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Research Article

Current Status of Third-Line Antiretroviral Therapy in Togo

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ABSTRACT

Objective: Evaluate the conditions and criteria for starting third line antiretroviral treatment for patients who have failed second line treatment.

Materials and methods: Retrospective cohort study from January 1, 2013 to December 31, 2018 for patients who were already on third line ART and then a cross-sectional study from January 1 to June 30, 2019 for patients to be put on third line antiretroviral treatment. It was conducted in at the Day Hospital of the Department of Infectious and Tropical Diseases of Sylvanus Olympio Teaching Hospital.

Results: Seventy-six patients have been put under third line antiretroviral treatment from June 30, 2019 among the 3383 patients in the active queue of patients regularly monitored. The average age of the patients was 43.53 years (12-69 years). Almost all patients were HIV-infected1 (n=75). The average duration of HIV infection diagnosis was 10.77 years (2-21 years). The average duration ART of first and second line was 8.8 years. The average rate of CD4 count at the time of failure was 110.3 cells/µl (0-664 cells/µl). The viral load was done in 79% with an average of 44,023,958.35 copies. Only 17 patients or 22.4% were able to complete genotyping. Weight loss/deterioration of general condition (n=49) was the sign presented by most patients.Darunavir and Raltegravir were associated with all combinations of third line antiretroviral therapy in most cases. Lethality was 12% (n=9).

Conclusion: Diagnosis of treatment failure is mainly based on clinical signs or events, CD4 count and to a certain extent viral load measurement. The use of genotyping, which is not available in Togo, depends on the patient's financial possibilities or capacities.

Keywords: Antiretrovirals; Treatment failure; Third-line; Retrospective

INTRODUCTION

The broad prescription of multi-therapies has had a significant impact on the health status of HIV-infected people. The incidence of opportunistic infections and AIDS cases and deaths has decreased, immune restoration and control of viral activity have been observed in a large number of patients [1]. However, in addition to this virological and immune success, one should not forget that some treated patients retain a detectable viral load and a significant immune deficiency [1].

The antiretroviral treatment guidelines developed by the World Health Organization (WHO) were first published in 2002, simplified in 2003 and updated in 2006. They continue to follow the principles of a public health approach, which aim to achieve the possible best results, especially in terms of quality of life and survival for people living with HIV [2]. In 2016, the WHO Unified Guidelines on the use of Antiretroviral Drugs for the treatment and prevention of HIV Infection recommended universal initiation of antiretroviral treatment and systematic monitoring of viral load for all people living with HIV. As treatment access expands, the number of people failing treatment is also expected to increase [3]. Treatment failures are

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diagnosed at a late stage due to the unavailability of viral load in the antiretroviral treatment systematic routine monitoring of antiretroviral treatment as recommended by the WHO, which would encourage the accumulation of resistance [4].

Indeed, the difficulty of access to means of measuring this therapeutic efficacy, especially the viral load, requires changes in therapeutic protocols based solely on clinical and immunological criteria [5].

In the framework of the fight against the HIV/AIDS epidemic, Togo has since 2001 opted for a multi-sectoral response, under the coordination of the National Council for the Fight against HIV/AIDS and Sexually Transmitted Infections (CNLS-IST). The average prevalence of HIV infection is estimated at 2.11% [6].

The care sites preferentially follow patients on first and second-line antiretroviral treatment throughout Togo. Second-line treatment failures are referred to the infectious and tropical diseases department of the Sylvanus OLYMPIO Teaching Hospital, which is the reference service for HIV/AIDS care. The decision to move to the third-line is taken in the referral service where patients are referred regardless of their place of residence in the country.

The main objective of this work was to take stock of the situation of third-line antiretroviral treatment patients and to identify the difficulties in the management of this category of patients in Togo.

MATERIALS AND METHODS

Type of study

A study was conducted on a retrospective cohort from 1 January 2013 to 31 December 2018 on patients who were already on third line antiretroviral treatment; and a cross-sectional study from 1 January to 31 December 2019 on patients to be put on third line antiretroviral treatment in whom second-line antiretroviral treatment failure is suspected or announced.

Framework of the study

The department of Infectious and tropical diseases of the Sylvanus OLYMPIO Teaching Hospital in Lomé was used as a study setting. This service is the national reference for the management of infectious diseases in general and HIV infection in particular. It is the service where all patients undergoing antiretroviral treatment are referred in case of suspicion or failure of second-line antiretroviral treatment regardless of their place of residence in Togo.

All patients on third-line antiretroviral treatment in Togo are registered in the database of the day hospital. However, it should be noted that not all these patients necessarily come to the day hospital at all times to obtain antiretroviral drugs. Arrangements have been made with the antiretroviral dispensing sites to make third line treatment available in order to bring patients closer to the place of care for those who live very far from the reference center.

Inclusion and non-inclusion criteria

All third line antiretroviral treatment patients regularly followed up in the active file of the department of Infectious and Tropical Diseases of the Sylvanus Olympio Teaching Hospital were included.

Patients registered in the database and whose medical records are not found were not included.

Operational definition of therapeutic failure

According to WHO criteria, treatment failure was defined by clinical, immunological and/or virological failure [7].

Virological failure was defined by an HIV1 plasma viral load greater than 1000 copies/µl determined by two consecutive measurements at least 3 months apart, with adherence support after the first virological test. A person must have been on antiretroviral therapy for at least 6 months to be able to determine whether a treatment regimen has failed [3].

In children over five years of age, immunological failure is defined by the persistence of a CD4 count inferior to 100 cells/ mm3. In adolescents and adults, immunological failure is defined by a CD4 count of 250 cells/mm3 or less following clinical failure, or the persistence of a CD4 count inferior to 100 cells/mm3 [3].

Clinical failure in children is defined as the occurrence of a new or recurrent clinical event indicating advanced or severe immunosuppression (WHO clinical stage 3 or 4 pathology, excluding tuberculosis) after 6 months of effective treatment. In adolescents and adults, clinical failure is a new or recurrent clinical event indicating severe immunosuppression (WHO clinical stage 44) after 6 months of effective treatment [3].

Data collection

The data were extracted from the ESOPE computerized database where all patients monitored are registered. The paper documents, particularly the medical management records, were also consulted for additional information.

Ethical consideration

The study was approved by the head of the Infectious and Tropical Diseases Department. The necessary measures were taken to guarantee the confidentiality of the information collected in the patients' medical care files. Patient identification numbers and file or folder numbers were used to identify the files.

RESULTS

Socio-demographic Data

During the study period, 91 patients were put on third line antiretroviral treatment and registered in the database of the Infectious Diseases Department of the Sylvanus OLYMPIO Teaching Hospital.

A total of 76 patients undergoing third line antiretroviral treatments are monitored among the 3583 patients in the active file of patients monitored regularly.

The average age of the patients was 43.53 years, with extremes of (12-69 years) and a male predominance of 44 men for 32 women, i.e. a male/female sex ratio of 1.375. Almost all patients were infected with HIV1 in 98.68% of cases (n=75). The average duration for diagnosis of HIV infection was 10.77 years (2-21 years).

Before third line treatment, patients had an average duration of first and second-line antiretroviral treatment of 8.8 years with extremes of (1-21 years).

Therapeutic profile

During first-line antiretroviral treatment, the combinations used by patients have been presented in the Table 1.

-Stavudine (D4T)+Lamivudine (3TC)+Nevirapine (NVP) in 47 cases;

-Zidovudine (AZT)+Lamivudine (3TC)+Nevirapine (NVP) in 61 patients;

-Tenofovir (TDF)+Lamivudine (3TC)+Efavirenz (EFV) in 31 cases (Table 1).

In the second line, the following combinations were mostly prescribed for patients in the third line (Table 2)

-Tenofovir (TDF)+Lamivudine (3TC)+Atazanavir boosted by ritonavir (ATV/r) in 48 patients;

-Tenofovir (TDF)+Lamivudine (3TC)+Lopinavir boosted by ritonavir (LPV/r) in 14 patients;

-Abacavir (ABC)+Lamivudine (3TC)+Lopinavir boosted by ritonavir (LPV/r) in 11 cases.

Immunological and virological profile

The criteria for determining failure of second line antiretroviral treatment were based on immune, virological and clinical status.

Antiretroviral combination	Number (n)	Percentage (%)
D4T+3TC+NVP	47	62
AZT+3TC+NVP	61	80.3
AZT+3TC+EFV	5	6.6
ABC+3TC+EFV	4	5.3
TDF+3TC+EFV	31	41
TDF+3TC+NVP	1	1.3

Note: ABC: Abacavir; AZT: Zidovudine; D4T: Stavudine; EFV: Efavirenz; NVP: Nevirapine; 3TC: Lamivudine; TDF: Tenofovir.

Table 1: Distribution of patients according to the antiretroviral therapeutic combinations used in first line.

Antiretroviral combination	Number (n)	Percentage (%)
TDF+3TC+LPV/r	14	18.4
TDF+3TC+ ATV/r	48	63.2
ABC+3TC+ATV/r	8	10.5
ABC+3TC+LPV/r	11	14.5
AZT+3TC+ATV/r	1	1.3
DDI+ABC+LPV/r	2	2.6
ABC+3TC+DRV/r	1	1.3

Note: ABC: Abacavir; AZT: Zidovudine; DDI: Didanosine; 3TC: Lamivudine; ATV/r: Atazanavir boosted with ritonavir; LPV/r: Lopinavir boosted with ritonavir; DRV/r: Darunavir boosted with ritonavir; TDF: Tenofovir.

Table 2: Distribution of patients according to the antiretroviral therapeutic combinations used in second line.

The average rate of CD4 cell count of patients at the time of failure of second line antiretroviral treatment was 110.3 cells/µl (0-664 cells/µl).

The average viral load of patients who achieved it at the time of the failure of second line antiretroviral treatment was 44,023,958.35 copies (970-2,400,000,000 copies). The viral load had not been achieved in 16 patients, a 79% achievement rate.

Genotyping to guide the prescription of third line antiretroviral therapy was performed by 17 patients (22.4%).

Clinical and therapeutic profile

Table 3 shows various manifestations noted in patients at the time of the second line treatment failure.

General signs were dominated by weight loss and/or alteration of general condition (49 cases); generalized prurigo (10 cases); HIV-related wasting and intermittent prolonged fever in 7 cases and chronic malnutrition in 4 patients respectively. Chronic diarrhea and chronic cough were predominantly reported by patients in treatment failure (Table 3).

Physical examination of patients was poor in the majority of cases (Table 3).

Only 7 patients had no clinical manifestations.

Opportunistic infections were dominated by tuberculosis (8 cases), oral candidiasis (8 cases) (Table 4).

Tuberculosis was diagnosed in several forms. Four patients presented with pulmonary tuberculosis under positive microscopy. Bacteriologically diagnosed pulmonary tuberculosis, peritoneal tuberculosis, lymph node tuberculosis and tubercular pericarditis were diagnosed in one case respectively.

Poor adherence to antiretroviral treatment was associated with treatment failures in 72 cases (94.7%) with frequent or intermittent cessation of antiretroviral treatment reported in 65 cases (85.5%).

Ritonavir-boosted Darunavir (DRV/r) and Raltegravir were the two main molecules associated with all combinations of third line antiretroviral treatment in most cases. The different third line therapeutic regimens are as follows:

-Tenofovir (TDF)+Lamivudine (3TC)+Raltegravir (RAL) +Ritonavir boosted Darunavir (DRV/r) prescribed in 47 patients;

-Abacavir (ABC)+Lamivudine (3TC)+Raltegravir (RAL) +Darunavir boosted with ritonavir (DRV/r) prescribed in 28 cases;

-Abacavir (ABC)+Lamivudine (3TC)+Darunavir boosted by ritonavir (DRV/r) in one patient (Table 5).

Nine deaths were reported in these patients after initiation of the third line antiretroviral treatment, a lethality rate of 12%.

Clinical signs	**Number (n)**
General signs	
Weight loss/deterioration of general condition	49
Severe physical asthenia	1
Facial puffiness	1
HIV-related cachexia	7
Temporal-spatial disorientation	1
Moderate dehydration	1
Prolonged intermittent fever	7
Conjunctival hyperemia	1
Chronic malnutrition	4
Edema of the lower limbs	3
Conjunctival pallor	8
Generalized prurigo	10
Behavior trouble	2

Functional signs	
Amnesia	1
Non-gestational amenorrhea	1
Headache	1
Chronic diarrhea	12
Dyspnea	1
Chronic cough	14
Tremor	1
Vertigo	1
Physical signs	
Multiple lymphadenopathy	2
Hemicorporeal motor deficit	2
Jaundice	1
Itchy papular skin lesions	1
Paraparesis	1
Apraxo-agnosic syndrome	1
Peritoneal effusion syndrome	1
Genital ulcers	2
Flat warts	1
Cutaneous xerosis	1

Table 3: Distribution of clinical signs observed in patients at the time of treatment failure.

Opportunistic conditions	**Number (n)**
Multiple skin abscesses caused by *Escherichia coli and Staphylococcus* spp.	1
Oral candidiasis	8
Dermatophytia	1
HIV-related encephalopathy	1
Acute yeast enteritis	1
Genital herpes	2
LEMP	1
Molluscum contagiosum	1

HIV-related nephropathy	2
Onychomycosis	1
Recurrent pneumonia	1
Chronic follicular proctitis	1
Kaposi's sarcoma	1
Cerebral toxoplasmosis	1
Tuberculosis*	8
Thoracic shingles	3

Note: (*): 4 cases of pulmonary tuberculosis with positive microscopy; 1 case of bacteriologically diagnosed pulmonary tuberculosis; 1 case of peritoneal tuberculosis; 1 case of lymph node tuberculosis; 1 case of tuberculous pericarditis. PML: Progressive Multifocal Leukoencephalitis.

Table 4: Distribution of opportunistic conditions diagnosed at the time of treatment failure.

Therapeutic regimen	**Number (n)**
TDF+3TC+RAL+DRV/r	47
ABC+3TC+RAL+DRV/r	28
ABC+3TC+DRV/r	1
Total	76

Note: ABC: Abacavir; 3TC: Lamivudine; RAL: Raltegravir; DRV/r: Darunavir boosted with ritonavir.

Table 5: Distribution of patients according to the therapeutic regimen of third-line antiretroviral treatment.

DISCUSSION

The distribution by therapeutic line of PLWHIV on antiretroviral treatment in 2019 in Togo shows a predominance of 90% of patients on first-line or 68,634 patients out of a total of 76,230 patients on antiretroviral treatment for all lines combined. Second-line patients accounted for 9.8% or 7505 patients and third-line patients accounted for only 0.1%. These data are consistent with those of the Yaoundé Central Hospital in Cameroon where 9.89% of patients were on second-line antiretroviral treatment [8].

The treatment protocols for first-line antiretroviral treatment used according to national guidelines are similar elsewhere in sub-Saharan Africa. Patients on third line antiretroviral treatment in the day hospital of the Infectious and Tropical Diseases Department of Sylvanus Teaching Hospital are a very small minority compared to the active caseload; they represented about 2.1% of all patients. Almost all of these third-line patients are monitored in the referral service. For patients with distance problems, particularly those living outside Lomé, the PNLS has taken steps to introduce third-line drugs in the dispensaries in their place of residence. It should be noted that despite the fact that antiretroviral treatment is free of charge, patients pose a real socio-economic problem in terms of carrying out the follow-up assessment that is not covered, moving them to the care structures and feeding or nutrition.

The epidemiology of HIV infection shows a predominance of women as everywhere else. The 2019 report of the PNLS shows that 72% of PLWHIV under antiretroviral treatment were women [6].

Male predominance is shown in the third line of antiretroviral treatment in our cohort. This suggests that women are much more aware and concerned about their health status than men. The reasons that may explain men's non-compliance are diverse. The fact that some men's wives are not informed of their status leads them to go into hiding to take their treatment. This observation is made on both sides, but most of the time it is noted that women manage to share their status with their spouse unlike men. The regular movement of men for professional reasons often leads to frequent and long interruptions of antiretroviral treatment; voluntary cessation of treatment for reasons of the patient's sense of well-being or for undesirable effects are regularly observed during their therapeutic follow-up, without forgetting the important role played by traditional medicine and pastors, some of whom lead

the population to believe that they have miracle solutions. Very quickly the population believes in these false allegations to the detriment of their antiretroviral treatments. These different factors are usually associated with the therapeutic follow-up of the majority of patients, which in the long run has an impact on their therapeutic success. Therapeutic failure is also noted in a minority of patients who are highly compliant with their antiretroviral treatment. This leads to the strong suspicion of primary resistances even before the initiation of antiretroviral treatments; but our technical facilities do not allow us to detect them before the initiation of triple therapy.

The general observation also made during our study is that non-observance or poor observance of antiretroviral treatment was the factor found in the majority of cases in patients in a situation of therapeutic failure. Lutresse, et al. in Cameroon concluded that non-adherence was significantly associated with treatment failure (86.6%; $p<0.0001$), reflecting an increased risk of failure in the case of poor adherence. Furthermore, they found that failure to take prophylaxis against opportunistic infections was twice more associated with the risk of treatment failure (0.0004) [8].

Virological failure was significantly more common among men ($p=0.03$) [9], in a study in Senegal and the same finding was also made in Vietnam [10].

The reasons put forward in Senegal to explain the predominant virological failure in men were the greater motivation of women to participate in the awareness sessions and the reinforcement of therapeutic adherence initiated in the follow-up structures [9].

In a cross-sectional study in Senegal involving 327 patients living with HIV aged 18 years and over, followed in a decentralized site for 11 months, the average age of these patients was 44 years (18-76 years) with a predominance of women (female/male sex ratio=3.3). The patients had an average follow-up period of 60 months (1-204 months) with therapeutic outcomes noted in 39% of cases in 128 patients, including 17% of virological failure. Unlike the male sex associated with the failure found in our study, the female sex ($p=0.04$) was associated with treatment failures. The other factors detected were: age <25 years ($p=0.009$), late initiation of antiretroviral therapy with a CD4 count <200 at baseline ($p=0.04$), high viral load >10,000 copies/mL [11].

In Burkina-Faso in children aged 6 months to 15 years infected with HIV1 on antiretroviral treatment, whose average age was 108 months ± 67, a study on the factors associated with treatment failure had made it possible to determine the following factors: female sex, adherence <95%, maternal death and WHO advanced stage of HIV infection (stages III/IV) [7]. The complexity of the treatment regimen (the dosage form, the number of tablets, the combination of tablets and syrup) was a factor associated with the treatment failure found in a cohort of children aged 1 to 18 years infected with HIV.

In a qualitative study, the medical history of patients reveals that treatment failures are linked to complex, multifactorial situations, resulting from factors attributable to patients (lack of compliance linked to various psycho-social problems), but also to healthcare structures (organization of the care system, training of healthcare professionals, availability of biological examinations and appropriate drugs). This study also concludes that the incidence of the occurrence of treatment failures should be considered as a testament to the quality of care provided [12].

The viral load is a systematic parameter in the criteria for treatment failure, but we note that it was not achieved by 16 patients. There are many reasons for this achievement blanket. The 2019 report of PNLS–IST activities shows low coverage of PLWHIV on antiretroviral treatment that have benefited from the load. This report notes a low coverage of 15.7% which significantly decreased in 2019 compared to the previous year when the coverage was 32%.

The Consolidated Guidelines on the Use of Antiretrovirals for the Treatment and Prevention of HIV Infection published in 2016 contain recommendations on routine monitoring and diagnosis of treatment failure. According to the WHO, viral load measurement is the preferred monitoring method to determine and confirm treatment failure [13]. The difficulty of measuring viral load in low-income countries has led the WHO to say that if viral load testing is not routinely available, the diagnosis of treatment failure should be based on CD4 count and clinical follow-up, with, when possible, targeted viral load measurement to confirm virological failure [13]. We observed in the practice of prescribers that clinical and immunological criteria were primarily taken into account in the diagnosis of treatment failures although the viral load coverage was 79%. This poor coverage is due to frequent breaks in inputs (reagents and consumables) during the year; Togo has seven viral load measuring devices subject to frequent breakdown [6]. To these reasons, must be added there is need to add the too long lead time for results when clinicians ask for them in order to make decisions. All these situations greatly discourages prescribers of antiretrovirals and, with regard to other factors, they often no longer request the viral load. Under these conditions, the diagnosis of treatment failure is made on the basis of the CD4 count and the viral load if the latter is available or on the occurrence of clinical events alone in the absence of the viral load. If for the diagnosis of first-line treatment failure, the CD4 criteria, the viral load and other clinical events are sufficient for a switch to second-line, the diagnosis of second-line treatment failure should go beyond these parameters.

Resistance testing (genotyping) should be of great help in prescribing third-line antiretroviral therapy in sub-Saharan Africa. Genotyping is an examination not available in the majority of countries in sub-Saharan Africa such as Togo. This explains in our study the low proportion of patients (n=17) who underwent genotyping when the second-line of antiretroviral treatment failed. Its realization is however possible through the intermediary of private laboratories which subcontract with laboratories most often in France. The cost varies from 190,000 to 436,000 CFA francs or around 291 to 667.4 USD depending on the resistance genotype. This cost is obviously not within the reach of our populations, the majority living below the poverty line. Indeed, Togo has a poverty incidence of 50.4% and the normalized average annual expenditure per capita is 384,736 CFA Francs (589 USD) with a national poverty line of 273,619

CFA Francs (419 USD) [14]. In view of these data, we understand the difficulties encountered by patients to treat themselves, as well as the nursing staff who are limited in the means of investigations through the additional examinations that patients honor painfully because of the very limited financial means. Faced with this situation, we also see the difficulty or even and the impossibility for patients to pay for genotyping, the cost of which greatly exceeds their financial capacity.

Considering all these factors, and to give the chance to patients whose general condition is deteriorating day by day, clinicians are obliged to consider both the immunological (CD4 count) and the clinical criteria (occurrence of a clinical event new or recurrent, diagnosis of an opportunistic condition) to diagnose the second line antiretroviral treatment failure and prescribe the third line one.

Poor adherence is the most frequent cause of treatment failure in PLWHIV [7], the availability of genotyping would make it possible to diagnose true treatment failures in certain cases and to maintain initial treatments by strengthening patient adherence since the treatment of the third requires a lot of tablets to be taken.

New or recurrent clinical events have been presented by almost all the patients, some of which have been investigated leading to the diagnosis of opportunistic conditions. Tuberculosis in several forms comes first among these opportunistic diseases confirming its place as the first opportunistic disease in HIV immunocompromised people.

The care of patients on the third-line of antiretroviral treatment in Togo faces several difficulties which have a negative impact on their therapeutic success.

These difficulties, especially the rupture of antiretrovirals, increase the level of stress in these patients; mostly during the counseling before the pre-initiation of third-line where the care provider or clinician emphasizes that they are at their last chance.

The major difficulty is linked to the availability of antiretroviral molecules in general, those of the third-line in particular. Frequently we note stock tensions for third-line molecules due to non-respect provisional delivery dates by the suppliers [6].

The first semester of 2019 was marked by stock tensions for certain molecules and the breakdown of third-line molecules. This situation is explained by the non-respect of the provisional delivery dates by the suppliers [6]. The end of 2020 is marked by the same difficulties putting patients on involuntary therapeutic termination.

In addition to these difficulties related to the suppliers of the molecules, we also note the breakdown of antiretroviral molecules due to the lack of stock management with the risks of expiration and shortages.

Another aspect of the shortage of third-line drugs is also linked to the fact that the main technical and financial partners, in particular the Global Fund, support the PNLS-IST by making antiretrovirals available on treatment sites.

The support of antiretroviral by technical and financial partners concerns first and second-line antiretroviral molecules. Third-line antiretroviral molecules are the responsibility of the Togolese State. Knowing the administrative delays experienced by our countries in sub-Saharan Africa, the delay in disbursing funds for the supply of third-line antiretroviral drugs may also explain the disruption of third-line antiretroviral molecules this class of antiretroviral drugs.

CONCLUSION

Between HIV infection diagnosis, first and second-line antiretroviral therapy; and the start of third-line antiretroviral therapy there has been an average of a decade in most patients. All the antiretroviral therapy lines recommended by the WHO guidelines for HIV care in low-income countries were followed by all patients.

The diagnosis of treatment failure is based primarily on clinical signs or events, CD4 count and to some extent viral load measurement.

The use of genotyping, which is not available in Togo, depends on the patient's financial possibilities or capacities. And most patients are unable to do the genotyping to actually diagnose second-line treatment failure and guide the prescription of third-line antiretroviral therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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