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Isoniazid Preventive Therapy Associated Hepatotoxicity among Children Living with HIV: Descriptive Case Series at Mildmay Uganda HIV/AIDS Clinic, Uganda

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Abstract

Provision of Isoniazid Preventive Therapy (IPT) as part of the comprehensive TB/HIV prevention intervention for people living with HIV & AIDS was recommended by WHO in 2011. Literature shows that Isoniazid (INH) associated hepatotoxicity is a common drug adverse event among people taking INH, and that it's associated with a high risk of mortality. These case series document INH associated hepatotoxicity in HIV-infected children receiving IPT in a resource constrained setting. They also further describe the challenges and lessons learnt while providing routine IPT among HIV-infected children in a resource-limited setting where laboratory tests for liver function monitoring are not performed routinely. The case series describe observed cases which presented to the Mildmay Uganda HIV/AIDS clinic between December 2013 and March 2014. The findings demonstrate that: 1) there was a 1.5% INH related hepatotoxicity incidence among children of four to ten years old; 2) 20% death rate—one out of the five children died and; 3) hepatotoxicity events on average occurred at 10.8 weeks after INH initiation while at the same time, all the cases had liver enzymes elevated above 10 times the upper normal limit values and reported late for medical intervention. The insidious onset of symptoms and signs of INH related hepatotoxicity coupled with lack of adequate resources needed to manage the condition were the major challenges to provision of routine IPT among children living with HIV in resource-limited settings in sub-Sahara Africa. Clinical vigilance, continuous education of clients and caretakers about the

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side effects or adverse events of INH and routine laboratory examination of liver function tests during follow-up of IPT in HIV-infected children are recommended to enhance early detection and prompt management of IPT associated hepatotoxicity.

Keywords

Isoniazid Preventive Therapy, Hepatotoxicity, TBHIV

1. Introduction

World Health Organization (WHO) recommended provision of Isoniazid Preventive Therapy (IPT) among people living with HIV as part of the TB prevention interventions in 2011 [1]. Hepatotoxicity is a common complication of Isonicotinic Acid Hydrazide (INH) or Isoniazid (an anti-tuberculosis drug), a condition that may lead to hepatic failure and subsequently hepatic encephalopathy requiring liver transplantation [2]. The existing body of literature reveals that drug-induced encephalopathies are important pharmacological side effects which occur seldom in clinical practice [3] and Isoniazid-induced encephalopathy is one of them [4]. INH hepatotoxicity presents a difficult management challenge and is associated with a high risk of mortality. A 5-fold and greater transaminases elevation or a 3-fold and greater elevation with symptoms is associated with high mortality risk that may exceed 50%, mainly due to hepatic failure unless liver transplantation is performed [2]. Symptoms and signs of hepatic damage, failure and eventually hepatic encephalopathy usually present late, making it harder for earlier detection of hepatic tissue damage, especially if routine laboratory monitoring is not done [2] [5] [6]. INH hepatotoxicity has been reported more frequently in developed countries than in less developed countries, such as Uganda [5] [7]-[9], where the burden of TB, HIV and AIDS pandemics is high and hence meriting accelerated adoption and implementation of the 2011 WHO recommendations on routine IPT among people living with HIV & AIDS [1]. Uganda is among the 22 world TB high burdened countries whose HIV prevalence is 7.3 percent [10] [11].

Although the burden of childhood TB among people living with HIV in Uganda is unknown, at Mildmay Uganda—a specialized HIV & AIDS care and treatment centre [12], unpublished reports indicate that children constitute 25 to 30 percent of all TB-HIV co-infected patients, while INH associated hepatotoxicity incidence among patients on routine IPT is 1.2 percent. This paper describes five case series of HIV positive children observed with INH associated hepatotoxicity while receiving routine IPT as part of the comprehensive TB/HIV prevention intervention for people living with HIV & AIDS in a resource constrained setting. All these children were on oral tablet INH of 10 mg/Kg taken once a day and none of them had ever previously experienced hepatotoxicity or active hepatitis events. All the five cases were fully assessed for IPT eligibility and none had a contraindication. Liver function testing wasn't a routine procedure while on IPT. One out of the five children died. In regard to the INH hepatotoxicity risk among children (especially at an increased dose of 10 mg/Kg), it's still unclear whether they have a minimal risk below threshold [13]. Previous studies have shown that older age is as a risk factor for hepatotoxicity in adults [14] [15] whereas children are reported to experience low risk [16]. Another study however did not demonstrate any age-specific difference for hepatotoxicity [17], while in another study age and gender were found not to be risk factors for hepatotoxicity [18].

2. Case Presentation

Case 1

A seven-year-old girl who initiated Highly Active Anti-retroviral Therapy (HAART) in 2007 and IPT in August 2013 developed INH hepatotoxicity which was later complicated by encephalopathy. She was reported dead one week after discharge from the In-Patient Unit. In 2007, she initiated Stavudine, Lamivudine and Nevirapine as HAART, but Stavidine was later substituted for Zidovudine in 2009 due to policy change phasing out Stavudine. Eleven weeks after initiation of INH, she reported to the clinic in company of her caretaker with a history of cough, fatigue and poor appetite for two weeks; and yellow eyes, passing dark urine, abdominal pains, nausea and vomiting and swelling of the face for one week. On physical examination, the patient was lethargic

and deeply jaundiced with a puffy face, but not febrile. There was no abdominal tenderness and the liver was not palpable. The abdominal ultrasound scan showed mild increase in liver parenchymal echogenicity with a rough echotexture but normal size and contour. Liver function tests indicated markedly raised transaminases, 30 to 40 fold above the upper normal limits. Renal function tests were within normal range while Hepatitis B and C tests were negative. Urinalysis showed Bilirubin 2^{+} and urobilinogen 33 micromol/l. A diagnosis of INH Hepatotoxicity was made basing on history, physical examination findings, Liver function test and abdominal ultrasound scan results. The Patient was admitted for supportive care and management of toxicities. On the day of admission, the patient stopped INH and Pyridoxine, and Nevirapine was also led out.

For the first three days of admission, the patient remained stable without new complaints. On the 4th day of admission, the patient's condition deteriorated mainly characterized by acute urinary retention, and reduced level of consciousness with Glasgow Coma Scale of 11/15. A diagnosis of INH hepatotoxicity with encephalopathy was made due to reduced level of consciousness. All drugs were stopped and the patient was given Lactulose, animal protein free diet feeding by the nasal gastric tube and Intravenous rehydration with normal saline. The patient however, experienced fluctuating levels of consciousness and episodes of aggressiveness. She later improved on supportive treatment and become clinically well—Glasgow Coma scale 15/15, she was able to carry on the activities of daily living and play. She was discharged on the 14th day of admission off all drugs and on an animal protein free diet with a review date of one week. Liver function test results on discharge were as follows: Alkaline Phosphatase (U/L): 387; Aspartate transaminase (U/L): 415.3; Alanine transaminase (U/L): 382.6; and Total Bilirubin (µmol/l): 352.7. Total Bilirubin, was twenty times higher than the normal limits, while Aspartate and Alanine transaminases were each ten times higher than the normal limits. Unfortunately, she fell sick before the appointment date and got admitted at a private Hospital in town where she died. There was no postmortem report from the hospital.

Case 2

A seven-year-old male reported to the clinic four weeks after initiating INH with a short duration (five days) history abdominal pain associated with passing of semi-formed stools. He had a skin rash which did not involve mucous membranes, neither the eyes nor the mouth. The child had initiated HAART (Zidovudine, Lamivudine and Nevirapine) at the age of one month while in a study setting in 2007, failed on first line HAART after nine months and was switched to second line, Didanosine, Abacavir and Lopinavir/Ritonavir. He had received Single dose Nevirapine at birth for Prevention of Mother to Child Transmission of HIV. Later Didanosine was substituted for Lamivudine in 2011 due to policy change to phase out Didanosine. At the time of diagnosis with the INH hepatotoxicity he had been on Abacavir, lamivudine and Lopinavir/Ritonavir for two years, and the diagnosis was made basing on the liver function test results, which were nine times the upper normal limit. The patient continued with HAART uninterrupted and was managed as an out-patient with supportive treatment. Monitoring liver function tests results done on the fourth day after stopping INH were within normal range: Aspartate transaminase (U/L): 36.8; Alaline transaminase (U/L): 33.2; and Total Bilirubin (µmol/l): 3.5. Currently, the child is well and continuing with HAART.

Case 3

A seven-year-old HAART naïve HIV positive female receiving HIV care developed severe INH associated hepatotoxicity, 21 weeks (five months) after taking IPT. She had received HIV care since 2007 for a period of about seven years. She reported to the clinic with a four-day history of fever, abdominal pain, vomiting and passing yellow coloured urine. There was no history of diarrhea and cough. Review of other systems had no significant symptoms and she had no previous history of having a liver disease. On medical examination, she was afebrile and deeply jaundiced. Liver function and bilirubin tests were done and results were raised above the normal upper limits, 40 times for the liver transaminases and 4 times for total bilirubin. Hepatitis B and C tests were also done and results were negative. A diagnosis of severe INH associated hepatotoxicity was made and the child was admitted to the paediatric inpatient unit at Mildmay Uganda for In-patient care. All medications were stopped and the child was managed by giving intravenous fluid and an animal protein free diet for supportive management. The child improved and was discharged after two weeks of admission. Liver function test results on discharge were as follows: Alkaline Phosphatase (U/L) 332.7, Aspartate transaminase (U/L): 44.2; Alaline transaminase (U/L): 69.8; and Total Bilirubin (µmol/l): 8.3. After INH hepatotoxicity resolved, she continued with Cotrimoxazole as prophylaxis for other HIV related opportunistic infections while at the same time preparation for HAART initiation began as per the Uganda National guidelines [19].

Case 4

A 12-year-old HIV positive female receiving HIV care and treatment (for seven years) developed severe INH associated hepatotoxicity 14 weeks after initiation of IPT. She initiated HAART in 2006 on Zidovudine, Lamivudine and Nevirapine regimen. She reported with a two weeks' history of fever and headache. On medical examination, she was afebrile and had marked conjunctiva jaundice. She was not anaemic and the systemic examination was normal. Liver function tests were done and results indicated raised liver transaminases five times the upper limit. Abdominal ultrasound scan indicated mild hepatomegally. Blood test results for malaria, Hepatitis B and C were negative. A diagnosis of INH associated hepatotoxicity was made and the child was admitted for In-patient supportive care on the paediatric ward. All medications were stopped, and the patient was given intravenous fluids and restricted animal protein diet. While admitted the liver enzymes kept rising and Prothrombin Time was done to determine the severity of liver damage. Prothrombin Time was 71.6 Seconds, fivefold higher than the upper normal limit (normal range: 9.8 - 14.2). International Normalized Ratio (INR) was 6.5, two-fold higher than the upper normal value (normal ratio range: 2 - 3). However, there was no history of bleeding tendencies. The patient was given Vitamin K. Prothrombin Time and INR results after ten days of admission were 20.7 seconds and 1.69 respectively. The patient was discharged on the 18th day after admission. Liver function test results on discharge were as follows: Alkaline Phosphatase (U/L): 287; Aspartate transaminase (U/L): 75.2; Alaline transaminase (U/L): 61.2; and Total Bilirubin (µmol/l): 111.5. After being discharged from the ward, she continued to attend clinical reviews in the Out-patient department on Cotimoxazole. HAART was restarted three months later after Alkaline Phosphatase, Aspartate transaminase, Alanine transaminase and Total Bilirubin levels had normalized.

Case 5

A four-year-old HIV positive boy was brought in by a care taker, seven weeks after initiating IPT with a five-day history of anorexia, yellow eyes, passing of yellow urine, abdominal pain and general body weakness. He had received HIV care since 2011 and HAART (Zidovudine, Lamivudine and Efavirenz) for 15 months. The child also had a past medical history of pulmonary TB disease in 2012 (2RHZ/4RH) and completed treatment. Test results were negative for hepatitis, and malaria. Liver enzymes were raised about twenty-fold above the upper normal limits. A diagnosis of INH associated hepatotoxicity was made, the child immediately stopped INH. The caretaker was advised on modifying the diet and restricted animal protein. HAART and Cotrimoxazole were continued uninterrupted and the patient was managed on ambulatory basis in the out-patient clinic without admission. Liver Function Tests normalized within eight days after stopping INH. Results were: Alkaline Phosphatase (U/L) 208, Aspartate transaminase (U/L) 44.7, Alanine transaminase (U/L) 16.8 and Total Bilirubin (µmol/l) 5.5.

A summary of the baseline characteristics of the 5 children prior to initiation of IPT is shown in **Table 1**.

3. Discussion

INH associated hepatotoxicity has previously been reported among people taking TB treatment and IPT, but mainly in developed countries [5] [7]-[9]. There is paucity of information regarding INH associated hepatotoxicity in resource limited settings especially among children living with HIV & AIDS—in particular, the sub Sahara African region which accounts for more than seventy percent of the world's burden of both HIV & AIDS pandemic and tuberculosis disease [10] [20]. Symptomatic INH associated hepatotoxicity incidence is

Table 1. Baseline characteristics before initiating IPT.

	Sex (M/F)	Age (Years)	CD4 cells (Absolute Count)	Percentage CD4 (CD3+ CD4+/CD45+)	ART Status (Yes/No)	ART Regimen When Initiating IPT
Case 1	F	7	839	43	Yes	Lamivudine, Zidovudine, Nevirapine
Case 2	M	7	1564	35	Yes	Abacavir, Lamivudine, Lopinavir/Ritonavir
Case 3	F	7	528	24	No	Naive
Case 4	F	12	1193	38	Yes	Zidovudine, Lamivudine Nevirapine
Case 5	M	4	1478	38	Yes	Zidovudine, Lamivudine, Efavirenz

estimated at 0.1 percent and is rare in individuals younger than 20 years of age [2] [21]. These five case series indicate a high incidence of INH associated hepatotoxicity in children—1.5 percent of the 322 children who were receiving IPT between August 2013 and March 2014. This is similar to what was found in another study done to assess the risk factors for INH toxicity among children with latent TB and TB [17]. It is however higher than 1.1 percent reported in a cohort study conducted in Botswana among adult people living with HIV & AIDS [6]. These findings are inconsistent with previous studies which indicated that high risk of INH hepatoxicity incidence is uncommon in children as compared to adults [12]. Findings are also inconsistent with the Botswana study findings which reveal that INH associated hepatotoxicity occurs after twelve weeks and is significantly associated with CD4 count less than 200 cells/mm^3. To the contrary, the case series indicate that INH hepatotoxicity incidence occurred in children (median age of seven years) with high CD4 count above 500 absolute cells or CD4 (%) above 24 percent, and earlier than twelve weeks [6]. The variations in the findings regarding incidence and its association with the CD4 immunological status between the case series and the Botswana study may have been compromised, though not exclusively, by the fact that the Botswana study did not have child participants. The case series reveal a new phenomenon of INH associated hepatitis in HIV infected children. The five cases were purposively selected, but there were other cases reported with INH hepatotoxicity in the clinic after March 2014. In regard to severity and mortality risk, the findings are consistent with previous studies which show that severe INH associated hepatotoxicity can easily be complicated by encepha-lopathy which has a poor prognosis and leads to death [2] [6]. Hence, severe cases require In-Patient Care for proper management of cases and assured attainment of good prognosis and treatment outcome. Unfortunately, a rock-solid bottleneck of un-accessible liver transplant services in developing countries such as Uganda will continue to undermine successful management of severe INH hepatotoxicity in case of extensive liver damage or failure.

On average, the duration between starting IPT and presentation of cases to the clinic was 11.4 weeks. The findings of these case series are consistent with previous findings in the literature which indicate that hepatotoxicity occurs several weeks after initiating INH, usually after one month [2] [5] [6]. The presenting features in these case series also were consistent with signs and symptoms reported in previous studies [5] [6] [21]. In the order of importance, they were: a) abdominal pain associated with nausea, anorexia, vomiting and sometimes passing loose stools; b) yellow eyes and passing dark urine and lastly; c) fatigue, headache and malaise. On medical examination, children were jaundiced and not febrile. In Botswana, the following combination of strategies was observed as an effective means of preventing death from INH hepatitis as opposed to repeated blood draws for monitoring LFTs, such as: short follow up review periods (at least monthly), education of patients' caretakers or IPT recipients on hepatic damage symptoms reinforced by immediate seeking of medical attention and stopping of INH as soon as symptoms occur [6]. However, the findings of these case series indicate that the above strategies are not sufficient. Despite the fact that caretakers received pre-IPT counseling sessions on adverse events and advise on what they needed to do in case hepatitis symptoms began to manifest, children reported late and the reasons for delayed presentation were unclear. In fact, the delay in seeking appropriate medical attention after onset of symptoms was noted as a serious challenge for early detection and prompt management of INH associated hepatotoxicity. The average duration of reporting symptoms was as late as two weeks. These findings thus underscore the need to emphasize patients or care givers' continuous education about INH hepatitis, clinical vigilance and laboratory monitoring since toxicity symptoms and signs manifest much later after hepatitis changes have occurred already and hepatotoxicity is tending to become severe immediate stoppage of INH upon onset of hepatitis symptoms.

Except for one child (Case 3) who was HAART naive, the other cases were on ARVs. As previously noted by Weisiger's finding [2], it was quite a challenge identifying a culprit drug (INH) from ARVs which also have a potential to cause hepatotoxicity. Previous studies indicate that ART is associated with INH hepatitis—the relative risk is higher among patients taking Nevirapine than those taking Efavirenz based HAART regimens—although the association was not statistically significant [6] [22]. Cases 2 and 5 were on Lopinavir/Ritonavir and Efavirenz respectively, they continued their HAART uninterrupted and recovered. Their LFTs normalized within eight days after INH was stopped. Cases 1 and 4 which had Nevirapine in their HAART regimen presented with severe forms of hepatitis and were given HAART holiday. They recovered much later than the other cases which were not on Nevirapine regimens. Liver function tests for Case 1 remained high (about nine times the upper limit) after two weeks of stopping INH and later the child died. Case 4 remained on HAART holiday for

several weeks and liver function tests normalized on the 25th day after stopping INH. Although, previous findings show that there is no statistically significant association between ARVs (especially Nevirapine) and developing INH associated hepatotoxicity [6] [22], Cases 1 and 4 show a clinical association between Nevirapine and severity of INH hepatotoxicty. It is important to note that the findings from previous studies which showed that the association of Nevirapine and INH hepatitis was not statistically significant were limited by the small number of patients that were studied [13] [19]. Hence, there is need for a bigger quantitative study to further explore the significance of the association between Nevirapine and INH hepatitis.

It is recommended that INH (and other hepatotoxic drugs) be withheld in case a patient's transaminase exceed 3 times the upper limit of normal level if associated with symptoms or 5 times the upper limit of normal if the patient is asymptomatic [2] [6] [22] [23]. The finding of the case series is consistent with the available literature emphasizing that stopping INH as soon as INH hepatotoxicity is diagnosed improves mortality risk. In fact, Liver transaminase levels decreased for all the cases after stopping INH. Secondly, it is recommended that after stopping INH, patients should be managed with supportive care [23]. Severe cases with significant elevation of Prothrombin Time and a 5-fold or greater transaminase elevation or a 3-fold and greater elevation symptoms and potential liver transplantation can also be hospitalized [5] [23]. The findings indicate that cases were managed with supportive care and actually improved except for one child who died. This is in keeping with the literature that states that INH hepatotoxicity toxicity is generally reversible after cessation of INH [18]. The grade of hepatotoxicity affects the duration for recovery of hepatotoxicity. However, the findings show that managing these cases is a great challenge in many poor countries such as Uganda due to insufficient resources coupled with the fact that liver transplant services are not available. Therefore, it is important to note that earlier detection and stoppage of INH among patients taking routine IPT in the early stages of hepatotoxicity increases survival, though it requires routine laboratory monitoring of liver function [21].

4. Conclusion

The case series demonstrate that a high incidence of INH associated hepatotoxicity may occur among HIV positive children receiving routine IPT, given as part of the comprehensive HIV care and treatment. Furthermore, children affected are more likely to present late to the clinics or hospitals for appropriate medical interventions. Since the onset of hepatotoxicity symptoms and signs may be insidious after starting IPT, cases are more likely to become severe due to delayed or missed diagnosis, hence carrying a high fatality risk or poor prognosis requiring in-patient care and skilled medical staff—which is most often not readily available in resource-limited settings. This fact underscores the need for: 1) vigilance during clinical visits' assessment to identify hepatotoxicity signs and symptoms and; 2) continuous education about the side effects and adverse events of INH among patients and caretakers of patients taking IPT. These interventions in turn improve suspicion, early detection and reporting of INH related adverse events both in the health facilities and in the community or at home. In addition, clinical monitoring alone has limitations in ensuring safety and earlier identification of organ damage, hence necessitating routine examination of liver function tests during the course of routine IPT. There is a need for research to: a) explore the effect or interaction of Nevirapine with INH in a bigger quantitative study and; b) assess possible risk factors or determinants of INH hepatotoxicity among HIV infected children taking routine IPT.

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Consent

Informed assent was obtained from the caretakers for all the five children—copies of the assent forms are available for review by the Editor in Chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors made equally substantial and intellectual contributions during the writing process of this paper.

Disclaimer

The contents of this manuscript are solely the responsibility of the authors and do not represent the official views of the CDC.

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Abbreviations

AIDS:	Acquired Immunodeficiency Syndrome
ART:	Antiretroviral Therapy
CDC:	Centers for Disease Control and Prevention
HAART:	Highly Active Anti-retroviral Therapy
HIV:	Human Immunodeficiency Syndrome
INH:	Isonicotinic Acid Hydrazide or Isoniazid
INR:	International Normalized Ratio
IPT:	Isoniazid Preventive Therapy
TB:	Tuberculosis
WHO:	World Health Organization