



## Research paper

## Quality of life among people living with HIV in England and the Netherlands: a population-based study

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## ABSTRACT

**Background:** HIV is now considered a chronic condition, and people living with HIV, when treated, have a similar life expectancy as compared to the general population. Consequently, improving and ensuring a good health-related quality of life (HrQoL) among people living with HIV (people living with HIV) is increasingly important and has risen on the global agenda in recent years. A ‘fourth 90’ as 90% of people with viral load suppression have a good HrQoL should therefore be adopted alongside the other 90-90-90 targets. This study aims to report the progress on HrQoL as the ‘fourth 90’ and compare against the general population in the Netherlands and England.

**Methods:** In the Netherlands, individuals attending the HIV outpatient clinic of a tertiary hospital were asked to complete the EQ-5D-5L from June 2016 until December 2018. In England, individuals attending one of 73 HIV outpatient clinics were randomly sampled to complete the Positive Voices survey, which included the EQ-5D-5L, from January to September 2017. HrQoL scores were combined with demographic data and compared to general population data.

**Findings:** The EQ-5D-5L was filled-out by 895 people living with HIV in the NL and 4,137 in England. HrQoL<sub>utility</sub> was 0.85 among Dutch and 0.83 among English people living with HIV. This equated to 98% and 94% of the general population HrQoL<sub>utility</sub> in the Netherlands and England, respectively. Of the EQ-5D domains, anxiety/depression was mostly affected, with one-third in Dutch (35%) and almost half (47%) of English people living with HIV reporting symptoms. This was higher compared to their respective general populations (21% NL and 31% England).

**Interpretation:** Overall, HrQoL<sub>utility</sub> for people living with HIV was high in both countries and highly comparable to the general populations. Nevertheless, there should be an increased focus on anxiety and depression in the people living with HIV population. The EQ-5D-5L proved an easy HrQoL measurement tool and identified areas for improvement by social and behavioural interventions.

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### 1. Introduction

Although transmission of HIV is preventable, significant transmission continues across Europe. In 2018, approximately 140,000 people acquired HIV [1]. Provided that people are treated with antiretroviral therapy soon after HIV acquisition, HIV is no longer a deadly disease, but has instead transformed to a chronic, lifelong condition with a

## Research in context

### Evidence before this study

HIV is now considered a chronic condition, and people living with HIV, when treated, have a similar life expectancy as compared to the general population. Consequently, improving and ensuring a good health-related quality of life (HrQoL) among people living with HIV is increasingly important and has risen on the global agenda in recent years. A 'fourth 90' as 90% of people with viral load suppression have a good HrQoL should therefore be adopted alongside the other 90-90-90 targets. This study aims to report the progress on HrQoL as the 'fourth 90' and compares against the general population in the Netherlands and England.

We searched PubMed for studies up to March 2020 with the term's "HIV" and "quality of life" or "Health-related quality of life" with no language or date restrictions.

Most studies were clinical trials which assessed the impact on quality of life when drugs were switched to single tablets or to different drug classes. Additionally, many studies were performed in Africa and analysed the effect on quality of life when patients started with ART instead of not receiving therapy. Therefore, we added the following criteria into our search "Europe", "health policy", and "general population" as we were searching for a comparison with the general population. This search resulted in finding the study from A.Miners et al. in which people living with HIV from the United Kingdom were compared with the general population between 2011 and 2012. They found that people living with HIV have a lower HrQoL as compared to the general population using the EQ5D-3L. In addition, we found the study from J.V Lazarus et al. who pledge to implement a 'fourth 90' to look beyond viral suppression among people living with HIV. None of these studies assessed HrQoL in terms of the 'fourth 90' and compared these results against the general population of two Western European countries. Moreover, both countries are on track on the UNAIDS 90-90-90 goals, which provides an optimal setting to look beyond viral suppression.

### Added value of this study

Our study is the first to show that the 'fourth 90' outlining HrQoL is achieved among people living with HIV. Nevertheless, in both countries mental health issues are a disproportionate burden among people living with HIV resulting in a lower HrQoL which needs addressing.

### Implications of all the available evidence

Our results have important implications in daily HIV-care as it clearly outlines that mental health issues needs more attention to improve the well-being of people living with HIV. Moreover, our research shows that standardized HrQoL measurements implemented in daily practice can guide individualized patient care, however more work is needed to identify the optimal HrQoL measurement to adopt as the 'fourth 90'.

instruments have been developed to measure HrQoL. The EuroQol 5-Dimensional 5-Level version (EQ-5D-5L) is an often used instrument which provides a health state that can be linked to the societal preferences for that specific health state, of which validity in HIV populations has been established [5-7]. Advantages of the EQ-5D-5L include its brevity, and ability to directly convert the results into a utility score for economic evaluation and comparisons [8,9].

There has been a great deal of research on HrQoL among people living with HIV. Among people living with HIV with a virologically controlled HIV infection, a substantially lower HrQoL has been reported compared to the general population [10]. However, improvements in HrQoL have been observed in people living with HIV due to the introduction of highly effective antiretroviral therapy with fewer side effects and an earlier start of therapy [11]. However, much of this research has been in the context of clinical pharmaceutical trials or evaluating interventions, so the results are not generalisable to the wider population.

The importance of addressing HrQoL in people with HIV has risen on the global agenda in recent years. In 2014, UNAIDS established their 90-90-90 HIV targets, which challenges health systems to ensure that 90% of people living with HIV know their status, 90% of those diagnosed receive antiretroviral therapy, and 90% of those receiving antiretroviral therapy are virologically suppressed. This was soon followed by a paper from Lazarus et al. with a plea to acknowledge that viral suppression is not the endpoint of HIV treatment and defined a 'fourth 90' as 90 % of people with viral load suppression have good HrQoL to be adopted alongside the other 90-90-90 targets [12].

In this study we aim to report the progress on HrQoL, as the 'fourth 90', and compare by gender and age group and to the general population. We defined a 'good' HrQoL in the people living with HIV population as achieving a utility score of at least 90% or higher of the general population's utility score. This study uses EQ-5D-5L data from people living with HIV in the Netherlands and England, two high-income Western-European countries where HIV care is open-access and free at the point of access, regardless of residency status. Additionally, both countries have met the 90-90-90 targets (England in 2016 and in the Netherlands in 2017) and are therefore suitable to identify progress towards HrQoL [13].

## 2. Methods

### 2.1. Study design and population

#### 2.1.1. The Netherlands

A cross-sectional survey was conducted at the outpatient clinic of the Erasmus University Medical Centre (Erasmus MC), an academic tertiary hospital in Rotterdam from June 2016 to December 2018. The Erasmus MC sees over 2,000 patients annually, which is approximately 8% of all people living with HIV in the Netherlands. Patients attending the outpatient clinic were approached to fill-out a paper-based EQ-5D-5L. Recruitment took place from June 2016 to December 2018.

In the Netherlands, there are an estimated 23,000 people living with HIV, of whom around 20,000 are diagnosed and linked to care in one out of 27 HIV treatment centres [14]. People living with HIV have access to biannual appointments with an infectious disease specialist or nurse practitioner, which may be increased for complex cases. Of those linked to care, 93% are on treatment and of those, 95% are virologically suppressed.

#### 2.1.2. England

Positive Voices is a national, cross-sectional survey of people living with HIV conducted by Public Health England. The survey recruited in 73 HIV outpatient clinics across England and Wales, which cumulatively represented 54,000 patients, or 60% of the

similar life expectancy as the general population [2]. Consequently, improving and ensuring a good health-related quality of life (HrQoL) among people living with HIV (people living with HIV) is increasingly important [3].

HrQoL is a multidimensional construct concerned with the impact of health on an individuals' perception of their wellbeing and level of functioning in important life domains including the physical, mental, emotional, and social wellbeing [4]. Over time, many validated

89,000 of all people accessing HIV care in England and Wales in 2017. Patients attending a participating clinic were randomly sampled from clinic registers to fill-out an omnibus-style survey, which included the EQ-5D-5L instrument. Recruitment took place from January to September 2017.

The United Kingdom is significantly larger compared to the Netherlands, with over 180 National Health Service centres that provide HIV treatment and care. People living with HIV have biannual appointments but may attend more frequently for complex cases or when newly diagnosed or starting treatment. In 2017 the United Kingdom there were approximately 101,600 people living with HIV of whom 92% were diagnosed [15]. From the diagnosed population 98% received antiretroviral therapy and 97% were virologically suppressed.

## 2.2. Data collection

### 2.2.1. The Netherlands

During the first two months of the study (June and July 2016) all individuals who visited the outpatient clinic of the Erasmus MC were approached to fill-out a paper-based EQ-5D-5L questionnaire prior to the consultation with an infectious disease specialist. Apart from Dutch the EQ-5D-5L was available in English, Spanish, French, and Portuguese. Whenever individuals refused to participate the reason for rejection was recorded.

Thereafter, the EQ-5D-5L was adopted as a suitable instrument to measure the HrQoL in people living with HIV  $\geq 18$  years of age. The study was continued from July 2017 until December 2018. People living with HIV were asked to fill-out the EQ-5D-5L by their infectious disease specialist during their HIV consultation. The EQ-5D-5L was available in five different languages (Dutch, English, French, Spanish and Portuguese).

Data from both study phases were combined with clinical data from the "Stichting HIV Monitoring" database (formerly known as ATHENA project) [14]. The Stichting HIV monitoring collects prospective demographic, clinical, and virological data from people living with HIV that receive care in one of the 27 HIV treatment centres. Individuals who did not consent to have their data collected by the Stichting HIV monitoring were excluded. Additionally, duplicate questionnaires from individuals who already filled-out the EQ-5D-5L were excluded, as well as questionnaires which had incomplete data on all five dimensions or were filled-out incorrectly. Selection bias was assessed by comparing the survey population to the total people living with HIV population in the Netherlands (Supplemental information S1) [14].

The study was reviewed and approved by the local Medical Ethics Committee (MEC-2016-264). Additionally, all participants were asked to sign an informed consent form and all data were anonymized.

### 2.2.2. England

Between January and September 2017, data was collected across 73 HIV clinics in England and Wales. Individuals were included if they were HIV-positive adults (aged  $\geq 18$  years) and who could complete the survey in English. Participants were provided with several options of the response format including in clinic (paper/online), by email (online), or by mail (paper). Surveys from Welsh participants and those with incomplete data on all five dimensions or were filled out incorrectly were excluded.

The national HIV surveillance database (the HIV and AIDS Reporting System), which includes all attendances at HIV NHS specialist services and England and Wales, was used as a national sampling frame to randomly sample patients for recruitment. Pre-selected individuals were assigned a unique six-letter survey identifier to avoid duplicate responses as well as to link the survey data to clinical and demographic data in the HIV and AIDS Reporting System. Survey

data were weighted to conform to the demographic profile of people with HIV in England in 2017. Further information on the survey methods, including sampling and recruitment, are published elsewhere [16].

The Positive Voices survey was designed in collaboration with people living with HIV, academics, clinicians, and NHS commissioners. Apart from the EQ-5D-5L this large-scale survey covers a range of socio-demographic, lifestyle, and behavioural factors including questions regarding medication, sex and relationships, and financial security. Selection bias was assessed by comparing the survey population to the total HIV population in England in 2017 (Supplemental information S2).

The study was reviewed and approved by the London – Harrow Research Ethics Committee (13/LO/0279).

## 2.3. The EuroQol 5-Dimensional 5-Level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a validated instrument to measure HrQoL and is an updated version of the EQ-5D-3L version, with improved sensitivity and reduced ceiling effects [17]. The EQ-5D-5L questionnaire contains five dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [9]. Each of these five dimensions consists of five severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Combining these domains and severity levels leads to a health state, which can be converted into a HrQoL utility score with a country-specific value set based on the valuation of the general public of the converted health state [18,19]. The HrQoL utility score is measured on an interval scale, where a utility score of 0 is equal to death and 1 is equal to a perfect health.

## 2.4. Data and statistical analysis

Patient characteristics such as binary social gender, age, transmission mode, and country of origin were extracted from the clinical datasets. Due to small numbers those who identified as non-binary or in another way (representing 0.5% of Positive Voices respondents) were excluded. We classified transmission by mode using the following categories: men-who-have-sex-with-men (MSM), heterosexual transmission, and *other transmission routes* (including injecting drug use, haemophiliac, perinatal transmission, and unspecified modes of transmission). Country of origin was classified based on geographical region (Sub-Saharan Africa, the Middle East, South America, South-East Asia), and other high-income countries (other European countries, North America, and Oceania).

Descriptive statistics presented the distribution of responders across each of the five different domains and compared to the general population. Utility scores were calculated from the EQ-5D-5L by using the country specific value sets (Dutch and English) [18,19]. We reported the mean (standard deviation) and distribution of utility scores by age and gender. Differences were assessed using the two-sample independent t-test and the  $\chi^2$ -test.

## 2.5. Comparison with the general populations

In order to compare the HrQoL of people living with HIV with the Dutch and English general population, previously published data from Versteegh et al. (NL) and Health Survey for England 2017 was used [18,20]. The EQ-5D-5L utility scores and the distribution per domain of the Dutch people living with HIV population was compared with the Dutch general population, using the paper of Versteegh et al. [18]. Age- and gender-weighted utility scores of people living with HIV were used to match the distribution of the Dutch general population. Versteegh et al. used a stratified sampling approach for adults ( $> 18$  years of age) with age, sex, and highest educational attainment as strata, including Dutch respondents (n=979) whom are

representative of the Dutch general population [18]. The population was 49.1% male, and the largest age category was 40-60 years old (39.5%). Most participants originated from the Netherlands (86.7%) (Supplemental information S2).

In order to compare the English people living with HIV with the English general population the EQ-5D-5L utility scores and the distributions per domain were provided on request from NHS Digital from the 2017 Health Survey for England, using the same value set [20]. Age and gender weighted utility scores of people living with HIV were used to represent the English general population. The 2017 Health Survey for England is an annual cross-sectional household survey of 7,136 adults (>16 years of age) representative of the English population. The population consists of 48.1% of males and the majority is aged below 40 years of age (38%) followed by 40-60 years (34%) (Supplemental information S2).

### 2.6. Role of the funding source

The study received funding (unrestricted grants) from: Gilead sciences, ViiV Healthcare, MSD, and MSD, Janssen pharmaceuticals. The funders had no role in the study design, data collection, data analysis or interpretation of the data. The authors made the decision to submit for publication

## 3. Results

### 3.1. Population in the Netherlands

During the first phase of the study, 375 individuals attending the infectious diseases outpatient clinic were considered for inclusion. A total number of 37 individuals were excluded because of HIV-2 infections, attended the outpatient clinic for a second or third time during the study period or visited for post-exposure prophylaxis. Of the 338 HIV positive people which met our inclusion criteria, 303 (89.6%) completed the EQ-5D-5L questionnaire (Figure 1). Reasons for not participating were *not feeling like filling-out a questionnaire* (6.5%),

*private problems* (0.3%), *reading problems* (1.2%) and other unspecified reasons (2.4%).

During the second phase of the study 1,213 EQ-5D-5L questionnaires were filled-out. After excluding questionnaires from the second, third, or fourth visits (n=591), incorrectly complete or incomplete EQ-5D-5L (n=21) and those who did not consent to the Stichting HIV monitoring (n=9), a total of 592 questionnaires were included in the analysis. An overall total of 895 questionnaires from Phase 1 and Phase 2 remained for further analysis (Figure 1).

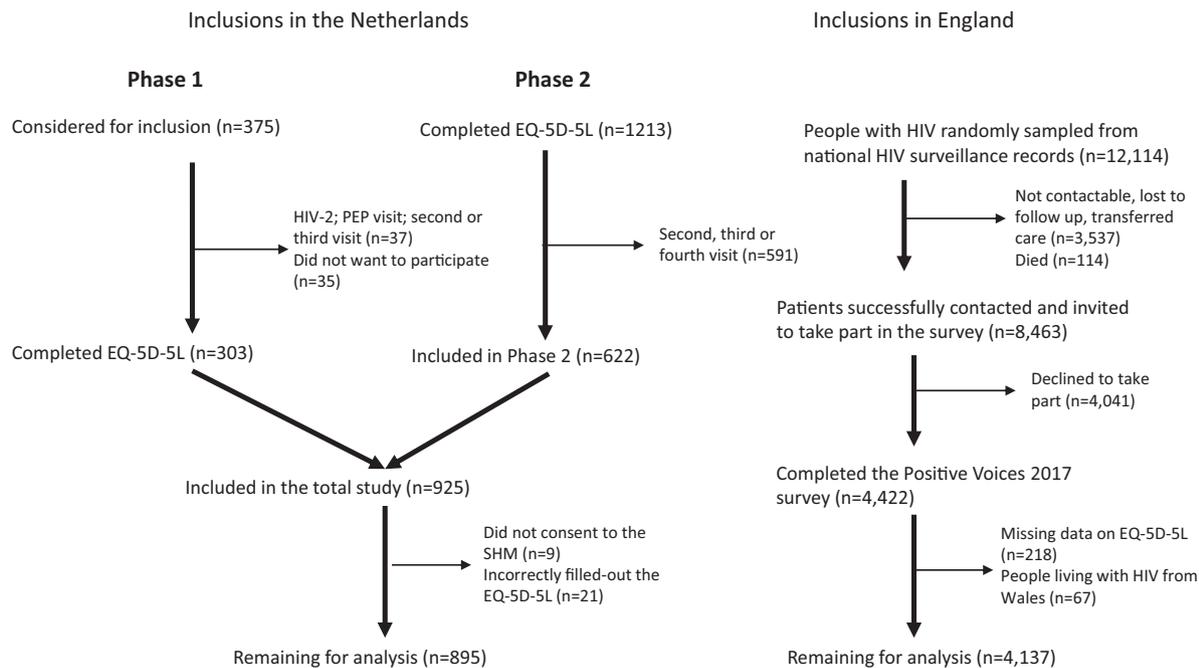
### 3.2. Population in England

12,114 patients from 73 participating HIV clinics in England and Wales were randomly sampled using the HIV/AIDS reporting system database, representing approximately 1 in 5 patients attending those clinics. Overall, 8,463 (70%) patients were successfully contacted by clinic staff to take part in the survey, of which 4,422 patients completed the survey (52.3% response rate). Most participants (87%) chose to complete the survey using the paper questionnaire and 13% completed the survey online. This sample represents about one in twenty (5%) people living with HIV in England and Wales in 2017.

The demographic profile of the Positive Voices 2017 survey respondents closely matched the demographics of all people accessing HIV in 2017 for gender, age, ethnicity, area of residence and treatment status ( $\pm 5\%$ ), but slightly overrepresented older white men and Londoners [16]. Survey data were weighted using an algorithm based on gender, ethnicity, HIV risk group, age and residence to account for differential sampling probability and small differences in response rates to ensure estimates were generalizable to the English HIV population. Individuals who were missing data on the EQ-5D-5L (n=218) and Wales (n=67) were excluded (Figure 1).

### 3.3. Baseline characteristics

In both countries most of the population was male, and substantially more males were included in the Netherlands than in England (p=0.005) (Table 1). Over half of participants were aged between 40-



**Figure 1.** Flowchart representing the inclusions during the first and second phase of the study in the Netherlands and in England. In the first phase of the study all individuals attending the infectious disease clinic were approached, after that the EQ-5D-5L was implemented in care and individuals were approach by the infectious disease specialist. The second phase only included the EQ-5D-5L questionnaire. We used only the first questionnaire for our analysis. The compliance in the first phase of the study was high approaching 90%.

**Table 1**

baseline characteristics of people living with HIV in the Netherlands and England. Other transmission routes included: injecting drug use (NL: 3% n=26 versus England 1% n=47), blood contact (NL: 0% n=2 versus England 0.75% n=30), perinatal (NL: 1% n=8 versus England: 0.75% n=29), and unknown routes of transmission (NL: 4% n=33 versus England: 1% n=45)

Baseline characteristics n (%)	People living with HIV		P-value
	Netherlands	England	
<b>Demographic characteristics</b>			
Gender			
Male	693 (77)	2945 (73)	0.005
Female	202 (23)	1100 (27)	
Age			
<40	223 (25)	904 (22)	<0.001
40-60	507 (57)	2617 (65)	
>60	165 (19)	525 (13)	
Transmission mode			
MSM	478 (60)	2165 (55)	<0.001
Heterosexual	248 (31)	1599 (41)	
Other	69 (9)	106 (4)	
Origin			
NL/England	474 (53)	2077 (52)	<0.001
High-income countries	77 (9)	504 (12)	
Sub-Saharan Africa	130 (15)	1120 (28)	
Middle East	19 (2)	23 (1)	
South-East Asia	40 (4)	102 (3)	
South America	155 (17)	173 (4)	

60 years, and of this age group there were more persons included in England as compared to the Netherlands ( $p < 0.001$ ). Additionally, a quarter of the people living with HIV from both countries was below 40 years of age. The main transmission route in both countries was MSM, but more MSM were included in the Netherlands than in England ( $p < 0.001$ ) (Table 1).

In the Netherlands almost half of the population originated from another country (47% n= 421), which was comparable to England (48%, n=1,922). The distribution of the different regions of origin was, however, different between the Netherlands and England ( $p < 0.001$ ). In the Netherlands, the most common regions of origin included South America and Sub-Saharan Africa while in England this included Sub-Saharan Africa and other high-income countries (Europe, North America, Australia, and New Zealand) (Table 1).

### 3.4. HrQoL<sub>utility</sub> of people living with HIV compared to the general population

In the Netherlands, people living with HIV have a mean adjusted HrQoL<sub>utility</sub> score of 0.850 ( $\pm$  standard deviation (SD) 0.17), which is comparable to the Dutch general population at 0.869 ( $\pm$ SD 0.17) (Table 2). People living with HIV in England have a slightly lower mean adjusted HrQoL<sub>utility</sub> score (0.832  $\pm$  SD 0.23) than the general population at 0.885 ( $\pm$  SD 0.22) ( $p < 0.001$ ). When stratified by

gender, male people living with HIV have slightly higher HrQoL<sub>utility</sub> scores than females in both countries. However, this was also seen in the general population (Table 2). In both countries, HrQoL<sub>utility</sub> scores decreased with age both in people living with HIV and in the general population. In the Netherlands and England, young people living with HIV (< 40 years of age) had a lower HrQoL<sub>utility</sub> score than the general population in the same age group (Table 2). Also middle-aged and elderly people living with HIV had lower utility scores than the general population, although this only reached statistical significance in England (Table 2).

Using this study's definition of the 'fourth 90' of a 'good' HrQoL, which was people living with HIV having an HrQoL<sub>utility</sub> score at or above 90% of the general population HrQoL<sub>utility</sub>, both countries met this target. In the Netherlands people living with HIV reached 98% and in England 94% of the utility score of the general population. When stratified by gender, English male people living with HIV scored 93% of the utility score of the male general population, which was lower than male people living with HIV in the Netherlands or female people living with HIV from both countries (Table 2).

### 3.5. Distribution of the five EQ-5D-5L domains

In the Netherlands, people living with HIV reported fewer problems with mobility compared to the general population, with 21% of people living with HIV versus 24% of the general population reporting any mobility problems (Figure 2). In contrast, in England, people living with HIV had more problems with mobility compared to the general population with 27% of people living with HIV versus 21% of the general population. Both in the Netherlands and English people living with HIV reported more problems with self-care compared to the general population (NL: 8% people living with HIV vs 4% general population  $p < 0.001$ ; England: 13% people living with HIV vs 8% general population  $p < 0.001$ ).

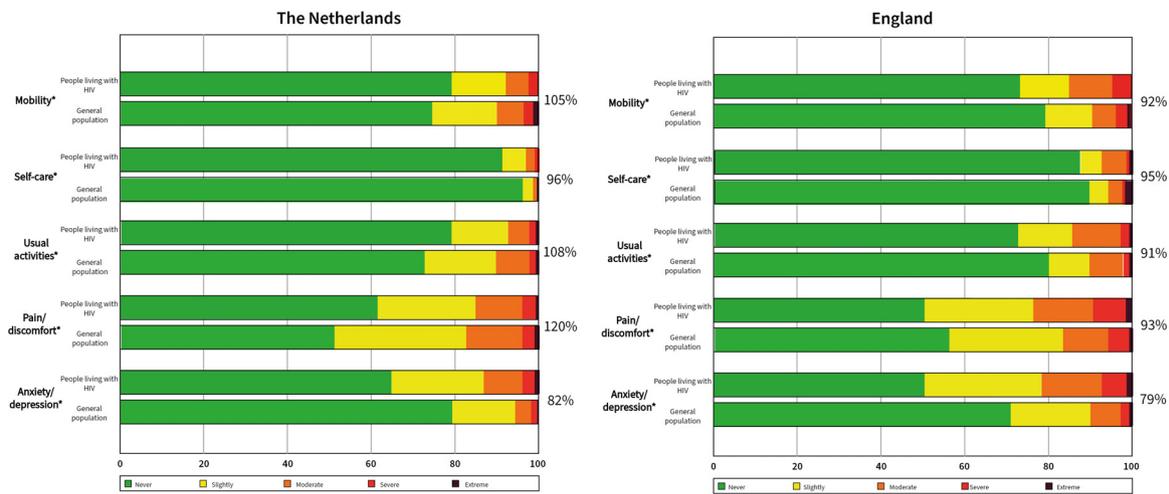
The EQ-5D domain with the greatest burden of reported symptoms for people living with HIV was pain/discomfort, with 39% of people living with HIV in the Netherlands and 47% people living with HIV in England reporting symptoms. In the Netherlands, people living with HIV reported less pain/discomfort as compared to the Dutch general population, in which 49% reported problems. In contrast, people living with HIV in England reported more pain/discomfort than the general population, where just 43% of the population reported problems.

Remarkably, in both countries, people living with HIV report more symptoms of anxiety/depression. Over one-third (35%) of the Dutch people living with HIV and almost half (47%) of people living with HIV in England reported anxiety/depression problems compared to one-fifth (21%) and one-third (31%) among the Dutch and English general population, respectively ( $p < 0.001$ ) (Figure 2).

**Table 2**

Baseline characteristics of living with HIV in the Netherlands and England in comparison to the general populations. Raw data regarding the distribution of the Data of the Dutch general population was kindly provided by Versteegh et al. and the Health Survey for England 2017 (18, 20). Dutch and English general people living with HIV outcomes were age and gender weighted to represent the distribution of the general population. Difference as compared to the general population are indicated with a \* for  $p < 0.05$  and \*\* for  $p < 0.001$ . § Age weighted utility score based on the distribution of age among the general populations. <sup>1</sup>Gender weighted utility score based on the distribution of gender among the general populations.

Baseline characteristics	Netherlands			England		
	People living with HIV	General population		People living with HIV	General population	
Mean utility score $\pm$ SD	0.850 $\pm$ 0.17	0.869 $\pm$ 0.17		0.832 $\pm$ 0.23**	0.885 $\pm$ 0.22	
90% target	98%	97%		94%	94%	
n(%)	979(100)	979(100)		7,136(100)	7,136(100)	
Gender§						
Male	0.865 $\pm$ 0.17	0.881 $\pm$ 0.17		0.833 $\pm$ 0.23	0.897 $\pm$ 0.21	
Female	0.837 $\pm$ 0.18	0.858 $\pm$ 0.17		0.831 $\pm$ 0.23	0.873 $\pm$ 0.20	
Age <sup>1</sup>						
<40	0.875 $\pm$ 0.15*	0.906 $\pm$ 0.14		0.882 $\pm$ 0.18**	0.924 $\pm$ 0.16	
40-60	0.851 $\pm$ 0.16	0.853 $\pm$ 0.19		0.817 $\pm$ 0.24**	0.883 $\pm$ 0.22	
>60	0.832 $\pm$ 0.21	0.844 $\pm$ 0.17		0.786 $\pm$ 0.24*	0.836 $\pm$ 0.24	



**Figure 2.** Comparison of the different EQ-5D-5L domains per severity level of the age and gender weighted HIV population (first bar) and the general population (second bar) in the Netherlands (left) and England (right). Raw data regarding the distribution of the Dutch general population was kindly provided by Versteegh et al. and the Health survey for England 2017 (18, 20). The percentage on the right indicates the percentage of people living with HIV who did not report any problems on this domain compared to the general population. \* indicates a difference with  $p < 0.05$ .

In the Netherlands, people living with HIV only scored worse than the general population on two domains: self-care and anxiety/depression, which differed in England, where people living with HIV scored worse on all five domains. In both countries, the most striking disparity compared to the general population was for anxiety/depression.

When stratified by age, younger people living with HIV (<40 years of age) in both countries reported more problems with anxiety/depression than older adults. Of young people living with HIV, 36% in the Netherlands and 47% in England reported symptoms of anxiety and depression compared to 20% and 33% among the general population ( $P < 0.001$ ) (Table 3). Young people living with HIV from England reported more problems with mobility, self-care, and usual activities compared to the general population of the same age group.

In the Netherlands, middle-aged people living with HIV (40–60 years of age) had similar or better symptom profiles for all domains except for anxiety/depression. In contrast, in England middle-aged people living with HIV scored worse on all EQ-5D-5L domains compared to the general population. In both countries middle-aged people living with HIV scored lower for anxiety/depression (Table 3).

In the Netherlands, elderly people living with HIV (>60 years of age) fared better for the mobility, usual activities, and pain/discomfort domains, but worse for the self-care and anxiety/depression domain. Over one-third (32%) of elderly Dutch people living with HIV report anxiety/depression issues compared to 15% in the Dutch general population. Additionally, 8% reported severe to extreme problems, which did not occur in the general population. In England, elderly people living with HIV had slightly lower scores on the domains self-care and usual activities, but much lower scores on anxiety/depression compared to the English general population. Of elderly English people living with HIV, 44% experienced anxiety/depression issues compared to 27% in the English general population (Table 3).

#### 4. Discussion

To the extent of our knowledge this is the largest cross-sectional study which compared the HrQoL<sub>utility</sub> of people living with HIV in two Western European countries, the Netherlands and England, with the general population. In both countries people living with HIV reported a highly comparable HrQoL<sub>utility</sub> as compared to the general

populations. In the Netherlands, HIV positivity did not impact mobility, usual activities, and pain/discomfort, while in England all domains were affected. In both countries people living with HIV experienced far more anxiety/depression issues compared to HIV-uninfected individuals. Strikingly, elderly people living with HIV (>60 years of age) were mostly affected, with anxiety/depression issues occurring almost twice as often as in the elderly general population. People living with HIV from both countries exceed the 'fourth 90' for the overall HrQoL<sub>utility</sub> score on HrQoL with 98% and 94% in the Netherlands and England, respectively. Nevertheless, both countries still observed a disproportionate burden of anxiety/depression among people living with HIV.

This study reports the progress towards the 'fourth 90', in two countries on track for the UNAIDS '90-90-90 targets' [13]. While reaching the '90-90-90 targets' has already delivered tremendous benefits for people living with HIV in both countries, the 'fourth 90' is important to ensure that long and healthy lives are possible [12,21]. Measuring HrQoL should be considered as a standard in HIV-care given several benefits in improving care. On a clinical level, measuring HrQoL can predict survival among people living with HIV receiving antiretroviral therapy and predict the occurrence of behaviour which negatively influence health status [22]. This practical information for clinicians can determine the involvement, adherence, self-care and subsequently prognosis of their patients. Also, prior to starting ART, HrQoL measurements could highlight aspects of a persons' health which require improvement to maximize the likelihood of a positive treatment outcome (23–25). On a population level, measuring HrQoL can identify areas where the health system is failing and can identify areas where needs are unmet and inform service planning and provision.

Our study demonstrated that anxiety/depression was a key issue, with up to twice as many people living with HIV reporting symptoms of anxiety and depression compared to the general population. Anxiety and depression were the main driver of poorer overall HrQoL<sub>utility</sub> in people living with HIV in both the Netherlands and England. Several factors could contribute to an increase in anxiety/depression among people living with HIV for example, coping with a recent HIV diagnosis, the onward effect on relationships, stigmatization, social isolation and loneliness, and the experience of living with a chronic illness. However, previous studies have shown that even compared to individuals with other chronic diseases, people living with HIV report more anxiety/depression issues [26]. Additionally, there is an

**Table 3**

Comparison of PLWH with the general population over EQ-5D-5L domain. The gender weighted levels of severity per EQ-5D-5L domains from PLWH over different age groups compared to general population of the same age group (The Netherlands = upper part and England = lower part of the table). A significantly difference of the PLWH and general population is indicated with \* for a  $p < 0.05$  and \*\* for a  $p < 0.001$ . Only England PLWH whom reported their age could be included in this analysis. Data from the general population has been kindly provided by Versteegh et al. and the Health Survey for England(18, 20).

Comparison of people living with HIV and the general population of the Netherlands						
Per EQ-5D-5L domain n(%)	<40 years of age People living with HIV in the Netherlands n=242	General population n=336	40 – 60 years of age Dutch people living with HIV n=514	General population=379	> 60 years of age People living with HIV in the Netherlands n=139	General population n=264
Mobility				**		
Able to walk about	215 (89)	300 (89)	410 (80)	265 (70)	93 (67)	158 (62)
Slight problems	21 (9)	28 (8)	63 (12)	79 (21)	29 (21)	47 (18)
Moderate problems	4 (2)	6 (2)	30 (6)	29 (8)	9 (6)	32 (13)
Severe problems	1 (1)	1 (0)	11 (2)	6 (2)	7 (5)	19 (7)
Unable to walk about	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Self-care						*
Able to wash or dress myself	235 (97)	330 (98)	473 (93)	366 (97)	118 (85)	246 (93)
Slight problems	5 (2)	4 (1)	21 (4)	8 (2)	14 (10)	10 (4)
Moderate problems	2 (1)	1 (0)	15 (3)	3 (1)	1 (1)	5 (2)
Severe problems	1 (0)	0 (0)	5 (1)	0 (0)	5 (3)	0 (0)
Unable to walk or dress myself	0 (0)	1 (0)	0 (0)	1 (0)	1 (0)	3 (1)
Usual activities				**		*
Able to do usual activities	195 (81)	275 (84)	402 (78)	257 (68)	107 (77)	180 (67)
Slight problems	36 (15)	37 (11)	74 (14)	68 (18)	19 (13)	53 (20)
Moderate problems	8 (3)	10 (3)	26 (5)	46 (12)	8 (5)	28 (10)
Severe problems	3 (1)	3 (1)	12 (2)	7 (2)	3 (2)	7 (3)
Unable to do usual activities	0 (0)	1 (0)	1 (0)	1 (0)	3 (2)	0 (0)
Pain/discomfort				**		**
No pain	164 (68)	217 (65)	291 (57)	181 (48)	81 (59)	102 (39)
Slight pain	53 (22)	92 (27)	138 (27)	120 (32)	39 (28)	98 (37)
Moderate pain	21 (9)	21 (6)	58 (11)	61 (16)	9 (7)	51 (19)
Severe pain	3 (1)	5 (2)	27 (5)	14 (4)	5 (4)	12 (5)
Extreme Pain	1 (1)	1 (0)	1 (0)	3 (1)	3 (2)	1 (0)
Anxiety/depression		**		**		**
Not anxious or depressed	154 (64)	265 (79)	333 (65)	289 (76)	94 (68)	223 (85)
Slightly	52 (22)	55 (16)	124 (24)	59 (16)	26 (19)	35 (13)
Moderately	32 (13)	13 (4)	42 (8)	21 (6)	6 (5)	6 (5)
Severely	3 (1)	3 (1)	11 (2)	8 (2)	10 (7)	0 (0)
Extremely	1 (0)	0 (0)	4 (1)	2 (1)	2 (1)	0 (0)
Comparison of people living with HIV and the general population of England						
Per EQ-5D-5L domain n(%)	<40 years of age People living with HIV in England n=904	General population n=2683	40 – 60 years of age People living with HIV in England n=2617	General population=2430	> 60 years of age People living with HIV in England n=525	General population n=2023
Mobility		**		**		
Able to walk about	803 (89)	2434 (90)	1874 (72)	1991 (81)	292 (56)	1263 (61)
Slight problems	50(6)	183 (7)	278 (11)	234 (10)	96 (18)	345 (17)
Moderate problems	35(4)	52 (2)	325 (12)	123 (5)	93 (18)	239 (12)
Severe problems	16 (2)	24 (1)	130 (5)	91 (4)	42 (8)	192 (9)
Unable to walk about	0 (0)	9 (0)	10 (0)	14 (1)	2 (0)	21 (1)
Self-care		**		**		**
Able to wash or dress myself	846 (94)	2614 (97)	2235 (85)	2282 (93)	427 (81)	1767 (86)
Slight problems	27 (3)	54 (2)	141 (5)	74 (3)	40 (8)	144 (7)
Moderate problems	22 (2)	27 (1)	182 (7)	74 (3)	51 (10)	82 (4)
Severe problems	6 (1)	0 (0)	44 (2)	24 (1)	4 (1)	41 (2)
Unable to walk or dress myself	3 (0)	0 (0)	15 (1)	0 (0)	3 (1)	21 (1)
Usual activities		**		**		**
Able to do usual activities	755 (84)	2406 (89)	1822 (70)	2010 (81)	324 (62)	1368 (67)
Slight problems	77 (9)	189 (7)	325 (12)	223 (9)	85 (16)	347 (17)
Moderate problems	45 (5)	81 (3)	309 (12)	124 (5)	80 (15)	204 (10)
Severe problems	22 (2)	27 (1)	126 (5)	74 (3)	28 (5)	102 (5)
Unable to do usual activities	5 (1)	0 (0)	35 (1)	25 (1)	8 (2)	41 (2)
Pain/discomfort				**		
No pain	632 (70)	1952 (73)	1375 (53)	1336 (55)	204 (39)	830 (40)
Slight pain	163 (18)	508 (19)	606 (23)	680 (28)	164 (31)	643 (31)
Moderate pain	67 (7)	161 (6)	359 (14)	291 (12)	97 (18)	415 (20)

(continued)

Severe pain	38 (4)	53 (2)	225 (9)	97 (4)	51 (10)	145 (7)
Extreme Pain	4 (0)	27 (1)	52 (2)	49 (2)	9 (2)	41 (2)
Anxiety/depression		**		**		**
Not anxious or depressed	431 (48)	1791 (67)	1314 (50)	1710 (69)	302 (58)	1492 (73)
Slightly	266 (29)	535 (20)	621 (24)	446 (18)	108 (21)	368 (18)
Moderately	125 (14)	267 (10)	428 (16)	198 (8)	81 (15)	143 (7)
Severely	52 (6)	80 (3)	175 (7)	74 (3)	26 (5)	41 (2)
Extremely	30 (3)	27 (1)	79 (3)	28 (1)	8 (2)	21 (1)

intersection of higher rates of mental health problems in marginalised population who are also at risk of HIV, such as LGBT populations, migrants, drug users, and prisoners [27]. People with mental health issues or psychiatric disorders may be more likely to acquire HIV [28,29]. Unrecognized and untreated mental health issues are associated with non-adherence and the increase of high-risk behaviour. This may facilitate HIV transmission, which can hamper the other '90-90-90 targets' [23-25]. Therefore, it is of importance to regularly screen for anxiety/depression issues in the provision of HIV-care and, if indicated, a more in-depth assessment followed by an appropriate treatment plan, including a multidisciplinary team for people living with HIV with moderate to extreme anxiety /depression symptoms [30].

We found that the HrQoL<sub>utility</sub> is impacted by different factors for older and younger people living with HIV, indicating the changing needs of the HIV population over the life course. Young people living with HIV mostly struggle with anxiety/depression issues, while elderly people living with HIV have additional problems with self-care and usual activities. Maintaining a good HrQoL among elderly people living with HIV is challenging but of importance given an ageing HIV population. Older people living with HIV have more co-morbidities, use multiple medication, experiences more changes in physical and cognitive wellbeing, and are more prone to stressors [31,32]. Additionally, apart from age-group differences our study found country specific differences. For instance, in England middle-aged people living with HIV experienced a lower HrQoL on all domains while Dutch middle-aged people living with HIV scored better on most. This demonstrates that HrQoL is country specific and cannot be adopted from other countries. Therefore, countries should measure their own HrQoL among people living with HIV.

One of the major strengths of this study is that we included a large fraction of all people living with HIV in the Netherlands (4%) and England (5%) and that our sample is generally representative of the national PLWH population from both countries. Another strength of this study is the comparison of gender and age groups of PLWH with similar groups of the general population. Moreover, the Netherlands and England can provide an example to other countries as both have universal access to ART, a focus on early case finding, and solid and multidisciplinary HIV-care, which might result in a higher HrQoL than previous studies [10].

Our study has several limitations. Firstly, as there is no consensus on the best definition of and measurement tool for HrQoL to assess progress towards the 'fourth 90', we defined this measure independently as a HrQoL<sub>utility</sub> score that is 90% of the general population. This approach has several caveats, in that the interpretation is highly dependent on the validity of the EQ-5D-5L instrument to accurately measure HrQoL<sub>utility</sub> for people living with HIV. Generic HrQoL measures such as the EQ-5D-5L, SF-36, and WHOQOL-BREF are widely used in HIV research [6]. While the EQ-5D-5L may be less sensitive to HIV-specific changes than other measurements, the EQ-5D-5L is useful due to its extensive validation, brevity, ease of administration and interpretation, the availability of several languages, and, importantly for this study, allows comparison to the general population. Additionally, the EQ-5D-5L is frequently used and recommended among

people living with HIV and provides responsiveness to treatment initiation, adverse events, and the development of opportunistic infections [4,8,33]. However, more HIV specific in-depth knowledge as, social circumstances, relationships issues, and stigmatization, should be measured with HIV-specific HrQoL instruments as for example, the WHOQOL-HIV or MOS-HIV or other patient-reported outcome measures such as stigma, social isolation, and patient engagement [6,8,34]. Although the EQ-5D-5L and other HrQoL instruments are very useful tools, they only measure a range of activities. Ideally, these should be offered with additional context specific measure of open-ended questions which can allow patients to expand on these modalities as well as express in their own words their lived experiences.

Secondly, there may be bias in the sample of people with HIV who participated in the surveys. In the Netherlands, the survey was conducted in a single urban HIV clinic representing 8% of all people with HIV in the Netherlands and significantly over-represented women and migrants. In England, the data was from a national survey with a random sampling strategy. However, the survey somewhat over-recruited older, white men and Londoners. In England, the survey data was weighted to account for these demographic differences. However, in both surveys non-respondents may systematically differ from respondents on the outcome of interest (quality of life) and in important factor socioeconomic status, self-stigma, and mental health status. Therefore, some residual bias will remain, although the directionality of this bias is not clear.

Thirdly, England and the Netherlands have a demographically different people living with HIV population and are therefore not directly comparable. From a methodological perspective, this analysis raised additional questions about the cross-country comparability of EQ-5D utility scores using different value sets and the complexity of interpreting the overall utility score. Nevertheless, this method has been performed in other studies comparing the HrQoL between different countries [35-37]. Importantly, data showed that HrQoL between countries differ and therefore it is of importance to have country specific measurements instead of adopting values from other countries.

Lastly, this study aimed to provide an overview of the HrQoL of people living with HIV compared to the general population and did not look at population specific factors, such as smoking, economic, and educational status. These factors, however, can negatively influence quality of life outcomes and are often more present in people living with HIV, such as smoking [10,38].

This study represents a first step in the process of how best to assess HrQoL in people living with HIV, by assembling large, existing data sources that use a standardised HrQoL measurement, and appraising the 'state of play' for HrQoL among the people living with HIV population in a standardised way that allows comparison to the general population. Indeed, our results identified important insights into gaps in the general health of people living with HIV at the population-level. However, there is a need for a standardised HrQoL measure or index to be developed, particularly considering mental health and HIV-specific issues such as stigma and ART use.

Measuring HrQoL is an important next step in HIV-care, due to the chronic nature of the disease and to promote health. Our study

showed that in two Western European countries, both on track for the '90-90-90 targets', the 'fourth 90' is already achieved. Although a high HrQoL<sub>utility</sub> was reported, both countries reported more anxiety/depression among the people living with HIV population compared to the general population, highlighting an area of health which needs more attention to improve the well-being of people living with HIV. Standardized HrQoL measurements implemented in daily practice can help to guide individualized patient care by pointing out areas which require attention. More work is needed to identify the optimal HrQoL measure for people living with HIV to adopt as the 'fourth 90'.

## 5. Author's contributions

Conceptualisation: SP, MK, BEN, ES, DvdV, CB, AV  
 Data curation: SP, MK, BEN, ES, LV, AS, MV, VD  
 Formal analysis: SP, MK, BEN, ES, LV, DvdV, CB, AV  
 Funding acquisition: BEN, DvdV, AS, CB, AV  
 Investigation: SP, MK, BEN, ES, LV, MV, VD, AV  
 Methodology: SP, MK, ES, DvdV, AS, MV, CB, AV  
 Project administration: SP, MK  
 Supervision: BEN, DvdV, CB, VD, AV  
 Visualisation: SP, ES, LV  
 Writing original draft: SP, ES  
 Writing review & Editing: All authors

## 6. Data availability statement

Data can be requested by contacting the corresponding authors.

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## Declaration of Competing Interest

SP reports an unrestricted educational grant from Gilead Sciences; DvdV reports unrestricted research grant from Gilead Sciences; CAB reports personal fees from speaker honoraria from ViiV outside the submitted work; AvS reports grants from Dutch Ministry of Health, Welfare and Sport, during the conduct of the study. MV: Dr. Versteegh is a member of the non-profit EuroQoL research foundation which develops EQ-5D; MK, ES, BN, LV, VD, AV have nothing to disclose.

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## Supplementary materials

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## References

- [1] ECDC. HIV/AIDS surveillance in Europe 2019-2018 data European Centre for Disease Prevention and Control (ECDC) 2019.
- [2] Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *Aids* 2012;26(3):335–43.
- [3] National AIDS programmes: A guide to monitoring and evaluation UNAIDS; 2000.
- [4] Clayson DJ, Wild DJ, Quarterman P, Duprat-Lomon I, Kubin M, Coons SJ. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. *Pharmacoeconomics* 2006;24(8):751–65.
- [5] Devlin NJ, Krabbe PF. The development of new research methods for the valuation of EQ-5D-5L. *Eur J Health Econ* 2013;14(1):S1–3 Suppl.
- [6] Cooper V, Clatworthy J, Harding R, Whetham J, Emerge C. Measuring quality of life among people living with HIV: a systematic review of reviews. *Health Qual Life Outcomes* 2017;15(1):220.
- [7] Tran BX, Ohinmaa A, Nguyen LT. Quality of life profile and psychometric properties of the EQ-5D-5L in HIV/AIDS patients. *Health Qual Life Outcomes* 2012;10:132.
- [8] Wu AW, Hanson KA, Harding G, Haider S, Tawadrous M, Khachatryan A, et al. Responsiveness of the MOS-HIV and EQ-5D in HIV-infected adults receiving antiretroviral therapies. *Health and quality of life outcomes* 2013;11:42.
- [9] Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37(1):53–72.
- [10] Miners A, Phillips A, Kreif N, Rodger A, Speakman A, Fisher M, et al. Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. *The Lancet HIV* 2014;1:e32–40.
- [11] Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 2019;393(10167):143–55.
- [12] Lazarus JV, Saffred-Harmon K, Barton SE, Costagliola D, Dedes N, del Amo Valero J, et al. Beyond viral suppression of HIV – the new quality of life frontier. *BMC Medicine* 2016;14(1):94.
- [13] UNAIDS. Fast Track: Ending the AIDS epidemic by 2030 2015.
- [14] Van Sighem A GL, Smit C, Stolte I, Reiss P. Monitoring Report 2017. *Humaan Immunodeficiency Virus (HIV) Infection in the Netherlands* 2017.
- [15] Nash S DS, Croxford S, Guerra L, Lowndes C, Connor N, Gill ON. Progress towards ending the HIV epidemic in the United Kingdom: 2018 report. November 2018. *Public Health England. Public Health England*; 2018 November 2018.
- [16] Kall M, Kelly C, Auzenbergs M, Delpech V. Positive Voices: The National Survey of People Living with HIV - findings from the 2017 survey. London: Public Health England; 2020. January [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/857922/PHE\\_positive\\_voices\\_report\\_2019.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857922/PHE_positive_voices_report_2019.pdf).
- [17] Selivanova A, Buskens E, Krabbe PFM. Head-to-Head Comparison of EQ-5D-3L and EQ-5D-5L Health Values. *Pharmacoeconomics* 2018;36(6):715–25.
- [18] MV M, MV K, MAAE S, de Wit GA, Prenger R, AS E. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health* 2016;19(4):343–52.
- [19] Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ* 2018;27(1):7–22.
- [20] Digital N. Health Survey for England: NHS Digital; 2019 [Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2017>].
- [21] Organization WH. Draft global health sector strategies. *HIV 2016* 2016–2021.
- [22] de Boer-van der Kolk IM, Sprangers MA, Prins JM, Smit C, de Wolf F, Nieuwerkerk PT. Health-related quality of life and survival among HIV-infected patients receiving highly active antiretroviral therapy: a study of patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort. *Clin Infect Dis* 2010;50(2):255–63.
- [23] Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. *Drugs* 2006;66(6):769–89.
- [24] Horberg MA, Silverberg MJ, Hurley LB, Towner WJ, Klein DB, Bersoff-Matcha S, et al. Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. *J Acquir Immune Defic Syndr* 2008;47(3):384–90.
- [25] Davis L, Uezato A, Newell JM, Frazier E. Major depression and comorbid substance use disorders. *Curr Opin Psychiatry* 2008;21(1):14–8.
- [26] Engelhard EAN, Smit C, PRv Dijk, Kuijper TM, Wermeling PR, Weel AEAM, et al. Health-related quality of life of people with HIV: an assessment of patient related factors and comparison with other chronic diseases. *AIDS* 2018;32(1):103–12.
- [27] Russell ST, Fish JN. Mental Health in Lesbian, Gay, Bisexual, and Transgender (LGBT) Youth. *Annu Rev Clin Psychol* 2016;12:465–87.
- [28] Grassi L. Risk of HIV infection in psychiatrically ill patients. *AIDS Care* 1996;8(1):103–16.
- [29] Carey MP, Carey KB, Maisto SA, Schroder KE, Venable PA, Gordon CM. HIV risk behavior among psychiatric outpatients: association with psychiatric disorder, substance use disorder, and gender. *J Nerv Ment Dis* 2004;192(4):289–96.
- [30] Robertson K, Bayon C, Molina JM, McNamara P, Resch C, Munoz-Moreno JA, et al. Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in Western Europe and Canada. *AIDS Care* 2014;26(12):1555–61.
- [31] Rodriguez-Penney AT, Iudicello JE, Riggs PK, Doyle K, Ellis RJ, Letendre SL, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS Patient Care STDS* 2013;27(1):5–16.
- [32] Balderson BH, Grothaus L, Harrison RG, McCoy K, Mahoney C, Catz S. Chronic illness burden and quality of life in an aging HIV population. *AIDS Care* 2013;25(4):451–8.
- [33] Robberstad B, Olsen JA. The health related quality of life of people living with HIV/AIDS in sub-Saharan Africa - a literature review and focus group study. *Cost Eff Resour Alloc* 2010;8:5.
- [34] Simpson KN, Hanson KA, Harding G, Haider S, Tawadrous M, Khachatryan A, et al. Patient reported outcome instruments used in clinical trials of HIV-infected adults on NNRTI-based therapy: a 10-year review. *Health Qual Life Outcomes* 2013;11:164.

- [35] Mastboom MJ, Planje R, van de Sande MA. The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life. *Interact J Med Res* 2018;7(1):e4.
- [36] Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. *Journal of Hospital Infection* 2017;96(1):1–15.
- [37] Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomas-Aragones L, et al. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. *Br J Dermatol* 2017;176(5):1170–8.
- [38] Johnston PI, Wright SW, Orr M, Pearce FA, Stevens JW, Hubbard RB, et al. Worldwide relative smoking prevalence among people living with and without HIV. *Aids* 2021;35(6):957–70.