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Evaluation of Early Warning Indicators of ARV Resistance to HIV in the Hospital of Tivaouane from 2008 to 2016

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Abstract

Introduction: HIV resistance to antiretroviral is currently a global concern, and requires increased surveillance in a context of widespread ARV treatment. **Objective**: To evaluate early warning indicators of HIV resistance to ARVs in the Hospital of Tivaouane (Senegal) where viral load was not routinely available. **Methods**: This is a cross-sectional retrospective study from 2008-2016. The extraction tool (May 2010 version) was used to analyze the EWI. **Results**: We collected 360 HIV positive patients followed on average for 3.57 years ± 3.02. 2009, 2010 and 2012 recorded 100% ARV prescribing rates. Throughout the study period, the percentage of patients lost to follow-up during the first 12 months of treatment was less than 20%. Virtually, all patients were still under primary ARVT over 12-month treatment. All patients (100%) withdrew their ARV drugs on time. No stock storage regarding various classes of ARVs was noted during the study period. **Conclusion**: At the end of this study we recommend to maintain regular follow-up of EWI, and combine it with the achievement of viral load.

Keywords

HIV, Resistance, EWI, Tivaouane

1. Introduction

HIV resistance to drugs has become a serious concern on a global scale. The WHO 2017 Report indicates in some places, a rate of resistance to some of the most used drugs against this virus, more than 10% [1]. Such resistance can cause

the failure of the treatment. To monitor and prevent HIV resistance to ARVs, since 2008, WHO has developed Early Warning Indicators (EWI) to estimate associated factors and R-ARV (Resistance to ARVs) without the need to perform resistance to ARV tests. In Senegal, the global resistance rate within the public health system, in Dakar, the capital, is put at 6.5% over M12 and 8.9% over M24 [2] [3]. With the decentralization of access to ARVs performed in Senegal within regions in 2001, the number of PLHIV under ARV treatment increased significantly from 1855 patients in 2004 to 2151 in December 2017 and close to 62% of these patients under ARV lived in a decentralized area where virologic monitoring is not yet effective, due to some technical requirements that are generally to be considered in monitoring patients, plus problems connected to the collect and transfer of samples to agreed laboratories in the capital [2]. The increased use of HIV treatment with ARVs in low- and middle-income countries is seen as a factor that has led to the resistance to some kinds of treatment.

It is in this context that we conducted this study in the Hospital of Tivaouane. The management and prescription of ARVs started from 2008 until 2017, the viral load as well as simplified alternative methods such as DBS for outlying areas was not routinely available, thus not allowing an optimal surveillance of therapeutic failures and of the resistance [3]. The objectives were:

- Evaluation of early warning indicators of resistance to HIV in this hospital from 2008 to 2016.
- Making recommendations for the prevention of resistance to ARVs.

2. Methology

Our study was carried on over the 8-year period (1st January 2008 to 31st December 2016), which concerns HIV-infected patients followed-up in the hospital of Tivaouane, a level-1 public health institution (PHI). The Medical and psychosocial care for Persons life of HIV (PLHIV) is ensured by a multidisciplinary staff composed of doctors from various specialized medical fields (a general practitioner, a dermatologist and an infectologist) and a pharmacist. Following screening and the start of treatment, patients are checked every second month for a consultation, except in case of emergency. Doctors are assisted in care-giving by a staff of caregivers responsible for further counseling and for the search for lost to follow-up patients. Basic biological tests and CD4 count are available for the purpose of follow-up. This hospital does not have any appliance to measure viral load. A device measuring viral load has been made available to the Thies medical region center since the end of March 2016 (Provincial capital).

The distribution of ARVs and stock management come under the responsibility of the pharmacist. Patients whose records were unusable and prophylaxis cases got after exposure to blood, other biological products and sex were not included.

Data was collected from individual patient, patient follow-up, and ARV dispensing records; drug stock cards, as well as data in the PLHIV treatment data-

base established by the National Council for the Fight against AIDS (CNLS).

As part of our study, five early warning indicators (EWIs) were selected from the eight proposed by WHO. This choice is justified by the fact that after situational analysis, only the five indicators were accessible and could be informed; it is as follow:

- EWI 1: Prescribing Practices for ARVT (Prescribing Indicator): Determine the percentage of patients starting ARVT in the site during a selected period, from those who were previously prescribed an appropriate fist-line ARVT.
  - ➢ The target is 100%.
- EWI 2: Patients lost to follow-up during the first 12 months: this is the percentage among patients starting ARVT in the site during a selected period, from those lost to follow-up within 12 months after the beginning of the treatment.
  - ➢ The target is less 20%.
- EWI 3a: Patients receiving first-line ARVT over 12 months (retention indicator): this is the percentage of patients starting ARVT in the site during a selected period from those who continue to follow an appropriate first intention ARVT 12 month later.
  - ➢ The recommended target is greater than or equal to 70%.
- EWI 4a: Withdrawal of ARV drugs on time: this is the percentage of patients withdrawing drugs in a selected month (denominator month) from those who have withdrawn on time prescribed ARV drugs within the next 2 months.
  - ➢ Target is greater than 90%.
- EWI 6: Steady delivery of ARVs: this is the percentage of the current month of a given year during which no stock shortage of various classes of ARVs occurred.
  - ➢ The target is 90%.

The data entry and analysis were carried out using Microsoft Excel 2016 software. The averages and percentages were compared using the chi2 test. Any difference below 0.05 was considered to be statistically significant.

For the calculation of EWIs, data entry and analysis were carried out using the EWI Extraction.

Tool developed by WHO (May 2010 version) [4].

3. Results

3.1. General Characteristics of PLHIV Followed in Tivaouane

From 2008 to 2016, 360 patients living with HIV were followed in the Hospital of Tivaouane. Their general characteristics are summarized in Table 1.

3.2. Early Warning Indicators of Resistance to HIV

- IAP1: ARVT prescribing practices (Prescribing indicator)

During the follow-up, we observed a variation of prescribing indicators

Table 1. General characteristics of PLHIV followed-up in Tivaouane.

Parameter		Number	Percentage (%)
Sex	Male	106	29
	Female	254	71
Meddle age ± standard deviation		42 ± 12.8	[6 months - 83 years old]
Occupation	Jobless	217	60
	Informal sector	130	36
	Other ones	13	4
Marital status	Bachelor	11	3
	Married	106	30
	Divorced	7	2
	Widower	18	5
	Not specified	218	60
Profile Serological	HIV1	306	85
	HIV2	32	9
	HIV1 + 2	19	6
Treatment	1st-line	178	92
	2nd-line	15	8
	3rd-line	0	0
Follow-up Medium duration ± Standard derivation		3.57 years old ± 3.02	[13 month - 10 years old]
Progressive Modalities	Death	71	20
	Ongoing follow-up	166	46
	Lost to follow-up	95	26
	Transfer	28	8

depending on the time. Only the years 2009, 2010 and 2012 recorded 100% rates, which were the target. Other years had rates ranging from 93.5% to 96.2% (Table 2).

- IPA 2: Patients lost to follow-up during the first 12 years of ART (Lost-to-follow-up indicator):

From 2008 to 2016, approximately 10% of patients were considered to be lost to follow-up over 12 months. This rate will drop over M24 and M36, and then increase over M60. Nevertheless, it remained below the target of less than 20% (see Table 3).

- IPA 3a: Patients on appropriate first-line ART over 12 months (retention indicator).

Among patients under first-line ART, more than 90% were still under this treatment after follow-up over 12 months (see Table 4). The recommended target is greater than or equal to 70%.

- EWI 4a: Withdrawing ARV drugs within indicating deadlines for this purpose.

Table 2. Distribution according to the evolution of ARV prescribing practices over years from 2008 to 2016.

Years	PLHIV starting their ARVT	PLHIV under appropriate treatment	EWI1 (%)
2008	46	43	93.5
2009	27	27	100
2010	30	30	100
2011	38	36	94.7
2012	25	25	100
2013	41	39	95.1
2014	33	31	93.9
2015	26	25	96.2
2016	23	22	95.7

Table 3. Distribution of patients based on changing terms.

	Follow over M12	Follow over M24	Follow over M36	Follow over M60
Dead patients	29	3	7	5
Transferred patients	6	2	1	1
Lost to follow-up patients	34	10	5	6
Total patients under ARVT	289	220	205	192
Proportion of Lost to follow-up	11.7%	4.5%	2.4%	3.1%

Table 4. Retention of patients over 12 months under first-line ART.

Years	Appropriate first-line treatment	Keeping first-line treatment over M12	Retention indicator over M12 (%)
2008	43	41	95.34
2009	27	25	92.59
2010	30	29	96.66
2011	36	36	100
2012	25	25	100
2013	39	38	97.43
2014	31	29	93.54
2015	25	23	92
2016	22	22	100

All patients (100%) withdrew their ARV drugs within deadlines.

- EWI 6a: Regular delivery of ARV

We didn't note any stock storage during our period of study.

4. Discussion

This study, on patients infected by HIV followed-up in the Hospital of Tivaouane from January 2008 to December 2016, allowed us to better apprehend their socio-demographic, clinic, para-clinical and progressive characteristics; and estimate EWIs of the resistance in this caregiving center at a decentralized level.

Results from the exploitation of data give rise to the following feedback:

- General characteristics of the population of the study

From 2008 to 2016, PLVIH have been followed in our structure; epidemiologically, our patients show (gender, middle-age, occupation, marital status) the same characteristics as those followed-up within other structures in Senegal [5] [6] [7] and in Sub-Saharan Africa [8] [9]. The average follow-up duration was 42.84 months. The most used treatment was the combination of 2 nucleotide analogues into a unique non-nucleotide analogue of the inverse transcriptase with higher proportion of schema made of Tenofovir. This protocol complies with first-line national (ISA ARV) and international recommendations. Only 15 patients from our cohort were under second-line treatment. No patient was under third-line treatment.

Without surveillance of viral load, the transition to second-line diets is sometimes delayed, and then cause a second accumulation of mutations of resistance, which can impair the effectiveness of the second-line ARVT [1] [3] [5].

4.1. EWI Characteristics

Early warning indicators are needed for assessing the risk of HIV resistance to antiretroviral, and should allow us to understand the risks of HIV resistance to ARVs due to failure in the management of the disease by ARVs.

In our study we took an interest in the following indicators:

- Prescription practices;
- Lost to follow-up patients during the first 12 months of ART;
- Retention of patients under first-line ART in the 12th month;
- Withdrawal of drugs on time;
- Stock storage.

Most of the studies on this theme are focused on several sites, which have not been the case in ours, which is focused on a single site, but this provides us an outline at local level.

4.2. Prescription Practices (EWI1)

Only the years 2009, 2010 and 2012 recorded 100% rates which were the target. This could be due to various changes to national guidelines over the study period regarding first-line protocols. Such changes were due either to a lack or withdrawal of some molecules, or to the sale of new ARVs, or to the standardization of protocols in relation to international standards.

Nevertheless, the threshold is higher than the one found in the work achieved

in Côte d'Ivoire, where only 11% of sites had reached the threshold of at least 70% of patients on appropriate first-line treatment [10].

4.3. Those Lost to Follow in the First 12 Months of Antiretroviral Treatment (EWI2)

In Senegal, the estimate at national level for retention regarding care showed that 75.7% of adults were kept after 12 months of treatment [2].

In our documentation, we recorded about 10% of lost to follow-up over 12, or a retention rate of 90%. Such figure is similar to that found in a study conducted in the Fann's Infectious Diseases Department, a reference Department as part of caregiving for PLHIV where it was 11.1% [9]. It is significantly lower than that found in Côte d'Ivoire where a total of 33% of patients were lost to follow-up during the first 12 months of antiretroviral treatment. However, it should be noted that, 20% of sites had less than 20% of lost to follow-up patients [10].

However, in Namibia, the retention rate was 79% after 12 months for adults, and 82% for pediatrics [11]. In Vietnam, it was 81.2% among adults, and 84.4% among children [12]. However, it should be noted that, in this latest study, retention regarding care rates between main sites and corner sites was similar for adults and pediatrics.

This finding is somewhat amazing, as decentralized sites can be expected to be better in keeping treated patients due to their convenience and reduced size. For example, Chan *et al.* demonstrated that patients treated in decentralized health centers in Malawi were 60% less likely to be lost to follow-up for the first 10 months of care [13]. However, a similar study conducted in Kenya showed that, patients in a primary health care facility were less likely to be lost to follow-up than those enrolled in a secondary health facility. Distance can also be a curb [14]. Maru showed that, with a statistically significant difference, patients whose residence was distant stopped their follow-up more easily [15].

4.4. Percentage of Patients Kept under First-Line Treatment over 12 Months (EWI3a)

Among patients under first-line ARVT, more than 90% were still under this treatment after 12-month follow-up. In Côte d'Ivoire, 51% of patients are still under appropriate first-line treatment over 12 months [10].

According to the 2016 EWI WHO report, 73.5% of individuals out of 7,062 clinics in 50 countries during the 2004-2014 periods were kept in care facilities 12 months after initiation of ARVT [16]. To keep adequate suppression of virus replication, the ARV treatment adherence level should be greater than 90%. The failure to comply with this results in the emergence of virus resistance causing therapeutic failure. The World Health Organization recommends second-line treatment in the event of failure of first-line treatment [16] [17].

4.5. Withdrawing Drugs on Time (EWI4a)

This is an important measure of the adherence of the patient linked with HIV

resistance, virologic failure, and increased mortality. Regular 48-hour treatment interruptions are certainly linked with virologic failure and the emergence of virus resistance, so it is important to follow-up withdrawals on time to ensure uninterrupted ARV adherence. In our documentation, data from pharmacy show a 100% rate. In Namibia, only 21% of adult sites and 33% of pediatric sites reached the target > 90% of patients getting treatment in time [11]. Also, in Zimbabwe in 2013, only 22% of adult sites and 4% of pediatric sites reached > 90% [18]. And according to the Cameroon 2013 Early Warning Indicators Report, only 33% of sites achieved this objective [19]. According to the 2012 Global Early Warning Indicators Report, in other African contexts, only 15% of the 321 adult sites monitoring on-site withdrawal of pills had reached their target of >90%. The 2016 Global Report on early warning indicators also showed that, out of 5,027 clinics in 9 countries during the 2010-2014 period, 85.5% (IC 95%: 72.1% - 93.1%) of taking pills were on time, below the WHO target of 90% [16].

4.6. Regular Delivery of ARVs (EWI6)

There was no ARV rupture during our study period unlike the (Kouadio J Y) study where only one site did not experience antiretroviral ruptures over the 12 months [10].

According to the 2016 Global Report on early warning indicators, 35.7% of clinics reported at least one stock, out of 1703 clinics in 35 countries [16]. Stocks in Namibia were due to poor inventory management practices, constraints related to space for storage and expiring ARVs, which resulted in unusable ARVs on sites.

Namibia has been working on strengthening supervision by regional pharmacists to ensure a good forecast of drugs, supply and distribution [11].

5. Conclusion

The results are definitely encouraging, but there are some shortcomings, particularly in terms of good practice regarding prescriptions and retention. We advocate a continuous update for physicians in relation to national recommendations concerning ARV treatment that is to be strictly observed, and the establishment of a formal and efficient active search system for the lost to follow-up patients, associating the medical staff, social works and families of patients. In addition, such results should be combined with the viral load now available to better assess the impact and importance of these resistance early warning indicators.

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