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Analysis of efficiency of Isoniazid Preventive Therapy Programme among Human Immunodeficiency Virus-infected clients

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Abstract

Measures have been taken to reduce the mortality rate of Human Immunodeficiency Virus-infected clients. The use of isoniazid preventive therapy was one of those measures. Irrespective of using isoniazid preventive therapy mortality rate increased. The aim of this article is to analyse the causes and the factors that led to mortality among Human Immunodeficiency Virus-infected people who received isoniazid preventive therapy. A retrospective quantitative, explorative, descriptive isoniazid preventive therapy design was used. The records of 80 deceased patients who received isoniazid preventive therapy were reviewed through the use of a checklist. Of the records (N = 80), 75% were for female. The most highly indicated causes of death were gastroenteritis (18.75%), cryptococcal meningitis (17.5%) and pneumonia (16.25%).The causes of death of the patients who died before completing the six months of isoniazid preventive therapy; (28.75%) were gastroenteritis (21.7%), symptoms and signs of bacterial pneumonia (17.4%), cryptococcal meningitis (13%), pulmonary tuberculosis (13%), septicaemia (13%), and murder (13%). A breakdown in isoniazid preventive therapy, cotrimoxazole prophylaxis therapy and antiretroviral therapy interventions and the lack of holistic care for people living with Human Immunodeficiency Virus led to opportunistic infections leading to mortality among patients receiving isoniazid preventive therapy. A reorganisation of services of care for Human Immunodeficiency Virus-infected persons, such as provision of cotrimazole prophylaxis therapy and isoniazid preventive therapy to ensure a holistic approach to care, is recommended.

Keywords: Antiretroviral therapy, demographic factors, hospitalisation, mortality.

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Introduction

Botswana has one of the world's highest Human Immunodeficiency Virus infection rates (17.6%) (Botswana Central Statistics Office, 2009). Botswana has also the highest burden of tuberculosis per capita, with a tuberculosis notification rate of 470 per 100 000 members of the population (Botswana Ministry of Health, 2009). Although a high notification rate could be viewed in a positive light as signifying a well- functioning notification process, the Ministry of

Health indicated that in 2008 there had been an increase of 8.5% in the number of relapse cases, compared with 5.9% in 2007. The re-treatment of tuberculosis cases increased to 11.4% in 2008, compared with 5.9% in 2007(Botswana Ministry of Health, 2010).

Mycobacterium tuberculosis remains one of the leading causes of morbidity and mortality globally (Zumla, Mwaba, Huggett, Kalettpata et al., 2009). The World Health Organization estimated that in 2008 there were 11.1 million cases of tuberculosis (World Health Organisation, 2009). This included some 9.4 million people who had contracted the disease that year, of which 1.4 million were new cases of tuberculosis that occurred in people living with Human Immunodeficiency Virus (World Health Organisation, 2009).

Due to the highest mortality rate of Human Immunodeficiency Virus-infected clients, the isoniazid preventive therapy regime was implemented to all Human Immunodeficiency Virus-infected clients who came for health care service. The isoniazid preventive therapy regimen applied in Botswana is 300 mg isoniazid daily for 6 months. Isoniazid is known for its effectiveness (92%) in reducing tuberculosis related to Human Immunodeficiency Virus-infection (Samandari, Agizew, Nyirenda, Tedla et al., 2011). The above study showed that some patients on isoniazid preventive therapy became sick, were hospitalised and died. Despite the confirmed efficacy of isoniazid preventive therapy, concerns about the durability of protection, toxicity, drug resistance and adherence have limited its uptake (Golub, Saracen, Cavalcante, Pachelo, Moulton, King, Efron, Moore, Chaisson & Durovi, 2007). The protection offered by isoniazid preventive therapy to those infected with Human Immunodeficiency Virus may depend on a number of factors, including the degree of immune suppression of the individual, duration of isoniazid preventive therapy, adherence to and potency of the regimen, as well as the general risk of re-infection in that setting (Woldehanna & Volmink 2004).

The isoniazid preventive therapy programme evaluation done in Botswana in 2008 indicated that at the initial screening, the evaluation of patients was often incomplete, as physical examinations were not conducted routinely. In most cases physical examination was not performed and symptom screening was minimal. Health workers reported that clients collected their Isoniazid refills from the pharmacy without seeing a doctor or nurse (Botswana MoH, 2008). It is not clear whether these clients were simply overlooked or attended other health facilities or services, or were defaulting (Botswana Ministry of Health 2008:14). It became necessary to investigate what contributed to the high mortality of Human Immunodeficiency Virus-infected people while on isoniazid preventive therapy.

To address the concern raised above, the decision taken was to analyse the records of all deceased Human Immunodeficiency Virus-infected people who had received isoniazid preventive therapy from 2005 to 2008 in Botswana. All the records in the isoniazid preventive therapy register of patients that had fallen sick and had died were used as the basis for the study. All the available records were investigated in order to analyse and document the causes of mortality of Human Immunodeficiency Virus-infected people on isoniazid preventive therapy. The aim of this article is to analyse the causes and the factors that led to mortality among Human Immunodeficiency Virus-infected people who have received isoniazid preventive therapy.

The significance of this study lies in the opportunity to develop strategies to improve the quality of care and to reduce mortality of Human Immunodeficiency Virus-infected people on isoniazid preventive therapy. It could further contribute to future recommendations and interventions to prevent further illnesses and deaths among Human Immunodeficiency Virus-infected people and those on isoniazid preventive therapy. Medical and laboratory technologists and nursing and pharmaceutical professionals would use the findings to plan care in such a way that Human Immunodeficiency Virus-infected patients are comprehensively screened for tuberculosis before enrolling on an isoniazid preventive therapy programme, where they are meticulously monitored for the duration of the isoniazid preventive therapy programme.

Isoniazid preventive therapy refers to the use of isoniazid tablets or suspension to treat patients who are infected with tuberculosis but do not have active tuberculosis disease, a condition known as latent tuberculosis infection (World Health Organisation report, 2011). For these patients, a six- to nine-month course of isoniazid monotherapy significantly reduces the risk of progression from latent tuberculosis infection to active tuberculosis. Because Human Immunodeficiency Virus fuels the tuberculosis epidemic in countries with high Human Immunodeficiency Virus prevalence, providing isoniazid preventive therapy for latent patent Human Immunodeficiency Virus not only reduces the individual patient's risk but also helps to mitigate tuberculosis transmission to others (World Health Organisation report, 2011). World Health Organisation recommended use of isoniazid preventive therapy in areas with high Human Immunodeficiency Virus prevalence areas (World Health Organisation report 2011). In view of high tuberculosis rates, Botswana rolled out its isoniazid preventive therapy program in 2001 and uses six months course of isoniazid monotherapy. Despite the confirmed efficacy of the isoniazid preventive therapy concerns about the durability of protection, toxicity, drug resistance and adherence have limited uptake (Golub, Saracen, Cavalcante, Pachelo et al., 2007). The protection offered by isoniazid preventive therapy to those with Human Immunodeficiency Virus- infected may depend on a number of factors including the degree of immune suppression of the individual, duration of

isoniazid preventive therapy, adherence to and potency of the regimen as well as the general risk of re-infection in that setting (Woldehanna & Volmink 2004:10).

Methodology

A retrospective, quantitative, explorative, descriptive study was done in two cities in Botswana. The population under study consisted of all Human Immunodeficiency Virus-infected people who received isoniazid preventive therapy and for World Health Organisation there were records of hospitalisation and death. The 80 records were archived safely in the offices of the Botswana and United States of America Centers for Disease Control and Prevention (Botusa) in Gaborone. Examined records were of patients who had received isoniazid preventive therapy for whom there were notes on admission or death, such as a death certificate or a documented verbal autopsy report (documented verbal history relating to the illness that led to the death of the individual, collected by health personnel from a relative or a caregiver). A census was used because of the manageable sampling frame of 80 records.

The records of patients receiving their first to sixth month of isoniazid preventive therapy in January 2005 to December 2008 were selected. During this period, isoniazid preventive therapy was administered under close monitoring in two sites in Botswana. Patients were allowed to attend the same clinic only until completion of their prophylaxis. The six-month time frame was chosen because it would also provide a good sample size for the analysis.

The frequency of variables such as age, cluster determinant 4 for lymphocyte cells, body-mass index, tuberculin skin test, highly-active antiretroviral therapy, cotrimoxazole prophylaxis therapy and gender was determined. Information was categorised and the variables under study were compared. The variables were not manipulated. There was no control over the independent variables, namely risk factors.

Ethical clearance was obtained from the Higher Degrees Committee of the Department of Health Studies at the University of South Africa. Permission to conduct the study and ethical clearance were granted by the Ministry of Health, Botswana Health Research and Development Committee. Permission was granted for the use of records that formed part of the Botusa project. Privacy and confidentiality were respected, and records were not misused. Records and the checklist were anonymous, as they bore no names, and the records were coded.

Data collection

Data were gathered from the existing records during July 2013. Existing records of those who had taken isoniazid preventive therapy between January 2005 and

December 2008 were used to extract the data. A checklist comprising self-developed structured questions to extract data from all the records was used. The checklist was pre-tested once on five records that did not relate to the population under study. These records pertained to Human Immunodeficiency Virus-infected patients who had been admitted to hospital, were receiving isoniazid preventive therapy, and had died. The advantage of using a checklist for extraction of data from the records was that the same set of questions and in the same sequence was used.

The checklist consisted of 36 items, divided into the following 5 sections:

1. Demographic data
2. Baseline physical examination
3. Hospitalisation and reasons for hospitalisation
4. Drug history
5. Information related to the death of the records

All 80 records were examined over a period of 2 weeks. On completion of the data collection, the data was entered into the computer on an Excel spreadsheet.

Data analysis

The Statistical Package for Social Sciences (SPSS) version 13.0 was used for the analysis of the collected data. Descriptive statistics included frequency tables and measures of central tendency such as mean, median, mode, variability, variance, standard deviation and range on ratio continuous variable. These were used to summarise each extracted response from all the records. Variables that were analysed included age group, cluster determinant 4 for lymphocytes cells count (CD4), and cotrimazole prophylaxis therapy. Explorative analysis was also applied wherever possible. This included summarising data using statistical charts in the form of pie charts, bar graphs for nominal variables and histograms for continuous variables.

In order to determine the causes of mortality among patients, the focus was on finding the modal causes of mortality. Frequency tables were used to analyse the corresponding variable. In order to explore the risk factors for mortality among patients receiving isoniazid preventive therapy, patients were divided into two distinct groups – those who had died during the six months of isoniazid preventive therapy administration, and those who had died afterwards. For the purposes of this article, the group of patients who died before the end of the six months of isoniazid preventive therapy will be referred to as “Group 1”, and the group of patients who died subsequently will be referred to as “Group 2”.

Results

Of the 80 patient records considered, 75% related to female patients, and 25% to male patients. In a study conducted in Botswana, Acquired Immune Deficiency Syndrome was found to be the leading contributor to mortality among females (9.1%) and the third most significant contributor to mortality among males (7.0%) (Setlhare, Forchev & Gabaitiri, 2009).

The cluster determinant 4 for lymphocytes cells count, of the majority of patients (78.87%) were below 400, while 4.23% had a cluster determinant 4 for lymphocytes cells count of 500–599, and a further 4.23% had a cluster determinant 4 for lymphocytes cells count of 600–699. In the case of patients whose data was complete, the records indicated that their corresponding count ranged from 18.7 to 907.

Group 1 (patients who had died during the 6 months of isoniazid preventive therapy administration on the basis of their tuberculin skin test results) comprised 23 patients: 1 for whom the tuberculin skin test result was positive and 22 for whom the tuberculin skin test result was negative. The relative risk of those who have tested positive to those who have tested negative was 0.182. Thus, a positive tuberculin skin test result could be said to reduce the risk of death during the isoniazid preventive therapy administration period. Group 2 (patients who survived beyond the six months of isoniazid preventive therapy administration on the basis of their tuberculin skin test results) comprised 57 patients: 15 for whom the TST result was positive and 42 for whom the tuberculin skin test result was negative.

Forty-seven patients reported signs and symptoms of a variety of diseases. The leading self-reported illnesses were gastroenteritis (19.15%) and common cold/influenza (19.15%). These were followed by pneumonia/pulmonary tuberculosis (14.89%). The least self-reported illnesses were herpes zoster (2.13%) and hepatitis (2.13%). 85% of patients were not hospitalised during the six-month period of isoniazid preventive therapy administration, while 15% of patients were hospitalised.

Twelve patients were hospitalised for various reasons. Of these, 25% were hospitalised because of signs and symptoms of gastroenteritis; 16.7% were hospitalised because of vaginal bleeding; 8.3% were hospitalised with the signs and symptoms of hepatitis; 8.3% were hospitalised with symptoms of meningitis; 25% were hospitalised due to signs and symptoms of pneumonia/pulmonary tuberculosis; 8.3% due to seizures, and 8.3% due to oral candidiasis.

Of the patients hospitalised, 25% were diagnosed with gastroenteritis, followed by 16.67% diagnosed with bacterial and decubitus pneumonia, sepsis and

pulmonary tuberculosis. Isoniazid was administered to all 80 patients. 71.25% completed six months of treatment with isoniazid, while 28.75% received isoniazid for less than six months because they died of various causes within the treatment period.

Of the 80 patients reported in this article, 17.5% consumed alcohol (the type of alcohol and the extent of alcohol intake were not indicated) and 82.5% did not consume alcohol in the six months during which they received isoniazid preventive therapy. According to the results, alcohol consumption during isoniazid preventive therapy was considered to be one of the factors possibly contributing to mortality among Human Immunodeficiency Virus-infected people receiving isoniazid preventive therapy. Alcohol consumption during isoniazid preventive therapy increased the risk of death before the end of the isoniazid preventive therapy programme.

Of the patients considered for the present study, 28.75% fell within Group 1, and 71.25% in Group 2. Those in Group 2 died between 1 and 29 months after the completion of treatment. Gastroenteritis, pneumonia and 'other' (causes unrelated to Acquired Immune Deficiency Syndrome) were the leading causes of death in the case of patients in Group 1. Of these, 21.7% developed gastroenteritis, and 17.4% developed pneumonia and 'other' (illnesses unrelated to Acquired Immune Deficiency Syndrome) respectively.

Discussion

The majority of patients (75%) were female. According to the Botswana AIDS Impact Survey the Human Immunodeficiency Virus prevalence rate among females was 20.4% compared with 14.2% among males rates (Botswana Central Statistics Office, 2009). The AIDS Impact Survey in Botswana revealed Human Immunodeficiency Virus prevalence rate of 19.1% in urban areas, compared with 17.1% in rural areas rates (Botswana Central Statistics Office, 2009).

Parker (2011) attributes the higher prevalence of Human Immunodeficiency Virus among women to the greater vulnerability of women to Human Immunodeficiency Virus, since they are often subjected to gender violence, and are usually unable to insist on the use of a condom. Women's vulnerability to Human Immunodeficiency Virus infection in Botswana is directly related to an interplay of factors, where immediate needs in a context of poverty, unemployment or low income flow into transactional and inter-generational sexual relationships in which high partner turnover and concurrent sexual partnerships have become the norm.

The position of women in society is one of the drivers of the Acquired Immune Deficiency Syndrome epidemic. Since the prevalence of Human

Immunodeficiency Virus among women is high, and studies indicate that women are unable to negotiate condom use, there is increased susceptibility to repeated infection, which in turn compromises the immune system of an individual and leads to opportunistic infections and death.

Records showed that all the patients underwent thorough examination, including checking of temperature, chest X-ray, tuberculin skin test and tuberculosis symptom screening, before receiving isoniazid preventive therapy. This was done to avoid administering isoniazid preventive therapy to patients with active tuberculosis. Records showed that those with a cough during initial assessment were examined further for active tuberculosis, and if they were free from active tuberculosis, they were enrolled for isoniazid preventive therapy.

When active tuberculosis is not ruled out and a patient receives isoniazid as immunotherapy, the patient can develop non-resistance to isoniazid. The importance of thorough examination to rule out active tuberculosis prior to the commencement of isoniazid preventive therapy is emphasised (Reddy, Brady, Gilman, Coronel et al., 2010). Adding chest X ray to a "Symptom" policy would reduce new isoniazid resistance and multidrug-resistant tuberculosis (Multiple Drug Resistant tuberculosis) cases (Samandari, Bishai, Luteijn, Mosimaneotsile et al., 2011).

In the case of 80% of the patients, the tuberculin skin test was negative. A negative tuberculin skin test indicates the absence of latent *Mycobacterium tuberculosis*. There was no observable benefit in administering isoniazid preventive therapy to Human Immunodeficiency Virus-infected people not infected with *Mycobacterium tuberculosis* (Samandari et al., 2011). Results of the simulated meta-analyses conducted by Bachhuber and Gross indicated a probable mortality benefit of isoniazid preventive therapy in purified protein derivative-positive individuals (Bachhuber & Gross, 2009).

A cluster determinant 4 for lymphocytes cells count ranging between 0 and 299 (a combination of 0–99, 100–199 and 200–299). It was suggested that people with Human Immunodeficiency Virus who have not taken antiretroviral therapy and have a cluster determinant 4 for lymphocytes cells count above 350 are at greater risk of death than the general uninfected population, although this increased risk seems to be of modest magnitude. Having a higher count does not exclude one from the risk of dying; individuals, who are Human Immunodeficiency Virus-infected and on isoniazid preventive therapy, regardless of the level of the cluster determinant 4 for lymphocytes cells count, need regular monitoring for other opportunistic infections, as these increase the risk of death (Lodwick, Sabin, Porter, Ledergerber et al., 2010).

Forty-seven patients (25%) were hospitalised. Of those hospitalised, 8.3% died before completion of the six months of isoniazid preventive therapy. None of the patients were hospitalised at the time they were enrolled for the treatment. The study revealed low cotrimazole prophylaxis therapy use among patients. 10% (8 patients) received cotrimazole prophylaxis therapy, but no adequate monitoring of cotrimazole prophylaxis therapy took place. Cotrimazole prophylaxis therapy administration was inconsistent, ranging from 1 month to 11 months. The reasons for discontinuation were not indicated, even though 75% of the patients still had a cluster determinant 4 for lymphocytes cell count of below 200 after termination of cotrimazole prophylaxis therapy. Of the 25% who qualified for cotrimazole prophylaxis therapy at the time of enrolment, only 40% received cotrimazole prophylaxis therapy. This is probably due to poor monitoring and evaluation integration, and weak patient referral tracking. The records showed that patients were asked each time they came for their isoniazid preventive therapy review whether they were taking cotrimoxazole. Records did not indicate why those who were no longer taking cotrimoxazole had stopped taking it. There was no indication of patients with a cluster determinant 4 for lymphocytes count of less than 200 being referred for cotrimazole prophylaxis therapy.

The leading causes of death were gastroenteritis (18.75%), cryptococcal meningitis (17.5%) and pneumonia (16.25%). Date, Vitoria, Granich, Banda, Fox and Gilks (2010) have provided evidence that despite the effectiveness of cotrimazole prophylaxis therapy in reducing morbidity and mortality, nationwide implementation seems to be impeded by the lack of consistent supplies of cotrimazole prophylaxis therapy and lack of monitoring of the administration of cotrimazole prophylaxis therapy (Date, Vitoria, Granish, Banda, Fox & Gilks, 2010). Lawn and Wood (2011) make the observation that careful screening and prophylaxis for co-infections is also important, because multiple pathologies appear to be the rule rather than the exception in Human Immunodeficiency Virus-infected patients.

The records indicated that 82.5% of the patients did not consume alcohol during the six months of isoniazid preventive therapy. (Parker 2011) holds that patients who consume alcohol have a higher chance of being non-adherent to the drugs administered to them than those who do not consume alcohol. Women who consume alcohol are at greater risk of being sexually abused by men who consume alcohol.

According to (Parker, 2011) alcohol consumption is associated with sexual risk and vulnerability to Human Immunodeficiency Virus infection. Males are more likely to engage in higher risk behaviour following drinking, whereas risk to women is related to alcohol consumption by a partner (Parker, 2011). The records showed that of the 14 patients that consumed alcohol, 42.86% died before completing six months of isoniazid preventive therapy. The reasons for

death were recorded as murder, cryptococcal meningitis, Kaposi sarcoma of the lungs, vomiting and pneumonia. Of the 80 patients, 37.5% were on antiretroviral therapy. Of the 62.5% not on antiretroviral therapy the records indicated that 38% were eligible for antiretroviral therapy, but were not using it. The reasons for not taking antiretroviral were not stated.

Although the deceased patients were on isoniazid preventive therapy, there were various documented causes of death. A tally of 41.25% of the patients did not have any of the self-reported illnesses reported during the months of receiving isoniazid preventive therapy. This shows that patients often have life-threatening illnesses that they do not report to health workers, despite visiting the clinics every month. In the case of the 80 patients surveyed, over 32 different illnesses leading to death were reported; in most instances, two or more illnesses were recorded as the cause of death. Tuberculosis was therefore not among the three leading causes of death.

Recommendations

The three most common cause of death of the deceased patients were attributed to gastroenteritis, pneumonia and cryptococcal meningitis. Proper monitoring systems to ensure that patients take cotrimoxazole regularly should be in place and applied by nurses and doctors. Registers of patients should be kept on the use of cotrimoxazole**.** These must be regularly monitored and evaluated in order to ensure adherence to the regimen, which in turn reduces mortality. Intensive tuberculosis case finding through tuberculosis screening should be done at the antiretroviral therapy clinics, and isoniazid preventive therapy can be administered to patients without active tuberculosis.

Based on the results it is recommended that all health professionals offer increased health education. Intensive cotrimazole prophylaxis therapy and isoniazid preventive therapy education programmes must be implemented if they are not yet available, and improved if they are already in place. It is recommended that a subsequent version of this study with a wider scope should be conducted, as the present study dealt with only a small portion of Human Immunodeficiency Virus/Acquired Immune Deficiency-infected deceased patients who received isoniazid preventive therapy in Botswana. The future study should include Human Immunodeficiency Virus/Acquired Immune Deficiency-infected children on isoniazid preventive therapy.

Given the poor monitoring and evaluation of cotrimazole prophylaxis therapy in the case of patients receiving isoniazid preventive therapy, it is recommended that a package of activities, including training, advocacy and reorganisation of services, be put together to stop Human Immunodeficiency Virus-infected

patients travelling unnecessarily to multiple clinics to initiate isoniazid preventive therapy.

Conclusion

Records revealed that all of the patients underwent had undergone examination, such as tuberculosis screening, before commencing isoniazid preventive therapy. In the case of 80% of the patients the tuberculin skin test was negative, and they therefore did not have latent *Mycobacterium tuberculosis*. The leading causes of mortality were as highlighted in the foregoing discussion.

The fact that tuberculosis was not a leading cause of death among Patent Latent Human Immunodeficiency Virus on isoniazid preventive therapy shows the benefit of isoniazid preventive therapy. Service integration for gastroenteritis, pneumonia and cryptococcal meningitis should be considered a priority, as they are leading causes of mortality.

Records studied on mortality of Human Immunodeficiency Virus-infected people on isoniazid preventive therapy were taken in two sites of the two cities in Botswana which provided isoniazid preventive therapy. It could be possible that patients World Health Organisation died at other sites might have had different contributory factors to mortality. Because there was missing information in some records on the use of cotrimazole prophylaxis therapy, it was not possible to analyse the data to see if it is a risk to use or not to use cotrimazole prophylaxis therapy. Given the retrospective nature of the study having existing records as the source of information, the results may not reflect recent progress at various facilities in the implementation of these policies.

The leading cause of death was gastroenteritis, pneumonia and Cryptococcal meningitis and this necessitates service integration. With tuberculosis not being one of the major causes of death for Patent Latent Human Immunodeficiency Virus on isoniazid preventive therapy, this shows the benefit of isoniazid preventive therapy. Understanding the local epidemiology, as well as understanding risks and the service needs of the Patent Latent Human Immunodeficiency Virus served are essential components of developing appropriate, comprehensive services and thereby enhancing quality, public health impact. Service integration provides patients with seamless comprehensive services from multiple programmes without repeated registration procedures, waiting periods, or other administrative barriers. Not only is services integration needed for Human Immunodeficiency Virus and tuberculosis, additional prevention service integration for gastroenteritis, pneumonia and Cryptococcal meningitis should be considered a priority as they are the leading causes of mortality. By eliminating missed opportunities Patent Latent Human

Immunodeficiency Virus are afforded more health benefits which could maximise survival.

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