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Review Article

Advances on Human Immunodeficiency Virus Type 2 Infection

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Abstract

Human immunodeficiency virus type 2 (HIV-2) was first isolated in West Africa but the number of diagnosed infections is rising in western countries due to migration and international travels. This prompts for an increased surveillance by health authorities and improved diagnostic assays. This review summarizes the advances on our understanding of the transmission, clinical presentation, antiretroviral therapy, diagnostic tests, molecular epidemiology and historical dispersal patterns of HIV-2 infection.

Keywords: *HIV; Phylogeny; AIDS; Epidemiology*

Abbreviations

HIV-2: Human Immunodeficiency Virus Type 2; HIV: Human Immunodeficiency Virus; HIV-1: Human Immunodeficiency Virus Type 1; CRF: Circulating Recombinant Form; VL: Viral Load; PBMCs: Peripheral Blood Mononuclear Cells; AIDS: Acquired Immune Deficiency Syndrome; HIVAN: HIV-Associated Nephropathy; PI: Protease Inhibitors; NRTI: Nucleoside Analog Reverse-Transcriptase Inhibitors; PI: Protease Inhibitor; TAMs: Thymidine Associated Mutations; ASC: Asylum Seekers Centre; tMRCA: Time of Most Recent Common Ancestor

Introduction

Human immunodeficiency virus (HIV) is one of the main contributor to global burden of disease. Patients can be infected by two different HIV virus, HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-2 originated in sooty mangabey monkeys (*Cercocebus atys*) of the coastal West Africa [1].

HIV-2 was initially isolated in West African patients and spread to other regions of Africa, Europe, the United States, India and to the former Portuguese colonies such as Brazil, Angola, Mozambique [2,3]. To date, HIV-2 is endemic in West Africa while among European countries the majority of the cases are reported in Portugal and France. The current number of HIV-2 cases in the above regions is higher than older estimates (Centers for Disease Control. Factsheet HIV Type 2. Available at: http://wonder.cdc.gov/wonder/prevguid/m0038078/m0038078.asp) due to widespread immigration to the United States and Europe and to commercial ties. These latter factors along with the international travels contributed also to the global diffusion of HIV-2 infection.

HIV-2 comprises eight different groups (A-H), of which groups A and B are responsible for the vast majority of cases identified so far. Furthermore, these two groups present a different circulation pattern in West Africa: group A is widely present in all areas, while group B is mainly found in Ivory Coast, Ghana, Burkina Faso and Mali [4]. The other groups have been reported in only a few individuals. Groups C, D, E, and F were found in rural areas of Sierra Leone and Liberia and group G in the Ivory Coast [5-7]. In HIV-2-infected individuals the presence of a circulating recombinant form (CRF), 01_AB, has been detected [8] by sequencing the complete virus genome from one Japanese patient infected in Japan and two Nigerians patients most likely infected in their country of origin. To date there is no other recombinant form described for HIV-2.

In Italy few studies have been published on this topic [9-16]; mostly case reports. In general, there is a lack of updated estimates on HIV-2 infection.

This review provides information and updates on the transmission, clinical presentation, antiretroviral therapy, diagnostic tests, molecular epidemiology, historical dispersal patterns of HIV-2 infection. Plagiarism has been double-checked with CopySpider v1.4.2 and Quetext (https://www.quetext.com/) using various setting, the results of the analysis have been discussed by all the authors and plagiarism has been excluded.

Transmission

HIV-2 has a lower transmission efficiency than HIV-1, even thought the transmission routes are the same: sexual contact, blood-borne exposure (blood transfusion, shared needles), and perinatal transmission [17]. The lower infectivity of HIV-2 is likely related to lower RNA levels, so sexual transmission is reduced by 5- to 9-fold, and vertical transmission by 10- to 20-fold, in comparison to HIV-1 [18]. In Gambia, the antenatal geometric mean plasma viral load in pregnant women with HIV-2 infection was 410 copies/mL, which was 37-fold lower than the viral load in women with HIV-1 infection (15,100 copies/mL). Actually, the mother-to-child transmission rate of HIV-2 was 4%, 6-fold lower than HIV-1 (24.4%) [19]. Similar observation was made in Ivory Coast in 1994 [20]. In this prospective cohort of women, the perinatal transmission rate was lower in subjects with HIV-2 (1.2%) than those with HIV-1 (24.7%) with a relative risk 21-fold lower for HIV-2. In addition, a prospective cohort study carried out on Senegal-heterosexual-female sex workers showed that the spread of HIV-2 was lower than that of HIV-1 [21] suggesting a lower infectivity of HIV-2 compared to HIV-1.

Clinical presentation and outcome

The HIV-1 and HIV-2 viruses have distinct natural histories, and differences in immune activation or viral proteins may play a role in their diffusion [22-25], although the available data are limited.

Compared to HIV-1, HIV-2 infection can have a longer asymptomatic latency period and slower progression to AIDS [26-28] as well as a slower T lymphocyte CD4 depletion [29,30] and a lower plasma viral load (VL) [28,31]. It was observed a high probability of AIDS-free survival 5 years after seroconversion (100%) compared to those with HIV-1-infection (67%) [27]. Still, HIV-2 infection can lead to clinical AIDS [32,33] and death [34-36].

The rate of progression to AIDS in HIV-2 patients is variable, some subjects develop advanced immunodeficiency and AIDS-related complications similarly to HIV-1 infection, whereas others have normal survival or progress very slowly [37,38]. These latter observations led some authors to hypothesize that HIV-2 might prevent subsequent HIV-1 infection. The authors measured the seroincidence of HIV-1 and HIV-2 among Senegalese female sex workers over a 9 years period. It was found that prostitutes infected by HIV-2 had a lower incidence of subsequent HIV-1 infection compared to seronegative women [39]. This observation was confirmed some years later by *in vitro* studies where peripheral blood mononuclear cells (PBMCs) obtained from HIV-2 infected subjects were resistant to *in vitro* infection by HIV-1 [40]. However, cohort based studies have concluded that HIV-2 does not protect against acquisition of HIV-1 infection [41-44].

The AIDS defining events can be similar in HIV-2 and HIV-1 patients (tuberculosis, esophageal candidiasis, wasting syndrome, cerebral toxoplasmosis, disseminated intracellular Mycobacterium avium, cryptococcosis, cryptosporidiosis, cytomegalovirus disease, Kaposi's sarcoma, AIDS dementia complex, recurrent bacterial pneumonia) [45-47], as reported in the Gambia's study where the wasting syndrome and pulmonary tuberculosis frequently occurred in both infections [33]. Similarly, cases of progressive multifocal leukoencephalopathy have been frequently reported also in HIV-2 patients [46-48].

Other clinical conditions such as cranial neuropathy [49] and non-immune thrombocytopenia in the setting of NK/T cell lymphoma [50] and HIV-associated nephropathy (HIVAN) [51] are reported less frequently in HIV-2 patients.

Treatment and resistance

Therapeutical options for HIV-2-infected patients are more restricted in comparison with HIV-1, for which antiretroviral compounds were designed. HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors, such as nevirapine and efavirenz, due to the presence of mutations at positions 181 and 188 of the reverse transcriptase, as well as to fusion inhibitors [52,53].

HIV-2 also showed a decreased susceptibility to some protease inhibitors (PI), with only darunavir, lopinavir and saquinavir being fully active among all nine of PI available [54-56]. Therapeutical management based on viral load monitoring and drug resistance testing is of great importance to avoid the emergence of complex resistance patterns. However, due to few available data and to the lack of randomized clinical trials, no genotypic drug resistance interpretation's algorithm is available for HIV-2 but a drug resistance mutations list has been drawn by a European Consortium and is regularly updated [57,58]. A prevalence around 5.0% of transmitted drug resistance was identified in different studies [58-61].

Regarding NRTI drug class acquired resistance, it has been described in the FrenchANRSHIV-2 cohort where the three key resistance mutations K65R, Q151M, and M184V were frequently selected in HIV-2-infected patients in virological failure [62]. Two of these mutations (K65R and Q151M) generate a high level of resistance for most of NRTI drugs, leading to a high level of cross resistance [62]. Thymidine Associated Mutations (TAMs) are rarely selected in case of virological failure with the exception of S215Y/F and codon 215 revertants. Additionally, K70N/R was described in some HIV-2-infected patients in virological failure [62,63]. The presence of TAMs does not confer an increase in NRTI resistance level, due to the fact that HIV-2 reverse transcriptase has a much lower ability to excise zidovudine monophosphate than HIV-1 reverse transcriptase [64,65].

Regarding PI drug class, the selection of the V47A mutation is very common in case of treatment failure with lopinavir [66]. Mutations V47A, I82F and I54M cause a high level of phenotypic resistance to lopinavir, and to darunavir for the I54M mutation [56]. Thus, the cross-resistance is higher than in the HIV-1 because of the limited number of active PI on HIV-2. Furthermore, the presence of a single I54M, I84V or L90M mutation affects the phenotypic susceptibility of the three most active PI against HIV-2 [54-56]. Recent studies confirmed the potency of integrase inhibitors on wild-type integrase HIV-2 clinical isolates [67], suggesting that combinations based on INSTIs are effective and safe treatment options for these individuals. However, resistance mutations to INSTIs resulted to be frequently selected in failing patients [68].

Testing

The screening of HIV-2 infection is indicated in at risk individuals or people in whom an HIV-1 western blot exhibits an unusual indeterminate result. The diagnostic tests capable of detecting HIV-2 infection used enzyme-linked immunosorbent and chemiluminescent immunoassay methods. While these immunoassays detect both HIV-1 and 2, they do not differentiate between the 2 types of HIV infection. FDA-approved rapid antibody test that detects and differentiates HIV-2 infection, that is, the Bio-Rad Laboratories Multispot HIV-1/HIV-2 Rapid Test [69]. Supplemental HIV-2 antibody tests are commercially available at reference testing laboratories, such as Focus Diagnostics, Inc. Quest Diagnostics Inc. (HIV-2 antibody immunoblot). Laboratory-developed HIV-2 western blot assays are performed by the California Department of Health Services and by various research laboratories. Supplemental HIV-2 antibody assays that are available commercially in other countries include the INNO-LIA HIV I/II Score (Innogenetics, NV) and HIV-2 Blot, version 1.2 (MP Biomedicals, LLC).

To our knowledge, one quantitative HIV-2 RNA assay (HIV-2 Real Time RT-PCR Kit, Lfe River™, Shanghai ZJ Bio-tech Co., Ltd., China) has been validated for *in vitro* diagnostics and is available on the market [13]. In a study by Rodes., *et al.* [70], NucliSens EasyQ assay (version 1.1) has been successfully used to quantify HIV-2 subtype A RNA in plasma of infected patients detecting HIV-2 in 34 (45%) of 75 specimens.

A qualitative assay used with the Abbott m2000 platform performed well in detecting HIV-2 RNA in PBMCs from patients serologically reactive to the virus, HIV indeterminate or HIV undifferentiated individuals with undetectable plasma RNA. So, the assay could be used for confirming HIV-2 infection in HIV testing algorithm.

Epidemiology

HIV-2 infection is primarily restricted to West Africa, isolated in patients with AIDS originating from Cape Verde and Guinea-Bissau [3,71]. One to 2 million people in West Africa (Guinea-Bissau, Gambia, Senegal, Cape Verde, Cote d'Ivoire, Mali, Sierra Leone, and Nigeria) are infected with HIV-2 [72] with a prevalence of 1% of the national population in the late 1980s (Centers for Disease Control. Factsheet HIV Type 2. Available at: http://wonder.cdc.gov/wonder/prevguid/m0038078/m0038078.asp). HIV-2 prevalence has been declining in several West African countries among younger people [73,74]. In rural area of northwestern Guinea-Bissau, the HIV-2 prevalence dropped from 8.3% in 1990 to 4.7% in 2000, while in the same period the same HIV-1 prevalence increased from 0.5% to 3.6% [75]. In West Africa, between 10 and 20% of HIV infections include HIV-2 with also dually infected or reactive HIV-1/HIV-2 individuals [76,77]. Other West African countries reporting HIV-2 are Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, São Tomé, Senegal, and Togo. HIV-2 prevalence in Angola, Mozambique or other African countries is higher than 1%. The seroprevalence of HIV-2 infection has been analysed in selected groups of patients as Indian female prostitutes. A total of 809 sera from Maharashtra and of 61 sera from Goa were analyzed. Among the HIV-positive sera from Bombay, 4% were positive for HIV-2 while in the Goa group, 33% resulted HIV-2 positive. HIV-2 infections were first detected in India in 1990 [78]. Before that time, Asia was believed to be free HIV-2 [78].

In a community-based prevalence study carried out in Guinea Bissau, 4.7% of the individuals screened were HIV-2 positive, and the seroprevalence increased with age. Among the seropositive HIV-2 individuals, the relative risk of dying for was 60.8 in children and 5.0 for adults [79].

Similarly, in a rural area of the same country, the prevalence of HIV-2 among the people tested was 7.9% [80].

The prevalence of HIV-2 is a growing concern in certain parts of Europe [13].

Since the year 1980s, HIV-2 infection has been reported in Portugal, probably spreading from Guinea-Bissau where the highest prevalence is registered (up to 8 - 10%) during the war of independence through contacts between colonial army and sex-workers [81]. In Italy attention regarding this neglected infection recently increased because of the migratory effect, leading a case of HIV-2 in a migrant individual in the Asylum Seekers Centre (ASC) as well as some cases in foreigners and native citizens in 2013 [9,11].

The cumulative number of notified HIV-2 infections in Portugal was 1,813 as of December 2008. In the early 1990s, HIV-2 infection accounted for approximately 10% of the annually diagnosed AIDS cases, while it decreased to 2.6% in 2000 and 2.3% in 2008.

he first case of HIV-2 seropositivity in Austria was confirmed in 1993 [82]. Six further cases of confirmed HIV-2 infections were noted in Austria in patients originated from West Africa.

In France HIV-2 represents 1 to 2% of new HIV diagnosis [4].

In Spain in the year 2016, 338 cases of HIV-2 infection, represented by 72% Sub-Saharan Africans and 16% native Spaniards with HIV-1 and HIV-2 coinfection in 9% of them, has been reported [83].

In 1987 in a West African woman migrated in the United States was reported the first case of HIV-2 already progressed to AIDS. In USA, New York city, a new algorithm for HIV diagnosis has been implemented leading to the discover of 62 confirmed or probable cases of HIV-

2 infection [84]. The majority of HIV-2 positive patients were from Africa but since the large number of immigrants from HIV-2 endemic areas, the current number of cases could be probably higher than older estimates.

HIV-2-Subtype A accounts for the majority of HIV-2 infections and is the predominant genotype in Guinea-Bissau and Europe [43,85].

Currently, in Italy few studies have been published on HIV-2 cases [9-16]. Some works reported only few cases in patients of African origin. Particularly, the study by Costarelli., *et al*. [15] focused on the screening for HIV- 2 infection in African patients followed at the Clinic of the Institute of Infectious and Tropical Diseases of the University of Brescia (Northern Italy), and investigated the HIV- 2 prevalence among HIV - positive African population. Among 220 HIV-positive African patients, only 141 (141/220, 64%) presented for blood examinations and were included in the survey. The authors found a total of 16 patients positive for HIV-2 (16/141, 11%).

The study by Ciccozzi., *et al*. [13] reported a case of HIV-2 infection in an Italian patient, whose sequence was related with that of a patient from France. This study also showed that the common ancestor of these two viruses was in Africa. Another study by Ciccozzi., *et al*. [12] reported an HIV-2 infection in a 44-year-old Italian woman, who contracted the infection in Italy after having a sexual relationship with a man from Senegal. The study by D'Ettorre., *et al*. [11] reported 12 HIV-2-infected patients. Of these patients, six were from Africa (50%), one from Portugal (9%), one from Cape Verde (9%), and four from India (36.5%). Maiello., *et al*. [86] reported a severe herpetic whitlow (HSV lesion) in a 33-year-old cook who became seropositive to HIV-1 and HIV- 2 in January 1992 because of sexual contacts with Nigerian prostitutes.

Phylogeny

This review provides information on the spatiotemporal dynamics of HIV-2, molecular epidemiology and phylogeographic reconstruction of the historical dispersal patterns of HIV-2 infection.

The date of the introduction of HIV-2 into humans was estimated in different works. When concatenated *env* and *gag* sequences were studied, the estimated time of most recent common ancestor (tMRCA) was 1940 ± 16 for HIV-2 group A and 1945 ± 14 for HIV-2 group B [87]. By analyzing separately *pol*, *env* and *gag* genes, the tMRCA estimates were 1905 (1857-1949), 1942 (1921-1959) and 1932 (1906-1955), respectively [88], for the group A, and 1914 (1868-1955), 1937 (1914-1958) and 1935 (1907-1961), respectively [88] for group B. Despite these analyses were conducted with a limited number of HIV-2 sequences, these findings were confirmed for HIV-2 group A in a large phylogeographic study [89] which estimated the virus introduction in 1938 (1928-1947). Another work reported for HIV-2 group B *pol* gene an origin in 1957 (1927-1980) [13].

Regarding the phylogeography, two main works have been published, one regarding HIV-2A [87] and the other HIV-2B [13].

The first work indicated that Guinea-Bissau and Cape Verde, together with Cote d'Ivoire and Senegal, acted as viral source populations in the early epidemic history of HIV-2A. Starting from these countries the virus spread at neighboring countries, while in Europe viral migration initially established in Portugal and France and later spread to other countries.

Differently, the phylogenetic analysis revealed, on 12 HIV-2 cases coming from different geographic regions but all registered in Italian medical care centers, that this variant seems to be closely related to sequences from Ivory Coast and/or France.

One sequence has been classified as a possible recombinant between type A and B, whereas four sequences classified as type A were from India and the remaining seven sequences as HIV-2 type A were all originating from different African countries [11].

From there, a close inspection of viral flow revealed a scenario of multiple introductions resulting in different paths of transmission clusters involving African and European countries.

Data regarding the introduction of HIV-2 in different countries remains to be clarified due to the limited availability of dated sequences. Recently, Cella., *et al*. [9] described a case of HIV-2 infection in a migrant individual in the Asylum Seekers Centre (ASC) in Italy. Bayesian

evolutionary analysis revealed that the HIV-2 sequence from this migrant dated back to 1986 and formed a subcluster that includes sequences from Guinea Bissau. This was coherent with the history of the migrant who lived in Guinea Bissau from his birth until 1998, when he was 13 years old, then lived in Gambia from where moved to Italy.

Conclusion

A molecular epidemiological surveillance system for HIV-2 is becoming critical because of the increase in migration from endemic areas to European countries and mostly in Italy as the most important first landing place from immigrants coming from African countries. A correct diagnosis of HIV-2 infection is essential for planning the best therapeutic treatment. Therefore, it is important to use valid diagnostic tools as quantitative Real-time PCR assays to determine the HIV-2 viral load and the phylogenetic analysis to identify in the infected patients the type of HIV-2 as well as trace the origin of the infection and the spread of the virus.

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