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Review

Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection

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ABSTRACT

One to two million people worldwide are infected with the human immunodeficiency virus type 2 (HIV-2), with highest prevalences in West African countries, but also present in Western Europe, Asia and North America. Compared to HIV-1, HIV-2 infection undergoes a longer asymptomatic phase and progresses to AIDS more slowly. In addition, HIV-2 shows lower transmission rates, probably due to its lower viremia in infected individuals. There is limited experience in the treatment of HIV-2 infection and several antiretroviral drugs used to fight HIV-1 are not effective against HIV-2. Effective drugs against HIV-2 include nucleoside analogue reverse transcriptase (RT) inhibitors (e.g. zidovudine, tenofovir, lamivudine, emtricitabine, abacavir, stavudine and didanosine), protease inhibitors (saquinavir, lopinavir and darunavir), and integrase inhibitors (raltegravir, elvitegravir and dolutegravir). Maraviroc, a CCR5 antagonist blocking coreceptor binding during HIV entry, is active *in vitro* against CCR5-tropic HIV-2 but more studies are needed to validate its use in therapeutic treatments against HIV-2 infection. HIV-2 strains are naturally resistant to a few antiretroviral drugs developed to suppress HIV-1 propagation such as nonnucleoside RT inhibitors, several protease inhibitors and the fusion inhibitor enfuvirtide. Resistance selection in HIV-2 appears to be faster than in HIV-1. In this scenario, the development of novel drugs specific for HIV-2 is an important priority. In this review, we discuss current anti-HIV-2 therapies and mutational pathways leading to drug resistance.

Contents

1. Introduction

According to the latest estimates from UNAIDS, there are approximately 34 million people worldwide living with the human immunodeficiency virus (HIV), with a prevalence rate (i.e.

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percentage of HIV-infected people 15–49 years old) of 0.8% (UNAIDS, 2013). Although HIV type 1 (HIV-1) is responsible for most of the global AIDS pandemic, there are about one to two million people infected with HIV type 2 (HIV-2), most of them in Senegal, Guinea Bissau, Gambia, Ivory Coast and Cape Verde (Gottlieb et al., 2008a). The highest prevalence has been observed in Guinea Bissau where up to 8–10% of the adult population could be infected (Poulsen et al., 1993). In addition to being endemic in West Africa, during the last two decades HIV-2 has spread to nineteen different countries in Europe, Asia and North America (Matheron et al., 1997; Nam et al., 2006; Barin et al., 2007; Gurjar et al., 2009; Valadas et al., 2009; Torian et al., 2010). In Europe, relatively high prevalences of HIV-2 infection have been reported in Portugal (Valadas et al., 2009) and France, where surveillance studies showed that around 2% of the new infections in 2003–2006 were caused by HIV-2 (Barin et al., 2007).

HIV-2 was first isolated in 1986 (Clavel et al., 1986, 1987). The genome organization of HIV-2 (Fig. 1) was determined from virus obtained from an AIDS patient from Cape Verde islands, and designated as the ROD isolate (Guyader et al., 1987). At present, HIV-2 strains are classified in eight groups named A through H (Damond et al., 2004; Santiago et al., 2005), although only groups A and B cause epidemics (Fig. 1). Isolates from group A are responsible for most HIV-2 infections worldwide, although it is most prevalent in Guinea Bissau (Rowland-Jones, 2006), while HIV-2 group B is more frequent in Ivory Coast and Ghana. ROD is a prototypic HIV-2 group A strain while EHO is usually considered the reference strain for group B. Phylogenetic relationships between HIV-2 groups A and B and HIV-1 clades and selected simian immunodeficiency viruses (SIV) are depicted in Fig. 2.

Recombinant HIV-2 containing sequences of groups A and B have been identified in Cameroon and the Ivory Coast (Gao et al., 1994; Yamaguchi et al., 2008), and evidence of a circulating recombinant form (HIV-2 CRF01_AB) has been recently reported in Japan (Ibe et al., 2010). Infections with groups C to G have been detected only in one or two individuals and available evidence indicates that in those cases infection did not lead to immune suppression (Gao et al., 1994). An exception is the highly divergent HIV-2 group H strain that was isolated from a man suffering immunodeficiency in the Ivory Coast (Damond et al., 2004). More recently, a large screening study in villages close to Tai National Park (in the south-west of Ivory Coast) led to the identification of a novel HIV-2 variant (HIV-2-071C-TNP03) infecting an 8-year old boy, and unrelated to any of the previously defined HIV-2 groups (Ayouba et al., 2013).

HIV-2 groups derive from independent transmissions from sooty mangabeys (*Cercocebus atys*) to humans (Santiago et al., 2005; for a recent review, see Peeters et al., 2013). Sooty

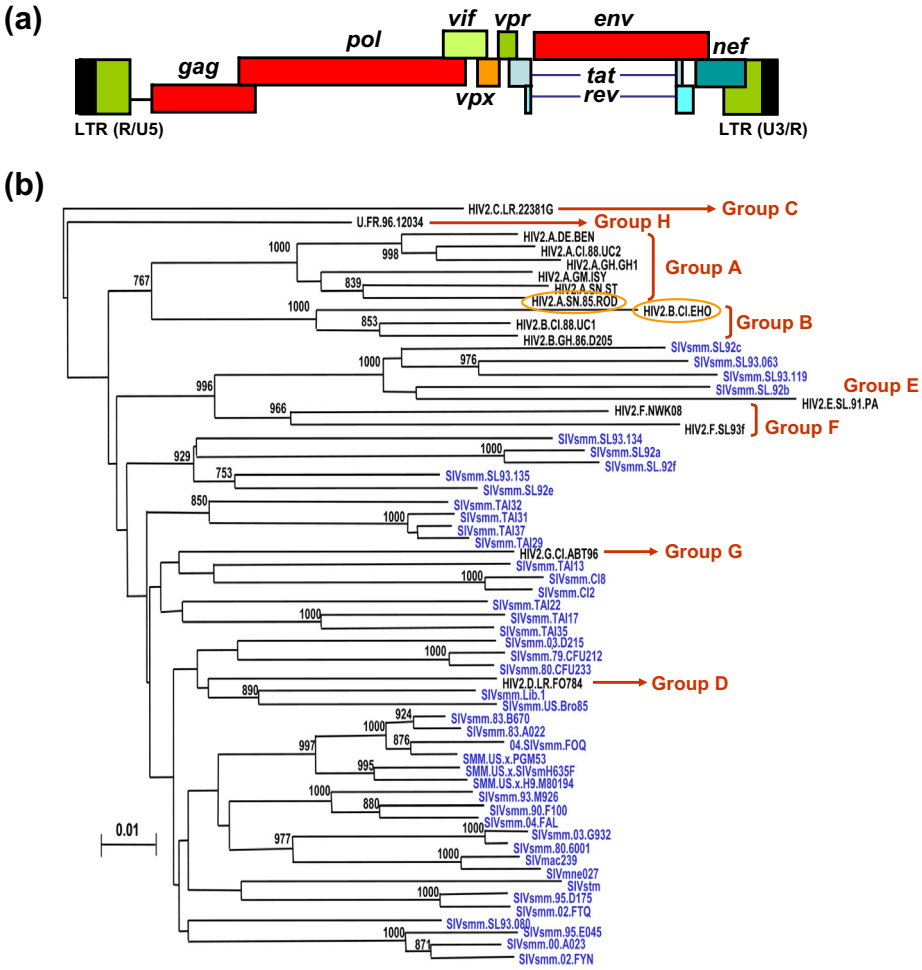

Fig. 1. HIV-2 genome organization and *gag* phylogenetic tree of HIV-2 and simian immunodeficiency virus strains. (a) Major (*gag*, *pol*, *env*) and accessory and regulatory genes (*vif*, *vpx*, *vpr*, *tat*, *rev*, *nef*) in the HIV-2 genome. Antiretroviral drug targets such as the protease, the reverse transcriptase and the integrase are encoded within the *pol* gene. (b) Phylogenetic tree based on *gag* nucleotide sequences and showing the group classification of HIV-2 isolates (adapted from Smith et al., 2008a). Reference HIV-2 strains such as ROD (group A) and EHO (group B) are indicated with an orange oval.