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ARTICLES

The use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of atrial fibrillation
Riyadh Mustafa Murtadha Al-Shehristani

Prevalence of antiretroviral treatment failure and associated factors in HIV infected
children on antiretroviral therapy at Gondar University Hospital, retrospective
cohort study
Abiyie Zeleke
The use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of atrial fibrillation

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Atrial fibrillation is a common cardiac arrhythmia that has many risk factors including some medications; however, the effect of non-steroidal anti-inflammatory drugs (NSAIDs) and its risk is not well assessed. This study was conducted to find out if there is an association between the use of non-steroidal anti-inflammatory drugs and risk of atrial fibrillation. The study was conducted at Al-Hussein Medical City Hospital in Karbala-Iraq as a retrospective case-control study between September 2014 and March 2015; including 90 patients with atrial fibrillation and 90 control subjects who were age and sex matched, and based on risk-set sampling. Current use of NSAID was started within one month and chronic use for more than one month was recorded. The current use of NSAIDs by patients with atrial fibrillation was found in 43 patients out of 90 (47.7%) of which new users were 29 (32.2%) and chronic users were 14 (15.5%), while it was found in 27 out of 90 (30%) of the control subjects who were current users of NSAIDs. That difference was statistically significant (p-value was 0.015), the odds ratio (OR) was 2.135 and 95% confidence intervals (CI) was 1.16-3.94. This study suggests that the current use of NSAIDs might be associated with increased risk of incidence of atrial fibrillation.

Key words: Non-steroidal anti-inflammatory drugs, atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac rhythm disorder observed in clinical practice that usually requires hospital admission. It is defined as a tachyarrhythmia characterized by predominantly uncoordinated atrial activation with consequent deterioration of atrial function (National Collaborating Centre for Chronic Conditions (UK), 2006).

It occurs generally due to abnormal electrical signals generated all over the atria, resulting in a quavering fibrillating atrial activity which leads to inadequate emptying of the atria. Consequently, the ventricular rate will be fast, chaotic and irregular which will also affect the emptying of the ventricles (Allessie et al., 2001).

The prevalence of AF doubles during each advancing decade of life, from 0.5% at the age of 50s to above 10% at the age of 80s (Heeringa et al., 2006). It is usually associated with increasing mortality and morbidity, mainly due to hemodynamic impairments that aggravate or even cause heart failure (Stevenson et al., 2004), and the increased risk of thromboembolic stroke resulting...
from stagnation of blood in the atria due to incomplete emptying (Wolf et al., 1991). There are many reported risk factors for AF (Rosiak et al., 2010):

1) Age; 2) hypertension; 3) heart diseases which include coronary artery disease, valvular heart disease, rheumatic heart disease, heart failure, cardiomyopathy, congenital heart disease, and pericarditis; 4) lung diseases such as chronic obstructive pulmonary disease (COPD) and pulmonary embolism; 5) hyperthyroidism; 6) other health conditions such as obesity, diabetes, renal failure and metabolic syndrome; 7) family history of AF and heart diseases; 8) external factors such as drinking too much alcohol, caffeine and other stimulants, smoking, and also psychological stress, fatigue and illness; 9) medications such as high-dose steroid therapy (Felson et al., 1988).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for treatment of pain and inflammatory conditions. The non-selective NSAIDs are known to cause gastrointestinal adverse effects (Laine, 2002) mostly by inhibiting cyclooxygenase (COX)-1 mediated production of prostaglandins, in addition to a range of nephrotoxic disorders (Whelton, 2001). The selective COX-2 inhibitors have improved gastrointestinal effect profile (Laine, 2002), but their renal and cardiovascular safety are often of concern because both renal (Whelton, 2001) and cardiovascular (Trelle et al., 2011; Aw et al., 2005) risks are frequently reported.

The use of both selective and non-selective NSAIDs may increase the risk of atrial fibrillation mainly through their renal and cardiovascular adverse effects; like fluid retention, electrolyte disturbances and blood pressure destabilization (Whelton, 2001; Trelle et al., 2011), but the evidence for such effects is still limited (Zhang et al., 2006; De Caterina et al., 2010).

So, confirming the association between the use of NSAIDs and the incidence of atrial fibrillation would have major clinical and public health consequences (Zhang et al., 2006), especially for older people because of the prevalent use of NSAIDs and the higher incidence of AF (De Caterina et al., 2010).

However, many confounding factors may increase the risk of AF, particularly by the underlying inflammatory disorders that lead to the use of NSAIDs (Engelmann et al., 2005).

The aim of this study was to find out if there is an association between the use of NSAIDs and the risk of incidence of the most common cardiac arrhythmia, atrial fibrillation.

METHODS

Study design

A retrospective case-control study was conducted in Al-Hussein Medical City Hospital in Karbala - Iraq. Patients with atrial fibrillation and control subjects were selected from the medical wards, the cardiac care unit (CCU) and from the outpatient clinic in the period from October 2014 to April 2015.

Case definition and inclusion criteria

Ninety adult patients (50 males and 40 females) were selected randomly with a diagnosis of acute atrial fibrillation, who were admitted to the CCU. Patients with chronic AF were excluded. In addition to that, 90 control subjects (54 males and 36 females) were selected randomly from the medical inpatients and outpatients departments using risk-set sampling, who share the same risk factors for AF as the patients group.

Data collection

A questionnaire was used to collect data from both patients and controls groups. A full medical history and medication history was taken from patients and control subjects. Age, sex, and body mass index (BMI) were recorded. Since there is a number of risk factors for AF that can also be associated with the use of NSAIDs (Engelmann et al., 2005), data was obtained from patients and controls on any previous history of disorders that may increase the risk of AF. Co-morbidities were also identified and recorded.

NSAIDs use

The current use of non-steroidal anti-inflammatory drugs (NSAIDs) was reported in both groups. The current users of NSAIDs were categorized into two groups: “new users” defined by having redeemed their first use within few days to 1 month, and “long term or chronic users” with chronic conditions such as arthritis that have been taking NSAIDs for a long time (more than 1 month). The use of NSAIDs which include non-aspirin non-selective NSAIDs (e.g. ibuprofen, diclofenac, naproxen, ketoprofen, meloxicam, piroxicam and mefenamic acid), and selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib, and etoricoxib) were recorded for both patients and control subjects.

Statistical analysis

The study variables are presented as means ± standard deviations (SD), and as numbers and percentages in contingency tables. Data was recorded and analyzed by using conditional logistic regression to calculate the odds ratios (OR) for atrial fibrillation among current users of NSAIDs, and T-test was used for continuous variables. P-value of < 0.05 was considered as significant.

RESULTS

Table 1 shows the demographic characteristics of patients and control subjects. There was obviously no significant difference between AF patients and control subjects regarding age, sex and BMI, so they are considered as matched groups. Table 2 shows age distributions among patients and control subjects:

Patient in the age range of 51-90 are the most exposed to AF and result in having greater risk for the disease, younger patients in the age range of 21-50 have lower incidence of AF, and control subjects with age range of 41-70 are the highest with other diseases that had great risk factors for AF. Table 3 shows the risk factors of AF for the occurrence of AF.
Table 1. Demographic characteristics of patients and control subjects.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AF patients</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ±SD)</td>
<td>61.4 ±15.2</td>
<td>60.3 ±14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>55.5%</td>
<td>60.0%</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (mean ±SD)</td>
<td>26.7 ± 4.4</td>
<td>26.4 ± 4.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2. Age distributions among patients and control subjects.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>AF Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>21-30</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>31-40</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>41-50</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>51-60</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>61-70</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>71-80</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>81-90</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 3. Risk factors for AF among patients and control subjects.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>AF Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Obesity</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>HT</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Smoking</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>CHD (IHD)</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>DM</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Family Hx.</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>CHF</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Lung dis.</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>CRF</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Each subject may have more than one risk factor.

Table 4. Current use of NSAIDs among AF cases and control subjects.

<table>
<thead>
<tr>
<th>NSAIDs use</th>
<th>AF Cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Current use*</td>
<td>43</td>
<td>47.7</td>
</tr>
<tr>
<td>New users</td>
<td>29</td>
<td>67.4</td>
</tr>
<tr>
<td>Chronic users</td>
<td>14</td>
<td>32.6</td>
</tr>
<tr>
<td>No use</td>
<td>47</td>
<td>52.3</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

* Odds ratio (OR) = 2.135; 95% Confidence intervals (CI) = 1.16 to 3.94; Z score = 2.4; P value = 0.015.

The most frequent risk factors that are found to be associated with AF were obesity 64.4%, hypertension 60% and smoking 56.6%. Other risk factors were: diabetes mellitus, coronary heart disease, congestive heart failure, chronic renal failure, lung disease, hyperthyroidism and family history of arrhythmia and heart diseases which have variable percentages in both patients and controls.

Table 4 shows the current use of NSAIDs among AF cases and control subjects. The current users of NSAIDs among AF cases was 43 patients (47.7%); of which the new users were 29 out of 43 (67.4%) and the chronic users were 14 out of 43 (32.6%) as shown in Figure 1, while the current users of NSAIDs among control cases was 27 subjects (30%); of which the new users were 19 out of 27 (70.3%) and the chronic users were 8 out of 27 (29.7%) as shown in Figure 2.

The odds ratio (OR) of AF among the current users of NSAIDs was 2.135, and 95% confidence intervals (CI) was 1.16 to 3.94. This was statistically significant (p-value was 0.015).

DISCUSSION

The most common cardiac arrhythmia worldwide that usually requires CCU admission is atrial fibrillation (AF). It is commonly associated with increased long term risk of stroke, heart failure and death (Fuster et al., 2011). The risk of AF is known to increase with age. In the elderly, slow heart rate which is mainly due to underlying alterations in autonomic tone and/or subclinical sino-atrial node dysfunction may potentially predispose older patients to escape rhythm, thus associated with an increased risk of AF (Benjamin et al., 2009). Therefore, older patients with age above 55 have more frequency of AF reaching about 70% as observed in this study.

Hypertension is a well-known risk factor for new-onset AF. Besides, other important cardiovascular risk factors, such as obesity, hyperlipidemia and cigarette smoking are less clearly related to the incidence of AF (Huxley et al., 2011). Obesity also as a risk factor of AF is strongly associated with osteoarthritis, which is one of the most common indications for NSAIDs and also the risk seemed to be higher in older people (Felson et al., 1988; Holliday et al., 2011).

After adjustment for age, sex, BMI and some other risk factors for AF among cases and controls, there was a statistically significant increase in the incidence of AF with the current use of NSAIDs. It was found that the odds ratio (OR) for AF among current NSAID users was 2.135 with 95% confidence intervals (CI) 1.16 to 3.94, which...
means that the risk of incidence of AF was about twice more in NSAIDs users.

These findings were comparable with that observed by other case-control study which found that the incidence rate ratio associating the current use of NSAIDs with AF was 1.33 (95% CI 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for selective COX-2 inhibitors as compared to non-users (Schmidt et al., 2011).

Another follow-up study reported that the current use of NSAIDs was associated with increased risk of AF as compared to never-use (hazard ratio (HR) was 1.76, 95% CI 1.07 to 2.88). Moreover, recent past use (within 30 days after discontinuation of NSAIDs use) was associated with an increased risk of AF as compared to never-use (HR was 1.84, 95% CI 1.34 to 2.51) when adjusted for age, sex and other potential confounders (Krijthe et al., 2014).

Furthermore, the newer and the chronic users of NSAIDs were recorded in this study. The percentages of newer users, who use NSAIDs for less than 1 month, and the chronic users, who use NSAIDs for more than 1 month, were nearly the same in both AF patients and control subjects with no statistically significant difference.

Although, there other studies reported an association between the use of NSAIDs and the risk of AF (De Caterina et al., 2010; Schmidt et al., 2011; Krijthe et al.,...
CONCLUSION AND RECOMMENDATIONS

This study suggests that there could be an association between the use of NSAIDs and risk of incidence of atrial fibrillation.

So, NSAIDS should be used very cautiously in older patients and especially those with a history of risk factors for AF, who are already at higher risk for adverse effects of these drugs, regardless of whether an association between NSAIDs use and AF do exist.

Furthermore, it is recommended to monitor the users of NSAIDs for the occurrence of AF especially in patients who have other risk factors.

Conflict of Interests

The authors have not declared any conflict of interests.

REFERENCES


Prevalence of antiretroviral treatment failure and associated factors in HIV infected children on antiretroviral therapy at Gondar University Hospital, retrospective cohort study

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As the use of highly active antiretroviral therapy (HAART) increases, the issue of drug resistance and subsequent anti-retroviral treatment (ART) failure appears as a challenge. The study aim to assess prevalence of ART treatment failure and associated factors amongst children on ART at Gondar University Hospital, North WEST Ethiopia, 2014. A retrospective cross-sectional study was conducted on children taking ART at Gondar University Hospital by using a systematic random sampling technique to include 225 under 15 Children on ART who took the drugs for at least six months. Data was collected from the patients’ medical records and analyzed by SPSS version 16.0. Binary logistic regression with multivariate analysis was used. Data from 225 children was analyzed, where the mean age was 10.8 years. The majority of children (77.4%) were in advanced clinical stage before initiation of HAART. About 60% of children were started with regimen of AZT-3TC-NVP. The original first line regimen was substituted in 44.9% of patients. About 101 patients who took ART for a mean of 60.3 months had poor adherence. There were 41 patients (18.2%) who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological. Out of all children with first line ART treatment failure, only 14 patients (34%) were detected and started on second line regimens. ARV prophylaxis for PMTCT (p=0.041), advanced clinical stage 3(p=0.046) and stage 4(p=0.035), base line CD4 less than 200 cells or 10% (p<0.001), tuberculosis co-infection (p=0.045), substitution of original regimen (p=0.001), poor adherence during follow up (p=0.002) and duration of ART above 60 months (p=0.033) were independent risk factors for ART treatment failure.

Key words: HIV/AIDS, clinical and immunological treatment failure, risk factors, Ethiopia.

INTRODUCTION

United nations programme on HIV/AIDS (UNAIDS)/World health organization (WHO) 2010 report estimated that, globally, about 33.3 million people are living with human immunodeficiency virus (HIV) in 2008 of which 30.8 million were adults and 15.9 million are women. Children under 15 years of age account about 2.5 million (7.5% of PLWHIV) (FMOH, 2010). Estimated number of PLHIV in Ethiopia in 2010 were
1,216,908 (41% males and 59% females) of which, 79,871 (6.6%) are children <15 years. 44,751 deaths occurred due to acquired immune deficiency syndrome (AIDS) in 2009 which made about 804,184 children AIDS Orphans in 2010 from the total anti-retroviral therapy Need in 2010 (Universal Access Target) 397,818, about 26,053 were children (FHAPCO/MoH, 2007).

Many studies have reported the success of highly active anti retroviral therapy in improving clinical and immunologic outcomes of children. However, as the use of HAART increases, the issue of drug resistance and subsequent treatment failure presenting as one or more of clinical, immunological or virological ART failure appears as a challenge (Tigist et al., 2012). The World Health Organization advocates a public health approach to ART, recognizing the potential role for plasma HIV-1 RNA testing but recommending clinical and immunological monitoring in most situations. However, little work has been done to assess the sensitivity and specificity of clinical and immunologic criteria to predict virologic failure, and we are aware of no other study evaluating these criteria in children (Emmett et al., 2010). From retrospective cohort study amongst 456 patients on NNRTI-based ART in Soweto, after a median of 15 months on ART, 19% (n = 88) and 19% (n = 87) had failed virologically and immunologically respectively. A cumulative adherence of <95% to drug-refill visits was significantly associated with both virologic and immunologic failure (p<0.01).

In the final multivariable model, risk factors for virologic failure were incomplete adherence (OR 2.8, 95%CI 1.2 to 6.7), and previous exposure to single-dose nevirapine or any other antiretroviral (adj. OR 2.1, 95%CI 1.2–3.9), adjusted for age and sex. As a conclusion, one in five failed virologically after a median of 15 months on ART. Adherence to drug-refill visits works as an early warning indicator for both virologic and immunologic failure (El-Khatib et al., 2011).

In an Ethiopian university hospital, among children on first line ART, clinical treatment failure and immunologic treatment failure were diagnosed in 6.2 and 11.5% respectively. The presence of chronic gastroenteritis or the appearance of a new opportunistic infection after starting treatment was associated with immunologic treatment failure.

Having chronic malnutrition (height for age in the third percentile or less) at initiation of ART, low CD4 at baseline, chronic diarrhea after initiation of first line ART, substitution of ART drugs and age less than 3 years old were found to be independent predictors of first line ART failure in children. Most of the first line ART failure cases were not detected early and those that were detected were not switched to second line drugs in a timely fashion. Children with the above risk factors should be closely monitored for a timely switch to second line highly active anti-retroviral therapy (World Health Organization (WHO) (2010).

ART failure is not a common diagnosis in most centers in Ethiopia. Very few patients among the needy are started on second line ART regimens. Previous studies have evaluated the patterns associated with switching from first line ART regimes to second line ART regimes; however, studies that evaluate the factors associated with first line ART regime failures in limited resource settings like Ethiopia and Africa at large are scarce (Workneh et al., 2009).

Hence, this study reported prevalence of first line ART treatment failure and associated factors which will help the personnel working on the ART program and clinicians to evaluate patients on ART in every visit for treatment failure and contributing factors. The study result can also be used as a baseline data for subsequent studies.

METHODOLOGY

Study setting

The study was conducted at Gondar University Hospital which is located in Gondar town. The Hospital is one of the teaching hospitals of Ethiopia, and referral hospitals in the Amhara Region with strong HIV /AIDS care and treatment center. The Hospital started delivering ART service in 2003. Free ART was started in 2005. Since the Hospital is the only referral hospital for the surrounding zones with wide catchment area, most patients have follow up in this hospital. Currently (up to June 30, 2013), there were 964 HIV positive children ever enrolled in chronic care. Of these children, 614 have ever started ART as to the National guide line. Patients are then followed based on the National guide line which recommends first visit after two weeks of initiation, every month for the next two to three months and every three months then after. They are followed with clinical staging at every visit and CD4 count /CD4 percentage every six month

Study period

The study was conducted from September to December, 2014 in HIV infected children on HAART from 2005 to 2013.

Study design

A retrospective cohort study was conducted on a children taking ART since March 2005 up to Dec 2013 at Gondar University Hospital to assess treatment failure and associated factors.
Study population

All HIV infected children who took first line ART for at least six months at the Gondar University Hospital were included in the study with the following inclusion criteria:

1. Under 15 years of age
2. A minimum of two follow-up visits with at least one visit six months post initiation of first line ART of any regimen.

Exclusion criteria:

1. If CD4 count/percentage not documented at least once after 6 month of ART.
2. If transferred out before treatment failure was detected.
3. If lost to follow up or died before detection of treatment failure.

Sampling technique and sample size

Systematic random sampling technique was used to select 259 patients from total of 614 patients on ART who took for six months. The formula used to select the sample was:

\[ n = \left( \frac{Z^2pq}{d^2} \right) \]

where

- \( n \) = sample size to be calculated for study
- \( n_0 \) = the minimum sample size from single population = 384
- \( Z \) = the standard normal value at confidence interval of 95% = 1.96
- \( p \) = population proportion in problem (estimated prevalence) =0.5
- \( q \) = 1 - \( p \) = 0.5
- \( d \) = degree of accuracy (estimated error) =0.05

The final study sample (n) will be:

\[ n = \left( \frac{n_0}{1 + \frac{n_0}{N}} \right) \]

(Reduction Formula because the total population is less than 10,000) where \( n \) = sample size to be calculated for study \( n_0 \) = the minimum sample size above. 

N = number of sampling population = patients on ART for at least six months = 614

So \( n = 236+23 \) (10% contingency for loss of subjects from any reasons) = 259

The data collected from 225 charts was analyzed (19 were excluded and 15 cards cannot traced)

Data collection procedures

Data was collected from the patients' medical records by using an English structured data retrieval form check list. Quality of data collected by data collectors was checked every day by principal investigator (author).

Data analysis procedures

The data was entered, cleaned and analyzed using SPSS version16.0. Cross tabulations between independent variables and dependent variable (treatment failure) were made to see relations. Binary logistic regression with multivariate analysis was used to see predictors of treatment failure (to compute p-value and adjusted odds ratio at 95% confidence interval) where p-value of less than 0.05 was taken significant

Operational definitions

Treatment failure is categorized as clinical, immunological and virological failure and defined as follows (FMH, 2008; Sebunya et al., 2013):

Clinical failure

Sever or recurrent infections or illness: recurrence or persistence of AIDS defining conditions (OIs and malignancies) or other serious infections.

Growth failure: persistent decline in weight growth velocity despite adequate nutritional support and without other explanation.

Progressive neurodevelopmental deterioration: lack/loss of neuro-developmental milestones or HIV encephalopathy.

Immunological failure

Incomplete immunological response to therapy: failure to improve CD4 values by ≥ 5% in child < 5 years with severe immune suppression (CD4 percentage< 15%) or failure to improve CD4 values by ≥ 50 cells/mm³ in a child 5 years or older and severe immune suppression (CD4 ≤ 200 cells/mm³)

Immunological decline: sustained decline of 5% CD4 below baseline at any age or decline to below baseline in absolute CD4 count in children 5 years or older.

Virologic failure: was not used because of the complexity of defining ART failure in children using viral load and the in accessibility of routine virologic tests in Ethiopia

Ethical consideration

The study proposal was approved by ethical committee for health research of the University of Gondar, collage of medicine and health sciences. A formal letter was received from hospital administration to review patients’ medical charts for data collection. Since it (the chart review) does not have direct contact with patients and doesn’t harm the patients, and data kept confidential with coding consent was not taken from each patient.

RESULTS

From the 225 children whose data was analyzed, 110 (48.9%) are males and 115 (51.1%) are females. Majority of children (59.5) lies in age group between 10 to 15 years and the mean age at time of study was 10.8 (range 3 to 14 years). Only 7 patients (3.1%) took ARV prophylaxis (PMTCT) where single dose NVP, single dose NVP with one week AZT or four week AZT was used (Table 1). As shown in Table 2 from the 225 sampled children on ART, about 137(60.9%) children started HAART with eligibility criteria of both WHO clinical stage and CD4 number/percentage. Majority of the children were in advanced clinical stage (stage3 and 4) and severe immune suppression before initiation of
Table 1. Socio demographic characteristics of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5 years</td>
<td>8</td>
<td>3.6</td>
</tr>
<tr>
<td>5-10 years</td>
<td>83</td>
<td>36.9</td>
</tr>
<tr>
<td>10-15 years</td>
<td>134</td>
<td>59.5</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110</td>
<td>48.9</td>
</tr>
<tr>
<td>Female</td>
<td>115</td>
<td>51.1</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100</td>
</tr>
<tr>
<td>ARV prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>3.1</td>
</tr>
<tr>
<td>No</td>
<td>218</td>
<td>96.9</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Base line characteristics of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>9.8</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>12.9</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>59.6</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>17.8</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100.0</td>
</tr>
<tr>
<td>CD4 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 200/ 10 %</td>
<td>75</td>
<td>33.3</td>
</tr>
<tr>
<td>200-350/10%-15%</td>
<td>79</td>
<td>35.1</td>
</tr>
<tr>
<td>Above 350/15%</td>
<td>71</td>
<td>31.6</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100</td>
</tr>
<tr>
<td>Tuberculosis co-infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>198</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HAART. About 60% (135 patients) of children started with regimen of AZT-3TC-NVP followed by D4T-3TC-NVP which accounts for 29.8% (67 patients). AZT-3TC-EFV, D4T-3TC-EFV, AZT-3TC-LPV/r and TDF-3TC-EFV are other first line regimens used. About 12% (27 cases) of patients have Tuberculosis co-infection during the initiation of the HAART.

As shown in Table 3, the original first line regimen was substituted in 101(44.9%) patients. The reasons for change were side effects, diagnosis of Tuberculosis, program shift from D4T to AZT or TDF and stock out of drugs. The side effects were common with AZT-3TC-NVP regimen, anemia being the commonest. About 27(12%) patients who were followed for a mean of 60.3 months (range 7 to 113 months), have poor adherence.

There were 41(18.2%) patients who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological 20 (48.8%), followed by immunological failure 14 (34.2%). Clinical failure alone accounts for about 7(17.0%). Out of all children with first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens. Mostly prescribed second line regimen is ABC-ddi-LPV/r (78.6%) followed by TDF-3TC-keleta (14.3%). The rest 27(66.0%) patients were not detected even though the first line treatment had failed (Table 4).

As shown in Table 5 ARV prophylaxis, advanced clinical stage, low CD4 count and tuberculosis co-infection before initiation of ART are independent factors that increase risk of treatment failure. Substitution of original regimen
Table 3. Follow up data of sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substitution of first line</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Side effect</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Diagnosis of TB</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Program shift</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>stock out</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>225</td>
</tr>
<tr>
<td>Adherence</td>
<td>Good</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>poor</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>225</td>
</tr>
<tr>
<td>Duration on ART</td>
<td>Below 36 months</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>36-60 months</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Above 60 months</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>225</td>
</tr>
</tbody>
</table>

Table 4. Treatment failure, type of treatment failure and second line drug intake among sampled children on ART from 2005-2013 at Gondar University Hospital, North West Ethiopia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunological</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>225</td>
</tr>
<tr>
<td></td>
<td>ABC-ddi-LPV/r</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>ddi-3TC-LPV/ r</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>TDF-3TC-keletra</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>14</td>
</tr>
<tr>
<td>Taking second line regimen</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>41</td>
</tr>
</tbody>
</table>

once or more for any reason and poor adherence during follow up had also increased the risk of ART treatment failure. Patients who took ART for longer duration (above 60 months) have high probability of first line ART treatment failure in comparison with those who took less than 60 months.

**DISCUSSION**

From this study, there were 41(18.2%) patients who had evidence of first line ART treatment failure of which the most common type is both clinical and immunological 20 patients (8.9%), followed by immunological failure 14(6.2%). Clinical failure alone accounts about 7(3.1%).

From the study by PLATO II in many countries more than 1000 children were followed for a median of 4.2 years from the time of ART initiation. Risk for triple-class failure was estimated to be 12% by year 5 of ART and 20% by year 8 (Holly, 2011). From retrospective cohort study amongst 456 patients on NNRTI-based ART in Soweto, after a median of 15 months on ART, 19% (n =
and 19% (n = 87) had failed virologically and immunologically respectively (El-Khatib et al., 2011). From case controlled study conducted in Uganda among 701 children on first line ART, 240 (34%) failed on first line ART (Sebunya et al., 2013). From retrospective cohort study done in Nigeria the rate of first line regimen failure was 18.8% (Isaakidis et al., 2010).

In retrospective cohort study done at Jimma university specialized hospital, among children on first line ART, clinical treatment failure and immunologic treatment failure were diagnosed in 6.2% and 11.5% respectively (8). From the retrospective cohort study conducted in Addis Ababa, there were 167 (14.1%) children with HIV/AIDS who had evidence of first line ART failure of which 70 (5.9%) had clinical treatment failure, 79 (6.7%) immunologic failure and 18 (1.5%) developed both immunologic and clinical failure (Tigist et al., 2012). From all studies above the prevalence of the ART treatment failure was comparable except that of Ugandan study which was higher and explained by the nature of study being case control with possible risk factors.

In this study, out of all children with first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens but the rest 66% of patients were not detected even though they have evidence of treatment failure.

From study conducted at Addis Ababa, Out of all children with first line ART failure, only 24 (14.4%) were identified. The mean time of detection of treatment failure was 19.7 months (SD = 14 months) and the mean time to switch to second line ART regimen, for those switched, was 24 months (SD = 11.67 months) (Tigist et al., 2012). The detection rate was higher in the current study which can be due to the high prevalence of treatment failure and the increased awareness for treatment failure as time goes.

In this study duration of ART above 60 months (p=0.033) was independent factor that increase the risk of ART treatment failure. From PLATO II study the factors for treatment failure were older age at time of study and longer duration on HAART (Holly, 2011). From the study conducted in Medical College and Research Institute of Bangalore, duration on ART for more than 3 years (P=0.0436) was associated with immunological failure. In multiple regression, duration on ART, age and nadir CD4 count (lowest ever) on treatment were predictors of immunological failure in these patients (Prabhakar et al., 2011). As it can be seen from these studies the chance of ART treatment failure was increasing as duration of ART increases which is 18.2% (in this study) with average duration of 60.2 months and 12% and 20% (PLATO II study) with mean duration of 60 months and 96 months respectively.

This study showed that ARV prophylaxis for PMTCT (p=0.041), base line CD4 less than 200 cells/µl (p<0.001) and poor adherence during follow up (p= 0.002) were also independent factors for ART treatment failure. In Medical College and Research Institute of Bangalore, low
CONCLUSION

The overall first line ART treatment failure was 18.2% (41 patients) in which the most common type is both clinical and immunological (8.9%) followed by immunological failure (6.2%), clinical failure alone accounts for 3.1%. Out of all children who have evidence for first line ART treatment failure, only 14 (34%) patients were detected and started on second line regimens. But about 37(66%) patients were not detected even though they have evidence of treatment failure during follow up. So close monitoring should be done to detect treatment failure early and shift to second line treatment.

ARV prophylaxis for PMTCT, advanced clinical stages (3 and 4), base line CD4 less than 200 cells/μl, tuberculosis co-infection, substitution of original regimen once or more for any reason, poor adherence during follow up and duration of ART above 60 months were independent factors that increase the risk of first line ART treatment failure. So this group of patients should be strictly evaluated for treatment failure at every visit since these factors increase the risk of first line ART treatment failure. Service providers should strengthen adherence counseling at every visit since it is a risk factor for treatment failure. Since there are many patients with first line ART treatment failure, second line drugs for children should be available.

The trend of shifting to second line treatment and the mean delay from detection of treatment failure and start of second line treatment was not determined in this study and can be studied in subsequent studies.

Limitation of the study

CD4 was not determined regularly every six months for some patients/ not documented. There was lack of viral load determination to assess virological treatment failure.

ACKNOWLEDGMENT

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Conflict of interests

The author has not declared any conflict of interests.

REFERENCES


