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Prevalence and Predictors of Clinical and Immunological Failure among Adults HIV Patients on HAART in Southern Benin

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Abstract: Objective: The purpose of this study was to determine the prevalence of antiretroviral therapy failure and to identify factors associated with failure in HIV infected patients on antiretroviral therapy. Methods: A six years retrospective cohort study was conducted. All HIV- infected patients on antiretroviral therapy for at least 12 months and followed in the outpatient treatment center at the CNHU-HKM in Cotonou were systematically included. The evaluation of the failure was clinical and immunological using the WHO 2010 criteria adapted by the Beninese national HIV/AIDS program. Data was extracted from ESOPE database and analyzed by SPSS 10.0. Multivariable linear regression was performed to identify predictors of antiretroviral treatment failure and $p < 0.05$ was considered to declare a statistical significance. Results: A total of 268 HIV infected patients were enrolled in the study. The overall prevalence of antiretroviral treatment failure was 35.4% (n=95), including thirty-one cases of clinical failure (11.6%), ten cases of immunological failure (6.3%) and forty-seven cases of clinico-immunological failure (17.5%). The mean age was 37 ± 22 years and the sex ratio was 0.71. Non-adherence to treatment was found to be the main cause of HARRT failure in 71.6% of cases (n=68). High levels of education, polygamy, advanced clinical stage (WHO stage IV) and a history of documented adverse effects were predictors of antiretroviral therapy failure. Difficulties in accessing routine viral loads and second-line molecules did not allow for early diagnosis and good management of HAART failure in Benin. Conclusion: The prevalence of clinical and immunological failure is high in this cohort. It is necessary to facilitate access to routine viral load as the main means of HAART monitoring and to make second-line molecules available.

Keywords: Failure, Antiretroviral Therapy, Predictors, Benin, West-Africa

1. Introduction

The advent of highly active antiretroviral therapy (HAART) has revolutionized the management of people living with the Human Immunodeficiency Virus (PLHIV) [1, 2]. These treatments, while not definitively curing the disease, ensure and guarantee a dramatic reduction in mortality and morbidity rates, improved patients quality of life, revitalization of the most affected communities and the transformation of the perception of AIDS, which gradually becomes a chronic disease with which patients can live [3-7].

The effectiveness of antiretroviral therapy is no longer in doubt. Antiretroviral therapy provides clinical and immunological restoration through sustained suppression of viral replication that becomes undetectable after six months of well-conducted therapy [3, 5, 8]. However, it is not unusual to find that some patients who have been on antiretroviral therapy for several months do not experience clinical, immunological and / or virological improvement [9-15]. Qualified as HAART failure, this situation is most often a headache for the caregivers, particularly in the context of

countries with limited resources. Due to its increasing frequency, the diversity of the factors that contribute to it and especially the difficulties associated with its management, it deserves a special attention for achieving the goal 90 90 90 of UNAIDS [16]. Many studies have been carried out in several countries on HAART failure and have shown that the problem does not arise with the same acuteness from one region to another [17-29]. In Benin, this study is the first to take stock of the situation of antiretroviral therapy failure after a few years of implementation of the Beninese antiretroviral access initiative. The purpose of this study was to determine the prevalence and predictors of HAART failures.

2. Methods

This was a six years retrospective cohort study conducted in the national and teaching hospital of Cotonou. All HIV-infected patients on antiretroviral therapy for at least 12 months and follow-up at the outpatient treatment center were systematically included. The HAART failure's evaluation was clinical and immunological because the viral load was not done regularly on the site. The WHO 2010 criteria adapted by the Beninese national HIV/AIDS program were used to assess clinical and immunological failures [30].

The data was exported from ESOPE database of the site to the SPSS 10.0 software in a pre-established registration mask. Some information was collected directly from the patient's medical record and integrated into the registration form. Multivariable linear regression was performed to identify predictors of antiretroviral treatment failure and $p < 0.05$ was considered to declare a statistical significance. The management of medical records was carried out in strict compliance with medical confidentiality. Any situation compromising the health of a patient discovered during the course of the study was properly managed in the interest of the patient with the medical team.

3. Results

Two hundred and sixty-eight (268) patients were included in this study. The mean age was 37 ± 22 years with extremes of 18 and 68 years and the sex ratio was 0.71. The majority of patients were educated, of whom 124 (46.3%) had reached secondary level. In 97.8% of cases patients were infected with HIV1 (n=262) and we noted 6 cases (2.2%) of double profiles (HIV1 + HIV2). The overall prevalence of HAART failure was 35.4% (n=95). Figure 1 shows the prevalence of the different types of failure diagnosed. Table 1 shows the modes of expression of the clinical or immunological failures. The occurrence of opportunistic infections coupled with immunological failure (more than 50% fall or absence of ascent of TCD4 lymphocytes) was found in 24 patients (25.3%). Regarding the occurence of HAART failure, most cases of failure (64.2%) occurred in the first 20 months of antiretroviral therapy with a 47.4% aggregation between M16 and M20 (Figure 2). Non-adherence to antiretroviral therapy was the leading cause of therapeutic failure in 68 patients (71.6%). All patients were on a first-line regimen. Therapeutic protocols varied widely depending on the availability of antiretroviral drugs (Table 2). Among the predictors of HAART failure, polygamy (p = 000.4), high level of education (P = 0.000), WHO clinical stage IV (p = 0.000) and a history of documented adverse effects (p = 0.000) were strongly associated with HARRT failure.

For the management of the cases of failure, no switch to second-line therapy was noted because of the unavailability of these molecules. Nevertheless thirteen patients (13.7%) had benefited from a change in treatment for reasons of intolerance. Fifty-eight patients (61.1%) had undergone a process to increase adherence to treatment. Failure was unknown in twenty-four patients (25.3%) who had no specific intervention.

Table 1. *Clinical and / or immunological modes of expression of HAART failure in the PLHIV cohort at the CNHU-HKM outpatient treatment center in Cotonou.*

Modes of expression	Frequency	%
Weight loss > 10% or cachexia (A)	04	04.2
Occurrence of opportunistic infections (B)	17	17.9
Fall > 50% of CD4 count or return to initial number (C)	17	17.9
A + B	10	10.5
A + C	08	08.4
B + C	24	25.3
A + B + C	15	15.8
Total	95	100.0

Table 2. *Initial therapeutic protocol in the PLHIV cohort at the CNHU-HKM outpatient treatment center in Cotonou.*

Therapeutic protocols	Frequency	%
3TC-ddI-EFZ	18	6.7
3TC-AZT-EFZ	37	13.8
3TC-d4T-EFZ	137	51.1
AZT-ddI-EFZ	8	3.0
d4T-ddI-EFZ	2	0.7
EFV-based regimens	202	75.3
3TC-ddI-NVP	1	0.4
3TC-d4T-NVP	4	1.5
NVP-based regimens	5	1.9
3TC-ddI-NFV	7	2.6
3TC-AZT-NFV	4	1.5
3TC-d4T-NFV	9	3.4
d4T-ddI-NFV	1	0.4
NFV-based regimens	21	7.9
3TC-ddI-IDV/r	5	1.9
3TC-AZT-IDV/r	13	4.8
3TC-d4T-IDV/r	15	5.6
AZT-ddI-IDV/r	4	1.5
d4T-ddI-IDV/r	3	1.1
IDV/r-based regimens	40	14.9
Total	268	100.0

3TC= Stavudine, ddI= Didanosine, AZT= Zidovudine, d4T= Stavudine, EFV=Efavirenz, NVP= Nevirapine, NFV= Nelfinavir, IDV/r = Indinavir/Ritonavir

Table 3. *Predictors of HAART failure in the PLHIV cohort at the CNHU-HKM outpatient treatment center in Cotonou.*

Variables		HAART failure		Total	Failure rate (%)	p
		Yes	No			
Gender	Female	50	66	111	45.0	
	Male	45	107	157	28.7	0.14
	Total	95	173	268	35.4	
Marital status	Single	13	22	35	37.1	0.319
	Monogamous	39	98	137	28.5	
	Polygamous	15	11	26	57.7	0.004
	Widowed	14	21	35	40.0	0.187
	Divorced	9	17	26	34.6	0.528
	Not specified	5	4	9	55.6	
	Total	95	173	268	35.4	
Level of education	Not educated	8	44	52	15.4	
	Primary	10	4	64	15.6	0.972
	Secondary	62	62	124	50.0	0.000
	Tertiary	12	6	18	66.7	0.000
	Non precise	3	7	10	30.0	
	Total	95	173	268	35.4	
Body Mass Index (BMI)	< 18.5	27	68	95	28.4	0.068
	18.5 - 25	56	84	140	40.0	
	25 – 30	12	19	31	38.7	0.894
	> 30	0	2	2	00.0	0.250
	Total	95	173	268	35.4	
Baseline WHO clinical stage	I + II	5	28	33	15.2	0.575
	III	35	105	140	25.0	0.133
	IV	55	40	95	57.9	0.000
	Total	95	173	268	35.4	
History of side effect	Yes	51	48	99	51.5	0.000
	No	44	125	169	26.0	
	Total	95	173	268	35.4	

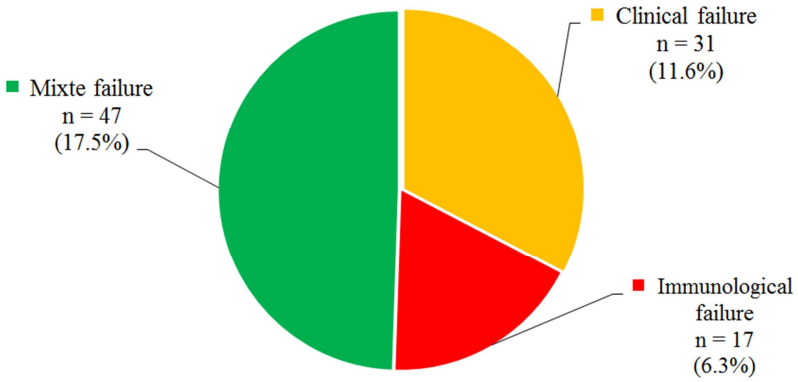

Figure 1. *Prevalence of different types of HAART failure in the PLHIV cohort at the CNHU-HKM outpatient treatment center in Cotonou.*

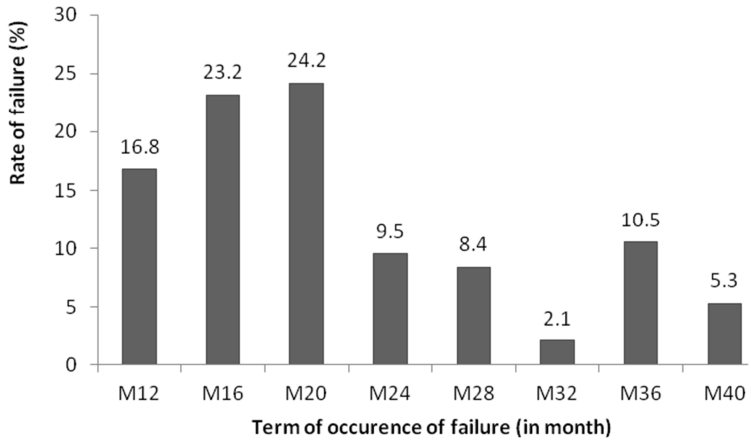

Figure 2. *Terms of occurrence of failures in the PLHIV cohort at the CNHU-HKM outpatient treatment center in Cotonou.*

4. Discussion

Limitations of the study: This study was conducted in a context where viral load was not routinely available for follow-up of PLHIV on antiretroviral therapy. The failure was therefore diagnosed on the basis of WHO clinical and immunological criteria. Several studies have shown limitations in the use of clinical and immunological criteria for ART follow-up because they not only underestimate the rate of failure but are late in expression [17, 19, 20, 22, 25, 28]. Nevertheless the WHO recommends their use in the context where the viral load is not available because they allow a diagnosis although belated of the failure.

Prevalence of HAART failure: At the end of our study, 35.4% of patients (n=95) were experienced HAART failure of which 11.6% were clinical failure (n=31), 6.3% were immunologic failure (n=17) and 17.5% were clinico-immunological failure (n=47). Some authors, based on clinical and immunological criteria obtained results similar to ours with a failure rate ranging from 32.1% to 38% [11, 18, 19]. In the same studies, virological failure was documented and represented rates ranging from 19.8% to 28%, respectively. Other studies found lower rates of clinical and / or immunological failure ranging from 17.6% to 19.6% while the rate of virological failure in these same studies ranged from 6% to 17.1% [21, 28, 31]. These studies revealed an overestimation of the rate of therapeutic failure when using WHO immunological and clinical criteria. Indeed, in most of these studies, evaluation was generally done during the first five years of ART. We thus note that for patients with more than two years of ART exposure, clinical and immunological criteria tended to overestimate the failure rate, whereas the reverse effect was observed at six months and one year of ART [17, 18, 22]. This is proof that viral load is the best tool for monitoring and early diagnosis of antiretroviral therapy failure. Several studies also highlighted immuno-virological discordance in the monitoring and evaluation of ART and concluded that immunological and clinical criteria did not detect early failure and should not be used alone [9, 19, 22, 25, 27]. Their use exposed patients to the risk of major clinical events associated with high mortality [10, 17, 23, 27]. It is therefore necessary and even urgent that all HIV care programs make available and adopt the routine viral load as the main means of monitoring the effectiveness of ART. This will facilitate not only the early diagnosis of the failure but also its management as it is often difficult to rely solely on clinical and immunological criteria for deciding switch to the second-line. Low rate of switch to second-line in resources limited countries are also related to difficulties to access viral load [11, 17, 19, 23, 25, 31]. This leads to indefinitely keeping patients in HAART failure under first-line treatment with the risk of compromising even second-line drugs and thus to promote the transmission of resistant viruses in the general population [24].

Causes and predictors of HAART failure: This study also showed the importance of strengthening adherence to ART through the implementation of an adherence assistance program at the HIV care sites. Indeed, the first cause of ART failure remains in our context the non-adherence or the poor observance [18]. Regarding the associated factors with the HAART failure, they vary from one context to another. We have identified five main factors: polygamy, high level of education, advanced baseline clinical stage (WHO stage IV), and a history of documented adverse effects. The baseline WHO clinical stage (III and IV) with an baseline CD4 count less than 200 or 100 cells/mm^3 are unanimous in the literature [10, 17, 18, 21]. On the other hand, authors have shown that a high baseline CD4 count and the absence of symptoms were associated with HAART failure [31]. Hence the reluctance of some practitioners in relation to the last WHO recommendations to systematically treat any HIV infected people regardless of their clinical and immunological status.

Management and outcome of failures: From the view of the therapeutic failure's management, fifty-eight patients (61.1%) benefited from an adherence consultation but only seventeen (29.3%) experienced a favorable outcome. Out of thirteen patients in whom the treatment was modified, only five (38.5%) experienced a good progress. In 100% of cases, the evolution remained unfavorable for those who did not benefit from any intervention. At the end of our study, the failure persisted in 74.7% of cases. This result highlighted the real problem of managing HAART failure in our context. Indeed the modifications carried out did not consist in a change of therapeutic line because the molecules of second line were not available in a stable way at the time. Observance being a dynamic phenomenon, it would be difficult to swear here that the fifty - eight patients who received therapeutic education became well adherent after the intervention of the consultants. Therefore one could be mistaken about the true cause of their failure. Would these patients already experience antiretroviral drug resistance? Would it not be drug interactions in this context where the majority of patients associate traditional therapies with antiretroviral drugs? All these questions remained suspended due to the impossibility of performing resistance tests such as genotyping, phenotyping and plasma antiretroviral assays.

5. Conclusion

The prevalence of clinical and immunological failures was relatively high in this cohort, hence the need to facilitate access to routine viral load and adopt it as a primary means of monitoring antiretroviral therapy. It is also necessary to make second-line antiretroviral drugs available and to strengthen the healthcare personnel's capacities on the diagnosis and the management of HAAR failures. This would significantly reduce the morbidity and mortality of patients who have failed antiretroviral therapy.

References

[1] Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. Antiviral Res. 2010; 85 (1): doi: 10.1016.

[2] Pavie J, Molina JM. Treatment of the human immunodeficiency virus in adults in 2005; Presse med. 2005; 34 (10): 38-44.

[3] Taverne, B., Desclaux, A., Sow, P. S., Delaporte, E., Ndoye, I. Evaluation de l'impact bioclinique et social, individuel et collectif, du traitement ARV chez des patients VIH-1 pris en charge depuis 10 ans dans le cadre de l'ISAARV – Cohorte ANRS 1215. Rapport final, mai 2012. Dakar. CNLS, CRCF, IRD, ANRS, 2012, 415 p.

[4] Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, Fox MP et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med, 2013, 10 (4): e1001418.

[5] Montaner JSG, Lima VD, Harrigan PR, Lourenc¸o L, Yip B, Nosyk B, et al. (2014) Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the "HIV treatment as prevention" experience in a Canadian setting. PLoS One 9 (2): e87872. doi: 10.1371

[6] Bor J, Herbst AJ, Newell M-L et Bärnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science. 2013; 339 (6122): doi: 10.1126.

[7] Caroline A Sabin. Do people with HIV infection have a normal life expectancy in the era of combination antiretroviral therapy? BMC Medicine 2013, 11: 251.

[8] Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, Shin SS. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. J Acquir Immune Defic Syndr. 2010; 54 (2): 167–79.

[9] Li X, Margolick J, B MD, Jamieson B, Rinaldo C, Phair J, Jacobson L. CD4+ T-cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy (HAART). J Acquir Immune Defic Syndr. 2011; 57 (5): 421–28.

[10] Marconi VC, Grandits GA, Weintrob AC, Chun H, Landrum ML, Ganesan A, Okulicz JF, Crum-Cianflone N, O'Connell RJ, Lifson A, Wortmann GW, Agan BK *et al.*, Outcomes of highly active antiretroviral therapy in the context of universal access to healthcare: the U. S. Military HIV natural history study. AIDS Research and Therapy 2010, 7: 14 doi: 10.1186.

[11] Iroezindu MO. Disparities in the magnitude of human immunodeficiency virus-related opportunistic infections between high and low/middle-income countries: is highly active antiretroviral therapy changing the trend? Ann Med Health Sci Res. 2016; 6 (1): 4–18.

[12] Boender TS, Sigaloff KCE, McMahon JH, Kiertiburanakul S, Jordan MR, Barcarolo J, Ford N, Rinke de Wit TF, Bertagnolio S. Long-term virological outcomes of first-line antiretroviral therapy for hiv-1 in low and middle-income countries: a systematic review and meta-analysis. Clin Infect Dis. 2015; 61 (9): 1453– 61.

[13] Johnston V, Fielding KL, Charalambous S, Churchyard G, Phillips A, Grant AD. Outcomes following virological failure and predictors of switching to second-line antiretroviral therapy in a South African treatment programme. J Acquir Immune Defic Syndr. 2012; 61 (3): doi: 10.1097

[14] Gupta-Wright A, Wood R, Bekker L-G, Lawn SD. Temporal association between incident tuberculosis and poor virological outcomes in a South African antiretroviral treatment service. J Acquir Immune Defic Syndr. 2013; 64 (3): 261–70.

[15] Aghokeng AF, Kouanfack C, Eymard-Duvernay S, Butel C, Edoul GE, Laurent C, Koulla-Shiro S, Delaporte E, Mpoudi-Ngole E, Peeters M. Virological outcome and patterns of HIV-1 drug resistance in patients with 36 months' antiretroviral therapy experience in Cameroon. Journal of the International AIDS Society 2013, 16: 18004.

[16] ONUSIDA. 90-90-90. Une cible ambitieuse de traitement pour aider à mettre fin à l'épidémie du sida. Programme Conjoint des Nations Unies sur le VIH/SIDA 2015. 33p.

[17] Vanobberghen FM, Kilama B, Wringe A, Ramadhani A, Zaba B, Mmbando D, Todd J. Immunological failure of first-line and switch to second-line antiretroviral therapy among HIV-infected persons in Tanzania: analysis of routinely collected national data. Trop Med Int Health. 2015; 20 (7): 880–92.

[18] Ahoua L, Guenther G, Pinoges L, Anguzu P, Chaix M-L, Le Tiec C, Balkan S, Olson D, Olaro C, Pujades-Rodríguez M. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. BMC Infect Dis. 2009; 9: 81. doi: 10.1186.

[19] Haas AD, Keiser O, Balestre E, Brown S, Bissagnene E, Chimbetete C, Dabis F, Davies M-A, Hoffmann CJ, Oyaro P, Parkes-Ratanshi R, Reynolds SJ, Sikazwe I, Wools-Kaloustian K, Zannou DM, Wandeler G, Egger M. Monitoring and switching of first-line antiretroviral therapy in Sub-Saharan Africa: collaborative analysis of adult treatment cohorts. Lancet HIV. 2015; 2 (7): e271–e278.

[20] Estill J, Salazar-Vizcaya L, Blaser N, Egger M, Keiser O. The cost-effectiveness of monitoring strategies for antiretroviral therapy of HIV infected patients in resource-limited settings: software tool. PLoS One. 2015; 10 (3): e0119299.

[21] Huang P, Tan J, Ma W, Zheng H, Lu Y, Wang N, Peng Z, Yu R. Outcomes of antiretroviral treatment in HIV-infected adults: a dynamic and observational cohort study in Shenzhen, China, 2003–2014. BMJ Open. 2015; 5 (5): e007508.

[22] Ingole N, Mehta P, Pazare A, Paranjpe S, Sarkate P. Performance of immunological response in predicting virological failure. AIDS Res Hum Retroviruses. 2013 Mar; 29 (3): 541–46.

[23] Ramadhani HO, Bartlett JA, Thielman NM, Pence BW, Kimani SM, Maro VP, Mwako MS, Masaki LJ, Mmbando CE, Minja MG, Lirhunde ES, Miller WC. The Effect of switching to second-line antiretroviral therapy on the risk of opportunistic infections among patients infected with human immunodeficiency virus in Northern Tanzania. Open Forum Infect Dis. 2016; 3 (1): of w018.

[24] Nichols BE, Sigaloff KCE, Kityo C, Hamers RL, Baltussen R, Bertagnolio S, Jordan MR, Hallett TB, Boucher CAB, Rinke de Wit TF, van de Vijver DAMC. Increasing the use of second-line therapy is a cost-effective approach to prevent the spread of drug-resistant HIV: a mathematical modelling study. J Int AIDS Soc. 2014; 17 (1): 19164. doi: 10.7448.

[25] Motasim Badri, Stephen D Lawn, Robin Wood. Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting. BMC Infect Dis. 2008; 8: 89. doi: 10.1186.

[26] Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HGM, Yankey BA, Dodoo ANO. Association between the occurrence of adverse drug events and modification of first-line highly active antiretroviral therapy in Ghanaian HIV patients. Drug Saf. 2016; 39 (11): 1139–49.

[27] Zoufaly A, an der Heiden M, Kollan C, Bogner JR, Fätkenheuer G, Wasmuth JC, Stoll M, Hamouda O, van Lunzen J. Clinical outcome of hiv-infected patients with discordant virological and immunological response to antiretroviral therapy. J Infect Dis. 2011; 203 (3): 364–71.

[28] Ferreyra C, Yun O, Eisenberg N, Alonso E, Khamadi AS, Mwau M, Mugendi MK, Alvarez A, Velilla E, Flevaud L, Arnedo M, Dalmau D, Roddy P, Bernasconi A, Palma PP. Evaluation of Clinical and Immunological Markers for Predicting Virological Failure in a HIV/AIDS Treatment Cohort in Busia, Kenya PLoS One. 2012; 7 (11): e49834.

[29] Kityo C, Gibb DM, Gilks CF, Goodall RL, Mambule I, Kaleebu P, Pillay D, Kasirye R, Mugyenyi P, Walker AS, Dunn DT. High level of viral suppression and low switch rate to second-line antiretroviral therapy among HIV-infected adult patients followed over five years: retrospective analysis of the DART trial. PLoS One. 2014; 9 (3): e90772.

[30] Programme National de Lutte contre le SIDA (PNLS), Bénin. Politique, normes et procédures pour la prise en charge des personnes vivant avec le VIH au Bénin. PNLS - Bénin, 2010.

[31] Yirdaw KD, Hattingh S. Prevalence and Predictors of Immunological Failure among HIV Patients on HAART in Southern Ethiopia. PLoS One 2015; 10 (5): e0125826.