Molecular Determining of HIV-1 with the Presence of Hepatitis B Virus and Hepatitis C Virus Co-infections

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Background: Because of the similar modes of transmission, simultaneous infection of viral hepatitis and HIV increasingly seen as a big problem related to humanity health.

Aim: In this study, we aimed to determine the drug mutations in hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infected HIV-1 patients in Turkey.

Study Design: Retrospective cross-sectional study.

Methods: The present was conducted between 2010 and 2017. HBsAg, Anti HCV and anti-HIV were tested with ELISA. All anti-HIV positive results by ELISA were verified for anti-HIV positivity by Western blot test, and Anti-HIV positive patients with HBsAg and/or Anti HCV positivity were included in the study. Subtyping and genotypic resistance analysis were performed by population sequencing of the viral protease and reverse transcriptase regions of the HIV-1 pol gene.

Results: We detected a total of 3,896 HIV-1 positive patients that their sera were sent from numerous hospitals across the country to PCR Unit for detection of drug resistance mutations and whose molecular laboratory tests were completed. The viral hepatitis co-infections were detected in 4.3% (n=170) in total and HBV and HCV co-infections were observed in 3.2% and 0.5% of all HIV-1 infected patients, respectively. Major HIV-1 subtypes were detected as a group M, subtype B (62.9%). However, 13.5% drug resistance mutation motifs were found in HIV-1 genomes of the patients that included to study.

Conclusions: In conclusion, because of similar transmission routes HIV positive patients have a risk for HBV and HCV co-infections. However, the ART drug resistance mutation pattern is observed to be similar with patients who are HBV and/or HCV negative. Patients with HIV-1 and their viral hepatitis co-infections should be recommended for careful surveillance.

Keywords: HIV-1, co-infection, hepatitis B virus, hepatitis C virus, molecular epidemiology

A recent report by the World Health Organization (WHO) states that approximately, 70 million people have been exposed to HIV and 35 million have died due to HIV and its problems. The cumulative count of people who are living with HIV was recorded as 36.7 million at the end of 2016. In 2016, one million people died due to HIV and associated complications (1). Even if the severity and speed of the rates change, HIV still continues to spread throughout the world. Therefore, it is an important issue in all aspects.

Because of the similar modes of contamination (contaminated medical injection, infected blood transfusion, sexual transition and intravenous drug use with unreliable materials), co-infection with viral hepatitis and HIV is often observed in the majority of countries. Additionally, co-infection with HIV and certain other infections, such as HBV or HCV infection, increases the urgency to start ART (2). Chronic HBV and HCV infections could cause increasing fibrosis in the liver. A fibrotic liver may cause cirrhosis and hepatocellular carcinoma and disease-related mortality or morbidity may be seen as a result. HBV and/or HCV may affect the HIV treatment regimen (3). In the clinical course of HIV infection, decreased CD4+ T lymphocyte counts, T-cell dysfunction and ultimately, immunodeficiency are observed. In addition, HIV causes B-cell functions like polyclonal activation, hypergammaglobulinemia, and decreased specific antibody responses. Therefore, in summary, the immunological response to pathogens is seen in decreased levels, causing patients to become susceptible to pathogens (4). Because of all these reasons, HIV and viral hepatitis co-infections deserve special attention.

Rates of chronic HBV in HIV-infected individuals vary significantly between regions and risk-based groups. Different patterns of transmission have been observed in studies. Approximately 5 - 20% of HIV positive patients are also co-infected with HBV (5). Rates of chronic HBV infection are much higher for patients who are infected with HIV than those non-infected by HIV, with 25% and 5%, respectively (6). The morbidity and mortality rates are significantly higher in those with HIV and HBV co-infection than with HIV alone, even with effective suppression of both HIV and HBV replication (7-9). On the other hand, HCV infection influences 20% of HIV positives, and this condition is mostly seen in low and middle-income countries (10).

It has been indicated in recent reports produced by the health authorities of the country that a total of 16,644 cumulative HIV/AIDS cases have been recorded in Turkey (11). In the last report of medical system is stated that approximately 12,000 patients have been used to highly active antiretroviral therapy (12). On the other hand, Turkey is a middle endemicity region for HBV prevalence. Even though differences are observed between regions, the prevalence of HBsAg was reported as 4.5% in the last meta-analysis (13). A study that evaluated HCV positivity reported the rate of anti-HCV positivity to be 1% in Turkey (14). It was reported that the contribution of HCV to cirrhosis increased during the last decade (15). In addition to the increase in HCV, HIV is a growing threat in Turkey, as explained above. From this perspective, co-infections may be observed in the same person. In a previous study, simultaneous infections of HIV-1 and HBV and HCV were 76% and 20%, respectively (17).

In the presence of the HIV infection, an increase may be seen at the progression of hepatitis caused by HBV and HCV.
Additionally, the presence of HBV and HCV may increase the effects of the HIV virus and contribute to a decrease in CD4 (19). In this study, we aimed to evaluate the prevalence of HIV and viral hepatitis coinfections as well as the molecular epidemiological characteristics of the HIV virus in order to describe the present situation and to understand of the possible altering in the near future.

METHODS

Patients:
The present retrospective cross-sectional study was conducted between 2010 and 2017. HBsAg, Anti HCV and anti-HIV were tested with ELISA. All anti-HIV positive results by ELISA were verified for anti-HIV positivity by Western blot test and Anti-HIV positive patients with HBsAg and/or Anti HCV positivity were included in the study. We detected a total of 3,896 HIV-1 positive patients that their sera were sent from numerous hospitals across the country to PCR Unit for detection of drug resistance mutations and whose molecular laboratory tests were completed. Totally, 3,896 patients that serum samples were sent for molecular analysis for antiretroviral drug resistances from numerous hospitals across the country to PCR unit were included to study. Approval was obtained from the local ethics committee, and the study was performed between 2010 and 2017. All patients were informed, and then consent was taken. The European AIDS Clinical Society (EACS) Guidelines were used for defining the clinical categorisation (20). K2-EDTA was used for collecting blood samples and after that, the samples were centrifugated, plasma aliquoted and then frozen at -80°C until testing.

Antibodies

Microparticle enzyme immunoassay kits (AxSYM; Abbott Laboratories, Abbott Park, IL, USA and Elecsys, Roche Diagnostics, Mannheim, Germany) were used for anti-HIV-1/2 antibody screening. All anti-HIV positive results determined by ELISA were verified for anti-HIV positivity by Western blot test (DIAPRO, HIV-1 LIA, Diagnostic Bioprobes Srl, Milano, Italy). Detecting for HBsAg was performed by enzyme immunoassay of ELISA (Enzyme-Linked Immunosorbent Assay) by (Architect System, Abbott Diagnostics, USA). Anti-HCV ELISA testing was applied by using a commercially current microparticle enzyme immunoassay kit (AxSYM; Abbott Laboratories, Abbott Park, IL, USA and Elecsys, Roche Diagnostics, Mannheim, Germany). Anti HDV antibodies were detected by commercial enzyme immunoassay.

HIV-1 RNA, HBV DNA, and HCV RNA detection

HIV-1 RNA was defined and counted by a trading RT-PCR assay – QIAsymphony + Rotorgene Q/artus HIV-1 QS-RGQ v1 (Qiagen GmbH, Hilden, Germany) COBAS Ampliprep/COBAS TaqMan HIV-1 Test (Roche Molecular Systems, Roche Molecular Systems, Inc. Pleasanton, CA, USA) and Abbott M2000 SP/Abbott RealTime HIV-1 Amplification Kit (Abbott Molecular Inc. Des Plains, IL, USA).

HBV DNA was defined on a Bio-Robot workstation using magnetic-particle technology (QIAasymporny SP; Qiagen GmbH, Hilden, Germany). HBV DNA was determined and counted by a trading RT-polymerase chain reaction (PCR) assay (Artus HBV QS-RGQ test; Qiagen GmbH, Hilden Germany) on the RT platform (Roto-Gene Q; Qiagen GmbH, Hilden Germany and COBAS Ampliprep/COBAS TaqMan HBV test Roche Diagnostics, Mannheim, Germany). HCV RNA procuring and quantification were completed by using a merchant RT PCR assay – QIAsymphony + Rotorgene Q/artus HCV QSRGQ (Qiagen GmbH, Hilden, Germany), COBAS Ampliprep/COBAS TaqMan HCV Test (Roche Molecular Systems, Inc. Pleasanton, CA, USA) and an Abbott M2000 SP/Abbott RealTime HCV Amplification Kit (Abbott Molecular Inc. Des Plains, IL, USA).

PCR amplification and sequence analysis of HIV-1

The protease (1 - 99 aa) and RT (40 - 250 aa) regions of pol gene in the HIV genome were amplified and sequenced. The cDNA Synthesis Kit was applied for HIV-1 cDNA synthesis (Thermo Scientific Inc, Fermentas, Lithuania) and M-MuLV RT enzyme. PCR procedure is as follows: 95°C for 10 min, and then 45 cycles at 95°C for 45 s, 55°C for 45 s, and 72°C for 45 s (21). Highly Pure PCR Product Purification Kit (Roche Diagnostics GmbH, Mannheim, Germany) was used for PCR product purifying. The HIV-1 sequencing reaction was applied on the ABI PRISM 310 Genetic Analyzer platform with DYEning ET Terminator Cycle Sequencing Kit (Amersham Pharmacia Biotech Inc, Piscataway, NJ, USA). The performed cycle sequencing reaction was as follows: 35 cycles consisting of 95°C for 20 s, 50°C for 20 s, and 60°C for 2 min. The sequence electropherogram was acquired and evaluated by Vector NTI v5.1 (InforMax, Invitrogen, Life Science Software, Frederick, MD, USA). The Sanger di-deoxy sequencing technique was used for the analysis of viral protease and reverse transcriptase regions of HIV-1. The Agence Nationale de Recherche Sur le Sida (ANRS, National AIDS Research Agency) explication algorithm (www.hivfrenchresistance.org) was used for specific primer pairs. The PCR conditions were performed as follows:

Reverse transcriptase (codons 40 – 250): outer primers (798 bp); MJ3: 5’- agtaggaactacactgcta -3’ (2480 to 2499) and MJ4: 5’-ctgttagttgtgtgcctct-3’ (3399 to 3420), inner primers (573 bp). A (35): 5’-tgatgtgacttaaaatcttctagttactttatt-3’ (2530 to 2558) and NE1 (35); 5’-ctactaatgctcagagatacgacatcagctct-3’ (3300 to 3334). Sequencing primer; A (20): 5’-aattccccattgctctatt-3’. Protense (codons 1–99); outer primers: 5’ prot 1: 5’-taatgttgaagactgcttcc-3’ (2082 to 2109) and d 3’ prot 1: 5’-gaaactgagatgagattgagtcag-3’ (2703 to 2734); inner (amplification: 507 bp fragment) and sequencing primers 5’ prot 2: 5’-tagagcaagagagacacacgca-3’ (2136 to 2163) and 3’ prot 2: 5’-aatgcttatttttcattgctaatcgc-3’ (2621 to 2650). The primer pairs used for PCR were presented in Table 1. The consensus reference sequence of HIV-1 subtype B (GenBank accession no. JN215195) that obtained from Los Alamos National
Laboratory (www.hiv.lanl.gov) database was consulted for the design of the primers.

Table 1: The primer pairs used for PCR

HIV-1 subtyping and drug resistance mutation detection

The HIVdb-Stanford University (www.hivdb.stanford.edu) and geno2pheno (http://coreceptor.bioinf.mpi-inf.mpg.de) tools were used for evaluating HIV-1 subtypes. However, HIV-1 mutations related to ART resistances were detected by using the Stanford Database. World Health Organization's Surveillance Drug Resistance Mutation (SDRM) list (2009), was used for the definition of Transmitted Drug Resistance Mutation (TDRM).

The WHO SDRM list contains general agreement on non-polymorphic drug resistance mutations at 43. position of HIV-1 protease and reverse transcriptase genes of >1000 subtypes that obtained from ART-naive patients (22). Statistical Analysis:

The SPSS 15.0 programme was used for statistical analysis. The significance in groups was tested with the Pearson chi-square for each HBV/HIV, HCV/HIV and HBV/HCV/HIV groups for ART resistance mutations, and p<0.05 was accepted as significant.

RESULTS

In the present study, a total of 3.896 HIV-1 positive patients whose molecular laboratory tests were completed by 93 infectious diseases clinic located in 33 cities in Turkey were detected and evaluated. Viral hepatitis co-infections were detected in 4.3% (170) of all HIV-1 infected patients in this study. HBV and HCV co-infections were observed as 3.2% and 0.9% in HIV positive patients, respectively. HBV+HDV, HBV+HCV and HBV+HCV+HDV total rates were detected as 0.15%.

HIV and viral hepatitis coinfected patients were included in the study, where 83% (141) of them were male and 17% (29) of them were female. The mean age was 39+/- 12. A total of 85.3% (145) of the patients were from Turkey and the rest (25) were from other countries. The demographic characteristics of the study patients have been presented in Table 2.

Table 2: Demographic characteristics of the study patients

The major transmission route for co-infection was determined to be sexual transmission in HBV and HCV co-infected groups, with 97.6% and 77.7%, respectively. All of the patients with IVDU history had HCV co-infection, while none of the HBV coinfected had IVDU history. Heterosexual and homosexual/bisexual transmissions were detected at rates of 44.7% and 33.5%, respectively.

The major HIV-1 subtypes were detected as subtype B (62.9%). Based on detailed analyses of the domestic subtypes, the subtypes were detected as subtype B and Circulating Recombinant Form (CRF) with rates of 62.9% and 24%, respectively. On the other hand, Circulating Recombinant Form (CRF) was determined in 48% of the foreign subjects. The differences between the major subtypes of domestic and foreign subjects were determined to be statistically significant according to chi-square (p=0.002).

In 170 coinfected HIV patients; HBV, HCV, HBV+HDV, HBV+HCV, HBV+HCV+HDV were detected as 75%, 21%, 1.8%, 0.6% and 1.2%, respectively. Also rates were found as; 3.2%, 0.92%, 0.07%, 0.02% and 0.05% respectively in total 3896

Drug resistance mutations were determined in 13.5% of all patients. The findings are presented in Table 3. NRTI, NNRTI and PI resistance mutations were investigated and the mutation rates were determined as 9.4%, 5.3%, and 1.8%, respectively. We did not observe any integrase inhibitory drugs resistance mutations in our study.

In the analyses, the NRTI, NNRTI and PI mutations were detected in 4.8%, 4% and 0.8% of the ART-naive group and 20%, 13% and 4% in the treatment-experienced group, respectively. The results were determined to be significant for NRTI and NNRTI (p=0.002, p=0.03, respectively) between groups. NRTI resistance (NRTI-R) mutations were observed in 9% and 5.1% of patients coinfected with HBV and HCV patients, respectively. NNRTI resistance (NNRTI-R) mutations were detected in 5.2% and 10.2% of patients in the HBV and HCV co-infected groups, respectively. Also, The PI resistance (PI-R) rates were evaluated as 1.5% and 2.5% in the HBV and HCV co-infected groups, respectively. The treatment-naive HBV co-infected patients were also analysed. NRTI-R, NNRTI-R, and PI-R were detected as 6.1%, 5.1%, and 1.0%, respectively. NRTI-R, NNRTI-R, and PI-R were not detected in any of the treatment-naive and HCV coinfected patients. We also compared with treatment experience status and ART drug resistance. The NRTI and NNRTI resistance were observed to be significantly higher in the experienced group according to Pearson Chi-square analysis (p=0.001) and (p=0.03, respectively). However, no statistically significant difference was observed between PI resistances and treatment experience status (p=0.11).

NRTI-R, NNRTI-R and PI-R have been evaluated in detail and the mutations are presented in Table 3.

Table 3: Antiretroviral drug resistance mutations in HIV and viral hepatitis coinfected patients

Some accessorial mutations (A62V, V75I, T215 H/N in NRTI, V90I, E138A in NNRTI, L10I, Q58E, A71V in PI drug class) are not defined in the WHO TDRM list (Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update). These mutations are likely to follow other mutations (15). We found A62V in 2 patients (1.2%), V75I in 1 patient (0.6%), T215H/N in 3 patients (1.8%) V90I in 1 patient (0.6%), E138A in 3 patients (1.8%), L10I in 1 patient (0.6%), Q58E in 1 patient (0.6%) and A71V in 1 (0.6%) patient in the study.

DISCUSSION:

HIV-1 and HBV co-infections were observed in 75% of the study population and sexual transmission was observed in 93% of the patients. Heterosexual contacts were observed to be more prevalent than homosexual/bisexual contact, with rates of 58.8% and 34%, respectively. The major transmission route for HIV is sexual intercourse in Turkey. Co-infections such as HBV/HCV may exhibit similar transmission dynamics (17). On the other hand, HCV co-
In conclusion because of similar transmission routes HIV positive patients have a risk for HBV and HCV co-infections. However, the ART drug resistance mutation pattern is observed to be similar with patients who are HBV and/or HCV negative. The molecular characterization of the HIV-1 genome for ART resistance is not different from non-coinfected patients. The increasing migration rates and demographic changes have a potential effect on infection transmission trends. Prevention of the viral hepatitis coinfection in HIV positives is important for community health, patient morbidity, mortality, life quality, drug burden and drug interaction. Patients with HIV-1 and viral hepatitis coinfections should be carefully monitored.
Conflict of Interest: No conflicts.
Funding Source: No funding source.

REFERENCES

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### TABLE 1. The primer pairs used for PCR

<table>
<thead>
<tr>
<th>Primer</th>
<th>Amplification of HIV-1 pol gene region</th>
<th>Reverse transcriptase domain</th>
<th>Protease domain</th>
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<tr>
<td><strong>Outer primer (codons)</strong></td>
<td>MJ3:5’-agtaggaccaacctgtca -3’ (2480-2499)</td>
<td>5’Prot 1:5’-aatatttttaggaagatctgcctcc-3’ (2082-2109)</td>
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<tr>
<td></td>
<td>MJ4:5’-ctgttagtggctgtctcttcct-3’ (3399-3420)</td>
<td>3’Prot 1:5’-gcaatatgtggtgtgatgtgctcttcaggg-3’ (2701-2734)</td>
<td></td>
</tr>
<tr>
<td><strong>Inner primer (codons)</strong></td>
<td>A(35):5’-tatttttaggaagatctgcctcc-3’ (2530-2558)</td>
<td>5’Prot 2: 5’-teaggecgagacagacacagc-3’ (2136-2163)</td>
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<tr>
<td></td>
<td>NE1(35):5’-ccctactaactctgtgatgtgactcagcctcagct-3’ (3300-3334)</td>
<td>3’Prot 2:5’-aatcctttttttctctctgtaatggc-3’ (2621-2650)</td>
<td></td>
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</tbody>
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GenBank accession no: JN215195

### TABLE 2. Demographic characteristics of the study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Patient, n</td>
<td>170</td>
</tr>
<tr>
<td>Gender, M/F, n (%)</td>
<td>141/29 (83%/17%)</td>
</tr>
<tr>
<td>Region/city</td>
<td>Marmara/Kocaeli, Istanbul, Bursa, Black Sea/Samsun, Giresun, Trabzon, Eastern Anatolia/Elazığ, Southeastern Anatolia/Sanlıurfa, Diyarbakir, Gaziantep, Central Anatolia/Ankara, Kayseri, Sivas, Aegean/Izmir, Canakkale, Mediterranean/Antalya, Mersin</td>
</tr>
<tr>
<td>Nationality of the patient, n (%)</td>
<td>Turkey 156 (92%), Ukraine 3 (1.8%), Turkmenistan 3 (1.8%), Uzbekistan 2 (1%), Libya 2 (1%), Tajikistan 1 (0.6%), Mali 1 (0.6%), Australia 1 (0.6%), Indonesia 1 (0.6%)</td>
</tr>
<tr>
<td>Behaviors at-risk for HIV infection n (%)</td>
<td>Sexual contact 158 (93%), Blood transfusion 1 (0.6%), Dental surgery 2 (1.2%), IVDU 8 (4.7%), Other 1 (0.6%)</td>
</tr>
<tr>
<td>Type of sexual preference, n (%)</td>
<td>Heterosexual 100 (58.8%), Homosexual 47 (27.6%), Bisexual 10 (5.9%), Transsexual 1 (0.6%)</td>
</tr>
<tr>
<td>ART history, n (%)</td>
<td>Naive 125 (73.5%), Experienced 45 (26.5%), ND 1 (0.6%)</td>
</tr>
<tr>
<td>HIV-1 RNA load, mean (IU/mL)</td>
<td>1.3+E6 IU/ml +/- 7.9+E6</td>
</tr>
<tr>
<td>Co-infection, n (%)</td>
<td>HBV 128 (75%), HCV 36 (21%), HBV and HDV-3 (2%), HBV and HCV-1 (0.6%), HBV and HCV and HDV-2 (1.2%)</td>
</tr>
<tr>
<td>CD4 + T cell count, cell/mm³</td>
<td>355 +/- 237</td>
</tr>
<tr>
<td></td>
<td>HBV coinfected 362 +/- 225</td>
</tr>
<tr>
<td></td>
<td>HCV coinfected 332 +/- 278</td>
</tr>
<tr>
<td></td>
<td>HBV and HCV coinfected 233</td>
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<tr>
<td>Drug class</td>
<td>Mutation</td>
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<tr>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>NNRTI</td>
<td>L100I, K101E/P, K103N/S, Y181C, G190A</td>
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<tr>
<td>PI</td>
<td>M46I, I54A/V, L76V, V82A, L90M</td>
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