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Frequency of viral infections in adolescent and adult in-patient Ethiopians with acute leukemia at presentation to a tertiary care teaching hospital: a cross-sectional study

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Abstract

Background Leukemic patients are prone to infectious agents such as viruses due to dysregulated immune system resulting from infiltration of the bone marrow by malignant cells, chronic stimulation, reactivation of some viruses and viral pathogenicity as well as rarely from acquisition of a new infections leading to severe complications. However, the prevalence of these infections has not been systematically documented in resource-limited settings such as Ethiopia.

Objective To determine the prevalence of HBV, HCV, and HIV among adult and adolescent in-patients with acute leukemia before the administration of chemotherapy, at the Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia.

Methods A cross sectional study was conducted on 176 adult and adolescent inpatient Ethiopians, who were diagnosed with acute leukemia from April 2019 to June 2021. Socio-demographic characteristics and relevant clinical data were collected. Peripheral blood samples were collected and tested for HBV, HIV, and HCV using Enzyme-Linked Immunosorbent Assay (ELISA) and real-time PCR. Chi-square tests were used to assess associations between variables.

Results Of the 176 patients, 109(62%) were males. The median age was 25[IQR,18–35] yr, with a range from 13 to 76 year. The prevalence of HBV (positivity for HBsAg plus HBV DNA), HCV and HIV was 21.6%, 1.7%, and 1.7%, respectively. HBsAg was positive in 19 cases (10.8%). Among 157 HBsAg negative patients, 52(33.1%) were positive for Anti-HBcAg; of these seropositive cases, 47.5% were positive for HBV DNA. Most DNA positive, HBsAg negative cases (79.0%) had DNA concentrations below 200 IU/ml indicating true occult HBV infection (OBI). Of the 176 cases, 122 had a history of blood transfusions, but no statistically significant association was found between HBV infection and blood product transfusion history (P = 0.963).

Conclusions The prevalence of HBV, HIV and HCV in patients with acute leukemia was similar to the national prevalence level of these infections. Given the HBsAg positivity and the high prevalence of occult hepatitis B infection

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in our study, these patients may be at increased risk for chemotherapy related hepatitis flares. Hence, clinicians caring these patients are strongly advised to screen their patients for HBV and also for HIV and HCV infections routinely.

Keywords Viral infections, HBV, HCV, HIV, OBI, Acute leukemia, Ethiopia

Background

Acute leukemia (AL) is caused by genetic lesions within hematological progenitor cells [1]. Viral infections are common in hematological malignancies including leukemia due to immunocompromise mainly related to bone marrow infiltration and crowding, but also from the effects of immunosuppressive chemotherapy [2–6].

Blood-borne viruses such as Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Human immuno-deficiency virus (HIV), are common in developing countries and may affect patients with hematological malignancies and potentially complicate their treatment outcomes [7, 8]. Hepatitis B and C infection in hematological patients are reportedly prone to reactivation of latent infections and may also from new infection [7]. Several studies have reported associations between HBV/ HCV with hematological malignancies [9–11].

Moreover, higher prevalences of co-infections of these viruses have been noted among cancer patients [12]. However, little is known about the frequency of blood born virus infections in acute leukemia patients in resource limited settings like Ethiopia. This study, therefore, aimed to determine the prevalence of blood born viruses namely HBV, HIV and HCV before initiation of chemotherapy in acute leukemia adolescent and adult patients admitted in a tertiary care teaching hospital in Addis Ababa, Ethiopia.

Materials and methods

Hospital setting and patients

A cross-sectional study was conducted on those adolescent and adult patients (aged 13 years and above) diagnosed with acute leukemias who were admitted at the hematology clinic of Tikur Anbessa Specialized Hospital (TASH) from April 2019 to June 2021. TASH was established in 1972, has more than 700 beds and more than 700 health professionals. It is the main referral hospital in the country to diagnose, treat and manage cancer patients including hematological malignancies. Historically the adult Hematology clinic serves patients aged 13 years and above as well as provides service for more than 20,000 patients annually [13].

A standardized form was used to collect socio-demographic characteristics and relevant clinical data. Patients were recruited at the time of admission before starting any type of chemotherapy. Following informed consent and/or assent for those aged 13 to 17 years, peripheral blood samples were collected from study participants. Three ml of blood was drawn in EDTA tube and centrifuged for plasma separation; the plasma was stored at -70 ^{0} C until analysis.

HBV, HIV and HCV Testing

The stored plasma samples were thawed and used for ELISA, rapid and PCR tests. HBsAg was detected by enzyme immunoassay (HBsAg ELISA-Beijing WantaiBiological Pharmacy Enterprise Co. Ltd, China), HBsAg negative samples were tested for both IgM and IgG by anti-HBcAg ELISA kits (Monolisa Anti-HBc PLUS, Bio-Rad, France) at the Armauer Hansen Research Institute (AHRI). Anti-HBcAg positive samples were tested for HBV DNA by PCR. DNA was extracted, amplified, and detected from 200 µl plasma samples using a commercially available Real-time PCR platform (Abbott m2000rt) with a lower detection limit < 1.18 Log IU/ml genome equivalent to 15 IU/ml at ALERT hospital laboratory to determine Occult hepatitis B infection (OBI).

HIV was screened by Enzyme linked immunosorbent assay (Micro ELISA–HIV Ag & Ab, J. Mitra & Co. Pvt. Ltd., New Delhi, India). Positive samples were repeated with rapid tests using the Ethiopian national algorithm: CHEMBIO, Chembio Diagnostic Systems. Inc, (Medford, NY, USA); ABON, Abon Biopharm Co. Ltd, P.R. (Hangzhou, China); SD HIV 1/2 3.0, Standard Diagnostics, Inc (Republic of Korea).

HCV was screened by Enzyme linked immune assay (anti-HCV ELISA–Beijing Wantai Biological Pharmacy Enterprise Co. Ltd, China) and positive samples checked with Wondfo one step rapid Ab assay for HCV, Guangzhou Wondfo Biotech Co., Ltd, China. All the tests were performed according to the manufacturer's instruction. All quality control steps were handled as per the standard operating procedures.

Statistical analysis

Data was entered into an excel spread sheet, transported into SPSS version 25 statistical software and analyzed by descriptive statistics including mean, median, range, standard deviation and percentage. The Chi square test was used for studying the association between various variables. A P-value < 0.05 was considered statistically significant.

Results

A total of 176 adolescent and adult acute leukemia patients were included in this study and 109/176 (61.9%) were males. The median age of the study participants was 25[IQR 18–35] years; age range (13–76) years. Most,

Table 1 Baseline demographic and clinical characteristics of adolescent and adult acute leukemia patients, n = 176

Variables	Count (%)
Age	
13–17	35(19.9)
18–39	105(59.7)
40–59	27(15.3)
60 and above	9(5.1)
Sex	
Male	109(61.9)
Female	67(38.1)
Clinical Assessment	
Complex of anemia	112(71.3)
Pancytopenia	10(6.4)
Leukocytosis	5(3.2)
Blast crisis	2(1.3)
Other	28(17.8)
Leukemia Diagnosis	
ALL	83(51.9)
AML	67(41.9)
Blast crisis*	2(1.2)
Mixed Leukemia	1(0.6)
Not specified	7(4.4)

Abbreviations used: ALL (Acute Lymphoblastic Leukemia), AML (Acute Myeloblastic Leukemia)

* Chronic myelogenous leukemia undergoing accumulation of undifferentiated blasts

59.7%, were in the age group of 18–39 years (105/176), while 19.9% of the study participants were grouped within the 13–17 age category, and 5.1% were of the 60–89 age group. The majority of the cases (83/160, 51.9%) were acute lymphoblastic leukemia (ALL) cases based on Leukemia diagnosis (Table 1). Two patients were previously diagnosed with chronic myelogenous leukemia undergoing acute blast crisis [14, 15].

Among 176 cases, detectable HBV (either HBsAg positive or Occult HBV infection (OBI)) was detected in 21.6% (38/176) of the participants. Males were more infected than females, 22.9% (25/109) versus 19.4% (13/67), respectively; however, these differences were not statistically significant (P = 0.580). Patients in the age group of 18–39 years were the most commonly infected comprising 24.8% (26/105), and those in the age group of 60 and above, 11% (1/9), were the least affected. These differences were not statistically significant (p = 0.590).

HBsAg was detected in 19/176 (10.8%) of the cases. Among the 157 HBsAg negative samples, we further observed that 52/157 (33.1%) were positive for anti-HBcAg. Of these 52, DNA extraction, amplification and detection was conducted in 40 and viral DNA was detected in 47.5% (19/40) of the analyzed samples. This represented 10.8% of all samples. From these 19 samples, 15 had HBV DNA concentration below 200 IU/ml, indicating true OBI. Among DNA positive cases, 16/19(84,2%) were males and this gender discrepancy was statistically significant (p = 0.034).

Most of the cases with positive DNA were in the 18–39 year old age group, 73.7% (14/19). In contrast, 15.8% (3/19), 5.2% (1/19) and 5.2% (1/19) of the study subjects were among the 13–17, 40–59, as well as 60 and above age groups, respectively (p = 0.728).

From the total cases, 145 had transfusion histories recorded. Of these, 84.1% (122/145) had been transfused with blood or blood products. Among all cases with complete records, 21.4% (31/145) were positive for HBV (either HBsAg positive or DNA positive). Of the 31 positive cases 26 had been transfused. Of those who were HBV positive and had been transfused, 12 (46.2%) had occult infection, whereas 14 (53.8%) were HBsAg positive. There was no statistically significant association between HBV infection and previous transfusion history (P = 0.963) (Table 2).

HIV seroprevalence was 1.7% (3/176). All the three infected cases were female (p = 0.026); two were in the age category of 40–59, and one in the 60 and above age group. HCV sero-prevalence was 1.7% (3/176) and all the three infected cases were male (p = 0.171), two were in the 18–39 age category, and one in 40–59 group (Table 3).

The prevalence of viral infections is consistent with pooled results reported by systematic reviews of HBV and HCV prevalences at the population level in Ethiopia [16] as well as HIV in Addis Ababa [17]. To probe the possible relationship of viral infection and leukemia further, we determined whether there were associations between viral infection and subtypes of leukemia. As shown in Table 4, none of the viruses were associated with subtypes of acute leukemia.

Table 2 Cases with available previous transfusion history data before Chemotherapy, n = 145

Laboratory results	Transfusion status			P value*
	Transfused cases (122)	Non transfused cases (23)	Total	
	Count (%)	Count (%)	Count (%)	
HBsAg pos	14(11.5)	1(4.3)	15(10.3)	0.303
HBV-DNA pos	12(9.8)	4(17.4)	16(11)	0.289
Total HBV (HBsAg pos and HBV-DNA pos)	26(21.3)	5(21.7)	31(21.4)	.0963

Abbreviation used: HBV (Hepatitis B virus), HBsAg (Hepatitis B surface antigen), pos (positive)

* Chi-square was used to analyze the association

Table 3 HBV, HCV and HIV distribution in gender of acute leukemia cases

Laboratory results	Gender			
	Male	Female	Total	P value*
	Count (%)	Count (%)	Count (%)	
Total HBV (HBsAg pos and HBV-DNA pos)	25(22.9)	13(19)	38(21.6)	0.580
HBsAg pos	9(8.3)	10(14.9)	19(10.8)	0.166
HBsAg neg, Anti-HBcAg pos and HBV-DNA pos	16(14.8)	3(4.5)	19(10.8)	0.034
HBsAg neg, Anti-HBcAg pos and HBV-DNA neg	10(9.2)	11(16.4)	21(11.9)	0.150
Ag and Anti-HIV pos	0(0)	3(4.5)	3(1.7)	0.026
Anti-HCV pos	3(2.8)	0(0)	3(1.7)	0.171

Abbreviation used: HBV (Hepatitis B virus), HIV (Human Immunodeficiency Virus), HCV (Hepatitis C virus), HBsAg (Hepatitis B surface antigen), HBcAg (Hepatitis B core antigen), pos(positive), neg(negative), Ag (Antigen),

* Chi-square was used to analyze the association

Table 4 Association of HBV, HCV and HIV with acute leukemias, n = 160

		Leukemia Diagnosis					Total Count (%)	P value*
		ALL Count (%)	AML Count (%)	Blast Crisis Count (%)	Mixed Leukemia Count (%)	Non-Specified Count (%)		
HBsAg	pos	7(8.4)	11(16.4)	0(0)	0(0)	0(0)	18(11.3)	0.156
	Neg	76(91.6)	56(83.6)	2(100)	1(100)	7(100)	142(88.8)	
HBV-DNA	Pos	8(9.6)	7(8.4)	0(0)	0(0)	2(28.6)	17(10.6)	0.603
	Neg	75(90.4)	60(89.6)	2(100)	1(100)	5(71.4)	143(89.4	
Total HBV	Pos	15(18.1)	18(26.9)	0(0)	0(0)	2(28.6)	35(21.9)	0.428
	Neg	68(81.9)	49(73.1)	2(100)	1(100)	5(71.4)	125(78.1)	
HCV	Pos	2(2.4)	1(1.5)	0(0)	0(0)	0(0)	3(1.9)	0.830
	Neg	81(97.6)	66(98.5)	2(100)	1(100)	7(100)	157(98.1)	
HIV	Pos	3(3.6)	0(0)	0(0)	0(0)	0(0)	3(1.9)	0.242
	Neg	80(96.4)	67(100)	2(100)	1(100)	7(100)	157(98.1)	

Abbreviations used: HBV (Hepatitis B virus), HBsAg (Hepatitis B surface antigen), HCV (Hepatitis C virus), Pos (positive), HIV (Human Immunodeficiency Virus), Neg (negative), ALL (Acute Lymphoblastic Leukemia), AML (Acute Myeloblastic Leukemia)

* p values according to Chi-square test

Discussion

In this study, we analyzed the prevalence of three chronic viral infections, HBV, HIV and HCV in patients with acute leukemia admitted to a tertiary care teaching hospital in Ethiopia. Our study indicates that HBV (included occult infection) was the most prevalent viral infection in these patients. HBV infection is a major public health problem worldwide particularly in low- and middle-income countries [18–24].

In Ethiopia the prevalence of HBsAg has reportedly ranged from 3.4 to 11.9% [25–33]. Several factors have been identified to play role for the increased burden of HBV in resource constrained settings. These include under diagnosis, inadequate system for prevention (such as vaccination), and suboptimal contact tracing and treatment and care of affected individuals. Additional factors include poor awareness of the community about infections and their transmission, treatment inaccessibility and unaffordability and in some occasions limited awareness of the health professionals of the current treatment guidelines. Increased internal and external migration rates, administrative and regulatory issues that hinder commitment of resource mobilization at the national health regulatory level, and weak coordination with international partners, also play role [34–39]. In our study, HBV was detected in 38(21.6%) of our cases, out of which 19(10.8%) were positive for HBsAg and the remaining 19(10.8%) were positive for HBV DNA test. The later were negative for HBsAg.

These findings are consistent with studies of leukemia patients reported from Korea, Iraq and Iran [40–42] as well as consistent with prevalence studies in Ethiopia of HBsAg [28, 30, 33]. HBV DNA has been detected in peripheral blood, even when levels of HBsAg or anti-HBcAg are undetectable. When HBsAg is negative, detectable HBV DNA is termed Occult HBV infection (OBI).

Because blood levels may be low (<200 IU) (true OBI) and the liver is also relatively inaccessible [43–45]. Occult HBV infection can be challenging to detect, particularly in immunocompromised patients such as in patients with leukemia [46–48]. OBI prevalence is variable depending

on the nature of the study [43, 45, 49–51] hence the HBV DNA test is recommended as a preferred reliable marker for identifying HBV infection [45]. In leukemia patients, of the growing concerns of chemotherapy-related flares of HBV, which can be fatal, have led to recommendations for DNA testing [52–55]. Indeed, in our study, 19 (10.8%) of the cases were positive for occult infection, similar to studies conducted in China and India [23, 48].

It is notable that we observed male predominance of occult HBV infection in our study population (P=0.034). However, the difference in non-occult HBsAg positivity was not statistically significant between males and females (P=0.166). Contrary to our findings, multiple previous studies have reported higher prevalence of HBsAg rates among males [40, 41, 56–58]. The pathogenesis of HBV infection due to gender difference may be related to sex exposure risks such as occupational, travel, social and life style differences [41], as well as due to immune effects related to reproductive hormones. Moreover, stimulatory effects of androgen in males on interleukin-6 (IL-6) enhances HBV gene expression / transcription and decreases viral immune response such as apoptosis which may also be associated with oncogenesis, whereas estrogen influenced IL-6 production in females resulting in mediating apoptosis. In addition, estrogen inhibits HBV RNA transcription [59–65]. The finding in our study that occult but not non-occult HBV infection was more prominent among males in this leukemia cohort would be consistent with an immune based mechanism related to reproductive hormones.

A possible explanation underlying occult HBV infection in this leukemia cohort may be related to the use of transfusions of blood and/or blood products, known to transmit HBV infection [40, 42]. Although the majority of patients in our study had been transfused with blood products, we did not find a statistically significant association between either total or occult HBV infection and previous transfusion history (P>0.05), a finding in line with other reports of HBV positivity [23]. Further studies may reveal whether patients such as these are at risk for hepatitis flares in the context of chemotherapy treatment.

Regarding HIV and HCV seroprevalence in our patients, HIV seroprevalence was 1.7% (3/176), and all were females, greater than 40 years of age. Similar to our study, HIV positivity has been reported in patients with hematological malignancies elsewhere [66, 67]. Although HIV infection in leukemia patients has not been systematically reported in Ethiopia, many studies in other population groups have indicated that females are affected more than males in Ethiopia [68–70], with some exceptions noted [8]. The gender difference in HIV infection may be related to the greater mucosal surface area exposure in females during sexual intercourse as well as under diagnosis and screening related to asymptomatic presentation of other sexually transmitted diseases in women [71, 72].

Our study showed that HCV sero-prevalence was 1.7% (3/176) and all the three cases were males, two were in the 18–39-year age category, and one in 40–59. These findings are consistent with overall reported seroprevalence of HCV in Ethiopia in multiple studies, ranging from 0.6 to 6% [26, 27, 73, 74].

We did not observe differences in HBV, HCV or HIV prevalence among AML and ALL subtypes of leukemia. This contrasts with the findings of study who reported that AML patients had higher prevalences of HBV viruses in Korea [40]. This could relate to age differences in the presentation of both leukemia and HBV infection [9, 40].

Limitations

Due to resource limitation, some of anti-HBcAg positive samples were not evaluated for DNA, however, sufficient information were obtained from the analyzed samples. Moreover, because we did not include a control population of non-leukemic patients, we cannot be certain that these viral infection prevalences are identical to those of the general population; however, they are consistent with previous systematic reviews of multiple population-based studies in Ethiopia.

Conclusions

This is the first study in Ethiopia examining the prevalence of viral infections among leukemia patients. Our study showed that the prevalence of HBV, HIV and HCV among leukemia patients is similar to the national prevalence reported in the general population. Of particular concern is the high prevalence of HBsAg positive and occult hepatitis B, which collectively comprised a significant proportion of leukemia patients. Given that these patients are at risk for chemotherapy related complications, clinicians are strongly advised to screen their patients for HBV, HIV and HCV infections.

Abbreviations

AHRI	Armauer Hansen Research Institute
AL	Acute Leukemia
ALERT	All African Leprosy Rehabilit- ation Training Center
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloblastic Leukemia
DNA	Deoxyribonuceic acid
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linkedimmunosorbent assay
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IL	Interleukin
IQR	Interquartile Range
OBI	Occult hepatitis B Infection
PCR	Polymerase Chain Reaction
SPSS	Statistical Package for the Social Sciences
TASH	Tikur Anbessa Specialized Hospital

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Authors' contributions
Conception and a study designed: J.A and R.H ; Laboratory data collection and performing laboratory testing: J.A, Z.R and A.S; Reviewing and analysis of data: B.G and A.T; Clinical data collection interpretation, review and write up: A.G, A.A and F.T; Manuscript preparation: J.A; Manuscript revision and supervision: R.H, A.T,B.G, A.M and A.M; Final approval of the manuscript: All authors approved the manuscript.

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Data Availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethical approval and Consent
The study was approved by the Institutional Research Board of Aklilu Lemma Institute of pathobiology Addis Ababa University/Ref No. ALIPB IRB/009/2011/2018, College of Health Science Addis Ababa University (CHS IRB) Protocol number: 001/19/IM, AHRI/ALERT Ethics Review Committee (AAERC) Protocol No.PO34/18 and Consent /assent were obtained from participants or their families/caregiver. Confidentiality was maintained throughout the study.

Competing interests
The authors declare no competing interests.

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