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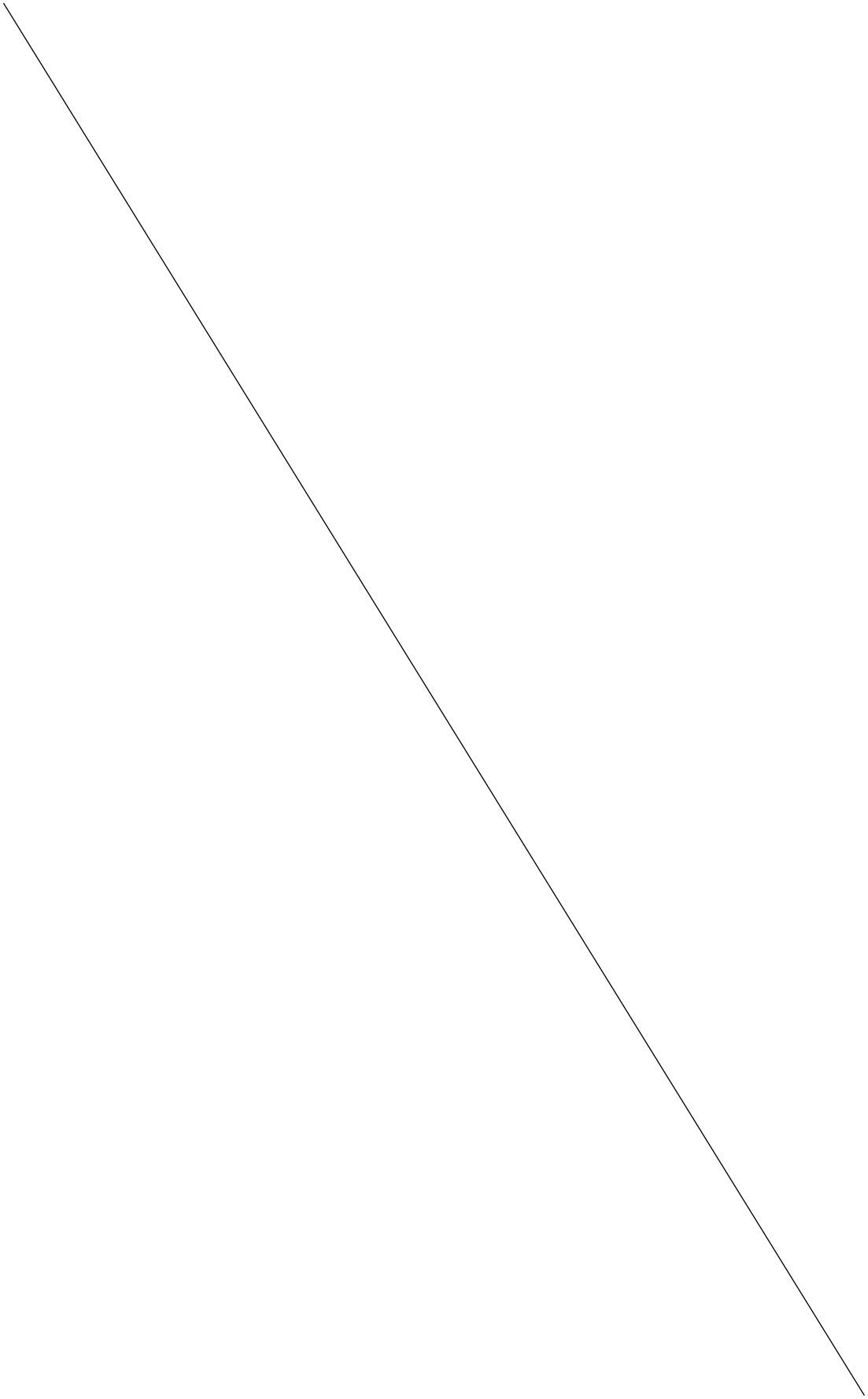

title

Boosted darunavir as a new therapeutic option for treatment-naive HIV-infected patients

authors

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summary

HIV infection is one of the major global public health problem. Currently, among the specialists, an estimated 33 million people are infected with HIV worldwide. At present, six main classes of antiretroviral drugs exist, and almost all of them are used in antiretroviral therapy regimen in treatment-experienced as well as treatment-naive patients. Protein inhibitors are selective inhibitors of the cleavage of HIV-encoded gag-pol polyproteins. Darunavir, previously known as TMC-114, is a new, second-generation PI. Darunavir has high potency, genetic barrier and very good clinical and metabolic tolerance. In twice-daily dose darunavir is used as a rescue therapy in treatment-experienced patients. However, after ARTEMIS study, it was recently approved in first-line antiretroviral therapy for treatment-naïve HIV-infected patients.

key words

HIV infection, antiretroviral treatment, protease inhibitors, darunavir, treatment-naïve patients

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Introduction

HIV infection is one of the major global public health problem. Currently, among the specialists, an estimated 33 million people are infected with HIV worldwide (1). Fortunately, after introduction of HAART (highly active antiretroviral therapy) which usually leads to the achievement of durable virologic suppression, HIV-infected persons have further chances to living almost like other patients with common chronic diseases. At present, six main classes of antiretroviral drugs exist: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (IIs), fusion inhibitors (FIs), and chemokine receptor antagonists (CRAs). Moreover, almost all of them are used as part of an antiretroviral therapy (ART) for treatment-experienced as well as for ART-naive patients.

First PIs were introduced in 1995, and till nowadays 9 agents from this class are approved to use. Indinavir (Crixivan), nelfinavir (Viracept), saquinavir (Invirase) and ritonavir (Norvir) belong to the first-generation PIs. The second-generation PIs – atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), lopinavir/ritonavir (Kaletra), and tipranavir (Aptivus) – have higher antiviral potency and may retain activity in the presence of resistance to first-generation agents. All PIs inhibit HIV-1 and HIV-2 protease activity. In consequence, they are selective inhibitors of the cleavage of HIV-encoded gag-pol polyproteins and the maturation of the virus particles. PIs are metabolized by the hepatic cytochrome P450 (CYP3A4 and CYP3A5) enzymes. Therefore, PIs are usually used with "boosted" dose of ritonavir (100-200mg) which acts as an inhibitor of PIs hepatic CYP3A and intestinal metabolism, thereby increasing PIs availability. PIs have rather short serum half-lives, ranging from 1.5-2 hours for indinavir and 7 hours for atazanavir (2). The most common adverse events associated with PIs are diarrhea, nausea, vomiting and metabolic complications such as dyslipidemia, lipodystrophy, hyperglycemia, insulin resistance and diabetes mellitus.

Darunavir (DRV), previously known as TMC-114, is a new, second-generation PI. In in vitro studies DRV was more potent then saquinavir, amprenavir, nelfinavir, indinavir, lopinavir and ritonavir. DRV is rapidly absorbed from gastrointestinal tract and reaches peak plasma concentrations within 2.5-4 hours. It should be taken with food which enhances its bioavailability by almost 30%. Its mean elimination half-life is approximately 15 hours (3).

Darunavir in treatment-experienced HIV-infected patients

Firstly, DRV was studied as early (TITAN; 48-week phase 3 study) or late rescue therapy (POWER 1 and 2; 96-week phase 2 studies) in treatment-experienced HIV-infected patients with resistance to other available PIs. In POWER study oral twice-daily 600 mg DRV dose boosted with 100 mg ritonavir was compared to investigator-selected boosted control PIs (CPIs), in TITAN study DRV/r was compared to twice-daily boosted lopinavir (400/100 mg). All studies above confirmed its high therapeutic efficacy and antiviral potency: in POWER and TITAN study, the virologic response achieved 57% in DRV/r-treated patients versus 10% in CPIs/r-treated patients and 77% in DRV/r-treated patients versus 67% in LPV/r-treated patients, respectively [3]. Moreover, in POWER study, 11 protease mutations associated with a reduced response to boosted DRV were identified (V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V). The most commonly selected mutations were V32I and I54L (4). DRV has extremely elevated genetic barrier because at least three DRV-associated mutations plus high number of other PIs-associated mutation must be detected to confirm DRV resistance. Genotypic resistance to DRV was detected in 7-9% of studied treatment-experienced patients with rescue therapy failure. In in vitro studies no DRV cross-resistance with other PIs was detected. Furthermore, it has been shown that DRV/r had also very good tolerability profile with lower rate of gastrointestinal adverse events and dyslipidemia than CPIs (5). Additionally, it has been demonstrated that subjects with significant baseline resistance to PIs have lower rates of viral suppression after 800/100 mg DRV/r twice-daily then after 600/100 mg DRV/r twice-daily dosage (31% vs. 47%, respectively). For patients with no genotypic DRV resistance-associated mutations at baseline, the rates of viral suppression were 62% and 67% for the 800/100 mg once-daily and 600/100 mg twice-daily DRV/r doses, respectively (6). Finally, DRV was approved by FDA (Food and Drug Administration) and EMEA (European Medicines Agency) as a therapeutic option for treatment-experienced HIV-infected patients with resistance to other available PIs in twice-daily 600/100 mg DRV/r dose. Finally, recently, the very interesting findings of MONET trial were presented during 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, Cape Town, South Africa. In this study the once-daily monotherapy with 800/100 mg DRV/r was compared with standard combinated ARV therapy with 2 NRTIs and DRV/r. Two hundred fifty six HIV-1 infected treatment-experienced patients with undetectable HIV viral load were enrolled in the study. As a result, DRV/r monotherapy had the same efficacy as cART: at week 48 the HIV RNA < 50 copies/ml was detected in 97.6% patients in DRV/r arm and 97.7% in cART arm, respectively. No phenotypic resistance to DRV/r during monotherapy was detected. Moreover, it was the first study which showed noninferiority of PI monotherapy in comparison to standard triple-therapy (7).

Darunavir in treatment-naive HIV-infected patients

The 800/100 mg once-daily DRV/r dose as a new therapeutic first-line option for treatment-naïve patients was approved by FDA on 21st October 2008. This decision was based on the results of the clinical trial ARTEMIS (Anti-Retroviral Therapy with TMC114 Examined In naive Subjects). In this study 800/100 mg once-daily DRV/r dose was compared to 800/200 mg LPV/r daily-dose plus tenofovir and emtricitabine as an optimized background regimen. Six hundred eighty-nine patients with HIV viral load at least 5000 copies/ml were enrolled in the study. Undetectable HIV viral load achieved 84% of DRV/r and 78% of LPV/r patients at 48 weeks and 79% of DRV/r and 71% of LPV/r patients at 96 weeks, respectively. Median augment

in CD4 cell count was comparable for two studied PIs: 137 vs 141 cells/ml at 48 weeks and 171 vs 188 cells/ml at 96 weeks, respectively. Moreover, at 48 weeks significantly higher virological response rates were observed with DRV/r in patients with high viral load at baseline (at least 100 000 copies/ml). At week 96, there was no difference in viral response degree in adherent patients (mean adherence > 95%), however in sub-optimally adherent patients (mean adherence < 95%), those receiving DRV/r had a greater response than those receiving LPV/r: in the DRV/r group, sub-optimally adherent patients had similar rates of response (76%) compared with adherent patients (82%; p = 0.3312), and in the LPV/r group -53% vs. 78%; p < 0.0001, respectively. DRV/r was generally very good tolerated by treatment-naïve patients, only 4% of DRV/r-treated patients vs 9% of LPV/-r treated patients discontinued therapy because of adverse events. The most common reasons of treatment withdraw were diarrhea (6%), headache (5%), abdominal pain (4%), nausea (3%), vomiting (2%) and rash (2%), however almost all of them were less frequently observed in DRV/r-treated patients then in LPV/r-treated group. Moreover, DRV/r influenced in statistically less degree on lipid and glucose profile. Finally, no DRV/r genotypic resistance at baseline in treatment-naïve patients were observed (8, 9).

The current recommended regimens for treatment-naïve patients are presented below.

NNRTI:

preferred	EFV*
alternative	NVP

* do not use in 1st pregnacy trimester or in young woman withhigh pregnacy potential

OR

PI:

preferred	ATV/r (qd) DRV/r (qd) FPV/r (bid) LPV/r (qd or bid)
alternative	ATV/r (qd) DRV/r (qd) FPV/r (bid) SQV/r (bid)

PLUS

NRTI:

preferred	TDF+FTC
alternative	ZDV+3TC ABC*+3TC ddI+FTC ddI+3TC

* if HLA B*5701 negative

Conclusion

The current evidence from DRV/r clinical trials supports its high antiviral efficacy and very good clinical as well as metabolic tolerance. In conclusion, once-daily DRV/r may be an preferable option in first-line antiretroviral therapy for treatment-naïve HIV-infected patients.

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title

Whether the resistance to human immunodeficiency virus (HIV)-infection exist?

authors

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summary

Studies of persons who remain uninfected despite exposure to HIV continue to provide valuable information on mechanisms of natural protection, which can be applied to future vaccine designs. They are arousing a huge public interest, leaving the belief that some people aren't sensitive to HIV infection. In this review, we focus on certain mechanisms associated with resistance to HIV and to the progression to AIDS, showing that the total insensitivity to infecting doesn't exist.

key words

susceptibility, resistance, HIV infection

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Introduction

Despite some successes in the field of HIV-1 prevention through strategies of education, prevention sexually transmitted infections, and early antiretroviral therapy over 6800 people are infected by human immunodeficiency virus type 1 (HIV-1) every day in 2007, mostly in the so-called "developing countries". HIV-1 exposure can lead to a broad spectrum of outcomes ranking from rapid progression to AIDS to survival for many years. Fortunately, despite documented exposure to HIV, less than a 100% of exposed individuals become infected. For example, the rate of infection in individuals exposed to an entire unit of infected blood is only about 90% (1).

Transmission of HIV results first in an acute (primary) infection, followed by an apparently asymptomatic period that averages ten years, although it may vary greatly among infected subjects. In the absence of the antiretroviral treatment, most patients progress into a generalized immune dysfunction that culminates in AIDS and death.

But the course of HIV infection is affected by inter-individual variability and intense efforts are currently underway to immunologically and genetically characterize individuals that show resistance to HIV disease. These individuals can be classified in two main groups: highly exposed, but seronegative individuals (ESN) and long-term non progressors (LTNP). This review will focus on first from these groups – exposed, seronegative persons.

Overview of HIV-1 replicative cycle

Mature HIV-1 virions have spherical morphology of 100-120 nm in diameter and consist of a lipid bilayer membrane that surrounds a dense truncated cone-shaped nucleocapsid (core) which contains the genomic RNA molecules. The HIV-1 genome consists of two identical 9,2 kb single stranded RNA molecules within the virion and encode three polyprotein precursors: the group-specific antigen (Gag), polymerase (Pol), and envelope (Env); two regulatory proteins: the transcriptional transactivator (Tat) and the regulator of virion gene expression (Rev), as well as four accessory proteins" the "negative effector" (Nef), viral infectivity factor (Vif), and the viral proteins: r (Vpr) and u (Vpu). The persistent form of the HIV-1 genome is proviral double-stranded DNA within infected cells (2).

The infection begins with the attachment of the virions to the cell surface mediated by an interaction between the extracellular domain of HIV-1 gp-120 and cellular receptors. Shortly after the discovery of HIV, it was recognised that the virus gain access to the cell via the CD4 receptor. But the second receptor, so called co-receptor, is also necessary for viral entry. Upon a conformational change in gp120 Env interact with the CC chemokines receptor 5 (CCR5: for R5, macrophage tropic or non-syncytium inducing strains) or CXC chemokine receptor 4 (CXCR4: for X4, T-cell tropic or syncytium inducing strains). A minority of HIV viruses are capable of using the CCR5 or the CXCR4 receptor. These interactions prompt a conformational change in gp41, which mediates the fusion between the virus and the host cell. By the entrée to the sensitive cell, HIV is uncoated, and viral reverse transcriptase (RT) copies the genomic RNA into double stranded cDNA. The completion of reverse transcription gives rise to the HIV-1 pre-integration complex (PIC), which is composed of double stranded viral cDNA, integrase (IN), matrix (MA), Vpu, RT, and the high-mobility group DNA-binding protein, HMGI(Y). After viral proteins are translated in the cytoplasm, they are assembled into new virions in lipid rafts on cellular membranes. In T cells the assembly and release occur at the cell surface, in macrophages and dendritic cells, HIV assembles on the endosomal membranes. Eventually, these organelles fuse with the plasma membrane and viral particles are released. The further maturation of virions occur after the formation of active protease dimmers, which cleave Gag and Pol polyprotein precursors into their functional subunits. The virus assumes its mature shape with a clearly defined inner cigar-shaped core and outer dodecahedral envelope (review: 3).

HIV-1 specific T-helper and cytotoxic T lymphocytes (CTL) response

Some exposed seronegative individuals do not seroconvert despite numerous documented exposures to HIV. HIV-specific CTL responses have been detected in babies born to infected mothers (4, 6), occupationally-exposed health care workers (6), the regular sexual partners of infected people. Early studies showed some commercial sex workers in Kenya remained persistently seronegative, despite > 3 years daily exposure to numerous HIV-infected sex partners (7). But years later some of these women seroconverted, and their common feature was a reduction in sex work – either stopping for over two months or reducing the numbers of clients per day – over the preceding year. In persistently uninfected controls, a break from sex work was associated with a loss of HIV-specific CD8+ responses (8). According to Letvin and Walker commentary, it will be very important to monitor the clinical course of HIV disease in these HIV-infected commercial sex workers. This unusual subpopulation of individuals, because of pre-existing memory CTLs specific for HIV prior to their infection, may actually have relative preserved CD4 T-lymphocyte populations and therefore sufficient immune function to control their HIV infection effectively in the absence of antiretroviral therapy (9). These individuals may therefore have relative benign clinical disease courses in the coming years (8), however it requires further research and a longer observation.

In the Multicenter AIDS Cohort Study (MACS) Detels and al. (10) observed that some men with many different partners with whom they practiced receptive anal intercourse remained seronegative. In later years they demonstrated that white blood cells, polymorphonuclear neutrophils, total lymphocyte count, CD8+ percentage and number, and CD3+ and CD4+ number were higher in the resistant men what support hypothesis that CD8+ cells may modulate the outcome of HIV-1 exposure (11). Paxton et al. (12) show that CD8+ lymphocytes from ESN subjects had greater anti-HIV-1 activity than did CD8+ lymphocytes from nonexposed controls and that their purified CD4+ lymphocytes were less susceptible to infection with multiple primary isolates of HIV-1 than were CD4+ lymphocytes from the nonexposed controls, but this relative resistance to HIV-1 infection did not extend to T-cell line-adapted strains and was associated with the activity of the CC chemokines RANTES (regulated upon activation, normal T expressed and secreted)/ named according to Zlot-

nik and Yoshi classification system (13) CCL5, macrophage inflammatory proteins – MIP-1α/ CCL3, MIP-1β/CCL4. Skurnick et al. (14) in study of 17 women – heterosexual partners of HIV positive men demonstrated that CD8+ cell activity appeared to be the dominant factor in nontransmission. Their results indicate also that characteristics of the donor men and the potential recipient women both contribute to nontransmission. The lack of transmission cannot be ascribed to reduction in CD4 cell infectivity. The CD4+ cells of 9 women were readily infected, and of 5 by their partner's virus. None of the women was homozygous for CCR5Δ32. Authors believe that this findings, supported by other data, makes a strong case for the primacy of the CD8 cell response in reducing the risk of HIV transmission. But, according to Marmor et al. (15) despite the evidence for CTL involvement in resistance to HIV infection, the available data does not yet establish causation, and the possibility that CTLs are surrogate markers of some other mechanism can't be ruled out.

Recently Card et al. (16) published findings that HIV-resistant individuals were shown to have reduced frequencies of T cells expressing the activation marker CD69 and elevated frequencies of regulatory T cells compared with HIV-negative control individuals. Card et al. concluded, that T regulatory cells may contribute to HIV resistance by minimizing the pool susceptible to infection by controlling levels of T cell activation. But in Cao et at. findings expansion of regulatory T-cells was positively correlated with CD4+ T cell activation among HIV-infected fast progressors (17).

Mucosal HIV-1 IgA

Most of the new cases of HIV infection occur as a result of sexual transmission, with the initial host-virus interaction occurring at the level of the genital tract epithelium. This may be the female genital mucosa (during vaginal sex), the rectal mucosa (during anal sex), or the oropharyngeal mucosa (during oral sex, or breast feeding). For this reason, the study of HIV-specific mucosal immune responses in highly exposed, persistently seronegative subjects has inspired research interest. Since IgA antibodies are a key element in the mucosal immune system (18) many investigators have been interested in examining HIV-1 specific IgA responses in ESN subjects, both at a mucosal and systemic level. IgA is present in various mucosal and exocrine fluids, including parotid saliva, cervicovaginal and intestinal secretions, milk, and bronchial lavage fluid, and can contain antibodies to HIV (19). IgA from parotid saliva, cervicovaginal fluid, and plasma of naturally infected individuals has been shown to be capable of neutralizing T cell line-adapted as well as primary HIV isolates (20). In addition to the conventional neutralization activity mentioned, human IgA antibody has also been shown to be able to act intracellularly to block HIV transcytosis from the apical to the basolateral side of epithelial cell monolayers, suggesting the potential to inhibit spread of HIV from mucosal epithelium to the lamina propria ("intracellular neutralization") (21, 22).

However Horton et al. (23) demonstrate that not strong correlation exists between HIV-specific cervical IgA levels and resistance to infection by HIV as previously believed. This findings do not preclude the possibility that functional differences in the cervical IgA of ESN women may play a role in resistance, but argue that HIV-specific responses may not be a universal protective factor.

MHC class I/II alleles

One important determinant of resistance and susceptibility to infections is the major histocompability complex (MHC). MHC alleles determine the molecular targets of the cellular immune response in a given host. Genetic polymorphism of MHC results from concentrated amino acid substitutions in the peptide-binding groove of HLA molecules that produce variability in peptide epitope binding and presentation to T cells.

A selective advantage against the disease has been demonstrated with increased heterozygosity at HLA class I region. According to the hypothesis of over dominant selection (heterozygote advantage) at the MHC, individuals heterozygous at HLA loci are able to present a greater range of antigenic peptides to CTLs than by homozygotes, resulting in a more protective immune response. Carrington et al. (24) presented evidence to suggest that maximum HLA heterozygosity of class I loci led to significantly delay in AIDS onset among patients infected with HIV, compared to individuals homozygous for one or more loci who progressed faster to AIDS.

HLA-B*57 and related alleles of HLA-B*58 supertype have been reported to be associated with low viraemia, delayed onset of AIDS and cytotoxic T lymphocyte-driven attenuation of HIV in Caucasoid and African population. However in many studies has been observed a strong association of B*35 with rapid progression to AIDS (review: 25).

Amongst HLA class II genes DRB1 is the most polymorphic locus and forms haplotypes with DRB3, DRB4 and DRB5. The study conducted amongst Kenyan sex workers cohort showed that three DRB1 alleles were associated with resistance to HIV infection: DRB1*010101, DRB1*010201, and DRB1*1102 however DRB1*030201, DRB1*070101, DRB1*1503, and DRB5*010101 were associated with susceptibility. The haplotype DRB1*1102-DRB3*020201 was associated with HIV-1 resistance, whereas the haplotypes DRB1*070101-DRB4*01010101 and DRB1*1503-DRB5*01010101 were associated with susceptibility (26). These associations with resistance/ susceptibility to HIV-1 were independent of previously reported alleles HLA-DRB1*01 (27).

In the same cohort HLA-DP antigen presenting peptides to CD4+ T cells, namely DPAI*010301 was associated with HIV resistance and slower seroconversion (28).

Chemokine receptor polymorphisms

Many chemokine receptors have been described as HIV co-receptors and co-receptor usage is a major determinant of viral cell tropism. CCR5 is the co-receptor used by R5 HIV strains which are recovered during first years following seroconversion, and therefore considered as responsible for disease transmission (29).

Liu et al. (30) and Samson et al. (31) identify a 32-base-pair deletion (Δ32) within the coding region CCR5 which generates a non-functional receptor that does not support membrane fusion or infection by macrophage and dual tropic HIV-1 strains. This deletion is common in Caucasians and found at lower frequencies in the Middle East and East Asians. A cline CCR5Δ32 allele frequencies in a north to south gradient has been found in Europe, with the highest frequencies in Finnish population (16%), and the

lowest in Sardinia (4%). The properties of CCR5Δ32 suggest that it was rapidly enriched in Caucasians because it conferred an advantage against some relatively recent and strong selective factors, possibly a catastrophic epidemic. Even appeared a view that the dispersal of Vikings may have greatly accelerated the dissemination of the resistance allele across Europe (32). The CCR5Δ32 variant is almost completely absent in sub-Saharian African populations, where the majority of HIV infections occurs and where many investigators have described numerous cohorts of ESN. Schliekelman et al. (33) has been projected that if the HIV epidemic continues for another 100 years, it will leave a signature on the human genome at the CCR5 locus and related HIV-resistance loci. Thus, alleles that provides disease resistance during historical epidemics may continue to be positively selected by the current HIV epidemic.

Individuals homozygous for the CCR5Δ32 allele do not express any of the CCR5 chemokine receptor on their cell surfaces, and in turn, they are largely resistant to infection by HIV-1.

Unfortunately rare HIV-infected homozygous for CCR5Δ32 have been reported. In 1997 O'Brien et al. (34) described a white man with severe haemophilia A, which received over 500 000 units of Factor VIII concentrate from 1978 through 1985 and was positive for antibodies to HIV in 1985. As is turned out that this man was infected with SI strain, which do not require CCR5 and can use CXCR4 as a coreceptor (35). French investigators found another individual homozygous for the CCR5Δ32 infected with HIV strain which did not use CCR5 as coreceptor for HIV entry (36). Oh et al. presents HIV-infected CCR5Δ32 homozygous individual which displays extremely rapid disease progression. According to Oh, this is the 12th case of HIV-infection in this genotype described worldwide (37).

At the heterozygous state, this mutation has been associated with a slower progression of the disease in HIV-1 infected individuals (38). In large cohort of German seroconverters the protective effect of CCR5Δ32 heterozygosity was confirmed (37). However, whether this mutation might have a protective role also in heterozygous exposed but uninfected individuals, remains controversial (30).

In Polish population Wąsik et al. (39) found higher prevalence of CCR5Δ32 mutant allele among seronegative participants (13,6%) compared with HIV-infected patients (9,7%), although this did not attain statistical significance.

The knowledge of mechanisms of HIV entry into cells has resulted in the development of a new class of HIV therapy called entry inhibitors. The first CCR5-based entry inhibitor, maraviroc, has been recently approved.

ENDOGENOUS ANTIRETROVIRALS

The ability to modulate HIV replication has recently been associated with mechanism other than MHC and chemokines as well. HIV participates in multiple interactions with the infected host cell during replication. Such intra-cellular interactions have generally been viewed as benefiting HIV growth and, therefore, are considered as facilitators of infection and transmission. Recent discoveries, however, have revealed that human (and non-human primate) cells harbor at least two intrinsic (or non-immune) intracellular resistance mechanisms that can suppress HIV infection. The first is mediated by members of the APOBEC (apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like) family of polynucleotide cytidine deaminases and was discovered through efforts to understand the role of HIV accessory/regulatory protein, Vif (virion infectivity factor), during viral infection (40). The second is mediated by TRIM (tripartite interaction motif) proteins and was revealed through studies of species-specific post-entry blocks to HIV and simian immunodeficiency virus (SIV) infections (41).

APOBEC3G was shown to reduce the fitness of Vif protein-deleted strains of HIV, thus preventing viral cDNA integration in the cell genome. The antiviral activity of APOBEC3G in wild-type viruses is counteracted by Vif and the resulting APOBEC3G-Vif bimolecular complex is then degraded via the ubiquitine-proteasome pathway (42). These observations have triggered a series of studies in the attempt to identify possible genetic variants of the APOBEC3G gene that might encode for a mutant protein able to overcome Vif mediated degradation, thus conferring resistance to HIV disease. Unfortunately no effective mutations have been detected in the APOBEC3G promoter but many studies seem to confirm that APOBEC3G exerts its antiviral role by varying its expression (possibly following immune modulation by cytokines, such as IFNα). Further support to this concept stems from data by Jin et al. (43) showing correlations between APOBEC3G levels and CD4+ T cell counts and viraemia in a cohort of long-term non progressors indicating a role of this protein in the control of HIV disease progression.

A second antiviral factor, TRIM5α, was recently shown to restrict the replication of a broad range of retroviruses through its interaction with the capsid of such viruses (44). TRIM5α restricts retroviruses in a species-specific manner as, for example, HIV replication is blocked by simian TRIM5α alone. But results obtained in a study analyzing the most human TRIM5α variants failed to show any significant associations between any of such variants and progression to HIV disease (45).

Recently Iqbal et al., using a unique proteomics approach in a large scale, cross-sectional cohort study, identified elafin/trappin-2 as a novel innate immune factor, which is highly associated with resistance, but a possibility remains that elafin/trappin-2 may be a biomarker of HIV-resistance and may not play an active role in a mechanism of protection (46).

Attempts to define the single factor associated with resistance to infection in HIV exposed seronegative individuals – and with delayed progression in HIV-infected patients – have produced a huge amount of data that have been only briefly summarized with this review. None of the factor analysed so far, though, can be unequivocally accounted for the sometimes observed resistance to HIV infection. According to Piacentini et al. (47) critical features of this kind of research, such as inaccurate selection or stratification of patients and inadequate statistical analyses that do not consider, for example, correction for multiple tests as well as the often problematic reproducibility of the data in independent cohorts, can partially explain failure to identify such "single" factor which the resistance to infection assures. The simplest way to justify the fact that we still do not know how HIV infection is modulated, nevertheless, highlighting, once again that any single factor will unlikely be responsible for a phenomenon as complex as resistance to HIV.

Information about mechanisms of natural protection to HIV are penetrating into the public opinion causing at least at some persons false sense of security. But nobody should consider itself resistant to HIV infection and still extremely important is compliance to all e well-known safety precautions in preventing the transmission of HIV.

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title

Genetic detection of HLA-B*5701 allele for prediction of Abacavir hypersensitivity among HIV-positive patients in Polish population

authors

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summary

Abacavir (ABC) is a potent nucleoside reverse transcriptase inhibitor used in combined antiretroviral therapy (cART) of HIV-positive patients. However, 5 to 8% of patients manifest hypersensitivity reaction to ABC (ABC HSR) during first 6 weeks after therapy initiation. ABC HSR can be fatal if therapy with ABC is continued or ABC is restarted. There is an association between ABC HSR occurrence and a carriage of the Major Histocompatibility Complex class I allele HLA-B*5701. Genetic screening, before ABC initiation, significantly reduces a risk of developing ABC HSR. In accordance with European AIDS Clinical Society's guidelines Molecular Diagnostics Laboratory has been testing towards HLA-B*5701 since 2008.

key words

abacavir, hypersensitivity, HSR, HLA-B*5701, SSP, SBT

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Background

Hypersensitivity reaction (ABC HSR) is associated with initiation of abacavir (ABC), a potent HIV-1 reverse transcriptase inhibitor, as a part of antiretroviral therapy in HIV+ patients (1). Hypersensitivity reaction can be fatal if therapy with ABC is continued or ABC is restarted. The clinical classification of ABC hypersensitivity includes at least two symptoms of fever, rash, nausea, vomiting, headache, respiratory and gastrointestinal symptoms, lethargy, myalgia or arthralgia if they occur less than 6 weeks after exposure and resolve within 72 h of withdrawal of the drug (2). According to worldwide data hypersensitivity reaction affects 5 to 8% of patients (3). In the year 2002, an association between a diagnosis of ABC HSR and carriage of the Major Histocompatibility Complex class I allele HLA-B*5701 was reported independently by two research groups (4, 5). Mallal et al has proposed that in white race genotyping for HLA B*5701 should be performed before prescription of ABC. Improvement of the diagnostics with such testing has resulted in a reduction in the incidence of ABC HSR (4). PREDICT-1 study demonstrated that the presence of the allele HLA-B*5701 had a positive predictive value of 61.2% and a negative predictive value of 95.5% (6). Genetic screening highly reduces the risk of developing ABC HSR (7), but there are evidences that ABC HSR can also develop in HLA B*5701 negative patients (8,9). It seems that not only one genetic marker (HLA-B*5701 allele) is responsible for developing of HRS in HIV+ patients. Mallal et al has proved that presence of HLA-DR7 and HLA-DQ3 alleles along with HLA-B*5701 allele had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97% (4).

Genetic screening for HLA-B*5701 typing before ABC initiation is cost-effective in the case of white race (10). In some ethnic groups HLA-B*5701 is not associated with hypersensitivity (11). Park et al had tested 534 Korean patients with HIV infection, no patients had the HLA-B*5701 allele (12). In the group of 320 Taiwanese HIV+ patients there was only one case of HLA-B*5701 presence (13).

The molecular techniques based on PCR are the most sensitive and accurate methods for detecting HLA-B*5701 allele (14), but new alternative tests are introduced, i.a. flow cytometry method (15).

European AIDS Clinical Society (www.europeanaidsclinicalsociety.org) guidelines recommend HLA-B*5701 testing for HIV positive patients at initial visit; U.S. Department of Health and Human Services (www.hhs.gov) recommends HLA-B*5701 testing when ABC use is being considered.

Since the year 2008 our laboratory has been testing HIV-infected patients for the presence of HLA-B*5701 allele. Initially we used sequence based typing method (PCR-SBT, Atria Genetics). SBT is a very accurate and specific technique enabling detection of new alleles, but is also relatively expensive, laborious and time-consuming. Currently we use a method based on PCR with sequence specific primers (PCR-SSP, Inno-Train, Olerup) which is much cheaper and faster. Detection and analysis of PCR product is performed in agarose gel electrophoresis. The detection of HLA-B*5701 is of great clinical value and determines the frequency of presence of this allele in Polish population.

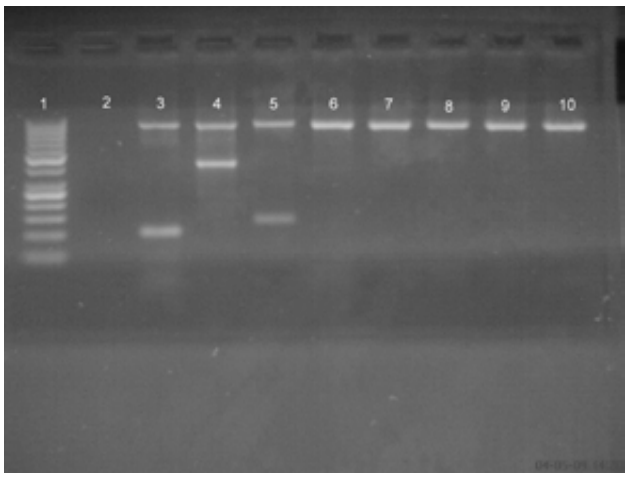
Materials and methods

Blood samples were obtained from HIV-infected patients before ABC-containing therapy was initiated or during first visit. All blood samples were collected from patients of Pediatrics Ward of Warsaw Medical University and Outpatient Clinics Of Warsaw Hospital for Infectious Diseases. Among Pediatrics Ward's patients 70% live outside of Warsaw, among these attending Outpatient Clinics – 25% (dr M. Szczepanska-Putz and dr I. Cielniak – personal information). Genomic DNA was isolated from whole blood by spin column method (NucleoSpin Blood, Macherey-Nagel). Quality of isolated genomic DNA was evaluated in agarose gel electrophoresis. Next, DNA was amplified by PCR (Perkin-Elmer GeneAmp 9600) according to manufacturers' protocols (Inno-Train HLA-B Ready Gene B5/57 cross PCR-SSP, low resolution, Atria Genetics). Finally, PCR products were analyzed as above (PCR-SSP method) or sequenced in ABI Avant 3100 (PCR-SBT, Atria Genetics). Samples suspected for the presence of HLA-B*5701 allele in PCR-SSP low resolution test (Inno-Train) were retested with PCR-SSP high resolution test (Olerup HLA-B*5701 SSP).

Results

Until now 238 patients have been tested for HLA-B*5701 presence – 168 (70,5%) males and 70 (29,5%) females. Majority of tested patients were Caucasian race (98,7%), except 3 patients (Asian, Black and Arab). Twenty patients were tested with PCR-SBT method, the rest of them with PCR-SSP method. Eleven out of 238 (4,6%) patients were positive in low resolution and were further diagnosed by high resolution testing (Fig. 1).

Figure 1. Example of electrophoretic analysis of PCR-SSP product (Inno-Train)



Lane 1 – marker, Lane 2 – negative control, Lanes 3 – 10 – PCR SSP product and internal control

Among these patients, in 10 out of 11 cases the HLA-B*5701 allele was confirmed in PCR-SSP high resolution test; one patient carried HLA-B*5714 allele. Among HLA-B*5701 positive patients there were 9 men. None of non-Caucasian race patients was HLA-B*5701 positive.

Figure 2. Sequence analysis of PCR-SBT product (Atria Genetics)

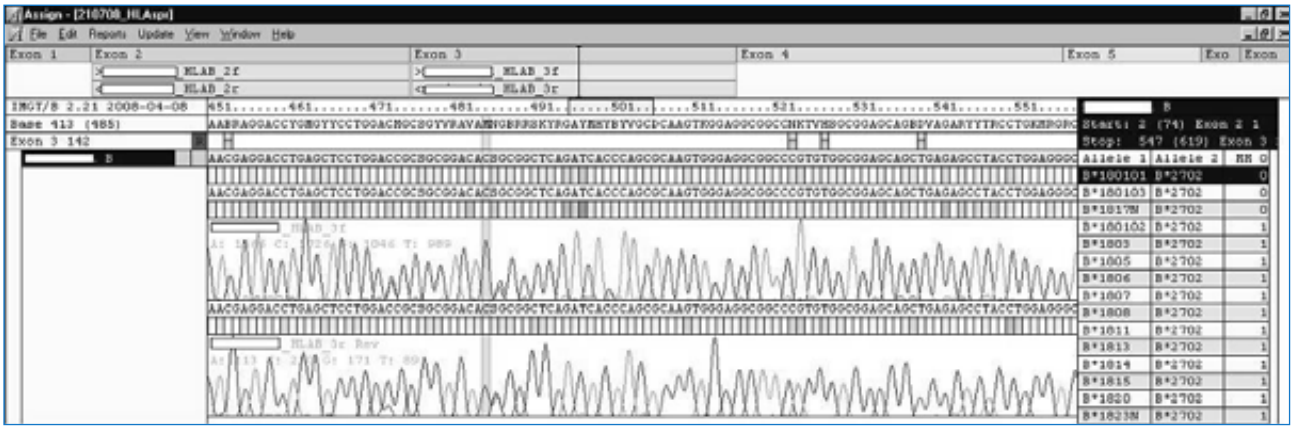
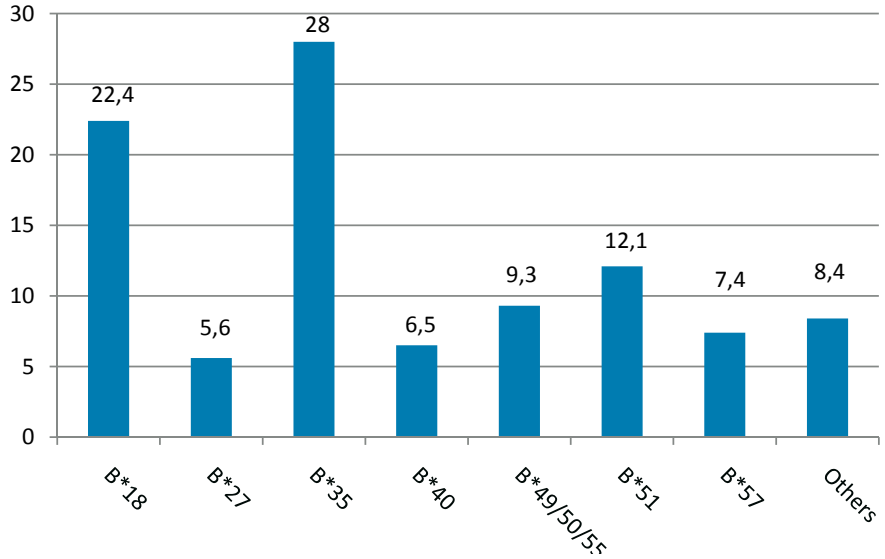


Figure 3. Percentage of HLA-B alleles detected by HLA-Ready Gene B5/57 cross test (Inno-Train, PCR-SSP method)



There were no cases of HLA-B*5701 allele detection using the SBT method (Fig.2).

Percentage of HLA-B alleles detected by HLA-Ready Gene B5/57 cross test is presented on Fig.3. Alleles with low frequency, i.a. B*15, B*58, B*78, were collected in "others" group.

Discussion

Obtained data shows that among tested HIV-infected patients HLA-B*5701 allele occurs with frequency of 4,2%. High percentage of patients living out of Warsaw makes our results representative for Polish population. Presence of HLA-B*5701 in Polish population is similar as in other Eastern European countries according to data collected in Allele Frequencies database (www.allelefrequencies.net). Polish HIV-infected patients population is ethnically homogenous: nearly 99% of population is Caucasian. This suggests that frequency of HLA-B*5701 allele is not underestimated by non-caucasian patients because the frequency of HLA-B*5701 varies in different ethnic populations: such as < 1% in sub-Saharan African, 1% to 2% in the Mediterranean, 5% to 20% in India, 0% in China and 4% to 10% in Thailand (16, 17).

Positive predictive value of the technology used is about 79%, negative predictive value – 99,4% (18). Thus we believe that genetic screening for HLA-B*5701 presence is a useful and cost effective tool in the treatment of HIV+ patients. New, rapid and sensitive tests are being generated which give a chance to reduce time to obtain typing results. We think that HLA-B*5701 typing will become a part of personalized medicine for HIV+ patients.

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title

Nephrotoxicity of Tenofovir true or myth?

authors

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summary

Among HIV (Human Immunodeficiency Virus) infected patients, combined antiretroviral therapy (cART) has significantly altered the treatment efficiency and life expectancy. Some antiretroviral agents may have influence on the function of various organs. We describe some aspects of the influence of kidney functions as Tenofovir (TDF) widely used as NRTI (Nucleoside Reverse Transcriptase Inhibitor).

Renal sufficiency is one of the main problems through the initiation and continuation of each treatment and is influenced by age, gender, coexisting diseases or concomitant medication. Understanding all mechanisms and actions of antiretroviral's in correlation with general status is key for safe and effective treatment.

key words

tenofovir (TDF), HIV (Human Immunodeficiency Virus) infection, nephrotoxicity, cART (combined antiretroviral therapy)

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Background

Renal dysfunction related to HIV infection can be overlapped to other viral coinfections (HBV, HCV), arterial hypertension, diabetes mellitus or using nephrotoxic drugs (1). Based on several studies we can find that even long term use of Tenfovir (TDF) may be safety for kidneys. Other trials suggest renal dysfunction as a main complication may even lead to TDF treatment discontinuation.

Initiating or changing the components of antiretroviral treatment is very difficult for both the patient and doctor. In response to some clinical observation results, we can reduce risk of CART (combined antiretroviral therapy) failure and protect patients against possible side effects and reduce risk of organ complications.

Tenofovir (TDF)

One of the most documented renal complications is Tenofovir disoproxil fumarate (Viread). Tenofovir is also one of the components of Truvada. It is a pill that contains two drugs used to fight HIV: Tenofovir (Viread) and emtricitabine (Emtriva) or Atripla a combination of three HIV medicines: efavirenz (Sustiva), emtricitabine (Emtriva) and tenofovir disoproxil fumarate (Viread). Tenofovir has a high antiviral activity against drug-resistant strains of HIV, this is one of the drugs of choice in the first-line combinations of antiretroviral therapy.

TDF dosage is 1 pill once daily and is generally well tolerated. Patients treated with TDF can develop proximal tubular dysfunction with higher-than-normal levels of creatinine in their blood and urine; this can suggest kidney disfunction. Using biochemical results we can detect less than-normal phosphorus levels in the blood. It was described as Fanconi Syndrome (FS) connected with TDF.

The Fanconi Syndrome is a disorder in which the proximal tubular function of the kidney is impaired, resulting in decreased reabsorption of electrolytes and nutrients as glucose, aminoacids, uric acid, phosphate and bicarbonate. This leads to: hypophosphatemia connected with phosphaturia, proteinuria, aminoaciduria, glycosuria, acidosis, hypokalemia, hyperchloremia. The main clinical features connected with the Fanconi Syndrome are: polyuria, polydipsia and dehydration.

The disease can be inherited as well as acquired. The acquired FS is often connected with concomitant treatment with nephrotoxic agents such as tetracyclines or when it is used among patients with former chronic renal disease.

Main inherited causes of Fanconi Syndrome in children are: cystinosis (the most common cause of FS in children), Wilson`s disease, Lowe Syndrome, tyrosinemia (Type I), galactosemia, glycogen storage diseases, and fructose intolerance (4).

In 2004 mechanizm of Fanconi Syndrome (FS) was described as unclear (2). Two years later results of Izzedine et al. trial in mutational screening of the genes for MRP2 (ABCC2) and MRP4 (ABCC4) performed using genomic DNA assessing among 13 HIV-infected patients presenting symptoms of TDF induced tubulopathy shown an assosciation of ABCC2 haplotypes with renal proximal tubulopathy induced by TDF in HIV-1 infected patients (3).

Some of nephrotoxic drugs mostly used among HIV infected patients are listed below:

- NSAIDS (non-steroidal anti-inflammatory agents),
- Aminoglycoside antibiotics,
- Bactrim (co-trimoxazole, trimethoprim-sulfamethoxazole),
- Amphotericin B (Fungizone),
- Pentamidine i.v.,
- Acyclovir (Zovirax),
- Foscarnet (Foscavir), adefovir (Hepsera), cidofovir (Vistide).

Tenofovir is only one among NRTIs which can be a cause of increased creatinine concentration but often without necessity of withdrawing.

Patients with complications listed below can interact with the renal transport of organic anions leading to proximal tubular intracellular accumulation of TDF (5):

- Low lymphocytes CD4 count,
- Low body weight,
- Arterial hypertension,
- Diabetes mellitus,
- Co-infections with HCV or HBV,
- Treponema pallidum infection,
- Previous exposure to nephrotoxic drugs,
- Boosted protease inhibitors,
- Using didanosine (ddI).

Some clinical cohort studies have shown little evidence of nephrotoxicity associated with TDF: In an analysis of data from more than 5000 patients in the Tenofovir Expanded Access Program, grade 3 or 4 abnormalities in serum creatinine or phosphorus were observed in only 0.3% and 0.6% of patients, respectively (6).

Patients treated with TDF must be monitored for glycosuria, phosphaturia, proteinuria, phosphoremia. Also an assessment for mitochondrial toxicity should be controlled NRTI treatment. In these situations therapy containing TDF should be stopped to avoid the risk of serious renal failure (7).

Despite side effects and the risk of renal toxicity in some trials with Tenofovir, it also demonstrated renal safety profile. In the trial GS 903 with 299 treatment-naive patients TDF were given a combination of Lamivudine and Efavirenz as an initial regiment. No cases of renal failure were reported within the 144 weeks and no significant differences in renal function were observed compared with patients taking Stavudine, Lamivudine and Efavirenz (8,9).

In the RECOVER trial only 0.4% of over 1000 patients treated with TDF discontinued due to renal failure (10).

Moreover, a report of 2-year's worth of analysis data of GS 902 and GS 907 (follow up 133 weeks) studies with TDF among 687 treatment-experienced patients indicated that < 1% of patient's discontinued TDF treatment due to renal events (1).

In the Chelsea and Westminster Hospital among 4000 patients, increases in serum creatinine were no more common among patients treated with TDF than among patients treated with other antiretroviral drugs. Moreover were less common than among patients who received no antiretroviral therapy et al. (11).

Only 9 (0.01%) patients of 1058 exposed to TDF in other cohort, developed increased creatinine levels without another obvious cause. The majority of patients in the cohort who experienced an increase in creatinine levels had other reasons for renal dysfunction. A review of the records of 447 patients treated for at least 12 weeks revealed rare (1.3%) occurrences of grade 1 and 2 nephrotoxicity, most of which were attributed to other causes (12). Similar results were in German cohort of 206 Tenofovir-treated patients with 227 patient-years of follow-up. In this study the median increase of creatinine was 0.11 mg/mL (13).

METHODS OF ASSESSMENT OF RENAL FUNCTION

The most common method to determine renal function is analyzing the blood concentrations of the waste substances of creatinine and urea, electrolytes kalium, natrium, magnesium. We should know that it can be inadequate to determine the kidneys function.

Blood urea nitrogen (BUN) and creatinine will not be raised above the normal range until 60% of total renal function is lost. One of the most accurate methods for the assessment of kidney function is glomerular filtration rate (GFR) – this is the volume of fluid filtered from the renal glomerular capillaries per time unit (Picture 1).

Picture 1. GFR formula

$$\text{GFR} = \frac{\text{Urine concentration} \times \text{Urine flow}}{\text{Plasma concentration}}$$

The GFR can be determined by injecting inulin into the plasma. Since inulin is neither reabsorbed nor secreted by the kidneys after glomerular filtration, its rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter.

Another prognostic marker for kidney disease is microalbuminuria. This is the assessment, calculating the amount of small albumin in the urine that cannot be detected by urine dipstick methods. In healthy individuals albumin is not normally present in urine because it is retained in the bloodstream by the kidneys. Microalbuminuria is diagnostically confirmed when albumin flow is from 20 to 200 μg/min in 24-hour urine collection. Macroalbuminuria is when the albumin result in urine is over 300 mg/L.

Creatinine clearance (ClCr) is calculated as creatinine concentration in the urine sample (UCr), urine flow rate (V), and the plasma concentration (PCr).

Picture 2. Creatinine clearance (ClCr) formula:

$$\text{ClCr} = \frac{\text{UCr} \times \text{V}}{\text{PCr}}$$

Since the product of urine concentration and urine flow rate yields creatinine excretion rate, which is the rate of removal from the blood, creatinine clearance is calculated as removal rate per min (UCr×V) divided by the plasma creatinine concentration. To allow comparison of results between people of different sizes, the ClCr is often corrected for the body surface area (BSA) and expressed compared to the average sized man as mL/min/1.73 m^2. While most adults have a BSA that approaches 1.7 (1.6-1.9), extremely obese or slim patients should have their ClCr corrected for their actual BSA.

Compared to the MDRD (*Modification of Diet in Renal Disease*) formula, the inulin clearance slightly overestimates the glomerular function. In some cohorts CrCl were estimated using the Cockcroft-Gault equation (Picture 4). It is named after the scientists who first published the formula, and it employs serum creatinine to predict the creatinine clearance (14).

Picture 3. Corrected creatinine clearance (ClCr) formula:

$$\text{ClCr (corrected)} = \frac{\text{UCr} \times 1{,}73}{\text{BSA}}$$

BSA can be calculated on the basis of weight and height common formula. BSA (m^2) = ([Height(cm) × Weight(kg)] / 3600)^{½}.

In studies using the Cockcroft-Gault equation age, diet, race, HIV transmission risk group, hypertension, viral load, and choice of other antiretroviral agents were not associated with decline in renal function (15).

Picture 4. Cockcroft-Gault Formula for Predicting Creatinine Clearance

$$\text{Estimated CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine [mg/dL]} \times 72} \times (0{,}85 \text{ if female})$$

In other studies, glomerular filtration rates (GFR) were calculated based on the modification of diet in renal disease (MDRD) equation (Picture 5) (16).

A recently advocated formula for calculating the GFR is one that was developed by the *Modification of Diet in Renal Disease Study Group*. The most commonly used formula is the "4-variable MDRD" which estimates GFR using four variables: serum creatinine, age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels (17).

Picture 5. MDRD Formula for predicting GFR in mg/dL

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{serum creatinine [mg/dL]})^{-1{,}154} \times (\text{age})^{-0{,}203} \times (0{,}742 \text{ if female}) \times (1{,}210 \text{ if African American})$$

For creatinine in μmol/L:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 32788 \times (\text{serum creatinine [mg/dL]})^{-1{,}154} \times (\text{age})^{-0{,}203} \times (0{,}742 \text{ if female}) \times (1{,}210 \text{ if African American})$$

For MDRD equation also includes serum albumin and blood urea nitrogen (BUN) levels. Where the creatinine and blood urea nitrogen concentrations are both in mg/dL. The albumin concentration is in g/dL.

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 170 \times (\text{serum creatinine [mg/dL]})^{-0{,}999} \times (\text{age})^{-0{,}176} \times (0{,}762 \text{ if female}) \times (1{,}180 \text{ if African American}) \times \text{BUN}^{-0{,}170} \times \text{Albumin}^{-0{,}318}$$

Overall, the investigators found that patients treated with cART were more likely to have a GFR below 60 mL/min /1.73 m^2 than uninfected men, but there was no difference ($p > 0.05$) for GFRs between 60 and 89 mL/min/1.73 m^2.

Among patients receiving cART using Tenofovir was associated with a GFR lower than non use (odds ratio [OR] was 1.7; 95% CI, 1.1-2.1 for a GFR of 60-89 mL/min/1.73 m^2 and OR, 2.0; 95% CI, 0.8-4.9 for a GFR < 60 mL/min/1.73 m^2).

This data, connects with similar observations from other randomized trials, and emphasize the renal safety of Tenofovir in patients who have normal renal function at baseline.

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was developed in an effort to create a formula more precise than the MDRD formula, especially when actual GFR is > 60 mL/min/1.73 m^2 [18]. Another tool to calculate GFR is estimated GFR (eGFR) is the Mayo Quadratic Formula (Picture 6) (19):

Picture 6. Mayo Quadratic Formula (MQF)

The equation MQF is: GFR = exp [1.911 + 5.249/SCr – 2.14/Scr^2 – 0.00686 × Age – 0.205 (if female)]

**Scr – single creatinine determination (mg/dL). When SCr < 0.8 mg/dL, use 0.8 for Scr*

This formula was developed by Rule et al. in an attempt to better estimate GFR in patients with preserved kidney function. The results of the MDRD and MCQ are expressed directly after adjustment to body surface area. It is well recognized that the MDRD formula tends to underestimate GFR in patients with preserved kidney function.

Conclusions

Results of numerous studies analyzing Tenofovir nephotoxicity in HIV infected patients seem to be conflicting. Some data indicate that use of Tenofovir can lead to a decline in renal function. Others show good tolerance and low incidence of renal complications. Some factors such as age, gender, height, weight, concomitant diseases and treatment should be considered before and during Tenofovir treatment. Methods to assess renal functio-n are as important as the factors previously discussed and we should regard all information about the patient. All these factors have an influence on renal sufficiency and it is necessary to know them to ensure the patients best possible treatment.

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title

Influence of HIV infection on highest cardiovascular risk

authors

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summary

WHO estimates that over 33 milion people living with HIV all over the world and 2,7 milion became infected in 2008. Even though in 2008 approximately 2,0 milion people died of AIDS (1). HIV infection, thanks to antiretroviral therapy, has became a manageable and chronic disease. In the 1980's patient with HIV infection very rarely lived longer than 10 years, nowadays situation of these patients changed dramatically, approximately 85% of them survive over 10 years (2,3).

In the post HAART era, as the HIV infected patients live longer, it is noticeable dramatic increase of the non-HIV-related conditions such as hypertension, cancer, diabetes or cardiovascular disease (CVD) (4). HIV infected patients show increased rates of cardiovascular disease compared with patients without HIV (5,6).

The risk of the cardiovascular disease is associated with host, virus and antiretroviral therapy factors. This review summarize the knowledge about the mechanism by which Human Immunodeficiency Virus itself can lead to cardiovascular disease.

key words

HIV, cardiovascular disease

address

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Human Immunodeficiency Virus – the structure and patomechanism of action

Human Immunodeficiency Virus is a member of the RNA retroviridae family. HIV is spread through damaged mucosal surfaces for example during unprotected sexual contact or by direct transmission into the blood. In short HIV is composed of two copies RNA, enzymes such as reverse transcriptase, proteases, ribonuclease and integrase, complex of glicoproteines: gp120, gp41. Virus infects lymphocytes, macrophages, dendritic cells, but mostly prefer to infect the CD4 cells. HIV attaches to cells and infects them via coreceptors for chemokines such as CCR5 and CXCR4. Within the cell HIV reverse transcriptase transcribed viral RNA to DNA. Then viral DNA migrates towards cell nucleus and via integrase integrates into the patient genome. Untreated and uncontrolled viral replication conducts to CD4 lymphocytes reduction and results immune system dysfunction. Once the level of the CD4 reduce < 200/mm^3, HIV infection turn to the acquired immunodeficiency syndrome (AIDS). HIV – associated malignancies and opportunistic infections can also manifest the AIDS [7].

The mechanisms of highest cardiovascular risk in HIV-infected patients

Endothelial dysfunction is the basic mechanism of the cardiovascular disease and is caused by chronic inflammation, platelet activation and hypercoagulability.

Human Immunodeficiency Virus can induce the endothelium dysfunction by cytokines secreted by activated monocytes and via direct effect – proteins *tat* and gp120 [8].

A simple evidence of the chronic inflammation in HIV-infection give a higher levels of the inflammatory markers such as C-reactive protein (CRP) and some interleukins: IL-6, IL-8 and TNF-alfa activated by the HIV *tat* protein [9]. HIV- infected patients with high level of CRP compare to control group are in the higher risk for cardiovascular disease [10]. Increased levels of IL-6 and IL-8 are correlated with higher levels of Von Willebrand Factor (vWF) and plasminogen activator, interestingly all this markers strictly depend on the HIV viral load [11].

HIV *tat* protein stimulates endothelial cells to produce adhesion molecules such as vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecule (sICAM-1). These markers induce chronic inflammation by incessant endothelial activation and successive endothelial disfunction. Both markers are increased in HIV infection [12].

Another protein of HIV – gp120, induce apoptosis and by this mechanism damage the endothelium [13].

Much is known about the nitric oxide (NO), the mediator which can cause, after reaction with oxygen radicals and production peroxynitrite, oxidative harm to the endothelium and decreased dilation [14]. NO is biosynthesized endogenously from arginine and oxygen by various nitric oxide synthase (NOS) enzymes, decreased expression of endothelial NO synthase (eNOS) and accelerated inducible NO synthase (iNOS) [15]. It is very interesting that the virus has the direct impact on the nitric oxide production. HIV *tat* protein remarkably decrease eNOS mRNA and weaken vasorelaxation in porcine arteries [16]. The protein gp120 cause direct endothelial damage by stimulating macrophages to product NO [17].

Injured endothelium predispose to deposit the atherosclerotic plaque within the arteries and cause cardiovascular disease.

Apart from the endothelial disfunction, HIV affects the cardiovascular system by the lipid changes and coagulation abnormalities [18,12].

HIV changes the lipid profile, lower HDL-C and LDL-C, increase TG [19]. These lipid abnormalities have been found to be related with higher viral load and lower CD4 cell amounts [20].

In HIV-infection are also increased E-selectin adhesion molecule and Von Willebrand Factor , which conduce the platelets adhesion to the endothelium [13]. Uncontrolled platelet activation in HIV infection often lead to tromboembolic events [21]. In vitro has been demonstrate the impact of the gp120 HIV protein through the CXCR4 and CCR5 receptors on the smooth muscle cells and the expression of the tissue factor on them [22]. Tissue factor starts the coagulation cascade and conduct to thrombosis. In HIV infection are also seen other coagulation abnormalities such as: decreased level of the protein S and antithrombin, increased anticardiolipin antibodies and lupus inhibitor [23].

The consequences of HIV-infection on the cardiovascular system

Myocardial infarction is a serious consequence of the cardiovascular disease. Recent US study showed the higher rates of MI among the HIV-infected patients – 11,13/1000 compared to the non-infected group 6,98/1000 [24]. Also, Kaiser Permanente study confirm the fact that the HIV infected patients have the higher risk of the cardiovascular events [25].

The risk of MI is increased in both HIV infected and uninfected patients similarly by the traditional cardiac risk factors such as male sex, increasing age, smoking, low HDL-C, high LDL-C, diabetes, hypertension [26]. Though the HIV infected population have a higher prevalence of these traditional cardiovascular risk factors [27].

Conclusions

As the HIV population live longer the risk for cardiovascular associated disorders will increase. The management of HIV-infected patient is a very difficult and complicated problem, doctor needs to balance between controlled HIV infection and other conditions usually associated with HIV such as diabetes, hypertension and hyperlipidemia.

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