CHARPTER II

LITERATURE REVIEWS

Antiretroviral therapy

Since the first case report of AIDS as a clinical syndrome 30 years ago [34], around 75 million people with human immunodeficiency virus (HIV) and 36 million people have died of AIDS [35]. There are 5 groups of drugs (26 drugs) classification of drugs approved by US-FDA for the HIV treatment including (1) Nucleotide reverse transcriptase inhibitors (NRTI); (2) Non-nucleoside reverse transcriptase inhibitors (NNRTIs); (3) Protease inhibitors (PIs); (4) Integrase inhibitors (INSTIs), and; (5) Fusion inhibitors (FIs) Time line of those drug and their discovery are summary in Figure 1 [36]. These highly active drugs improve the survival rate and quality of life HIV-infected patients [37]. Standard guidelines recommend a drug treatment in asymptomatic patients with HIV (including pregnant) with CD4 count ≤ 350 or lower with 3 or more antiretroviral drugs (Table 1-2) [38,39].

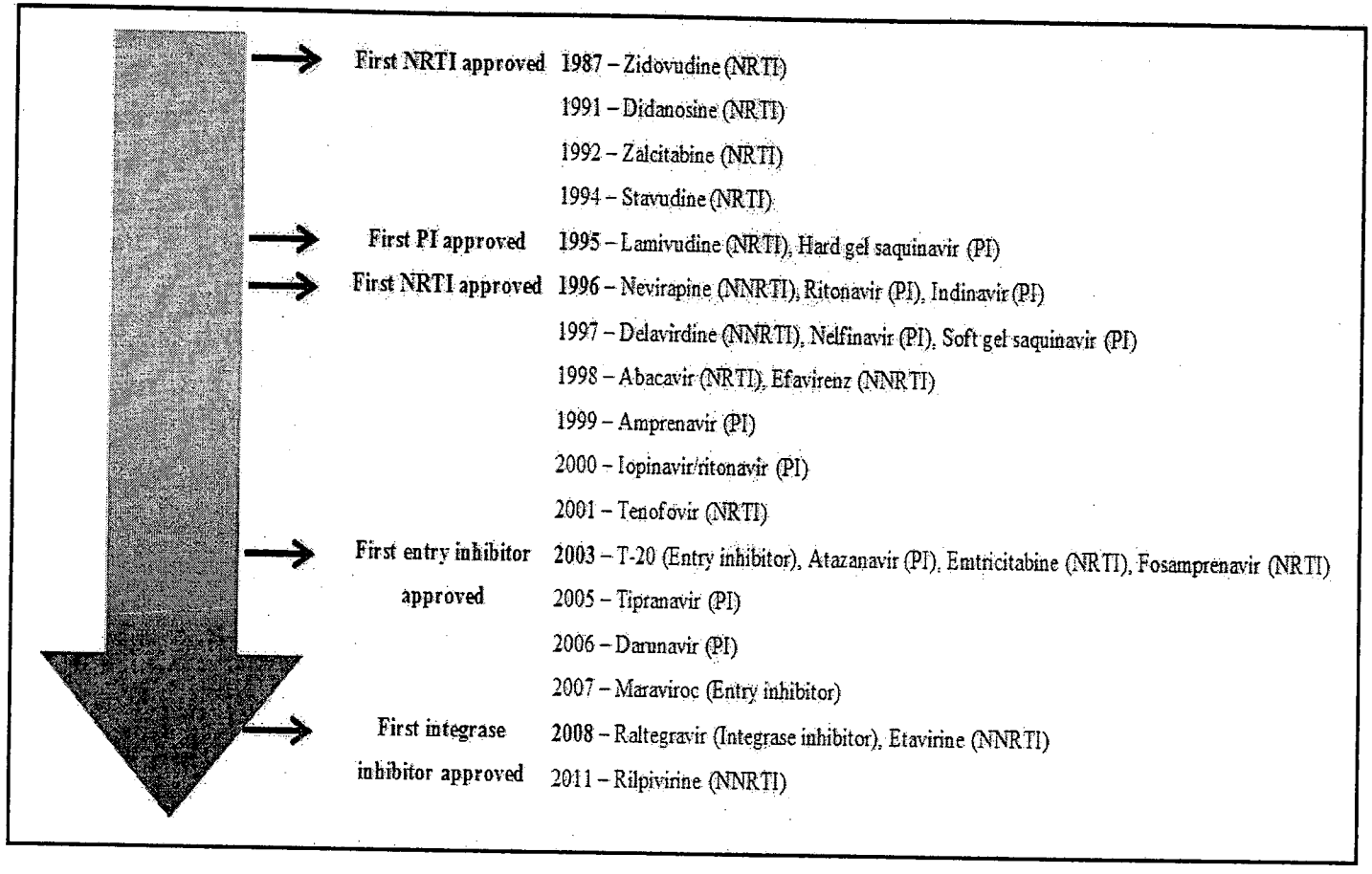

Figure 1 Timeline of antiretroviral

Source: Adapted from Pavlos R, et al. [36]

Table 1 Criteria for ART Initiation in specific populations [38]

Target population	Clinical condition	Recommendation
Asymptomatic individuals (including pregnant women)	WHO clinical stage 1	Start ART if CD4 ≤350
Symptomatic individuals (including pregnant women)	WHO clinical stage 2	Start ART if CD4 ≤350
	WHO clinical stage 3 or 4	Start ART irrespective of CD4 cell count
TB and hepatitis B coinfections	Active TB disease	Start ART irrespective of CD4 cell count
	HBV infection requiring treatment	Start ART irrespective of CD4 cell count

Table 2 Regimens for initiating treatment of HIV infection

Guidelines	NRTIs	NNRTIs	PIs
World Health Organization [38]	Zidovudine + Lamivudine (see Footnote 1) Tenofovir + Lamivudine Tenofovir + Emtricitabine	Nevirapine Efavarenz	-
National Guidelines on HIV/AIDS Diagnosis and Treatment: Thailand 2010 [39]	**Preferred:** Zidovudine + Lamivudine Tenofovir + Lamivudine Tenofovir + Emtricitabine	Nevirapine Efavarenz	Lopinavir/Ritonavir (see Footnote 2)
	Alternative: Abacavir + Lamivudine Stavudine + Lamivudine Didanosine + Lamivudine	Nevirapine Efavarenz	Atazanavir/Ritonavir Darunavir /Ritonavir Saquinavir /Ritonavir

Abacavir

Abacavir (Figure1) is a nucleoside reverse transcriptase inhibitor (NRTI) used with other antiretroviral agents in the treatment of HIV infection. Abacavir is converted to active metabolite (carbovir triphosphate), an analogue of deoxyguanosine-5'-triphosphate (dGTP) this active metabolite competitively inhibits the HIV reverse transcriptase enzyme and acts as a chain terminator of DNA synthesis [40].

Abacavir is generally well tolerated but can cause hypersensitivity in 5-8% of patients during the first 6 weeks of treatment [41]. These symptoms include renal or hepatic failure, fever, rash, nausea and, vomiting [26].

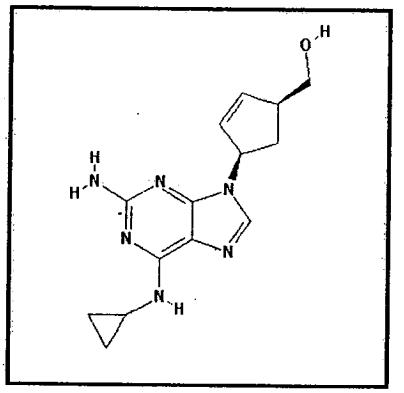

Figure 2 Structure of abacavir

Source: Product Information: Ziagen®, abacavir sulfate tablets and oral solution [40]

Nevirapine

The chemical structure of nevirapine is depleted in Figure 3. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with other antiretroviral agents in the treatment of HIV infection. Nevirapine binds directly to the reverse transcriptase and blocks RNA-dependent and DNA-dependent DNA polymerase activities causing a disruption of the enzyme at its catalytic site [42].

Nevirapine has a long-term ADR profile. Its common ADRs are rash, hypersensitivity syndrome, and hepatitis. For hepatitis it typically occurs in approximately 5% of patients during the first treatment within 2–8 weeks. SJS and TEN occur in 0.3% of patients within 8 weeks of nevirapine treatment initiation [12].

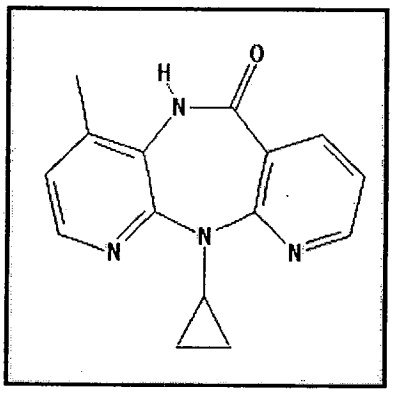

Figure 3 Structure of nevirapine

Source: Product Information: Viramune® [43] tablets and oral suspension [42]

Stavudine

Stavudine (Figure 4) is a nucleoside reverse transcriptase inhibitor (NRTI) used with other antiretroviral agents in the treatment of HIV infection. It is phosphorylated by cellular kinases into stavudine triphosphate. The metaboliteate inhibits the HIV reverse transcriptase by competing with, thymidine triphosphate and incorporating into the DNA strand. Major ADRs of this drug are lipodystrophy, neuropathy and lactic acidosis [38].

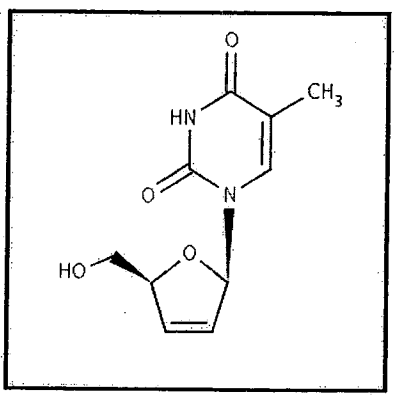

Figure 4 Structure of stavudine

Source: Product Information: ZERIT® (stavudine) capsules and oral solution [44]

The human leukocyte antigen (HLA) system

The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, is located on chromosome 6. It encodes cell-surface receptors that capture and present self- and pathogen-derived peptides to T cells receptor (TCR). HLA is divided into 3 groups, HLA Class I, II and III, Nonetheless, only HLA Class I and II are association with drug-induced ADRs [45]. Thus, in this review, we shall focus on these 2 classes and omit the remaining, HLA class III.

HLA Class I [45] consists of α heavy chain, composed of three domains α1, α2 and α3. This heavy chain is bound to a β_2-microglobulin molecule. The heavy chain consists of 2 peptide-binding domains, an Ig-like domain, and a transmembrane region with a cytoplasmic tail (Figure 5). HLA Class I is divided into 3 major groups, HLA-A, HLA-B, and HLA-C. The proteins produced from these genes are present on the surface of almost all cells. On the cell surface, these proteins are bound to protein fragments (peptides) that have been exported from within the cell. MHC class I proteins display these peptides to the immune system (CD8+). If the immune system recognizes the peptides as foreign entities (such as viral or bacterial peptides); it responds by triggering a self-destruction process of the infected cell.

HLA Class II [45] consists of 2 α heavy chain and 2 β_2-microglobulin molecule. Each chain has a peptide-binding domain, an Ig-like domain, and a transmembrane region with a cytoplasmic tail (Figure 5). There are six main HLA class II genes in humans, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1. They are usually present on antigen-presenting cells (APCs) (i.e. B cells, macrophages, dendritic cells, langerhans cells), thymic epithelium, and activated T cells.

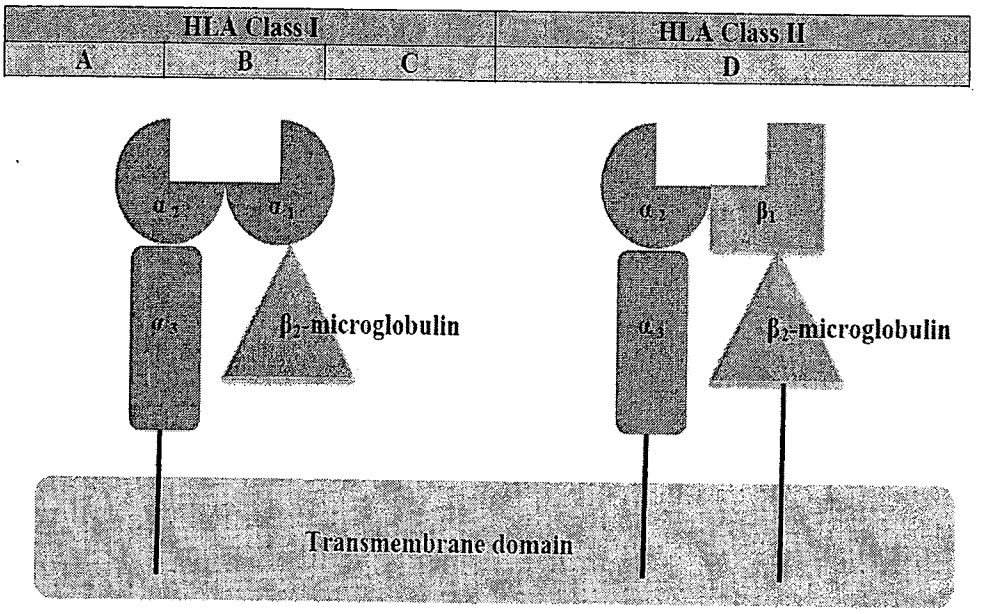

Figure 5 HLA class I and HLA class II molecule

Source: Adapted from Abbas A, et al. [46]

Role of genetics and HLA genotypes in ADRs

ADRs are one of the causes of morbidity and mortality in healthcare. In USA, the cost of drug-related morbidity and mortality was about US$136 billion [47]. This is an obvious burden from drugs treatment.

There are two major categories of ADRs, Type A and Type B. Type A ADR is predictable from a pharmacological activity of the drug, and type B ADR is not predictable or idiosyncratic. The severity of Type B ADR is more pronounce than type A ADR [48]. However, over the last few decades several studies reported strong genetic association between HLA genotypes and specific drug-induced ADRs. For example, a strong association between the HLA-B*1502 allele and carbamazepine induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in some Asian populations (i.e., Han Chinese, Thai and Malaysian) was documented [17, 18, 19, 20]. In Japanese, HLA-A*3101 is association with carbamazepine induced SJS/TEN [49]. In addition, individuals having HLA-B*5801 also displays a high incidence of allopurinol-induced SJS/TEN [21]. In ADRs of the anti-HIV drugs, the

association between HLA-B*5701 with abacavir HSRs abacavir are generally accepted [26, 31, 32].

The mechanism by which HLA genotypes associated with the ADRs is still not fully understood. However, several models have been proposed to explain how small molecules are recognized by T cells in HLA. These models are including the hapten concept model, the p-i model, and the altered repertoire model.

The hapten concept model

This model proposes that small drugs or their metabolites (less than 1000 Da) cannot elicit immunogenicity by themselves. Nonetheless, they irreversibly bind with a larger protein molecules or a peptide by a covalent bond. Subsequently, that newly formed molecule binds directly to the HLA and be presented to the T-cell receptor (TCR). Then it becomes antigenic [15, 36, 50]. However, this model cannot explain a phenomenon caused by drugs with a high molecular weight.

The p-i model (pharmacologic interaction)

This model proposes that drugs or their metabolites bind directly and reversibly via a non-covalent bond with the TCR or HLA molecules without the requirement for a specific peptide ligand. This interaction results in active immune response of the T cell [15, 36, 50] (Figure 6)

For the interaction between drug and TCR, HLA molecules were not restricted. For example in Watkins, et al study, sulfamethoxazole binds to CDR2β of specific TCR (Vβ20-1) without interaction with peptide or HLA molecule. Subsequently, this complex interacts with a specific peptide and HLA molecule. This interaction results in triggering the immune system [51].

For the direct interaction between drug and HLA molecule was presented in the carbamazepine induced SJS/TEN model, which was shown that HLA-B*1502 loaded with endogenous peptides were able to bind carbamazepine directly [52].

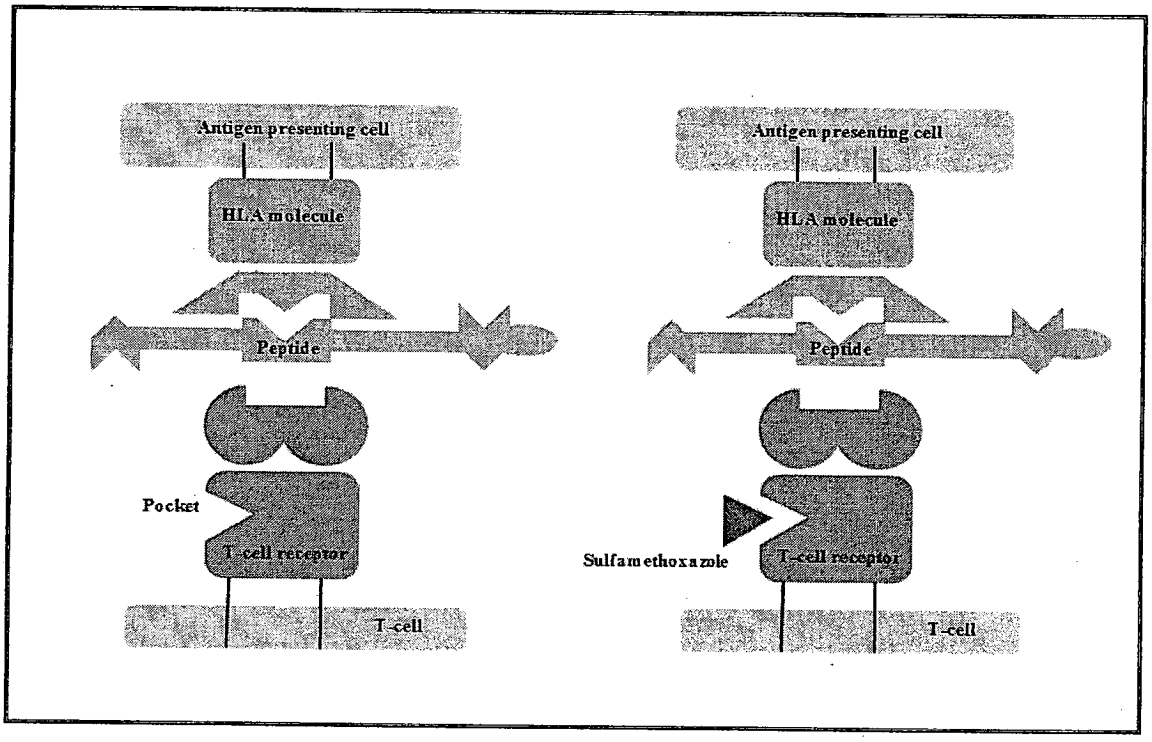

Figure 6 Models of the interaction between drug and TCR

The altered repertoire model (Figure 7)

The major concept of this model is, the binding of drug and HLA molecule alters the specificity of the antigen-binding cleft via non-covalent binding. Subsequently, a new repertoire of self-peptide ligand is presented to the TCR [36, 53, 54]. This concept was presented by Illing P, et al. [54] in abacavir induced HSR model, which was shown that abacavir bind to the pocket-F of HLA-B*5701 lead to selection of peptide with Valin at position 9. In Adam J, et al. study [55], 3D conformation of SI9 is very similar between complex of abacavir and HLA-B*5701and HLA-B*5801 (Figure 8). In additional, naturally peptides fitting into HLA-B*5801 peptide binding groove can bind into the complex of abacavir and HLA-B*5701 and increased the proportion of HLA-B*5801 allo-reactive T cell clones from 5% to 42%.

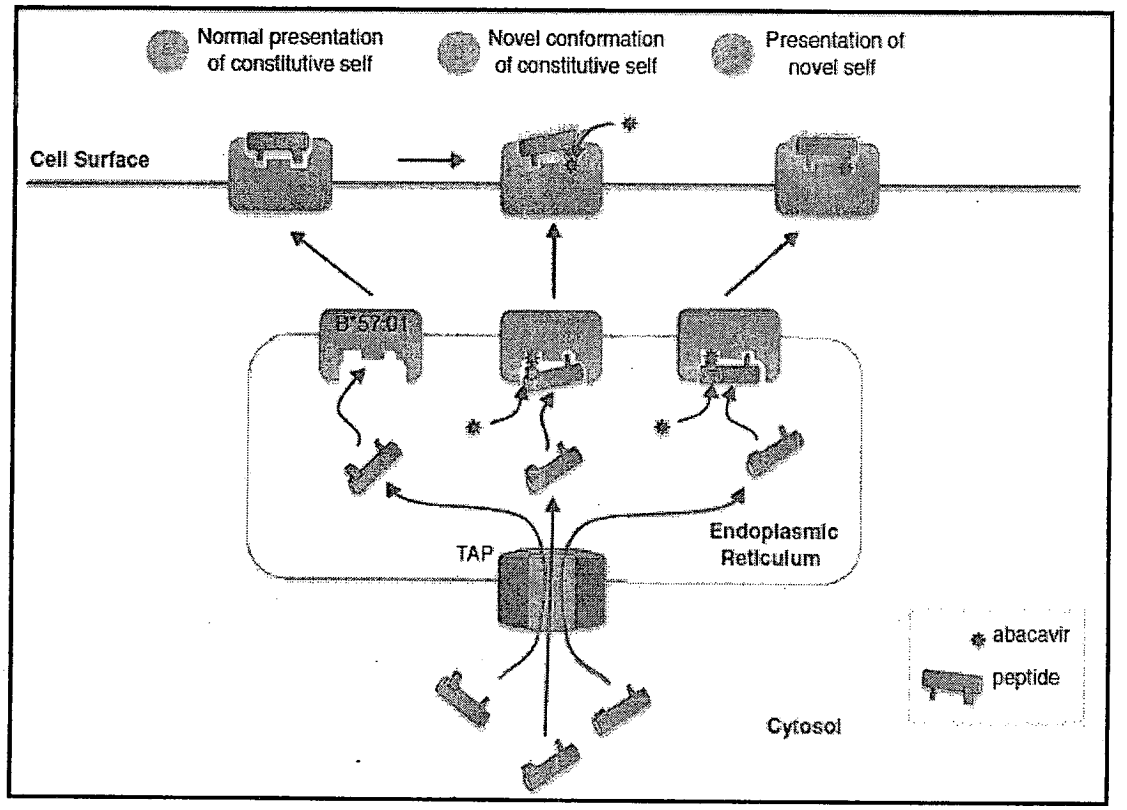

Figure 7 Models for generation of immunogenic HLA-B*5701 and abacavir peptide complexes

Source: Illing P, et al. [56]

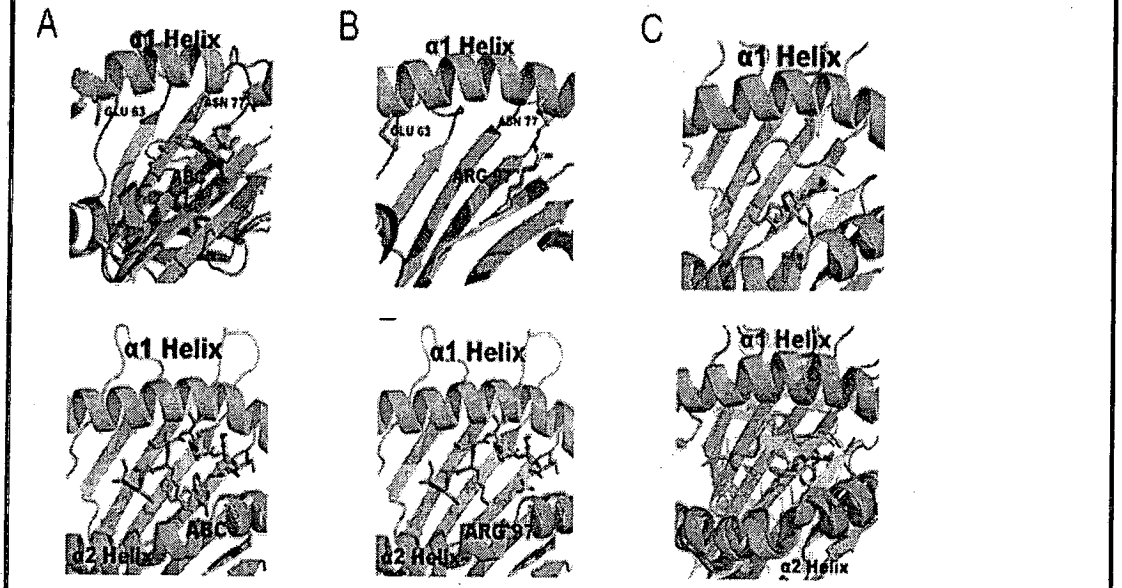

Figure 7. Molecular modelling of HLA-peptide complexes. A. HLA B*57:01 peptide binding cleft with bound abacavir (orange) is shown empty (upper panel) or filled with the SI9 peptide (lower panel). B. The position of Arg97 is highlighted in yellow on the HLA-B*58:01 molecule without (upper panel) or with the anchored SI9 peptide (lower panel). C An overlay of the (HLA-B*57:01+abc) complex (turquoise) and HLA-B*58:01 (purple) with modelled SI9 peptide is shown. SI9 highlighted in orange is bound to (HLA-B*57:01+abc) and SI9 highlighted in purple is bound to HLA-B*58:01. Abacavir and Arg97 found in the F9 pocket are highlighted in orange and yellow, respectively. The 3D conformation of SI9 is very similar between (HLA-B*57:01+abc) and HLA-B*58:01.

Figure 8 The 3D conformation of SI9 is very similar between abacavir-HLA complex and HLA-B*5801.

Source: Adam J, et al. [55]