

Kingdom of Cambodia
Nation Religion King



**Documentation on causes of death among people
living with HIV at ART Services in Cambodia**



National Center for HIV/AIDS, Dermatology and STD

May 2022

Supported by US-CDC in Cambodia

Prepared by:

1. Dr. SOMANYTHD CHHAY MENG
2. Dr. KAOEUN CHETRA

Technical Assistance:

1. Dr. CHAN SODARA
2. Dr. KHOL VOHITH
3. Dr. SAU SOKUN MEALINY
4. Dr. SAMRITH SOVANNARITH
5. Dr. NGAUV BORA

Acknowledgements

On behalf of National center for HIV/AIDS and dermatology and STD (NCHADS), we would like to express our sincere thanks to all contributors to all process of development this important documentation: Siem Reap Provincial Hospital, Battambang Provincial Hospital, Kampot Provincial Hospital, Sery Sophon Referral Hospital, Preahnorodom Sihanouk Tbuong Khmum Referral Hospital, Neak Loeung Referral Hospital, Doun Keo Provincial Hospital, Sampeov Meas Provincial Hospital, Sihanouk Provincial Hospital, Moung Russey Referral Hospital, Prey Veng Provincial Hospital, Kampong Trach Referral Hospital, Sothnikum Referral Hospital, Svay Rieng Provincial Hospital, Odormeanchey Provincial Hospital, National clinic (ex: Khmer-Soviet Friendship Hospital and ex: Social Health Clinic) colleagues at NCHADS' units including Research Unit, AIDS Care Unit, Technical Bureau, and Data Management Unit.

It is the first documentation of the courses of deaths among PLHIV on ART in Cambodia, with the main purposes to identify the leading causes by reviewing NCHADS' program data, patients records in selected 17 ART sites from January to December 2020. Good understanding the causes of deaths among PLHIV will help program managers, decision makers, and clinicians to improve the quality of care and treatment for PLHIV, and then to reduce the number of deaths.

Finally, we would also like to express our sincere thanks to US-CDC for providing technical assistance and financial supports for the documentation of this important topic – morbidity and mortality among PLHIV on ART in Cambodia.

Phnom Penh, 16 May 2022

**Director of National Center for HIV/AIDS
Dermatology and STD**



Dr. OUK VICHEA

List of Abbreviations and Acronyms

Abbreviation	Definition
ARV	Antiretroviral
ART	Antiretroviral Therapy
CD4	T-CD4+ Lymphocyte
HAART	Highly Active Antiretroviral Therapy
SOP	Standard Operational Procedure
MOH	Ministry of Health
NCHADS	National Center for HIV/AIDS Dermatology and STD
OI	Opportunistic Infection
PLHIV	People Living with HIV/AIDS
Prov RH	Provincial Referral Hospital
RH	Referral Hospital

Table of Contents

Acknowledgements	i
List of Abbreviations and Acronyms	ii
List of tables	iv
Executive Summary	1
I. Introduction	3
II. Rationale	3
III. Objective	4
IV. Methods	4
V. Results	5
Table 1: Socio-demographic characteristics of PLHIV who died in 2020	6
Table 2: Clinical characteristics of PLHIV who died in 2020	7
Table 3: Recorded causes of PLHIV who died in 2020	8
VI. Discussion	9
VII. Limitation	10
VIII. Conclusion	10
IX. References	12

List of tables

Table 1: Socio-demographic characteristics of PLHIV who died in 2020	6
Table 2: Clinical characteristics of PLHIV who died in 2020	7
Table 3: Recorded causes of PLHIV who died in 2020	8
Table 4: Top ten causes of PLHIV who died in 2020	9

Executive Summary

Introduction

Human Immunodeficiency Virus (HIV) remains a major public health problem in the world. In the recent years, AIDS-related mortality of PLHIV has been decreasing, is associated with the early diagnosis and prompt treatment initiation with highly active antiretroviral therapy (HAART) and thus the life expectancy (LE) of PLHIV has gradually increased to be similar with those who have not infected with HIV.

The monitoring of the underlying causes of death among PLHIV is important so that strategic actions to reduce morbidity and mortality can be taken on time.

Methods

Desk review was conducted in this study by using data from NCHADS' program database and patient charts at ART clinic from 01 January 2020 to 31 December 2020. 17 ART clinics were selected to review a total of 433 PLHIV who died and received ART treatment were recorded the information related to death.

Results

Of 433 deaths, more than half (57%) of PLHIV were in the age group of more than 45 years old, followed by 21.5% were in the age group of 35-44 years. Male PLHIV represented slightly more than half of the samples. Mainly, 62% of them were married, 21% were separated, 14% were single. Commonly, 37% of them were farmer, 17% were recorded as unemployed, 15.2% were workers, and 11.5% were self-employed. PLHIV (57%) were between 5 and 15 years from starting ART to dead, while 32.5% were less than 5 years and 5.5% were more than 15 years. Among of them, 24% had last CD4 > 500 cells/mm³, 23% had between 301 and 500 cells/mm³, 14% had less than or 100 cell/mm³ and 12% had from 101 to 300 cells/mm³ before death respectively.

Furthermore, half of PLHIV (50%) had less than 40 copies/ml of last viral load (VL) results, while 17% had more than 1000 and only 3% had between 40 and 999 copies/ml respectively.

Anyway, only 20% of deaths who had more than 40 copies/ml of last VL were eligible for the last assessment on ARV adherence and nearly 40% of the 433 deaths received Tuberculosis preventive treatment (TPT).

Meanwhile, 40.4% and 24% of PLHIV who died were found in groups of treatment regimens TDF+3TC+EFV, and TDF+3TC+DTG, respectively.

The results the causes of death, 92% of causes were recorded in 2020. It was found that AIDS-related infection accounted for 38.1% of all recorded, followed by 33% of non-AIDS-related non-infection, and 14.1% of AIDS-related non-infection. Only 4.6% of injury were recorded as causes of death.

The most common causes of death were classified into four groups:

- AIDS-related infections the leading cause of death are Tuberculosis, Pneumonia, Diarrhoea, and Meningitis
- Non-AIDS-related non-infections the main cause are Heart diseases, Cirrhosis, and renal failure
- AIDS-related non-infections originated cause Wasting syndromes and Cancer;
- Besides, injury originated road accident 3% is also one of the top ten leading causes.

Conclusion

The result of the study show, 57% of people living with HIV were between 5 and 15 years of starting treatment ART to the deaths of people living with HIV in care in 2020 in Cambodia.

Our results demonstrated that not only mortality of all AIDS-related infections (N = 38%), but also Non-AIDS-related non-infection (N=33%) is the second classification leading cause of death, However, AIDS-related non-infection(N=14%) and Injury (N=4.62%) were the third and fourth highest classification among PLHIV related deaths in 2020, respectively.

Furthermore, the differences in the definition of AIDS death and the accuracy of AIDS diagnosis must be taken into account. To improve the quality of classification of causes of death, miss classification of diagnosis in community, therefore, we propose to conduct in-depth study on mortality of PLHIV in community by using verbal autopsies. We adopted deep clearance of data to make key variables more accurate, so that national programs should build more capacity to health care providers at ART sites.

Moreover, to improve the quality of life as well as to reduce mortality among HIV-positive people receiving treatment and care, especially national programs should take immediate actions to improve strategies to prevent, screen, and management on AIDS-related infection, AIDS-related non-infection, Non-AIDS-related non-infection, especially TB, Pneumonia, and Non-Communicable Diseases, and strengthening referral linkages and integrated related HIV co-morbidities services such NCD, mental health, and cervical cancer screening and treatments at the ART clinics in the country.

I. Introduction

Human Immunodeficiency Virus (HIV) remains a major public health issue in the world. Since the beginning of the HIV epidemic, approximately 78 million people have been infected by HIV, and 35 million people have died because of AIDS-related diseases (1).

In the recent years AIDS-related mortality is decreasing, is associated with the early diagnosis and prompt treatment initiation with access to highly active antiretroviral therapy (HAART) and thus life expectancy of PLHIV has increased. Highlighting the importance of further efforts towards prevention, it has changed considerably HIV infection to chronic disease and other causes among PLHIV associated deaths. Therefore, life expectancy of PLHIV has live longer to be similar to those who have not been infected with HIV (2, 3).

Since the introduction of the combined antiretroviral therapy (cART), has drastically changed of HIV/AIDS epidemic. However, this goal has not yet been achieved [6,7,8]. It has been predicted that increasing to access to HAART, and longer survival time would lead to more variations in the death causes among PLHIV (4-6). AIDS-related deaths have been reduced in 2019, around 690 000 [500 000–970 000] people died from AIDS-related illnesses worldwide, compared to 1.7 million [1.2 million–2.4 million] people in 2004 and 1.1 million [830 000 – 1.6 million] people in 2010. and AIDS-related mortality has declined by 39% since 2010. In Cambodia, AIDS-related deaths (all ages) in 2015, around 2000 [1400–3100], compared to 1300 [1000–1900] people died from AIDS-related in 2019, and in 2020, there were 763 deaths of which 24 were children across the country. Then the deaths of PLHIV in Cambodia is still a public health concern (7). In a study by Takeshi the causes of death among PLHIV were determined in 165 deaths as AIDS-defining infection 15%, AIDS-defining malignancy 24%, Non-AIDS-defining malignancy 23%, Non-AIDS, non-malignancy 12%, injury (include suicide) 11%, Stroke, heart or vascular 4%, and Unknown 11% (8).

II. Rationale

Given the promising national progress in scale-up of prevention and treatment services, Cambodia has set a national goal of reaching 95% of PLHIV diagnosed, 95% of diagnosed PLHIV on treatment, and 95% of PLHIV on treatment are virally suppressed, and moving towards the elimination of new HIV infection, as well as to decrease AIDS-related mortality as a public health threats by 2025 (9).

Quality of data on causes of death among PLHIV is challenging in Cambodia. Many patient charts are blank at the cause of death of the patient at the ART clinic while some others are not readable script. The issue of missing and inaccurate data led to unqualified information. Recording and reporting causes of death of HIV-infected patients are challenging due to some factors problems to record the cause of death. Improving data recording and reporting system will lead to quality information and lead to right decisions when using information.

The previous studies have documented factors that influence mortality among HIV-infected people including HAART treatment, late diagnosis, poverty, and little or no education(10, 11). Factors related to PLHIV-associated deaths, however, have not been as extensively researched.

The monitoring of the underlying causes of death in PLHIV is important so that actions to reduce morbidity and mortality can be taken in the right ways.

III. Objective

1. To describe proportion of death by socio-demographic and clinical characteristics
2. To identify proportion of death due to AIDS-related infection
3. To identify proportion of death due to AIDS-related non-infection
4. To identify proportion of death due to non-AIDS-related infection
5. To identify proportion of death due to non-AIDS-related non-infection
6. To identify proportion of death due to injury
7. To describe top ten of causes of death

IV. Methods

4.1. Study design and setting

Desk review was conducted in this study by using data from NCHADS database and patient chart at ART clinic from 01 January 2020 to 31 December 2020. 17 ART clinics were selected for retrieving data including Siem Reap Provincial Hospital, Battambang Provincial Hospital, Kampot Provincial Hospital, Serey Sophon Referral Hospital, Preahnorodom Sihanouk Tbuong Khmum Referral Hospital, Neak Loeung Referral Hospital, Doun Keo Provincial Hospital, Sampeov Meas Provincial Hospital, Sihanouk Provincial Hospital, Moung Russey Referral Hospital, Prey Veng Provincial Hospital, Kampong Trach Referral Hospital, Sothnikum Referral Hospital, Svay Rieng Provincial Hospital, Odormeanchey Provincial Hospital, National clinic (ex: Khmer-Soviet Friendship Hospital and ex: Social Health Clinic).

4.2. Sampling and sample size

Sampling frame: list of ART clinics where the number of PLHIV deaths in year 2020 will be selected for the documentation purposes.

From preliminary review of data in NCHADS ART database, 17 ART clinics with total 433 deaths occurred during January to December 2020 in 12 provinces were included for the desk review at site.

4.3. Data analysis

Analyses were performed in Stata V14. Basic and clinical characteristic of death were included for descriptive analysis using frequency and proportion.

4.4. Data analysis Operational Definitions

- AIDS-related infection

Illnesses among HIV people that occur more frequently and are more severe because of damaged immune systems. HIV-related OIs include tuberculosis (TB), pneumonia, Salmonella infection, candidiasis, toxoplasmosis, cryptococcus, Diarrhea....(12)

- Death due to AIDS-related non-infection

Illness with extremely transmission resolving spontaneously and cause no symptoms or non-infectious complication on the incidence of disease including lung, cervical cancer and wasting syndromes (13, 14)

- Death due to non-AIDS-related infection

HIV people influence by the natural co-infection which hastening progression to end-stage of any infected disease including Chronic hepatitis B, C, peritonitis. (15)

- Death due to non-AIDS-related non-infection

Phenomenon has been accompanied by an increasing number of patients diagnosed by frequently chronic conditions that are linked with advancing age and chronic inflammation including cardiovascular disease (Stroke, hypertension, Myocardial infarction...), chronic kidney disease, type 2 diabetes mellitus, renal failure ...).(16, 17)

- Death due to injury

Unintentional injuries are the leading cause of death. The leading causes of death for unintentional injury include: Injuries result from road traffic crashes, falls, drowning, burns, poisoning, and acts of violence against oneself or others, among other causes(18)

V. Results

5.1. Socio-demographic characteristics of PLHIV who died in 2020

Of 433 deaths, more than half (57%) of PLHIV were in the age group of more than 45 years old, followed by 21.5% were in the age group of 35-44 years, 10.6% were in the age group of

25-34 years and slightly close to 8% were in the age group of 15-24 years. Only 3% were in the age group of less than 15 years. Male PLHIV represented slightly more than half of the samples. Mainly, 62% of them were married, 21% were separated, 14% were single. In the meantime, 4% were unknown of their marital status. Commonly, 37% of them were farmer, 17.0% were recorded as unemployed PLHIV, 15.2% were workers and 11.5% were self-employed. Also, 11% of them were not reported their occupation (Table 1).

Table 1: Socio-demographic characteristics of PLHIV who died in 2020

Characteristics (N=433)	Frequency	Percentage
	(n)	(%)
Age group		
<15	13	3.0
15-24	34	7.8
25-34	46	10.6
35-44	93	21.5
45+	247	57.0
Sex		
Female	181.	41.8
Male	252	58.2
Marital status		
Single	60	14.0
Married	267	62.0
Widowed/separate	90	21.0
Unknown	16	4.0
Occupation		
Farmer	160	37.0
Unemployed	72	17.0
Worker	66	15.2
Self-employed	50	11.5
Uniform group (arm-force)	22	5.0
Government Civil Servant	10	2.3
Employee	5	1.1
Unknown	46	11.0
Missing	2	0.5

5.2. Clinical characteristics of PLHIV who died in 2020 (N=433)

As shown in Table 2, PLHIV (57%) were between 5 and 15 years of starting ART to dead, while 32.5% were less than 5 years and 5.5% and 5% were more than 15 years and still HIV-related to opportunistic infections (OIs) patients respectively. Among them, 24% had last CD4 > 500 cells/mm³, 23% had between 301 and 500 cells/mm³, 14% had less than or 100 cell/mm³ and 12% had from 101 to 300 cells/mm³ before death respectively. However, 27% of PLHIV death were found as no CD4 tested with some reasons.

Furthermore, half of PLHIV (50%) had less than 40 copies/ml of last viral load (VL), while 17.0% had more than 1000 and only 3.0% had between 40 and 999 copies/ml respectively. However, 30% of PLWHIV who died were found as no VL last tested for some reason.

Anyway, only 20% of deaths who had more than 40 copies/ml of last VL were eligible for the last assessment on ARV adherence. The results of the ARV adherence assessment showed that 77% of them had poor adherence, while 20% were good and only 3% had moderate adherence.

Nearly 40% of the 433 deaths received Tuberculosis preventive treatment (TPT). In that figure, 77% of patients received TPT completion, 19% of them had no completed for some reason and only 4% died before TPT completion.

Meanwhile, 40.4% and 24% of PLHIV who died were found in groups of treatment regimens TDF+3TC+EFV and TDF+3TC+DTG, respectively.

Table 2: Clinical characteristics of PLHIV who died in 2020

Characteristics (N=433)	Frequency	Percentage
	(n)	(%)
Year starting ART to dead		
<5	141(Man=87)	32.5
5-15	245(Man=133)	57.0
>15	24(Man=16)	5.5
OIs	23	5.0
Last CD4 before dead		
≤100	62	14.0
101-300	52	12.0
301-500	101	23.0
>500	102	24.0
No CD4 Tested	116	27.0
Last viral load value		
<40	215	50.0
40-999	13	3.0
1000+	74	17.0
No Viral load tested	131	30.0
Eligible for Assessment on ARV adherence (n=87)		
Yes	35	40.0
No	52	60.0
Last assessment on ARV adherence (n=35)		
Good adherence	7	20.0
Moderate adherence	1	3.0
Poor adherence	27	77.0
Received TPT		
No	262	60.5
Yes	171	39.5
TPT Status (n=171)		
Yes, Completed	131	77.0

Yes, Not Completed	32	19.0
died before completion	8	4.0
Treatment regimen		
TDF+3TC+EFV	175	40.4
TDF+3TC+DTG	104	24.0
AZT+3TC+NVP	35	8.0
TDF+3TC+ATV/r	34	8.0
AZT+3TC+EFV	20	5.0
ABC+3TC+ATV/r	9	2.0
TDF+3TC+NVP	9	2.0
ABC+3TC+DTG	6	1.4
AZT+3TC+ATV/r	6	1.4
ABC+3TC+LPV/r	4	1.0
ABC+3TC+EFV	3	0.7
TDF+3TC+LPV/r	3	0.7
AZT+3TC+LPV/r	1	0.2
OI	23	5.0
Missing	1	0.2

5.3. List recorded causes of PLHIV who died in 2020

Table 3 presented recorded causes of death among PLHIV. 92% of causes were recorded in 2020. It was found that AIDS-related infection accounted for 38.1% of all recorded causes of death, followed by 33% of non-AIDS-related non-infection and 14.1% of AIDS-related non-infection. Only 4.6% of injury were recorded as causes of death.

Table 3: Recorded causes of PLHIV who died in 2020

Recorded causes of death (N=433)	Frequency	Percentage
	(n)	(%)
Yes	398	92.0
No	35	8.0
Recorded causes		
AIDS-related infection	165	38.1
AIDS-related non-infection	61	14.1
Non-AIDS-related infection	9	2.1
Non-AIDS-related non-infection	143	33.0
Injury	20	4.6
Unknown	35	8.1

5.4. List top ten causes of PLHIV who died in 2020

In this review, the most frequent causes of death were classified into four groups: **AIDS-related infections the leading cause of death are Tuberculosis, Pneumonia, Diarrhoea, and Meningitis, Non-AIDS-related non-infections Heart diseases, Cirrhosis, renal failure. AIDS-related non-infections are Wasting syndromes and Cancer, Besides, injury** originated road accident, is also one of top ten leading causes. Their distribution of top ten causes of death is shown in Table 4.

Table 4: Top ten causes of PLHIV who died in 2020

No.	Cause of death (n=433)	Frequency	Percentage
		(n)	(%)
1	TB	53	12.2
2	Pneumonia	52	12.0
3	Heart diseases	49	11.3
4	Cancer (cervical cancer 3%)	45	10.4
5	Wasting syndromes	37	8.5
6	Diarrhea	30	6.9
7	Cirrhosis	25	5.7
8	Meningitis (cryptococcus...)	21	4.8
9	Road accident	13	3.0
10	Renal diseases	12	2.8

VI. Discussion

Although cART significantly improved the life expectancy of PLHIV, the results of this study demonstrated that 57% of deaths were between 5 and 15 years from starting treatment ART to death of PLHIV, Occurred during the period of analysis in 2020. Most PLHIV who died were not only cause by all AIDS-related infections (n = 38%), was a significant classification of deaths, such as tuberculosis, pneumonia, diarrhea, and meningitis were the leading causes of death, but also non-AIDS-related non-infection (N=33%) is the second classification leading cause of death originating from heart diseases, Cirrhosis, renal failure and AIDS-related non-infection(N=14%) is the third classification of death originating from Wasting syndromes, and cancer, Most cancers, in 3% of cases, are cervical cancer, and injury (N=4.62%) were the fourth highest classification among PLHIV related deaths in 2020. like studied mortality among Swiss HIV patients. This is consistent with other studies, as well(4, 6, 19).

Even though AIDS-defining diseases are the leading cause of death in PLHIV. The leading causes of death of PLHIV were suicide, and accidents accounting for 4.6%. This rate was lower than that reported in many cohorts, such as 32.7% in a population-based cohort study in Spain(20).

The overall finding concurs with what is known about the late cause of death of PLHIV. Thus, this usually leads to an impact on the HIV care and inaccuracy in the database.

VII. Limitation

The empirical results reported here should be considered in light of some limitations. The first is incomplete medical documents, especially CD4, Viral load, TPT, accesses to ART adherence, the second is blank in the cause of death document, and the third is the burden of health care providers, so there is no time to concentrate. Therefore, the collection and recording of the data were not timely and accurate as well.

These major limitations in this study could be addressed in future studies, for instance First, the study focused on identifying the cause of death by using the standard verbal autopsies method.

VIII. Conclusion

AIDS-related infection is the leading cause of death originating from Tuberculosis and Pneumonia, diarrhea, and meningitis, Non-AIDS-related non-infection is the second causes of death originating from heart disease, and AIDS-related non-infection is the third classification originating from Wasting syndromes and cancer and injury (N=4.62%) originated road accident 3% and suicide were the fourth highest classification among PLHIV related deaths in 2020. It seems that after receiving antiretroviral therapy, no effective measure has been put in place to control Non-AIDS-related Non-infection to PLHIV in Cambodia. Numerous epidemiological studies have shown that young people living with HIV are more likely to be under pressure from their parents, friends and society and to have a reaction rate of (21, 22). Further research on suicide, accidents in PLHIV are necessary to identify specific risk factors.

Further, the differences in the definition of AIDS death and the accuracy of AIDS diagnosis must be taken into consideration. To improve the quality of classification of causes of death, Miss classification of diagnosis in the community, Therefore, we could be addressed in the future deep study focused on identifying the cause of death by using standard verbal autopsies method. We adopted a deep clearance of data to make key variables more accurate, so that the national programs should build capacity for health care providers.

Applying effective strategies is needed to achieve an on-time diagnosis of individuals with HIV and provide them with care, prevention, and treatment of HIV to increase patient survival. Thus, a better understanding of patterns and diagnoses for specific causes of death in the ART era may help to develop appropriate care for PLHIV and inform guidelines for risk management.

In line with the available evidence, the findings of the current research revealed that HIV care and treatment could substantially reduce AIDS-related infection and non-AIDS-related non-infection among PLHIV.

Therefore, to reduce mortality rate among PLHIV, in particular, the national programs should lake an immediate action to improve the strategies to ensure early HIV diagnosis, timely ART, good treatment adherence and long-life retention in care with viral load suppression.

In addition, efforts to screening for prevention and treatment, especially, on TB, Non-Communicable Diseases, should be considered a public health priority, and improve on AIDS-related infection, non-AIDS-related non-infection that related the PLHIV death in Cambodia. and strengthening referral linkages and integrated related HIV co-morbidities services such NCD, mental health, and cervical cancer screening and treatments at the ART clinics in the country.

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