Infect Chemother. 2023 Mar;55(1):69-79
https://doi.org/10.3947/ic.2022.0059
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Original Article

Check for updates

Rate of and Risk Factors for Loss to Follow Up in HIV-Infected Patients in Korea: The Korea HIV/AIDS Cohort Study

Hye Seong [1,2,3], Yunsu Choi [4,5], Minjeong Kim [6], Jung Ho Kim [1,2], Joon Young Song [3], Shin-Woo Kim [7], Sang Il Kim [8], Youn Jeong Kim [9], Dae Won Park [3], Boyoung Park [4], Bo Youl Choi [4,5], and Jun-Yong Choi [1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[2]AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[4]Department of Preventive Medicine, Hanyang University College of Medicine, Seoul, Korea
[5]Institute for Health and Society, Hanyang University, Seoul, Korea
[6]Division of Data Technology, Tokyo Electron Korea Ltd, Hwaseong, Gyeonggi-do, Korea
[7]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, Korea
[8]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[9]Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Open Access

ABSTRACT

Background: Owing to antiretroviral therapy (ART), acquired immune deficiency syndrome (AIDS)-related mortality has significantly decreased. Retaining in care is an essential step for human immunodeficiency virus (HIV) care cascade. This study investigated the incidence of and risk factors for loss to follow-up (LTFU) in Korean people living with HIV (PLWH).

Materials and Methods: Data from the Korea HIV/AIDS cohort study (including prospective interval cohort and retrospective clinical cohort) were analyzed. LTFU was defined as not visiting the clinic for more than 1 year. Risk factors for LTFU were identified using the Cox regression hazard model.

Results: The study enrolled 3,172 adult HIV patients (median age, 36 years; male 92.97%). The median CD4 T cell count at enrollment was 234 cells/mm^3 (interquartile range [IQR]: 85 - 373) and the median viral load at enrollment was 56,100 copies/mL (IQR: 15,000 - 203,992). The total follow-up duration was 16,487 person-years, and the overall incidence rate of LTFU was 85/1,000 person-years.In the multivariable Cox regression model, subjects on ART were less likely to have LTFU than subjects not on ART (hazard ratio [HR] = 0.253, 95% confidence interval [CI]: 0.220 - 0.291, P <0.0001). Among PLWH on ART, female sex (HR = 0.752, 95% CI: 0.582 - 0.971, P = 0.0291) and older age (>50: HR = 0.732, 95% CI: 0.602 - 0.890; 41 - 50: HR = 0.634, 95% CI: 0.530 - 0.750; 31 - 40: HR = 0.724, 95% CI: 0.618 - 0.847; ≤30: reference, P <0.0001) were associated with high rate of retention in care. The viral load at ART initiation ≥1,000,001 (HR = 1.545, 95% CI: 1.126 - 2.121, ≤10,000: reference) was associated with a higher rate of LTFU.

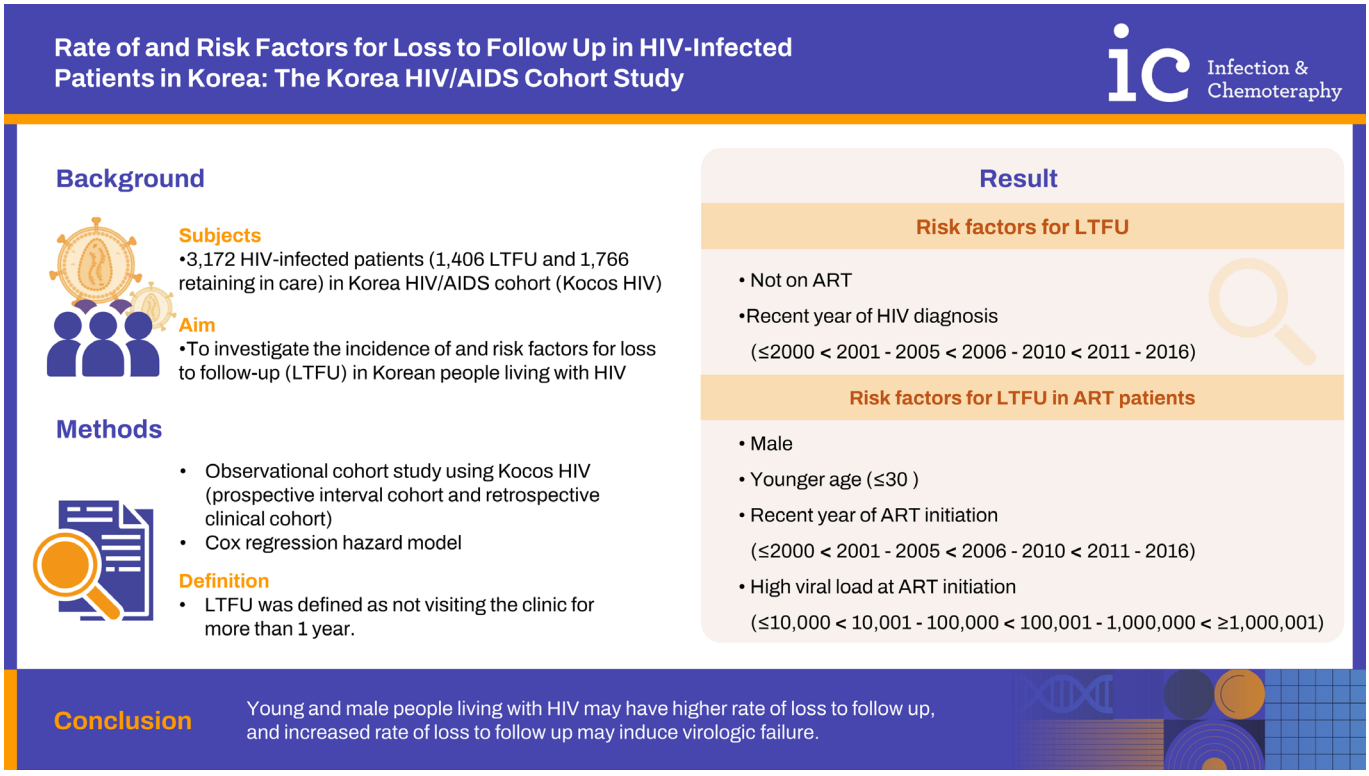
Conclusion: Young and male PLWH may have a higher rate of LTFU, and an increased rate of LTFU may induce virologic failure.

Keywords: Antiretroviral therapy; Human immunodeficiency virus; Loss to follow up; Korea HIV/AIDS cohort; Risk factor

Received: May 4, 2022
Accepted: Nov 2, 2022
Published online: Feb 20, 2023

Corresponding Author:
Jun-Yong Choi, MD, PhD
Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-02-2228-1974, Fax: +82-02-393-6884
Email: seran@yuhs.ac

GRAPHICAL ABSTRACT



INTRODUCTION

Human immunodeficiency virus (HIV) has been a significant global public health problem worldwide [1], having claimed nearly 40.1 million people living with HIV at the end of 2021 [2]. In 2021, 650,000 people died from HIV-related illnesses, and 1.5 million people acquired HIV [2]. Global prevention and treatment programs such as the United Nations program on HIV/AIDS (UNAIDS) have tried to reduce the incidence and mortality caused by HIV.

In this century, owing to antiretroviral therapy (ART), acquired immune deficiency syndrome (AIDS)-related mortality is the lowest. ART inhibits HIV replication, transmission and improves HIV-infected patients' immune function [1]. The first and essential step to ending AIDS as a public health threat is to provide ART treatment, including regular visiting and monitoring [3]. The retention in care is vital not only for successful individual therapy but also for preventing HIV-related disease [4].

This study aimed to evaluate the incidence and risk factors for loss to follow-up (LTFU) in Korea HIV/AIDS cohort (Kocos HIV). We would also find out how well the retention in care is being achieved and investigate characteristics for LTFU of the Korean HIV/AIDS cohort.

MATERIALS AND METHODS

1. Study design and time-period

It was an observational cohort study using Korea HIV/AIDS cohort, in which 16 mid- and large-scale general hospitals operate across six cities [5]. In this study, we determined the LTFU rate using the baseline data of the HIV/AIDS cohort study at the time of enrollment. The clinical retrospective cohort was registered by December 2016, while the interval prospective cohort was enrolled from December 2006 to December 2016. We united the clinical cohort with the interval cohort and analyzed the data. The patients HIV infected but under 18 years were excluded.

After registering both HIV cohorts, informed consent was obtained. Trained researchers of each center collected information using a standardized protocol: medical history, socioeconomic status, physical findings, laboratory findings including immunological and virological status, and opportunistic diseases [6].

This study utilized a part of the collected data including age, CD4 counts, viral load at diagnosis, sex, HIV transmission route, year of diagnosis, and ART-related variables (year of ART initiation, age at ART initiation,

https://doi.org/10.3947/ic.2022.0059

CD4 counts at ART initiation, viral load at ART initiation, and fist ART regimen).

2. Ethics statement

This study was approved by Institutional Review Board (IRB) of the Severance hospital (IRB approval number: 4-2019-0419), and written informed consent was obtained from all participants.

3. Definitions

The LTFU definitions in other studies vary ranging from 90 days to 365 days with no clinic visit [7-10]. According to the recommendation of Shepherd et al., we defined LTFU based on the study outcome of interest, available encounter data, and the cohort visit schedule [7]. For the clinical retrospective cohort, when a patient has had 365 days or more since the last clinic visit, we considered it LTFU. In the prospective cohort, LTFU was defined at least one of the followings: (1) When the reason for the termination of the investigation is "Dropping out (not visited for more than two years)"; (2) When the survey interval is 365 days or more; (3) When the investigation interval of each visit is less than 365 days but the period from the last visit date to December 31, 2016, is 365 days or more. If the visit to the clinic and treatment has not been interrupted for more than 365 days during the study period, it is classified as In Care group. When multiple LTFUs occur in a person, the first LTFU occurrence is considered a follow-up period.

4. Statistical analyses

The Wilcoxon rank-sum test was used to analyze differences between LTFU and In Care groups, while the Chi square test or Fisher's exact test was used for categorical data. The poisson regression model and the Cox proportional hazard regression analysis were performed to evaluate LTFU incidence rate and Hazard ratio, respectively. Variables with P <0.05 in the multivariable Cox regression analysis were stratified to draw the Kaplan–Meier curve. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Clinical characteristics of the Korea HIV/AIDS Cohort study

Among 4,108 HIV-infected patients (1,443 prospective and 2,665 retrospectives), 3,172 patients were finally enrolled (1,407 LTFU and 1,766 in care; 2,949 males and 223 females; median age, 36 years) (**Fig. 1**, **Table 1**). Sexual

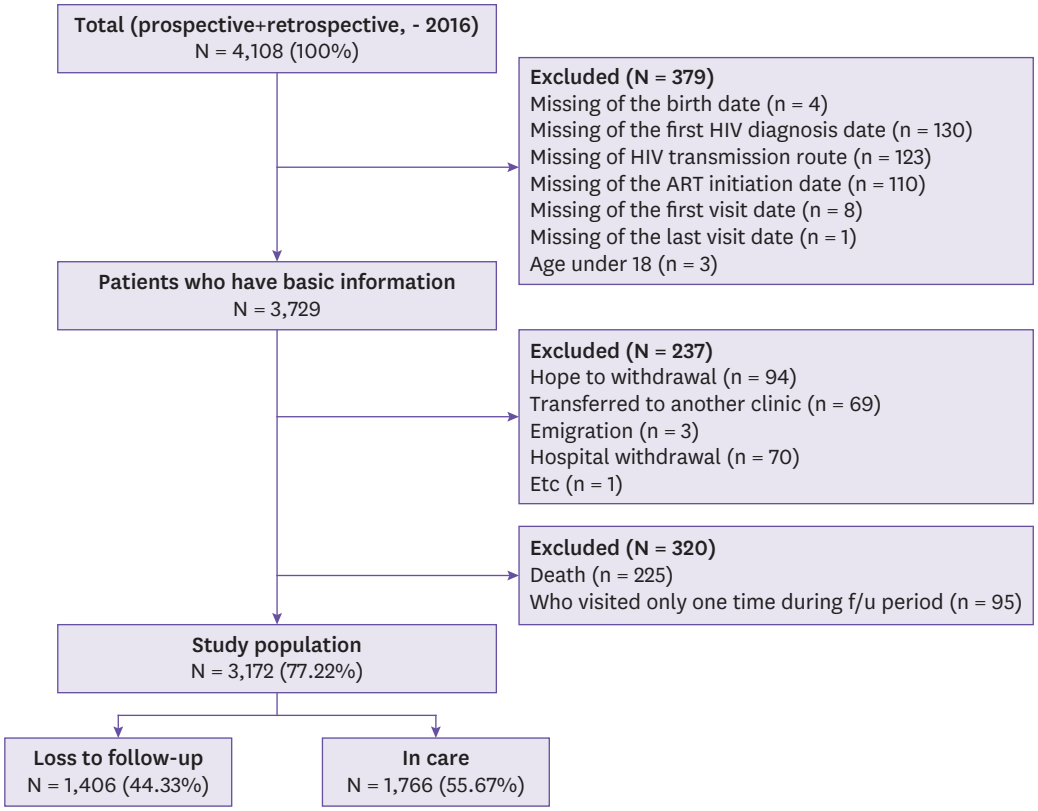


Figure 1. A flow chart describing the patients enrolled into Korean HIV/AIDS cohort, 1987-2016.
HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy.

https://doi.org/10.3947/ic.2022.0059

contact was the main route of HIV transmission (n = 2,003, 63.15%). The median CD4 T cell count and viral load at enrollment were 234 cells/mm^3 (interquartile range [IQR]: 85 - 373), 56,100 copies/mL (IQR: 15,000 - 203,992), respectively. At enrollment, 86% of the patients (n = 2,733) were receiving antiretroviral agents. The most preferred regimen was the nucleoside/nucleotide reverse transcriptase inhibitor plus protease inhibitor regimen (n = 1,404, 51.37%).

When compared to the patients retention in care (median age, 37 years, IQR: 29 - 46), patients who became LTFU were younger (median age, 35 years; IQR: 27 - 44) (*P* <0.001). The proportion of patients with CD4 count <100 cells/mm^3 (n = 223, 15.86% *vs.* n = 340, 19.25%; *P* <0.001) and the median viral load were lower in LTFU patients than in care patients (49,154.5, IQR: 11,700 - 180,000 *vs.* 59.500, IQR: 17,062 - 229,462; *P* = 0.068).

Ninety-four percent (n = 1,663) of the patients that retention in care were under ART, higher than the patients became LTFU (n = 1,070, 76.10%). Compared to the median age and CD4 cell counts at ART initiation for patients who remained in care, patients who became LTFU tend to be younger (37, IQR: 82 - 304 *vs.* 39, IQR: 30 - 48; *P* = 0.0358) and have lower CD4 count (207, IQR: 82 - 304 *vs.* 219, IQR: 83 - 338; *P* <0.001). The viral load at ART initiation was significantly different between the two groups while revealing no significant differences in median value; the median viral load in LTFU was higher than that of in care (57,000, IQR: 14,100 - 180,000 *vs.* 53,500, IQR: 12,481.5 - 190,000; *P* = 0.9031).

Table 1. Baseline characteristics of 3,172 enrolled patients

Characteristics	In care (%)	Total (%)	Loss to follow-up (%)	*P*-value
Total	1,766 (55.67)	3,172 (100.00)	1,406 (44.33)	<0.0001
Sex				0.2727
Male	1,634 (92.53)	2,949 (92.97)	1,315 (93.53)	
Female	132 (7.47)	223 (7.03)	91 (6.47)	
HIV transmission route				
Sexual contact	1,171 (66.31)	2,003 (63.15)	832 (59.17)	<0.0001
Homosexual	481 (41.08)	862 (43.04)	381 (45.79)	
Heterosexual	452 (38.60)	734 (36.65)	282 (33.89)	
Bisexual	200 (17.08)	295 (14.73)	95 (11.42)	
Unknown	38 (3.25)	112 (5.59)	74 (8.89)	
Injecting drug user	0 (0.00)	3 (0.09)	3 (0.21)	
Others	4 (0.23)	8 (0.25)	4 (0.28)	
Unknown	591 (33.47)	1,158 (36.51)	567 (40.33)	
Year of diagnosis				<0.0001
≤2000	110 (6.23)	263 (8.29)	153 (10.88)	
2001 - 2005	350 (19.82)	740 (23.33)	390 (27.74)	
2006 - 2010	542 (30.69)	1,015 (32.00)	473 (33.64)	
2011 - 2016	764 (43.26)	1,154 (36.38)	390 (27.74)	
Age at Diagnosis				0.0022
≤30	544 (30.80)	1,047 (33.01)	503 (35.78)	
31 - 40	509 (28.82)	926 (29.19)	417 (29.66)	
41 - 50	410 (23.22)	707 (22.29)	297 (21.12)	
>50	303 (17.16)	492 (15.51)	189 (13.44)	
Median (Q1 - Q3)	37 (29 - 46)	36 (28 - 45)	35 (27 - 44)	<0.0001
CD4 counts (cells/mm^3) at diagnosis				<0.0001
<100	340 (19.25)	563 (17.75)	223 (15.86)	
100 - 199	202 (11.44)	310 (9.77)	108 (7.68)	
200 - 349	339 (19.20)	588 (18.54)	249 (17.71)	
≥350	340 (19.25)	582 (18.35)	242 (17.21)	
Unknown	545 (30.86)	1,129 (35.59)	584 (41.54)	
Median (Q1 - Q3)	228 (81.5 - 367)	234 (85 - 373)	241.5 (88 - 385)	0.3727

(continued to the next page)

https://doi.org/10.3947/ic.2022.0059

Table 1. (Continued) Baseline characteristics of 3,172 enrolled patients

Characteristics	In care (%)	Total (%)	Loss to follow-up (%)	*P*-value
Viral load (copies/mL) at diagnosis				<0.0001
≤10,000	198 (11.21)	362 (11.41)	164 (11.66)	
10,001 - 100,000	474 (26.84)	774 (24.4)	300 (21.34)	
100,001 - 1,000,000	325 (18.40)	520 (16.39)	195 (13.87)	
≥1,000,001	96 (5.44)	151 (4.76)	55 (3.91)	
Unknown	673 (38.11)	1,365 (43.03)	692 (49.22)	
Median (Q1 - Q3)	59,500 (17,062 - 229,462)	56,100 (15,000 - 203,992)	49,154.5 (11,700 - 180,000)	0.0068
ART				<0.0001
No	103 (5.83)	439 (13.84)	336 (23.90)	
Yes	1,663 (94.17)	2,733 (86.16)	1,070 (76.10)	
Year of ART initiation				<0.0001
≤2000	45 (2.71)	128 (4.68)	83 (7.76)	
2001 - 2005	239 (14.31)	493 (18.04)	255 (23.83)	
2006 - 2010	542 (32.59)	921 (33.7)	379 (35.42)	
2011 - 2016	838 (50.39)	1,191 (43.58)	353 (32.99)	
Age at ART initation				0.021
≤30	426 (25.62)	712 (26.05)	286 (26.73)	
31 - 40	497 (29.89)	862 (31.54)	365 (34.11)	
41 - 50	424 (25.50)	679 (24.84)	255 (23.83)	
>50	316 (19.00)	480 (17.56)	164 (15.33)	
Median (Q1 - Q3)	39 (30 - 48)	38 (30 - 47)	37 (30 - 46)	0.0358
CD4 counts (cells/mm^3) at ART initiation				<0.0001
<100	434 (26.10)	702 (25.69)	268 (25.05)	
100 - 199	280 (16.84)	468 (17.12)	188 (17.57)	
200 - 349	487 (29.28)	817 (29.89)	330 (30.84)	
≥350	352 (21.17)	509 (18.62)	157 (14.67)	
Unknown	110 (6.61)	237 (8.67)	127 (11.87)	
Median (Q1 - Q3)	219 (83 - 338)	212 (82.5 - 324)	207 (82 - 304)	0.0140
Viral load (copies/mL) at ART initiation				<0.0001
≤10,000	314 (18.88)	494 (18.08)	180 (16.82)	
10,001 - 100,000	621 (37.34)	983 (35.97)	362 (33.83)	
100,001 - 1,000,000	428 (25.74)	675 (24.70)	247 (23.08)	
≥1,000,001	81 (4.87)	133 (4.87)	52 (4.86)	
Unknown	219 (13.17)	448 (16.39)	229 (21.40)	
Median (Q1 - Q3)	53,500 (12,481.5 - 190,000)	55,600 (13,400 - 185,000)	57,000 (14,100 - 180,000)	0.9031
First ART regimen				<0.0001
NRTI	32 (1.92)	70 (2.56)	38 (3.55)	
NRTI + INI	389 (23.39)	499 (18.26)	110 (10.28)	
NRTI + PI	797 (47.93)	1,404 (51.37)	607 (56.73)	
Others	445 (26.76)	760 (27.81)	315 (29.44)	

HIV, human immunodeficiency virus; Q1, first quartile; Q3, third quartile; ART, antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; INI, integrase inhibitor; PI, protease inhibitor.

https://doi.org/10.3947/ic.2022.0059

2. Incidence of LTFU

For 3,172 patients, the total follow-up duration was 16,487 person-years, and the overall incidence rate of LTFU was 85/1,000 person-years (**Table 2**, **3**). More than half of LTFU event was occurred within 5 years from enrollment. The loss to follow-up incidence rates was the highest in the first year from enrollment (1678.280) and year 2015 (342.431). The number of LTFU patients and LTFU incidence rates according to follow-up duration or LTFU year are shown in **Figure 2**.

3. Factors associates with LTFU

In univariate Cox regression, the risk factors associated with LTFU were male sex (*P* = 0.0026), HIV transmission route (*P* <0.0001), year of HIV diagnosis (*P* <0.0001), CD4 counts at diagnosis (*P* <0.0001), Viral load at diagnosis (*P* <0.0001), and ART (*P* <0.0001). In the multivariable Cox regression model, subjects on ART were less likely to have LTFU than subjects not on ART (hazard ratio [HR] = 0.253, 95% confidence interval [CI]: 0.220 - 0.291, *P* <0.0001) as well as subjects diagnosed HIV before 2000 year (2001 - 2005: HR = 2.368, 95% CI: 1.86 - 3.013; 2006 - 2010: HR = 3.869, 95% CI: 2.983 - 5.018; 2011 - 2016: HR = 5.981, 95% CI: 4.534 - 7.888; ≤2,000: reference, *P* <0.0001) (**Table 4**, **Fig. 3**).

Among 2,702 PLWH on ART, as presented in **Table 5** and **Figure 4**, female sex (HR = 0.752, 95% CI: 0.582 - 0.971, *P* = 0.0291) and older age (>50: HR = 0.732, 95% CI: 0.602 - 0.890; 41-50: HR = 0.634, 95% CI: 0.530 - 0.750; 31 - 40: HR = 0.724, 95% CI: 0.618 - 0.847; ≤30: reference, *P* <0.0001) were associated with lower rate of LTFU. A recent viral load ≥1,000,001 (HR = 1.545, 95% CI: 1.126 - 2.121, ≤10,000: reference) was associated with higher

Table 2. Loss to follow-up incidence rates by follow-up duration[a] (years)

Follow-up year	Total N	LTFU N	Person-years	Incidence per 1,000 person-years
Total	3,172	1,407	16,487.080	85.340
≤1	426	307	182.925	1,678.280
≤2	375	209	560.271	373.033
≤3	562	182	1,360.505	133.774
≤4	351	137	1,226.292	111.719
≤5	255	102	1,137.423	89.676
≤6	180	79	992.797	79.573
≤7	154	67	1,002.185	66.854
≤8	118	52	890.857	58.371
≤9	109	41	933.023	43.943
≤10	132	50	1,256.741	39.785
≤11	120	37	1,262.255	29.313
≤12	86	28	990.497	28.269
≤13	77	24	960.591	24.985
≤14	58	23	782.455	29.395
≤15	38	17	549.286	30.949
≤16	31	17	477.658	35.590
≤17	24	8	396.147	20.195
≤18	24	12	417.882	28.716
≤19	9	2	165.713	12.069
≤20	6	1	116.006	8.620
≤21	14	5	286.128	17.475
≤22	6	2	129.837	15.404
≤23	6	2	136.928	14.606
≤24	5	1	117.696	8.496
≤25	3	0	74.181	0.000
≤26	2	2	50.701	39.447
≤27	0	0	0.000	0.000
≤28	0	0	0.000	0.000
≤29	1	0	28.783	0.000

[a]Follow-up duration: from the date of positive confirmation to the last observation or death date.

N, numbers; LTFU, loss to follow up.

Table 3. Loss to follow-up incidence rates by year

Year	Total N	LTFU N	Person-years	Incidence per 1,000 person-years
Total	3,172	1,407	16,487.080	85.340
1987	1	0	0.734	0.000
1988	2	0	1.642	0.000
1989	7	0	5.622	0.000
1990	12	0	9.438	0.000
1991	17	0	14.364	0.000
1992	30	0	24.068	0.000
1993	42	2	37.099	53.910
1994	58	1	49.904	20.038
1995	78	0	69.479	0.000
1996	99	0	91.770	0.000
1997	125	1	112.110	8.920
1998	165	8	140.904	56.776
1999	200	6	172.334	34.816
2000	245	10	217.115	46.059
2001	321	17	268.594	63.293
2002	425	18	362.255	49.689
2003	542	27	467.101	57.803
2004	692	24	592.902	40.479
2005	889	35	760.408	46.028
2006	1,087	32	968.647	33.036
2007	1,252	61	1,129.838	53.990
2008	1,393	90	1,239.604	72.604
2009	1,485	133	1,267.951	104.894
2010	1,463	96	1,237.263	77.591
2011	1,466	81	1,287.238	62.925
2012	1,556	97	1,333.770	72.726
2013	1,592	92	1,369.666	67.170
2014	1,647	70	1,443.416	48.496
2015	1,678	505	1,474.751	342.431
2016	1,160	0	302.462	0.000

N, numbers; LTFU, loss to follow up.

https://doi.org/10.3947/ic.2022.0059

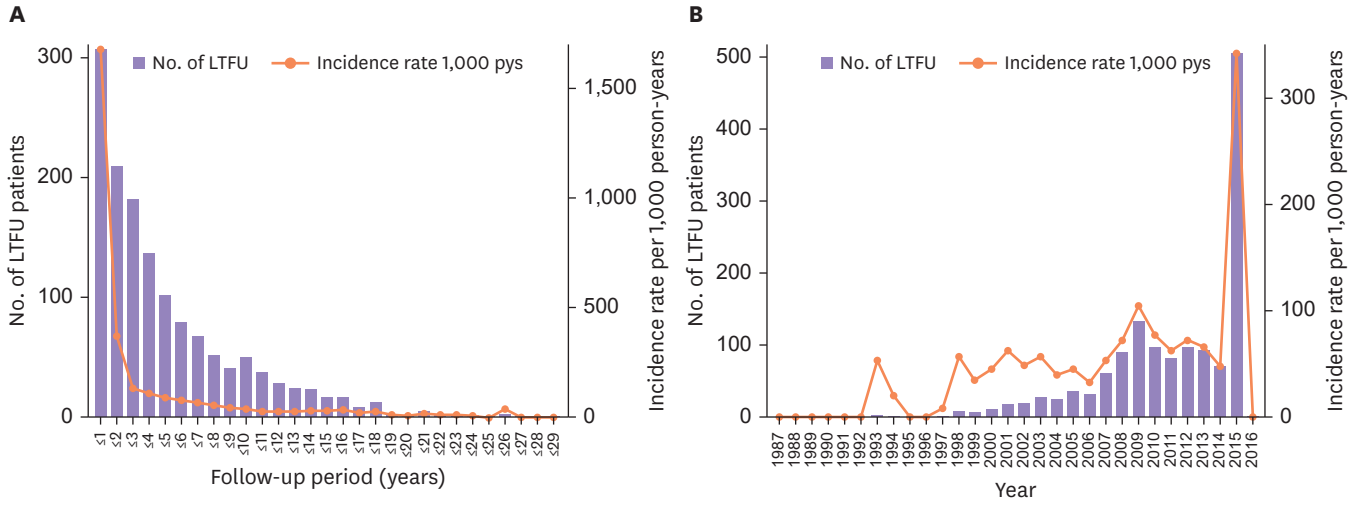


Figure 2. Number of loss to follow-up (LTFU) patients and LTFU incidence rates.
(A) LTFU incidence rates by follow-up duration, (B) LTFU incidence rates by loss to follow-up year.

rate of LTFU. Also, initiation of ART in year 2011-2016 was associated with more LTFU than the initiation of ART before year 2000 (2011 - 2016: HR = 2.204, 95% CI: 1.628 - 2.985; ≤2,000: reference, *P* <0.0001).

DISCUSSION

Successful ART requires retention in care, regular visiting, and monitoring. This study utilized both prospective and retrospective Kocos HIV for assessing the incidence rate and factors of LTFU. We identified that a considerable number of patients were LTFU, and various factors are associated with LTFU.

The overall incidence rate of LTFU in Kocos HIV was 85 per 1,000 person-years for a 10-year observation. This finding is lower than 109 per 1,000 person-years of the South Africa cohort [1] but higher than 28.3 per 1,000 person-years of TREAT Asia HIV Observational database Low-Intensity TransfEr (TAHOD-LITE), a multiregional Asian cohort [8].

Retention in care is important for HIV-infected patients to prevent further HIV transmission, progression, and mortality. Like other studies, we found ART was an essential factor for retention in care by reducing LTFU [11]. Efforts to improve ART adherence, including adherence support services, may lead to lower rates of LTFU [12, 13].

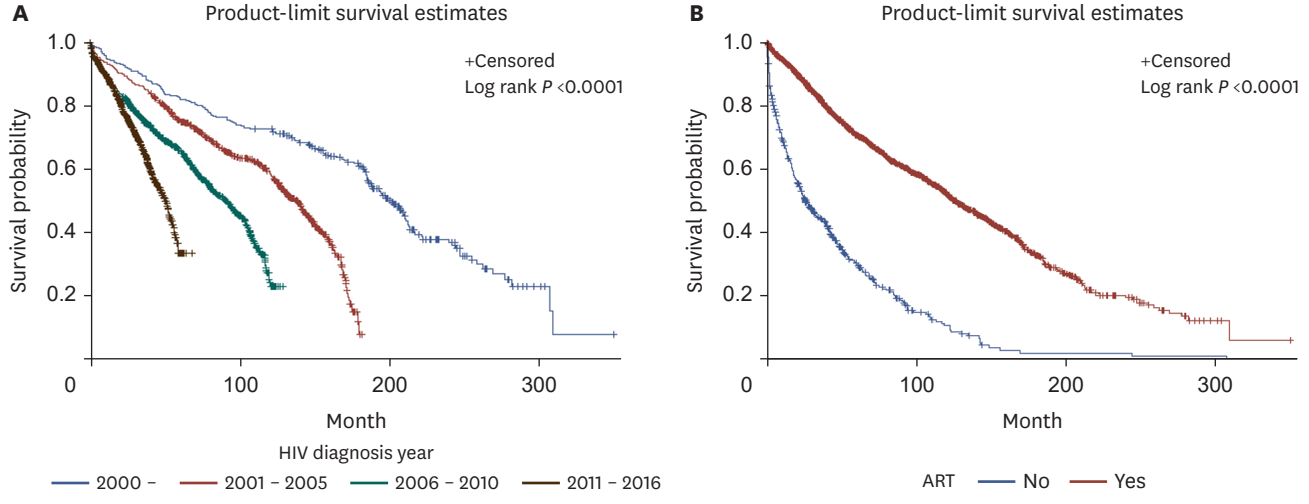


Figure 3. Kaplan-Meier curves for loss to follow-up (LTFU) stratified by risk factors.
(A) LTFU rates by HIV diagnosis year, (B) LTFU rates by antiretroviral therapy.

https://doi.org/10.3947/ic.2022.0059

Table 4. Factors associated with loss to follow-up (prospective + retrospective)

Characteristics (n = 3,139)	Events/ person-years	Rates per 1,000 person-years (95% CI)	Univariate			Multivariable		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex								
Male	1,315/15,065	87.29 (82.69 - 92.13)	Reference		0.0026	Reference		0.2844
Female	91/1,434	63.47 (51.68 - 77.94)	0.719	0.581 - 0.891		0.883	0.702 - 1.109	
HIV Transmission Route								
Homosexual	381/4,541	83.91 (75.90 - 92.77)	Reference		<0.0001	Reference		0.2684
Heterosexual	282/3,960	71.209 (63.37 - 80.02)	0.845	0.724 - 0.986		0.909	0.771 - 1.071	
Sexual contact - unknown	95/1,445	65.736 (53.76 - 80.38)	0.781	0.623 - 0.977		0.857	0.683 - 1.074	
Other/unknown	648/6,553	98.882 (91.56 - 106.80)	1.176	1.036 - 1.335		1.015	0.890 - 1.158	
Year of HIV Diagnosis								
≤2000	153/3,424	44.69 (38.14 - 52.36)	Reference		<0.0001	Reference		<0.0001
2001 - 2005	390/5,860	66.56 (60.27 - 73.50)	2.612	2.063 - 3.306		2.368	1.86 - 3.013	
2006 - 2010	473/4,671	101.27 (92.54 - 110.82)	4.748	3.704 - 6.086		3.869	2.983 - 5.018	
2011 - 2016	390/2,545	153.23 (138.76 - 169.22)	7.546	5.803 - 9.813		5.981	4.534 - 7.888	
Age at HIV Diagnosis								
≤30	503/5,445	92.38 (84.65 - 100.82)	Reference		0.2054	Reference		0.1227
31 - 40	417/5,253	79.39 (72.12 - 87.38)	0.876	0.769 - 0.998		0.886	0.777 - 1.011	
41 - 50	297/3,641	81.57 (72.80 - 91.40)	0.899	0.779 - 1.039		0.847	0.732 - 0.982	
>50	189/2,161	87.48 (75.85 - 100.88)	0.958	0.810 - 1.134		0.915	0.771 - 1.087	
CD4 counts (cells/mm^3) at Diagnosis								
<100	223/2,644	84.34 (73.97 - 96.17)	Reference		<0.0001	Reference		0.3130
100 - 199	108/1,365	79.11 (65.51 - 95.53)	0.934	0.742 - 1.175		0.923	0.731 - 1.165	
200 - 349	249/2,596	95.91 (84.71 - 108.60)	1.132	0.944 - 1.356		1.128	0.934 - 1.361	
≥350	242/2,158	112.16 (98.88 - 127.22)	1.304	1.086 - 1.564		0.958	0.780 - 1.175	
Unknown	584/7,736	75.49 (69.61 - 81.87)	0.889	0.761 - 1.038		0.967	0.773 - 1.209	
Viral load (copies/mL) at Diagnosis								
≤10,000	164/1,393	117.70 (101.00 - 137.17)	Reference		<0.0001	Reference		0.0942
10,001 - 100,000	300/3,052	98.29 (87.78 - 110.07)	0.836	0.691 - 1.011		0.922	0.759 - 1.119	
100,001 - 1,000,000	195/1,914	101.86 (88.52 - 117.20)	0.864	0.702 - 1.063		1.028	0.823 - 1.285	
≥1,000,001	55/524	104.90 (80.54 - 136.64)	0.880	0.649 - 1.195		0.961	0.701 - 1.317	
Unknown	692/9,615	71.97 (66.80 - 77.54)	0.606	0.510 - 0.720		0.758	0.597 - 0.962	
ART								
No	336/1,225	274.29 (246.47 - 305.24)	Reference		<0.0001	Reference		<0.0001
Yes	1,070/15,274	70.05 (65.98 - 74.38)	0.256	0.226 - 0.290		0.253	0.220 - 0.291	

CI, confidential interval; HR, hazard ratio; HIV, human immunodeficiency virus; ART, antiretroviral therapy.

Among the 1,407 total LTFU, 307 (21.8%) participants were LTFU 12 months after enrollment. Among ART receiving PLWH, younger age (≤30) at ART initiation and male sex were at higher risks of becoming LTFU. These are consistent with previous cohort studies [8, 14, 15]. Higher viral load at ART initiation was also associated with a higher rate of LTFU. Patients with a higher viral load were more likely to be in the acute stage of HIV infection, so the period to diagnosis may be short. Hence, they could have less experience with symptomatic infections such as opportunistic infections and less feel the need for treatment. Lower CD4 counts at ART initiation were not associated with a higher rate of LTFU. Previous studies have shown varying findings on whether CD4 cell count is associated with LTFU [12, 15, 16]. Further research is needed to reveal the associations between viral load and CD4 count at ART initiation and LTFU.

Our study has limitations. First, some Kocos HIV data are missing, including CD4 counts and viral load at diagnosis or ART initiation. It might affect the results of the analysis. Second, we chose the LTFU definition of 365 days according to the recommendation of Shepherd et al. However, the LTFU definitions in other studies vary, ranging from 90 days to 365 days with no clinic visit [7 - 10]. Third, to unite the clinical retrospective cohort with the prospective cohort, we applied the same LTFU duration, but the detailed definition is slightly different due to its investigational differences. Fourth, LTFU may contain some patients who were transferred to other hospitals and are still in care, so the total LTFU could be overestimated. In addition, in this study, male and female sex were defined according to the last digit of the resident registration number. Therefore, according to the definition, some people who have received gender

Table 5. Factors associated with loss to follow-up in ART patients (prospective + retrospective)

Characteristics (n = 2,702)	Events/ person-years	Rates per 1000 person-years (95% CI)	Univariate			Multivariable		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex								
Male	998/13,882	71.89 (67.57 - 76.49)	Reference		0.0035	Reference		0.0291
Female	72/1,392	51.72 (41.05 - 65.15)	0.698	0.549 - 0.888		0.752	0.582 - 0.971	
HIV Transmission route								
Homosexual	308/4,245	72.56 (64.89 - 81.13)	Reference		0.0027	Reference		0.0573
Heterosexual	229/3,798	60.29 (52.97 - 68.63)	0.825	0.695 - 0.980		0.906	0.754 - 1.089	
Sexual contact - unknown	76/1,366	55.65 (44.45 - 69.68)	0.772	0.601 - 0.993		0.791	0.614 - 1.019	
Others/unknown	457/5,865	77.92 (71.09 - 85.40)	1.065	0.922 - 1.231		1.064	0.915 - 1.238	
Year of ART initiation								
≤2000	83/1,535	54.08 (43.61 - 67.06)	Reference		<0.0001	Reference		<0.0001
2001 - 2005	255/4,298	59.34 (52.48 - 67.09)	1.280	0.992 - 1.651		1.383	1.044 - 1.831	
2006 - 2010	379/5,407	70.09 (63.38 - 77.52)	1.594	1.244 - 2.043		1.636	1.232 - 2.174	
2011 - 2016	353/4,035	87.49 (78.82 - 97.11)	2.076	1.608 - 2.680		2.204	1.628 - 2.985	
Age at ART initation								
≤30	286/3,163	90.42 (80.52 - 101.53)	Reference		<0.0001	Reference		<0.0001
31 - 40	365/5,411	67.46 (60.88 - 74.74)	0.732	0.626 - 0.855		0.724	0.618 - 0.847	
41 - 50	255/4,283	59.55 (52.67 - 67.32)	0.646	0.545 - 0.765		0.631	0.530 - 0.751	
>50	164/2,417	67.84 (58.21 - 79.06)	0.754	0.622 - 0.913		0.732	0.602 - 0.890	
CD4 counts (cells/mm^3) at ART initiation								
<100	268/4,056	66.08 (58.62 - 74.48)	Reference		0.5397	Reference		0.4055
100 - 199	188/2,692	69.85 (60.55 - 80.58)	1.048	0.870 - 1.263		1.049	0.866 - 1.270	
200 - 349	330/4,380	75.35 (67.64 - 83.93)	1.142	0.972 - 1.342		1.165	0.980 - 1.383	
≥350	157/2,324	67.56 (57.78 - 79.00)	1.020	0.837 - 1.242		1.022	0.825 - 1.267	
Unknown	127/1,823	69.67 (58.54 - 82.90)	1.025	0.830 - 1.267		1.131	0.906 - 1.412	
Viral load (copies/mL) at ART initiation								
≤10,000	180/2,870	62.72 (54.19 - 72.58)	Reference		0.0008	Reference		0.0470
10,001 - 100,000	362/4,767	75.95 (68.51 - 84.19)	1.224	1.023 - 1.464		1.172	0.976 - 1.407	
100,001 - 1,000,000	247/3,357	73.59 (64.96 - 83.36)	1.185	0.977 - 1.436		1.213	0.989 - 1.487	
≥1,000,001	52/548	94.93 (72.34 - 124.58)	1.541	1.131 - 2.099		1.545	1.126 - 2.121	
Unknown	229/3,733	61.34 (53.89 - 69.82)	0.923	0.758 - 1.125		1.048	0.842 - 1.304	
First ART regimen								
NRTI	38/637	59.69 (43.43 - 82.03)	Reference		0.1284	Reference		0.4528
NRTI + INI	110/1,393	78.96 (65.50 - 95.18)	1.540	1.055 - 2.246		0.882	0.577 - 1.350	
NRTI + PI	607/8,789	69.06 (63.78 - 74.78)	1.282	0.919 - 1.788		1.063	0.737 - 1.532	
Others	315/4,455	70.71 (63.31 - 78.96)	1.326	0.942 - 1.868		1.009	0.689 - 1.476	

HR, hazard ratio; CI, confidential interval; HIV, Human immunodeficiency virus; ART, antiretroviral therapy; NRTI, nucleoside transcriptase reverse inhibitor; INI, integrase inhibitor; PI, Protease inhibitor.

reassignment may be included, and this part may not have been identified. However, these people are thought to be a minority of the entire HIV/AIDS cohort, and it is unlikely that they will impact the overall statistics.

This study shows that the LTFU rate was the highest in the first year of enrollment. More than half of the LTFU events occurred within five years of registration. ART was associated with retention in care by reducing LTFU. Further efforts would be needed to recognize and support patients at risk for LTFU, including younger age (≤30), male sex, and with higher viral load.

https://doi.org/10.3947/ic.2022.0059

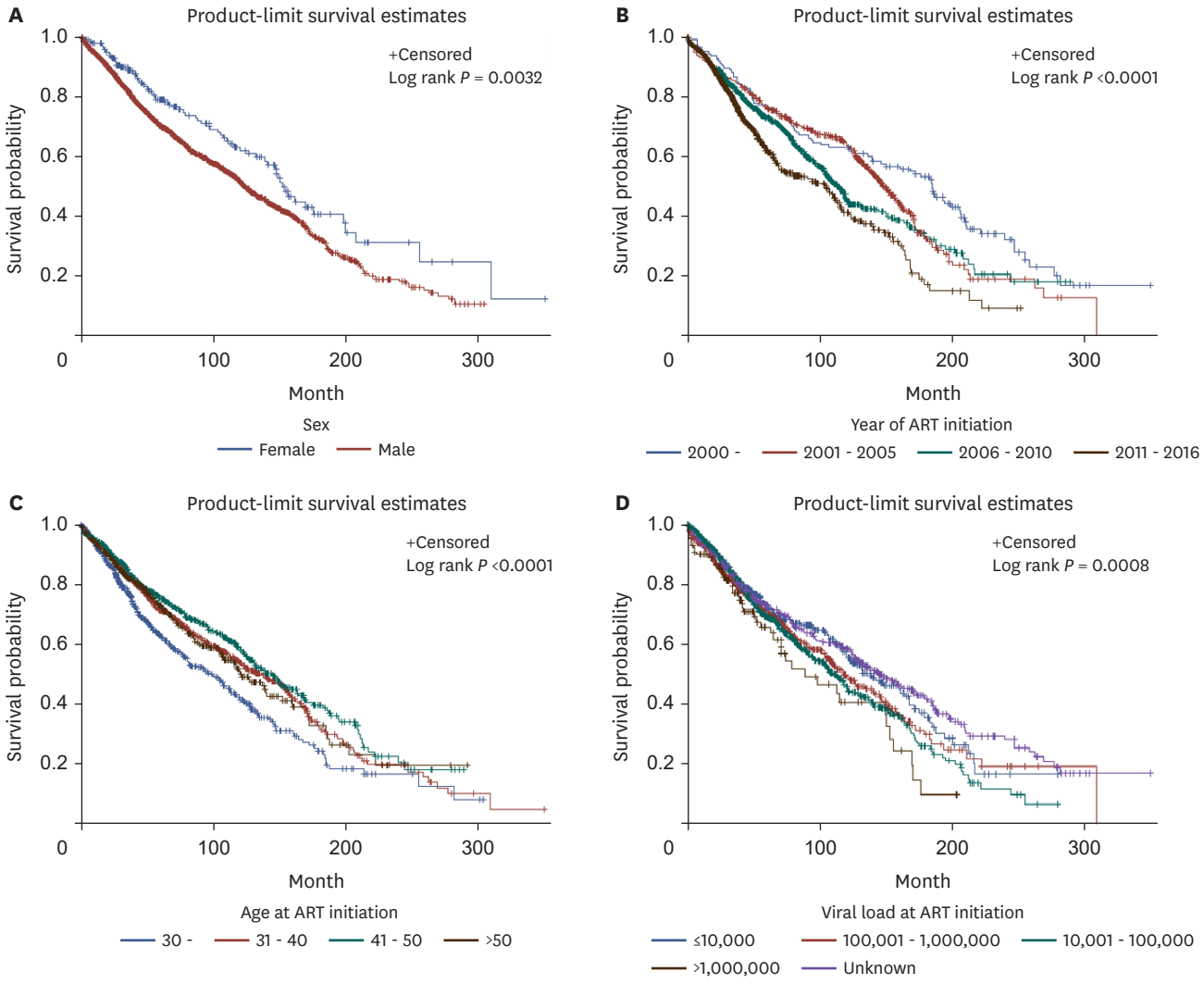


Figure 4. Kaplan-Meier curves for loss to follow-up (LTFU) stratified by risk factors in patients with antiretroviral therapy (ART). (A) LTFU rates by gender, (B) LTFU rates by the year of ART initiation, (C) LTFU rates by age at ART initiation, (D) LTFU rates by HIV viral load at ART initiation.

ORCID iDs
Hye Seong
https://orcid.org/0000-0002-5633-7214
Yunsu Choi
https://orcid.org/0000-0001-7682-7993
Minjeong Kim
https://orcid.org/0000-0003-1736-3695
Jung Ho Kim
https://orcid.org/0000-0002-5033-3482
Joon Young Song
https://orcid.org/0000-0002-0148-7194
Shin-Woo Kim
https://orcid.org/0000-0002-3755-8249
Sang Il Kim
https://orcid.org/0000-0002-2758-0012
Youn Jeong Kim
https://orcid.org/0000-0001-5870-1801
Dae Won Park
https://orcid.org/0000-0002-7653-686X
Boyoung Park
https://orcid.org/0000-0003-1902-3184
Bo Youl Choi
https://orcid.org/0000-0003-0115-5736
Jun-Yong Choi
https://orcid.org/0000-0002-2775-3315

Funding
This study was supported by the National Institute of Infectious Diseases, National Institute of Health, Korea Disease Control and Prevention Agency (#2022-ER1907-00, #2022-E1901-00, and 2019-ER5101-00) and a grant from the Ministry of Health & Welfare, Korea (HI14C1324).

Conflict of Interest
JYS is editorial board of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

https://doi.org/10.3947/ic.2022.0059

Author Contributions

Conceptualization: JYC, HS. Data curation: JHK, JYS, SWK, SIK, YJK, DWP. Formal analysis: YSC, MJK. Funding acquisition: JYC. Investigation: HS, JYC, YSC, MJK, BYC. Methodology: YSC, MJK, BYC. Project administration: JYC. Resources: BYP, BYC. Supervision: JYC, BYC. Validation: JYC, BYC, HS, MJK. Visualization: MJK. Writing - original draft: HS. Writing - review & editing: HS, YSC, MJK, JHK, JYS, SWK, SIK, YJK, DWP, BYP, BYC, JYC.

REFERENCES

1. Mberi MN, Kuonza LR, Dube NM, Nattey C, Manda S, Summers R. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004-2012: a cohort study. BMC Health Serv Res 2015;15:259.
PUBMED | CROSSREF
2. World Health Organization (WHO). HIV: fact sheet. Available at: https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Accessed 30 November 2022.
3. Korean Society for AIDS. Summary of 2021 clinical guidelines for the diagnosis and treatment of HIV/AIDS in HIV-infected Koreans. Infect Chemother 2021;53:592-616.
PUBMED | CROSSREF
4. Cho YM, Chin B. Assessment of human immunodeficiency virus care continuum in Korea using the national health insurance system data. Infect Chemother 2021;53:477-88.
PUBMED | CROSSREF
5. Choi BY, Choi JY, Han SH, Kim SI, Kee MK, Kim MJ, Kim SW, Kim SS, Kim YM, Ku NS, Lee JS, Lee JS, Choi Y, Park KS, Song JY, Woo JH, Kang MW, Kim J. Korea HIV/AIDS cohort study: study design and baseline characteristics. Epidemiol Health 2018;40:e2018023.
PUBMED | CROSSREF
6. Kim YJ, Woo JH, Kim MJ, Park DW, Song JY, Kim SW, Choi JY, Kim JM, Han SH, Lee JS, Choi BY, Lee JS, Kim SS, Kee MK, Kang MW, Kim SI. Opportunistic diseases among HIV-infected patients: a multicenter-nationwide Korean HIV/AIDS cohort study, 2006 to 2013. Korean J Intern Med 2016;31:953-60.
PUBMED | CROSSREF
7. Shepherd BE, Blevins M, Vaz LM, Moon TD, Kipp AM, José E, Ferreira FG, Vermund SH. Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: application to an HIV program in Mozambique. Am J Epidemiol 2013;178:819-28.
PUBMED | CROSSREF
8. De La Mata NL, Ly PS, Nguyen KV, Merati TP, Pham TT, Lee MP, Choi JY, Ross J, Law MG, Ng OT. Loss to follow-up trends in HIV-positive patients receiving antiretroviral treatment in Asia from 2003 to 2013. J Acquir Immune Defic Syndr 2017;74:555-62.
PUBMED | CROSSREF
9. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, Wood R, Laurent C, Sprinz E, Seyler C, Bangsberg DR, Balestre E, Sterne JA, May M, Egger M; Antiretroviral Therapy in Lower Income Countries (ART-LINC) CollaborationART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006;367:817-24.
PUBMED | CROSSREF
10. Weigel R, Hochgesang M, Brinkhof MW, Hosseinipour MC, Boxshall M, Mhango E, Nkwazi B, Tweya H, Kamlaka M, Chagwera F, Phiri S. Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi. BMC Infect Dis 2011;11:31.
PUBMED | CROSSREF
11. Orrell C, Kaplan R, Wood R, Bekker LG. Virological breakthrough: a risk factor for loss to followup in a large community-based cohort on antiretroviral therapy. AIDS Res Treat 2011;2011:469127.
PUBMED | CROSSREF
12. Greig J, O'Brien DP, Ford N, Spelman T, Sabapathy K, Shanks L. Similar mortality and reduced loss to follow-up in integrated compared with vertical programs providing antiretroviral treatment in sub-saharan Africa. J Acquir Immune Defic Syndr 2012;59:e92-8.
PUBMED | CROSSREF
13. Nakiwogga-Muwanga A, Alamo-Talisuna S, Musaazi J, Kambugu A, Ssekawungu P, Katabira E, Colebunders R. Inadequate monitoring in advanced stages of disease with lack of supportive counseling increases attrition among patients on antiretroviral treatment at a large urban clinic in Uganda. J Int Assoc Provid AIDS Care 2014;13:547-54.
PUBMED | CROSSREF
14. Van Cutsem G, Ford N, Hildebrand K, Goemaere E, Mathee S, Abrahams M, Coetzee D, Boulle A. Correcting for mortality among patients lost to follow up on antiretroviral therapy in South Africa: a cohort analysis. PLoS One 2011;6:e14684.
PUBMED | CROSSREF
15. Alvarez-Uria G, Naik PK, Pakam R, Midde M. Factors associated with attrition, mortality, and loss to follow up after antiretroviral therapy initiation: data from an HIV cohort study in India. Glob Health Action 2013;6:21682.
PUBMED | CROSSREF
16. Clouse K, Pettifor A, Maskew M, Bassett J, Van Rie A, Gay C, Behets F, Sanne I, Fox MP. Initiating antiretroviral therapy when presenting with higher CD4 cell counts results in reduced loss to follow-up in a resource-limited setting. AIDS 2013;27:645-50.
PUBMED | CROSSREF