Update Article

HIV - 1 SUBTYPES, ITS IMPLICATIONS AND VIRAL DYNAMICS

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ABSTRACT

Subtyping of HIV has important implications for developing candidate vaccine and understanding the biological behaviour and dynamics of HIV transmission in various populations. The third variable region (V3) in the envelope gene of HIV-1 has been shown to be a major determinant influencing a number of biological characteristics of the virus. HIV-1 evolves by rapid mutation and by recombination, both processes actively contributing to its genetic diversity. Most of the multiple genetic subtypes and intersubtype recombination of HIV-1 that comprise the global pandemic have not been characterized by full genome sequencing. The development of an effective human immunodeficiency virus type-1 (HIV-1) vaccine is likely to depend on knowledge of circulating variants of genes other than the commonly sequenced *gag* and *env* genes.

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KEY WORDS : Genetic variations; HIV-1 subtypes; Recombinants; Viral dynamics.

Introduction

Human immunodeficiency virus (HIV) is the most significant emerging pathogen. Since recognition in 1981 of the acquired immune deficiency syndrome (AIDS), HIV has produced a world wide epidemic. The first indication that AIDS could be caused by a retrovirus came in 1983 when Barre-Sinoussi et al [1] at the Pasteur Institute recovered a reverse transcriptase containing virus from the lymph node of a man with persistent lymphadenopathy syndrome (LAS). However, further studies in 1983 by Montagnier and co workers [2] indicated that this human retrovirus was similar to HTLV in infecting CD4⁺ lymphocytes. Gallo et al [3] reported characterization of another human retrovirus distinct from HTLV which they called HTLV III. Levy and co-workers in the year 1984 [4] reported identification of a retrovirus from an AIDS patient in San Francisco and named it as AIDS associated retrovirus (ARV). Rabson et al in the year 1985 [5] found that the proteins and the genome of the ARV were distinct from HTLV. For all these reasons, in 1986 the International Committee on Taxonomy of viruses [6] recommended giving the ARV a separate name, the human immunodeficiency virus (HIV).

Genetic Subtypes of HIV-1 :

HIV-1 has been divided into three genetic groups, based on phylogenetic reconstruction using nucleotide sequences [7,8,9]. The majority of the isolates fall into

the "M" or Major group while a small number of divergent constitute the "O" or Outlier group. The "N" group till date consists of a few isolates obtained in Cameroon, which are distinct from the M and O group isolates in the phylogenetic relationship. The "M" group again has been subdivided into distinct subtypes or clades "A to K" [10] (Table-1). Divergent or "Outlying" strains of HIV-1 outside group "M" has been reported and is provisionally categorized as group "O". Within group "O" some isolates may differ at least as much from each other as the various group "M" subtype differ from each other. HIV-2 has also been phylogenetically classified into subtypes, although the number of sequence isolates remain limited. These subtypes may have evolved from a common human precursor along with the fitful nature of global virus spread. When the increase in HIV-1 genetic variation was analysed within a geographic area in which a single subtype was introduced, a gradual increase in genetic diversity was observed over time [11].

Viral dynamics and genetic variants :

The genetic variation of HIV is extremely high with rapid turnover of HIV virions and infected persons maintain a substantial viral burden during the entire course of infection. Genetic changes in the virus not only between host but even within an individual host at variable times after infection, lead to the formation of a diversified viral population, often referred to as

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TABLE 1

Subtypes	Genotypes	Country of origin
A (Central Africa)	A1	Rwanda
	A2	Ivory coast
	A3	Rwanda
B (North America, Western Europe)	B1	Brazil
	B2	Thailand
	B3	USA
C (South Africa, India)	C1	Malawi
	C2	Zambia
	C3	India
	C4	Brazil
D (Central Africa)	D1	Uganda
	D2	Uganda
	D3	Uganda
E (Thailand)	E1	Thailand
	E2	Thailand
	E3	Central Africa
F (Brazil)	F1	Brazil
	F2	Brazil
G (Russia, Gabon)	G1	Russia
	G2	Gabon
	G3	Gabon
H (Cameroon, Zaire)	H1	Cameroon
	H2	Zaire

quasispecies. Over time, HIV quasispecies also change as one set of variant is replaced by another, presumably a fitter set of variant [12]. More closely related strains share greater genetic similarity as expressed by the sequence of component nucleotides. Rate of mutation and selection pressures vary in different parts of retroviral genome. The polymerase (*pol*) gene, which codes for reverse transcriptase and the *gag* gene which codes for the protein core of the virus, are relatively well conserved among the lentiviruses as compared to the greater variation found in the envelope (*env*) gene which codes for the envelop glycoprotein. Mathematical analysis of the kinetics with which virus particle number drops, and CD4 cells increase in the circulation indicates that the magnitude of the ongoing virus infection and the production required to sustain steady state level of viremia is extraordinarily high [13]. In majority of productively infected cells, the virus replicates at an extraordinarily high rate, generating 10^9 to 10^{10} virions per day with a half-life in plasma of only 6 hours. This results from a relatively short virus life cycle (the time from virion binding to the cell to the release of progeny) of approximately 1.2 days. At least 99% of this large pool of circulating virus must be produced from recently infected cells. CD4 positive lymphocytes, one of the major cell targets that are responsible for virus production in vivo, must also be produced in a very high

number to sustain the high level of HIV replication and release into the circulation. The average life span of these infected cells has been calculated to be approximately two days, with a turn over of an average of two billion cells per day or approximately 5% of the total CD4 lymphocyte population. Viral kinetic studies suggest that the mutant virus population increases exponentially, doubling approximately every two days.

Thus, a rapid and virtually complete replacement of wild type virus by drug resistant virus in the plasma can be demonstrated in only 14-28 days. Viral reverse transcriptase is very error prone and thus appears to give rise readily to changes in genome. As a consequence, even a fairly modest mutation rate of 10^{-5} per base per generation would yield 10^8 - 10^9 mutants per day. Thus, there are endless possibilities for rapid adaptation of the virus to its environment resulting in immune escape mutants. Because of its high mutation rate and strong selection for the emergence of phenotypic variants, the HIV *env* gene evolves rapidly through nonsynonymous nucleotide substitutions and short in frame insertions and deletions [14,15,16]. Such mutations radically alter the properties of the virus and together with silent synonymous nucleotide substitutions, provide the genetic variation used for phylogenetic analysis and molecular epidemiological investigations. The genetically distinct mutants are also immunologically distinct as suggested by cross neutralization experiments using sera and viral isolates from individuals infected with different subtypes indicated that neutralization titres were generally higher using viruses and sera of the same subtypes [17].

Significance of subtyping and its implications :

There are three main reasons for genetic subtyping. First, since different subtypes express different envelope proteins, it is likely to have an effect on vaccine development. This is more so since the principal neutralizing domain within the V3 loop of gp 120 is also a hypervariable sequence. Knowing that genetic variants can escape immune surveillance, information on genetic subtypes becomes important. Secondly, study of subtypes has implications on the biological behaviour of the virus. Mutational trends within the V3 loop among different subtypes may reflect the acquisition of specific biological properties during evolution of HIV-1. Finally, the subtypes help us understand the global HIV epidemic.

The development of globally effective HIV vaccines and immunotherapies is complicated by the high degree of HIV genetic variability, especially in the

envelope glycoprotein, gp120 [18,19]. However, a greater understanding of heterotypic infections occurring between HIV-1 and HIV-2, mixed infections caused by viruses of distinct subtypes within those two HIV-1 and HIV-2 types and multiple infections resulting from different viral strains of the same phylogenetic clade is also needed. This is important because of their potential contribution in broadening the genetic diversity of HIV through recombinant events. Such mixed infections may have a profound and as yet unforeseen impact on viral pathogenesis and on the evolution of the HIV/AIDS pandemic. In addition, naturally occurring mixed infections may have important implications for immunotherapies. If multiple, mixed infections can be sequentially acquired, then vaccination with a component derived from specific HIV variant may not confer protection against subsequent infection with HIV of a different subtype [20,21,22]. Thus, a clearer definition of the role of these infections will have relevance to future vaccine development. Moreover, information on the presence of HIV multiple infections caused by distinct viral subtypes circulating within a population and the long term observation of patients dually infected with distinct HIV strains may contribute to a better understanding of pathogenesis of HIV infections.

Recombinants and HIV mixed infections :

Most of the reported mixed infections represent the mixture of HIV-1 and HIV-2 that have been found mainly in Africa [23], but also in Brazil [24] and India [25], the geographic areas where both types of viruses are present. In contrast, mixed infections caused by viral strains of distinct HIV subtypes within two major HIV-1 and HIV-2 types have been suggested by the discovery of recombinant viral sequences consisting of parts from viruses belonging to different subtypes of HIV-1 [26] or HIV-2 [27,28]. The monitoring of the presence of the co-infection as well as events of superinfection by a second strain of HIV-1 is crucial to know the effectiveness of the immunity induced by the initial infection in conferring protection against subsequent challenges. The development and evaluation of the currently used diagnostic tests have been based primarily on the subtype B strains from North America and Europe. Thus, the sensitivity of these tests in detecting divergent strains like group O and group M subtypes, other than subtype B requires further evaluation. In addition, the rapid tests used in many developing countries are reliably sensitive to prevailing typically non-B subtypes which is another source of concern. Active surveillance and characterization of the prevailing HIV strains are essential to

validate the sensitivity of HIV tests in clinical practice and research use.

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