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Update of HIV-2 diagnostics and resistance testing

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Epidemiology

HIV-2 and its different groups, A to H, are orginating from West African sooty mangabey monkeys. By this transmission route HIV-2 is a zoonosis with a consecutive permanent transmission cycle in humans, mainly by sexual contact as described for HIV-1, perhaps as early as 1924 or latest 1956 (Lemey et al, 2003; Poulsen et al, 2000;Valadas et al, 2009). World wide around 1 to 2 million people are HIV-2 infected, the main number lives in West Africa, but also in Europe, in Portugal and France, and in further countries as Angola, Mocambique, and India. A cluster of HIV-2F was reported from Sierra Leone in 2008 (Smith et al, 2008).

In France among the 10.184 newly diagnosed HIV cases from January 2003 to June 2006 186 (1.8%) were infected with HIV-2 and 12 (0.1%) with HIV-1 group O (Barin et al, 2007). Most of the HIV-2 infected subjects originated from Africa especially from Ivory Coast, Mali and Senegal; among the 22 European subjects 20 were from France and 2 from Portugal. Three of the HIV-2 infected cases were man who have sex with man (MSM) (Barin et al, 2007).

The number of patients in Portugal is estimated with more than 1.000, who are mainly infected with HIV-2 A, and patient's origin from all over West Africa up to Cameroon. The epidemiologic pattern in Portugal is heterogeneous: the majority of patients in the South are from Guinea Bissau and Cap Verde Island, while in the North mainly Portuguese people are infected. Transmission of HIV-2 by blood transfusion has occurred (Gomes et al, 2003). The number of newly diagnosed HIV-2 infected is far below 100 per year (Valadas et al, 2009).

Epidemiological data from Germany are scare. According to data given at the conference around 100 HIV-2 infected are living in Germany. Patients are treated and followed up in München, Frankfurt, Düsseldorf, Berlin and Hamburg. Data from the Robert Koch Institute in Berlin (RKI) state a number of HIV-2 infected between 29 to 35, mentioning as well around 78 dual infections (for specification between dual reactivity and dual infection see below). There is a trend for HIV-2 being overgrown by HIV-1M (da Silva et al, 2008).

Clinical course

In contrast to sooty mangabey monkeys which have a high viral load of 10^6 to 10^7 particles per ml blood, viral load in humans is generally low and thus not a good marker for clinical follow up of patients. The main parameter for patient follow up remains the CD4 cell number. In most patients with a CD4 cell number >500/µl no viral load is measurable. In patients with CD4 cells between 350-500/µl a deterioration is expected after 6 months, in those < 350/µl a deterioration within 3 to 4 months.
HIV-2 enters cells via the CD4 receptor as HIV-1, but additionally using coreceptors as BOB, BONZO, CCR3 and not only CCR5 or CXCR4. Around 80% of HIV-2 infected are slow progressors (MacNeil et al, 2007), in 20% the clinical course is similar to HIV-1M.

Treatment

Compared to the available therapy of HIV-1M, the success rate to treat the HIV-2 infection is disappointing. Experiences from follow up of patients tell to start early with the treatment. NNRTI do not inhibit the reverse transcriptase. Substances that can be used

generally are 2 NRTI and 1 PRI. Combination of Tenofovir (TDF) and Emtricitabin (FTC) or Abacavir (ABC) and Lamivudin (3TC) are recommendable, while Stavudine (D4T) and Didanosin (DDI) are of minor efficacy for inhibition of the reverse transcriptase. Resistance associated mutations are Q151M, which is seldomly seen in HIV-1M, and M184V and K65R. Protease inhibitors that are frequently used are boosted Lopinavir (LPV) and Saquinavir (SQV) and Darunavir (DRV). Protease mutations inducing failure are L90M, V71I and I84V, perhaps also V47A. Further PRI in use are Amprenavir (APV), Atazanavir (ATV) and Tripanavir (TPV).
Raltegravir (RAL) is inhibiting also the HIV-2 integrase. For blocking the CCR5 receptor with Maraviroc (MVC) there is no clinical experience, but there is some in vitro activity seen.

Diagnostics
Antibody detection is done by the commercially available HIV-1/HIV-2 combination assays, and reactivity confirmed by western blot (Marcelino et al, 2006). Dependent on the antibody titer and epitope recognition only around 10% of double reactive specimens in the HIV-1 and HIV-2 western blot are pure HIV-2 infections. In Germany, related to the high HIV-1 prevalence, a very low number of sera with double reactivity indicate double infection. In conclusion a western blot for HIV-1 and HIV-2 has to be performed simultaneously, when necessary with serum dilution 10 and 100 fold.
In ambiguous cases PCR analysis of the proviral DNA from lymphocytes is the preferred method for analysis of dual infection; conserved amplification sites are published in the LTR and integrase of HIV-2.
Double infections are rare: in France 0.2% of the HIV-2 infected were coinfected with HIV-1 (Barin et al, 2007). In Germany there should presently be only 1 or 2 HIV-1/HIV-2 dual infected cases.

Viral load: quantitative determination of the HIV-2 RNA in plasma cannot be performed by commercially available assays (Ariyoshi et al 2000). The presently used in house assays amplify all HIV-2A, some problems may arise with HIV-2B (Berry et al, 2001) and more problems with the other HIV-2 groups. It is recommendable to use proviral DNA of the patient's lymphocytes as a further amplification control, besides the test control.

Drug resistance testing: primer for the amplification of the protease, reverse transcriptase and integrase are available. As described for the viral load determination group A viral RNA can be amplified and sequenced. The problem arises with the definition of key amino acids and their relevance for the activity of the enzyme, and the 'natural resistance' linked to the mutated amino acids compared to HIV-1M (Gottlieb et al, 2008). The interpretation algorithm of ANRS (Agence National de Recherche Scientifique) (Damond et al, 2005) and the British Guidelines offer some help (Smith et al, 2001). HIV-GRADE is until now not adapted to HIV-2.

Drug resistance testing and quantification of the viral load for HIV-2 are performed in Germany in München (Pettenkofer Institute), Frankfurt (Institute of Medical Virology), Hamburg (Labor Lademannbogen, Labor Fenner), Berlin (Robert Koch Institute, Labor Berg, Institute of Virology Charité).

Reference material
Presently this is only available in small amounts in München and Frankfurt. There are enough virus isolates to establish a national reference bank.

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