A SNAP-SHOT OF FIRST-LINE ART TREATMENT FAILURE CASES FROM MPUMALANGA PROVINCE ON THE DECENTRALISED PHARMACOVIGILANCE PROGRAMME DATABASE

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REVIEW ARTICLE

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ABSTRACT

The increase in ART use comes with the inevitable increase in cases of ART treatment failure, especially that patients are living longer on ART. The main objective of this short study was to conduct an interim review of the Pharmacovigilance database at the National Pharmacovigilance Centre of South Africa in order to profile cases of treatment failure with first-line antiretroviral therapy among HIV-infected patients in Mpumalanga Province. From 2851 ADR reports, 853 were reported for male patients, 1699 females and 299 had no gender reported. A total of 271 patients were diagnosed with treatment failure. 170 of these were female, 78 male and for 23 of the reports, gender was unreported. The mean age of the patients who were reported to have treatment failure was 36 years. The highest number of treatment failure was reported from the age group 31 - 40 years with the majority being females. A strong correlation was observed between female sex and treatment failure. The South African National Pharmacovigilance Centre decentralized Pharmacovigilance database is a useful tool that can be used to consistently monitor and document ART treatment failures.

Keywords: Immunological, Virologic, ART, HIV/AIDS.

INTRODUCTION

The success of anti-retroviral therapy (ART) in improving clinical, virological and immunological outcomes of HIV/AIDS is well documented.(1-3). However, as the use of ART increases, it is inevitable that some patients will develop ART failure, and this percentage is expected to increase as patients are living longer on ART. As the number of individuals taking ART in sub-Saharan Africa and South Africa in particular expands rapidly, ART failure is also rapidly increasing in magnitude as a major public health.

ART failure may present as one or more of clinical, immunological or virological failure/s. According to the WHO, clinical failure is defined as the occurrence of new opportunistic infections or malignancies. Immunologic failure is a rapid, serial rate of decline to the cut-off values for severe immunodeficiency or a fall in CD4 count by 50% from the recorded peak in the absence of any concurrent illness and/or persistent CD4 levels <100 cells/mm^3 after 12 months on ART. Virological failure occurs when ART fails to suppress and sustain a person's viral load (VL) to less than 200 copies/mL. It may also manifest as rise in the viral load that was previously suppressed. The three types of treatment failure may happen alone or together. (4) According the Southern African HIV Clinicians Society, virological failure is defined as two consecutive VL measurements of more than 1 000 RNA copies/ml, despite adherence and other issues addressed in the interval. (5) In general, virological failure happens first, followed by immunologic failure, and then clinical

progression. They may happen months to years apart but it has been reported that Virological failure precedes immunological failure by about 4 to 8 months. (Figure 1) (6)

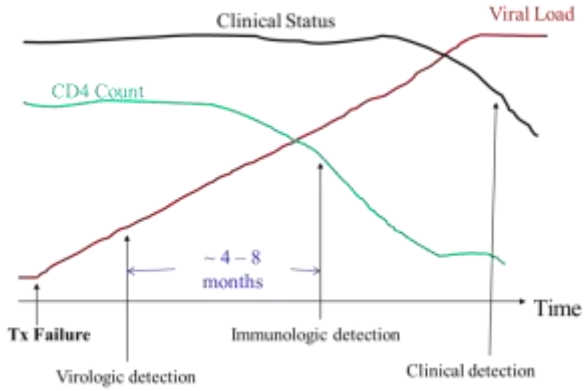

Figure 1: Time-Sensitivity of different failure definitions for detecting treatment failure (6)

It should be noted however that although clinical failure/detection comes towards the end of this order, it is the major predictor in most African countries that rely mainly on clinical outcomes with CD4 counts and viral load testing not being readily available.(7) In South Africa like most other African countries, non-compliance with treatment guidelines is a major problem that contributes to treatment failure.

Factors associated with, or may increase the risk of ART failure may include socio-demographic factors; baseline clinical factors {e.g. high pre-treatment viral load, low pre-treatment CD4 count, prior World Health Organization (WHO) stage}; drug-drug interactions (between the ART and concomitantly administered drugs); drug side-effects; drug toxicity; inadequate adherence to treatment, previous treatment failure; drug resistance; anti-HIV medications poorly absorbed by the body; other illnesses or conditions and/or substance abuse leading to poor treatment adherence. Other important factors include transmitted drug resistance also referred to as "Primary drug resistance" and Prescription errors. (8)

South Africa's Mpumalanga province is a resource-limited area and according to the provincial government, in the period 2008/09 there were 35,698 people on ART, in 2009/10 that number rose to 70,064, in 2010/11 it went to 1,11,402 then 1,44,069 people in 2011/12. In their 2013 provincial department of health report, Mpumalanga reported a colossal 2,09,727 people on the public ART programme. (9, 10) Considering this exponential increase in ART initiations in the province, the potential number of ART failures that may arise is an important public health concern that needs to be closely monitored.

Our main objective was to conduct a higher level review of the Pharmacovigilance database at the National Pharmacovigilance Centre (NPC) in order to profile cases of treatment failure with first-line antiretroviral therapy among HIV-infected patients in Mpumalanga Province. As we reported from the NPC previously, this database is created from spontaneous ADR reports for ART patients from the 26 decentralised Pharmacovigilance clusters in the province. (11, 12) A cluster is formed where structures or systems exist between a (sub) district hospitals and clinics, such as up or down referrals of patients. If there isn't a structure or system, geographic proximity is used/recommended to form the cluster. PV clusters consist of multidisciplinary healthcare provider teams including Doctors, Nurses, Pharmacists, Social workers, Laboratory technicians and Dieticians. All these healthcare practitioners (HCPs) participate in forming strategies of integrating ADR reporting in their daily activities. Patient-level information such as demographic data, laboratory results, ADRs, treatment outcomes, concomitant conditions and medications all linked through an anonymous patient identification number are reported on the ADR reports that the clusters send to the NPC for capturing onto the database. (10)

METHODS

We retrospectively reviewed the NPC Pharmacovigilance database for reported cases of treatment failure. Key search words included clinical, immunological, virologic, failure and/or treatment failure. The search covered data entered between July 2011 and July 2014 from Mpumalanga province. The data were analysed using STATA 10 statistical software package. (13) Descriptive statistics including counts, percentages, medians, ranges, means, and standard deviations were calculated.

This paper does not report on the use of experimental or new protocols and was not set

up as a study or research project but is part of the South Africa National Department of Health Pharmacovigilance programme. The brief retrospective review was done internally as part of an evaluation, so as to improve patient quality of care. ART as HIV/AIDS treatment exposes patients to a high risk of treatment failure so it is vital that this information is published in a reputable open source journal in public interest. The autonomy of the patients is protected as their identity was withheld from the data reviewers. Neither informed consent nor ethics approval was sought or deemed necessary because this is an epidemiological review in which it was impossible to identify the participants, a situation which is not unprecedented. This information will also benefit the people whose autonomy is only remotely likely to be harmed by its publication. (14)

RESULTS

The search returned 2851 ADR reports from Mpumalanga province, 853(29.92%) were reported for male patients, 1699(59.59%) females and 299(10.49%) had no gender reported. A total of 271 (9.51%) patients were diagnosed with treatment failure. 170 (62.73%) of these were female, 78 (28.78%) male and for 23 (8.49%) of the reports, gender was unreported. The mean age of the patients who were reported to have treatment failure was 36 years (SD=12).

The reports were categorised into five age groups namely Under 18, 18 – 30, 31 – 40, 41 – 50 and 51+. Overall, the incidence of treatment failure per age group was found to be 9.73% (25), 16.97% (46), 38.75% (105), 15.50% (42) and 13.28% (36) respectively (Table 2). The highest number of treatment failure was reported from the age group 31 - 40 years with the majority being females (62, 59.04%). A strong correlation was observed between female sex and treatment failure and was found to be statistically significant (*p* value < 0.001).

Table 1: Age distribution of patients with treatment failure in the Mpumalanga Province

Characteristic	Number of ADRs	Number of ADRs	Incidence (%) = reported/*n*	*P* Value
Age (years)				
Under 18	*Male 10*	25	9.23	
	Female 14			
	Unknown 1			
18 - 30	*Male*13	46	16.97	
	Female 33			
31 - 40	*Male 33*	105	38.75	
	Female 62			
	Unknown 10			
41 - 50	*Male 22*	42	15.50	
	Female 18			
	Unknown 2			
51+	*Male 19*	36	13.28	
	Female 17			

p value < 0.001

**Age not reported = 16, Both Age and Gender not reported = 7*

We found that 150 patients (55.35%) were reported to have virologic failure, 3 immunological (1.11%), 11 were diagnosed with both virologic and immunological (4.06%), while 113 of the reports were generally classified only as treatment failure (41.70%) without stating whether Virological, immunological and/or clinical. Time to

detection of treatment failure indicates the time between ART initiation and detection of failure of first-line ART. The mean time of detection of treatment failure (Virological, immunological or clinical) was found to be 34.5 months (SD = 18.8 months).Although males experienced treatment failure earlier than females as seen in the Kaplan-Meier curve (Figure 2), there was no significant difference in the survival experience between males and females (log rank *p* value=0.22).

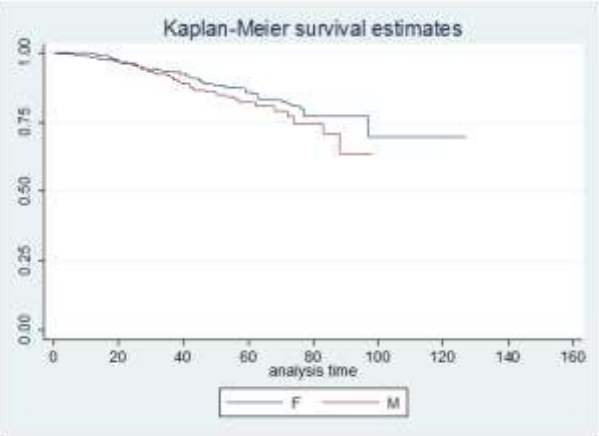

Figure 2: Kaplan-Meier survival estimates in the population

DISCUSSION

Mpumalanga province has a reported total of 2,22,000 people on ART and only 2851 (1.3%) suspected ADR reports have been received by the NPC over the last 3 years, suggesting gross under-reporting. (15) out of these, 271 were reported first-line ART treatment failures (9.71%). By mid-2014, an estimated 5.51 million South Africans were living with HIV/AIDS and 21,50,880 of them are currently receiving ART. (16, 17) Considering the number of South Africans on ART and the gross under reporting alluded to above, the population of ART treatment failures could be much higher and are a ticking time-bomb that will present great strain on the South African health system in the near future.

The results of this study suggest that patients between the age 31 and 40, especially females, showed the highest risk of treatment failure but that males experienced failure earlier. Furthermore, it found that treatment failure (clinical, virological and immunological combined) in the population of people living with HIV/AIDS on ART in this population occurs approximately 34.5 months after initiation. Given our findings in this snap-shot/exploratory study, we are currently undertaking a more detailed study of the data in an attempt to pinpoint which specific factors, socio-demographic, baseline clinical {e.g. high pre-treatment viral load, low pre-treatment CD4 count, prior World Health Organization (WHO) stage}, drug-drug interactions (between the ART and concomitantly administered drugs), drug side-effects, drug toxicity or inadequate adherence to treatment and/or transmitted drug resistance are contributing to the high levels of treatment failure observed.

CONCLUSION

Adverse events have been reported to be the most frequent reason for first-line antiretroviral therapy discontinuation or switch, (18, 19) Investigation of variables associated with their occurrence in a routine clinical practice setting is of increasing interest. Such an understanding is crucial to tailor antiretroviral regimens on patients' characteristics in order to increase the probability of ART tolerability and more importantly, to reduce the possibility of treatment failure. That said, South African HCPs should be encouraged classify their reports of treatment failure as clinical, virological and/or immunologic instead of generalising.

This brief study has given a snap-shot profile of cases of treatment failure with first-line antiretroviral therapy among HIV-infected patients in Mpumalanga Province from the decentralized Pharmacovigilance database during the period 2011 to mid-2014. It has shown that the NPC decentralized Pharmacovigilance database is a useful tool that can be used to consistently monitor and document ADRs as well as monitor treatment failures.

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CONFLICT OF INTEREST

No conflict of interest declared

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