

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

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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.

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**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
PRH	Provincial Referral Hospital
RH	Referral Hospital

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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. Seven-teen ART clinics were selected to review a total of 433 records of PLHIV who were reported dead during indicated period.

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 represented slightly more than female.. 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. More than half (57%) of deaths 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 CD4 between 301 and 500 cells/mm³, 14% had less than or 100 cell/mm³ and 12% had from 101 to 300 cells/mm³ respectively.

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

Only 20% of deaths who had more than 40 copies/ml of last VL received enhanced adherence counseling and assessment on ARV adherence. For TB preventive therapy, nearly 40% of them had completed/received the course

Meanwhile, more than 40% and only 24% of PLHIV who died were found in groups of treatment regimens TDF+3TC+EFV, and TDF+3TC+DTG, respectively.

Ninety-two percent of deaths had cause recorded in 2020. It was found that AIDS-related infection accounted for almost 39% of all recorded causes, followed by 33% of non-AIDS-related non-infection, more than 14% of AIDS-related non-infection, about 5% of injury, 1.4% associated with non-AIDS infections, and 8.1% were not recorded cause of death.

Conclusion

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

About 39% of death associated with AIDS-related infections, Dead due to non-AIDS-related non-infection was 33%, AIDS-related non-infection was 14% and Injury (was about 5%.

TB and pneumonia were the leading causes of death among deaths associated with AIDS-related infections that were accounted for almost 55%.

Clinical screening for TB, and provision of TPT to all PLHIV were highly recommended. Introducing health care services for non-communicable diseases at the ART clinics is recommended too.

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, this 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).

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. AIDS-related mortality has declined by 39% since 2010. In Cambodia, AIDS-related deaths (all ages) in 2015 were 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 one of the three zeros – to reduce AIDS-related death rate to 13.2 per 100,000. (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 the causes of death of HIV-infected patients are challenging due to some unidentified problems. Improving the data recording and reporting systems would lead to quality information and lead to the right decisions when using information.

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 preliminary data from NCHADS database and patient chart at ART clinic from 01 January 2020 to 31 December 2020. Seven-teen 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, Moug 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 were selected for the documentation purposes.

From preliminary review of data in NCHADS ART database, there were 739 adult patients and 24 children died at 69 ART clinics in 25 provinces in 2020 in Cambodia. We selected 17 ART clinics where there were 15 deaths or more during January to December 2020 for the study. The total sample size was 433, death among adult was 419 equals to 57% of total adult dead in 2020, and 14 children which was equal to 58% of total children dead in 2020. The 17 ART clinics selected locate in 12 provinces in Cambodia.

4.3 Data analysis

Analyses were performed in Stata V14. General information 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 infections included in our analyzes were tuberculosis (TB), pneumonia, pneumocystis pneumonia, Salmonella infection, candidiasis, toxoplasmosis, cryptococcus, and diarrhea

- Death due to AIDS-related non-infection

AIDS-related non-infection included in our analyzes are anemia, lung cancer, cervical cancer, mental health, and wasting syndromes.

- Death due to non-AIDS-related infection

Non-AIDS-related infections included in our analyzes were digestive infections, malaria, hepatitis, peritonitis, and urinary tract infection.

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

Non-AIDS non-infection included in our analyzes are heart disease, cancer, cirrhosis, hypertension, hemorrhage, diabetes, and other which include other 13 health conditions such as adenoma prostatic, birth-defect, gallstone, osteoporosis, thalassemia, nephrotic syndrome chronic, etc.

- Death due to injury

Unintentional or intentional injuries are one of the leading causes of death. Death due to injury included in our analyzes were: road traffic accident, electroshock, drowning, food poisoning, and suicide.

V. Results

5.1 Socio-demographic characteristics of PLHIV who died in 2020

Of 433, more than half (57%) of deaths 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. Death among male 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, 17.0% were recorded as unemployed, 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	Frequency (N=433)	Percentage (%)
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

As shown in Table 2, 57% of deaths were between 5 and 15 years after starting ART, while 32.5% were less than 5 years and 5.5% were more than 15 years. On the other hand, 5% of deaths did not start ART yet.

Regarding CD4 status, 24% of deaths 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 deaths had no CD4 counts recorded in their chart.

Furthermore, half of deaths (50%) had last viral load (VL) less than 40 copies/ml, while 17.0% had more than 1000 and only 3.0% had between 40 and 999 copies/ml respectively. However, 30% of deaths had no viral load results recorded in the chart.

About 20% of deaths who had viral load more than 39 copies/ml had 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.

Regarding treatment regimens, 40.4% and 24% of deaths were on TDF+3TC+EFV and TDF+3TC+DTG, respectively.

Table 2: Treatment history and clinical status of deaths

Characteristics	Frequency(N=433)	Percentage (%)
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 Recorded causes of death among PLHIV in 2020

Table 3 presents recorded causes of death in 2020 among PLHIV. Ninety-two percent of deaths had causes recorded. The most frequent causes of death were grouped in five groups. First was **AIDS-related infections**, second, **non-AIDS-related non-infection**, third, **AIDS-related non-infection**, fourth was non-AIDS related infection, and fifth was **injury**. 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 4.7% of deaths were due to injury.

Table 3: Classification of cause of death

Recorded causes of death	Frequency (N=433)	Percentage (%)
Yes	398	92.0
No	35	8.0
Grouped Recorded causes of death		
AIDS-related infection	168	38.1
Non-AIDS-related non-infection	143	33.0
AIDS-related non-infection	61	14.1
Non-AIDS-related infection	6	2.1
Injury	20	4.7
Not recorded	35	8.0
Total	433	100

Among causes of death associated with AIDS-related infections, the leading causes reported were tuberculosis, pneumonia, chronic diarrhoea, meningitis (without identified germ), cryptococcus meningitis, acute diarrhoeas, pneumocystis pneumonia (PCP), and candidiasis.

Table 4: Cause of deaths AIDS-related Infections

No.	Infection	Number	Percent
1	Tuberculosis	53	31.6
2	Pneumonia	39	23.2
3	Chronic diarrhea	21	12.5
4	Meningitis	11	6.6
5	Cryptococcus meningitis	10	6.0
6	Acute diarrhea	9	5.4
7	Pneumocystis pneumonia	9	5.4
8	Candidiasis	5	3.0
9	Septicemia	3	1.8
10	Acidosis	2	1.2
11	Hepatis B	2	1.2
12	Abscess of lung	1	0.6
13	Hepatis A	1	0.6
14	Pleurisies	1	0.6
15	Toxoplasmosis cerebral	1	0.6
	Total	168	100

Among non-AIDS related non-infections, heart disease, cancer, cirrhosis, and hypertention were the most common cause of death among people living with HIV.

Table 5: Cause of death non-AIDS related non-infections

No.	Non-AIDS related non-infection	Number	Percent
1	Heart disease	33	23.1
2	Cancer	28	19.6
3	Cirrhosis	25	17.5
4	Hypertention	16	11.2
5	Hemorrhage	11	7.7
6	Renal failure	10	7.0
7	Diabetes	7	4.9
8	Other	13	9.1
	Total	143	100

Of the 61 deaths classified as AIDS-related non-infection, almost 61% were due to Wasting syndromes and 21% were recorded as cervical cancer respectively.

Table 6: Cause of deaths AIDS-related non-infection

No.	AIDS related non-infection	Number	Percent
1	Wasting syndrome	37	60.7
2	Cervical cancer	13	21.3
3	Lung cancer	4	6.6
4	Mental health disorder	4	6.6
5	Anemia	3	4.9
	Total	61	100

There were only six cases of non-AIDS-related infection causes that were reported, and of these 50% were digestive tract infections.

Table 7: Cause of deaths non-AIDS related infections

No.	Non-AIDS related infection	Number	Percent
1	Digestive tract infection	3	50.0
2	Malaria	1	16.7
3	Peritonitis	1	16.7
4	Urinary tract infection	1	16.7
	Total	6	100

Regarding 20 cases of injury, 70% were road traffic accident and 15% were suicide.

Table 8: Cause of deaths due to Injury

No.	Injury	Number	Percent
1.	Road traffic accident	14	70.0
2.	Suicide	3	15.0
3.	Drowning	1	5.0
4.	Electric shock	1	5.0
5.	Food poisoning	1	5.0
	Total	20	100

5.4 List top ten causes of death among PLHIV in 2020

As mentioned early, of 433 deaths, 398 had cause recorded. The list of all reported causes of death was shown in Table 9.

Table 9: List all reported cause of death among PLHIV in 2020

No.	Cause of death	Number	Percent
1	Tuberculosis	53	13.31
2	Pneumonia (without identified causal microorganism)	49	12.31
3	Wasting syndrome	37	9.30
4	Heart disease	33	8.30
5	Diarrhea (Acute or Chronic)	30	7.53
6	Various cancer but not cervical cancer	28	7.03
7	Cirrhosis	25	6.30
8	Meningitis	21	5.30
9	Hypertension	16	4.02
10	Road traffic accident	14	3.52
11	Cervical cancer	13	3.26
12	Hemorrhage	11	2.76
13	Renal failure	10	2.51
14	Other AIDS-related infections	7	1.75
15	Diabetes	7	1.75
16	Other injuries	6	1.50
17	Other non-AIDS related infection	6	1.50
18	Candidiasis	5	1.25
19	Lung cancer	4	1.00
20	Mental health	4	1.00
21	Other lung infections not TB	3	0.75
22	Anemia	3	0.75
23	Other Non-AIDS related non-infection	13	3.30
	Total	398	100.0

Referring to the above list, the most common top ten causes of death were tuberculosis, pneumonia, wasting syndrome, heart disease, diarrhoea, cancer, cirrhosis, meningitis, hypertension, and road traffic accident that all combined were accounted for 79.5% of all deaths among PLHIV in 2020. Cervical cancer that was accounted for 3.4% of all deaths was ranked number eleventh besides the top ten above.

Table 10: Reported Top ten causes of death among PLHIV in 2020

No.	Cause of death	Number	Percent
1	Tuberculosis	53	13.31
2	Pneumonia (without identified causal microorganism)	49	12.31
3	Wasting syndrome	37	9.30
4	Heart disease	33	8.30
5	Diarrhea (Acute or Chronic)	30	7.53
6	Various cancer but not cervical cancer	28	7.03
7	Cirrhosis	25	6.30
8	Meningitis	21	5.30
9	Hypertension	16	4.02
10	Road traffic accident	14	3.52
11	Cervical cancer	13	3.26

VI. Discussion

Although ART significantly improved the quality of life of PLHIV, the results of this study demonstrated that 57% of deaths were between 5 and 15 years from starting antiretroviral treatment. More than (38%) PLHIV died by AIDS-related infections in which tuberculosis, pneumonia, diarrhoea, and meningitis were the leading causes.

According to the 2019 Global HIV Programme report, Tuberculosis (TB) remains the leading cause of death among people living with HIV (PLHIV). In 2019, TB accounted for an estimated 30% of the 690 000 AIDS-related deaths in the world(10).

Pneumonia is still one of the most common opportunistic infections in HIV patients, The occurrence of pneumonia increased rapidly, resulting in death rate up to 40%(11).

Cryptococcal meningitis is a serious opportunistic infection and a major cause of morbidity and mortality among PLHIV with advanced disease. It is responsible for an estimated 15% of all HIV-related deaths globally(12).

VII. Limitation

There were several limitations for our study. First, samples were selected from 17 ART clinics where there were 15 or more patients died. It was accounted for 57% of the population of 739 in which non-recorded cause of death (blank) was 44%. Although we found only 8% of our samples did not have cause of death recorded, this might be underestimated. Simplify recording and reporting tool to ease the recording will reduce the missing value and increase the quality of data.

Second, the accuracy of the dead diagnosis since the cause of death recorded in patient's chart some time different from cause of death recorded in database at site, or even it was not readable. This may lead to misclassification of cause of death whether AIDS-related or non-AIDS-related infection or non-infection. Further study using community verbal autopsies is recommended. Furthermore, as recommended above to simplify recording and reporting tools meaning there should be selecting box on patient's chart and in database to ease healthcare providers to record the cause of death.

Third, there may be underreported of cause of death due to TB since some diagnoses were not specified the causal microorganism such as pneumonia, meningitis, and pleurisy. The same way may happen for cryptococcus meningitis.

VIII. Conclusions and Recommendations

AIDS-related infections were accounted for more than 38% of all causes of death among PLHIV in Cambodia following by non-AIDS-related non-infections that were accounted for 33%. The most common AIDS-related infection was TB and pneumonia, while the most common non-AIDS-related non-infection was heart diseases and cancer.

For AIDS-related non-infections, wasting syndrome and cervical cancer were the most common causes of death reported, while road traffic accident was accounted for 70% of all deaths due to injury.

There were only several deaths – 2.1%, that were reported due to non-AIDS related infections.

Among all causes of death, the top ten were tuberculosis, pneumonia, wasting syndrome, health disease, diarrhea, cancer, cirrhosis, meningitis, hypertension, and road traffic accident.

Recommendations: The National Center for HIV/AIDS, Dermatology and STI program should:

- Strengthen TB screening and provision of TPT to all PLHIV at all ART clinics in the country.
- Simplify recording and reporting tool both in patient's chart and database by having pre-designated box to ease the recording and reporting cause of death at site level.
- Conduct a further study using community verbal autopsy to triangulate findings of this study.
- Consider introducing non-communicable disease (chronic diseases) services at all ART clinics, or at least at clinics with high volume of PLHIV.

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