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Trends in life expectancy of HIV-positive adults on ART across the globe: comparisons with general population

Gilles Wandeler, MD, MSc^{1,2,3}, Leigh F. Johnson, PhD⁴, and Matthias Egger, MD, MSc^{2,4}

¹Department of Infectious Diseases, Bern University Hospital Bern, University of Bern,

Switzerland ²Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

³Department of Infectious Diseases, University of Dakar, Senegal ⁴Centre for Infectious Disease Epidemiology and Research (CIDER), University of Cape Town, South Africa

Abstract

Purpose of review—Improved virological and immunological outcomes and reduced toxicity of antiretroviral combination therapy (ART) raise the hope that life expectancy of HIV-positive persons on ART will approach that of the general population. We systematically review the literature and summarize published estimates of life expectancy of HIV-positive populations on ART. We compare their life expectancy with the life expectancy of the general or, in sub-Saharan Africa, HIV-negative populations, by time period and gender.

Recent findings—Ten relevant studies were published from 2006 to 2015. Three studies were from Canada, two from European countries, three from sub-Saharan Africa and two were multi-country studies. Life expectancy increased over time in all studies and regions. Expressed as the percentage of life expectancy in the HIV-negative or general population, estimated life expectancy at age 20 years in HIV-positive people on ART ranged from 60.3% (95% CI 58.0–62.6) in Rwanda (2008–2011) to 89.1% (95% CI 84.7–93.6) in Canada (2008–2012). The percentage of the life expectancy in the HIV-negative or general population achieved was higher in HIV-positive women than in HIV-positive men in all countries, except for Canada where the opposite was the case.

Summary—Life expectancy in HIV-positive people on ART has improved worldwide in recent years, but important gaps remain compared to the general and HIV-negative population, and between regions and genders.

Keywords

HIV infection; life expectancy; antiretroviral therapy; Africa; North America; Europe

Correspondence: Prof. Matthias Egger, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, CH-3012 Bern, Switzerland, matthias.egger@ispm.unibe.ch.

Conflicts of interest

The authors have no conflicts of interest to declare.

INTRODUCTION

Worldwide, survival of HIV-infected populations has improved with the increasing availability of antiretroviral therapy (ART). By 2014, 40% of eligible HIV-infected individuals had initiated ART globally [1]. In the same year, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced the 90-90-90 targets, which aim for 90% of all people living with HIV to know their HIV status, 90% of all people with diagnosed HIV infection to receive sustained ART and 90% of all people receiving ART to have HIV viral suppression [2]. As shown by the increasing CD4 cell counts observed at ART initiation worldwide, a trend towards earlier ART initiation is seen in most countries [3,4].

With the scale up of ART, the reduction in early mortality seen in high-income countries 20 years ago [5] has also become evident in sub-Saharan Africa. For example, in a recent study from Botswana, mortality in the year after ART initiation decreased from 7% to 2% between 2002 and 2012 [6]. Improved virological and immunological outcomes and reduced toxicity of newer ART combinations led to the hope that life expectancy of HIV-infected persons on potent ART will soon approach that of the general population [7]. A study of 14 cohort studies from Europe and North America found that life expectancy at age 20 years was 43.1 years in the years 2003 to 2005, about two thirds of the life expectancy in the general population of these countries [8].

Few studies have examined life expectancy in low- and middle-income countries where sub-optimal treatment of opportunistic diseases, high prevalence of co-infections such as tuberculosis and viral hepatitis, and limited access to second-line ART options remain important challenges. Furthermore, retention in care and ART adherence are often poor due to the barriers to HIV care faced by many patients, including structural barriers, for example costs for transport, clinical barriers, for example long waiting times, and psychosocial factors such as stigma [9]. We performed a systematic review of the literature to summarize estimates of life expectancy of HIV-positive populations on ART, and compared their life expectancy with that calculated for HIV-negative or general populations, by gender and time period.

IDENTIFYING AND CALCULATING ESTIMATES OF LIFE EXPECTANCY

We searched MEDLINE and EMBASE on 17 February 2016 for studies assessing life expectancy of HIV-infected populations on ART. We combined free text words and medical subject headings (MESH) describing the age group, ART status and the outcome (see Appendix for search strategies). We also screened the reference lists of identified publications. No language restrictions were applied. We examined the titles and abstracts and, in a second step, the full text of potentially eligible articles. We extracted data on the demographic and behavioural characteristics of the population studied as well as information related to statistical methods and outcome ascertainment. The main outcome of interest was life expectancy at the age of 20 years overall and stratified by sex and calendar period. We excluded modelling studies and studies of selected populations, such as cohorts of persons who inject drugs (PWID) or men who have sex with men (MSM). If several studies described life expectancy within the same cohort, we included the most recent estimates. Of

30 potentially eligible studies, 20 were excluded because they did not present relevant data on life expectancy on ART, were based on the same study population as another study or only presented life expectancy estimates in selected groups of patients (Figure 1). Among 10 studies included, three were from Canada [10–12], two from European countries [13,14], three from African countries [15–17] and two were multi-country studies [8,18] (Table 1).

We compared estimates of life expectancy at 20 years of age in patients on ART with the corresponding estimates for the general population. In African countries with generalized HIV epidemics, mortality rates estimated for the HIV-negative population were used since HIV-related mortality contributes substantially to adult mortality in the general population. If not reported in the articles, we calculated life expectancies from published life tables. For Uganda and Rwanda we used the United Nations Population Division estimates for 2005–2010 [19], and for Canada the estimates for 2009–2011 from Statistics Canada [20].

COMPARATIVE LIFE EXPECTANCY

Life expectancy on ART at age 20 years was lower in HIV-positive individuals on ART from African countries compared to high-income countries in North America and Europe, however, the composition of study populations, the calendar periods studied, and the methods used to ascertain deaths and estimate life expectancy varied between studies (Table 1).

Trends over time

Five studies examined trends over time [10,12,14,15,17]. When comparing the earliest with the most recent calendar period, life expectancy increased in all studies and regions (Table 2, Figure 2). In the most recent calendar period life expectancy, expressed as the percentage of the life expectancy in the HIV-negative or general population, ranged from 60.3% (95% CI 58.0–62.6) in Rwanda 2008–2011 [17] to 89.1% (95% CI 84.7–93.6) in Canada 2008–2012 [12]. Although there are several potential explanations for these improvements, the earlier initiation of ART during the course of disease will have played an important role. During the calendar periods considered in this review, the World Health Organization increased the recommended CD4 count thresholds for the start of ART from 200 to 350 and 500 cells/ μ L [21–23]. The level of cellular immunity has a strong impact on early mortality on ART as well as on long-term mortality from non-communicable diseases [24]. In South Africa, life expectancy was 50% higher in patients who started ART with CD4 cell counts above 200 cells/ μ L compared to those starting below 50 cells/ μ L, and twice as high in Uganda if ART was initiated above 250 cells/ μ L compared to below 50 cells/ μ L [15,17]. Of note, the South African study adjusted for differences in baseline CD4 counts when comparing the two periods, which partly explains the more modest increase in the estimated life expectancy shown in Table 2 and Figure 2 [15].

Gender differences

Six studies investigated gender differences in life expectancy at age 20 years [10,12,14–17]. As shown in Table 3 and Figure 3, the percentage of the life expectancy in the HIV-negative or general population achieved over the entire study period was higher in HIV-positive

women than in HIV-positive men in all countries, except for the two studies from Canada. The largest absolute differences between men and women were estimated in Rwanda and Uganda [16,17], whereas smaller differences were observed in the UK and South Africa [14,15]. The higher mortality in men can be explained by the more advanced stage of disease and lower CD4 cell count at ART initiation in men compared to women. The opposite trend observed in the two Canadian studies [10,12], with a higher life expectancy in men compared to women, may be due to the different risk factors for HIV transmission prevalent among women and men living with HIV in Canada. Women who use or used injection drugs, women from HIV-endemic countries or with partners from such countries, women involved in sex work, women in prisons, indigenous women and trans women constitute the majority of women with HIV in Canada [25]. In contrast, MSM dominate among HIV-positive men living in Canada [25]. Of note, the higher HIV-unrelated background mortality in men compared to women is controlled for when expressing gender-specific life expectancy as a percentage of the life expectancy in the HIV-negative or general population.

Impact of injection drug use

In Europe and North America, a substantial proportion of HIV-positive persons are active or past injection drug users, an important risk factor of mortality. In the Swiss HIV Cohort study, a nationwide cohort of HIV-infected individuals, active drug use (injected and non-injected) was an important predictor of death, and patients with past injection drug use were 2.3 times more likely to die during follow-up than individuals without drug use [26]. In the three Canadian studies included in this review, life expectancy of PWID was about half the life expectancy in other HIV-positive individuals [10–12]. Differences in life expectancy across studies from high-income countries might be partly explained by the proportion of PWID in each population: the two studies with the lowest life expectancy estimates also had the highest proportion of PWID [10,11], whereas life expectancy was highest among studies with fewer PWIDs [8,12–14,18]. Although injection drug use has increased in several large African cities [27], data on drug consumption is only rarely reported and generally not systematically assessed. Indeed, no information on IDU was available from the three African studies included in this review.

METHODOLOGICAL CHALLENGES

Several limitations and methodological challenges need to be considered when interpreting and comparing estimates of mortality or life expectancy on ART reported by different studies and from different settings. For example, an important limitation is that analyses tend to rely on data from treatment and care programmes with electronic medical record systems that may not be representative of all programmes in the country. Below we consider some of these challenges in greater detail.

Loss to follow-up and ascertainment of deaths

Estimations of life expectancy in HIV-infected populations rely on the complete ascertainment of deaths, however, the proportion of patients lost-to follow-up in HIV care programs can be high, especially in sub-Saharan Africa [28]. As patients who are lost to

follow-up experience higher mortality than those remaining in care [29], failing to account for deaths in these patients leads to the underestimation of mortality, and overestimation of life expectancy. The studies included in this review addressed this issue in different ways. The study from Uganda [16], and the analysis of the Canadian Observational Cohort collaboration [12] assumed that 30% of patients lost to follow-up had died whereas in Rwanda, investigators assumed that about 50% of patients lost to follow-up had died [17]. In South Africa the authors used the civil identity document (ID) number of patients lost to follow-up to check their vital status in the national population registry: 94% of known deaths are identified using this method [30]. However, about 14% of patients lost to follow-up had no ID [15]. Inverse probability weighting was therefore used to ensure that LTFU patients with IDs were weighted up to represent the patients without IDs [15]. The mortality estimates from South Africa are therefore likely as accurate as those from the UK and British Columbia [10,14], where the HIV cohort data were also linked to civil registries. Unfortunately in some studies, the ascertainment of mortality in patients lost to follow-up was not addressed [13].

Comparisons with the general or HIV-negative population

The question whether HIV-positive people on ART have a “normal” life expectancy is difficult to address because life-expectancy varies widely, influenced by socio-economic status, lifestyle factors and, in HIV-positive people, by HIV-related factors. The biological effects of HIV infection cannot easily be disentangled from effects associated with lifestyles and behaviours. Ideally, HIV-positive people would be matched to HIV-negative individuals from the general population for age, sex, smoking, alcohol, nutrition, drug use, co-infections, co-morbidities, socio-economic status and other risk factors to compare life expectancy. However, these data are not available from the vital registration systems used to estimate life expectancy in the general population. Matching HIV-positive people to members of the general population for variables that are associated with lifestyles and behaviours, for example educational attainment, is one way to address this issue. The Swiss HIV Cohort Study recently showed that life expectancy of HIV-positive people with higher education was lower than the life expectancy of their equally well educated peers from the general population [31].

Comparisons across calendar periods

The risk of death is much higher in the first months after starting ART but declines with increasing duration of therapy, particularly in patients with low CD4 cell counts [32]. Duration of ART should therefore be standardised when comparing different calendar periods [33]. This was done in several of the studies included in this review. The South African study [15] defined four categories of ART duration categories and, in a sensitivity analysis, estimated life expectancy for patients who had survived to 2 years since ART initiation. The UK study did not stratify the analysis by ART duration but performed a sensitivity analysis restricted to those who survived at least six months after starting treatment [14]. The Rwandan study restricted mortality analyses to the first 3 years of follow-up [17]. In contrast, the Canadian studies do not appear to have considered the duration of ART [10,12].

Statistical issues

Most studies which reported on life expectancy in HIV-infected populations used the abridged life table method, which does not allow multivariate analysis of the data, for example to assess to what extent the increase in life expectancy in later years was due to increases in CD4 cell counts [33]. The South African study [15] used a multivariate relative survival model adjusting for CD4 count and duration of ART, which explains the smaller improvement in life expectancy over time, and the small difference between genders observed in this study compared to the other studies. It should also be noted that estimates of life expectancy from abridged life tables method and the relative survival model can differ, particularly in patients starting ART at young ages [15]. Another issue is the estimation of mortality rates for the oldest, open age category (typically 65), which may be difficult because there are only few older HIV-positive patients in the cohorts [14].

CONCLUSIONS

Our review shows that life expectancy in HIV-positive people on ART has improved worldwide in recent years, but important gaps remain compared to the general and HIV-negative population, and between regions and genders. Life expectancy is the number of years that a person of a particular age would live, assuming that current age-specific mortality rates remain constant. Estimating life expectancy in people living with HIV is not straightforward, particularly in sub-Saharan Africa where ascertainment of deaths is often incomplete. Comparisons with the general, HIV-negative population are difficult to interpret, particularly in high-income countries where HIV infection is associated with life styles and behaviors that affect life expectancy independently of HIV.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. xxx).

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Appendix to Wandeler et al Curr Opinion in HIV and AIDS 2016: Searches in Ovid MEDLINE and EMBASE

Database(s): **Ovid MEDLINE(R)** 1946 to February Week 2 2016, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** February 17, 2016, **Ovid MEDLINE(R) Daily Update** February 17, 2016

Search Strategy:

#	Searches	Results
1	exp Anti-Retroviral Agents/tu [Therapeutic Use]	36744
2	exp Antiretroviral Therapy, Highly Active/	17819
3	Antiviral Agents/	62116
4	((anti and hiv) or antiretroviral* or (anti and retroviral*) or HAART or (anti and acquired immunodeficiency) or (anti and acquired immunodeficiency) or (anti and acquired immuno-deficiency) or (anti and acquired immune* and deficiency)).tw.	69186
5	or/1–4	144766
6	exp HIV Infections/dt, mo [Drug Therapy, Mortality]	63035
7	(hiv or hiv?1 or hiv?2 or human immun#deficiency virus or human immun#-deficiency virus or (human immun# adj3 deficiency virus) or acquired immun#deficiency syndrome or acquired immun#-deficiency syndrome or (acquired immun# adj3 deficiency syndrome)).tw.	274892
8	or/6–7	288038
9	exp Life Expectancy/	14745
10	exp Longevity/	16648
11	exp Mortality/	304617
12	(life expectanc\$3 or (life adj3 exten\$4) or years of potential life lost or years of life lost or additional years or mortality rate*).tw.	126090

Search Strategy:

#	Searches	Results
13	or/9–12	419525
14	5 and 8 and 13	3171
15	exp animals/ not humans/	4188359
16	14 not 15	3147
17	cohort*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	414012
18	16 and 17	867
19	exp children/ not adults/	1066585
20	18 not 19	802
21	(life expectanc\$3 or surviv\$3 or mortality).ti.	221418
22	20 and 21	372
23	limit 22 to yr="1996 -Current"	365

Database(s): **Embase** 1974 to 2016 February 17

Search Strategy:

#	Searches	Results
1	exp antiretrovirus agent/	153956
2	exp highly active antiretroviral therapy/	32866
3	exp antiviral agent/	740477
4	((anti and hiv) or antiretroviral* or (anti and retroviral*) or HAART or (anti and acquired immunodeficiency) or (anti and acquired immunodeficiency) or (anti and acquired immuno-deficiency) or (anti and acquired immune* and deficiency)).tw.	89463
5	or/1–4	777778
6	exp Human immunodeficiency virus infection/	320593
7	(hiv or hiv?1 or hiv?2 or human immunodeficiency virus or human immunodeficiency virus or (human immun# adj3 deficiency virus) or acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or (acquired immun# adj3 deficiency syndrome)).tw.	331665
8	or/6–7	429445
9	exp life expectancy/	36058
10	exp longevity/	20770
11	exp mortality/	778290
12	(life expectanc\$3 or (life adj3 exten\$4) or years of potential life lost or years of life lost or additional years or mortality rate*).tw.	169185
13	or/9–12	873165
14	5 and 8 and 13	10881
15	exp animals/ not humans/	9183074
16	14 not 15	6246
17	cohort*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	582945
18	16 and 17	1110
19	exp children/ not adults/	2279968

Search Strategy:

#	Searches	Results
20	18 not 19	975
21	(life expectanc\$3 or surviv\$3 or mortality).ti.	286053
22	20 and 21	333
23	limit 22 to yr="1996 -Current"	325

KEY POINTS

- Life expectancy of HIV-positive people on combination antiretroviral therapy (ART) has increased in recent years, both in high-income and low-income and middle income countries. Most of this increase is likely due to the increase over time in CD4 cell counts at the start of ART.
- Life expectancy in people on ART is still below the corresponding HIV-negative life expectancy. It ranges from 60% of HIV-negative life expectancy in Rwanda to 90% in Canada, and is higher in women than in men in most countries.
- Achieving life expectancy on ART that is close or equal to HIV-negative life expectancy may be feasible with early start of ART and long-term retention and adherence.

Figure 1.
Flow chart of identifying relevant studies.

Figure 2.
Life expectancy at age 20 years in HIV-positive individuals initiating ART, by earlier and later calendar period.

Figure 3.
Life expectancy at age 20 years in HIV-positive men and women initiating ART.

Table 1
 Characteristics of studies reporting on life expectancy of general HIV-infected populations on antiretroviral therapy

Region/Study (Year)	Country	Period of observation	Methods	Death ascertainment	Number of HIV-positive individuals	Proportion of men (%)	Proportion of PWID (%)	Life expectancy at 20 (years)
Sub-Saharan Africa								
Johnson (2013) [15]	South Africa	2001–2010	Relative survival model	Linkage with civil registry	37,740	40%	Not specified	33.3
Mills (2011) [16]	Uganda	2000–2009	Abridged life-tables	Home visits in patients lost to follow-up	22,315	32%	Not specified	26.7
Nsanzimana (2015) [17]	Rwanda	1997–2014	Abridged life-tables	Home visits in patients lost to follow-up	72,061	39%	Not specified	29.9
Europe								
Guaraldi (2014) [13]	Italy	1997–2011	Abridged life-tables	Not specified	9,671	74%	26%	42.7
May (2011) [14]	UK	1996–2008	Abridged life-tables	Linkage with civil registry	17,661	75%	0%	41.1
North America								
Lima (2015) [10]	Canada	2003–2013	Abridged life-tables	Linkage with civil registry	3,653	82%	36%	34.5
Lloyd-Smith (2006) [11]	Canada	1996–2003	Abridged life-tables	Not specified	1,573	85%	46%	31.0
Patterson (2015) [12]	Canada	2000–2012	Abridged life-tables	Not specified	9,997	82%	27%	37.5
Samji (2013) [18]	USA, Canada	2000–2007	Abridged life-tables	Linkage with civil registry in some cohorts	22,937	77%	20%	51.4
Multi-regional								
ART Cohort Collaboration (2008) [8]	North America, Europe	1996–2005	Abridged life-tables	Linkage with civil registry in some cohorts	10,854	67%	8%	43.1

PWID, persons who inject drugs

Table 2

Estimates of life expectancy at age 20 years by calendar period.

Study	Country	Earliest period			Latest period		
		Period	LE in HIV+ individuals	Percent of LE in general/HIV – population (95% CI)	Period	LE in HIV+ individuals	Percent of LE in general/HIV – population (95% CI)
Johnson (2013) [15]	South Africa	2001–2006	34.7 (33.0–36.3)	69.7 (66.3–72.9)	2007–2010	36.8 (35.1–38.5)	73.9 (70.5–77.3)
Nsanzimana (2015) [17]	Rwanda	1997–2007	21.1 (19.5–22.7)	44.1 (40.7–47.4)	2008–2011	28.9 (27.8–30.0)	60.3 (58.0–62.6)
May (2011) [14]	UK	1996–1999	30.0 (27.7–32.4)	51.6 (47.7–55.8)	2006–2008	45.8 (42.5–49.1)	78.0 (73.1–84.5)
Lima (2015) [10]	Canada	2003–2005	28.8 (25.3–32.4)	46.8 (41.1–56.7)	2009–2012	49.8 (46.5–53.1)	81.0 (75.6–86.3)
Patterson (2015) [12]	Canada	2000–2003	30.8 (29.0–32.6)	50.7 (47.7–53.6)	2008–2012	54.2 (51.5–56.9)	89.1 (84.7–93.6)

LE, life expectancy

Table 3

Estimates of life expectancy at age 20 years by gender.

Study	Country	Period of observation	Men		Women			
			LE in HIV+ men (95% CI)	LE in men from general /HIV- population	Percent of LE in general/HIV- population (95% CI)	LE in HIV+ women (95% CI)	LE in women from general /HIV- population	Percent of LE in general / HIV- population (95% CI)
Johnson (2013) [15]	South sAfrica	2001–2010	27.6 (25.2–30.2)	44.8	61.6 (56.3–67.4)	36.8 (34.0–39.7)	52.9	69.6 (64.3–75.0)
Mills (2011) [16]	Uganda	2000–2009	19.1 (16.6–21.6)	47.0	40.6 (35.3–46.0)	30.6 (28.7–32.5)	49.5	61.8 (58.0–65.7)
Nsanzimana (2015) [17]	Rwanda	1997–2014	22.2 (20.2–24.2)	46.2	48.1 (43.7–52.4)	33.2 (32.2–34.2)	48.9	67.9 (65.8–69.9)
May (2011) [14]	UK	1996–2008	39.5 (38.6–40.4)	57.8	68.3 (66.8–69.9)	50.2 (49.3–51.1)	61.6	81.5 (80.0–83.0)
Lima (2015) [10]	Canada	2003–2013	37.5 (35.1–39.9)	60.8	61.7 (57.7–65.6)	27.2 (23.4–31.0)	64.9	41.9 (36.1–47.8)
Patterson (2015) [12]	Canada	2000–2012	39.2 (37.8–40.6)	60.0	65.3 (63.0–67.7)	32.4 (31.3–33.5)	64.2	50.5 (48.8–52.2)

LE, life expectancy