

Do the HIV-1 subtypes circulating in Italy resemble the Red Queen running in Carroll's novel?

Massimo Ciccozzi¹, Isabella Bon², Marco Ciotti³

¹Department of Infectious, Parasitic and Immunomediated Disease, Istituto Superiore di Sanità, Rome, Italy;

²Section of Microbiology of the Department of Haematology and Oncologic Sciences, University of Bologna;

³Laboratory of Molecular Virology, University Hospital Tor Vergata, Rome, Italy

SUMMARY

The human immunodeficiency virus type 1 (HIV-1) pandemic is currently in its third decade and approximately 35 million people are infected worldwide. HIV-1 genetic variability results in 9 phylogenetic subtypes and several circulating recombinant forms (CRFs). In Italy, the first phase of the HIV epidemic was mainly confined to the intravenous drug users (IDU) risk group, moreover most studies have focused on different aspects of the non B subtype such as drugs and therapeutic protocols, laboratory methodologies (heteroduplex mobility assay, PCR screening methods) for the identification of phenotypic variants. These studies were mostly locally conducted. In this context, the Red Queen Hypothesis might be suggestive. In the first original expression that comes from Chapter 2, *Through the Looking Glass*. To improve our knowledge, in the near future, we will need to investigate the demographic and spatiotemporal history of different HIV-1 subtypes circulating in Italy in a large data set of sequences, involving a sample size comparable with the Italian population. To monitor the genetic evolution of the HIV-1 in a large data-set represent an essential strategy to control the local as well as the global HIV-1 epidemic and to develop efficient preventive and therapeutic strategies, with a great impact in clinical practice.

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The human immunodeficiency virus type 1 (HIV-1) pandemic is currently in its third decade and approximately 35 million people are infected worldwide. Despite some progress, the worldwide epidemic has not been slowed, and the proportion of newly HIV-1 infected individuals is increasing. One of the hallmarks of HIV-1 is the virus's ability to generate multiple genetic variants (more fit and virulent) as a consequence of high rates of mutation and recombination during viral replication.

HIV-1 genetic variability results in 9 phylogenetic subtypes (A-K), approximately equidistant from one another, and several circulating recombinant

forms (CRFs), derived from recombination events occurring between different HIV-1 subtypes co-circulating in a specific geographic region (Buonaguro *et al.*, 2007a, 2007b, 2008).

In Italy, the first phase of the HIV epidemic was mainly confined to the intravenous drug users (IDU) risk group, with an absolute predominance of HIV-1 B clade, as other Western Countries. However, the transmission pattern is changing over time and, in the 2004-2005 period, heterosexual contacts accounted for the 40.3% of total HIV-1 infections (Suligoi *et al.*, 2009) and also an increasing spread of HIV-1 non-B genetic variants has been observed. This phenomenon seems to be strictly linked to the growing number of immigrants from non-Western Countries, where several non-B clades and CRF are prevalent. This gradual change in HIV-1 epidemic is coupled with the recent identification of HIV-1 isolates genetically related to novel subtypes for the Italian epidemic (Giuliani *et al.*, 2009). In Italy, the estimated percentage of infection with non-B sub-

Corresponding author

Massimo Ciccozzi

Department of Infectious

Parasitic and Immunomediated Disease

Istituto Superiore di Sanità

Viale Regina Elena - Italy

E-mail: massimo.ciccozzi@iss.it

types has been reported to range from 4.6% to 19.4%, confirming a significant increase in non-B subtype (Balotta *et al.*, 2001; Tramuto *et al.*, 2004; Monno *et al.*, 2005; Ciccozzi *et al.*, 2007; Baldanti *et al.*, 2008; Longo *et al.*, 2008; Buonaguro *et al.*, 2008; Giuliani *et al.*, 2009). Moreover most studies have focused on different aspects of the non B subtype such as drugs and therapeutic protocols, laboratory methodologies (heteroduplex mobility assay, PCR screening methods) for the identification of phenotypic variants (Romano *et al.*, 2000; Visco-Comandini *et al.*, 2001; Amendola *et al.*, 2002; Visco-Comandini *et al.*, 2003; Buonaguro *et al.*, 2004; Nicastrì *et al.*, 2004; Buonaguro *et al.*, 2005; Tagliamonte *et al.*, 2006; Buonaguro *et al.*, 2007; Razzolini *et al.*, 2007; Monno *et al.*, 2009; Bracciale *et al.*, 2009). In this context, the Red Queen Hypothesis might be suggestive. In the first original expression that comes from Chapter 2, *Through the Looking Glass* (Carroll, L. 1872), the Red Queen begins to run, faster and faster, to the top of the hill; Alice is also running following the Red Queen, but she is astonished observing that nobody is moving and when they stopped running, they were in exactly the same place. The Red Queen answered back: "Now, here, you see, it takes all the running you can do to keep in the same place". Even if the "Red Queen" hypothesis is normally used to describe two similar ideas, it could explain the Italian epidemiologic data on the real and true prevalence of HIV-1 non-B subtypes circulating in our country.

To date, little is known on HIV-1 subtypes diffusion, the role of viral evolution in the transmission and disease progression. Most studies, performed on a limited number of patients, not always representative of the HIV Italian infected population, reported different percentages of the prevalence of non B variants circulating (Balotta *et al.*, 2001; Tramuto *et al.*, 2004; Monno *et al.*, 2005; Ciccozzi *et al.*, 2007; Buonaguro *et al.*, 2008; Longo *et al.*, 2008; Baldanti *et al.*, 2008; Giuliani *et al.*, 2009).

To improve our knowledge in the near future we will need to investigate the demographic and spatiotemporal history of different HIV-1 subtypes circulating in Italy in a large data set of sequences, involving a sample size comparable with the Italian population. Although in the local population the HIV-1 subtypes appear to have a lim-

ited evolution, the continuous introduction and diffusion of these genetic variants could progressively change the overall scenario and drive the need of adapting the diagnostic and treatment strategies currently used (Tagliamonte *et al.*, 2006; Buonaguro *et al.*, 2007). Moreover, few data are currently available on the genetic background of a viral isolate (as indicated by subtype) and the true meaning of resistance-associated mutations. Further studies are necessary to understand how the HIV-1 is changing over time in Italy, focusing on the molecular characterization of several viruses's sub-genomic regions, and to shed light on the hidden modifications of HIV-1 genome under antiviral pressure, able to favor resistance, even without clear evidence of its appearance. Moreover it will be important to estimate the putative origin and the time frame for the introduction of each new HIV-1 clade and CRF in Italy. In this regard, the general strategy of sequencing and performing phylogenetic analyses only on the *pol* genomic region could result in missing the identification of novel CRFs in the Italian epidemic. Finally, the study and monitoring of the genetic evolution of the HIV-1 on a large data-set represent an essential strategy to control the local as well as global HIV-1 epidemic and to develop efficient preventive and therapeutic strategies, with a great impact in clinical practice.

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