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The development of Resistance to Antiretroviral Therapy for HIV Infected Individuals: a Systematic Review

REVIEW

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Abstract

Background: Antiretroviral treatment (ART) has reduced morbidity and mortality due to AIDS. However, treatment options can be impaired by the development of antiretroviral drug resistance. Resistant virus strains can be transmitted to new hosts and, subsequently, can lead to antiretroviral treatment failure.

Methods: Th A systematic review of articles on resistance to antiretroviral therapy for HIV-infected individuals, published from January 1, 2014 to June 16, 2014, on SCOPUS and PUBMED databases wascarried out. Search terms were "AIDS" (Medical Subject Headings [MeSH]), "HIV" (MeSH), “treatment” (keyword), “resistance” (keyword) and "antiretroviral therapy" (MeSH). Of the 118 retrieved studies, 24 met the eligibility criteria.

Results: The main classes of antiretroviral drugs are Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Nucleoside Reverse Transcriptase Inhibitors (NRTIs), and Protease Inhibitors (PIs). Antiretroviral treatment selects for drug resistance. Resistant strains become prevalent in the population and are transmitted to new patients.

Discussion: A higher prevalence of certain mutations are present and characterize resistant strains that are prevalent in the population making it more difficult to treat these infected individuals. Poor compliance with antiretroviral therapy increases the potential for developing these and other resistant strains.

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Conclusions: Knowledge of drug resistance generated by mutations is useful for optimizing treatment regimens and to get better responses. Promoting compliance is important to limiting the selection of new resistant strains.

Keywords
AIDS, HIV, Antiretroviral Therapy, Treatment, Resistance, Drugs.

Introduction

The wide use of combination antiretroviral therapy (cART), for example, succeeded in sustained inhibition of viral replication and reduced significantly the morbidity and mortality of HIV related disease. [1-5] However, treatment options have been impaired by the development of antiretroviral drug resistance. Resistant virus strains can develop in a patient but are likely to be acquired from others leading to antiretroviral treatment failure. [6, 7]

Antiretroviral therapy resistance is a concern not just for individual patients, but also for society due to the high potential transmission of drug-resistant HIV. This compromises the effectiveness of available first-line regimens for a substantial portion of the population and increases the need for costly second-line drugs. [8]

This study is based on the following research questions: what are the main mutations conferring resistance to antiretroviral treatments and how do individuals acquire resistant strains? This issue has gained great impact in recent years with the constant and intense research on the many HIV antiretroviral therapies. Thus, this systematic review aims to present the main classes of drugs for ART and the resistance mechanisms that could lead to antiretroviral treatment failure.

Methods

We performed a qualitative systematic review of articles about the resistance to antiretroviral drugs used to treat HIV/AIDS in previously chosen electronic databases.

A search of the literature was conducted via PubMed and SCOPUS online databases in June 2014 and was limited to articles published from January 1, 2014 to June 16, 2014. The reason for limiting the search to 2014 was that several studies on the subject of HIV and resistance to antiretroviral therapies are performed every year, being necessary to recovery most recent data on resistance to antiretroviral drugs. Initially, the search terms browsed in SCOPUS database were:

1. "AIDS" (Medical Subject Headings [MeSH] term);
2. "HIV" ([MeSH])
3. "treatment" (keyword).
4. "resistance" (keyword); and
5. "antiretroviral therapy" ([MeSH])

The following searches were performed: 1 OR 2 AND 3 AND 4 AND 5. In addition to MeSH terms, we opted to add the keywords "treatment" and "resistance" to the search strategy, because, despite not being included in the MeSH thesaurus, they are frequently used to describe studies that deal with the theme object of the present review. The search strategy and the retrieved articles were reviewed on two separate occasions to ensure adequate sampling. A similar search strategy was performed in the PubMed database, using the aforementioned terms and their correspondent terms.

The article analysis followed previously determined eligibility criteria. We adopted the following inclusion criteria: (1) references written in English; (2) studies pertaining resistance to antiretroviral therapy for HIV-infected individuals; (3) original articles with online accessible full text available in database SCOPUS,

PubMed or CAPES (Higher Education Co-ordination Agency) Journal Portal9, a virtual library linked to Brazil's Ministry of Education and subjected to content subscription; (4) articles that included in the title at least one combination of terms described in the search strategy; (5) case reports, descriptive studies, cross-sectional studies, cohort studies, controlled clinical trials and case-control studies; (6) articles that appear in more than one database will be included only once, giving priority to the SCOPUS database. Exclusion criteria were: (1) studies that did not include the proposed topic; (2) non-original studies, including editorials, reviews, prefaces, brief communications and letters to the editor.

Then, each paper in the sample was read in entirety, and data elements were then extracted and entered into a matrix that included authors, journal, description of the study sample, and main findings.

This study did not require an assessment of an ethics committee because it is a systematic review. Similarly, for the same reason, this manuscript did not involve patient consent. The study was conducted based on literature obtained according to our inclusion criteria.

Results

Initially, the aforementioned search strategies resulted in 118 references. After browsing the title and abstract of the retrieved citations for eligibility based on study inclusion criteria, 91 articles were excluded and 27 articles were further retrieved and included in the final sample **(Figure 1)**. Articles from SCOPUS and PubMed database matched the inclusion criteria of the present study.

Table 1 provides an overview of all studies included in the final sample and of all data elements

Figure 1: Flow diagram of study.

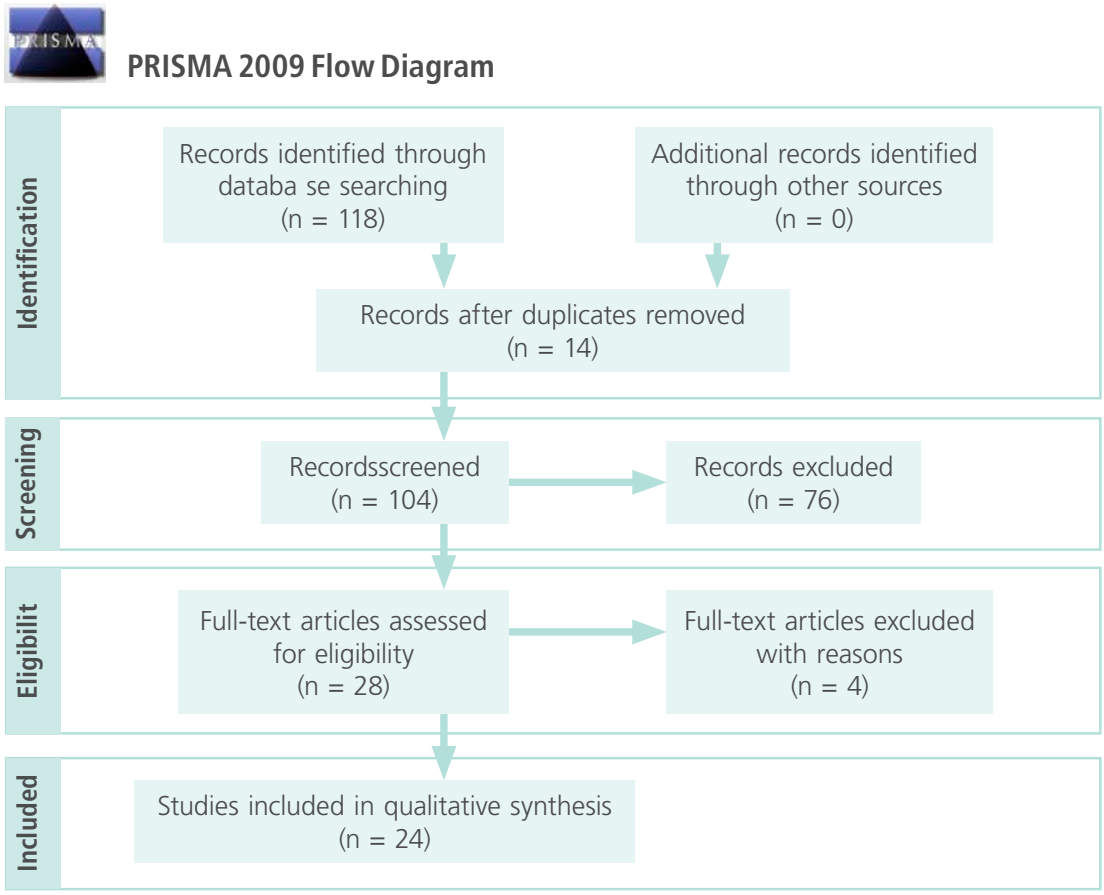

Table 1. Resistance to antiretroviral therapy for HIV-infected individuals: studies and main findings.

Journal	Sample	Sample	Study Particularities
Drescher, SM. Et al. [1]	Clinical Infectious Diseases	ART-naive men who have sex with men with infection date estimates between 1996 and 2009 (1674).	Many individuals harboring viral TDR belonged to transmission clusters with other Swiss patients, indicating substantial domestic transmission of TDR in Switzerland. Most TDR in clusters could be linked to sources, indicating good surveillance of TDR in the SHCS-DRDB. Most TDR sources were ART naive. This, and the presence of long TDR transmission chains, suggests that resistance mutations are frequently transmitted among untreated individuals, highlighting the importance of early diagnosis and treatment.
Zu Knyphausen, F.et al. [7]	PLoS ONE	Data of 1,667 HIV-infected individuals who seroconverted between 1996 and 2010 were analysed.	Overall prevalence of TDR remained stable at a rather high level. No significant differences in the frequency of virologic failure were identified during first-line cART between patients with TDR and fully-active cART, patients with TDR and nonfully active cART and patients without TDR.
Cambiano, V. et al. [8]	AIDS	We estimate 652 000 people (90% uncertainty range: 543 000-744 000) are living with nonnucleoside reverse transcriptase inhibitor (NNRTIs)-resistant virus in South Africa, 275 000 in majority virus [Non-nucleoside reverse transcriptase inhibitor resistant virus present in majority virus (NRMV)] with an unsuppressed viral load.	Prevalence of resistance is projected to increase substantially. However, introduction of policies to increase ART coverage is not expected to lead to appreciably higher prevalence of HIV positive people with resistance and viral load more than 500 copies/ml. Concern over resistance should not stop expansion of treatment availability.
Fall-Malick, F-Z et al. [10]	Journal of Medical Virology	Eighty-six subjects were included and 65 samples were amplified successfully and sequenced.	Phylogenetic analysis revealed 17 HIV-1 variants with the predominance of CRF02_AG (n=42; 64.6%). A high rate of DRM was found in this study and shows the potential need for a structured virological surveillance including viral load quantification and genotyping. Further studies may also be needed in regards to the great variability of HIV-1 strains in Mauritania.
Mulu, A. et al. [15]	BMC Infectious Diseases	Consecutive HIV-1 infected adults (N = 100) and children (N = 100) who have been receiving ART for up to 6 years at Gondar University Hospital, Ethiopia.	Majority of both adults (82%) and children (87%) who received ART showed high viral suppression and immunological recovery. This indicates that despite limited resources in the setting virological efficacy can be sustained for a substantial length of time and also enhance immunological recovery irrespective of age. However, the presence of drug resistance mutations and low level viraemia among clinically asymptomatic patients highlights the need for virological monitoring.
Baesi, K. et al. [17]	Journal of Medical Virology	All 30 participants naïve to ART and 62 of 70 (88.6%) participants receiving ART had detectable viral loads.	These findings document an alarmingly high frequency of multiple HIV drug class resistance in Iran, confirm the presence of TDR, and highlight the need for systematic viral load monitoring and drug resistance testing, including at diagnosis. Expanded access to new antiretroviral medications from additional drug classes is needed.

Journal	Sample	Sample	Study Particularities
Azam, M. et al. [21]	Archives of Virology	Drug resistance genotyping of a partial reverse transcriptase gene was done in 103 HIV-1-infected patients.	Major amino acid substitutions were seen at positions 41, 90, 98, 103, 106, 108, 138, 181, 184, 190, 215, and 219, which confer high/intermediate levels of resistance to most RTIs, independently or together. Our results show that there is an urgent need to tailor ART drug regimens to the individual to achieve optimum therapeutic outcome in North India.
Ong, LY. et al. [25]	Journal of Medical Virology	. Plasma specimens from N=100 HIV+ HAARTnaïve adult were collected between March 2008 and August 2010.	Transmitted drug resistance prevalence among HAART-naïve patients was low in this cohort of patients in Kuala Lumpur despite introduction of HAART 5 years ago. Owing to the high genetic diversity, continued molecular surveillance can identify the persistent emergence of HIV-1 URF and novel CRF with significant epidemiological impact.
Santoro, MM. Et al. [28]	Clinical Infectious Diseases	The genotyping success rate was evaluated in 12 828 human immunodeficiency virus type 1 (HIV-1) plasma samples with viremia >50 copies/mL, tested using the commercial ViroSeq HIV-1 Genotyping System or a homemade system.	In patients failing cART with LLV, HIV-1 genotyping provides reliable and reproducible results that are informative about emerging drug resistance.
Abdissa, A. et al. [31]	BMC Infectious Diseases	Two hundred sixty five patients had VL data available at baseline and at 6 months.	Our data confirm that the currently recommended first-line ART regimen is efficient in the vast majority of individuals initiating therapy in Jimma, Ethiopia eight years after the introduction of ART. However, the documented occurrence of transmitted resistance and accumulation of acquired HIVDR mutations among failing patients justify increased vigilance by improving the availability and systematic use of VL testing to monitor ART response, and underlines the need for rapid, inexpensive tests to identify the most common drug resistance mutations.
Phanuphak, P. et al. [32]	Journal of Acquired Immune Deficiency Syndromes	1471 Asian treatment-naive patients.	TDR was associated with failure in the context of non-fully sensitive regimens. Efforts are needed to incorporate resistance testing into national treatment programs.
Lambert-Niclot, S. et al. [38]	Journal of Antimi-crobial Chemo-therapy	Two groups of patients: the first group (n = 998) failing a nucleoside reverse transcriptase inhibitor (NRTI) plus boosted protease inhibitor (PI)-based regimen and the second group (n = 3733) failing an NRTI plus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.	In patients failing an NRTI plus NNRTI-based regimen, to know the feasibility of a switch to rilpivirine/ emtricitabine/tenofovir disoproxil fumarate, reliable resistance information should be available at the time of use of concurrent NNRTI therapy.

Journal	Sample	Sample	Study Particularities
Mulu, A. et al. [39]	BMC Infectious Diseases	Viral RNA was determined in 160 baseline plasma samples.	Strong evidence for consistent HIV-1C clade homogeneity and low influx of other variant into the country was found. The level of drug resistance observed in chronically infected treatment naïve patients which exceeds the WHO estimates suggests the need for incorporation of HIV-1 drug resistance testing prior to ART initiation. The occurrence of monophyletic transmission clusters affecting (24/160) individuals indicates their potential risk related practice. Thus, an intensified public health intervention program and monitoring of HIV drug resistance testing appears indispensable.
Azam, M. et al. [40]	Journal of Infection in Developing Countries	Fifty-four HIV-1 strains isolated from treatmentnaive patients (n = 54) were included in this study.	This study confirms that HIV-1 subtype C predominates in northern India. Protease secondary mutations associated with drug resistance to protease inhibitors (PIs) were present with high frequency in the HIV-1 C subtype strains isolated from north Indian ARV treatment-naive patients, but no primary resistance mutations were found in this region.
Ross, LL. et al. [41]	PLoS ONE	Viral transmission clusters (VTCs) were initially predicted from a phylogenetic analysis of population level HIV-1 pol sequences obtained from 690 antiretroviral-naïve subjects in 2007.	Our analysis shows specific geographical and drug resistance trends that correlate well with transmission clusters defined by HIV sequences of similarity. Furthermore, our study demonstrates the utility of molecular and epidemiological analysis of VTCs for identifying population-specific risks associated with HIV-1 transmission and developing effective local healthcare strategies.
Vande-nhende, M-A. et al. [42]	PLoS ONE	Twenty-nine ART-naive patients followed up in the ANRS-CO3 Aquitaine Cohort.	Low frequency DRMs detected before ART initiation and at VF in patients experiencing VF on first-line ART can increase the overall burden of resistance to PI, NRTI and NNRTI.
Antunes DA. et al. [44]	PLoS One.	Bioinformatics tools were used to evaluate the impact of the unusual mutations D30V and V32E over the dynamics of the PR-Nelfinavir complex.	The D30V mutation triggered a subtle change in the PR structure, which was also observed for the well-known. Nelfinavir resistance mutation D30N, while the V32E exchange presented a much more dramatic impact over the PR flap dynamics.
Xiaobai Z. et al. [45]	PLoS One.	Deep sequencing was performed on samples from 90 ART-naïve subjects.	ART-naïve subjects from Hunan Province China infected predominantly with subtype AE frequently possessed HIV variants with WHO NRTI/NNRTI TDRs by deep sequencing that would affect the first line ART used in the region.
Johnston, V. et al. [46]	Journal of Infectious Diseases	Using prospectively collected data from patients in South Africa(417).	No adherence, suggested by subtherapeutic ART with/without major resistance mutations, significantly contributed to failure when switching regimen. Unresolved no adherence, not NRTI resistance, drives early second-line failure.

Journal	Sample	Sample	Study Particularities
Mata-Munguía, C. et al. [47]	BMC Bioinformatics	Protease sequences isolated from 151 Mexican HIV-1 patients that were naïve to, or subjected to antiretroviral therapy, were examined.	The structural correlation of natural polymorphisms and unusual mutations with drug resistance is useful for the identification of HIV-1 variants with potential resistance to PIs. The D29V mutation likely confers a selection advantage in viruses; however, in silico, presence of this mutation results in unstable enzyme/PI complexes, that possibly induce resistance to PIs.
Megens, S. et al. [48]	Virology	Origin and the effect of insertion D67D-THGERDLGPA within HIV-1 RT from a patient failing antiviral therapy.	These results suggest that a particular sequence within human chromosome 17 is prone to horizontal gene transfer into the HIV-1 RT finger subdomain. This insertion confers selective advantage to HIV-1 by its contribution to multi-drug resistance and restoration of impaired replication capacity.
Ibrahim, Y. et al. [55]	Malaysian Journal of Public Health Medicine	A health facility-based cross sectional study conducted among adults' people living with HIV in Omdurman HIV/AIDS centre, Sudan.	Educational level and social support against HIV-related stigma and discrimination were not significantly associated with adherence. Adherence to antiretroviral therapy among the respondents is very poor. Urgent interventions based on modifiable factors and mainly targeting females and younger age group are needed to improve adherence to antiretroviral therapy among people living with HIV.
Bulteel, N. et al. [66]	Journal of Infection	5455 patients received either (or both) 3TC, TDF and EFV or FTC, TDF and EFV contributing 6465 treatment episodes over 9962 person-years follow up.	We have not found evidence of an increased risk of development of M184V and K65R in patients exposed to 3TC.
Choi, J-Y. et al. [67]	Journal of Clinical Virology	The amplified HIV-1 pol gene in 535 patients requested for genotypic drug resistance testing from 2004 to 2009 by the Korea Centers for Disease Control and Prevention was sequenced and analyzed annually and totally.	About 50% and less than 10% of patients infected with HIV-1 have multidrug and multiclass resistance linked to 16 antiretroviral drugs, respectively. The significance of this study lies in its larger-scale examination of the prevalence of drug resistant variants and multidrug resistance in HAART experienced patients in South Korea.

Abbreviations: ART = antiretroviral treatment, TDR = transmitted drug resistance, SHCS = swiss HIV cohort study, DRDB = drug resistance database, HIV= human immunodeficiency virus, cART = combination antiretroviral therapy, NNRTI = non nucleoside reverse transcriptase inhibitor, NRMV = Non-nucleoside reverse transcriptase inhibitor resistant virus present in majority vírus, DRM = drug resistance mutations, IQR = interquartile range, RTI = reverse transcriptase inhibitors, HAART = Highly active antiretroviral therapy, URF = unique recombinant forms, CRF = circulating recombinant form, LLV = low-level viremia, V L= viral load, HIVDR = HIV drug resistance, NRTI = nucleoside reverse transcriptase inhibitor, RNA= ribonucleic acid, WHO = World Health Organization, PI = protease inhibitors, ARV = antiretroviral, VTC = viral transmission cluster, ANRS = Agence Nationale de Recherche sur le Sida, VF= virological failure, PR= protease, 3TC = Lamivudine, FTC = emtricitabine, TDF = tenofovir, EFV= efavirenz.

used during the data analysis process. Study designs included 1 descriptive study, [45] 7 cross sectional studies [10, 17, 19, 44, 47, 55, 68] and 19 cohort studies. [1, 7, 8, 15, 21, 25, 28, 31, 32, 38-40, 41, 42, 46, 48, 66, 67, 82]

Discussion

The increased use of antiretroviral therapy has reduced significantly the number of deaths related to HIV/AIDS and improved the life expectancy of people living with HIV. [10] It has been suggested that scaling up of ART results in a level of virological suppression at the population level that will reduce HIV transmission. [11-15] With the increased numbers of patients being treated, there is increased potential for development and spread of resistant virus. Individuals infected with HIV acquire antiretroviral resistance in one of two ways: (1) transmitted drug resistance (TDR) occurs when antiretroviral-naive individuals are infected with viruses already harboring resistance mutations, and (2) acquired drug resistance (ADR) emerges from the selective pressure of antiretrovirals in individuals without fully suppressed viral loads either because of poor adherence or the use of a non-suppressive regimen. [16, 17] As access to antiretroviral therapy (ART) expands in resource-limited countries, concerns will increase regarding the numbers of patients failing treatment and the subsequent emergence of drugresistant viruses. Resistant virus selected during treatment may subsequently be transmitted to newly infected individuals, undermining the effectiveness of currently recommended or available first-line ART. [18, 19] Also, factors associated with the development of drug resistance include poor adherence, suboptimal ART doses, and initiation of therapy late in the course of HIV infection. [20, 21]

Highly active antiretroviral therapy (HAART) has been shown to reduce significantly the mortality and morbidity of patients infected with HIV at various disease stages. [2, 22-25] Although HAART may limit the extent of selection during treatment, the success of HAART could still be compromised by the emergence of HIV drug resistance. [10, 26] Resistance can be acquired as the pool of variants within the population increases. [19] Resistance to an antiretroviral drug class is defined by the presence of at least one primary resistance mutation (PRM), as included in the mutation list paneled by the International Antiviral Society in 2013 [27], within the genes for the nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non nucleos(t)ide reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). [28]

Viral replication under suboptimal antiretroviral pressure leads to accumulation of resistance mutations. As the number of mutants increases, future therapeutic choices become more limited [29] especially with regard to monotherapy. In addition, mutations conferring resistance to one drug frequently confer cross resistance to other antiretroviral drugs within the same class. [30, 31] The significance of drug-specific or drug class-specific transmitted drug resistance to treatment outcome is not fully understood, especially when one or more drugs or drug classes in the regimen are still effective. [32]

Non nucleoside reverse transcriptase inhibitors (NNRTIs) are important and common components of highly active antiretroviral therapy (HAART). Rilpivirine, a second-generation NNRTI, is active against wild-type viruses and retains activity against some NNRTI-resistant HIV-1 strains. [33-35] This drug is currently indicated in the USA and Europe in combination with other antiretroviral drugs for the treatment of antiretroviral-naive HIV-1-infected patients with (HIV-1 RNA≤100000 copies/mL). [36] Rilpivirine resistance-associated mutations (RAMs) were defined as K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C and M230I/L. [27, 36] According to an algorithm developed by a national agency for AIDS research (ANRS), rilpivirine resistant strains were defined as having at least

one mutation among K101E/P, E138A/G/K/ Q/R/S, V179L, Y181C/I/V, Y188L, H221Y and M230I/L/V or as having L100I+K103N. Although, rilpivirine is not recommended in patients failing an NNRTI regimen. [37-40]

Ross et al. [41], in a phylogenetic analysis of HIV using population sequencing and ultra deep sequencing (UDS) data from 690 antiretroviral-naive HIV-infected subjects, observed 18 additional NNRTI, NRTI, and major PI resistance mutations. The authors detected a prevalence of between ≥ 1 and < 6% of which 12/18 (67%) were different types of NNRTI-related mutations (major: K101E, K103N, E138A, E138G, E138K; minor: K101E, V106I, E138A, E138G, E138K). The remaining 6/18 types of mutations detected at low prevalence were major PI-related mutations (D30N, M46I, M46L, V82A). The newly detected mutations that were observed in > 1 viral genotype were the major PI mutations M46I (2 subjects) and V82A (2 subjects), and the reverse transcriptase (RT) mutation V106I (7 subjects). A total of 16 subjects had virus with NNRTI and major PI mutations detected by UDS that were not detected by population sequencing with the frequencies of < 6%. For the major PI-associated mutations, these were detected by UDS in virus from 6 subjects. The PI major mutations included D30N,

M46I, M46L and V82A with the D30N and M46I mutations occurring in 2 separate samples from the same viral transmission cluster (VTC). For 10 viral samples from 8 VTCs, NNRTI mutations were detected only by UDS and at frequencies of 6% and included K101E, K103N, V106I, E138A, E138G, and E138K. Nevertheless, Vandenhende et al. [42] found that accessory PI mutations are polymorphic, but their accumulation could impact the susceptibility to some PI such as Lopinavir or Nelfinavir.

According to the International AIDS Society, 23 mutations in 16 codons of the protease gene relating to major drug-resistance to PIs were identified by phenotypic resistance assays. [43, 44] Xiaobai et al. [45] identified PI TDR mutations by deep sequencing (24% of subjects), but these were found in isolation and at low variant frequency. The most frequent and highest HIV variant level identified was T74S in 10 subjects (11.5%). The low-level variants were interpreted by Stanford.hivdb.edu, 9.2% of subjects had intermediate or high-level PI-associated resistance (driven by V32I, I47V, G48V, I50V & V82A/T); with only 2% of subjects had HIV variants having multiple PI mutations. At an individual level, switching nonadherent patients to a boosted PI-based regimen that is less susceptible to development of resistance may be appropriate and is the recommended strategy in many high-income settings. [46] Among the PIs, indinavir (IDV) demonstrated a higher affinity for mutant protease proteins. [47]

High-level resistance to antiviral drugs generally arises by stepwise accumulation of mutations rather than insertions or deletions [27] but insertions and deletions contributing significantly to drug resistance have been described. [48] Insertions of two amino acids have mainly been reported at RT position 69 in clinical isolates from HIV-1 patients failing ART. These insertions typically confer NRTI resistance in association with thymidine analog mutations (TAMs). [49, 50-53] In Megens et al. [48], a virus strain without the insertion already displayed some NRTI resistance due to the TAM1 mutations and the level of resistance was strongly enhanced after the addition of the insertion. Surprisingly, NNRTI resistance was observed in the absence of major NNRTI-associated mutations and the level of resistance was further elevated after the selection of strains with K103N and Y181C mutations. [54]

Ibrahim et al. [55] also showed, in a health facility-based cross sectional study, that poor adherence to antiretroviral therapies could have serious consequences for individuals who are infected with HIV including failure of prevention of viral replication, an increased possibility of developing viral resistance, the progression of the disease to stages of clinical complications, and reduction of survival. [55-

58] Factors associated with poor adherence based on the findings of this study include gender, age, employment, marital status, and health status. [55] The results reveal that females, younger people and unemployed individuals were more likely to be associated with poor adherence to antiretroviral therapy. Lack of support from either the family or community is also an important risk factor for poor adherence to antiretroviral therapy. [55] Moreover, low adherence to ART is associated with an increased risk of resistance to HIV-1 reverse transcriptase inhibitors (RTIs). The emergence of drug resistant virus limits antiretroviral choice due to cross-resistance to other antiretroviral agents [59, 60] and is strongly associated with progression of HIV-1 infection and increased mortality. [61-66]

Choi et al. [67] assumed that the earlier that patients were diagnosed and treated, the higher the level of drug resistance that would develop in them. Based on the treatment history of these patients, mutations giving resistance to the extensively used NRTIs were more prevalent than to PIs. [67] As the efficacy of the combination antiretroviral therapy (cART) decreased, the number of patients at risk to resistant virus increased with a possible concomitant increase in risk of TDR. [7] The consequences of prolonged continuation of non suppressive cART were observed in a cross-sectional study conducted by Mutwa et al. [68] Their genotypic results, with 90% of children with virologic failure and available genotyping determinations, showed the development of major NRTIs and NNRTI-associated resistance mutations. [68-72]

A major obstacle to the long-term efficacy of ART is the emergence of drug resistance mutations in the polymerase gene of HIV-1, the primary target for ART. This reduces anti-retroviral (ARV) drug susceptibility [73] and limits the therapeutic options of newly infected patients. [74] The transmission of resistant variants to uninfected individuals has become a serious clinical and public-health concern. [73] Knowledge of prevalent drug resistant variants is useful for optimizing therapeutic schemes and obtaining a better patient response. [21, 75] Despite stable ART, many patients experience episodes of low-level viremia (LLV), defined as plasma viral load (pVL) measurements between 50 and 1000 HIV-1 RNA copies/mL. This low level of virus production in the presence of ART increases the potential for mutants to arise and their selection. An increased risk of virologic failure has been associated with episodes of LLV in several studies, [74-79] but not in others. [80-82] Finally, it is important to expand the surveillance for antiretroviral resistance amongst these patients as well as treatment naive patients in order to facilitate the early detection of transmitted drug resistant strains to individual patients as well as the population. [25].

Conclusion

Recent findings reveal that the development of resistance to antiretroviral therapy by HIV-infected patients is associated with increased access to drugs used in the treatment, and with low adherence. The appearance of these resistant strains is associated with specific mutations that not only reduce the effect of the drug class in use on the patient but also provide the emergence of cross-resistance with other classes. Poor adherence to treatment, the use of sub-optimal doses and treatments initiated too late for efficacy provide conditions that allow the emergence of resistant mutations classes of drugs currently used in treatment of HIV/AIDS as NNRTIs, NRTIs and PI's and contribute to the reduction of effectiveness of treatment.

Knowledge of the mutations that confer drug resistance is useful for optimizing treatment regimens. Selection of resistant viruses by poor adherence to antiretroviral treatment and the acquisition of resistant viruses are important factors for the failure of antiretroviral treatment. With knowledge of the prevalent mutations conferring resistance to the antiHIV drugs, alternative drugs can be used. As

such, it is necessary to continue the evaluation of mutations causing resistance to antiretroviral therapy and the development of more effective ways of managing HIV/AIDS.

References

1. Drescher SM, Von Wyl V, Yang WL, et al. Treatment-naive individuals are the major source of transmitted HIV-1 drug resistance in men who have sex with men in the Swiss HIV cohort study. *Clin Infect Dis*. 2014; 58(2): 285-294.
2. Murphy EL, Collier AC, Kalish LA, Assmann SF, Para MF, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med*. 2001; 135: 17-26.
3. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998; 338: 853-860.
4. Jacobson MA, French M. Altered natural history of *AIDS*-related opportunistic infections in the era of potent combination antiretroviral therapy. *AIDS*. 1998; 12 Suppl A: S157-163.
5. Ray M, Logan R, Sterne JA, Hernandez-Diaz S, Robins JM, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*. 2010: 24: 123-137.
6. Booth CL, Geretti AM. Prevalence and determinants of transmitted antiretroviral drug resistance in HIV-1 infection. *J Antimicrob Chemother*. 2007; 59: 1047-1056.
7. Zu Knyphausen F, Scheufele R, Kücherer C, et al. First line treatment response in patients with transmitted HIV drug resistance and well defined time point of HIV infection: Updated results from the German HIV-1 seroconverter study. *PLoS ONE*. 2014; 9(5).
8. Cambiano V, Bertagnolio S, Jordan MR, Pillay D, Perriëns JH, Venter F, et al. Predicted levels of HIV drug resistance: Potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation. *AIDS*. 2014; 28(SUPPL. 1): S15-S23.
9. Periodicos.capes.gov.br [homepage on the Internet]. Brasília: Higher Education Co-ordination Agency of Brazil's Ministry of Education; 2000. Available from: http: //www.periodicos.capes.gov.br/. Accessed June 16, 2014.
10. Fall-Malick FZ, Tchiakpé E, Ould Soufiane S, et al. Drug resistance mutations and genetic diversity in adults treated for HIV type 1 infection in Mauritania. *J Med Virol*. 2014; 86(3): 404-410.
11. Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV-1 drug resistance detection. *Clin Infect Dis*. 2010; 50: 98-105.
12. Auvert B, Males S, Puren A, et al. Can HAART reduce the spread of HIV? A study in a township of South Africa. *J Acquir Immune Defic Syndr*. 2004; 36: 613-621.
13. Grant RM, Lama JR, Anderson PL, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010; 363: 2587-2599.
14. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010; 329: 1168-1174.
15. Mulu A, Liebert UG, Maier M. Virological efficacy and immunological recovery among Ethiopian HIV-1 infected adults and children. *BMC Infect Dis*. 2014; 14(1).
16. Toor JS, Sharma A, Kumar R, et al. Prediction of drug-resistance in HIV-1 subtype C based on protease sequences from ART naive and first-line treatment failures in North India using genotypic and docking analysis. Antiviral Res. 2011; 92: 213-218.
17. Baesi K, Ravanshad M, Ghanbarisafari M, et al. Antiretroviral drug resistance among antiretroviral-naive and treatment experienced patients infected with HIV in Iran. *J Med Virol*. 2014; 86(7): 1093-1098.
18. Hamers RL, Schuurman R, Sigaloff KC, et al. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. Lancet Infect Dis. 2012; 12: 307-317.
19. Nichols BE, Sigaloff KCE, Kityo C, et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: A modeling study. *AIDS*. 2014; 28(1): 73-83.
20. Xing H, Ruan Y, Li J, et al. HIV drug resistance and its impact on antiretroviral therapy in Chinese HIV-infected patients. *PLoS ONE*. 2013; 8(2): e54917. doi: 10.1371/journal.pone.0054917
21. Azam M, Malik A, Rizvi M, et al. Trends of drug-resistance-associated mutations in the reverse transcriptase gene of HIV type 1 isolates from North India. *Arch Virol*. 2014; 159(4): 719-25.
22. Sungkanuparph S, Chakriyanuyok T, Butthum B. Antiretroviral therapy in *AIDS* patients with CMV disease: Impact on the survival and long-term treatment outcome. *J Infect*. 2008; 561: 40-43.
23. Ragni MV, Nalesnik MA, Schillo R, et al. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia*. 2009; 152: 552-558.
24. Marconi VC, Grandits GA, Weintrob AC, et al. Outcomes of highly active antiretroviral therapy in the context of universal access to healthcare: The U.S. Military HIV Natural History Study. *AIDS*. 2010. Res Ther 7: 14.

25. Ong LY, Razak SNH, Lee YM, et al. Molecular diversity of HIV-1 and surveillance of transmitted drug resistance variants among treatment Naïve patients, 5 years after active introduction of HAART in Kuala Lumpur, Malaysia. *J Med Virol*. 2014; 86(1): 38-44.

26. Jordan MR. Assessments of HIV drug resistance mutations in resource-limited settings. *Clin Infect Dis*. 2011; 52: 1058-1060.

27. Johnson VA, Calvez V, Gunthard HF, et al. Update of the drug resistance mutations in HIV-1: March 2013. *Top Antivir Med*. 2013; 21: 6-14.

28. Santoro MM, Fabeni L, Armenia D, et al. Reliability and clinical relevance of the HIV-1 drug resistance test in patients with low viremia levels. *Clin Infect Dis*. 2014; 58(8): 1156-1164.

29. Pillay D. The emergence and epidemiology of resistance in the nucleoside experienced HIV-infected population. *Antivir Ther*. 2001; 6(Suppl 3): 15-24.

30. Ghosn J, Chaix M-L, Delaugerre C. HIV-1 resistance to first- and second generation non-nucleoside reverse transcriptase inhibitors. *AIDS Rev*. 2009; 11: 165-173.

31. Abdissa A, Yilma D, Fonager J, et al. Drug resistance in HIV patients with virological failure or slow virological response to antiretroviral therapy in ethiopia. *BMC Infect Dis*. 2014; 14(1).

32. Phanuphak P, Sirivichayakul S, Jiamsakul A, et al. Transmitted drug resistance and antiretroviral treatment outcomes in non-subtype B HIV-1-infected patients in south east asia. *J Acquired Immune Defic Syndr*. 2014; 66(1): 74-79.

33. Azijn H, Tirry I, Vingerhoets J et al. TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTIresistant HIV-1. *Antimicrob Agents Chemother*. 2010; 54: 718-727.

34. Guillemont J, Pasquier E, Palandjian P et al. Synthesis of novel diarylpyrimidine analogues and their antiviral activity against human immunodeficiency virus type 1. *J Med Chem*. 2005; 48: 2072-2079.

35. Janssen PAJ, Lewi PJ, Arnold E et al. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2cyanoethenyl]-2, 6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, rilpivirine). *J Med Chem*. 2005; 48: 1901-1909.

36. European Medicines Agency. Edurantw 25 mg Film-coated Tablets: Summary of Product Characteristics. 2012. http: // www.ema.europa.eu/ docs/en_GB/document_library/EPAR_-_ Product_Information/human/002 264/WC500118874.pdf (24 September 2013, date last accessed).

37. Tebas P, Palella F, Gazzard B et al. SPIRIT study: switching boosted PI to rilpivirine in combination with Truvada as a single tablet regimen week 24 results. In: Abstracts of the Fourteenth International Workshop on Comorbidities and Adverse Drug Reactions in HIV, Washington, DC, 2012. Abstract O18. *Antivir Ther*. 2012; 17 Suppl 2: A16.

38. Lambert-Niclot S, Charpentier C, Storto A, et al. Rilpivirine, emtricitabine and tenofovir resistance in HIV-1-infected rilpivirine-naive patients failing antiretroviral therapy. *J Antimicrob Chemother*. 2014; 69(4): 1086-1089.

39. Mulu A, Lange T, Liebert UG, Maier M. Clade homogeneity and Pol gene polymorphisms in chronically HIV-1 infected antiretroviral treatment naive patients after the roll out of ART in Ethiopia. *BMC Infect Dis*. 2014; 14(1).

40. Azam M, Malik A, Rizvi M, et al. Zero prevalence of primary drug resistanceassociated mutations to protease inhibitors in HIV-1 drug-naive patients in and around Aligarh, India. *J Infect Dev Ctries*. 2014; 8(1): 79-85.

41. Ross LL, Horton J, Hasan S, et al. HIV-1 transmission patterns in antiretroviral therapy-naïve, HIV-infected North Americans based on phylogenetic analysis by population level and ultra-deep DNA sequencing. *PLoS ONE*. 2014; 9(2).

42. Vandenhende MA, Bellecave P, Recordon-Pinson P, et al. Prevalence and evolution of low frequency HIV drug resistance mutations detected by ultra deep sequencing in patients experiencing first line antiretroviral therapy failure. *PLoS ONE*. 2014; 9(1).

43. Rhee SY, Gonzales MJ, Kantor R, et al. Human immunodeficiency virus reverse transcriptase and protease sequence database. *Nucleic Acids Res*. 2003; 31: 298-303.

44. Antunes DA, Rigo MM, Sinigaglia M, et al. New insights into the in silico prediction of HIV protease resistance to nelfinavir. *PLoS ONE*. 2014; 9(1) : e87520.

45. Xiaobai Z, Xi C, Tian H, et al. Prevalence of WHO transmitted drug resistance mutations by deep sequencing in antiretroviral-naive subjects in Hunan Province, China. *PLoS ONE*. 2014; 9(6): e98740.

46. Johnston V, Cohen K, Wiesner L, et al. Viral suppression following switch to second-line antiretroviral therapy: Associations with nucleoside reverse transcriptase inhibitor resistance and subtherapeutic drug concentrations prior to switch. *J Infect Dis*. 2014; 209(5): 711-720.

47. Mata-Munguía C, Escoto-Delgadillo M, Torres-Mendoza B, et al. Natural polymorphisms and unusual mutations in HIV-1 protease with potential antiretroviral resistance: A bioinformatic analysis. *BMC Bioinform*. 2014; 15(1).

48. Megens S, Vaira D, De Baets G, et al. Horizontal gene transfer from human host to HIV-1 reverse transcriptase confers drug resistance and partly compensates for replication deficits. *Virology*. 2014; 456-457(1): 310-318.

49. Larder BA, Bloor S, Kemp SD, et al. 1999. A family of insertion mutations between codons 67 and 70 of human immunodeficiency virus type 1 reverse transcriptase confer multinucleoside analog resistance. Antimicrob. *Agents Chemother*. 1999; 43: 1961-1967.

50. Mas A, Parera M, Briones C, et al. Role of a dipeptide insertion between codons 69 and 70 of HIV-1 reverse transcriptase in the mechanism of AZT resistance. *EMBOJ*. 2000; 19, 5752-5761.

51. Meyer PR, Lennerstrand J, Matsuura SE, et al. Effects of dipeptide insertions between codons 69 and 70 of human immunodeficiency virus type 1 reverse transcriptase on primer unblocking, deoxynucleoside triphosphate inhibition, and DNA chain elongation. *J. Virol*. 2003; 77, 3871-3877.

52. White KL, Chen JM, Margot NA, et al. Molecular mechanisms of tenofovir resistance conferred by human immunodeficiency virus type 1 reverse transcriptase containg a diserine insertion after residue 69 and multiple thymidine analog-associated mutations. Antimicrob. *Agents Chemother*. 2004; 48, 992-1003.

53. Winters MA, Coolley KL, Girard YA, et al. A 6-basepair insert in the reverse transcriptase gene of human immunodeficiency virus type 1 confers resistance to multiple nucleoside inhibitors. *J. Clin. Investig*. 1998; 102, 1769-1775.

54. Lee GQ, Bangsberg DR, Muzoora C, et al. Prevalence and virologic consequences of transmitted HIV-1 drug resistance in Uganda. *AIDS Res Hum Retroviruses*. 2014; 30(9): 896-906.

55. Ibrahim Y, Sutan R, Latif KBA, et al. Poor adherence to antiretroviral therapy and associated factors among people living with HIV in Omdurman City, Sudan. Malays J *Public Health Med*. 2014; 14(1): 90-101.

56. Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *Journal of Acquired Immune Deficiency Syndrome*. 2000; 23: 386-395.

57. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. *AIDS Read*. 2000; 10: 177-185.

58. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical Infectious Disease*. 2001; 33: 1417-1423.

59. Metzner KJ, Rauch P, Braun P, et al. Prevalence of key resistance mutations K65R, K103N, and M184V as minority HIV-1 variants in chronically HIV-1 infected, treatment naive patients. *J Clin Virol*. 2011; 50: 156e61

60. Saha R, Saha I, Sarkar AP, et al. Adherence to highly active antiretroviral therapy in a tertiary care hospital in West Bengal, India. *Singapore Med J*. 2014; 55(2): 92-8.

61. Svicher V, Alteri C, Artese A, et al. Different evolution of genotypic resistance profiles to emtricitabine versus lamivudine in tenofovir-containing regimens. *J Acquir Immune Defic Syndr*. 2010; 55: 336e44.

62. Hogg RS, Bangsberg DR, Lima VE, et al. Emergence of drug resistance is associated with an increased risk of death among patients first starting HAART. *PLoS Med*. 2006; 3: e356.

63. Kozal MJ, Hullsiek KH, Macarthur RD, et al. The incidence of HIV drug resistance and its impact on progression of HIV disease among antiretroviral naive participants started on three different antiretroviral therapy strategies. *HIV Clin Trials*. 2007; 8: 357e70.

64. Zaccarelli M, Tozzi V, Lorenzini P, et al. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIVinfected patients. *AIDS*. 2005; 19: 1081e9.

65. Zaccarelli M, Tozzi V, Lorenzini P, et al. The V1181 mutation as a marker of advanced HIV infection and disease progression. *Antivir Ther*. 2007; 12: 163e8.

66. Bulteel N, Bansi-Matharu L, Churchill D, et al. The emergence of drug resistant HIV variants at virological failure of HAART combinations containing efavirenz, tenofovir and lamivudine or emtricitabine within the UK Collaborative HIV Cohort. *J Infect*. 2014; 68(1): 77-84.

67. Choi JY, Kwon OK, Choi BS, et al. The prevalence of antiretroviral multidrug resistance in highly active antiretroviral therapy-treated patients with HIV/*AIDS* between 2004 and 2009 in South Korea. *J Clin Virol*. 2014; 60(2): 154-160.

68. Mutwa PR, Boer KR, Rusine J, et al. Long-term effectiveness of combination antiretroviral therapy and prevalence of HIV drug resistance in HIV-1-infected children and adolescents in Rwanda. *Pediatr Infect Dis J*. 2014; 33(1): 63-69.

69. Hirsch MS, Gunthard HF, Schapiro JM, et al. International *AIDS* Society-USA. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International *AIDS* Society-USA panel. *Top HIV Med*. 2008; 16: 266-285.

70. Luber AD. Genetic barriers to resistance and impact on clinical response. *MedGenMed*. 2005; 7: 69.

71. Towler WI, Barlow-Mosha L, Church JD, et al. Analysis of drug resistance in children receiving antiretroviral therapy for treatment of HIV-1 infection in Uganda. *AIDS Res Hum Retroviruses*. 2010; 26: 563-568.

72. D'Aquila RT, Schapiro JM, Brun-Vézinet F, et al. Drug resistance mutations in HIV-1. *Top HIV Med*. 2003; 11: 92-96.

73. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA*. 1999; 282(12): 1135-1141.

74. Arora SK, Gupta S, Toor JS, et al. Drug resistance associated genotypic alterations in the pol gene of HIV type 1 isolates in ART-naive individuals in North India. *AIDS Res Hum Retro*. 2008; 24(2): 125-130.

75. Dai L, Mahajan SD, Sykes DL, et al. Prevalence of Transmitted HIV-1 Drug Resistance (TDR) Associated Mutations and Predicted Drug Sensitivity in Newly Diagnosed HIV-1 Patient Cohort in a Western New York, 2005-2011. *J Antivir Antiretrovir*. 6: 022-027. doi: 10.4172/jaa.1000090.

76. Cohen C. Low-level viremia in HIV-1 infection: consequences and implications for switching to a new regimen. *HIV-1 Clin Trials*. 2009; 10: 116-124.

77. Delaugerre C, Gallien S, Flandre P, et al. Impact of low-level-viremia on HIV-1 drug-resistance evolution among antiretroviral treated-patients. *PLoS ONE*. 2012; 7: e36673.
78. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004; 18: 981-989.
79. Pilcher CD, Miller WC, Beatty ZA, et al. Detectable HIV-1 RNA at levels below quantifiable limits by Amplicor HIV-1 monitor is associated with virologic relapse on antiretroviral therapy. *AIDS*. 1999; 13: 1337-1342.
80. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA*. 2005; 293: 817-829.
81. Mira JA, Macías J, Nogales C, et al. Transient rebounds of low-level viraemia among HIV-1-infected patients under HAART are not associated with virological or immunological failure. *Antivir Ther*. 2002; 7: 251-256.
82. Gonzalez-Serna A, Min JE, Woods C, et al. Performance of HIV-1 drug resistance testing at low-level viremia and its ability to predict future virologic outcomes and viral evolution in treatment-naive individuals. *Clin Infect Dis*. 2014; 58(8): 1165-1173.