

## Review Article

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# Individualization of antiretroviral therapy - Pharmacogenomic aspect

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**Combination therapy with three drug regimens for human immunodeficiency virus (HIV) infection significantly suppresses the viral replication. However, this therapeutic impact is restricted by adverse drug events and response in terms of short and long term efficacy. There are multiple factors involved in different responses to antiretrovirals (ARVs) such as age, body weight, disease status, diet and heredity. Pharmacogenomics deals with individual genetic make-up and its role in drug efficacy and toxicity. In depth genetic research has provided evidence to predict the risk of developing certain toxicities for which personalized screening and surveillance protocols may be developed to prevent side effects. Here we describe the use of pharmacogenomics for optimal use of HAART (highly active antiretroviral therapy).**

**Key words** HAART - HIV- NNRTI - NRTI - personalized medicine - pharmacogenomics

## Introduction

Introduction of highly active antiretroviral therapy (HAART) has drastically reduced mortality associated with HIV infection, but variability in efficacy and toxicity is challenging. The advances in molecular biology has changed pharmacogenetics to a great extent to develop pharmacogenomics<sup>1</sup>. Host genetic factors are accountable for the variability in antiretroviral (ARV) response along with sex, body mass index, heredity and disease progression. Sometimes genetic variability is solely responsible for these variations<sup>2,3</sup>. A single-nucleotide change is a DNA sequence variation occurring commonly within a population at the same locus of the gene which may alter functioning of the protein product extensively. Single-nucleotide change hardly affects functioning of the protein produced by that gene, but some changes

affect functioning. Single nucleotide polymorphisms (SNPs) are significant with respect to genes of drug metabolic pathway including enzymes, drug carrier proteins involved in pharmacokinetics and disease progression. The influence of SNPs on personal responses to pharmacotherapy is complicated. Genetic variations in pathways of drug absorption, disposition, metabolism and excretion (ADME) contribute to inter-patient differences. Therefore, genes encoding for transport proteins, drug metabolizing enzymes or nuclear receptors have been the main targets of HIV pharmacogenomic studies. So far, numerous associations of SNPs with susceptibility to ARV drug adverse reactions or risks of virological failure have been reported<sup>4</sup>. This review focuses on some important aspects of pharmacogenomics to maximize efficacy and minimize toxic effects of HAART.

## Pharmacogenomics

Combination antiretroviral therapy (cART) for HIV - HAART or cART has improved the prognosis of HIV infection close to normal life expectancy. With HAART, different combinations of antiretroviral drugs are available for untreated and treated individuals. There are six categories of drug regimens available as follows: (1) Nucleoside reverse transcriptase inhibitors (NRTIs), (2) Non-nucleoside reverse transcriptase inhibitors (NNRTIs), (3) Protease inhibitors (PIs), (4) Integrase inhibitors (IIs), (5) Fusion inhibitors (FIs), and (6) Chemokine receptor antagonists. The choice of treatment is mainly influenced by HIV disease stage, co-morbidities, co-medication with potential drug-drug interactions, pregnancy or pregnancy potential, expected cART toxicity, and results of genotypic resistance testing and synergism/antagonism of the combination on HIV virus life cycle. Table I gives summary of some key reported genetic variants for HAART. Table II provides information on pharmacogenetics of adverse reactions due to HAART.

*1. Nucleoside reverse transcriptase inhibitors (NRTIs):* NRTI is a nucleoside analogue antiretroviral drug and its chemical structure constitutes a modified version of a natural nucleoside. These inhibit viral replication of retroviruses by stopping extension of oligomer due to absence of 3' hydroxyl group essential for addition of incoming new nucleotide. This prevents further synthesis of viral nucleic acid by interfering with the reverse transcriptase enzyme<sup>45</sup> (Fig. 1). These drugs get activated on endocytosis after phosphorylation to form active triphosphate compound (pro-drugs). The known drug toxicities are linked with lipid metabolism, liver steatosis and lactic acidosis. Additional evidence relates NRTI drugs to disruption of mitochondrial function, oxidative stress and peripheral neuropathy<sup>46</sup>.

Zidovudine (ZDV) (Azidothymidine, AZT) - Thymidine analogue - ZDV has been prescribed after U.S. Food and Drug Administration (FDA) approval in 1987 as a part of drug regimen to treat HIV infection, till it was found more harmful than tenofovir<sup>47</sup>. ZDV was found to be associated with severe anaemia in a randomized trial in untreated HIV patients using efavirenz (EFV) in addition to ZDV + lamivudine (3TC) / tenofovir (TDF) + emtricitabine (FTC) where ZDV was removed in 5.5 per cent population under study<sup>48</sup>. A previous study showed that 16.2 per cent of patients developed ZDV induced anaemia in the population of eastern India<sup>49</sup>, 58 per cent of the patients on ZDV showed reduced viral load (<400 copies/ml)

as compared to 71 per cent cases on TDF only because ZDV had to be withdrawn in 11 per cent (vs 5%) of the cases after drug adversities in 144 wk<sup>49</sup>. Observed ZDV related toxicities include drop in haemoglobin level and neutrophils count, and nausea due to gastrointestinal disturbances within a few weeks on initiation of the trial. Also, fat deposition in upper and lower extremities was significantly reduced on ZDV treatment<sup>50</sup>.

A pharmacogenetic study has reported higher levels of ZDV-triphosphates (up to 49%) in HIV cases heterozygotes for *ABCC4* G3724A on ZDV treatment as compared to wild type GG homozygote<sup>51</sup>. Another variant *ABCB1* GT or TT has shown significantly reduced levels of HIV viral load than that in individuals having wild type GG genotype<sup>52</sup>. Kwara *et al*<sup>53</sup> have shown 196 per cent oral drug clearance associated with *UGT2B7\*1c* carriers on ZDV therapy when compared to non carriers. These studies emphasize on extensive analysis using large cohorts for understanding potential role of pharmacogenomic factors in ZDV pharmacokinetics and pharmacodynamics<sup>5</sup>.

Stavudine (d4T) - Thymidine analogue - Stavudine (2',3'-didehydro-2',3'-dideoxythymidine) was made available for patients showing virological failure or intolerance to ZDV after its approval in May 1996<sup>54</sup>. After one year, it became the preferred drug for ART. But it was found to be associated with susceptibility to body fat side effects. Therefore, in 2009, the World Health Organization (WHO) restricted its use due to long-term, irreversible side effects<sup>55</sup>.

Lamivudine (3TC) - Cytidine analogue - Lamivudine (2',3'-dideoxy-3'-thiacytidine) is another nucleotide analogue used in combination therapy for delaying developments of acquired immunodeficiency syndrome (AIDS) and hence, avoiding disease related complications or cancer. Higher intracellular concentrations of 3TC-triphosphate have been reported to be associated with multidrug resistance protein 4 (MRP4) T4131G change and MRP2 polymorphism<sup>49</sup>.

Tenofovir disoproxil fumarate (TDF) - Adenosine analogue - Tenofovir, one of the most effective and commonly prescribed antiretroviral drugs belongs to a class of nucleotide reverse transcriptase inhibitors (NtRTIs). Nucleotide analogues have phosphate group in addition to pentose and nucleic base of nucleoside. Unlike nucleoside analogues, NtRTIs are chemically preactivated and thus require less processing in the body. A single G>A substitution at 1249 nucleotide

**Table I.** Summary of genetic variants associated with antiretroviral (ARV) pharmacokinetics, toxicity and efficacy

Class	Drug	Gene	Polymorphisms	Clinical impact (Efficacy/Toxicity)	Ref.	
NRTIs	ZDV	<i>ABCC4</i>	A1203A	Higher intracellular ZDV - TP	5	
		<i>UGT2B7*1c</i>	c.735A>G	196% Higher ZDV oral clearance	5	
		<i>ABCB1</i>	G2677T	Greater reduction of HIV RNA	5	
	d4T	<i>POLG</i>	R964C and E1143G		6	
	3TC	<i>ABCC4</i>	T4131G	Higher intracellular 3TC - TP	6	
	ABC	<i>HLA-B HLA-B*57:01</i>	NA	Toxicity - HSR	7,8	
		<i>HLA complex P5</i>	335T>G	Toxicity - HSR	9-12	
	TFV (NtRTI)	<i>ABCC2</i>	CATC Haplotype (-24, 1249, 3563, 3972) 24CC	Toxicity - KTD	13,14	
			<i>ABCC4</i>	3463A>G	Higher intracellular TFV-DP	15
			<i>ABCC4</i>	-669C>T	Toxicity - KTD	14
NNRTI	EFV	<i>CYP2B6</i>	516C>T, 785A>G and 983T>C	Higher plasma levels/CNS adverse effects	16-24	
		<i>ABCB1</i>	3435C>T	Possible influence in plasma EFV levels	25-28	
	NVP	<i>CYP2B6</i>	516C>T and 983T>C	Higher plasma levels	17,19, 29-31	
		<i>ABCB1</i>	3435C>T	-	32,33	
		<i>HLA-DR</i>	HLA- DRB1*0101	Toxicity - HSR	34,35	
		<i>HLA-C</i>	HLA-Cw*8	Toxicity - HSR	36	
		<i>HLA-B</i>	HLA-B3505	Toxicity - skin rash	37	
PIs	ATV	<i>UGT1A1</i>	*28	Toxicity - Gilbert's syndrome and Higher levels of bilirubin	38-40	
		<i>ABCB1</i>	3435C>T and 2677G>T	Lower plasma levels	39, 41	
		<i>NR1I2</i>	63396C>T	Lower plasma levels	42	
	RTV	<i>ABCA1, APOA5, APOC3, APOE, CETP</i>	-	-	6	
	IDV	<i>UGT1A1*28</i>	-	-	6	
		<i>CYP3A4*1B / CYP3A5*1</i>				
II	RAL	<i>ABCB1</i>	3435C>T	Allele T is associated with lower RAL plasma exposure	43	
EI	MVC	<i>CCR5</i>	Δ32	-	6	

ZDV, zidovudine; d4T, stavudine; 3TC, lamivudine; ABC, abacavir; TFV, tenofovir; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; RTV, ritonavir; IDV, indinavir; RAL, raltegravir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; II, integrase inhibitor; EI, entry inhibitor; HSR, hypersensitivity; KTD, kidney tubular dysfunction; DP, diphosphate; NA, not applicable; TP, triphosphate

**Table II.** Pharmacogenetics of adverse reactions due to HAART

Regimen	Pharmacogenetics	Side effects
<b>NNRTI – based regimen</b>	ZDV	3724G>A, c.735A>G, G2677T
	d4T	R964C, E1143G
	3TC	T4131G
	2 NRTIs + 1 NNRTI	ABC 335T>G
	TFV	CATC Haplotype (-24, 1249, 3563, 3972) 24CC, 3463A>G, -669C>T
(1) ZDV/d4T + 3TC + NVP	516C>T, 785A>G, 983T>C, 3435C>T	(i) Low genetic barrier to resistance
(2) ZDV/d4T + 3TC + EFV	516C>T, 983T>C, 3435C>T, HLA-DRB1*0101, HLA-Cw*8 and	(ii) Cross-resistance among NNRTIs
(3) TFV + 3TC + NVP/EFV	NVP HLA-B3505	(iii) Potential for hepatic and skin toxicity (NVP>EFV)
<b>Triple NRTI – based regimen</b>	ZDV	3724G>A, c.735A>G, G2677T
	d4T	R964C, E1143G
	3TC	T4131G
	(1) AZT + 3TC + ABC	ABC 335T>G
	(2) d4T + 3TC + ABC	
<b>PI - based regimen</b>	ZDV	3724G>A, c.735A>G, G2677T
	d4T	R964C, E1143G
	3TC	T4131G
	(1) 2 NRTIs + ATV/r or LPV/r	ABC 335T>G
	(2) 2 NRTIs + NFV	ATV UGT1A1*28, 3435C>T, 2677G>T, 63396C>T
		(i) Lower efficacy/high rates of clinical failure than EFV-based regimens
		(ii) ABC hypersensitivity
		(i) Higher pill burden
		(ii) Gastrointestinal side effects common
		(iii) Metabolic complications common
		(iv) Refrigeration requirements for some PI drug (RTV, LPV/r)
		(v) High chances for interactions with other medications

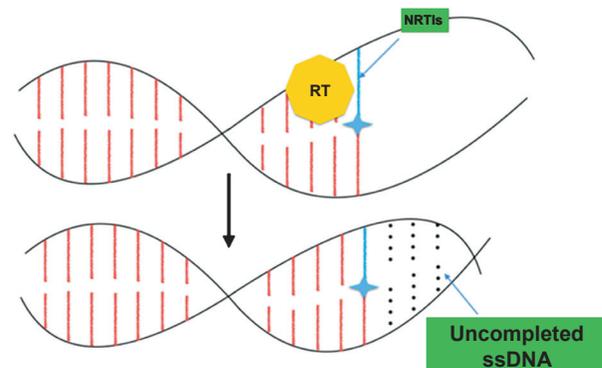
ZDV, zidovudine; d4T, stavudine; 3TC, lamivudine; ABC, abacavir; TFV, tenofovir; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; RTV, ritonavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; HLA, human leucocyte antigen; PI, protease inhibitor

Source: 4, 44

of ATP-binding cassette, sub-family C, member 2 (*ABCC2*) gene is reportedly linked with TDF adverse reaction causing renal tubulopathy<sup>6</sup>. Interestingly, TDF is not a substrate for MRP2, but for MRP4<sup>15</sup>. More recently, a naïve association between *ABCC4* 3463A>G genotype and renal toxicity has been reported showing tenofovir concentrations 35 per cent higher in carriers of the 3463G variant<sup>44</sup>.

Abacavir (ABC) - Guanosine analogue - Hypersensitivity to ABC occurs in about five per cent of HIV infected patients usually by the second week of ABC treatment. In some cases, hypersensitivity reaction is seen by six weeks<sup>56</sup>. A polymorphism in HLA gene HLA-B\*5701 needs to be screened prior to initiation of ABC treatment to avoid hypersensitivity reaction. An inexpensive laboratory test is available to detect this gene<sup>57</sup>. HLA B57 frequency is 5-20 per cent in India<sup>58</sup>. An Indian study<sup>58</sup> demonstrated that HLA B17 frequency in HIV patients on antiretroviral therapy was due to the different composite ethnic groups studied. The testing for HLA B17 antigen along with HLA B\*5701 allele subtype can be used as pharmacogenetic

testing to prevent abacavir hypersensitivity reaction among Indian patients<sup>58</sup>. This testing is now mandatory in many countries before prescribing abacavir<sup>9</sup>. HCP5 335 T>G polymorphism in P5 gene of HLA is preferred

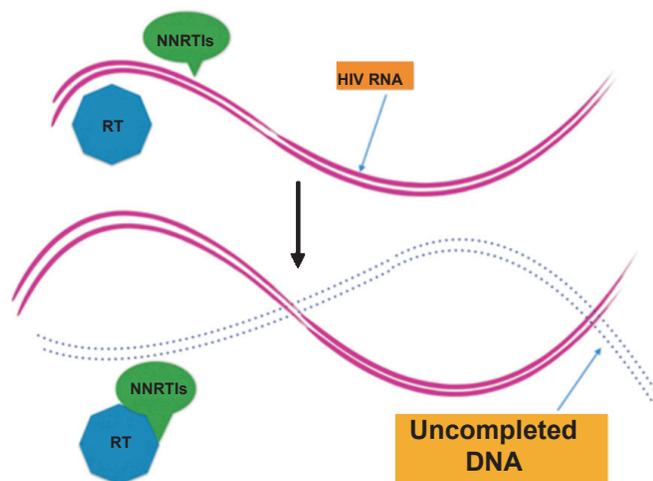


**Fig. 1.** Mode of action of nucleoside reverse transcriptase inhibitor (NRTI). On incorporation of NRTI the chain is terminated. ssDNA, single strand DNA.

SNP marker over HLA B\*5701 for ABC sensitivity due to simplicity and economicity<sup>10-12</sup>.

**2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** Non-nucleosides are directly active drugs as against prodrug NRTIs. These prevent HIV replication by targeting the enzyme reverse transcriptase, binding to a site near to but different from the active site for substrate. It decreases DNA synthesis drastically (Fig. 2). ADME pathways genes are studied extensively focusing on CYP450 enzyme<sup>4</sup>. Detoxification of NNRTI takes place in liver by CYP450 enzyme. SNPs associated with these isoenzymes play crucial role in inter-individual differences in metabolism and disposition of NNRTIs<sup>59</sup>. Polymorphisms result in decreased expression of enzymes and their activity in liver microsomes. As a result, there is considerable inter-individual variability in NNRTI ADME. Also, genes encoding drug transporters and HLA are considered in the pharmacogenetic studies of NNRTI. SNPs in *MDR1* gene, which encodes for P-glycoprotein (P-gp) affect oral absorption and desorption of NNRTIs. P-glycoprotein acts as a NNRTI carrier. The association between variants of *MDR1* gene and NNRTI plasma concentrations has been studied comprehensively<sup>44</sup>.

**Nevirapine (NVP)** - In 1997, NVP was approved as NNRTI<sup>60</sup>. In developing countries, it is the preferred first line drug in combination with two NRTIs due to its efficacy, moderate price and adjustable dosage<sup>60</sup>. NVP causes elevation of liver enzymes which may occasionally be severe. About 15-20 per cent patients

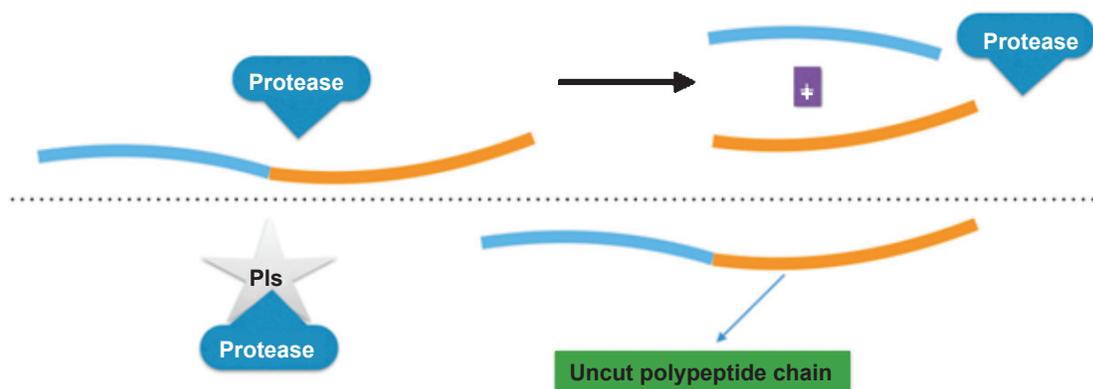


**Fig. 2.** Mode of action of non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs block enzyme activity by binding directly to reverse transcriptase (RT) enzyme.

experience rash and NVP needs to be withdrawn in about 7 per cent of them<sup>61</sup>. NVP-induced rashes were reported in 2.14 per cent of HIV positive individuals from India<sup>62</sup>. It is noteworthy that liver damage may appear after many months<sup>63</sup>. NVP induced hypersensitivity is associated with HLA-DRB1 allele and *MDR1* gene polymorphism<sup>32,34,64</sup>. The polymorphism *ABCBI-3435C>T* is linked with a decreased risk of hepatotoxicity in patients receiving NVP<sup>25,30</sup>. NVP plasma concentration is affected by G516T and 983 T>C substitutions in *CYP2B6* gene. Also, significantly higher NVP plasma levels are reported in black patients heterozygous for T983C SNP<sup>16,17</sup>. Although sex, age, body mass index, habits, habitat and pathological liver condition are major criteria in influencing pharmacokinetics of NVP, but in most of the studies only body weight is included<sup>29,44,57</sup>.

**Efavirenz (EFV)** - EFV is the first line drug for untreated HIV infected cases. EFV shows a narrow therapeutic range and there is a potential risk of high level of therapeutic concentrations that are related with virological failure or neurological manifestations. It is metabolized by *CYP2B6* in liver. The G516T SNP in *CYP2B6* (*CYP2B6\*6*) is reported to have a major impact on the pharmacokinetics and pharmacodynamics of EFV<sup>65</sup>. Black patients are predisposed to the CNS effects due to high prevalence of the genotype *CYP2B6-516TT*<sup>18,19</sup>. Also, there is SNP variability due to 785 A>G, 983 T>C, 593 T>C and 1132 C>T substitutions in *CYP2B6* rendering slow metabolism of EFV<sup>65</sup>. This affects its pharmacokinetics with increased drug levels, which result in CNS events or virological failure, necessitating *CYP2B6* allele genotyping. Efavirenz disrupts sleep architecture<sup>66</sup>.

**3. Protease inhibitors (PIs):** HIV hijacks host genetic code on invading CD4 cell and utilizes host cell machinery for its replication. The viral gag-pol polyprotein is excised into active protein particles of newly formed virus by viral protease, a molecular scissor. This step is inhibited by blocking the protease enzyme using PIs by preventing a proteolytic splicing and results into non-infectious virus particles (Fig. 3). Toxic effects of PIs include lipodystrophy, dyslipidaemia, tolerability problems and gastrointestinal disturbances<sup>67</sup>. Often drug interactions are substantiated due to PIs<sup>68</sup>. PIs are mostly metabolized by *CYP3A4*. PIs act both as inhibitors of and substrate for *CYP3A4*. *CYP3A4* also metabolizes both simvastatin and lovastatin. When PIs act as inhibitor of *CYP3A4*, the levels of simvastatin



**Fig. 3.** Mode of action of protease inhibitors (PIs). PIs are substrate analogue (mimic protein cutting site), and prevent generation of new viral proteins.

and lovastatin may increase drastically<sup>69,70</sup>. This in turn increases the risk of toxicity of liver and skeletal muscle<sup>71</sup>.

Ritonavir (RTV) - Ritonavir is included in combinational regimen because it blocks host enzymes involved in metabolism of PIs. It is the most powerful of all the PIs even in low doses. The primary role of RTV in boosted PI regimens is to improve the pharmacokinetics of the second PI. RTV inhibits host enzymes of drug metabolic pathways causing their levels to rise in bloodstream, and increasing efficacy of other PIs with reduced dose and frequency rendering them more compliant. It also blocks its own metabolism by inhibiting cytochrome P450<sup>72</sup>. Liver enzymes metabolize protease inhibitors only when their activity is modified. All PIs decrease hepatic enzyme activity. These increase cholesterol and triglycerides levels, cause abnormal fat deposition in various parts of the body, and diabetes. These can be associated with polymorphisms of genes like ATP-binding cassette transporter A1 (*ABCA1*), apolipoprotein A5 (*APOA5*), apo lipoprotein C3 (*APOC3*), apo lipoprotein E (*APOE*), and cholesterol ester transfer protein (*CETP*)<sup>73</sup>. *APOE* and *APOC3* variant alleles are associated with lipodystrophy among HIV patients. Genetic screening can reduce risk of hypertriglyceridaemia associated with RTV<sup>74,75</sup>.

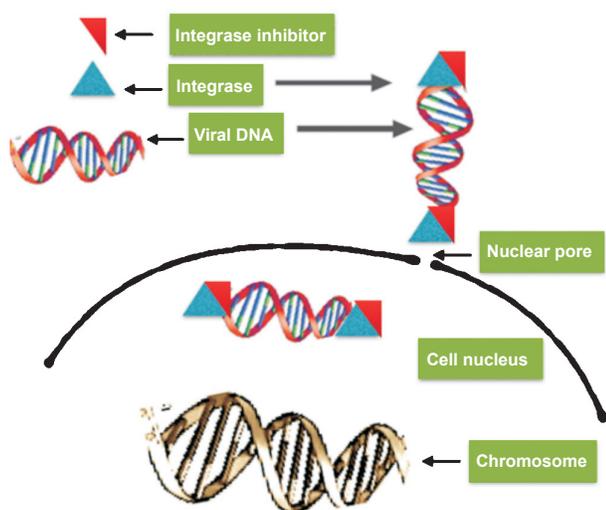
Atazanavir (ATV) - In March 2004, ATV arrived in market as daily prescription in single dose. Increased lipid levels associated with this drug make oneself susceptible to cardiovascular event<sup>74</sup>. Fifty per cent

of cases on ATV show rise in bilirubin levels and above one third have grade 3-4. This is also true for lipodystrophy<sup>75,76</sup>. Some patients even develop jaundice as hepatic conjugation is hampered due to a mechanism similar to Gilbert's Syndrome. A genetic predisposition is identified<sup>77</sup>. This side effect is provoked by competitive inhibition of UDP glucuronosyl transferase 1 family polypeptide A1 (*UGT1A1*), the microsomal enzyme causing glucuronidation, which allows bilirubin excretion. Inconsequential rise needs withdrawal of ATV in a few patients due to overt jaundice<sup>78</sup>. A previous Indian study has reported increased prevalence of of (TA)7/(TA)7 genotype in neonates (allele frequency 0.366)<sup>38</sup>. *UGT1A1* promoter variant is associated with hyperbilirubinaemia<sup>79</sup>. The presence of SNP *UGT1A1*\*28 is strongly associated with the occurrence of jaundice because of decreased enzyme activity<sup>52,57,80</sup>.

Indinavir (IDV) - Highly penetrating IDV reaches genital compartments and CNS, but it is not preferred nowadays<sup>39</sup>. This medicine needs to be used with caution in India due to presence of extensive 'renal stone belt' to avoid the risk of nephrolithiasis<sup>81,82</sup>.

4. *Integrase inhibitors (IIs)*: HIV integrase is an important enzyme in its replication through integrating viral DNA with host genome<sup>83</sup>. Integrase inhibitor is a desirable anti-HIV drug as integrase enzyme is absent in human cells; its selective inhibition without side effects is possible (Fig. 4).

Raltegravir (RAL) - Raltegravir is an aphthyridine carboxamide derivative that inhibits integrase. Integrase catalyses the step-wise process of integrating HIV-1



**Fig. 4.** Integrase inhibitors (IIs) - mode of action. IIs inhibit enzyme activity (bind to enzyme) and prevent insertion of proviral DNA.

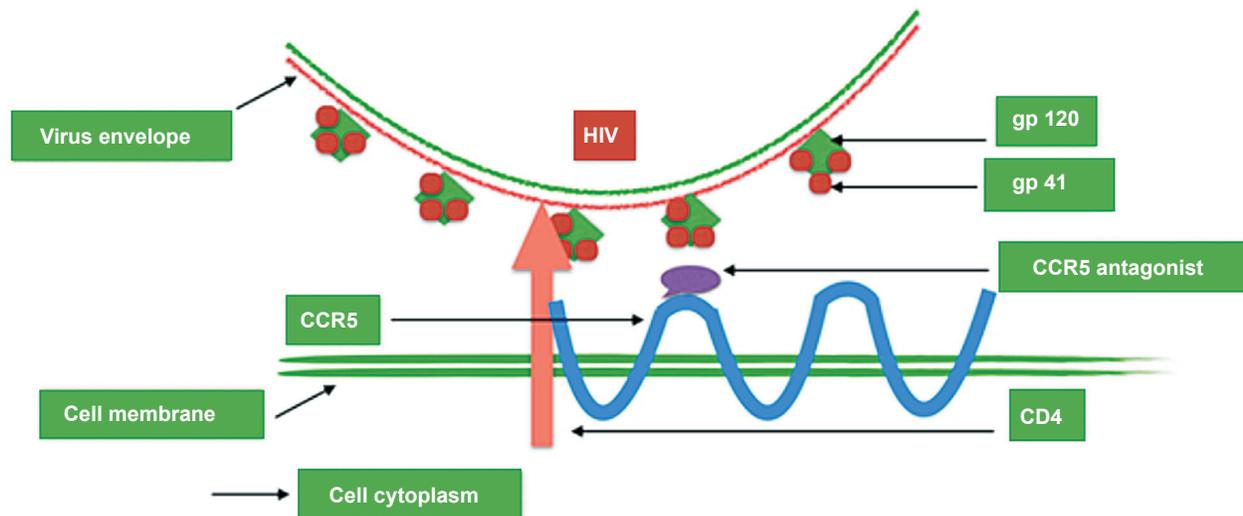
DNA into the host genome. In the process, assembly of integrase with viral DNA forms stable pre-integration complex, which follows endonucleolytic processing of the viral DNA ends, and joining of the viral and host DNAs. Covalent bonding takes place in 5' phosphate groups exposed on nicking cellular DNA strands of host and viral DNA to produce provirus. RAL does not allow pre-integration complex to bind to host DNA<sup>84</sup>. It prevents replication of HIV-2 and acts against R5 and X4 tropic viruses. RAL is a substrate of the P-gp, and consequently, polymorphisms in transport proteins may explain the large intra- and inter-individual variations of RAL exposure<sup>85,86</sup>. A recent study in Spanish HIV RAL-cohort reported that the polymorphism at *ABCB1*-3435C>T was associated with RAL concentrations<sup>43</sup>. Patients carrying CT or TT genotypes displayed lower median RAL concentrations than those with the CC genotype. Although pharmacokinetic/pharmacodynamics (PK/PD) analyses do not suggest a threshold RAL concentration associated with reduced efficacy, patients carrying CT/TT genotypes at the *P-gp* gene might be more prone to virological failure<sup>4,43</sup>. *UGT1A1*\*28/\*28 genotype is associated with higher RAL plasma concentrations compared to that of *UGT1A1*\*1/\*1 genotype<sup>87,88</sup>.

**5. Fusion inhibitors (FI):** Thirty-six amino acids long peptide of the FI enfuvirtide (T-20) is similar to a portion of gp41, necessary for binding to heptad repeat 1 (HR1). It interferes with HR1 and HR2 interaction and thereby, inhibiting the conformational change crucial

for viral fusion to CD4 cells. Decreased efficacy of T-20 is associated with a single amino acid substitution in HR1<sup>57</sup>. The drug is efficacious with hardly any side effects. However, its high cost, intolerance on long term use, complex mode of administration and limited pharmacokinetic properties are the limiting factors, and in future, studies should focus on these aspect to enhance its clinical advantage<sup>89</sup>.

**6. Entry inhibitors (EI):** HIV enters human body through fusion of viral envelope proteins with binding domain on host CD4 + (cluster of differentiation 4) cell. EIs interfere with this fusion step and stop virus from entering into the cell, thereby restricting HIV from infecting a cell and multiplying. Theoretically inhibitors can interfere with every step of HIV entry into the host cell. EIs mainly target either the viral envelope glycoprotein gp120 or gp41 or the C-C chemokine receptor CCR5 or CXCR4 receptors on a CD4 cell surface<sup>90</sup>. Intracellular HIV inhibition is not possible by EIs as against other drug classes.

Maraviroc (MVC) - Maraviroc belongs to entry inhibitors called as CCR5 receptor antagonist. HIV makes entry into host cell using a CCR5 receptor present on CD4+ immune cells. MVC prevents entry of HIV by inhibiting its fusion with the CCR5 receptors (Fig. 5). It allosterically binds to CCR5 by inducing conformational changes within CCR5 and hence, inhibiting its binding to viral gp120<sup>91</sup>. It acts against CCR5 tropic viral strains but is inactive against CXCR4 tropic HIV strains. CCR5-Δ32 is an allele of CCR5. An allele  $\Delta ccr5$  of the  $\beta$ -chemokine receptor gene *CCR5* has been found to confer protection against HIV-1<sup>92</sup>. In Europeans the prevalence of this allele is 5-14 per cent but is uncommon in Africans and Asians<sup>93</sup>. This protective allele was found to be absent in majority of Indians. Its sporadic occurrence in southern and northern parts of India presume Caucasian admixture<sup>92</sup>. The HIV R5 entry is prevented because of Δ32 deletion leading to a non-functional receptor. Homozygosity for this allele gives strong protection against HIV infection whereas the heterozygosity is associated with milder disease progression<sup>94</sup>. However, genetic variations in the CCR5 gene have not been shown to affect virological response to MVC<sup>95</sup>. On the other hand, MVC is substrate of CYP3A4 and P-gp; hence, dose adjustment is frequently required when co-administered with drugs that alter its pharmacokinetics<sup>96,97</sup>. MVC is identified as substrate of the transport protein OATP1B1 and the variation 521T>C is linked with higher MVC plasma levels<sup>98</sup>.



**Fig. 5.** Mode of action of maraviroc. It prevents gp120 from binding to the CCR5 co-receptor and prevents the fusion peptide from gp41 inserting into the cell membrane.

Thus, the only genetic test that is mandatory to perform before starting MVC treatment is the determination of viral tropism<sup>4,99</sup>.

### Conclusion and clinical relevance

The objective of any therapy is to maximize the therapeutic outcome and to minimize the side effects. HAART represents very effective ART but is brought with innumerable side effects. The side effects like cutaneous hypersensitivity may be avoided with proper genetic testing which predisposes to susceptibility such as HLA-B\*5701 associated ABC adverse reaction. Similarly, certain drugs like maraviroc may not be prescribed to HIV positive individuals with CCR5 tropic HIV. However, a large number of HAART drugs show change in pharmacokinetics due to variations in genes of drug metabolic pathway enzymes like CYP450, ATP binding cassette and UGT1A1. Individualized approach to personalized HAART is influenced by host factors and is known as pharmacogenomics. It is also influenced by certain viral characteristics and the drug administered. Application of pharmacogenomics with understanding of medicine, viral characteristic of HIV is at the doorstep to guide the personalized prescription in which the right medication will be given to the right person. Several measures need to be taken for application of pharmacogenetic research in making a genetic test available for public. Many factors affect successful translation such as pharmacodynamics and pharmacokinetic properties of

drug adversities, laboratory facilities, quality assurance and quality control (QA and QC) measures and type of tests<sup>100</sup>. The reported associations have to undergo stringent validation in independent, ethnically diverse populations having highest number of HIV positive individuals.

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