Abstract

Human Immunodeficiency Virus (HIV) infection has been a global problem and all measures were undertaken to prevent and treat the infection. However, challenges were multifaceted. From Social and behavioral problems to the drug resistance of the virus were all there to challenge our ability to fight with HIV. We have evolved from those days of panic now and drugs seem to be working as evident by the falling rate of new infections and transmissions. The world is thinking about curing HIV and research is ongoing on various fronts. One aspect which needs separate attention and wide studies is host pharmacogenomics. We may get wonder drugs, but to make them work, we also need to know about the host system and if the system is ready to make a right use of the drug and there would be no toxicity. The present review discusses all such aspects to highlight the importance of host pharmacogenomics while considering the cure of HIV infection.

Introduction

The success of antiretroviral therapy (ART) in restricting the transmission [1] and raising the life expectancy of the infected individuals [2], have provided the evidence and courage to think about curing Human Immunodeficiency Virus (HIV) infection. The measurable outcomes of using highly active antiretroviral therapy (HAART) have improved the overall scenario as there has been a decrease in Acquired Immunodeficiency Syndrome (AIDS)-related deaths, reduction in the use of drugs for opportunistic infections, and a decrease in the numbers of patients hospitalized with AIDS-related illnesses. HIV can now be classified as a chronic disease; until a cure is found, patients are likely to require lifelong therapy. With the evidence till date, it seems that the cure may become a possibility with effective drugs only. Currently used drugs have succeeded partially, in restricting viral multiplications, however, the latent reservoirs serves as a new source of replication and drug resistant virus. Cure research is all about targeting these hidden virus and clearing them using the available antivirals. The strategy seems promising and has proved effective with upcoming evidence [3]. A very recent work discovered a biomarker that is found only on the surface of HIV-infected white blood cells that can be used to eradicate reservoirs of the viral infection throughout the body [4]. A few problems in doing so are the emergence of drug resistance strains of the virus and drug toxicities to the host which may require newer drugs.

Hence, an additional but important area that needs to be considered in relation to HIV therapy is the genetic variability of the host genes which participate in drug metabolism. This concept of pharmacogenomics is imperative with respect to the efficacy of the treatment and handling the toxicity of antiretrovirals. This can aid in tackling the failure of current drug regimens and reducing the short- and long-term toxicities of the drugs. It has been demonstrated by various studies that in a small group of individuals there is a change in nucleotide (polymorphism) in the genes which are responsible for the conversion of antiretroviral drugs into their active forms, their transport and their levels in the blood. This polymorphism of a single nucleotide (SNP), can alter the whole cycle of drug utilization and hence may sometimes result in drug toxicities [5-7]. Hence, it may happen sometimes that the drug is effective on infecting virus but is not reaching the target because of the host genetic constitution. The treatment may fail or may induce various types of toxicities in such cases. The need is to individualize the therapy in order to achieve the best potency, adherence, and tolerability, to minimise toxicity.

Why Genomic Characteristics of Some Individuals becomes a Hurdle in a Cure?

The treatment has been a great success in terms of limiting new infections and extending the lifespan of the HIV-1 infected individuals. However, a group of individuals lands into the failure of treatment. This could have clinical, immunologic, virologic reason, or any combination of the three. It means, either their immune system has come to a point wherefrom recovery becomes impossible, or they harbor a virus that is resistant to the current regimen or have issues with adherence. Another big reason that is not accounted for is the genetic makeup of the patient. These individuals may carry a gene which is polymorphic and is not accounted for is the genetic makeup of the patient. These individuals may carry a gene which is polymorphic and is
These factors can basically be classified into two groups- one that involves host genes which interact with the virus at one or the other stage during the viral life cycle and controls the immune response. The other group constitutes genes responsible for drug metabolism. The first group has genes for Chemokine receptor, Chemokine genes involved in HIV budding, genes responsible for HIV-1 restriction, genes for immune response and cytokines. The second group, directly related to pharmacogenomics, involve the genes responsible for absorption, distribution, metabolism and excretion of the drugs. Mutations/polymorphism in these genes could cause alterations in gene expression or protein structure. This alteration leads to variations in protein quantity and quality. Changes in drug-receptor or drug-enzyme interactions due to structural alterations of enzymes or receptors could also result in variations in drug responses. The responses could be 'no drug response' or 'an increased drug response' leading to adverse drug reactions or toxicities. Polymorphisms in genes responsible for drug transport can affect pharmacokinetic properties of an administered drug and ultimately its plasma concentration as well as concentrations in the target tissues.

**Enzymes and their Polymorphism**

Inter-individual genetic variations have been associated with and used to identify potential for disease, drug response, and adverse reactions. The application of genetic data for the prediction of response to medications and adverse drug reactions is becoming a reality in some clinical fields. For instance, human leukocyte antigen (HLA)-B*5701 allele is being used as a pharmacogenetic marker for abacavir hypersensitivity. Standardizing the test of HLA-B*5701 allele for various populations can be useful to help HIV-infected individuals requiring treatment [8]. The capability of a drug regimen to treat an infection mostly depend on how the drug is getting into the system and what course it takes after its entry. In HIV infection, drug molecules which are Nucleoside reverse transcriptase inhibitors (NRTIs), Nucleotide reverse transcriptase inhibitors (NtRTI), Non- Nucleoside reverse transcriptase inhibitors (NNRTI), Protease Inhibitors (PI) etc. are employed in various combinations for the treatment. These drugs are metabolized by specific metabolic pathways and polymorphism in one or the other enzymes of these pathways may lead to a diversification of enzyme activity resulting in a changed course of drug action. Table 1 enlists a few enzymes which participate in these pathways.

**Utility of Polymorphism Detection**

Patients treated with abacavir (ABC) may develop a potentially fatal ABC-associated hypersensitivity syndrome (ABC-HS), typically characterized by fever, malaise, rash, vomiting/diarrhoea and/or dyspnoea/cough. ABC-HS has been strongly associated with HLA-B*57:01 carriage and screening for this allele is recommended [14]. Sequence-based or RFLP-based genotyping and polymerase chain reaction (PCR) sequencing of specific oligonucleotide probes are the most widely used techniques. However, the usage is limited to fewer centres at this point of time and need to be employed in other settings too. As minimizing adverse effects of antiretroviral therapy is critical to controlling the infection and maintaining treatment adherence, probing more and more such polymorphism in different populations becomes very important. Evidence generated with such studies can be directly converted into diagnostic tests which would further aid in reducing adverse reactions.

**Table 1: Enzymes which metabolize various drugs used in HIV infection.**

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Metabolizing enzymes</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs and NtRTI</td>
<td>UGT1A1 and UGT2B7 isozymes</td>
<td>[22,23]</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>CYP2B6, UGT2B7, CYP2C19, YP3A4/5, CYP2B6, CYP3A4/5</td>
<td>[24]</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>CYP3A4/5, CYP2C19</td>
<td>[25,26]</td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>UGT1A1</td>
<td>[27,28]</td>
</tr>
<tr>
<td>CCR5 co-receptor inhibitor (Maraviroc)</td>
<td>CYP3A4/5</td>
<td>[29]</td>
</tr>
</tbody>
</table>
Upcoming Evidences

Some of our studies tried to probe a few genes for their polymorphism and their association with adverse events. We reported polymorphism in Glutathione Transferases (GST) wherein, GSTT1-null and STM1-null genotypes alone and in combination may predict the acquisition of hepatotoxicity. The carriers GSTM1-null+GSTT1-null genotype among nevirapine user showed the risk of hepatotoxicity in HIV-infected individuals. Also, the CYP1A1m1 gene may have a role in the development of ARV associated hepatotoxicity and could be helpful in identifying a predictor for the choice of drug (5-7). NNRTIs are predominantly metabolized by CYP450 enzyme system, including 3A4, 2D6, 2B6, 2C9 and 2C19 isoenzymes. Also, they act as inhibitors or inducers of these enzymes, further complicating the potential for significant interactions with other drugs [15,16]. Study of CYP2B6, CYP2C9, CYP2C9, CYP2D6 may provide predictor for nevirapine-induced severe hepatotoxicity. Taking leads from various studies, new drugs are being developed to avoid the reported toxicities and utilizing different pathways. A series of integrase stand transfer inhibitors (InSTIs) has been developed and being used in order to have better efficacy and safety. Some InSTIs like Elvitegravir (EVG), raltegravir (RAL) and dolutegravir (DTG) are recommended as first-line options for treatment-naive patients by the European AIDS Clinical Society, British HIV Association, International AIDS Society-USA and DHHS [17]. RAL and DTG are not metabolized via cytochrome P450 (CYP) which result in fewer drug interactions and less toxicity risk in patients. However, Elvitegravir is predominantly metabolized via cytochrome P450 (CYP)3A4 and study of CYP3A4 polymorphism may provide predictor for Elvitegravir [18].

Ethnicity Issues- Variety of Variations

Inter-individual response to drugs in patients greatly varies because genetic background of the population is different. The drugs used in the treatment of individuals have varying clinical implications resulting from genetic polymorphisms in drug metabolizing enzymes (DMEs). Global mixing of Asian, African, European, and Native American ancestries with each other and within their own populations, has resulted in different ethnic groups with varying degrees of genetic diversity. Differences in genetic ancestry might introduce genetic variation, which has the potential to alter the therapeutic efficacy of various drugs including the antivirals. Hence large consortium-based sequencing studies are required to provide a diverse genome map of different admixed populations, which can be used for future pharmacogenetic studies. These studies may include candidate gene studies, genome-wide association studies, and whole-genome admixture-based approaches accounting for ancestral genetic structure, complex haplotypes, gene-gene interactions, and rare variants to detect and replicate novel pharmacogenetic loci. The other issues for developing such studies and linking their outcomes with the predictions of treatment success or failure are the availability of a well-powered sample size, information about lifestyles including ethnicity, substance use and other environmental factors.

The Contribution of Environmental Factors

Environmental factors such tobacco, alcohol and dietary factor play very important role in HIV disease progression. In a recent study from China, among HIV-infected participants, the proportions of those experiencing harmful effects of tobacco and alcohol on AIDS were 53.6% and 72.5%, respectively [19]. Another study showed that heavy alcohol consumption had a negative impact on the CD4 cell count of HIV-infected people not on combined antiretroviral therapy [20]. Along with many other past studies, a recent study from New York City metropolitan area showed that recent tobacco smoking was independently associated with unsuppressed viral load and low CD4 cell count [21]. Not only these, the food habits, use of traditional medicines along with ART etc. may have a positive or negative effect on the metabolism of drugs and hence may influence the expected outcomes of the treatment.

Conclusions

With the discussion above, we can say that progress have been made in the area of treatment and hopes are high that one day we would be able to clear the HIV reserves from the human body. With the support of upcoming evidence, we may have better diagnostic modalities available for individuals who become eligible for treatment or when there is a test and treat policy implemented. This would aid in knowing the best fitting regimen for a given individual. However, for those who have polymorphic genes, we need to have the alternate arsenal available. This further necessitates intensive research in new drug discovery with better efficacy and minimal side effects to complete our preparation for HIV-cure.

References


