

Health-adjusted life expectancy in HIV-positive and HIV-negative men and women in British Columbia, Canada: a population-based observational cohort study



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Summary

Background We sought to understand whether people living with HIV (PLHIV) ever on highly active antiretroviral therapy (ART) follow a pattern where morbidity is compressed into the last years of life or lessened as people age. We aimed to estimate health-adjusted life expectancy (HALE) among adults living with and without HIV, and examine dependency between causes of comorbidities.

Methods The Comparative Outcomes and Service Utilization Trends (COAST) study is a retrospective cohort of adults (≥ 20 years) including all known PLHIV and a 10% random sample of the general population of British Columbia, and with longitudinal data spanning from April 1, 1996, to Dec 31, 2012. We determined the prevalence of select comorbidities (cardiovascular, respiratory, liver, and renal diseases, and non-AIDS defining cancers because of their high prevalence among PLHIV) by age and sex by use of case-finding algorithms. Deaths were obtained from a vital event registry from British Columbia, Canada. Comorbid-specific HALE was estimated from 20 years of age by HIV status and sex. For each comorbidity, a healthy state was defined as the proportion of life expectancy comorbid-free, and was adjusted on the probability of occurrence of other different comorbidities. The sensitivity of HALE estimates was assessed to the sequencing of select comorbidities for the dependent comorbidity adjustments.

Findings Our sample consisted of electronic health records from 9310 HIV-infected and 510 313 uninfected adults over the period April 1, 1996, to Dec 31, 2012. These individuals contributed 49 605 deaths and 5 576 841 person-years over the study period. At exactly age 20 years, HALE was about 31 years (SD 0·16) among men living with HIV and 27 years (0·16) among women living with HIV. In the HIV-negative population, HALE was around 58 years (SD 0·02) for men and 63 years (0·02) for women. These results seem independent of ordering. However, PLHIV, particularly women living with HIV, had much shorter overall life expectancies than did their HIV-negative counterparts in the general population [29·1 years (SD 0·1) vs 65·4 years (0·1)], and thus spent less time in a healthy state.

Interpretation Although we noted little differences in the levels of morbidity compression by HIV status, PLHIV—especially women living with HIV—spent less time in a healthy state. Expanded service delivery interventions to address complex care needs of ageing PLHIV are crucial to address shorter life expectancies, and improve their healthy states.

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Introduction

Life expectancy in high-income countries has steadily increased since the 20th century because of changes in fertility patterns, advances in medicine, and improved living conditions.¹ This positive shift in years lived emphasises the need for better investigative methods to measure longevity and morbidity,² and to understand changes in health status over an individual's life course more clearly.³ To this end, health adjusted life expectancy (HALE), developed by Sullivan,⁴ is an important way to compartmentalise states of health by characterising the number of years a person can expect to live in good and ill health, while considering age-specific mortality, morbidity, and disability.

Three competing theories help to explain the relation between life expectancy and the length of the healthy state: compression of morbidity, expansion of morbidity,

and dynamic equilibrium.^{5,6} Compression of morbidity assumes that therapeutic and preventive efforts will compress chronic diseases to a shorter period later in life, resulting in reduced periods of disease.⁵ By contrast, the expansion of morbidity attributes advances in medicine to decreased fatality rates, thus increasing prevalence rates.^{5,7} Dynamic equilibrium, however, suggests that although decreased mortality rates lead to an increase in milder chronic diseases, severe chronic diseases will be reduced, resulting in an improved quality of life.⁶

Although these theories highlight the interplay of mortality and morbidity at both individual and population levels, there is an urgent need to determine this relationship within the ageing population living with HIV. Thus, we sought to understand whether this cohort of HIV-positive and negative men and women follow a pattern where morbidity is compressed into the last years

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Research in context**Evidence before this study**

Health-adjusted life expectancy (HALE) is an index used to capture morbidity and mortality factors of a population, and can thus be used to understand the effects of HIV and comorbid conditions on an ageing population living with HIV. However, examining all causes of comorbidity in the measure of HALE, without considering people with more than one condition, would overestimate the severity of the time a population is spent in an unhealthy state. We did a systematic review of the scientific literature by searching PubMed, CINAHL (Ebscohost), Global Health (Ovid), Embase(Ovid), and the Cochrane Central Register of Controlled Trials databases for studies published up to Nov 30, 2016. Our search terms included "healthy life expectancy" or "health-adjusted life expectancy" and "comorbidity" or "morbidity" with no language restrictions.

Added value of this study

Using data from the Comparative Outcomes and Service Utilization Trends (COAST) study, we estimated HALE, with adjustment for potential dependent comorbidities for select conditions among people living with HIV (PLHIV) and those living without HIV (HIV-negative) in the British Columbian population. To our knowledge, this is the first study to characterise the length of the health state for both PLHIV and HIV-negative individuals, as well as the effect of dependent comorbidities on the measurement of HALE. Age-specific

morbidity rates were calculated by dividing the number of people with select comorbidities by the number of person-years over the study period, and reported by age group and sex. Because of their prevalence among PLHIV, we chose to study the following key comorbid conditions: cardiovascular disease, respiratory disease, liver disease, renal disease, and non-AIDS defining cancers. More than half of comorbidities reported are paired or dependent with another condition. In the case of PLHIV, we found comorbidities were mostly paired with liver and renal diseases, whereas they were paired with cardiovascular diseases in the HIV-negative population. The ordering of comorbidity pairs has little effect on the estimation of HALE; however, these adjusted HALE measures are noticeably higher, and the time spent in an unhealthy state is much shorter than the unadjusted measures.

Implications of all available evidence

After adjustment for codependencies, we noted little differences in the levels of morbidity compression between PLHIV and their HIV-negative counterparts; however, men and women living with HIV had reduced life expectancies and measures of HALE. Our findings highlight the urgent need to better address the complex care needs of PLHIV through expanded service delivery targeted at comorbidities and chronic-disease management.

of life or lessened as a function of ageing. We aimed to estimate HALE, with adjustment for codependencies between select comorbidities, among people living with HIV (PLHIV) and those living without HIV in British Columbia, Canada.

Methods**Study design and participants**

The Comparative Outcomes and Service Utilization Trends (COAST) study is a retrospective cohort of adults (≥ 20 years) including all known PLHIV and a 10% random sample of the general population of British Columbia, and with longitudinal data spanning from April 1, 1996, to Dec 31, 2012. COAST is based on deidentified health-related data arising from a unique linkage between the BC Centre for Excellence in HIV/AIDS (BCCfE) and the British Columbia electronic repository of administrative health records held by the British Columbia Ministry of Health and other provincial agencies for research, Population Data BC. In this study, our combined dataset for individuals in COAST included physician billings, hospital discharge abstracts, cancer-related diagnoses, and deaths (obtained from British Columbia Ministry of Health databases Medical Services Plan [MSP] Payment Information File, MSP Registration & Premium Billing, Discharge Abstract Database [Hospital Separations], BC Cancer Agency Registry Data, and BC Vital Statistics

Agency Deaths). Additionally, the BCCfE, which centrally manages all antiretroviral prescriptions in the province, provided data for antiretroviral therapy, viral load, and clinical manifestations, such as AIDS defining illness, comorbidities, and mortality.⁸

Two cohorts of individuals aged 20 years and older were created for this study. The PLHIV cohort was constructed from all adults known to be living with HIV in British Columbia who have had a record of at least one detectable HIV plasma viral load and ever been prescribed highly active antiretroviral therapy (ART) in British Columbia between April 1, 1996, and Dec 31, 2012. The HIV-negative cohort was constructed from a 10% random sample of all adults in the total British Columbia population meeting the age criterion between April 1, 1996, and Dec 31, 2012, and with no known HIV diagnosis determined using a previously reported algorithm.⁹ Individuals were followed until the end of the study period.

Ethical approval was obtained from the University of British Columbia/ Providence Health Care (#H09-02905) and Simon Fraser University (#2013s0566) research ethics boards.

Outcomes

The primary outcome variable in our analysis was HALE. This measure estimates the number of healthy years an individual is expected to live at birth by subtracting

the years of ill health from overall life expectancy.⁴ In addition to HALE, we estimated the prevalence of five comorbidities, which were used to estimate HALE. Because of their prevalence among PLHIV, we considered cardiovascular, respiratory, liver, and renal diseases, and non-AIDS defining cancers. All comorbidities were predefined, and we used International Classification of Diseases (ICD) 9 and 10 codes and directly standardised to 1991 Canadian population.

HALE is composed of two sets of partial measures: age-specific death rates and age-specific rates of population morbidity.⁵ Age-specific death rates allowed us to measure mortality and life expectancy for select age groups, whereas age-specific rates of population morbidity (defined by cumulative prevalence of the five comorbidities noted above) allowed us to measure the extent of morbidity for these conditions in our two study populations. These two measures were combined mathematically with an abridged life table approach developed by Sullivan⁵ to estimate the HALE and proportion of time spent in a healthy state. HALE was reported at 20 years of age for men and women with corresponding standard error.

We examined the relation between life expectancy and the length of the healthy state by constructing a measure the proportion of time spent in an unhealthy state. This measure was defined as the ratio of (LE-HALE)/LE where LE is life expectancy, and in this case the relative expansion of unhealthy state occurs when this ratio increases and compression of unhealthy state occurs when this ratio decreases.¹⁰

We also considered the dependency of the five select comorbidities in our calculation of HALE. As Colin and colleagues¹¹ note, if we did not consider that study participants might have more than one of these select comorbidities, we could potentially over estimate person years lived with disability (PYLD) across all five select morbidities in our estimation of HALE. Therefore, for each comorbidity pair, we estimated the ratio of the prevalence of people with two conditions to the product of the two total prevalence rates for each of the conditions. We do this cumulatively in each adjusting step. The resulting dependent comorbidity factors were used to adjust for dependent comorbidity in summation of PYLD across all five comorbidities and in the calculation of HALE. We examined the sensitivity of the HALE estimates in our study to the sequencing of these five select comorbidities for the dependent comorbidity adjustments.¹¹

Statistical analysis

Data are presented within categories as frequencies (n [%]) or as median (range). CIs and rates were reported to one significant digit. Data were analysed with SAS software, version 9.3 (SAS Institute Inc, Cary, NC, USA). HALE and prevalence estimates were programmed by use of spreadsheets developed in Microsoft Excel for Mac 2011,

version 14.5.9 (Microsoft Corporation, Redmond, WA, USA). In the following presentation of results, all differences between PLHIV and HIV-negative controls were significant at $p < 0.0001$ unless otherwise specified.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our sample consisted of 9310 PLHIV aged 20 years and older on ART and 510 313 adults who were uninfected with HIV followed from April 1, 1996, to Dec 31, 2012. Compared with HIV-negative men and women in our sample, PLHIV were more likely to be men, to live in metro Vancouver, and to have been followed for a shorter period of time (table 1). Rates of mortality, crude and directly adjusted to the Canadian population, were significantly higher among both men and women living with HIV (table 2).

Men and women living with HIV had high prevalences of renal and liver diseases compared with those in HIV-negative counterparts. Among PLHIV with liver disease, hepatitis C accounts for 25% (2024 of 8145) of person-years lived with liver disease in men and 54% (1003 of 1799) of person-years lived with liver disease in women (data now shown). By contrast, among HIV-negative men and women, only 6% (3348 of 53 460)

	PLHIV (n=9310)	HIV negative (n=510 313)
Sex		
Men	7702 (83%)	256 440 (50%)
Women	1680 (17%)	253 873 (50%)
Age (years)		
Median (IQR)	40 (34-47)	36 (24-50)
Years since enrolment		
Median (IQR)	9 (4-14)	13 (5-17)
Residence		
Metro Vancouver	4732 (51%)	86 470 (17%)
Other	4529 (49%)	410 729 (81%)
Unknown	49 (1%)	13 114 (3%)
Deaths		
Men	1606 (82%)	24 394 (51%)
Women	352 (18%)	23 253 (49%)
Crude death rate (per 1000 person-years)		
Men	29.1	9.0
Women	33.6	8.3
Adjusted death rate (per 1000 person-years)		
Men	30.0	8.3
Women	36.5	5.8
PLHIV=people living with HIV.		

Table 1: Baseline characteristics of the study population by HIV status

	Adjusted prevalence (%)	Relative risk (95% CI)
Men		
Cancers		
PLHIV	3.2	1.6 (1.6-1.7)
HIV-	1.9	..
Cardiovascular diseases		
PLHIV	5.5	0.7 (0.7-0.8)
HIV-	7.3	..
Liver diseases		
PLHIV	13.2	7.3 (7.3-7.3)
HIV-	1.8	..
Renal diseases		
PLHIV	6.3	5.1 (5.1-5.2)
HIV-	1.2	..
Respiratory diseases		
PLHIV	4.4	0.9 (0.9-0.9)
HIV-	4.8	..
Women		
Cancers		
PLHIV	1.6	0.8 (0.8-0.8)
HIV-	1.8	..
Cardiovascular diseases		
PLHIV	2.8	0.5 (0.5-0.5)
HIV-	5.2	..
Liver diseases		
PLHIV	14.5	9.8 (9.8-9.9)
HIV-	1.5	..
Renal diseases		
PLHIV	9.8	10.2 (10.1-10.2)
HIV-	1.0	..
Respiratory diseases		
PLHIV	7.7	1.3 (1.3-1.3)
HIV-	5.8	..

All significantly different at $p<0.0001$. PLHIV=people living with HIV. HIV-=HIV negative.

Table 2: Relative risk of the age-adjusted prevalence of select individual comorbidities among British Columbians, by sex and HIV status

and 5% (2226 of 44 845) of person-years lived due to liver disease can be attributed to hepatitis C (data not shown).

Substantial variation was noted in the distribution of paired select individual comorbidities (appendix p 2). Among PLHIV, these individual comorbidities are more likely to be paired with liver and renal diseases, whereas they are more likely to be paired with cardiovascular diseases among HIV-negative individuals. Individuals with only one cause or select individual morbidity range from a quarter to half in men and women, indicating that unadjusted HALE measures would greatly overestimate disability.

49 605 deaths and 5576 841 person-years were accumulated during this study. 21% (1958 of 9310) of PLHIV ever on

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	HALE, years (SE)	Proportion of time spent in an unhealthy state
Men		
All cause, unadjusted		
PLHIV	24.4 (0.17)	0.28
HIV-	47.4 (0.04)	0.22
All cause, adjusted		
Cancers		
PLHIV	31.5 (0.10)	0.06
HIV-	58.1 (0.02)	0.04
Cardiovascular diseases		
PLHIV	31.8 (0.16)	0.06
HIV-	58.1 (0.02)	0.04
Liver diseases		
PLHIV	31.7 (0.09)	0.06
HIV-	57.7 (0.02)	0.04
Renal diseases		
PLHIV	31.8 (0.09)	0.06
HIV-	58.0 (0.02)	0.04
Respiratory diseases		
PLHIV	32.0 (0.08)	0.05
HIV-	58.2 (0.02)	0.04
Women		
All cause, unadjusted		
PLHIV	20.0 (0.17)	0.31
HIV-	51.9 (0.04)	0.21
All cause, adjusted		
Cancers		
PLHIV	26.9 (0.19)	0.08
HIV-	63.3 (0.02)	0.03
Cardiovascular diseases		
PLHIV	27.8 (0.16)	0.05
HIV-	63.3 (0.02)	0.03
Liver diseases		
PLHIV	28.3 (0.10)	0.03
HIV-	62.7 (0.02)	0.04
Renal diseases		
PLHIV	26.9 (0.19)	0.08
HIV-	63.2 (0.02)	0.03
Respiratory diseases		
PLHIV	28.3 (0.10)	0.03
HIV-	63.4 (0.02)	0.03

The proportion of time spent in an unhealthy state was defined as the ratio of (LE-HALE) / LE. PLHIV=people living with HIV. HIV-=HIV negative. HALE=healthy life expectancy. LE=life expectancy.

Table 3: Sensitivity analysis of HALE based on all-cause disease prevalence by using different adjusting order, by gender and HIV status

ART died compared with 9% (47 647 of 510 313) in the uninfected cohort. Life expectancy at exact age 20 years between those ever on ART and those uninfected was 33.7 years (SE 0.1) versus 60.5 years (0.1) for men and 29.1 years (0.1) versus 65.4 years (0.1) for women. Among

PLHIV, women had a significantly lower life expectancy at this exact age than men (29·1 years [SE 0·1] vs 33·7 years [0·1]; $p<0\cdot001$).

Substantial difference was observed between unadjusted and adjusted HALE measures (table 3, appendix p 3). However, the ordering of comorbidities makes little difference in the estimate of HALE and suggests that the level of contraction is similar by sex and HIV status. Although men and women living with HIV spent a similar proportion of their life in a healthy state, the years lived in this state were much shorter for PLHIV than for their HIV-negative counterparts (table 3, figure). This difference was especially noticeable among women living with HIV.

Discussion

After adjustment for dependency between comorbidities, we noted little difference in the proportion of time spent in a healthy state for both PLHIV and their HIV-negative counterparts. However, the time spent in this state was less for men and women living with HIV. Furthermore, much of the pairwise dependency could be attributed to liver and renal diseases among PLHIV and cardiovascular disease among their HIV-negative counterparts.

Consistent with previous work,^{12–16} our findings show that burden of disease was higher for PLHIV on ART than for those in the HIV-negative population. For example, Kendall and colleagues¹² reported that PLHIV in Ontario (Canada), particularly women, had a significantly higher prevalence of almost all chronic conditions than did people without HIV. Additionally, Goulet and colleagues¹⁵ reported that in their primarily male cohort, those individuals living with HIV had higher rates of liver and renal disease than did those who were not infected with HIV. Although these and other studies present findings on the range of comorbidities and risk factors affecting the lives of PLHIV, we add to the literature by integrating HALE measures to generate insight into how a substantially higher burden of comorbidity can directly affect the health life expectancy of PLHIV compared with their HIV-negative counterparts.

To our knowledge, this study is the first to characterise the length of the health state for both PLHIV and HIV-negative individuals, and show differences in shortened life expectancy among women and men living with HIV. In our sensitivity analysis, we observed similar levels of compression of chronic diseases, resulting in reduced periods of disease in both HIV-positive and HIV-negative men and women. Like their HIV-negative counterparts, we thus saw a compression of comorbidities in the last few years of life for PLHIV. The shortened life among women living with HIV has previously been observed in Canada. Other national or international studies have either found longer life expectancies among women than men or have found no sex-related differences.¹⁷

We also argue that the substantial differences in health life expectancies could be attributed to previous history of injection drug use among PLHIV. The effect

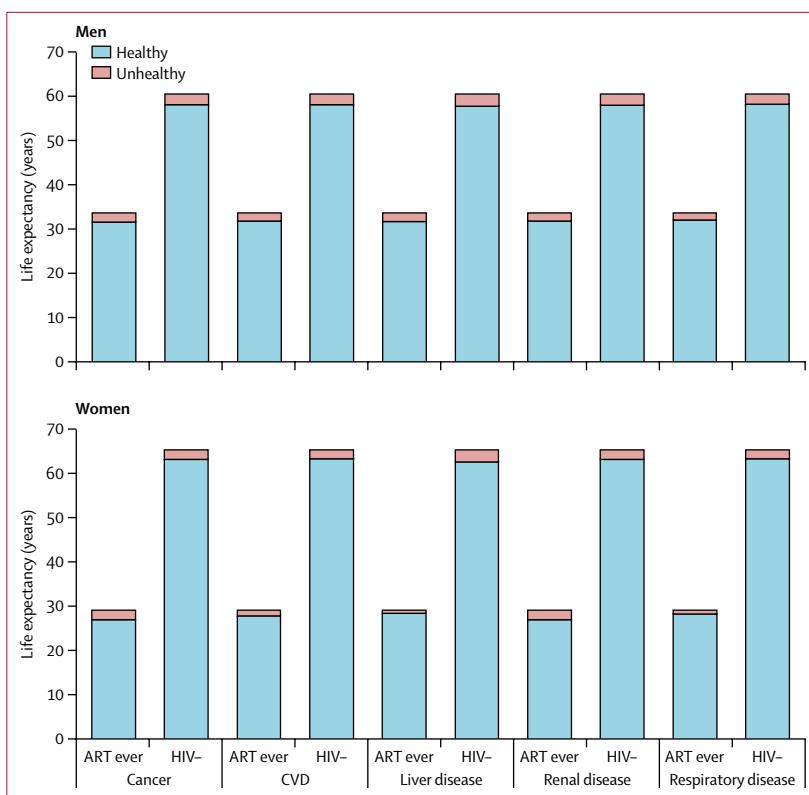


Figure: Life expectancy at exactly age 20 years taking into adjustment all-cause disease prevalence
ART ever=ever on highly active antiretroviral therapy. HIV-=HIV negative. CVD=cardiovascular diseases.

of liver-related illnesses and hepatitis C on morbidity and mortality rates among PLHIV who inject drugs or have a history of injection drug use.^{18–20} Lesko and colleagues²¹ reported higher rates of end-stage renal and liver diseases among PLHIV who inject drugs compared with non-injecting PLHIV. Although the increased burden of liver and renal disease affecting PLHIV in our sample might be caused by current or previous use of injection drugs, these diseases could be mitigated through access to direct-acting antiviral regimens and tenofovir alafenamide-based antiretroviral regimens.²² Although current costs of direct acting antiviral drugs and antiretroviral regimens based on tenofovir alafenamide restrict use, access strategies being implemented at the provincial level might successfully expand their use, reducing future infections in PLHIV.²³

Our study has several strengths and limitations that should be noted. In terms of strengths, the large and population-based nature of the COAST study from which our analytic sample was defined, allowed us to assess small differences in the outcomes of interest. The cohort of PLHIV included the vast majority of all known PLHIV in British Columbia on ART because our case ascertainment method included everyone in the BCCFE's registry. The cohort of HIV-negative people comprised individuals from the same time period and universal health-care system as the ART group, which helped us to

minimise selection bias that can be introduced by use of such a comparator. Government funded health care is available to all residents of British Columbia if they are a Canadian citizen, landed immigrant, government-assisted refugee, post-secondary international student with a study permit, or temporary worker with a work permit for 6 months or longer. Additionally, antiretroviral therapy, laboratory monitoring, and medical care for PLHIV and those not infected do not generally require any copayments or deductibles in British Columbia, which might be present in some other Canadian jurisdictions or elsewhere. Therefore, potential biases that could result from multiple health-care payers and differential access to health-care services in the ascertainment of comorbidities in this study are minimised.

In terms of limitations, our results could have been affected by loss to follow-up. However, we believe that loss to follow-up was minimised by use of large, population-based administrative data sources, as well as the extensive data linkage that we did across the several data sources included in the COAST study. Our ascertainment of comorbidities could also have been affected by the reliance on administrative data rather than self-reported or physician-reported records. Additionally, we did not assess the burden of mental health comorbidities, which are also likely to be increased among PLHIV.¹¹ We are also limited by our ability to ascertain outcomes that occurred outside of British Columbia. However, these limitations probably affected the HIV-positive and HIV-negative cohorts equally. Finally, we would expect to see differences between these populations decrease if we restricted our analysis to more recent years or to those individuals who initiated ART without any previous antiretroviral therapy use. In this study, to ensure robustness of our results, we focused on everyone who has ever started ART, as well as the entire time period when these drugs were available in the province.

In conclusion, our results show that PLHIV spend proportionally about the same amount of time in a healthy state as their HIV-negative counterparts in British Columbia. However, PLHIV, especially women, have much shorter overall life expectancies than their HIV-negative general population counterparts, and thus spend notably less time in a healthy state. Because life expectancy for many PLHIV is increasingly comparable to HIV-negative populations,²² we show here that it remains imperative to address the challenges this population faces in achieving a healthy state to improve quality of life over the life course.

Contributors

RSH, OE, ABC, WZ, SJ, VDL, and JSGM conceived the study, interpreted the findings, and drafted the report. WZ did the statistical analyses with help from RSH, VDL, SJ, and OE. RSH, OE, VDL, RB, JS, and JSGM helped with data acquisition. All authors contributed to the study design, interpretation of the results, and drafting of the report. RSH, WZ, OE, and VDL collected and revised the data, and were involved in the data analysis and revision of the report for important intellectual content. All authors read and approved the final report.

Declaration of interests

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