, body care, rest, sleep, eating and recreation; it is either self-administered or given by an interviewer and takes up to 20 min to complete [4, 13]. Scores are based on percentages; higher scores correlate to increased dysfunction and can be summed into a total percentage as well as broken down into different domains. It focuses more on physical limitations, which may be ideal in situations where the degree of patient disability needs to be assessed [4].

The Euroqol-5D (EQ-5D) [23] is a scale with two components—a questionnaire and a visual analog scale (EQ-VAS) [12]. The first part has five dimensions and can define up to 243 health states [12]. The five dimensions include: mobility, self-care, pain/discomfort, anxiety/depression and usual activity [24]. It has been validated for use in multiple studies in HIV patients and has shown good psychometric properties with fewer ceiling effects in HIV patients than in the general population [12]. It is available in multiple languages, can be self-administered or by proxy, electronically and over the telephone. Given its emphasis on activities of daily living and self-care, it may be helpful in the clinic setting to address which areas may need intervention.

The Health Utilities Index (HUI) [25, 26] can describe up to 972,000 disease states [12]. Like the EQ-5D, its psychometric properties within the field of HIV have been well established, and it appears to be very responsive to different HIV disease states [12]. It may be self-administered or given by an interviewer and may also be completed electronically, similar to the EQ-5D. It has also been translated into multiple languages. It asks the recipients to recall the events of the last 2 weeks [24]. It has eight domains: vision, ambulation, dexterity, emotion, cognition, hearing, speech and pain [24].

There are other health utilities tools that have been utilized in multiple HRQOL studies, including the Time Trade-off (TTO) [27] and the standard gamble (SG) [28, 29]. The TTO asks patients if they would rather live 15 years in their current health state versus a shorter amount of time in perfect health. Finally, the SG asks the patient what is the maximum chance of death they are willing to exchange for perfect health.

The WHO developed two tools to look at quality of life: WHOQOL-100 and WHOQOL-BREF [30]. These tools were developed across 15 centers worldwide and with the hopes that this would increase cross-cultural validity. The WHOQOL-BREF has 26 items derived from the WHO-QOL-100. The domains measured include: physical health, psychological health, social relationships and environment. In addition to the WHOQOL-100 and WHOQOL-BREF, there have been other measures adapted for more specific disease states including HIV with the WHOQOL-HIV [31]. This tool has 120 items, and the WHOQOL-HIV-BREF, which is adapted from the WHOQOL-BREF, has 31 items. The WHOQOL-HIV also takes into account body image, which is quite important for patients with HIV/AIDS and therefore may be useful in clinical settings where lipodystrophy is addressed.

In addition to the generic scales discussed above, there are several HIV-specific HRQOL assessment instruments. The HIV Overview of Problem/Evaluation System scale (HOPES) is a 168-item tool that looks at 35 subscales [32]. The domains that this tool focuses on include: physical, sexual, significant other, psychosocial, body image and stigma. It is self-administered, and, depending on responses, patients may skip sections [13, 15]. Additionally, because it is problem oriented, it is useful to help identify and develop interventions that may be needed for individual patients [15]. One criticism of the HOPES scale is that the questions are worded in the negative and thus may be skewed to interpretations that are more downbeat than would otherwise be expected [15]. The negatively worded items can also be upsetting for the patients. Also, given the number of items, it may be too lengthy to use in a brief patient encounter [4].

The General-Health Self Assessment (GHSA) [33] includes 49 items in six domains [4]. They include physical functioning, general health perception, HIV-related symptoms, role function and health care utilization. These domains/modules were adapted from previous tools, among them the SF-36, HIV Patient-Assessed Report of Status and Experience (HIV-PARSE) survey and the MOS-HIV scale. It can be administered by an interviewer, or patients can respond on their own.

HIV-related Quality of Life Questions (HIV-QOL) [34] was developed utilizing input from patient-specific concerns related to their HIV disease [34, 35]. It has 40 separate items and was adapted from several sources, including the Functional Status Questionnaire [36] (which looks at activities of daily living), the MOS, a disability scale derived from the Health Interview Survey [37] and a memory scale adapted from the Memory Assessment Clinic Self-Rating Scale [38]. It also includes a symptom checklist and a pain measurement scale. The dimensions measured include general health perception, life satisfaction, physical functioning, disability, fatigue, pain, emotional well-being, memory problems and other symptoms [9, 34].

The Functional Assessment of HIV Infection (FAHI) [39] was originally adapted from a cancer scale—the Functional Assessment of Cancer Therapy-General (FACT-G) [4, 12]. It has 44 items that correlate with five domains: physical well-being, emotional well-being, social/family well-being, functional well-being and relationship with their physician. It is self-administered. It has a total score but may also be broken down into domain scores [4].

The HIV/AIDS-Targeted QOL Instrument (HAT-QOL) [40] was developed with input from HIV-infected patients [4, 12]. It is self-administered and has a total of 42 items and 9 domains: overall function, health worries, sexual function, disclosure worries, financial worries, life satisfaction, medication concerns, HIV mastery and provider trust. Studies demonstrating its validity have been somewhat mixed [4, 12]. Given that ceiling effects have been noted, it has been suggested that it be administered alongside other HRQOL measures, which may make the process much lengthier and not ideal in brief encounters [4].

The Multidimensional QOL for Patients with HIV/AIDS (MQoL-HIV) [41] looks at ten domains and has 40 items [12]. The domains include physical health, physical functioning, mental health, social functioning, cognitive functioning, social support, financial status, sexual functioning, partner intimacy and access to care. These domains were generated by conducting interviews with both HIV providers and patients [12]. It can be self-administered. It appears that while ceiling effects are not a significant issue, it may be less responsive to change than other tools [4].

The HRQOL 601–602 measure was developed by the AIDS Clinical Trials Group (ACTG) Outcomes Committee and is closely related to the SF-20 with minor modifications in wording of the questions [42–44]. It has a visual analog scale, scored from 0 to 100 to look at general health perception (100 representing higher/best possible quality of life). It also looks at eight domains including physical functioning, energy/fatigue, social functioning, role functioning, cognition, pain, health perception and emotional well-being.

The MOS-HIV health survey [45–47] is one of the most studied and utilized HIV-specific HRQOL scales. It was developed from the SF-20 and currently has 35 items that fall into 10 domains: physical functioning, pain, social functioning, role functioning, emotional well-being, energy/fatigue, cognitive functioning, health distress, health transition, general health and overall quality of life [4, 12]. It was developed for use mainly in clinical trials, is self-administered and takes approximately 10 min to complete [12]. It has also been shown to be very responsive in terms of adverse events, opportunistic infections and AIDS-defining events [4, 12].

The ACTG created an Assessment of Body Change and Distress (ABCD) to help delineate the role lipodystrophy plays on HRQOL. There are 22 questions and it is self-administered. Similarly the ACTG symptoms distress module (ASDM) [48] was created to assess symptoms related to ART. It has 22 questions, and each question is scored from 0 to 4 [49]. A higher score means that patients have increased symptoms or are more bothered by their symptoms [49].

In addition, with the changing nature of health care delivery (i.e., electronic medical records, decreased face-to-face time with providers), other methods of measuring HRQOL have been

developed, including those that utilize computers, portable tablets [50] and also single-item measures [51].

4.1 Developing HIV-Specific HRQOL Evaluation Tools

There is a large body of literature on the creation of different HRQOL assessments. While the US Food and Drug Administration (FDA) does not have any specific guidelines regarding HRQOL and ARV development, they do have guidelines regarding patient-reported outcomes measurement and drug and device development. Specifically, they require that the instrument be appropriate for the outcome measured and the clinical population studied and have excellent psychometric properties [52]. Below are brief descriptions of some of the tools created and the methods behind their development.

The patient-reported outcome instrument to measure HRQOL in persons living with HIV and AIDS (PROQOL-HIV) [53] was designed to create a new tool in the modern era of highly active ART (HAART) that would be sensitive to the changes that new regimens have brought about. In addition, it was designed to be more responsive to changes in HRQOL in patients living with HIV/AIDS over time and give some sense of what HIV infection can do to HRQOL over a long period of time. It was also designed to be used across a broad range of cultures and therefore was developed in nine countries with multiple languages used. Significantly, many of the questions were drawn from interviews with patients directly. They identified several novel issues: concerns for the future, concerns related to infecting others, self-esteem, work disruption, sleep issues and treatment issues. In the end, the authors identified 11 major themes: general health perception, emotions, social relationships, energy/fatigue, cognitive functioning, physical and daily activity, symptoms, treatment, coping and future.

Spire et al. [54] wanted to develop a short form questionnaire that was more sensitive to HIV treatment effects—both positive and negative—in one instrument that was brief and self-administered. To that end, they formulated the HIV Symptom Quality of Life Adherence (HIV-SQUAD®) by adapting questions from the WHO-QOL-HIV BREF, the Anti-PROtease Cohort (APROCO) Adherence Questionnaire and a non-specified ART side effects questionnaire. At baseline and after the third month of the study, the 600 enrolled patients filled out these three scales. The group then chose which questions to include, creating the shorter questionnaire. There were a total of 12 HRQOL questions and 13 symptom questions, and they created a VAS to determine adherence. The tool was scored in four dimensions: physical, psychological, short-term symptoms and the VAS. They then tested the reliability of the tool by assessing the Cronbach's alpha—for their physical score the coefficient was 0.84, but the psychological score's coefficient was less than 0.7, indicating that reliability did not meet the accepted standard. However, they were able to show that the test was able to discriminate between patients at different CD4 counts, hepatitis co-infection (type not specified) and changes in HIV viral load.

The development of the Instituto Superiore di Sanità Quality of Life (ISSQol) symptom scale focused on domains that have become more important as ARV treatment has become more sophisticated and the progression of HIV disease has changed [55]. This group wanted to focus on quality of life in the domains of parenthood, life planning, medical staff

interaction and treatment impact in addition to what they determined were the core domains (i.e. mental health, physical well-being, social and role functioning,etc.). In order to construct the questionnaire, they conducted a literature review and had focus groups with HIV-positive patients. Two questionnaires were then sent out to two groups of 100 HIV-infected patients each, and no significant differences were noted between groups. All patients were on ART. The second questionnaire was modified based on the responses from the first and feedback given by the patients as to what questions were inappropriate or not useful. After the second questionnaire results were returned, 15 domain items were included in the final tool. The final tool was validated with an additional 350 patients. They found their instruments had reasonable (above 0.70) Cronbach's alpha coefficients.

The Medication Attribution Scale (MAS) was developed as a means to assess how HIV-infected individuals perceived the effects of their ARVs [56]. The investigators were interested in what effect taking ARV medications on a daily basis had on patients. They first interviewed 33 HIV-infected individuals and asked whether or not they attributed functional limitations to their ARV regimen. As they found that patients did indeed attribute significant quality of life limitations to the ARV drugs, as opposed to the disease itself, the study group began developing questions to better elicit the attribution. The group assigned each domain a scale of 0–10 with 10 being most limited and 0 with no limitations. The domains included: social and role functioning, physical functioning, sexual functioning, body pain/discomfort attributed to side effects, energy, cognitive functioning and mental health. All scores were then summed with a range of 0–100. They then distributed the MAS and MOS General Health Survey (MOS-GHS) [57, 58] to HIV-infected patients in South Georgia and Florida (n = 62), in addition to general questions related to the benefit of ARVs, CD4 counts, AIDS symptoms and demographics. Of their sample, the majority were White, young, with CD4 counts <500/mm^3 and were generally symptomatic. In the summated score, they found that patients did indeed attribute many of the problems in quality of life (especially in energy, role and sexual domains) to their ARVs and that lower scores were more likely to correlate with self-imposed drug holidays. The group found that their score did indeed have good internal reliability with a high Cronbach's alpha coefficient.

4.2 Validation of HRQOL Tools

A significant body of literature exists examining the validity of HRQOL tools. Below, we provide a few demonstrative examples of how these tools were validated; however, there have been many other studies that have also looked at the validity and reliability of many instruments [59–61].

The validity of the HIV-QOL and MOS-HIV was tested in a sample of 99 gay men who ranged from asymptomatic to having an AIDS diagnosis [35]. They demonstrated that the reliability and validity of both tools were in the acceptable Cronbach's alpha coefficient range (i.e., greater than 0.7) and could be utilized for study though recognized that their patient population was not entirely applicable to other populations. In order to determine concurrent validity, the authors looked at how each subscale for the tools correlated and whether or not this was statistically significant. They postulated that for the pain, cognitive and memory scales, the relationship was well matched, but it was not statistically significant

for the basic activities of daily living [35]. With regard to construct validity, the scales were looked at with regard to disease severity, and both the mean and standard deviation were calculated. The overall health, physical functioning, pain, role and social functioning as well as energy and fatigue from the MOS-HIV were all different for different disease states, and this was statistically significant. For the HIV-QOL the energy and fatigue, neurological, sleep, intermediate activities of daily living, total symptom scale and disability days also showed differences between disease states. In the post hoc analysis for the MOS-HIV, however, there were no differences between stages, but differences were present between patients who were symptomatic and asymptomatic. For the HIV-QOL, the post hoc comparison demonstrated differences in neurological, total symptom and disability days only between the asymptomatic and AIDS groups, while the intermediate activities of daily living was different between all groups.

In 1996, the FACT and FAHI tools for HIV were validated in a population of HIV patients [39]. FACT is a general HRQOL tool that is specific for oncologic patients, but was adapted for HIV patients with the addition of a 9-item subscale designed specifically to address the unique psychosocial impact of HIV. They found that while the FACT had high reliability, validity for HIV patients with the addition of the 9-item subscale (the FAHI) had a lower Cronbach's coefficient, suggesting that the HIV subscale was not specific enough in suggesting changes. In 1998, this group aimed to translate the FACT tool for Spanish-speaking patients within the US and looked at all patients with malignancy, including 18 patients with an HIV-related malignancy [62]. This study documents their process of translation/creation of the Spanish language and culturally competent tool and was found to have a high Cronbach's alpha coefficient for the HIV-related malignancy arm.

A large literature review was conducted for the MOS tools, including MOS-HIV, SF-36, SF-12, SF-21, SF-56 and SF-38 in 1997 [45]. The review detailed the domains and number of items available in each scale as well as described in detail each scale and its potential application. They also examined the reliability and internal validity of each scale looking at the Cronbach's alpha. Additionally, the group discussed the studies that utilized these tools such as the ACTG studies, as well as studies that looked at prophylaxis of opportunistic infections, studies that validated the instrument in different languages and among different patient populations. The group also details how to interpret results of the MOS-HIV scores. They concluded that the MOS scales are reliable and valid for use in HIV-infected patients and that each scale has strengths and weaknesses depending on the cohort studied, but that these tools are useful in clinical trials including HIV drug therapy trials.

Using patients from the ACTG 175 trial, the GHSA was validated [33]. A total of 1,694 questionnaires were submitted, and 1,602 were completed. After their analysis, Lenderking's group found that the GHSA had high internal and construct validity, in addition to a Cronbach's alpha coefficient greater than 0.7. Additionally, patients who were more symptomatic had lower scores for HRQOL than patients who had fewer symptoms, but even mild symptoms were correlated with lower cognitive functioning scores.

One group aimed to look at both MOS-HIV and EQ-5D and assess their reliability, validity and discriminatory capacity at different stages of HIV infection [63]. They recruited 242

patients with a range of CD4 counts and HIV viral loads and administered both scores, including the EQ-VAS scale. They found that both scores had high reliability and validity and correlated well with CD4 counts and viral loads, suggesting they had good discriminatory capacity. However, the MOS-HIV MHS was unable to detect changes in HRQOL based on CD4 count or viral load. Additionally, as the scales were only administered once, they were unable to assess the reliability of the measure.

A total of 224 patients across a spectrum of HIV stages (measured by CD4 count) were used to validate the WHOQOL instrument and the SF-36 in Taiwanese patients with HIV [64]. All patients received both scales. The group found that the validity and reliability of the WHOQOL and SF-36 instruments were quite good and had Cronbach's alpha coefficients in the acceptable range. They concluded that both the WHOQOL and SF-36 tool were useful to measure HRQOL in this population. Additionally, they found both scales correlated well with disease severity, as patients who had lower CD4 counts had lower HRQOL.

The HUI3 was tested for validity and reliability in patients with advanced AIDS [65]. The group also looked at responsiveness to AIDS-defining events and adverse events, and compared the HUI3 to MOS-HIV and EQ-5D/ VAS. The patients were enrolled in the Options in Management with Antiretrovirals (OPTIMA) study (which looked at the utility of ARV treatment interruption and standard versus mega-ARV treatment), which included 368 subjects, with the majority being male and white. The HUI3 did demonstrate good concurrent validity when compared to the MOS-HIV in the majority of subscales with the exception of vision, speech and hearing (85 %). With regards to responsiveness to adverse events, the MOS-HIV and the VAS had higher areas under the curve (AUC) and therefore had better discriminatory capacity. The EQ-5D was unable to distinguish these events better than chance and therefore did not perform as well as the HUI3. However, with regards to AIDS-defining events, the MOS-HIV, EQ-5D and VAS all had higher AUCs than did the HUI3. They concluded that the HUI3 was a good tool to look at HRQOL and at changes within HRQOL as an outcome of clinical events. Additionally, they looked at the responsiveness of these measures to adverse events and AIDS-defining events. They found that the MOS-HIV had the highest AUC and therefore was the most responsive tool—especially with regards to the physical and distress domains. The HUI3 was also sensitive to change, but the EQ-5D was unable to pick up on adverse events at a rate greater than chance. However, in the responsiveness to AIDS-defining events, while the MOS-HIV was most responsive, the EQ-5D was better than the HUI3.

In another study using the same treatment group, the preference-based measures SG, TTO, EQ-5D and HUI3 were compared to MOS-HIV to determine HRQOL in the OPTIMA trial patients [66]. SG, TTO, EQ-5D and HUI3 were able to detect changes in HRQOL similar to the MOS-HIV, and those patients with more advanced disease and poorer physical health had lower scores.

In addition to general validity studies, there have been quite a few studies that aim to validate the different scales in specific patient populations, for example, IDU [67], certain co-morbidities [68–76] and different languages/ cultures [77–83], etc. Some of these are discussed in detail in the Wu review article from 1997 [45].

4.3 Comparison of HRQOL Tools

There are many studies that compare different HRQOL instruments in a given population or particular aspect of HIV infection. In this section, we present a few of these comparative studies as illustrative examples; however, many more have been performed [84–88]. As discussed previously, within the psychometric field, it is important to find tools that demonstrate high validity and reliability, and to that end there have been a number of studies to evaluate which scales are best.

The MOS-HIV and MQOL-HIV instruments were compared in order to determine which scale was better at measuring HRQOL in the HIV population—both treatment naïve and those on ART [78]. They administered the scales to 558 patients with HIV infection and 80 healthy blood donors. They repeated the test in 98 HIV patients within 2 weeks to study test reliability. Additionally, in order to determine construct validity they gave all participants the EQ-5D; 275 patients completed the MOS-HIV and 280 completed the MQOL-HIV. There were more data missing/ incomplete responses on the MQOL-HIV scale. Cronbach's alpha coefficients were better for the MOS-HIV scale than the MQOL-HIV (some of the domains from the MQOL had scores less than 0.7). Additionally, the MOS-HIV seemed to have better construct validity when compared to the EQ-5D.

A further sub-group analysis aimed to look at the difference between the MOS-HIV and the MQOL-HIV in order to determine which scale was best at detecting changes within patients' HRQOL when starting or switching ARV regimens [77]. In this study 296 HIV-infected patients at 23 Spanish hospitals were evaluated at baseline and 3 months later after either starting or switching ARV therapy—nucleoside reverse transcriptase inhibitors (NRTIs) vs. protease inhibitors (PIs); specific regimens were not given. This group concluded that the MQOL-HIV was less sensitive for detecting change than the MOS-HIV scale as the MOS-HIV scale was able to identify changes in more subscales and thus was the recommended assessment tool.

Another group compared the MOS-HIV with the HOPES scale [89]. Given that the HOPES scale is amenable to suggesting clinical interventions given its more specific questions, they hoped that correlating the MOS-HIV to the HOPES would increase the ability to use the MOS-HIV to suggest some clinical intervention such as social worker support, nutrition, etc. They focused mainly on the domains of physical functioning, energy/fatigue and mental health and attempted to match these categories with MOS-HIV-specific subdomains and questions in the HOPES scale. They also attempted to look at patient's responses between subgroups that they defined as quartiles within the MOS-HIV scoring system in order to create a method by which clinicians can intervene in their patients' lives based on needs identified from the MOS-HIV scores. They found that patients who scored in the top quartile of MOS-HIV scores had few problems with physical or mental health functioning, but patients in the next lower quartile demonstrated functional declines that may require further intervention by the clinician. Thus, they concluded that the MOS-HIV could be used to help determine unmet needs by patients and help providers with care plans.

The EQ-5D was compared to the MOS-HIV in patients with advanced AIDS (CD4 $<100/mm^3$) in an ACTG study to look at cytomegalovirus prophylaxis [90]. There were 990

patients, and both tools were administered at each study visit. In addition to looking at the validity of the EQ-5D, they also looked at the responsiveness of the scale by studying the effects of adverse events within the first 4 weeks of the trial and those patients who developed opportunistic infections. The majority of the EQ-5D domains did correlate with respective dimensions on the MOS-HIV with the exception of the self-care domain. They found that in general the MOS-HIV was better at assessing changes related to adverse effects, with the exception of the EQ-5D VAS, which was the best at distinguishing HRQOL decrements associated with opportunistic infections.

Given the nature of this field, it is perhaps not surprising that though there have been many studies that have addressed and compared different HRQOL tools, there is not one instrument that is superior to the others. Additionally, depending on the situation—clinical trial versus clinical practice—one instrument may be more ideal than another depending on the time, resource allocation, patient population, etc.

5 Variables Affecting HRQOL

Studies have been performed using various HRQOL instruments to assess the impact of HIV seropositivity on HRQOL in this population. Overall, the majority of the studies have indicated that, for patients without symptoms, HRQOL is lower than for persons not infected and declines with increasing symptoms. Various other factors influence HRQOL in these patients: drug-related side effects, CD4 counts and HIV viral load, socioeconomic status and gender [91–98].

5.1 Symptom Burden

HRQOL in subjects from the Multicenter AIDS Cohort Study (MACS) was compared between different groups of patients with varying symptoms [99]. The subjects were mostly MSM and bisexual well-educated white males. A total of 2,295 patients were included: HIV seronegative, HIV seropositive with no symptoms, seropositive with one symptom and seropositive with more than one symptom. SF36 was used to measure HRQOL in all subjects. The HRQOL scores of seronegative subjects were similar to asymptomatic seropositive subjects in the mental health domains, but seropositive subjects had significantly lower physical health composite scores and general health perceptions. Even one HIV-related symptom significantly reduced the HRQOL score in all domains. Similar findings were seen in patients with CD4>500/mm^3 that had similar physical health scores as seronegative individuals.

In another study, HRQOL of HIV-infected patients participating in the HIV Cost and Services Utilization Study (HCSUS) was compared with the general US population and also with patients suffering from other chronic conditions in order to determine the morbidity burden of HIV [100]. In this study, the authors assessed the patients using a questionnaire comprising nine domains, which were essentially similar to SF36 with the addition of disability days. The comparison groups included patients with seizures, multiple sclerosis, gastroesophageal reflux disease (GERD), end-stage renal disease (ESRD), type 2 diabetes mellitus and localized prostate cancer. The study included 2,864 HIV-infected patients. They found that physical functioning of asymptomatic HIV patients was similar to the

general population but was significantly worse for the symptomatic HIV-infected patients. Also AIDS patients had significantly worse physical health scores (PHS) than other chronic disease patients with the exception of patients suffering from ESRD and multiple sclerosis. On the other hand, the mental health score (MHS) was not significantly different between asymptomatic and other HIV stage patients, but was worse than for other chronic disease patients, with the exception of depression. This study indicated early on the significant morbidity burden and need for social and mental support in patients suffering with HIV.

Miners et al. [101] compared HRQOL of patients with HIV (95 % on ART) from the general UK population using MOS-HIV and EQ-5D scales and found that even after the introduction of HAART and the resulting decrease in mortality and morbidity, the HRQOL of HIV patients was significantly decreased compared to the general population in all domains. They did not find any strong relationship between the HRQOL score and markers of disease progression. Women had lower PCS (MOS-HIV scale). There was also a significant relation between minimum CD4 count and MCS and EQ-5D utility score with patients who have a lower minimum CD4 count having higher HRQOL. There were no significant associations between variables such as current CD4 count, HIV viral load level or AIDS-defining illness.

5.2 Clinical Progression Parameters

CD4 count and HIV viral load are commonly used for monitoring disease activity. Many groups have sought to understand whether they also predict HRQOL in HIV patients. Overall, the majority of studies have found a direct relationship between these variables and HRQOL. Cross-sectional studies have found a direct relationship between CD4 count and HRQOL and a negative association between HIV viral load and HRQOL [91, 102–104]. Gill and colleagues evaluated 513 HIV-infected patients with HIV PARSE to evaluate HRQOL. Patients with CD4 count >500/mm^3 and undetectable viral load had higher physical function and role function scores. The main effect of viral load was seen in the difference between the undetectable and detectable viral load groups. However, the CD4 count had a stronger and consistent relation between various cut points and HRQOL.

HRQOL results from the San Diego Owens HIV clinic were used to determine the prognostic value of the EQ-5D [105]. The EQ-5D was distributed to every HIV patient at each clinic visit, and they hypothesized that EQ-5D scores would have prognostic value as to hospitalization, survival and emergency department utilization after controlling for CD4 count. To this end, they retrospectively reviewed data for a total of 965 patients, the majority of whom were white and male. Fifty-nine percent were on or had been started on ART. They found that the median VAS/EQ-5D scores were closely related to CD4 count, but less impacted by HIV viral load, and increased as the CD4 count increased. Patients with CD4 counts of <50, 50–199 and >200/mm^3 had scores of 65.4, 70 and 75, respectively, with higher scores indicating improved quality of life. In regards to their primary endpoint, death, the adjusted hazard ratio was 0.73 for higher VAS scores; therefore, higher scores were associated with survival. Additionally, higher VAS scores were related to fewer emergency department visits and fewer hospitalizations.

In another study both HRQOL measures and health utility measures were looked at in the context of clinical parameters—CD4 count, viral load, time to diagnosis and ART—to determine HRQOL [106]. The study coordinators also measured depression and alcohol use. They utilized the Centers for Epidemiologic Studies Depression scale (CESD-10) and used two questions from the ACTG clinical trials to assess alcohol use. They placed patients into six categories and attempted to perform regression analysis to compare the groups. They also measured respondent's responses to religious coping mechanisms. For the HRQOL measurement, they utilized the HAT-QOL tool. For the HUI, they used the health rating scale (RS), TTO and SG. The RS [106] score was based on a VAS from 0 to 100 (100 indicating better quality of life). They had a total of 443 respondents. Based on HAT-QOL responses, six health classes were identified: class 1 high functioning, classes 2 and 3 moderate and classes 4–6 low functioning. Among the patients in classes 4–6 (who also had generally more severe disease), their scores were lower on the HAT-QOL than their scores on the HUIs. Classes 1–3 generally had higher TTO; SG scores though class 3 indicated being willing to trade time. Classes 4 and 5 were willing to trade more time and gamble for perfect health, while class 6 had higher TTO/SG scores than class 5.

In another study using data from the OPTIMA trial, the goal was to determine how HRQOL of patients with advanced HIV/AIDS is affected by non-AIDS serious adverse events (SAEs) [24]. SAEs were defined as: not an AIDS-defining event, which resulted in death or significant disability/hospitalization. To that end, HRQOL was measured using the MOS-HIV, EQ-5D and HUI3 at consistent intervals and correlated the HRQOL data obtained with the timing of SAEs. A total of 368 patients were included, the majority of whom were male with a mean CD4 count of 127/mm^3 with a median follow-up time of 3.9 years; 240 patients had ≥1 non-AIDS SAEs, 98 had ≥1 AIDS-defining event (ADE), and 128 died during the study. They found that patients with SAEs and ADEs demonstrated decreased scores for HRQOL, especially within 8 weeks of a study visit, though scores also remained lower at 16 weeks after the SAE. For patients who experienced an SAE, the scores remained lower longer than for patients who had an ADE. Additionally, they found that the patients who died had significantly depressed HRQOL scores within 90 days of the death. They also looked at CD4 count and viral load and found that improvements in these parameters did indeed improve HRQOL but that the effect seemed smaller for the plasma viral load than the CD4 count.

6 HRQOL in Patients Starting ART

Several studies have been performed to measure HRQOL of HIV patients in relation to ART. Over the years, the pendulum has swung towards starting ART at a higher CD4 count [107]. As our understanding about the long-term benefits and side effects of ART have increased, many groups have attempted to study HRQOL in these patients before and after ART. There are also a few studies looking at HRQOL at different HIV stages. It is especially important to evaluate the effect of HAART on HRQOL of asymptomatic and early stage HIV patients who have a higher HRQOL at baseline, as this group is most likely to have a deterioration of HRQOL on treatment [108–110]. These studies have also helped us to find positive and negative predictors of HRQOL in these patients. What should be noted is that while various instruments have been used in clinical trials to measure HRQOL,

the majority of these instruments do not have treatment dimensions. Additionally, the content validity of the tools was determined mainly in epidemiological studies and not within the treatment studies themselves.

A study conducted in North Italy compared survival, disability and HRQOL between a pre-HAART cohort of patients in 1994 (25 % of patients on ARV monotherapy) to a group of patients in 1998 [111]. They used the Nottingham Health Profile. There was significant improvement in clinical outcomes after 6-month follow-up in the 1998 cohort in numbers of hospital admissions and length of stay. This was accompanied with a significant increase in HRQOL scores in the energy and emotional domain in the post-HAART group.

Similar findings were seen in another study performed in France [109]. A total of 1,054 patients were included, out of which 654 completed the MOS SF-36 scale at baseline and then again at 1 year. Along with significant improvement in clinical markers of HIV infection, there was improvement in all the HRQOL domains. Overall, significant improvement was seen in MCS, but it did not reach statistical significance in the PCS (although there was improvement in all domains except body pain). Significant factors associated with a normal HRQOL at 1 year were undetectable HIV viral load, baseline CD4 $<500/mm^3$ and shorter time since seropositivity (<8 years). The same cohort of patients in the above study was included in another observational study published in 2006 [112]. In this study, the effect of a newly started PI-based ART regimen on HRQOL was measured with a follow-up of 5 years. The findings of the original study were confirmed, showing an increase in HRQOL scores in the first year, but that was followed by relative stabilization for the next 4 years.

Another study evaluated HRQOL in symptomatic vs. asymptomatic HIV-infected patients starting treatment on a PI-based regimen with either ritonavir/saquinavir or ritonavir/saquinavir/stavudine using the MOS-HIV scale (nested study within the Prometheus study) [110]. Although, treatment with these ART regimens alone has fallen out of practice in the developed world, the notable finding in the study was improvement in HRQOL in symptomatic patients and worsening in asymptomatic patients (social and cognitive domains). Also mental health, health distress and social function showed positive changes in ART naïve patients as compared to patients already on therapy. The authors attribute this finding to favorable outcomes in terms of undetectable viral load at 12 weeks in the ART naïve group in the parent study, which is most likely secondary to less optimal treatment and development of resistance in patients already on ARTs.

It is now important to study HRQOL in asymptomatic patients as more data are suggesting starting ART early in the course of HIV infection. Low-Beer [108] conducted a study in British Columbia, Canada, looking at HRQOL of patients starting a new HAART regimen including a PI (most regimens contained ritonavir and indinavir); 179 patients were included in the study and followed up for 1 year. The MOS-SF scale (the specific scale not described by the authors) was required to be completed by patients at baseline and 1-year after starting the new ART regimen. After 1 year, an overall significant decline in mental health was seen in the study group. However, when patients were stratified into two groups, high and low HRQOL at baseline, it was clear that patients with low HRQOL at baseline had significant

improvement in role, physical and social functioning and overall health perception, while there was a decline in scores in all these fields in patients with high HRQOL at baseline, most likely secondary to side effects of ART in previously relatively well-functioning patients. Both groups had significant improvement in CD4 counts and HIV viral load.

A study done in patients with advanced HIV infection starting an HIV PI-based regimen included 70 patients and used multiple scales including Karnofsky Performance Status (KPS) Score, Brief Pain Inventory (BPI), Hamilton Depression Rating Scale (HDRS) and Edmonton Functional Assessment Tool (EFAT) to assess HRQOL [113]. These patients were followed up for a brief period of 3 months. Clinical variables (CD4 count and HIV viral load) improved significantly but there was no significant change in the HRQOL measures with the exception of depression and number of symptoms. It is also important to note that these patients were in an inpatient setting and were from lower socioeconomic strata; hence, the improvement in depression might just represent a better living situation and not reflect a real improvement in HRQOL.

7 HRQOL with Specific ART Regimens

Following approval of the first ARV, zidovudine, and studies showing the reduction of mortality and virologic and immunologic efficacy with its use, HRQOL studies were conducted to see the impact of side effects on patients. Wu et al. [114, 115] conducted a sub-study of the randomized placebo-controlled trial that showed the mortality benefit of patients on zidovudine. There was a general decline in QOL in both groups but less so in patients receiving zidovudine. A summary of these studies can be found in Table 2. However, some studies noted that the increase in HRQOL due to slow disease progression in the zidovudine group was almost balanced by a reduction in HRQOL due to its adverse effects [33, 116]. Overall, the results of these early studies were not very conclusive of an improved HRQOL on treatment in any patient group secondary to adverse effects of early ARVs.

Introduction of HAART in 1996 resulted in significant improvement in the treatment of HIV. It led to a considerable reduction in HIV viral load and increase in CD4 count and decreased the overall mortality. This impressive improvement was also associated with numerous side effects. With the increasing number of ARVs, HRQOL studies became more important to seek a balance between efficacy and adverse effects.

In the late 1990s, studies were performed demonstrating that three-drug ART regimens including two different ARV classes were superior to two drugs or single drug regimens in terms of virologic, immunologic and clinical outcomes. These studies were often followed by an HRQOL sub-study.

Studies have been done to see whether four-drug ART regimens are better than three-drug regimens as the initial HAART regimen, and they have not shown any additional virologic or immunologic benefit over the three-drug regimen [120, 121]. A nested sub-study of the INITIO trial was done to see whether the HRQOL in asymptomatic HIV patients initiating HAART with NRTIs (didanosine + stavudine) and efavirenz or nelfinavir or both were significantly different [122]. The MOS-HIV scale was used in the study to measure HRQOL

with results grouped in PHS and MHS. PHS increased in all three groups with no significant differences among the three groups, but the MHS increased only in the efavirenz and nelfinavir group and not in the four-drug group. The authors concluded that the low MHS scores in the four-drug regimen were possibly due to the complexity of the regimen.

Addition of PIs to an NRTI-based regimen has shown positive effects on HRQOL in several studies. ACTG 320 included patients who had been on zidovudine for at least 3 months and were randomized to either zidovudine/lamivudine or zidovudine/lamivudine/indinavir [123]. The virologic and immunologic benefit of adding a PI was clearly evident in the parent study. HRQOL was then measured using a QOL 601–602 scale, and after 24 weeks of treatment, scores in the triple drug arm had increased in all domains with statistically significant increases in general health scores, as well as in the pain, energy/fatigue and role function domains [43]. The main effect was seen in the strata of patients with CD4<50/mm^3. A similar increase in HRQOL was seen in a Spanish study done with ART-naïve patients and those already on NRTIs. All patients were placed on two NRTIs and indinavir. The MOS-HIV scale was used, and although an improvement in HRQOL was seen in both groups, the effect size was much larger in ARV-naïve patients as compared to the pretreatment group over 3 months.

The major HIV PI-related side effects are diarrhea and metabolic abnormalities including dyslipidemia, hyperglycemia, insulin resistance and lipodystrophy. They also have significant interactions with other drugs. Most of the studies assessing HRQOL in patients on PIs are older studies using first generation PIs. The newer PIs, which include lopinavir, atazanavir, fosamprenavir, darunavir and tipranavir, have fewer side effects and pill burden, and they have been shown to have a positive impact on HRQOL. In a prospective, randomized, open-label multi-country study, boosted lopinavir (PIs can be combined with low-dose ritonavir to boost their serum levels thereby reducing dosages and side effects) was substituted in patients experiencing side effects on other PIs (indinavir, nelfinavir) or efavirenz, nevirapine. A total of 849 patients were randomized to obtain the pre-study NRTI plus boosted lopinavir either immediately or after 4 weeks and were followed up for 8 weeks [49]. Using the MOS-HIV scale, ACTG-ASDM and a depression scale, significant improvement in all scales in patients from all prior ARV treatment groups was seen. Sixty-five percent of patients on prior nelfinavir regimens had improvement in diarrhea over an 8-week period.

HRQOL of patients on atazanavir was compared with boosted lopinavir in a multinational randomized controlled trial [124]. Although atazanavir was virologically inferior to boosted lopinavir in this study, the metabolic profile was in favor of the atazanavir arm. This study included 290 patients who had failed ART regimens including PIs and were randomized to atazanavir or boosted lopinavir each with two NRTIs. Moderate improvement was seen at 24 weeks of treatment in general health, pain, mental health, energy/fatigue, health distress and HRQOL in the atazanavir group with moderate worsening of physical function. In the boosted lopinavir group, general health, health distress and HRQOL improved. This study also measured utility scores, which improved in the atazanavir group but not in the ritonavir-boosted lopinavir group. Malan et al. [125] demonstrated improved HRQOL with ritonavir-boosted and unboosted atazanavir using the MOS-HIV scale as early as 24 weeks with

sustained improvement at 96 weeks. A substudy of a landmark trial (CASTLE) compared the gastrointestinal side effects of ritonavir-boosted atazanavir and boosted lopinavir using the Irritable Bowel Syndrome QOL (IBS-QOL) questionnaire and found that the HRQOL of patients improved in the atazanavir/ ritonavir arm over a 6-month period (>2 point increase) but not for ritonavir-boosted lopinavir [126].

Huang and group [127] assessed the HRQOL in patients starting on boosted tipranavir (patients in RESIST trial) as compared to patients on other PI regimens (lopinavir, indinavir, saquinavir). The MOS-HIV scale was used to measure HRQOL. There were no significant baseline differences in the MOS-HIV domains in the two groups. The study showed that both patient groups had improved scores in the majority of the domains with the exception of pain and social functioning, which decreased in the comparator PI group. Pain was significantly different between the two groups. This study showed that patients on this new PI maintained HRQOL over 48 weeks of study.

The functional HRQOL of patients in the darunavir POWER 1 and 2 trials was assessed using the FAHI instrument [128]. Analysis of the FAHI scores at week 48 showed improvement of HRQOL with ritonavir-boosted darunavir treatment in contrast to deterioration in HRQOL with treatment with comparator PI regimens. Significant improvement from baseline was achieved in the ritonavir-boosted darunavir group for the physical and emotional well-being subscale scores and the total FAHI.

There are no published data on HRQOL of patients on fosamprenavir compared to other PIs but the side effect profile is relatively similar to other newer PIs.

Numerous studies have evaluated the efficacy of HA-ART after switching patients from a PI to an NNRTI-based ARV regimen. Over the years many studies have shown fewer side effects and greater adherence on NNRTI-based regimens compared to PIs while maintaining virologic efficacy. One study compared patients switching from a PI-based regimen (nelfinavir, indinavir, ritonavir-boosted saquinavir) to efavirenz and patients continuing on the same regimen [129]. The HRQOL score in patients assessed using a 5-point scale adapted from the MOS-HIV scale improved in patients who switched to efavirenz while that of patients on the same regimen of PIs did not change. Patients reported improvement due to lesser impact on their daily life and simpler regimen, fewer adverse events and better physical and emotional status.

Similar results were observed in a study, which randomized 262 virologically suppressed patients on a PI-based regimen (nelfinavir, indinavir, ritonavir-boosted lopinavir or saquinavir) to either efavirenz/lamivudine/ didanosine or efavirenz + prior NRTI regimens [130]. HRQOL was measured using the FAHI and Illness Intrusiveness Rating Scale (IIRS). Significant increases in HRQOL (physical and emotional domains) were seen with similar virologic outcomes along with an increase in treatment adherence at week 48 as compared to baseline in both arms. No significant differences in HRQOL between the two efavirenz-based regimens were seen, and the authors concluded that the difference in HRQOL was secondary to switching from a PI to NNRTI and the once daily versus twice daily regimen did not make any difference.

In another recent observational, non-randomized study including 239 virologically suppressed patients on a PI regimen (ritonavir boosted lopinavir, nelfinavir, indinavir, saquinavir, atazanavir) who were switched to either nevirapine (68 %) or efavirenz (32 %), HRQOL was measured using the hospital anxiety and depression scale (HAD), a symptoms questionnaire (nine items on lipodystrophy and 21 other symptoms) and WHO-QOL and SF-12 scales [131]. Patients were assessed using all these scales at baseline and at months 1, 6 and 12. Significant improvement was seen in HRQOL using all the scales at 1 year: anxiety in the HAD scale, bothersome lipodystrophy symptoms, physical domain, independence and spirituality at 6 months. There was no difference between the efavirenz and nevirapine groups, which could be due to fewer patients in the efavirenz group or more patients with neuropsychiatric symptoms being switched to nevirapine rather than efavirenz.

van Leth et al. [132] published a study in 2004 assessing HRQOL in patients treated with nevirapine or efavirenz or both. The MOS-HIV questionnaire was used to measure HRQOL at baseline and 48 weeks. This is substudy of the 2NN study, which was a randomized trial comparing the efficacy of HAART regimens containing efavirenz or nevirapine or both. Similar to the primary study, which showed greater frequency of treatment failure when both efavirenz and nevirapine were used together as compared to either one of them, this study showed improvement in HRQOL with efavirenz and nevirapine over 48 weeks in all domains (MHS more than PHS) but a lesser increase when both drugs were in the regimen although the difference was not statistically significant.

Major advances in ART development have made administration of daily dosing as simple as one pill once a day. There are a number of effective once daily ART regimens available. Tenofovir/emtricitabine/efavirenz was the first fixed-dose combination pill approved in the US in 2006. This is also a preferred regimen according to the DHHS guidelines due to its efficacy, ease of administration and minimal side effect profile. Studies have been conducted to assess whether ART regimen simplification translates into improved HRQOL [133–135].

In a recent study, 234 patients who were stable on zidovudine/lamivudine (Combivir®) and efavirenz with HIV-1 RNA <400 copies/ml for more than 3 months prior were randomized to either continue the same regimen or switch to once daily tenofovir/emtricitabine (Truvada®) and efavirenz [133]. There was no difference in the rate of virologic suppression or HRQOL as measured using the SF-12 scale despite improvement in adherence, decrease in treatment intrusiveness and concern about side effects (measures with HAART IIRS) over a 48-month period. It is surprising to see no improvement in HRQOL, which might be due to the low sensitivity of the scale used in this study. Hodder et al. [135] also saw that the HRQOL was maintained when patients were switched from a stable ARV regimen (NNRTI or PI-based) to fixed-dose once daily tenofovir/emtricitabine/efavirenz. There was a small, non-significant increase in PHS score (SF-36 scale) over 48 weeks in the group switched to the once daily regimen but MHS scores were maintained. There was a definite increase in treatment satisfaction and improved ease of use. Finally, virologically suppressed patients on tenofovir + emtricitabine + efavirenz or tenofovir + lamivudine + efavirenz as individual prescription drugs were switched to fixed dose combination tenofovir/emtricitabine/efavirenz and monitored over a 6-month period [136]. The authors also concluded that there

was a significant increase in adherence from a baseline rate of 97 %. However, the clinical relevance of this increase is questionable given this high baseline rate. Also HRQOL of patients improved as measured by modified MOS SF-36 scale.

Etravirine, a second generation NNRTI, was approved by the FDA in 2008 after a 24-week placebo-controlled trial in treatment experienced patients. HRQOL was assessed using the FAHI questionnaire in that patient population. Although a ceiling effect was seen using the FAHI measure and both etravirine and placebo groups had high baseline scores, there was a statistically significant increase in physical well-being, emotional well-being and total scores for both groups. Functional and global well-being scores improved but only for the etravirine group. The impact of these results in deciding the treatment regimen in terms of HRQOL is unclear because of the small overall change in effect size in all dimensions [137].

The only approved fusion inhibitor, enfuvirtide, was approved in 2004 following two phase 3 studies in treatment-experienced patients showing the addition of enfuvirtide to an optimized background ART regimen led to a significantly greater reduction of HIV viral load as compared to an optimized ART regimen alone [138, 139]. The major side effect of enfuvirtide is the local injection site reaction as it has to be administered subcutaneously twice daily. Cohen et al. [140] conducted a study to assess the impact of this injectable ARV on the quality of life of patients receiving enfuvirtide in the major clinical trials up to 24 weeks. The MOS-HIV scale was used to measure HRQOL in this study. Improvement in the HRQOL score was noted in all the domains except social functioning and was most significant in general health and mental health scales. Social functioning was the only negatively impacted scale, which can be attributed to the mode of administration. Similar results were seen by another group who evaluated HRQOL in 16 enfuvirtide-treated patients in routine clinical practice using EQ-5D and ISSQoL [141]. A positive impact on HRQOL was seen in most of the domains except social functioning at the end of 6 months.

Raltegravir, an HIV integrase inhibitor, was approved in 2007 and in 2009 was approved as a first line HIV treatment agent. It has been shown to be effective in randomized, placebo-controlled trials in treatment-experienced patients for virologic suppression (BENCHMARK 1 and 2). A number of studies have evaluated HRQOL after the switch from enfuvirtide to raltegravir [142–144].

Grant et al. [143] conducted a study to evaluate the effect on HIV viremia and HRQOL secondary to switching suppressed patients from enfuvirtide to raltegravir. Their study included 14 patients with injection site reactions to enfuvirtide and switched to raltegravir and followed them for 24 weeks. HRQOL was measured at baseline and after 24 weeks using the MOS-HIV scale (11 domains). Although 2 out of 14 patients experienced virologic failure with low-level viremia (one resolved with changing to another ARV and the second one without any intervention), overall the switch was safe and effective. However, the HRQOL did not significantly change from baseline to 24 weeks. There was improvement in a number of domains including physical functioning, social functioning and energy, but the only significant improvement was seen in health transition (a domain that compares physical and emotional condition to 1 month prior), which could be due to a small number of patients in the study.

More recently, in a prospective, randomized, open-label trial including 169 patients, of whom 85 were maintained on enfuvirtide while 84 were switched to raltegravir, the MOS-HIV scale was used to measure HRQOL [142]. They found that the score increased for all dimensions in the switch group at 24 weeks of follow-up. Scores increased for physical summary, pain and social functioning with a Cohen's d measure of 0.38, 0.49 and 0.39, respectively, showing clinical significance.

8 Co-Morbidities/Side Effects and the Effect on HRQOL

As patients live longer with HIV, side effects of HIV medication and AIDS-related complications themselves lead to significant issues with HRQOL. Diarrhea, lipodystrophy, neuropathy, fatigue, CNS effects and pill burden can all have a significant effect on HRQOL. Additionally, PIs, especially indinavir and atazanavir, also have been associated with the side effect of hyperbilirubinemia, which may result in clinical jaundice. The incidence of hyperbilirubinemia varies with different PIs and doses and according to whether the PI is boosted by ritonavir or not. However, it has not been shown to have an adverse effect on HRQOL in clinical trials [145].

Lipodystrophy, which has been defined as central obesity, wasting of extremities, breast and cervical fat pad enlargement and facial fat atrophy, causes significant detriment to patients' self-esteem as well as metabolic complications [146–149]. While HIV itself can cause changes in metabolism, the PI and NNRTI classes of ARVs are associated with lipodystrophy [146, 150]. Given the alterations in patients' appearance, lipodystrophy can lead to stigmatization and have a profound effect on patients' self esteem and HRQOL [148]. It can also affect their adherence to medications. There have been several studies that have sought to define the impact of lipodystrophy on HRQOL [148, 150–154] as well as studies that have looked at interventions for lipodystrophy [150, 155–167].

Guaraldi and colleagues [148] reviewed the lipodystrophy and HRQOL literature in 2008. As they discuss in their review, body image can be detrimentally affected by lipodystrophy. What they found from review of the literature, however, was that this was not always correlated with lower HRQOL. A number of tools have been created to measure body image dissatisfaction/perception, and some like the ACTG ABCD scale for use in lipodystrophy studies. However, the group found that having lipodystrophy did not necessarily mean that patients scored lower on HRQOL measures.

There have been many studies that have looked at interventions for lipoatrophy and the changes that result in HRQOL. The injectables currently in use for lipoatrophy treatment include polyacrylamide gel and hyaluronic acid. The majority of the studies have demonstrated a trend toward improvement in HRQOL scores for these patients, though not all were statistically significant, with improvements seen in the mental health component and social functioning domains especially [155, 160–162], though improvement was also seen in the physical domains as well [155]. These studies have used both HIV-specific HRQOL tools such as the MOS-HIV [155, 165] as well as dermatologic and body image-specific tools such as the ABCD or Dermatologic Life Quality Index (DLQI) [158, 159, 163, 164]. In addition to improvement in HRQOL, many of these studies have looked at

depression subscales and have also demonstrated improvements in patients who are treated for lipodystrophy [157, 158, 160, 164].

In addition to lipodystrophy, diarrhea is another very significant side effect of ARVs. It has also been a problem in patients with AIDS off ART. In an early study, Tramarin et al. [168] evaluated HRQOL in 100 patients on ART with diarrhea and compared them to over 400 HIV-infected controls who were matched for CD4 count but who did not report diarrhea, using the MOS-HIV. They divided the case/control population by CD4 count and had patients rate their diarrhea on a severity scale. All patients with diarrhea scored lower on all 11 domains of the MOS-HIV compared to the matched controls. Patients with AIDS (CD4 <200/ mm^3) had statistically lower scores in five domains: quality of life, energy, general health, social functioning and health transition. Patients with severe diarrhea had significantly lower scores in the social and role-functioning domains.

Siddiqui et al. [169] examined the prevalence and HRQOL in 163 patients in New York City (including Veterans) compared to 253 non-HIV-infected controls that were seen in the same outpatient clinics. One hundred fifty patients were on ART, and the authors used the SF-36. A total of 28 % of the HIV-infected patients reported having more than three bowel movements per day versus 7 % of control subjects. With regards to HRQOL, HIV patients (and especially those with diarrhea) scored significantly lower in all domains with the exception of cognitive functioning and mental health than the controls.

9 Conclusion

With the advent of the ART era and the addition of a large arsenal of ARV medications, outcomes of HIV disease have changed significantly. With improved longevity, certain challenges have arisen, especially within ensuring quality of life for patients. Along with this challenge, the field of HIV-associated HRQOL assessment has grown. There are now dozens of tools to choose from when designing studies, and depending on the setting, one tool may be favored over another. At this time, there is no one tool that is best used for every circumstance. Given the constraints of clinic staff, study coordination, etc., what is appropriate for a clinical trial may not be the best measurement tool in a busy outpatient clinic or within the hospital. Most HRQOL studies are performed in a well-controlled study population, and therefore findings may be difficult to apply broadly to patients in clinical practice. For example, the MOS-HIV has been used in many ARV drug trials and is favored for its ease of use and experience. However, it may be somewhat difficult to interpret as an outpatient HRQOL measure. As the clinical encounter becomes even briefer, it will be important to continue to explore new measures or technologies and adapt existing tools to fit these new challenges.

While published ART guidelines state that quality of life must be considered in determining patient ARV regimens, it is not clear how much impact these HRQOL studies have on shaping the guidelines. Therefore, it is imperative for clinicians and regulatory bodies to be aware of the HRQOL literature when making ART decisions and establishing guidelines.

As discussed above, next generation HIV-1 PIs have shown promising results in terms of safety and efficacy, but HRQOL data for these drugs using validated instruments is still

scarce. Additionally, there is a paucity of data that have looked at combinatorial regimens. Given the combinatorial direction of ART, this is a significant lack of information. The approval of more fixed-dose ARV drug combination pills also creates the opportunity to look at HRQOL in patients with a wider range of clinical history as the majority of data currently comes from stable and virologically suppressed patients.

As short-term side effects with the newer generation ARVs decrease, long-term side effects, including metabolic, cardiovascular, and skeletal effects, are becoming more evident. For patients with HIV/AIDS whose HIV infection is well-controlled, diabetes and cardiovascular disease are as critical to morbidity and mortality as their non-infected counterparts. As it stands, none of the HRQOL studies have looked at these side effects as determinants of HRQOL, and this will become especially important as the HIV/AIDS cohort ages. Finally, given that patients are on ART for the rest of their lives and a population of HIV-infected older adults is emerging, it becomes important to conduct HRQOL studies with longer follow-up periods and especially in the HIV-infected elderly population.

What is evident from the literature is that even asymptomatic HIV infection has a significant impact on HRQOL of patients. Overall, the HRQOL of patients improves with HAART as compared to pre-HAART studies that demonstrated a decline. There are a myriad of factors influencing HRQOL including symptoms, medication side effects, socioeconomic factors and medical comorbidities. While the critical determinant of selecting an ARV regimen for a patient will remain HAART efficacy, HRQOL is becoming increasingly important to ensure overall well-being and must be taken into account when formulating an ART management plan.

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Table 1

Tools for measuring HRQOL

Generic tools[a]
Quality of Well-Being (QWB)
Sickness Impact Profile (SIP)
Medical Outcomes Studies (MOS) including SF-12, SF-20, SF-36, etc.
Nottingham Health Profile (NHP)
Karnofsky Performance Measure (KPS)
Psychological General Well-Being Scale
Cleary Health-Related Quality of Life Scale
Time Trade Off (TTO)
Standard Gamble (SG)
Spitzer QL index
Euroqol EQ-5D (EQ-5D)
Health Utilities Index (HUI)
Quality-Adjusted Life Years (QALY)
World Health Organization Quality of Life Assessment Instrument (WHOQOL, BREF)
McGill Quality of Life Scale
Dartmouth Primary Care Cooperative Information Project (COOP)
Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWIST)
Quality of Life Index QL-Index
Health Assessment Questionnaire (HAQ)
Health Assessment Questionnaire Disability Index (HAQ-DI)
RAND Health Insurance Experiment (HIE)
Linear Analog Self-Assessment Questionnaire (LASA)
Body Pain Index (BPI)
Specific tools[b]
HIV Impact Scale
HIV/AIDS-Targeted Quality of Life (HAT-QOL)
HIV Symptom Index (HIV-SI or SDM)
Symptom Quality of Life Adherence (HIV-SQUAD)
HIV Overview of Problems Evaluation System (HOPES)
Medical Outcome Study-HIV Health Survey (MOS-HIV)
AIDS Health Assessment Questionnaire (AIDS-HAQ)
AIDS Clinical Trial Group QOL Health Survey (ACTG-QOL)
Functional Assessment of HIV Infection (FAHI)
General Health Self Assessment Questionnaire (GHSA)
HIV Patient Reported Status and Experience (HIV-PARSE)
HIV Cost and Service Utilization Study (HCSUS)
Medication Attribution Scale (MAS)
HIV-QOL Questionnaire (HIV-QL31)
WHOQOL-HIV, WHOWOL-HIV BREF

	Patient Reported Outcome instrument to measure HRQOL in People with HIV/AIDS (PROQOL-HIV)
	Living With HIV Scale (LWH)

[a] Used in a number of disease states, not HIV specific

[b] Created for use in HIV patients

Table 2

Studies of antiretroviral therapy and quality of life

Author	Study	Drug regimen	Scale used	Follow-up	Patients	Significant finding
Wu et al. [114]	QOL in a placebo controlled trial of AZT in patients with AIDS and ARC	AZT vs. placebo	QWB and KPS	1 year	32	QWB scores were better for AZT at 24 weeks and 1 year. When death was not considered, functional scores were transiently better at 24 weeks but no difference at 1 year
Gelber et al. [116]	QOL of AZT therapy in mildly symptomatic HIV infection	AZT vs. placebo	Q-TWiST	18 months	711	14.5 months (AZT) vs. 14.7 months (placebo) without any serious AE or disease progression. AZT was associated with more Q-TWiST if QOL after HIV disease progression was assumed to be 10–20 % worse than QOL after an SAE
Wu et al. [117]	Functional status and wellbeing in a placebo controlled trial of AZT in early symptomatic HIV infection	AZT vs. placebo	MOS HIV survey	1 year	70	QOL was similar in both groups after 1 year (reduced from baseline)
Lenderking et al. [118]	QOL and AZT in asymptomatic HIV patients	AZT vs. placebo	Q-TWiST	18 months	1,384	Reduction in QOL in patients on AZT almost balanced the increase in QOL due to delay in disease progression
Bozzette et al. [119]	AZT compared to ddI on health status and functioning in advanced HIV infection	AZT vs. ddI	HIV-PARSE		356	Sub study of ACTG 116/117. No difference in QOL in AZT or ddI group regardless of prior AZT exposure
Nieuwkerk et al. [110]	QOL in asymptomatic and symptomatic HIV patients	PI-based regimen with either SQV/r vs. RTV/SQV/d4T	MOS-HIV	48 weeks	208	Improvement in QOL in symptomatic patients and worsening in asymptomatic patients (social and cognitive domains)
Low-Beer et al. [108]	HRQOL among HIV patients after PI use	2 NRTIs + PI	MOS-SF-20	1 year	179	Overall maintained QOL but decreased MHS
Brechtl et al. [113]	QOL in advanced HIV patients starting HAART	PI containing regimen	KPS, BPI, HDRS, EFAT	3 months	70	No improvement in QOL scores
Fumaz et al. [130]	Switch from PI based regimen to NNRTI	PI vs. EFV containing regimen	MOS-HIV 5 point item scale	48 weeks	100	Improvement in QOL with EFV containing regimen while no change when PIs were continued
Carrieri et al. [109]	QOL after 1 year of HAART	PI-containing ARV regimen	MOS SF-36	1 year	654	Significant improvement in MHS but overall improvement in all domains. Variables affecting QOL were symptoms, virologic success, baseline CD4 and time since HIV positivity
Mukherjee et al. [125]	Effect of ATV on patient QOL and utility compared to LPV/r in study 043	ATV vs. LPV/r	EQ-5D and MOS-HIV	24 weeks	290	ATV group improved in 6 domains (general health, pain, mental health, energy/fatigue, health distress, and quality of life) and worsening in physical function. LPV/r improved in 3 domains (general health, health distress and quality of life)

Author	Study	Drug regimen	Scale used	Follow-up	Patients	Significant finding
Coplan et al. [43]	Effect of adding IDV on QOL in advanced HIV on treatment with AZT + 3TC	AZT + 3TC vs. AZT + 3TC + IDV	QOL 601–602	24 weeks	1,143	Significant increase in general health scores, as well as in the pain, energy/fatigue, and role function domains in three drug regimen mainly driven by CD4 < 50 strata
Cohen et al. [140]	QOL with ENF	ENF + OBR vs. OBR	MOS-HIV	24 weeks	1,013	Improvement in the QOL score was noted in all the domains except social functioning
Sprinz et al. [49]	Switch to LPV/r in patients not tolerating their HAART regimen	NNRTI or PI regimen to LPV/r containing regimen	MOS-HIV, ASDM, Depression scale	8 weeks	849	Significant improvement in QOL in patients experiencing Grade-2 adverse effects
Dubois et al. [128]	QOL in treatment experienced HIV patients treated with boosted darunavir	DRV vs. CPI	FAHI	48 weeks	637	Significant improvement from baseline was achieved in the DRV/r group for the physical and emotional wellbeing subscale scores and the total FAHI
Bucciardini et al. [122]	HRQOL in 3 drug vs. 4 drug regimen	ddI + d4T + EFV/ NFV or both	MOS-HIV	3 years	153	PHS scores increased in both groups but only MHS increased in three drug regimen
Bucciardini et al. [141]	QOL in HIV patients with ENF in combination with optimized background therapy	ENF + OBR	ISSQoL and EQ-5D	6 months	16	Positive impact on QOL was seen in most of the domains except social functioning
Grant et al. [143]	Effect of switch from EFN to RAL	ENF to RAL	MOS-HIV	24 weeks	14	No significant change in QOL
Jayaweera et al. [134]	QOL on once daily EFV regimen in treatment naïve patients	ddI + 3TC + EFV vs. d4T-ER + 3TC + EFV	MOS-HIV	96 weeks	135	QOL increased on both groups of patients (significant increase in total wellbeing score over 96 weeks in regimen 1 and over 12 weeks in regimen 2)
Malan et al. [125]	QOL improvement in treatment naïve patients with boosted and unboosted ATV	3TC + d4T + ATV/r or ATV	MOS-HIV	96 weeks	200	Significant improvement in PHS and MHS with both regimens at 24 weeks
Huang et al. [127]	QOL on boosted TPV	TPV vs. other PI including regimens	MOS-HIV	48 weeks	984	Overall similar adverse effects but more treatment related adverse effects in TPV group. Maintained QOL over 48 weeks with pain being the only significantly different domain between the two groups
Campo et al. [130]	Switch from PI to EFV based regimen	PI based regimen to EFV based regimen	FAHI and IIRS	48 weeks	262	Significant increase in QOL in both physical and emotional domains
Potard et al. [131]	QOL after switch from virologically effective regimen to regimen with EFV/NVP	NNRTI naïve patients on cART to NNRTI containing regimen	HAD, WHO-QOL, SF-12	BL, 1, 6 and 12 months	239	Physical, independence and spirituality domains of QOL improved significantly at 1 year along with decreased anxiety and perceived symptoms
Boulet et al. [142]	Impact of QOL due to switch from ENF to RAL	ENF vs. RAL	MOS-HIV	24 weeks	169	QOL scores increased significantly in PHS, pain and social functioning in RAL group
Hodder et al. [135]	Patient reported outcomes after switch to single tablet regimen	SBR vs. single tablet EFV/ FTC/ TDF	SF-36	48 weeks	300	QOL maintained with improved ease of use and treatment satisfaction. Overall, PHS scores improved significantly in single tab group

Author	Study	Drug regimen	Scale used	Follow-up	Patients	Significant finding
Cooper et al. [133]	Continuation of ZDV/3TC or switch to TDF/FTC, each with EFV	Combivir® + EFV vs. Truvada® + EFV	SF-12	48 weeks	234	No improvement in QOL

BL baseline, *QOL* quality of life, *AZT* zidovudine, *ARC* AIDS-related complex, *QWB* quality of well-being, *KPS* Karnofsky Performance Score, *AE* adverse events, *ddI* didanosine, *ACTG* AIDS Clinical Trials Group, *SQV* saquinavir, *r/RTV* ritonavir, *d4T* stavudine, *PI* protease inhibitors, *NRTI* nucleoside reverse transcriptase inhibitors, *MHS* Mental Health Score, *HAART* highly active antiretroviral therapy, *BPI* Brief Pain Inventory, *HDRS* Hamilton Depression Rating Scale, *EFAT* Edmonton Functional Assessment Tool, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *EFV* efavirenz, *NVP* nevirapine, *ATV* atazanavir, *LPV* lopinavir, *IDV* indinavir, *3TC* lamivudine, *ENF* enfuvirtide, *OBR* optimized background regimen, *ASDM* ACTG symptoms distress module, *CPI* comparable PI regimens, *SBR* stay on baseline regimen, *DRV* darunavir, *PHS* physical health score, *SAE* serious adverse events, *FTC* emtricitabine, *TDF* tenofovir disoproxil fumarate, *EQ-5D* Euroqual-5D, *MOS-HIV* Medical Outcome Study HIV, *Q-Twist* quality-adjusted time without toxicity, *RAL* raltegravir, *ISSQoL* Instituto Superiore di Sanità Quality of Life, *KPS* Karnofsky Performance Status, *FAHI* Functional Assessment of HIV Infection, *IIRS* Illness Intrusiveness Rating Scale, *PARSE* Patient-Assessed Report of Status and Experience