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ABSTRACT

Sumário: A grande variabilidade genética do vírus HIV surge como consequência dos mecanismos biológicos intrínsecos do vírus, que lhe permitem evoluir e mutar. Através de estudos filogeográficos foi possível determinar as rotas de difusão espacial da epidemia e estabelecer uma distribuição geográfica dos diferentes subtipos. Todavia, num mundo em que as populações estão em constante movimento e em que a migração é cada vez mais comum, os limites desta distribuição geográfica estão a tornar-se menos claros e definidos. O subtipo B continua a ser a forma mais prevalente na União Europeia, porém casos de infecção por subtipos não-B estão a ser registados a um ritmo alarmante. Tendo em conta que as estratégias para lidar com a epidemia foram criadas com base nos conhecimentos adquiridos através do subtipo B, o aparecimento destas novas estirpes representa um risco para a saúde da população europeia em geral. Existem poucos dados disponíveis no que toca aos mecanismos, susceptibilidade aos anti-retrovirais, sensibilidade dos testes de diagnóstico e progressão patológica dos subtipos não-B. No entanto, nos estudos que foram realizados, não se constatou nenhuma diferença entre os subtipos no que diz respeito à resposta aos anti-retrovirais, embora não se ponha de parte que possam advir resistências farmacológicas num futuro próximo, resultantes dos polimorfismos genéticos do vírus. O mesmo se aplica à sensibilidade dos testes de diagnóstico. É, portanto importante que os departamentos da saúde, políticos e sociais, reconheçam o papel central desempenhado pelas comunidades imigrantes na alteração do *pool* genético do vírus HIV-1. As populações imigrantes são particularmente vulneráveis em diversas áreas e são, por isso, mais susceptíveis de transmitir a infecção HIV. Estudos focaram que na base deste problema estão a desigualdade social, a pobreza, limitações linguísticas e o isolamento social. É importante que estes indivíduos não sejam vistos como uma ameaça mas sim como áreas de potencial actuação para impedir a progressão da epidemia. Para concretizar este objectivo é, portanto, necessário um esforço conjunto para aplicar medidas preventivas que integrem acções comportamentais e biomédicas. **Palavras chave:** Virus HIV-1, mecanismos biológicos, variabilidade genética, migração, distribuição geográfica dos subtipos, subtipo B, infecção HIV, subtipo não-B, estratégias, susceptibilidade anti-retrovirais, sensibilidade dos testes de diagnóstico, progressão da doença, comunidades

imigrantes, desigualdade social, isolamento social, medidas preventivas, medidas biomédicas.

Migration and HIV Infection Incidence

Mestrado Integrado em Medicina

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ABSTRACT

Summary The HIV-1 virus has intrinsic biological mechanisms that enable it to evolve and mutate, justifying its extensive genetic heterogeneity. Phylogeographic studies of viral sequences have determined the spatial diffusion of the epidemic, suggesting a geographical distribution of the different subtypes. However in a increasingly globalized world, in which more people are travelling and migration is more frequent, this defined subtype-geographic distribution is changing and becoming less clear. B-subtype is still the most prevalent subtype in the European Union but new cases of HIV-1 infections by the non-B subtypes are being reported at an alarming rate. This poses as a threat to the health of the general European population, since the management strategies are built on the knowledge acquired from subtype B. Our knowledge on the mechanisms, antiretroviral drug susceptibility, diagnostic assays sensitivity, disease progression on non-B subtypes is limited. Nevertheless, the virological and immunological responses to antiretroviral therapy appear similar across subtypes but the data suggest that naturally occurring polymorphisms may induce drug resistance in a near future. This is also applicable to the diagnostic tests. This urges the health, political and social departments to be aware of the central part played by immigrant communities and of the changes in the HIV-1 genetic pool that they may cause. It is important to acknowledge that migrants are particularly vulnerable in so many areas and are more susceptible of transmitting the HIV infection. Studies have shown that on the basis of this problem are the social inequality, poverty, linguistic limitations and social isolation. Therefore, it is important, in order to not aggravate the situation, that these individuals are not seen as a threat but as an area in which the health department must also act in order to stop this pandemic. In conclusion, an effort should be made to adapt the health and political strategies, apply preventive measures, integrating behavioral and biomedical approaches. **Keywords:** HIV-1 virus, biologic mechanisms, genetic heterogeneity, migration, subtype-geographic distribution, B-subtype, HIV infection, non-B subtype, management strategies, antiretroviral drug susceptibility, diagnostic assays sensitivity, disease progression, immigrant communities, social inequality, social isolation, preventive measures, biomedical approaches.

REVIEW

Introduction

Since the first cases of the acquired immunodeficiency syndrome (AIDS) were reported, 29 years ago [1], the transmission of the virus and the evolution of the disease remain elusive. This is due, on one hand, to the complexity of the molecular pathogenesis of the virus; and on the other, to its ability to mutate and therefore evade the hosts immune system (mutational escape) [2]. The glycosylation of the external glycoprotein, the direct targeting of the CD4 molecule and the integration into the host-cell genome are examples of the intricacy of the molecular pathogenesis of the virus; Mutational escape results in a remarkable degree of viral diversity that allows the rapid adaptation of the virus to the immune response and to the antiretroviral therapy. Throughout the years many scientific breakthroughs have been made in characterizing the HIV virus genomic code. Nevertheless, the genetic evolutionary process, through which new HIV-1 strains emerge is a very dynamic process, is constantly mutating and is not fully understood. This extensive genetic diversity generates variants that are categorized into distinct molecular subtypes or into distinct recombinant forms. Molecular epidemiological studies show that, with the exception of sub-Saharan Africa, where almost all subtypes, circulating recombinant forms, and several unique recombinant forms have been detected, there is a particular geographic distribution pattern for the HIV-1 subtypes [3]. Guidelines for management of the HIV infection pandemic differ from area to area and are dependent of this geographical distribution pattern. But in an increasingly “globalised” world, where the viral migration process is more frequent, these distributional patterns may become less evident and, as a consequence, may jeopardize the applicability of these management plans. The genetic viral diversity in association with the “globalization” of the different viral strands may have implications on the diagnostic tests accuracy, responses to antiretroviral therapy (including the development of resistance), disease progression and, therefore, poses as a threat to the public and general health status.

Objective

The purpose of the present paper is to review selected aspects of the genetic diversity of HIV-1 virus, its association to migration routes and its social, diagnostic, pathologic and therapeutic implications, as well as present some authors' opinions on several preventive measures.

Methods

A research under the "HIV infection MESH migration" was conducted in MEDLINE and subsequently a qualitative selection of the most relevant articles to the purpose of the review was made. An email requesting those articles with no available free access was sent to the authors having received response from some of them. Ultimately, some of the references believed to be relevant were also sought.

HIV classification and genetic diversity

The HIV virus is an evasive and dynamic virus that suffers constant molecular evolution. As a result, the HIV epidemic is characterized by a great genetic variability and complexity that continuously pose as a challenge to the scientific community. Subsequently to an attentive phylogenetic molecular study of the HIV virus, it was classified in three groups: major (M), outlier (O), and non-major and non-outlier (N) [4]. The N and O groups are limited to Cameroon and west central Africa respectively [5, 6] therefore their contribution to the global evolution of the epidemic and consequently to the objective of the present review is limited. The group M is the global predominant circulating HIV-1 group, it has been divided into subtypes, denoted with letters, (B and A, C, D, F, G, H, J, K, also called non-B subtypes) and sub-subtypes, denoted with numerals (A1, A2, A3, A4, F1, F2). The subtypes are phylogenetically linked strains of HIV-1 that are approximately at the same genetic distance from one another. Genetic variations within a subtype can be 15 to 20%, whereas variation between subtypes is usually 25 to 35%. [7]. Subtypes are also linked geographically or epidemiologically. Moreover, the virus is denoted by an even greater genomic diversity for the virus has several intrinsic mechanisms that endorse a rapid viral

evolution: lack of proofreading ability of the reverse transcriptase and recombination events. These mechanisms integrate the virus replication cycle and are responsible for the constant advent of new strains. The HIV reverse transcriptase lacks proofreading activity, the ability to confirm that the DNA transcript it makes is an accurate copy of the RNA code, and, therefore, confers a high mutation rate enabling it to produce millions of variants within any infected person in a single day [8]. Another process that can lead to further viral diversity is recombination [9], and occurs when one person is co-infected with two separate strains of the virus, these swap parts of their genetic material resulting in unique recombinant forms. The rapid turnover of HIV-1 in vivo [10] and the host selective immune pressure [11] are mechanisms that further contribute to the diversity of the virus genetic code. If a unique recombinant form spreads to at least three epidemiologically unlinked individuals it will be classified as a circulating recombinant form. [12]. An example is subtype A strain of low density that was originated from CRF03_AB, a unique recombinant form, in the former soviet Union [13], or subtype F that emerged in South America in the form of a recombinant strain [14]. An example of a Unique recombinant form that was identified recently is the CRF14_BG that arose among injection-drug users in Spain and Portugal and, presently, continues to spread [15]. These circulating recombinant forms alone account for 18% of the worldwide infections [16] and represent the predominant local form in Southeast Asia [17] (CRF01-AE) 9 and in Western and West Central Africa (CRF02-AG) [18].

Subtypes migration, transmission and disease progression

History is littered with examples of how migration plays a central role in the dissemination of the HIV infection. For instance, the subtype B epidemic in the United States and elsewhere, was the result of a single point of introduction of the virus from Haiti around the 1960s [19]; the introduction of HIV-1 into Europe occurred mainly through homosexual contacts or needle sharing in or from the USA or through heterosexual contacts with individuals from Central Africa [20]. The HIV-1 group M infection originated in Africa from the simian immunodeficiency virus (SIVcpz) infecting chimpanzees [21] and originated a worldwide pandemic. All in all, the virus “traveled”, settled, reproduced itself and was transmitted, generating an epidemic in different parts of the globe. Curiously, it seems that different viral subtypes are responsible for the epidemic on different areas of the world and this suggests that the

emigrational process and the viral transmission did not occur in the same way throughout the globe. It is important to bare in mind that this migrational phenomenon is a dynamic process that is constantly happening and that is continuously influencing the present geographic distribution of the epidemic. Subtype C is the most prevalent form, accounting for almost 50% of all HIV-1 infections worldwide. Subtype Bs predominance in the industrialized regions, as in North America and Western Europe, is maintained but migration routs may be changing this in a near future. In the UK, for instance, subtypes A, G, C and D, most commonly found in African regions, together with an array of recombinant forms, are becoming more prevalent due, probably, to a high number of migrants from countries with a high prevalence of such subtypes, notably, sub-Saharan Africa.

The mechanisms through which this distribution pattern of the HIV-1 subtypes occurs are not fully understood nor are the migrational routs through which they happen. Some authors [22] suggest the process involves the accidental introduction of a viral strand followed by a “founder effect”, in other words, the viral clade is introduced in a population by an isolated event and ulteriorly is transmitted locally (fast-colonization outcome); or through a prevalent route of transmission in which the viral strand is being constantly introduced in the population. Recently, some studies have been conducted to shed some light on this subject. A phylogeographic study conducted by Luca Mendoza, *et al* [23] provided important clues about HIV-1 subtype B spatial diffusion across Europe, providing a new insight into the subject. They suggest that the viral strands are introduced from several sources and subsequently spread locally, but the pattern is not uniform across all the European countries. Some countries are more of a (1) source of different virus strands (Greece, Portugal, Serbia and Spain); or (2) sinks (Austria, Belgium and Luxembourg) of virus migration, others present (3) bidirectional migration, being both sources and sinks (Denmark, Germany, Italy, Israel, Norway, the Netherlands, Sweden, Switzerland and the UK). The only exception was Poland where a significant number of sequences fell within a monophyletic cluster. Their results also suggested that the virus mobility matched the host mobility, such that in order to reduce further spread of the epidemic, prevention measures should not only be directed towards national populations, but also towards migrants, travelers and tourists. Nevertheless, more studies must be conducted to confirm the data and quantify the exact

epidemiological contribution of migrants, travelers and tourists to the dissemination of such strains.

Apart from an apparent association between the geographical area and the HIV subtype, it seems that there is also, within a specific region, an association between the subtype and the risk-transmission behavior: intravenous drug users (IDUs); men who have sex with men (MSM); Unprotected intercourse among heterosexuals. In Europe, subtype B seems to be associated to IDU and homosexual risk groups as non-B subtypes and circulating recombinant forms are progressively being introduced by heterosexual contact between migrants and/or immigrants from regions where HIV-1 is endemic. This association could be justified by different subtype biological properties, yet it has not been consistently demonstrated and L.Buonaguro *et al* [22] believes that rather than a result of virological intrinsic factors this association is more probable to derive from genetic, demographic, economic, and social factors.

It has also been reported that these risk behaviors contribute in different ways to the transmission of the disease according to the region of the world. For instance, in Eastern Europe and Central Asia in 2005, 67% of the HIV infections were due to needle sharing among IDUs, as for Western Europe, unprotected intercourse among heterosexuals remains the most accountable [24, 25].

Some authors [22] believe that the virus biological characteristics may influence the disease progression. It has also been determined that HIV strains that are capable of using the CXCR4 co-receptor (X4 viruses) are associated with a more rapid disease progression [26]. All HIV-1 can use these coreceptors but the percentage of X4 virus appears to be lower in subtype C than in subtype B [27]. Barbara S. Taylor *et al* [28] mention several trials conducted to determine whether the virus subtype could be associated with a more rapid progression to AIDs or even death: In a large Swedish study of patients infected with subtype A, B, C or D, disease progression did not differ significantly according to subtype or ethnic group. On the other hand, a cohort study in Uganda suggested that HIV-1 disease progress more rapidly, and that the risk of death was greater, among persons infected with subtype D, with recombinant forms, or with multiple subtypes than among those infected with subtype A. The data on this subject is controversial, mostly because it is difficult to set aside confounders, such as access to

medical care, nutritional status, host genetic factors and mode of viral transmission, therefore, requiring further investigation.

HIV and the accuracy of the diagnostic tests;

Throughout the years death rates from HIV have fallen substantially mainly due to the constant improvement of the antiretroviral therapy. In the present, late diagnosis seems to be responsible for a high proportion of HIV mortality rates [29], giving special relevance to prevention campaigns and to the accuracy of the diagnostic tests. The scientific community still seems to agree that, currently, the serological and molecular diagnostic tests for HIV-1 are sufficiently specific and sensitive to the most prevalent forms [30]. But, the continuous mutation of the genetic code of the virus isn't reassuring and it is a potential risk that jeopardizes the specificity and sensitivity of the tests. To maintain the accuracy of such tests frequent evaluations may be required in the future in order to avoid the dissemination of unidentified infections.

Genetic diversity and drug resistance;

The increase in frequency of non-B subtypes in industrialized regions can have strong economic and public health implications. If a treatment is not effective on an individual, resources are being wasted, the patient is not being correctly attended to and is a risk for the public health in general. Most information on the response to ART (anti-retroviral treatment) was obtained through studies conducted on subtype B that accounts only for 12% of the global infections. [3]. This discrepancy in the availability of clinical data for non-B subtypes is exacerbated by the fact that, until the past few years, antiretroviral treatment had been largely unavailable in many countries with non-B subtypes of HIV-1. No significant differences in the response to triple antiretroviral therapy and the progression to AIDS or survival up to 48 months after starting treatment have been found between sub-Saharan Africans and Northwest Europeans [31]. However, treatment responses may not be equivalent in the longer term. Data from Holland showed that the virological response (plasma HIV-1 RNA level below 50 copies/mL) at 48 to 96 weeks was below than what was expected in non-indigenous patients [32]. Confounders, such as late presentation amongst migrants may justify this discrepancy.

Studies suggested that from 15% to 43% of HIV-positive individuals do not present for HIV testing until late in infection [33], therefore, the antiretroviral treatment is only initiated when patients are in an advanced stage of the disease. Clinical ramifications include the simultaneous management of antiretroviral agents and acute opportunistic infection, with overlapping adverse drug reactions and drug vs drug interactions [34]. For instance, co-infection with HIV and mycobacterium tuberculosis is common, and both therapeutic programs interact with cytochrome P 45 so the simultaneous treatment with antituberculous drugs, especially rifamycins, and antiretroviral agents requires particular focus for successful outcomes in both infections [35].

HIV resistance to antiretroviral therapy can be divided into two categories: primary resistance, which reflects acquisition of a drug-resistant strain of HIV by a newly infected person; and secondary, or acquired resistance, emerges after a period of treatment and suboptimal adherence to HIV ARTs presents as a risk factor. The HIV-1 polymorphisms confer drug resistance directly or by changing the “genetic barrier,” defined as the number of viral mutations required to develop escape mutations able to overcome the drugs effect [36].

Some trials have been conducted to elucidate the scientific community on the effectiveness of ARTs on non-B viral strands isolated or in comparison to B-subtypes. It has been reported that when exposed to tenofovir in culture, subtype C develops mutations more rapidly than other subtypes [37]. As for Nelfinavir resistance appears to occur in both B and non-B subtypes, differing on the location of the mutation [38]. It has also been reported that the reduced genetic barrier for the V106M substitution in subtype C confers high-level resistance to all NNRTIs. Moreover, natural resistance to NNRTIs has been observed in patients carrying group O HIV-1 viruses [39]. Curiously specific polymorphisms in protease positions may confer greater susceptibility to protease inhibitors to other non-B subtypes [40]. Nevertheless, although interesting, most of this data has not been consistently proven and most studies show that the antiretroviral drugs currently used are equally active on all HIV-1 subtypes [41] (with the exception of group O viruses, which are resistant to NNRTIs). What some authors [42] argue is that subtype-related differences and the rate of drug resistance emergence strongly suggest the need for HIV-1 pre-subtyping to guide selection of the appropriate therapeutic strategy but only as a preventive measure, to avoid the emergence of resistant strains.

HIV diversity and migrant communities

Nowadays, we live in an era in which travelling, whether it is for pleasure, for professional reasons or to change dwelling, has become extremely frequent. The number of international migrants (people residing in a country other than their country of birth for 12 months or more) has increased over the past years, from about 76 million in 1965 to 188 million in 2005 [42]. The central problem is that these individuals bring pathogenpassengers that enlarge the complexity of the diseases assigned to a geographic area or country. The HIV epidemic in Europe is an example of this, it has been profoundly influenced by the global epidemic mainly because of the constant movement, in and out of Europe, of migrants or residents. As a result, new virus strains, unknown strains, are being introduced by these individuals, and the genetic pool of the virus in the European epidemic is being modified and amplified. The Scientific knowledge on the HIV virus biologic characteristics, behavior, response to ARTs and so on, are based on studies that have been conducted mostly on the B subtype, since it is the most prevalent subtype in the developed countries (see **HIV classification and genetic diversity above**). Consequently, strategies, whether economic, political, diagnostic, therapeutic or social, have been built based on the knowledge obtained from this subtype. Therefore, the data that suggests a differential strain related pathogenicity and that these strains may influence the diagnostic tests accuracy and the therapeutic outcomes in association with the increase in prevalence of such strains should alarm the European community, for these management strategies may not be applicable or effective in a near future. In conclusion, migrant communities are an important area of intervention to reduce the dissemination of non- B clades, prevent the loss of effectiveness of the management strategies and avoid a greater loss of control over the epidemic.

The public health problematic

When attending to the public health in general the health of the individual is as important as the health of the general population. Therefore, when an individual is sick,

to the extent of the health care system capacity, he will be treated to his best interest. Nevertheless, the system must always keep in mind the “greater good”, the health of the rest of the population. So, the public health problematic is an equation that integrates the risk of the individual and the risk of the general population. Regarding chronic diseases as HIV infection, the problematic is even more complex for it also involves risk-producing environments, policies and is rooted in a larger social, cultural, political and economic backcloth. The public health sector must intervene at multiple levels of the social ecology to promote the health of the population and prevent, in this case, the further dissemination of the disease. It is important to have an intrinsic knowledge of the disease, parallel to knowledge of the social circumstances, in order to apply preventive measures, educate the citizens and alter the behavior of the individuals. In practical terms the public health professional acts on: the development of programs that ensure the health status of a population; Participates in the elaboration and application of laws and public health guidelines; promotes the development of screening campaigns and vaccination programs; evaluates social conditions (housing, hygiene, water supply...). The public health professional may work in public and private hospitals, pharmaceutical industries or social institutes. All in all, the exercise of this area of medicine is the result of a dynamic and multidisciplinary action.

Lydia R *et al* [43] defend that an effective secondary prevention program (they consider secondary prevention programs to be those that aim to reduce HIV transmission by already-infected persons, migrants are included in this group of individuals) must go beyond the traditional prevention components of risk education, encouraging condom use, behavioral skills practice, and emotional support. Secondary prevention requires a broader approach, in which biomedically and epidemiologically informed behavioral interventions constitute an essential component of multidisciplinary HIV care. So, it is clear that a multidimensional action must be taken about when facing the HIV pandemic and the part played by ethnic minorities that implicates a range of professionals, support organizations, coalitions, prevention campaign and epidemiological studies.

Frances Dunn Butterfoss *et al* [44] arguments that the development of coalitions of community agencies, institutions and concerned citizens to combat health chronic conditions as the HIV pandemic, is, probably, the best way to promote health. Coalitions may be defined as "an organization of diverse interest groups that combine their human and material resources to effect a specific change, the members are unable to bring about independently" by Brown [45].

Many European countries, Portugal included, lack epidemiological vigilance programs, limiting further more the implementation of preventive measures. Some authors propose that the first step to gain some control over the epidemic is to implement a national epidemiological vigilance program of sexually transmitted diseases [46]. It would enable the creation of national databases, that would quantify the number of infected, geographic distribution of the viruses subtypes and recombinant forms; the most prevalent ways of transmission in that region and its association with the virus subtypes; the migration pattern of the virus; the number and origin of migrants and tourists, their contribution to the prevalence of the disease in the population and the most prevalent risk-behaviors in these groups. This information is essential to create policies and guidelines adapted to the reality of the epidemic and enhance their effectiveness. For instance, preventive messages should be sent in different languages but without the information on the origin of migrants and tourists it is hard to determine the specific language in which they should be transmitted. Even the content of prevention campaigns depends on the epidemiologic data, for example, the most common risk-behaviors in a community determines which is the information that should be sent in their respective language. Besides, since resources are limited, it is important to know which nationalities are more prevalent, to know in which communities is more productive to act on, the most cost-effective intervention.

Some countries, mainly western European countries, have set some efforts on creating a consistent national database. Still, there is little generic information on HIV and migrants and most studies have focused on African sub-Saharan migrants, that is not necessarily the most prevalent nor the most representative, more studies should be conducted to fill the blanks on this subject. Anyhow, such studies showed that sub-saharan African immigrants bear a disproportionate and increasing share of the HIV prevalence and are responsible for most cases of sexually transmitted infections throughout those countries [47]. As referred above, the predominant way of transmission in Western Europe is unprotected sexual intercourse. So, this converging evidence suggests the possibility that recombinant forms are being introduced into Western Europe through sexual networks at an alarming rate. The co-circulation of multiple subtypes and CRFs in the same population increase the probability that individuals will be superinfected with different HIV-1 genetic forms, jeopardizing the

chances of a successful treatment. Emphasizing, once more, the importance of intervening on these clusters.

Although, surveys and intervention programs to change risk-behaviors are important to educate the population and transmit knowledge on the disease, it has been proven that information delivered individually rather than in groups and delivered by professionals rather than peers; is more effective and improves medication adherence [48], a conducted study reported that brief (3-5 min) transmission risk messages delivered by medical providers at every nonurgent clinic visit resulted in a significant reduction in unprotected penetrative intercourse for those patients who had more than one sexual partner at baseline [49]. Hence, Lydia *et al*, [43] support that medical providers have a promising and cost-effective opportunity to deliver secondary prevention messages to a very large number of HIV-positive individuals, given their long-term relationships and frequent contacts with the patients. These authors emphasize a shift from community-based interventions to interventions based in the health care settings. Moreover, several authors state that clinical environments are generally seen by most HIV positive migrants as safe spaces where their problems can be openly discussed [42].

Throughout history migrant communities have been blamed for importing and transmitting infections. Migrants are many times identified as threats generating a hostile political and social discourse towards these individuals in many countries. Migrants are isolated individuals, they are part of a process of transition associated with leaving “home” and negotiating a new culture, circumstances which may make them especially vulnerable to engage in risk-behaviors, mostly sexual, as was mentioned above. As a consequence of this social isolation, they don’t access the information required to understand the disease and although they know what HIV infection is, most of these individuals don’t consider themselves at risk of contracting the infection and don’t seek aid when ill, let alone for prevention purposes. The challenges encountered by physicians attending migrant patients are, therefore, considerable, involving issues of power and trust, language barriers and cultural divergences. Besides, the socio-political environment in which these individuals live is limited, hunger and inadequate housing is present in many cases. It becomes complicated to give high quality clinical HIV care and obtain the best therapeutic outcomes. In spite of this, a good doctor-patient relationship has the ability to overcome many of these unmet social needs, as mentioned above. Therefore, some efforts should be made to educate and prepare health

professionals to deal with these circumstances, as well as alert them to the importance of their contribution. All in all, ideally, a full range of services, (psychological, health care...) should be incorporated and co-located. It is also important to refer that in many European countries, with Portugal as an exception, free access to health care national system is not a reality, although the initial diagnostic HIV test is free the appropriate treatment is not. It is obvious that the probability of an untreated patient being conscious and beware of risk-transmission behaviors is very low.

Another issue that is directly linked to the success of doctor-patient relationships is the adherence to therapy. It has been shown that a higher viral load is associated with greater risk of HIV transmission, pointing out the importance of an optimal adherence to ART in order to prevent the transmission to non-infected sexual or needle-sharing partners. Moreover, the non-adherence to therapy enhances the probability of the appearance of resistant strains, which leads to treatment failure and disease progression. There is some controversy whereas, in a near future, the transmission of drug resistant strains will be significant. Some authors state that it already is [43], for some European studies reported a range of 5% to 26% of treatment-naïve patients with a drug-resistant virus [51]. Unfortunately, poor adherence and transmission risk behaviors are often correlated. A recent study found that individuals who were less adherent to antiretroviral therapy (ART) were 46% more likely to engage in sexual transmission risk behaviors than were adherent patients [51]. So, some authors defend that there is a strong probability that these resistant strains will spread within sexual networks, which are themselves associated to a lower socio-economic status and or ethnicity/race (stratification of drug resistant strains to particular communities). If this does, indeed, happen, providing clinical care to disadvantaged communities will become more of a challenge, as drug resistant strains of HIV that are more difficult to treat appear more commonly in these communities or ethnic minorities [52], needless to say that it is urgent to intervene.

CONCLUSIONS

The advent of new HIV-1 viral strands, further enriching the already heterogenic genetic pool of the virus, is happening at an alarming rate. The different viral strands present a geographic distribution throughout the globe but this distribution seems to be mutating and becoming less clear due to migration of the viral strands, associated to risk-behaviors engaged by migrants. Some studies suggest that the circulation of many different recombinant forms and subtypes within the same community increases the probability of appearance of new viral strands, as well as the co-infection of the same individual by different strains of the virus. The loss of these geographic distribution limits along with the mixture of the diverse genetic clades in the same population enables these phenomenon's to occur. Ethnic communities have been proven to be socially isolated, unaware of the risks of contracting the infection. These individuals live in poor environments in which their social needs are not attended to and in which the access to the health care system is limited. These facts, all together make these individuals prone to engage in risk-behaviors and be responsible for a great share of the transmission prevalence of the virus. It is urgent to act within these communities, to support these individuals and control the dispersal of new and unknown (non-B) viral clades through European countries. This requires a multidisciplinary action that would ideally enclose a range of social services, health professionals, prevention campaigns and coalitions. It is necessary to create laws and guidelines in order to develop a consistent intervention program that could indeed make a difference and prevent the establishment of these different viral strands in European communities. Although not totally clear, some authors believe that these strands may jeopardize the specificity and sensibility of the diagnostic tests as well as the response to ARTs and influence the disease progression endangering the therapeutic outcomes. All in all, if such data were to be confirmed and these strands would become common in the epidemic in European countries it would have a great social, political and most importantly economic impact. It is significant to mention the lack of epidemiologic data as a major limitation that needs to be addressed

ABBREVIATIONS

AIDS = acquired immune deficiency syndrome; **ART**= antiretroviral therapy; **HIV** = human immunodeficiency virus; **NNRTIs** = Non-nucleoside Reverse Transcriptase Inhibitor

COMPETING INTERESTS

The author declares that has no competing interests.

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