Journal of Microbiology, Immunology and Infection 57 (2024) 85—96

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Early HIV diagnosis enhances quality-adjusted life expectancy of men who have sex with men living with HIV: A population-based cohort study in Taiwan

Tung Lo [a,1], Chi-Tai Fang [a,b,c,*,1], Yu-Yao Lee [a,1], Chung-Ching Shih [b,c,d], Fang-Ying Chu [a], Jung-Der Wang [e,f]

[a] *Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[b] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[c] *National Taiwan University School of Medicine, Taipei, Taiwan*
[d] *Center for Infection Control, National Taiwan University Hospital, Taipei, Taiwan*
[e] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[f] *Department of Occupational Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

Received 25 August 2023; received in revised form 8 November 2023; accepted 28 November 2023
Available online 1 December 2023

KEYWORDS
Early HIV diagnosis;
Quality-adjusted life expectancy;
Quality of life;
Health utility;
Late HIV diagnosis

Abstract *Background:* Whether early HIV diagnosis is beneficial for HIV patients themselves remains uncertain, given the stigma and social discrimination associated with an HIV diagnosis. This study aimed to measure the impact of early HIV diagnosis on quality-adjusted life expectancy (QALE) in comparison with late HIV diagnosis, from real-world data in Taiwan under universal access to antiretroviral therapy (ART).
Methods: This population-based cohort study included 14,570 men who have sex with men (MSM) in the national HIV registry and a quasi-random sample (n = 127) of MSM patients to measure quality of life using the EQ-5D health utility instrument. We integrated quality of life data into the extrapolated cohort survival curve to estimate the QALE in patients with early versus late HIV diagnosis (≤30 days before AIDS diagnosis). Loss-of-QALE were estimated by comparing the cohort with age-, sex-, and calendar-year-matched referents simulated from vital statistics. Difference-in-differences was estimated to quantify the effect of early HIV diagnosis.

* Corresponding author. Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei 100 Taiwan.
E-mail addresses: a8617355@hotmail.com (T. Lo), fangct@ntu.edu.tw (C.-T. Fang), yuyao0307@gmail.com (Y.-Y. Lee), 2irene.s@gmail.com (C.-C. Shih), fychu276313@gmail.com (F.-Y. Chu), jdwang121@gmail.com (J.-D. Wang).
[1] Contribute equally as the first author.

https://doi.org/10.1016/j.jmii.2023.11.004

Results: Early HIV diagnosis is associated with a loss-of-life expectancy of 3.11 years, with an average health utility of 0.95, in contrast to those diagnosed late (loss-of-life expectancy 8.47 years, with an average health utility of 0.86). After integration of survival and life quality, early HIV diagnosis results in a reduction of loss-of-QALE by 8.28 quality-adjusted life years among MSM living with HIV.
Conclusions: Under universal access to ART, early HIV diagnosis is highly beneficial for people living with HIV themselves, with a net gain of 8.28 healthy life years compared with those diagnosed late.

Introduction

A prolonged sexually transmitted HIV outbreak, predominantly affecting men who have sex with men (MSM) and fueled by non-opioid recreational drug use, has occurred in Taiwan since 2005.[1,2] Despite the continuous decrease in the number of new HIV diagnoses since 2018,[2] a persistently high proportion (30 %—40 %) of new HIV patients have been diagnosed late in the course.[3,4] This has resulted in missed opportunities for timely antiretroviral therapy (ART) to reduce their infectivity, and for behavioral interventions to promote condom use in order to protect others.[5,6]

On the other hand, whether early HIV diagnosis is beneficial for individuals living with HIV themselves remains less clear, given the stigma and social discrimination associated with an HIV diagnosis.[7] Although the Strategic Timing of Antiretroviral Therapy (START) trial[8] and collaborative HIV treatment cohorts in Europe and North America[9—13] reported a lower HIV-associated mortality risk with early HIV treatment, previous studies have been limited by relatively short follow-up times,[8] the lack of adjustment for lead-time bias,[9—13] and not taking quality of life into account.[8—13] In particular, quality of life is the key to thriving with HIV.[14]

Since 1997, Taiwan has provided universal access to highly active ART for all citizens living with HIV.[5] In this nationwide, population-based cohort study, we assessed the impact of early HIV diagnosis on the loss-of-quality-adjusted life expectancy (QALE) in MSM living with HIV, compared with an age/sex-matched reference population. This metric is not affected by lead-time bias.[15—17] We measured quality of life using the EuroQol-5D,[18] and estimated the loss of QALE by extrapolating 10-year survival curves to a lifetime, using iSQoL 2.0,[19,20] a software package developed by Academic Sinica to accurately predict long-term survival.

Methods

Study design

This was a nationwide, population-based cohort study of all diagnosed MSM living with HIV in Taiwan, based on the national HIV registry. The primary outcome was the difference in loss-of-QALE between early-diagnosed and late-diagnosed MSM living with HIV. The study consisted of two parts. First, we extrapolated the 10-year survival curves, which were followed up and stratified by the timing of diagnosis, to a lifetime (up to 78 years after diagnosis). This allowed us to estimate the loss-of-life expectancy compared with an age- and sex-matched reference population (at the time of HIV diagnosis). Second, we measured the quality of life of people living with HIV using the health utility EuroQol-5D instrument by interviewing a quasi-random sample of HIV patients followed up at National Taiwan University Hospital (Taipei, Taiwan). Finally, we integrated the quality-of-life data into the extrapolated survival curve to estimate the loss-of-QALE compared with an age/sex-matched reference population.

Ethical statement

The study procedure was reviewed a priori and approved by the Research Ethics Committee of National Taiwan University Hospital (#201410005RIND). All participants in the quality-of-life survey gave written informed consent. Informed consent was waived by the Research Ethics Committee for delinked data from the Taiwan National HIV registry.

Definition of AIDS

Since January 1, 2005, the definition of acquired immunodeficiency syndrome (AIDS) in Taiwan followed the United States Centers for Disease Control and Prevention (USCDC) 1993 revised case definition.[21] Patients were reported as having AIDS if they were diagnosed to have an AIDS-defining illness or if their CD4 cell count falls below 200 cells/mm^3.[21]

Definition of early vs. late HIV diagnosis

To simulate the two alternative scenarios for an individual at risk: screening for HIV (while being asymptomatic) versus no screening (seeking treatment only after the onset of AIDS), we defined a late HIV diagnosis (no screening, having AIDS at the time of HIV diagnosis) as occurring $\leq$30 days before the date of AIDS diagnosis

(taking the time needed for diagnosing AIDS into account); and an early HIV diagnosis (by screening, before the onset of AIDS) as either occurring >30 days before the date of AIDS diagnosis or remaining AIDS-free by the end of the follow-up period.[22]

National HIV registry

The National HIV registry includes all people with HIV diagnosed since 1986. Variables in the registry include nationality, date of birth, sex, date of HIV diagnosis, risk group for HIV transmission, date of AIDS diagnosis and date of death (if applicable). We used the latest edition publicly released for academic research, which included all persons diagnosed before 2016, with validation of survival status up to December 31, 2015, through linkage to the National Death Registry by the Taiwan Centers for Disease Control (CDC). Taiwan CDC categorized HIV transmission into eight mutually exclusive HIV risk groups: homosexual behaviors, bisexual behaviors, heterosexual behaviors, injecting drug use, mother-to-child transmission, hemophilia, blood transfusion, and the undisclosed. We included all men aged ≥13 years, diagnosed since January 1, 2005, and whose HIV risk group was homosexual or bisexual behavior as MSM in the present study. Foreigners were excluded.

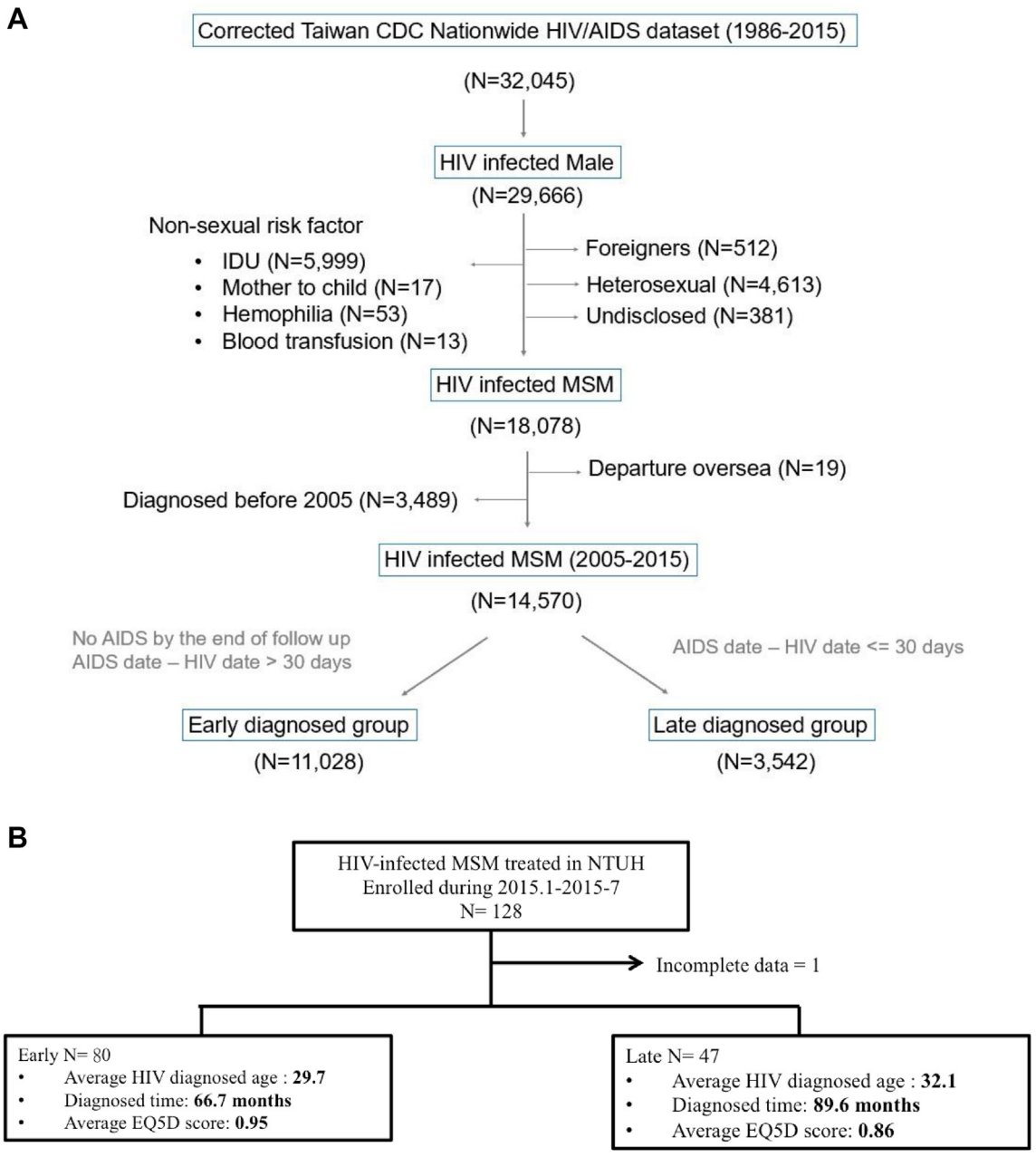

Figure 1. Flow chart of HIV patients enrollment (A) Delinked Taiwan national HIV registry cohort dataset (B) 128 patients who received EQ-5D measurement.

Extrapolation of survival curve

Accurate long-term survival extrapolation is based on the principle that, when the HIV-associated hazard is stable, the logit survival ratio between the HIV patient cohort and an age/sex- and calendar-year-matched reference cohort (the survival function of which was generated from the life tables of the Taiwan general population using the Monte Carlo method)[23] will converge to a straight line, allowing linear extrapolation.[22,24] However, with limited follow-up time, the logit survival ratio curve may not yet converge to a straight line at the end of follow-up, and simple linear extrapolation may underestimate long-term survival. iSQoL 2.0 employed a rolling extrapolation procedure to address this problem.[20] First, a restricted cubic spline model was used to fit the logit survival ratio curve, which becomes approximately a straight line at the end of follow-up, thus allowing linear extrapolation for a short time interval beyond the follow-up limit. Second, a rolling algorithm was utilized, extrapolating a short time interval at each time step, to fit the converging curve of the logit survival ratio for long-term extrapolation.[20] Using iSQoL 2.0, we extrapolated the 10-year survival curves, which were followed up and stratified by the timing of diagnosis, to a lifetime (up to 78 years after diagnosis).

Enrollment of patients for quality-of-life measurement

We interviewed a quasi-random sample of HIV patients receiving follow-up care at National Taiwan University Hospital (Taipei, Taiwan), referred by their HIV case managers, to obtain quality-of-life measurements. To be eligible for participation, patients had to be men aged 20 years or older, with registered HIV risk group of homosexual or bisexual behavior. Informed consent was obtained from all participants prior to the interviews.

Table 1 Characteristics of 14,570 men who have sex with men that were newly diagnosed with HIV during 2005–2015 in Taiwan.

	Early diagnosed (N = 11,028)		Late diagnosed[a] (N = 3542)		P value
	n	%	n	%	
Risk group of HIV transmission					<0.0001
Homosexual behaviors	9707	(88 %)	2953	(83 %)	
Bisexual behaviors	1321	(12 %)	589	(17 %)	
Age at HIV diagnosis (years)					<0.0001
Mean (standard deviation)	28.6	(7.4)	33.5	(9.1)	
5–14	2	(0 %)	0	(0 %)	
15–24	3760	(34 %)	512	(14 %)	
25–34	5200	(47 %)	1655	(47 %)	
35–44	1648	(15 %)	948	(27 %)	
45–54	358	(3 %)	332	(9 %)	
≥55	60	(1 %)	95	(3 %)	
Marital status					<0.0001
Married	166	(2 %)	132	(4 %)	
Unmarried	8665	(79 %)	2658	(75 %)	
Divorced/separated/widowed	51	(0.5 %)	47	(1 %)	
Undisclosed	2146	(19 %)	705	(20 %)	
Occupation					<0.0001
Unemployed	1372	(12 %)	619	(17 %)	
Student	1714	(16 %)	271	(8 %)	
Housekeeping	8	(0 %)	2	(0 %)	
Sex worker	4	(0 %)	1	(0 %)	
Paid job	7185	(65 %)	2337	(66 %)	
Undisclosed	745	(7 %)	312	(9 %)	
HIV screening channel					<0.0001
Criminal justice system	198	(2 %)	10	(0 %)	
Blood donation center	430	(4 %)	32	(1 %)	
Military routine	570	(5 %)	53	(2 %)	
Healthcare services	8323	(75 %)	3104	(88 %)	
Miscellaneous	1507	(14 %)	343	(10 %)	
Death	316	(3 %)	395	(11 %)	<0.0001
Mean follow-up time	51 months		45 months		
Death rate	2.87 % (316/11,028)		11.15 % (395/3542)		

[a] Having AIDS at the time of HIV diagnosis, operatively defined as receiving AIDS diagnosis within 30 days of HIV diagnosis.
Data are n (%) or mean (standard deviation).

Table 2 Characteristics of 127 men who have sex with men living with HIV participating EQ-5D utility measurement.

	Early diagnosed (N = 80)		Late diagnosed[a] (N = 47)		P-value
	n	%	n	%	
Male Sex	80	(100 %)	47	(100 %)	<0.0001
Age at HIV diagnosis (years)					<0.0001
Mean (SD)	29.8 (8.6)		32.1 (10.4)		
0–14	0	(0 %)	0	(0 %)	
15–24	25	(31 %)	8	(17 %)	
25–34	45	(56 %)	24	(51 %)	
35–44	6	(8 %)	12	(26 %)	
45–54	4	(5 %)	2	(4 %)	
≥55	0	(0 %)	1	(2 %)	
Education					
Illiterate	0	(0 %)	0	(0 %)	<0.0001
Junior high school	2	(3 %)	2	(4 %)	
High school	13	(16 %)	15	(32 %)	
University or above	65	(81 %)	30	(64 %)	
Duration from HIV diagnosis to enrollment (Years)	5.56		7.35		0.0036
0–2	28	(35 %)	10	(21 %)	
3–4	13	(16 %)	11	(23 %)	
5–6	19	(24 %)	2	(4 %)	
7–8	8	(10 %)	8	(17 %)	
9–10	4	(5 %)	5	(11 %)	
≥11	8	(10 %)	11	(23 %)	
Screening or diagnosis channels					<0.0001
Health care visits	22	(28 %)	32	(68 %)	
Screening in hospital (Anonymous)	22	(28 %)	6	(13 %)	
Screening in hospital (Named)	20	(25 %)	4	(9 %)	
Screening in non-governmental organization	7	(9 %)	1	(2 %)	
Military physical examination	5	(6 %)	2	(4 %)	
Blood donation screening	2	(3 %)	1	(2 %)	
Routine screening in prison	1	(1 %)	1	(2 %)	
Home testing	1	(1 %)	0	(0 %)	
Screening in harm reduction program services	0	(0 %)	0	(0 %)	
CD4 count of first time diagnosed					<0.0001
<200	0	(0 %)	47	(100 %)	
200–349	18	(23 %)	0	(0 %)	
350–299	31	(37 %)	0	(0 %)	
≥500	28	(36 %)	0	(0 %)	
Unknown	3	(4 %)	0	(0 %)	
Utility measurement score					
EQ-5D	0.95 ± 0.09		0.86 ± 0.19		<0.0001
EQ-5D VAS score	73.1		70		0.025
Today's health status comparing with the past year					0.158
Better	27	(34 %)	21	(45 %)	
Similar	44	(55 %)	18	(38 %)	
Worse	9	(11 %)	8	(17 %)	
Barthel index	99.7 ± 13.1		95.67 ± 2.3		0.036
Employment status					<0.0001
Employed	58	(72 %)	28	(60 %)	
Jobless	7	(9 %)	9	(19 %)	
Part time job	4	(5 %)	4	(9 %)	
Students	3	(4 %)	2	(4 %)	
Sex workers	0	(0 %)	0	(0 %)	
Others	8	(10 %)	4	(9 %)	
Marital status					
Unmarried	77	(96 %)	43	(91 %)	
Married	1	(1 %)	3	(6 %)	
Divorce	1	(1 %)	1	(2 %)	

(*continued on next page*)

Table 2 (*continued*)

	Early diagnosed (N = 80)		Late diagnosed[a] (N = 47)		P-value
	n	%	n	%	
Separated	0	(0 %)	0	(0 %)	
Widowed	0	(0 %)	0	(0 %)	
Others	1	(1 %)	0	(0 %)	
Self-reported sexual experience					
Homosexual sex	77	(99 %)	47	(100 %)	0.001
One-night stand	37	(46 %)	14	(30 %)	
Heterosexual sex	10	(13 %)	11	(23 %)	
Prostitution	1	(1 %)	2	(4 %)	
Never	1	(1 %)	0	(0 %)	
Comorbidity					
Yes	32	(40 %)	26	(55 %)	0.059
No	48	(60 %)	21	(45 %)	
Experience of using drugs, alcohol and tobacco					
Cigarettes	41	(53 %)	22	(47 %)	<0.0001
Alcohol	36	(46 %)	19	(40 %)	
Sedative-hypnotics	24	(31 %)	10	(21 %)	
Recreational drugs	21	(27 %)	10	(21 %)	
Anti-depressants	11	(14 %)	5	(11 %)	
Marijuana	5	(6 %)	4	(9 %)	
Cocaine	2	(3 %)	0	(0 %)	
Opioid	0	(0 %)	0	(0 %)	

[a] Having AIDS at the time of HIV diagnosis, operatively defined as receiving AIDS diagnosis within 30 days of HIV diagnosis.

Measurement of quality of life

Quality of life was measured using the EuroQol-5D (EQ-5D-3L) questionnaire.[18] EuroQol-5D is a well-validated, preference-based measure of health, widely used in cost-utility analysis.[25] It is now available in 158 languages, including traditional Chinese. The preference weights were generated using time trade-off methods to allow integration with the survival curve to compute quality-adjusted life-years (QALYs); these reflect the social value of health and are country-specific.[25] Each participant self-completed 5 questions, which encompassed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three levels of severity (no problems, moderate problems, and severe problems).[18] The health state vector derived from the five dimensions was transformed into a utility value using the scoring functions from Taiwan.[26]

Loss-of-quality-adjusted life expectancy

We integrated the quality-of-life data into the extrapolated survival curve to estimate the loss-of-QALE compared with an age/sex-matched reference population. To obtain the QALE of the reference population, we considered three scenarios for the health utility value of the reference population: (1) 1.0 (main analysis); (2) age- and sex-matched health utility values from the 2009 Taiwan National Health Interview Survey for the general population in Taiwan (sensitivity analyses to consider the effect of aging); (3) age- and sex-matched health utility values from the 2009 Taiwan National Health Interview Survey for the general population in Taiwan, but excluding those aged 80 years or more, to avoid potential bias due to sparse data in this age group (sensitivity analyses).

Data analysis

We conducted a logical check of the national HIV registry data to correct administrative delay. We considered the date of AIDS diagnosis or the date of death as the date of HIV diagnosis if the date of AIDS diagnosis or date of death preceded the notification date of HIV diagnosis. We also considered the date of death as the date of AIDS diagnosis if the date of death preceded the notification date of AIDS diagnosis. Survival extrapolation and loss-of-QALE computation were performed using iSQoL 2.0 (Integration of Survival with Quality of Life) software,[19] which was developed by Professor Jing-Shiang Hwang at Academia Sinica (Taipei, Taiwan).

Results

Patient enrollment

The CDC nationwide HIV/AIDS dataset (1986—2015) from the Taiwan national HIV registry included 32,045 individuals with HIV, of whom 14,570 MSM (diagnosed during 2005—2015) met the inclusion criteria for this study (11,028 individuals in the early diagnosis group and 3542 individuals in the late diagnosis group) (Fig. 1A). A total of 128 MSM patients living with HIV participated in the quality of life study (80 participants in the early diagnosis group and 47 participants in the late diagnosis group. Timing of HIV diagnosis could not be obtained for one of the participants) (Fig. 1B). All participants in the quality of life study provided written informed consent.

Characteristics of patients

Table 1 shows characteristics of the 14,570 MSM included in this nationwide, population-based study. Most were diagnosed in the age range of 25—34 years. The mean age of HIV diagnosis in the early HIV diagnosis group is 4.9 years younger than that in the late HIV diagnosis group (28.6 vs. 33.5 years, $p < 0.001$), consistent with the presence of lead-time bias. Table 2 shows the characteristics of the 127 participants in the quality-of-life measurement. The duration from HIV diagnosis to enrollment ranged from less than 1 year to more than 10 years (Table 2). Table 3 shows that the 127 patients and the national cohort (N = 14,570) were similar in all socio-demographic variables, including risk groups (homosexual vs. bisexual), age at HIV diagnosis, marital status, occupation, and HIV screening channels (Table 3), and that the former can serve as a quasi-random sample for the latter.

Loss-of-Life expectancy

Figs. 2 and 3 show the observed 10-year survival curve and extrapolated survival curve to a lifetime for the early diagnosis group and late diagnosis group. Early versus late-diagnosed MSM living with HIV had a mean life expectancy of 46.5 years (35.9—48.4 years) versus 36.7 years (32.1—40.0 years) after HIV diagnosis, with a loss-of-life expectancy (compared with age/sex-matched reference population) of 3.11 years (1.37—13.74 years) and 8.47 years (5.10—12.98 years), respectively (Fig. 4 and Table 4). Thus, early HIV diagnosis reduces loss-of-life expectancy by 5.36 years (Table 4).

Loss-of-QALE

The quality of life in the early HIV diagnosis group is significantly superior to that in the late HIV diagnosis group (mean: 0.95 vs. 0.86, $p < 0.001$) (Table 2). There was no significant trend of increase or decrease over 10 years after HIV diagnosis in both early diagnosis group and late diagnosis group (Fig. 5). After integrating the quality of life data for MSM living with HIV into their projected lifetime survival function, early and late-diagnosed MSM living with HIV had a loss-of-QALE of 5.52 (2.73—15.6) QALY and 13.80 (9.37—19.43) QALY, respectively. Early HIV diagnosis reduces the loss-of-QALE by 8.28 QALY (Fig. 6; Table 4). Sensitivity analysis using health utility values from the 2009

Table 3 Comparison of characteristics of the quasi-random sample for EQ-5D utility measurement (n = 127) and the population-based cohort (N = 14,570).

	Early diagnosed		*P* value	Late diagnosed[a]		*P* value
	Quasi-random sample (n = 80)	Cohort (N = 11,028)		Quasi-random Sample (n = 47)	Cohort (N = 3542)	
Risk group of HIV transmission			0.89			0.22
Homosexual behaviors	70 (87 %)	9707 (88 %)		36 (77 %)	2953 (83 %)	
Bisexual behaviors	10 (13 %)	1321 (12 %)		11 (23 %)	589 (17 %)	
Age at HIV diagnosis (years)			0.33			0.88
Mean (standard deviation)	29.8 (8.6)	28.6 (7.4)		32.1 (10.4)	33.5 (9.1)	
5—14	0 (0 %)	2 (0 %)		0 (0 %)	0 (0 %)	
15—24	25 (31 %)	3760 (34 %)		8 (17 %)	512 (14 %)	
25—34	45 (56 %)	5200 (47 %)		24 (51 %)	1655 (47 %)	
35—44	6 (8 %)	1648 (15 %)		12 (26 %)	948 (27 %)	
45—54	4 (5 %)	358 (3 %)		2 (4 %)	332 (9 %)	
≥55	0 (0 %)	60 (1 %)		1 (2 %)	95 (3 %)	
Marital status			0.58			0.56
Married	1 (1 %)	166 (2 %)		3 (6 %)	132 (4 %)	
Unmarried/Undisclosed	78 (98 %)	10,811 (98 %)		43 (91 %)	3363 (95 %)	
Divorced/separated/widowed	1 (1 %)	51 (0.5 %)		1 (2 %)	47 (1 %)	
Occupation			0.98			0.97
Unemployed/Undisclosed	15 (19 %)	2125 (19 %)		13 (28 %)	933 (26 %)	
Employed/Student	65 (81 %)	8899 (81 %)		34 (72 %)	2608 (74 %)	
Sex worker	0 (0 %)	4 (0 %)		0 (0 %)	1 (0 %)	
HIV screening channel			0.79			0.03
Criminal justice system	1 (1 %)	198 (2 %)		1 (2 %)	10 (0 %)	
Blood donation center	2 (3 %)	430 (4 %)		1 (2 %)	32 (1 %)	
Military routine	5 (6 %)	570 (5 %)		2 (4 %)	53 (2 %)	
Healthcare services	64 (80 %)	8323 (75 %)		42 (89 %)	3104 (88 %)	
Miscellaneous	8 (10 %)	1507 (14 %)		1 (2 %)	343 (10 %)	

[a] Having AIDS at the time of HIV diagnosis, operatively defined as receiving AIDS diagnosis within 30 days of HIV diagnosis.
Data are n (%) or mean (SD).

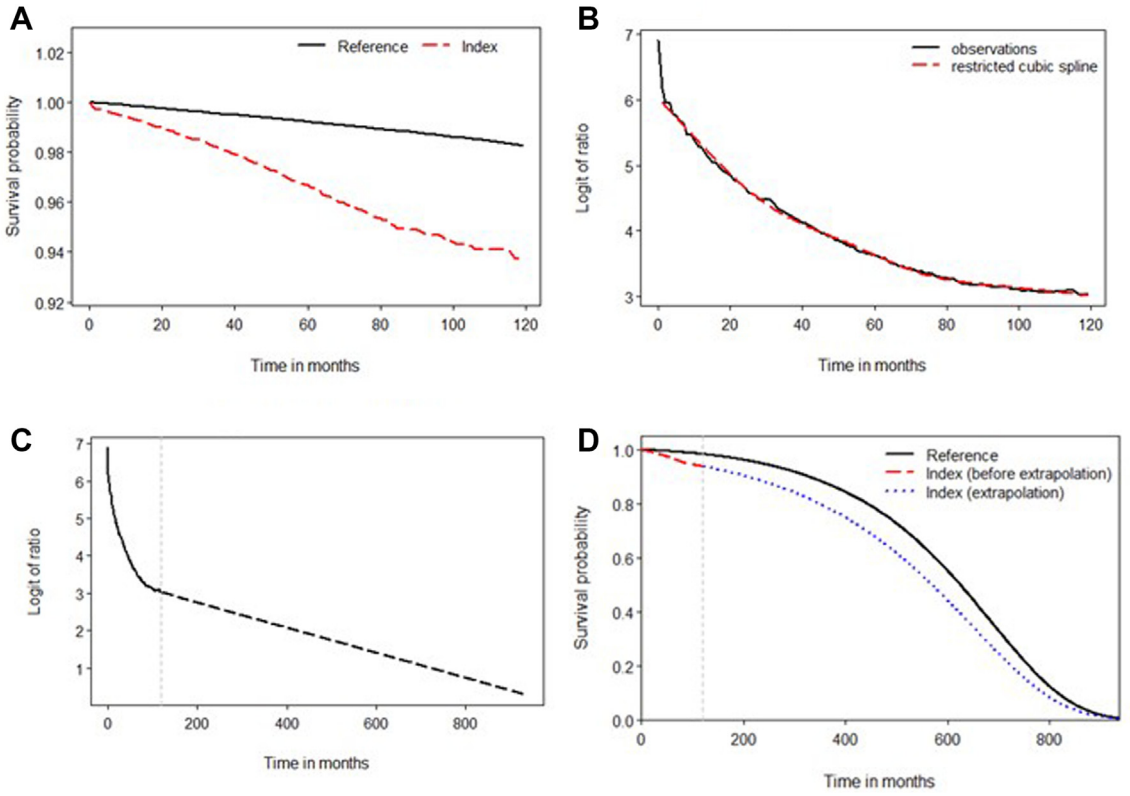

Figure 2. Early HIV diagnosis group (A) Survival curve (B) Logit W curve (C) Extrapolated Logit survival ratio curve and (D) Extrapolated survival curve.

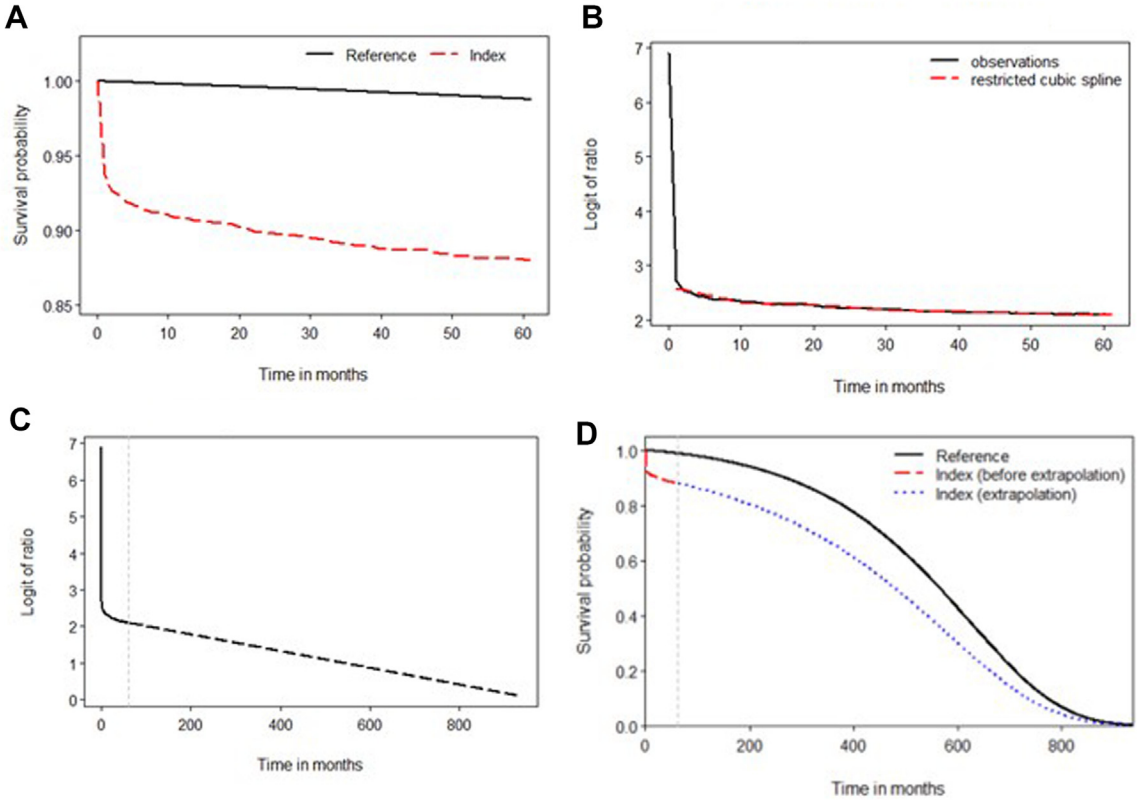

Figure 3. Late HIV diagnosis group (A) Survival curve (B) Logit W curve (C) Extrapolated Logit survival ratio curve (D) Extrapolated survival curve.

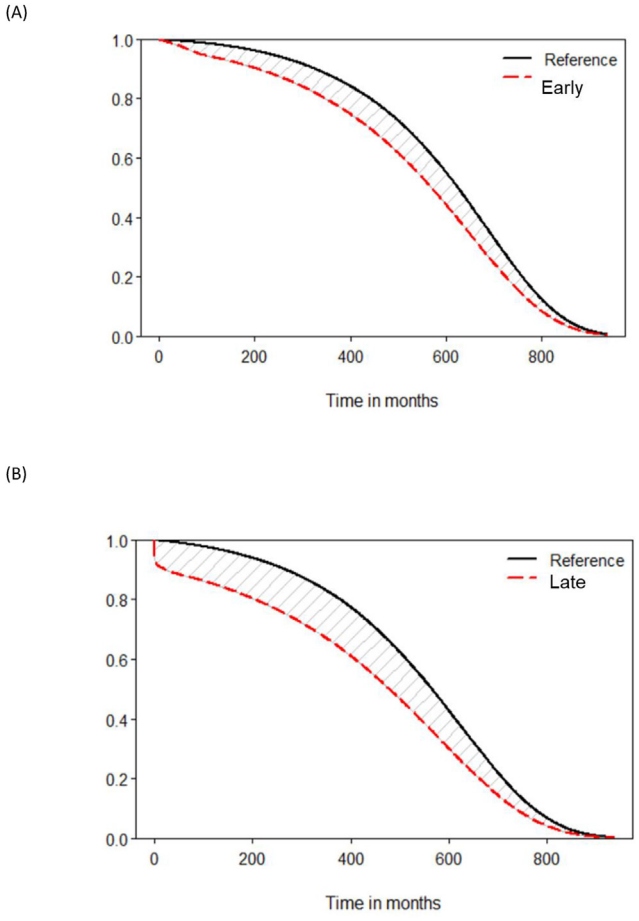

Figure 4. Loss of life expectancy (marked with diagonal lines) compared with age/sex-matched reference populations. (A) Early HIV diagnosis group. (B) Late HIV diagnosis group.

Taiwan National Health Interview Survey as the quality of life for the age/sex-matched reference population, whether or not excluding those aged 80 years or more, did not significantly alter the primary outcome (Table 5).

Discussion

Our results show that early HIV diagnosis before the onset of AIDS is associated with a loss-of-life expectancy of merely 3.11 years compared with the age/sex-matched reference population as well as a nearly normal quality of life (health utility 0.95). This is in sharp contrast to late HIV diagnosis-associated loss-of-life expectancy (8.47 years) and negative impact on quality of life (health utility 0.86). Overall, early HIV diagnosis results in a reduction of loss-of-QALE by 8.28 QALYs among MSM living with HIV. Therefore, early-diagnosed MSM living with HIV experience a net gain of 8.28 healthy life-years compared with those diagnosed late, after adjusting for lead-time bias and age at HIV diagnosis.

To our knowledge, the present study is the first real world study to incorporate quality of life into life expectancy estimates when evaluating the impact of early HIV diagnosis on the outcomes of people living with HIV. Using the Taiwan national HIV registry dataset, which includes all patients diagnosed with HIV in Taiwan, this study provides a real-world estimate of the impact of early HIV diagnosis on the quality-adjusted life expectancy of MSM living with HIV. We found that in the setting of universal access to ART in Taiwan, early HIV diagnosis before the onset of AIDS helps MSM living with HIV gain more than eight healthy life years.

The strength of this study is the use of an age/sex- and calendar-year-matched reference population to estimate the reduction of loss-of-LE, providing an unbiased estimate for the net survival gain after adjusting for the effects of both age at HIV diagnosis and lead-time bias. Unlike the START trial[8] and HIV treatment cohorts in Europe and North America,[9—13] which included only those patients who started ART, our study included all HIV-diagnosed MSM cases reported to Taiwan CDC, with follow-up starting from the day of HIV diagnosis. Therefore, our results answer the important question of whether early HIV diagnosis through screening is beneficial for the patients living with HIV themselves.

Our study may underestimate the benefit of early HIV diagnosis. First, the timing of HIV diagnosis in the present study was categorized into early HIV diagnosis (>30 days before the AIDS diagnosis) versus late HIV diagnosis (≤30 days before the AIDS diagnosis), because the Taiwan national HIV registry dataset did not contain information on the CD4 count at the time of HIV diagnosis. It is probable that an early HIV diagnosis at the time point when the CD4 count is greater than 500 cells/mm^3 may confer more survival benefit than an HIV diagnosis at the time point when the CD4 count is 350 cells/mm^3 (that would be classified as

Table 4 Comparison of life expectancy (LE) and quality-adjusted life expectancy (QALE) between men who have sex with men living with HIV diagnosed early vs. late.

	Early diagnosed group (Mean, 2.5 %—97.5 %)	Late diagnosed group (Mean, 2.5 %—97.5 %)	Difference in differences
LE after HIV diagnosis (Years)	46.5 (35.9—48.4)	36.7 (32.1—40.0)	
LE of age- and sex-matched reference population (Years)	49.7 (49.5—49.9)	45.1 (44.8—45.4)	
Loss-of-LE (Years)	3.11 (1.37—13.74)	8.47 (5.10—12.98)	5.36
QALE after HIV diagnosis (QALYs)	44.1 (34.1—46.7)	31.3 (25.8—35.7)	
QALE of age- and sex-matched reference population (QALYs)	49.7 (49.5—49.9)	45.1 (44.8—45.4)	
Loss-of-QALE (QALYs)	5.52 (2.73—15.6)	13.80 (9.37—19.43)	8.28

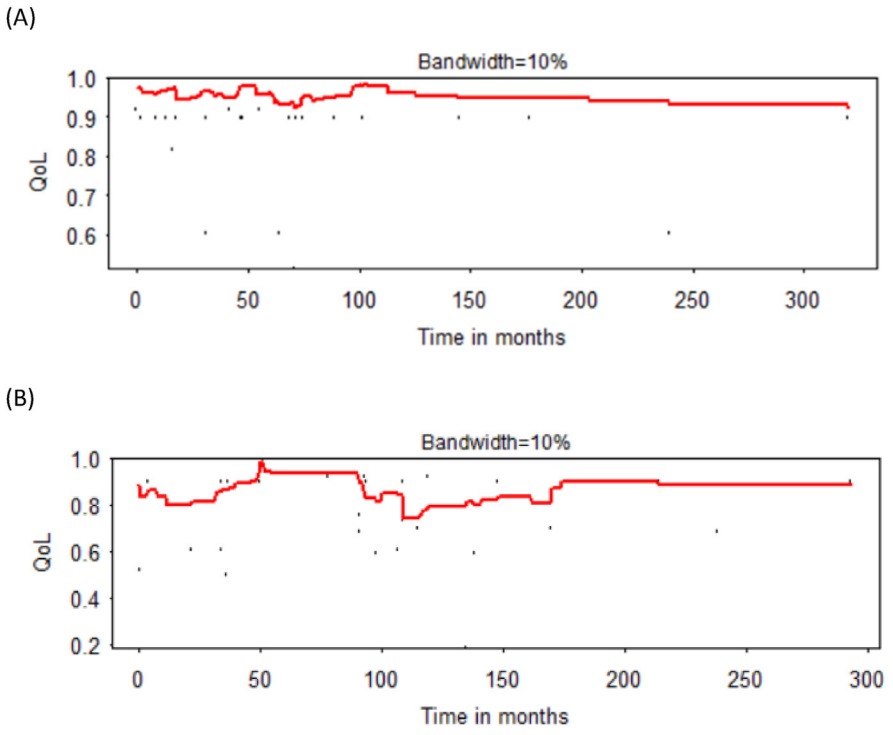

Figure 5. EQ-5D scores after HIV diagnosis with kernel smoothing (A) Early HIV diagnosis group (B) Late HIV diagnosis group.

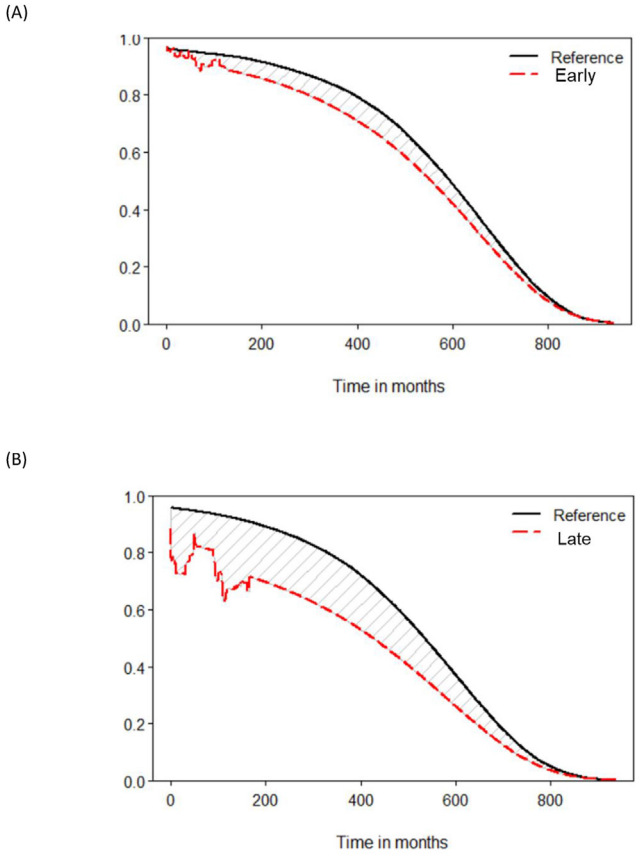

Figure 6. Loss of quality-adjusted life expectancy (marked with diagonal lines) compared with age/sex-matched reference populations with health utility of 1.0. (A) Early HIV diagnosis group. (B) Late HIV diagnosis group.

early HIV diagnosis under the less precise categorization used in our study), especially if ART is started immediately.[8] Second, after the onset of symptomatic AIDS, there might be a period of low quality of life under an unstable medical condition in the late diagnosis group. However, because we can only enroll stable patients, the quality of life of late presenters in the acute stage will be overestimated, resulting in an underestimated loss-of-QALE. Therefore, the actual reduction in loss-of-QALE due to early HIV diagnosis may be greater than the estimate in our studies.

Our study is subject to several important limitations. First, selection bias may exist, because we measured health utility of patients at a single medical center and integrated the quality-of-life data into national HIV cohort survival curve. However, previous studies[27,28] showed that patients treated at National Taiwan University Hospital had clinical characteristics similar to that of patients treated at other designated hospitals. Moreover, this quasi-random sample of 127 patients and the national cohort (N = 14,570) seems to be similar in all socio-demographic variables, including HIV risk groups (homosexual vs. bisexual), age at HIV diagnosis, marital status, occupation, and HIV screening channels (Table 3). The national HIV treatment guidelines and the HIV case management system ensure all patients receive the same high-quality medical care. Second, the life expectancy estimate is an extrapolation of the currently observed survival curves of HIV patients, under the assumption that HIV will remain an incurable disease for the next 78 years. However, even if a breakthrough occurs in HIV cure research,[29] early-diagnosed HIV patients would still likely benefit from curative treatment more than late-diagnosed HIV patients. Third, during the lifetime

Table 5 Sensitivity analysis of loss-of-QALE, by different assumption on quality of life of reference population.

Health utility value of reference population	Loss-of-QALE in Early diagnosed group (QALYs)	Loss-of-QALE in Late diagnosed group (QALYs)	Reduction in loss-of-QALE by early HIV diagnosis (QALYs)
Health utility = 1.0	5.52	13.80	8.28
Taiwan 2009 Health Interview Survey	2.33	10.66	8.33
Taiwan 2009 Health Interview Survey (excluding those aged 80 years or more)	2.66	10.87	8.21

extrapolation of quality of life, we assumed that the quality of life for patients living with HIV will continue to stay at the level of health utility as measured in the quality-of-life survey in this study, without considering the effect of aging in this population. Such an assumption could result in an overestimation of QALE after HIV diagnosis in both early-diagnosed and late-diagnosed groups, but it might not significantly affect the accuracy of the estimated impact of early HIV diagnosis on reducing the loss-of-QALE, as illustrated by the sensitivity analysis that takes the aging of the reference population into account.

Our study was conducted in Taiwan, an economically prosperous country that provides universal access to highly active ART for all citizens living with HIV.[5,24] The benefit of early HIV diagnosis, with a gain of 8.28 healthy life years, should be interpreted in this context of universal access to ART. Therefore, our results cannot be generalized to resource-limited regions where coverage of ART is low. In such settings, the priority should be expanding the coverage of ART to all patients living with HIV.[30—32]

One of the seven goals for public health training in the 21st century highlighted by Prof. Martin McKee is to "ensure that our students' approaches to public health are firmly grounded in human rights."[33] Whether expanding HIV testing to achieve early HIV diagnosis is actually beneficial to MSM living with HIV is a major concern for both individual patients and society as a whole. Our results show that, in the setting of universal access to ART, early HIV diagnosis before the onset of AIDS helps MSM living with HIV gain 8.28 healthy life years. Therefore, early HIV diagnosis is highly beneficial for people living with HIV themselves.

The findings of this study resolve the potential human rights concerns associated with screening for HIV among vulnerable populations and may serve as the ethical basis for the expansion of HIV testing and counseling services among MSM.

Financial Support

This work was supported by Taiwan Ministry of Science and Technology (MOST) (grants no. MOST-104-2314-B-002-035-MY2 and MOST-106-2314-B-002-115-MY3, to Chi-Tai Fang) and Population Health Research Center from Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Taiwan Ministry of Education (grant number NTU-112L9004). The publication of this article was supported by Infectious Disease Research and Education Center, Ministry of Health and Welfare and National Taiwan University (Taipei, Taiwan). The funders had no role in study design, data analyses, interpretation, or manuscript writing.

Author contributions

TL interviewed HIV patients using EQ-5D instrument to obtain quality of life data, conducted data analysis, constructed Table 2, and plotted Fig. 1B; CTF conceived and designed this study, obtained funding, obtained Taiwan national HIV registry dataset, constructed Table 3, and supervised data analysis; YYL conducted data analysis, constructed Table 1, Table 4, and Table 5, and plotted Figs. 1A, 2 and 3, Fig. 4, Fig. 5, and Fig. 6; CCS helped the interview of HIV patients to obtain quality of life data; FYC helped data analysis; JDW provided EQ-5D scoring function in Taiwan and the methodology; CTF and LT wrote the manuscript; All authors critically reviewed the manuscript and approved the final version for submission; TL, CTF, and YYL contributed equally as the first authors.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

A preliminary version of this work, using iSQoL 1.0 to analyze Taiwan national HIV registry for those diagnosed before 2015, was the Master thesis of the first author, Tung Lo, at National Taiwan University (2015) (Advisor: Chi-Tai Fang). An updated analysis, using iSQoL 2.0 to analyze Taiwan national HIV registry for those diagnosed before 2016, was included in part of the Master Thesis of the co-first author, Yu-Yao Lee, at National Taiwan University (2020) (Advisor: Chi-Tai Fang). We thank Taiwan Centers for Disease Control and Dr. Chang-Hsun Chen for providing Taiwan National HIV registry dataset for this study.

References

1. Lee YC, Liu WC, Hsieh YL, Wu CH, Wu PY, Luo YZ, et al. Non-opioid recreational drug use and a prolonged HIV outbreak among men who have sex with men in Taiwan: an incident case-control study, 2006-2015. *J Formos Med Assoc* 2022;**121**: 237—46.
2. Taiwan Centers for Disease Control (CDC). *Statistics of HIV/AIDS*. 2023. available at: https://www.cdc.gov.tw/En/

Category/MPage/kt6yIoEGURtMQubQ3nQ7pA. [Accessed 10 August 2023].
3. Chen YH, Fang CT, Shih MC, Lin KY, Chang SS, Wu ZT, et al. Routine HIV testing and outcomes: a population-based cohort study in Taiwan. *Am J Prev Med* 2022;**62**:234—42.
4. Tsai YC. On behalf of Taiwan centers for disease control. HIV epidemiology in Taiwan. In: *Taiwan public health association 2019 annual meeting*; 2019. September 27, 2019, Taipei.
5. Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. *J Infect Dis* 2004;**190**:879—85.
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;**365**:493—505.
7. Young SD, Monin B, Owens D. Opt-out testing for stigmatized diseases: a social psychological approach to understanding the potential effect of recommendations for routine HIV testing. *Health Psychol* 2009;**28**:675—81.
8. The Insight START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;**373**:795—807.
9. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;**360**:119—29.
10. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, et al., When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; **373**:1352—63.
11. May M, Gompels M, Delpech V, Porter K, Post F, Johnson M, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ* 2011;**343**:d6016.
12. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013;**8**:e81355.
13. Trickey A, Sabin CA, Burkholder G, Crane H, d'Arminio Monforte A, Egger M, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV* 2023;**10**:e295—307.
14. Cluver LD, Sherr L, Toska E, Zhou S, Mellins CA, Omigbodun O, et al. From surviving to thriving: integrating mental health care into HIV, community, and family services for adolescents living with HIV. *Lancet Child Adolesc Health* 2022;**6**:582—92.
15. Yang SC, Wang JD, Wang SY. Considering lead-time bias in evaluating the effectiveness of lung cancer screening with real-world data. *Sci Rep* 2021;**11**:12180.
16. Yang SC, Lai WW, Lin CC, Su WC, Ku LJ, Hwang JS, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. *Lung Cancer* 2017;**108**: 183—91.
17. Yang SC, Lai WW, Chang HY, Su WC, Chen HH, Wang JD. Estimation of loss of quality-adjusted life expectancy (QALE) for patients with operable versus inoperable lung cancer: adjusting quality-of-life and lead-time bias for utility of surgery. *Lung Cancer* 2014;**86**:96—101.
18. EuroQoL Group. EQ-5D. https://euroqol.org/(accessed August 11, 2023).
19. Hwang JS at Academia Sinica. iSQoL2. https://sites.stat.sinica.edu.tw/isqol/(accessed August 11, 2023).
20. Hwang JS, Hu TH, Lee LJ, Wang JD. Estimating lifetime medical costs from censored claims data. *Health Econ* 2017;**26**: e332—44.
21. Centers for Disease Control and Prevention. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep 1992* 1993;**41**(RR-17):1—19.
22. Fang CT, Chang YY, Hsu HM, Twu SJ, Chen KT, Lin CC, et al. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy. *QJM* 2007;**100**: 97—105.
23. Hwang JS, Wang JD. Monte Carlo estimation of extrapolation of quality-adjusted survival for follow-up studies. *Stat Med* 1999; **18**:1627—40.
24. Fang CT, Chang YY, Hsu HM, Twu SJ, Chen KT, Chen MY, et al. Cost-effectiveness of highly active antiretroviral therapy for HIV infection in Taiwan. *J Formos Med Assoc* 2007;**106**: 631—40.
25. EuroQol G. EuroQol-a new facility for the measurement of health-related quality of life. *Health Pol* 1990;**16**:199—208.
26. Lee HY, Hung MC, Hu FC, Chang YY, Hsieh CL, Wang JD. Estimating quality weights for EQ-5D (EuroQol-5 dimensions) health states with the time trade-off method in Taiwan. *J Formos Med Assoc* 2013;**112**:699—706.
27. Chen LY, Sun HY, Chuang YC, Huang YS, Liu WD, Lin KY, et al. Patient-reported outcomes among virally suppressed people living with HIV after switching to Co-formulated bictegravir, emtricitabine and tenofovir alafenamide. *J Microbiol Immunol Infect* 2023;**56**:575—85.
28. Lin KY, Yang CJ, Sun HY, Lee YT, Liou BH, Hii IM, et al. Care cascade of tuberculosis infection treatment for people living with HIV in the era of antiretroviral therapy scale-up. *Sci Rep* 2022;**12**:16136.
29. Maina EK, Adan AA, Mureithi H, Muriuki J, Lwembe RM. A review of current strategies towards the elimination of latent HIV-1 and subsequent HIV-1 cure. *Curr HIV Res* 2021;**19**: 14—26.
30. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. 2013. http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1. [Accessed 14 April 2014].
31. Joint United Nations Programme on HIV/AIDS (UNAIDS). *Fast track: ending the AIDS epidemic by 2030*. 2014. Geneva, Switzerland.
32. *UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic*. 2014 (available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf.
33. McKee M. Seven goals for public health training in the 21st century. *Eur J Publ Health* 2013;**23**:186—7.