

Prevalence and Factors Associated with Non-AIDS Mortality in HIV-1 Patients Under cART followed-Up At Cta – CHNU FANN in Dakar.

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Abstract

Introduction: The antiretroviral combination therapy (cART) has reduced the risk of HIV transmission and AIDS mortality. However, despite this therapeutic success, mortality observed in patients infected with HIV is higher than that observed in general population. This reflects a growing proportion of deaths resulting from non-AIDS diseases. The knowledge of causes and factors associated with these deaths would help to optimize the quality of care for PLHIV. This is the reason why we focused this study on "Prevalence and factors associated with non-AIDS mortality in HIV-1 patients under cART followed-up at CTA-CHNU in Dakar Fann".

Methodology: This is a descriptive and analytical cross-sectional study based on the medical records of HIV-1 patients under cART followed-up at the CTA of CHNU Fann in Dakar. It was conducted from January 2009 to December 2014. It included patients aged between 18 and 65, infected with HIV-1, under first-line treatment and having been of follow-up for at least twelve months in the center, with CD4 > 200 cells / mm³ and undetectable viral load.

Result : During the period, 758 patients were eligible for this study. The average age was 44 with an IQR [24-65], a male predominance (65%), i.e. a sex ratio of 1.9. The population was urban in majority (93%). Half (53%) of patients had an income generating activity and (49%) were living with a partner. The extremes of CD4 / CD8 ratio ranged between 0.18 and 2.22 with an average of 0.74. Of all the patients, (8.58%) presented a health history and 22 (2.90%) patients died. The risk of death was related to the age at 44 years ($P=0,000$), smoking ($P=0,001$), high LDL cholesterol value ($P=0,017$) and CD4 / CD8 < 0.74 ($P=0,005$).

Conclusion: Antiretroviral treatment has significantly improved the quality of life of PLHIV. However factors such as old age, smoking, hypercholesterolemia and a low CD4 / CD8 ratio are strongly associated with non-AIDS mortality in well-controlled patients. Communication programs for effective prevention should be set up to accompany the care of PLHIV.

Keywords: non-AIDS mortality, prevalence, associated factors, first-line cART, CTA, Dakar.

I. Introduction

The majority of people infected with HIV live in sub-Saharan Africa [1]. In these countries, AIDS-related morbidity and mortality remain the highest in the world due to limited access to diagnosis and treatment of HIV [1]. In recent years, efforts have been made to expand access to antiretroviral combinations (cART) in several low-income countries. Since 2010, an increase of 84% regarding access to antiretroviral therapy has been noted [2]. AIDS-related deaths have decreased by 35% since the peak observed in 2005 [1]. Moreover, nearly 90% of people aware of their HIV status have been placed under treatment [2]. Antiretroviral therapy has reduced the risk of HIV transmission and AIDS-related mortality, hence improving their survival [3, 4, 5, 6, 7, 8]. However, despite success to the combination of antiretroviral therapy, mortality in HIV patients is higher than what is observed among the general population. This reflects an increasing proportion of deaths caused by non-AIDS diseases. The causes and factors associated with these deaths are variable, depending on several factors [4, 5, 9,10, 11, 12]. Various factors are associated with the occurrence of non-AIDS deaths in these patients. These are: age; anemia; thinness; malnutrition; cardiovascular events; metabolic syndrome; lifestyle including alcohol, tobacco, intravenous drug use [5, 9, 13, 14, 15]. Similarly, low CD4 / CD8 ratio during effective antiretroviral therapy is associated with a high risk of morbidity and mortality [16, 17, 18,19].

We conducted this study on "Prevalence and factors associated with non-AIDS mortality in HIV patients under cARV followed at the CTA of Fann CHNU ", to know the factors associated with mortality in order improve the quality of care in HIV patients.

II. Method

This is a descriptive and analytical cross-sectional study from the records of HIV-1 positive patients under antiretroviral treatment, followed-up as outpatients at CTA CHNU Fann in Dakar. It was conducted over 6 years, from January 2009 to December 2014.

CTA is an affiliated health facility to the Ibrahima Mar Diop Clinic of Infectious and Tropical Diseases based at Fann National University Hospital (CHNU Fann) in Dakar. It is a national reference center dedicated to the ambulatory monitoring of PLHIV.

Patients aged between 18 and 65, followed as outpatients at the ambulatory treatment center, infected with HIV-1, placed under first-line treatment for at least a year, with a CD4 count > 200 / mm³, with available TCD4 / TCD8 report and an undetectable viral load were included in this study.

HIV-2 patients, loss to follow-up and those having received a non-standard first-line treatment including the combination of three nucleoside reverse transcriptase were excluded from our study.

We retrospectively analyzed the data entered into "ESOPE" database, which was exported to Excel and completed, for some missing variables from file sources (A2, Bone, register ART). We carefully reviewed the medical records to determine the presence or absence of non-AIDS events. The data were transferred to the Stata software 12.1 College Station, Texas 77845 (USA) for analysis. We evaluated the quantitative variables: (age, body mass index, WHO clinical stage, CD4 +, CD8 + and CD4 / CD8 ratio, viral load, creatinine clearance in mg / l calculated with the Cockcroft & Gault formula ($[(140 - \text{age}) \times \text{weight} \times k / 7.2 \times [\text{Cr}] = 1$ with male and female = 0.85) with glucose as value between 65-110 mg / dl, high-density lipoprotein (HDL: 40 - 70 mg / dl), low density lipoprotein (LDL <150 mg / dl), total cholesterol (96-270 mg / dl), and enzymatic triglyceride methods (40-165 mg / dl), duration between start of treatment and occurrence of event) and qualitative variables : (sex, marital status, obesity, diabetes, HBsAg, Alcohol, tobacco, event, death).

The variable of interest (event 'yes versus no') was estimated in proportions. Variables related to the event, with a p-value less than 0.25 in the bivariate analysis were included in a multivariate model. Any variable associated to death with a p-value <0.05 were retained in the final model.

III. Ethical Aspect

The study was performed on anonymous files. The identity and address of patients will remain confidential and will not be subject to any publication.

IV. Results

4.1. descriptive study

4.1.1. socio-demographic characteristics:

As a whole, 758 patients were included in this study. The average age of patients was 44 years with [IQR = 24-65]. Male predominance is noted with 496 (65%) representing a sex ratio of 1.9. Patients in union were more representative with a proportion of (49%). The urban population was the mostly represented with (93%). Half (53%) of patients had an income generating activity.

4.1.2. Comorbidities and risk factors:

Comorbidities such as alcohol (0.53%), diabetes (2%), tobacco (3%), obesity (10%) were found. Risk factors such as hyperglycemia (2%), hypertriglyceridemia (10%), hyper-LDL cholesterol (15%), hypo HDL cholesterol 50mg / dl (IQR 24-639), total cholesterol 183mg / dl (IQR 91- 386) and creatinine clearance 90mg / l (IQR 38-257) were also observed.

4.1.3. Clinical and immunological characteristics:

Stage 4 patients were (33%). Patients with a lower BMI (69%). The average CD4 count is 550 [223-1898] cells / mm³, the average CD8 826 [274-2000] cells / mm³ and the average CD4 / CD8 0.74 [0.18 to 2.22].

4.1.4. Progression aspects.

Of the 758 patients included, 66 (8.58%) had a health event and 22 patients died, this represents a sub treatment lethality of (2.90%).

4.2. Analytical study.

4.2. 1. Analysis bivariate.

The bivariate analysis was used to determine factors associated with the occurrence of an event (lethality) Non-AIDS.

The average time of occurrence of an event is 4 years followed by a minimum of 3 years and a maximum of 7 years.

Male sex, age from 44 years old and marital status, was not associated with lethality.

This lethality was significant in smoking patients (P=0,000); in skinny patients (P=0.02); in patients with hyperglycemia (P=0.01).

The lethality is about 3 times lower in patients with a CD4 / CD8 ratio (OR = 0.72) (P=0.005).

4.2.2 multivariate analysis.

The risk of death was multiplied by 3.66 times in patients from 44 years old (P=0,000); 10.58 times higher in smoking patients (P=0,001) ; 3.98 times in patients with high LDL cholesterol value (P=0,017); 2.43 times in patients with a T4 / T8 category <0.74 with a statistically significant difference (P=0,005). Advanced age, smoking, high cholesterol and a low CD4 / CD8 ratio are factors associated with risk of death.

Table N°1: General characteristics of the population in study (N=758).

| Variable (n = 758) | Total |
|--------------------------------------|--------------------|
| Socio -demographic Variables | |
| Age (years)* | 44 (24 -65) |
| Male [n (%)] | 496 (65,44) |
| Urban [n (%)] | 706 (93,14) |
| Married [n (%)] | 373 (49,21) |
| Income driving activity [n (%)] | 399 (52,64) |
| Co-morbiditiesand risk factors | |
| Diabetes (%) | 1,72 |
| Alcohol (%) | 0,53 |
| Smoking (%) | 2,64 |
| AgHbs + (%) | 0,79 |
| BMI (kg/m ²) [n (%)] | |
| 18.5 | 524 (69,22) |
| 25 | 155 (20,48) |
| 30 | 78 (10,30) |
| Stage 4 AIDS (%) | 33 |
| Creatinine clearance** | 90 (38- 257) |
| Hyperglycemia (%) | 1,98 |
| Hypertriglyceridemia (%) | 9,88 |
| Hyper LDL cholesterol (%) | 15,15, |
| Hypo HDL cholesterol ** | 50 (24 - 639) |
| Total cholesterol** | 183 (91 -386) |
| immunovirological variables | |
| Viral load <50 copies / mL [n (%)] | 758 (100) |
| CD4 (cells / mm3) ** | 550 (223 – 1898) |
| CD8 (cell / mm3) ** | 826 (274 – 2000) |
| Ratio CD4 / CD8 ** | 0,74 (0,18 – 2,22) |
| Evolution | |
| ART duration and occurrence of event | |
| Event [n (%)] | 66 (8,58) |
| Death [n (%)] | 22 (2,90) |

*Variable expressed in average (standard deviation);

** Variables expressed in median (interquartile range)

Table 2: Factors associated with the event (N = 758).

| Variables | OR | Bivariate Analysis [IC _{95%}] | P-value |
|--------------------|------|---|--------------|
| Male | 2.23 | [0.99 – 5.47] | 0.052 |
| Age > 44 years | 6.54 | [1.42 – 30.05] | 0.01 |
| Married | 2.18 | [0.71 – 6.68] | 0.16 |
| Alcohol | 0.05 | [0.002 – 0.14] | 0.000 |
| Smoking | 10 | [3.03 – 32.91] | 0.000 |
| BMI Categories | | | |
| Thinness | 3.31 | [1.18 – 9.29] | 0.02 |
| Overweight | 0.65 | [0.23 – 1.78] | 0.40 |
| Obesity | 0.40 | [0.05 – 3.02] | 0.37 |
| TCD4/TCD8 category | 0.72 | [0.21 – 1.22] | 0.005 |
| Hyperglycemia | 5.60 | [1.51 – 20.72] | 0.01 |

Table 3: Factors associated with death (multivariate) (N = 585).

| Variables | Deaths | Adjusted OR | IC95% | P |
|-----------|--------|-------------|--------------|----------------|
| Age > 44 | Yes | 3.66 | [2.05–6.54] | P=0,000 |
| | No | 1 | | |
| Tobacco | Yes | 10.58 | [2.64–42.44] | P=0,001 |

| | | | | |
|--------------------|--------|------|---------------|----------------|
| | No | 1 | | |
| Hyper LDL | Yes | 3.98 | [1.27- 12.46] | P=0.017 |
| | No | 1 | | |
| TCD4/TCD8 category | < 0.74 | 2.43 | [1.31- 4.48] | P=0.005 |
| | ≥ 0.74 | 1 | | |

IV. Discussion

During the study period, 758 patients were eligible for this study.

The modifiable cardiovascular risk helped to identify the following factors:

Alcohol (0.53%), diabetes (1.72%), tobacco (2.64%), obesity (10.30%) and HDL cholesterol which values vary between 24g / L and 639g / L with an average of 50 g / L.Sabin CA, 2013, United States [20] and Duprez et al, 2009 [21], Sabin CA, 2013, USA [20] and Duprez et al, 2009 [21], have shown that these cardiovascular risk factors exist more in HIV people, who are known for their lifestyles and behaviors than in the general population. Late etiologic diagnosis and management of these factors appear to increase of the morbidity and mortality.

This shows the interest of public awareness for the prevention of cardiovascular risk factors. Early detection seems to be a protective factor.

Extremes of CD4 / CD8 ratio ranged between 0.18 and 2.22 with a median of 0.74. Serrano-Villar et al S, V Leung et al, Hadrup SR et al [16, 17,18] have shown that low CD4 / CD8 ratio for an effective antiretroviral therapy is associated with a high risk of morbidity and mortality. This report can be useful for the Monitoring cART response and could identify sub-group of people experiencing therapeutic failure.

Regarding the distribution of the study population according to death, lethality under treatment based on the 758 patients included in the study is 2.90%. This rate is definitely high. Masiá M et al, 2013, Spain [17] had found that non-AIDS lethality was also high by 28.9% of all deaths, with an incidence rate of 3.75 [2.84 to 4.94] per 1000 person-years. The bivariate analysis permitted the determination of factors associated with the occurrence of non-AIDS event (lethality). The average age of occurrence of an event is 4 years of follow-up with a minimum of 3 years and a maximum of 7 years.

The lethality was multiplied by 10 in smoking patients (P=0,000).Sabin CA, 2013, London [20]; Helleberg et al, 2013, Denmark [22] and OD Jarrett et al, 2013, United States [23] reported that smoking reduces life expectancy of PLHIV than HIV itself. The life style of PLHIV exposes them to a higher mortality risk compared to the general population. The lethality was multiplied by 3.31 in skinny patients (P=0.02).Jarrett OD et al, 2013, USA [23] ; Johannessen A et al, 2008, Tanzania[24] and the NUSTART study (Nutritional Support for Starting Africans Antiretroviral Therapy) in 2015 [25], Ontario, showed that malnourished PLHIV are at high risk of mortality despite the cART caused by metabolic troubles and anorexia.

The conviction of health care providers that HIV monitoring by cART as well as other infections will be sufficient to invert the trend of deficits, might have contributed to the neglect of the nutritional follow-up in the HIV patients' treatment Policy.

It is urgent to integrate nutritional care to HIV programs but especially to conduct nutritional intervention studies in HIV patients in developing countries, where malnutrition is often the result of poverty and food insecurity [15].

The lethality was multiplied by 5.60 in patients with Hyperglycemia, (P=0.01).This result is similar to S Kalra et al, 2013, India [26]. Other studies have identified risk factors for the development of hyperglycemia and diabetes in PLHIV. ARVs increase the likelihood of developing diabetes: Protease inhibitors (PI), indinavir and ritonavir, nucleoside reverse transcriptase inhibitors (NUC) such as Stavudine, Zidovudine and Didanosine. Nonetheless the treatment with Nevirapine is useful and is a protective factor for pre-diabetes. Hyperglycemia with or without diabetes increases the risk of occurrence of metabolic and infectious complications in PLHIV [26, 27, 28].

This shows the interest of regular monitoring of glycaemia in PLHIV. The lethality is about 3 times lesser in patients with CD4 / CD8 ratio (OR = 0.72) (P=0.005).

This result is in accordance with those of Menozzi M, 2014, Italy [29] and the Serrano –Villar et al. 2014, United States [16]. A low CD4 / CD8 during an effective antiretroviral therapy is associated to a high risk of morbidity and mortality. This highlights the interaction between the acute activation of the immune system and the immune senescence in the pathogenesis of cardiovascular diseases. This result shows that the CD4 / CD8 ratio is useful for the monitoring of the response to antiretroviral therapy and may identify individuals requiring a change of therapy line.

The risk of death was multiplied by 3.66 times in patients aged 44 years and above (P=0,000).

This result is similar to Van Sighem A et al, 2005, The Netherlands [30] and Morlat et al, 2014, France [31] who found an increase of cardiovascular death among PLWHIV under cART from the age of 40.Hasse B et

al, 2011, Switzerland [32] have found that non-AIDS comorbidities, particularly in cardio Private-vascular and diabetes mellitus, are important in PLHIV and tend to increase with age.

Age being a non-modifiable cardiovascular risk factor, it is particularly important to detect and prevent non-AIDS comorbidities. The risk of death was 10.58 times higher in smoking patients ($P=0,001$). Morlat et al, 2010, France [31], found a similar result. Smoking is associated with high occurrence of death among PLHIV.

Yet, smoking is one of the main risk factors for the disease and death which may vary among PLHIV modifiable. [33] The risk of death was multiplied by 3.98 in patients with high LDL-cholesterol value ($P=0,017$). Dyslipidemia is common among PLHIV under cART and is presented as an isolated metabolic abnormality or accompanied with a lipodystrophy syndrome in which there is a redistribution of fat and generally a resistance to insulin [28]. Jarrett OD et al, 2012 United States [23] have demonstrated that dyslipidemia is associated with increase of mortality risk among long-term HIV patients after 36 months of follow-up. Indeed, the lipo-atrophy is associated with female gender, age and exposure to didanosine for more than 6 months; On the contrary, lipo-hypertrophy is associated with overweight and high triglycerides [27]. Early detection of these metabolic abnormalities can be an important tool to identify HIV people infected at increased risk of death over the time. The risk of death was multiplied by 2.43 times in patients reporting a CD4 / CD8 category <0.74 ($P=0,005$). Serrano-Villar S et al, 2014, USA [16] found a similar result. In fact, the low CD4 / CD8 ratio during effective antiretroviral therapy is associated with the activation of T cells and important immunosenescence with a high risk of morbidity and mortality. The CD4 / CD8 ratio is immune dysfunction evaluation criterion useful for monitoring the response to cART and could identify people experiencing therapeutic failure.

II. Conclusion

Owing to currently available drugs, HIV/AIDS has become a chronic disease and people have a better life quality. However, despite a well-controlled treatment, factors such as advanced age, smoking, high cholesterol and low CD4/CD8 are highly associated with the risk of death. It is adamant therefore to strengthen communication for early detection and adequate care.

Declaration of absence of conflict of interest:

The authors declare having no conflict of interest.

Contributions of authors:

Ngom Gueye Ndeye Fatou, Abdoul Salam Hamadama; Diallo Abdoullahy ; Ndour Cheikh Tidiane: Design, Data Collection, Statistical Analysis And Manuscript Review. Other Authors: Design and Manuscript Review. All the Authors Have Read And Approved The Final Version Of The Manuscript

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